Automatic and manual prediction of epileptic seizures based on ECG

Manef BEN MBAREK
manef2009@gmail.com
Université de Monastir
Ines ASSALI
Université de Monastir
Salah HAMDI
Laboratoire de Technologie et Imagerie Médicale, Faculté de Médecine de Monastir, Université de Monastir, 5019, Monastir, Tunisie
Asma BEN ABDALLAH
Université de Monastir
Olivier DAVID
Institut de Neurosciences des Systèmes - Inserm UMR1106 - Aix-Marseille Universit´e - Facult´e de M´edecine
Mouna AISSI
Hopital Universitaire Fattouma Bourguiba
Marcel CARRERE
Institut de Neurosciences des Systèmes - Inserm UMR1106 - Aix-Marseille Universit´e - Facult´e de M´edecine
Mohamed HEDI BEDOUI
Laboratoire de Technologie et Imagerie Médicale, Faculté de Médecine de Monastir, Université de Monastir, 5019, Monastir, Tunisie

Research Article

Keywords: Electrocardiogram, Epilepsy, Prediction, Epileptic Seizures, threshold, Heart rate variability analysis

Posted Date: January 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2456761/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Signal, Image and Video Processing on March 15th, 2024. See the published version at https://doi.org/10.1007/s11760-024-03063-x.

Abstract

This study presents a new attempt to quantify and predict changes in the ECG signal in the pre-ictal period. In the proposed approach, threshold techniques were applied to the standard deviation (STD) of two Heart rate variability features (The number of heartbeats per two minutes and approximate entropy) computed to ensure prediction and quantification of the pre-ictal state. We analyzed clinical data taken from two epileptic public databases, Siena Scalp EEG and Post-Ictal Heart Rate Oscillations in Partial Epilepsy and a local database. By testing the proposed approach on the Siena scalp EEG database, we achieved a sensitivity of 100%, specificity of 95%, and an accuracy of 96.4% whereas using acquisitions from the post-Ictal database, we achieved a sensitivity of 100%, specificity of 91% and an accuracy of 94% and using the local database we achieved a sensitivity of 100%, a specificity of 97% and an accuracy of 97.5%. Furthermore, the proposed approach predicted 58.7%, 57.2, and 40% of the seizures before the onset by more than 10 min for the data taken from post-ictal, local and Siena database, respectively. Using the automatic threshold technique, we were able to achieve a sensitivity, specificity, and accuracy of 85%, 81%, 82% using our local database respectively, whereas using acquisitions take from the Siena Scalp EEG database, we achieved a sensitivity of 75%, specificity of 85% and an accuracy of 82%. Besides, using the post-ictal database, we achieved a sensitivity of 90%, a specificity of 83% and an accuracy of 85%.

1 Introduction

Epilepsy is one of the most common neurological disorders [1]. This disorder is mainly characterized by a perdurable predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. This disorder is characterized by recurrent and unpredictable interruptions of normal brain function called epileptic seizures. An epileptic seizure is defined conceptually as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2], [3]. Epilepsy has become the second-highest incidence of cerebrovascular diseases and about 1% of the world's population suffers from epilepsy [4–5]. Epilepsy disorder affects all ages [6]. In the USA, more than 500 thousand patients are older than 65 years and more than 300 thousand patients are younger than 14. Despite the introduction of new antiepileptic drugs in the last decades, one-third of people with epilepsy continue to have seizures despite treatments [7]. Epileptic seizures are often thought to have a well-defined onset time determined by EEG and or clinical signs (semiology). However, some persons suffering from epilepsy can feel the seizures coming before it is registered on EEG (prodrome which is an early symptom that indicates the onset), indicating that physiological changes happen in the pre-ictal period before the seizures arise [8]. In most cases, the EEG monitoring which presents the gold standard in neurology for clinical monitoring of seizure activities is usually unavailable [9]. Moreover, monitoring the seizure activity based on the use of EEG signals is not always easy and accessible for several reasons and can be made only by highly trained neurologists expert which presents an expensive task and time consuming [10]. In addition, abrasive paste and electrolyte gel are sticky products that make hair scalp dirty and could be harmful [11]. Furthermore, specialists are wasting time trying to reduce the impedance of electrodes to an acceptable value where a countdown begins when the gel dries causing the disappearance of the transudative properties [12]. For that reason, ECG is a very useful signal as it is routinely monitored, and compared to EEG, a trained specialist is not required for ECG recording. Besides, ECG signal has a higher signal-to-noise ratio than EEG signal [9].

The epileptic seizures (partial and generalized) affect behavior of autonomic function during all periods: preictal, ictal, and post-ictal. Moreover, the sympathetic nervous activity is activated by seizures which leads to an increase in heart rate and blood pressure [13]. For that reason, several works tried to demonstrate and quantify the significant changes in ECG signal in the preictal period. A power spectrum analysis on 6 seizures taken from three patients (2 females, 1 male) in [8] showed a clear significant increase of the curve of the reciprocal HF-power just around the onset time of epileptic seizure. The authors used ECG data from 25 to 30 min pre-seizure up to 30 to 300 seconds post-seizure of ECG. Moreover, a random season of 30 min ECG acquisition not within 4 hours of seizures was used as a non-seizure control period. In fact, no significant changes were reported in this study for the LF, VHF, LF/HF, and LF/(LF + HF) frequency features analyzed. [14] presents an investigation of the changes in the ECG in the pre-ictal period. In this study, four clustering techniques (K-means clustering, Agglomerative hierarchical clustering, Density-based spatial clustering (DBSCAN), and Expectation-maximization (EM) clustering) were used in order to quantify changes in the pre-ictal period using three-features combination extracted from 32 HRV features (linear and non-linear). HRV features were extracted from 120 min of signal preceding the seizures and time preceding the seizure prediction horizon (SPH) of 10 min. Using the clustering techniques, the author was able to distinguish 41% of the seizures and 90% of the patients. In addition, changes predicted in the intervals 40 − 0 min before seizures were more prominent than in other intervals with 47 seizures 53% of all the seizures studied. In the same study, for the interval of 80 − 40 min only 21 seizures, which is 28% of all the seizures studied allow to obtain predictions. Then, for the last finding interval 80–120 min, 25 seizures, which present 24% of all the seizures studied were predicted. Furthermore, the authors reported that time-domain features RRmax, RRmin, and RRmean were the most relevant features. Moreover, they found that the following features in terms of predictability are LF/HF, pNN50, NN50, and

RQA ENT. Other works on prediction of epileptic seizures based only on ECG such [15], where the authors used a set of 8 linear and non-linear features (which are: RRI, Mean HR, LF, HF, LF/HF, SD1, SD2 and SD2/SD1) extracted from the data taken from a public database [16] which consists of 11 seizures taken from 7 subjects. Besides, using the threshold technique, authors reported a prediction sensitivity of 86.2%. In fact, a thresholding value was fixed for each patient. They also reported that features likes mean HR, LF/HF, and SD2/SD significantly increased while the RRI significantly decrease. Moreover, most of the observed changes in the features occurred 15 minutes before the seizures. In the work [17], authors studied the data taken from the public database [16]. Moreover, to predict the epileptic seizure, authors used a threshold technique and SVM using temporal features and spectral features. The temporal features are the Hjorth features: activity, mobility and complexity where the spectral features are spectral entropy and means of absolute derivation. These authors reported that the threshold technique was better than the SVM for epileptic seizure prediction and reported a prediction performance of 94.2% as accuracy, a sensitivity of 84.1% and a specificity of 94.5%. The work [18] studied 170 seizures taken from 16 patients where time and frequency domain features were computed. Adaptative threshold techniques were used and a threshold value was fixed for each patient separately. The proposed approach achieved a sensitivity of 75% and a false positive rate per hour (FP/h) rate of 0.21 with fixed a seizure occurrence period (SOP) of 4:30 and an intervention tile (IT) of 110 seconds. The author also reported that between 30 – 15 minutes before the seizure's onset: mean HR, RRI, LF/HF, and SD2/SD1 showed significant changes. In the approach proposed by [19], seizure prediction approach was proposed based on the use of an SVM classifier with Eigen decomposition HRV features based on covariance matrices. These authors of this work used a total of 34 seizures taken from 12 patients (a total of 55.2 hours of inter-ictal recording) and 123.6 hours of ECG acquisitions taken from healthy subjects. The proposed approach predicted seizures onset from 5 min to just before the seizure with a sensitivity of 94.1%, false-positive per hour (FP/h) of 0.49 in patients with epilepsy, and 0.19 in healthy patients.

This work aimed to study changes in the ECG signal in the pre-ictal period to explore the feasibility of creating an automatic epileptic seizure prediction approach, in which the result of the application of the statistical operator standard deviation (STD) on the computed HRV features is used as input for a thresholding technique in order to quantify the changes in the input pre-ictal ECG signal. The feasibility of our study was carried out using ECG acquisitions of a public and local databases consisting of 31 patients and a healthy public database consisting of forty patients.

2 Material And Methodology

2.1. Dataset

2.1.1. Siena Scalp EEG Database (version 1.0.0)

To address our objective (establishing the feasibility of our methodology to quantify the epileptic seizures), we focused exclusively on ECG acquisitions of epileptic patients from a public database. The Siena Scalp EEG Database is free to use on the Physionet platform (https://physionet.org/content/siena-scalp-eeg/1.0.0/). The database consists of data acquired from 14 epileptic patients: 9 males (ages 36–71) and 5 females (ages 20–58), within the Unit of Neurology and Neurophysiology at the University of Siena, Italy. The data contains synchronized EEG-ECG recordings of pathologic patients acquired based on the use of EB Neuro and Natus Quantum LTM amplifiers, and reusable silver/gold cup electrodes. The electrodes used in the acquisition were arranged according to the international 10–20 system. During data acquisition, patients were asked to stay in bed as much as possible, either asleep or awake [20]. All the data recorded were revised by expert clinicians according to the criteria of the International League Against Epilepsy. More information about the patients, seizures, and signals' duration can be seen in Table 1.

Table 1
Siena Scalp EEG Database Patients [17]

patient	age	gender	seizure	localization	lateralization	EEG_channel	ECG_channel	N° seizures	Signal's_duration
PN00	55	Male	IAS	T	R	29	2	5	198 min
PN01	46	Male	IAS	T	L	29	2	2	809 min
PN03	54	Male	IAS	T	R	29	2	2	752 min
PN05	51	Female	IAS	T	L	29	2	3	359 min
PN06	36	Male	IAS	T	L	29	2	5	722 min
PN07	20	Female	IAS	T	L	29	2	1	523 min
PN09	27	Female	IAS	T	L	29	2	3	410 min
PN10	25	Male	FBTC	F	Bilateral	20	2	10	1002 min
PN11	58	Female	IAS	T	R	29	2	1	145 min
PN12	71	Male	IAS	T	L	29	2	4	246 min
PN13	34	Female	IAS	T	L	29	2	3	519 min
PN14	49	Male	WIAS	T	L	29	2	4	1408 min
PN16	41	Female	IAS	T	L	29	2	2	303 min
PN17	42	Male	IAS	T	R	29	2	2	308 min

2.1.2. Post-Ictal Heart Rate Oscillations in Partial Epilepsy 1.0.0

The Post-Ictal database is available free on the Physionet platform. The database consists of 10 seizures recorded from 7 women patients aged from 31 to 48 years old. The duration of the recorded ECG signals vary from two to four hours with a sampling rate of 200 Hz, 12 bits per sample, and 5 mV. Besides, for each acquisition, the exact time of onset and offset of seizures were specified by an expert [17].

2.1.3. Local data:

The local database consists of 14 ECG acquisitions taken from 13 patients aged between 8 and 42 years old. Experimental data were selected from the F-TRACT database of spontaneous video-SEEG seizures (research protocol INSERM IRB 14–140). The patients gave their consent to undergo invasive recordings and peripheral recordings as part of a presurgical evaluation of their drug-resistant epilepsy. SEEG/ECG recordings were performed using a video-EEG monitoring system (Micromed, Treviso, Italy) that allowed for simultaneously recording up to 256 monopolar contacts. Sampling rate was either 256 or 512 Hz, with an acquisition band-pass filter between 0.1 and 90 Hz or between 0.1 and 200 Hz respectively, depending on amplifier capacities at the date of recordings. Data were acquired using a referential montage with reference electrode chosen in the white matter. The table below presents a description of the patient's health (age, gender, epilepsy type and lesion) [21]

Table 2
Local database description

Patient Code	Age	Gender	Epilepsy type	Lesion
Patient 1	12	Female	Left frontal dysplasia	Left frontal dysplasia
Patient 2	22	Female	Bilateral temporo-frontal	bilateral peri-ventricular junction heterotopia
Patient 3	14	Male	Right frontal temporal parietal	thickening of right temporo-parietal junction, T2
Patient 4	14	Male	Left Temporal insular	No
Patient 5	35	Female	Right frontal	No
Patient 6	15	Female	Right temporal insular	No
Patient 7	15	Male	Left parietal insular	No
Patient 8	13	Female	Right frontal	frontal dorsolateral / premotor
Patient 9	8	Female	No information	No information
Patient 10	42	Female	No information	No information
Patient 11	39	Male	Right temporal	right temporo-polar juxta-cortical focal lesion
Patient 12	38	Male	No information	No information
Patient 13	31	Male	Left central insular parietal	No

2.1.4. Data manipulation

To study changes in the ECG signal in the pre-ictal phase, we took 1 hour of ECG signal before seizures and 5 min after seizures. If the acquisition does not contain at least 1h of signal before seizure, we use all the provided pre-ictal in our work. Moreover, We only used data from the patients where at least one readable ECG acquisition is available. In fact, the Siena scalp database was made only for epileptic EEG analysis. For that reason, some of the ECG acquisitions are unreadable where they can contain a lot of noise, especially from 20 min before the seizure's onset which allow to study the variation of the input ECG signal in the pre-ictal period. The existence of such noises is due to either patient movements or bad connection of the ECG electrodes with patients skin.

From the Siena scalp database, we were able to study only acquisitions from 11 patients after deleting all unreadable and very noisy ECG acquisitions. From the 11 patients, only 34 seizures were studied after getting rid of the unreadable acquisitions. In addition, Patient PN16 was excluded from this study because both of his seizures were recorded during sleep. From the Post-Ictal database, all the seizures were used in our study.

Moreover, in order to improve our analysis, we also used inter-ictal segments in our study taken from all the studied patients. We extracted 8h of pre-ictal period from the Post-Ictal database, 29 hours from the Siena scalp EEG database and 14 hours from the local database. The heart rate takes some time after seizures to back to the basic signal rate. The first five minutes after seizures are considered as post-ictal instabilities and we do not take it into consideration. In our work, the inter-ictal period will be considered from at least 5 min after the onset. And also, inter-ictal segments are considered before the one hours signal in front of the onset which is the pre-ictal segments. In addition, we only extracted inter-ictal segments where at least 20 min of continuous signal so we can analyze all changes in the segments. Moreover, to maximize the number of segments of the inter-ictal period, the whole inter-ictal signal extracted was divided into sub-segments of 20 min length each to obtain 24 inter-ictal segments from the Post-Ictal database, 87 inter-ictal segments from the Siena scalp EEG database and 63 inter-ictal segments from the local database.

2.2. Pre-processing and features extraction

In order to improve the R peaks detections, we apply multiple noises (such as the baseline wander, Power-line Interference, and Electromyography noise) removal functions. For that reason, we used a notch filter followed by the application of two Butterworth filters (high pass and low filters with order 2). Furthermore, our notch filter was used to remove the power-line interference with a 50Hz cutoff (this cutoff should be 50/60Hz). Then, the cutoff of the high-pass and the low-pass filters were set to 20Hz and 10 Hz respectively.

The next step in our approach is our detection of the R peaks series. For that reason, we used the QRS detection approach proposed in [22] which is based on the use of two moving average windows with a thresholding technique to detect the QRS complexes and extract the R-peak series from the input signal.

In order to demonstrate the variations of the ECG signal, we extracted time-domain analysis and non-linear features that reflect dynamic changes of the input signal during the different stages of the signal: pre-ictal, seizure onset, and after seizure. Then, the time domain analysis features extracted are directly calculated from the time series of the extracted RR intervals (RRi). Then, we compute the number of the RRi distances extracted from the signal segment. The number of the RRi distance in the signal segment (NRRi) will directly reflect the dynamic changes (increase and decrease) of the heart rate.

Next, in order to quantify unpredictability of a time series and complexity of mechanisms that regulate the HRV, a nonlinear metrics approximate entropy (ApEn) is computed. The ApEn is devised in order to quantify the regularity, correlation, and persistence in time series. At first, the ApEn was developed in order to analyze medical data, essentially the heart rate [23]. Which mean, a high ApEn values refer to the independence between the data signals (a low number of repeated patterns and randomness), and low ApEn values refer to a very persistent system (repetitive and predictive). In addition, a zero value of ApEn indicates a fully predictable series [24]. As for the Sample entropy, two variables will be needed to compute the ApEn, a factor noise factor r and a template's length m (the different vector's window length). Moreover, the higher the value of m and the smaller the value of r describe details of sharper parameters. Taken a sequence of number $u = \{u(1), u(2), \ldots, u(N)\}$ with length N, real positive value r and integer m where $0 \leq m \leq N$. We define two blocks $x(i) = \{u(i), u(i+1), \ldots, u(im-1)\}$and $x(j) = \{u(j), u(j+1), \ldots, u(j+m-1)\}$. Next, the distance of those two blocks is computed as follow:

$$d[x(i), x(j)] = Max_{k=1,\ldots,m}(|u(i+k-1) - u(j+k-1)|) \quad (1)$$

Then

$$c_i^m(r) = \frac{numberofj \leq N-m+1, suchthatd[x(i), x(j)] \leq r}{(N-m+1)} \quad (2)$$

c_i^m counts the number of consecutive blocks of length m within the resolution r which are similar to a given block Computing:

$$\varphi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} logc_i^m(r) \quad (3)$$

Then, the ApEn can be computed as follow [24–25]

$$ApEn(m, r, N) = \varphi^m(r) - \varphi^{m+1}(r) \quad (4)$$

In order to have more information about the signal, a sliding window with an overlapping was used. Besides, to select the optimal sliding window and the overlapping window, we selected randomly 10 acquisitions from different patients to test several variations of sliding windows starting from 30 seconds up to 300 seconds. Then, the overlapping windows starting from 10 seconds up to 60 seconds of ECG signal were tested to search for an optimum. Figure 1 shows an example of the use of the sliding window technique with an overlapping window where in this example, W_0 presents an overlapping window of 10 seconds.

Finally, after testing several sliding and overlapping windows, a sliding window of 120 seconds with an overlapping of 10 seconds reflected the best combination to quantify the changes of the ApEn curves in the pre-ictal period.

2.3. Prediction

After computing the RRI, our approach consists of computing two linear and non-linear features: NRRi and approximate entropy (ApEn) using a sliding window with an overlapping technique. Then, based on the results of computing both NRRi and ApEn features, the standard deviation (STD) was computed using a sliding window of six values. Mathematically, the STD is computing by the following equation $[26]$.

$$STD = \sqrt{\frac{\sum(X_i - \bar{X})}{n-1}} \quad (5)$$

Where Xi presents the value at position i, $\bar{X}$ presents the means of all values in the sample, n is the number of the values in the sample.

Figure 2 shows the result of computing the ApEN feature based on the use of RRi extractred from ECG signal taken from patient PN09-3 from the Siena scalp EEG database. Besides, the same figure demonstrates the results of computing the STD operator using ApEn. In same way, Figure 3 demonstrates the result of computing the NRRi features STD operator using NRRi results extractred from the same acquisition used in Figure 2.

In order to certify a crisis alert, the STD calculation results calculated from these two features were combined. In addition, the threshold method was used on the STD results to ensure crisis prediction. The threshold value with the best prediction results was selected. In our work, tests were applied on the pre-ictal and the inter-ictal segments to select the best threshold value where each patient was separately studied. Furthermore, a crisis alert is predicted if and only if the threshold exceeded both the STD curves of ApEn and NRRi.

3 Results And Discussion

In order to measure performance of our proposed approach, pre-ictal and inter-ictal data taken from both epileptic databases were tested. From the Siena scalp EEG database, we were able to extract 34 seizures taken from 11 patients studied. Moreover, none of noisy or in-sleep acquisitions were taken into consideration. Besides, all of the 10 seizures from the Post-Ictal database were analyzed. In addition, we used 8h of the inter-ictal signal taken from the Post-Ictal database and 29h of inter-ictal signal taken from the Siena scalp EEG database. The whole inter-ictal signal extracted was divided into sub-segments of 20 min length each to obtain 24 inter-ictal segments from the Post-Ictal database, 87 segments from the Siena scalp EEG database and 63 inter-ictal segments from the local database.

In order to characterize the predicting of the epileptic seizure, three criteria were introduced which are sensitivity, specificity, and accuracy. The sensitivity reflects the probability of a positive detection whereas specificity reflects the probability of true detection of the non-seizure segment (inter-ictal segment):

True positive (TP): pre-ictal segment identified as a pre-ictal segment.

False-negative (FN): pre-ictal segment incorrectly identified as an inter-ictal segment.

False-positive (FP): inter-ictal segment identified as a pre-ictal segment.

True negative (TN): inter-ictal segment identified as an inter-ictal segment.

The three criteria proposed are computed as follows:

$$Sensitivity = \frac{TP}{TP + FN} * 100 \quad (6)$$

$$Specificity = \frac{TN}{TN + FP} * 100 \quad (7)$$

$$Accuracy = \frac{(TP + TN)}{(TP + FP + TN + FN)} \quad (8)$$

Based on the three criteria proposed, we compared our analysis with two other works that used the threshold technique to predict epileptic seizures. As all the analysis were extracted from the Post-Ictal database, we present in the following table our results:

Table 3
The comparison of the proposed approach performance with the approaches from the stat of art using post-ictal database

	Sensitivity	Specificity	accuracy
[15]	88.3%	86.2%	-
[17]	94.2%	84.1%	94.5%
Proposed approach	100%	91%	94%

As can be seen in Table 4, our proposed approach achieved a highest value of sensitivity and specificity compared to the other works. However, the proposed approach in [17] achieved a better accuracy than our approach, where the work [15] did not mention his accuracy. Moreover, the proposed approach also showed a prediction latency much better than both approaches seen in the stat of arts. However, none of the two works have specified in his proposed methodology the length of the pre-ictal and inter-ictal segment studied compared to us. Besides, no information was mentioned about the number of inter-ictal segments used to measure the performance of their approaches.

We also compared the prediction latency of the proposed approach with the other approaches seen in the state of arts as it can be seen in Table 4. In fact, in some acquisitions, we can see that there's no very huge different between the prediction delay of our approach compared with [17] (both threshold and SVM results) such as for patient 1, patient 5. Otherwise, our approach predicted the epileptic seizure before 43.08 min, 22.32 min and before 46.5 min, 35.84 min for both seizures of patient 2 and patient 6 respectively.

Table 4
Comparison between the prediction delay of our work with the stat of arts works using the post-ictal database

Patient		[15]	[17]	[17]	Our approach
	Seizure number	Threshold	Threshold	SVM	threshold
Patient 1	Seizure 1	-	0 s	20 s	15 s
Patient 2	Seizure 1	-	30 s	7 s	43.08 min
Patient 2	Seizure 2	-	6 s	9 s	22.32 min
Patient 3	Seizure 1	-	20 s	26 s	25.8 s
Patient 3	Seizure 2	-	3 s	3 s	37.8 s
Patient 4	Seizure 1	-	8 s	20 s	10 s
Patient 5	Seizure 1	-	0 s	53 s	24 s
Patient 6	Seizure 1	-	35 s	35 s	46.5 min
Patient 6	Seizure 2	-	-	-	35.84 min
Patient 7	Seizure 1	-	0 s	28 s	56.4 s

Similarly, we tested the performance of the proposed approach on the local database as can be seen in Table 5. The proposed approach achieved a sensitivity of 100%, a specificity of 97% and an accuracy of 97.5%. The local database consists of acquisitions taken from 14 patients with different seizures type which prove the feasibility of the proposed approach to predict the epileptic seizures using ECG of different seizures type. Moreover, from 63 inter-ictal segments, only two false alerts were returned by our approach.

Table 5
The Performance of the proposed approach using the local database

	Sensitivity	Specificity	Accuracy
Local data base	100%	97%	97.5%

Table 6 presents the delay prediction of the proposed approach using the local database data. All patients in this database are presented with only one seizure expect patient 13. Our proposed approach was able to achieve a prediction delay starting from few seconds before the seizure up to more than 15 min before the seizure.

Table 6
Prediction delay of the proposed approach using the local database

Patient	Seizure number	delay
Patient 1	Seizure 1	6s
Patient 2	Seizure 1	50 min
Patient 3	Seizure 1	7.4 min
Patient 4	Seizure 1	10.5 min
Patient 5	Seizure 1	81 s
Patient 6	Seizure 1	16.21 min
Patient 7	Seizure 1	25.2 s
Patient 8	Seizure 1	3 s
Patient 9	Seizure 1	13.14 min
Patient 10	Seizure 1	25.8 s
Patient 11	Seizure 1	48.04 min
Patient 12	Seizure 1	21.18 min
Patient 13	Seizure 1	54 min
Patient 13	Seizure 2	60 min

We also measured the performance of the proposed approach using the epileptic database Siena scalp EEG database as can be seen in Table 7. The Siena scalp database is composed of acquisitions with IAS, focal onset without impaired awareness (WIAS), and bilateral seizures, where the majority of the acquisitions are IAS. For that reason, the performance of the proposed approach was measured firstly using only IAS acquisitions and then with all the acquisitions extracted from the database.

As it can be seen In Table 7, using only the acquisitions with IAS seizure, our approach was able to achieve a sensitivity of 100%, specificity of 95%, and an accuracy of 96.4%. However, using all the acquisitions (different seizures type) we achieved a sensitivity of 85%, a specificity of 94%, and an accuracy of 91.5%. Unfortunately, we cannot compare this performance with other approaches because to the best of our knowledge, we are the first work that studied the effect of epileptic seizures on the ECG signal using the new public database Siena scalp.

Using only data taken from patients with the IAS seizures, from the 61 inter-ictal segments, our approach sent a false alert only on 3 inter-ictal segments where they showed unexpected changes in both curves. In fact, expect all patients with temporal epileptic seizures in the Siena scalp EEG database, patient PN14 is the only one who had WIAS where we were able to study only two seizures (the rest contain a lot of noise), and our approach predicted only one of the two seizures studied. Subject PN10 presents only patients in the database who suffer from Bilateral epileptic seizures. Our approach was able to predict only 5 seizures from 8 seizures studied. No more investigations could be made to assume why no seizure alert was triggered for those acquisitions taken from both PN10 and PN14 patients, especially due to a lack of patient data with the same type of seizures.

Table 7
The performance of the proposed approach using the Siena scalp EEG database

	Sensitivity	Specificity	Accuracy
Only IAS	100%	95%	96.4%
All patients	85%	94%	91.5%

Figure 4 presents the prediction delay of the proposed approach using the Siena scalp and the local database. The blue and orange points reflect the prediction delay for the Siena and the local databases, respectively. As it can be seen in these Fig. 4, the prediction delay vary from a few seconds before the seizure up to more than 15–20 min before the seizure depending on patients. In Addition, for almost all patients with more than one seizure acquisition, the prediction time of the different seizures were close to each other. Moreover, green points reflect the mean prediction delay of the Siena database acquisitions, which reflects our high prediction delay achieved.

Table 8 presents the percentage of the predicted seizures by the time of prediction, either between 0 to 5 min, 5 to 10 min or predicted before the seizure by more than 10 min. As it can be seen, in the table, our approach was able to predict 58.7% and 57.2% of the seizure before more than 10 min for both post-ictal and local database, respectively. For the Siena database, our approach was able to predict only 40% of the seizures before 10 min from the onset.

Table 8
Percentage of the predicted seizure by the prediction time

Database	Prediction time		
	[0–5min]	[5min – 10min]	10 min <
Post-ictal database	37.9%	3.4%	58.7%
Local database	35.7%	7.1%	57.2%
Siena database	60%	0%	40%

Figure 5 shows an example of the STD operator calculation on the ECG signal taken from the epileptic patient 9 taken from the Siena scalp EEG database. In this example, the red discontinuous line presents the moment of the seizure. In fact, our approach was able to quantify and predict epileptic seizures before 33.6 seconds.

In this work, we also proposed an automatic threshold technique for onset prediction. We believe that for normal patients, the variation of both features (ApEn and NRRi), especially the NRRi, which presents the heart rate changes, varies around the value of the mean. For that reason, the proposed approach consists of using the mean of the STD computed from both ApEn and NRRi features. Moreover, based on the use of the STD curves computed, the automatic threshold approach proposed consists of using a five min data segment with one minute overlapping. Next, for each segment, the threshold value is computed following list of equations:

$$Thresh = Mean + \beta \, (9)$$

- Where $Mean$ presents the mean value of the input data segment.
- β is a value computed from $Mean$ where the value of β will be in the range of values [0 – $Mean$], where the min value of β will equal to 0 and the max will equal to the value of $Mean$
- For selecting the β value, a Grid-search algorithm will be used to test all the possible threshold values.
- We first test all the possible values of β using only the Inter-ictal period to find the values which will return the less false alerts. Then, the pre-ictal periods will be used to select the proper β value that will return the best performance (maximum onset prediction and the less false alerts results) to be selected.
- The β value will be selected for each patient separately.

Table 9 presents the results of testing the performance of the automatic threshold prediction approach using the same three databases used with the manual threshold technique. In fact, acquisitions of less than 10 min in length will not be taken into consideration in this

part of the work.

Table 9
The performance of the automatic threshold approach using local database

	Sensitivity	Specificity	Accuracy
The local Database	85%	81%	82%
Siena Scalp EEG Database	75%	85%	82%
Post-ictal Database	90%	83%	85%

From the results presented in the tables above, the prediction approach using the manual threshold value selection gave a better result. In fact, the proposed automatic threshold technique is based on the mean of the two features computed. In fact, even for the inter-ictal period, if the changes (peak) in both curves' features is instantly, even if these changes are small compared to pre-ictal period, this kind of change is considered as a prediction by our automatic proposed approach (false alert). Another weak point in our proposed automatic threshold technique is the gradual increase of the value. If the values of both curves increase gradually in time, the threshold value also will increase gradually with the curves which will lead to unpredicted seizure. For those reasons, a manual threshold selection technique gave of course better results. In the inverse, the manual threshold selection is not sensible of this kind of those problems. Figure 6 presents an example of application of the automatic threshold approach proposed on the second acquisition of patient number 6 from the Siena Scalp EEG database.

For almost all the acquisitions studied, significant changes for both features NRRi and ApEn were seen in the pre-ictal period of the input ECG signal. In fact, a significant decrease was seen in the NRRi features, especially right before the seizure. This increase can be explained by the fact that about 82% of epileptic seizures are associated with ictal tachycardia which proceeds the epileptic seizures [19]. In addition, the features ApEn showed significant change in the pre-ictal period, and a clear decrease was seen for almost all the patients right before the seizure which can be associated with the increase in the sympathetic activity [19].

In this work, not only ApEn and NRRi features were studied. In fact, to quantify complexity of mechanisms that regulate the HRV, we started with several features such as ApEn, sample, fuzzy, Shannon and spectral entropy. Moreover, to study temporal changes in the HRV, we studied several features such as the standard deviation of the RR interval (SDNN), the root means of the root mean square of successive differences (RMSSD), the proportion of NRRi divided by the total number of RRs (pNN50). However, not all features studied showed significant changes to be used in our approach to ensure a good quantification and a good prediction of the epileptic seizures except both NRRi and ApEn which showed a significant correlated change in the pre-ictal period and inter-ictal period. In this part of the paper, we describe some significant changes in the other features studied which can be used to predict epileptic seizures. Only acquisitions taken from the Siena scalp EEG database are studied, where no information about localization, lateralization, or even the seizure types was given for the acquisitions taken from the post-Ictal database. Besides, the local database contains mixed acquisitions for adults and children, and we still don't know if the HRV will react in the same way for both categories.

A significant change in the sample and fuzzy entropy curves was seen starting approximately 30 min before the seizure for patients PN06, PN10 (bilateral seizure), and PN14 (starting from the interrupted green line, where the red line presents the start of the seizure). Whereas for patient PN09, these changes occurred starting before the seizure by 15 min. In the same way, for both fuzzy and sample entropy curves, a clearly significant decrease is seen either at the moments of the seizure or just after the seizure for all the acquisitions studied. These decreases are not seen for only patient PN10-2 as can be seen in Fig. 7 and Fig. 8.

Studying the SDNN feature in the pre-ictal period showed a slight decrease of the SDNN curve for patient PN06 starting before the seizure by 25 min (in blue color), PN10 (bilateral seizure) showed a significant decrease between 30 min to 8 min before the seizure, while a significant change was seen for patient PN09 14 min before the seizure. Moreover, a significant increase in the SDNN curve was seen starting from the moment of the seizure for patients PN06, PN09, and PN14 as can be seen in Fig. 9.

The proposed epileptic seizure prediction approach is based on the threshold technique. For that reason, we can't measure the performance of the proposed approach to differentiate between the Pre-ictal period of epileptic patients and the ECG of healthy subjects. For that reason, we are going to use a statistical operator in order to distinguish between features computed from epileptic and healthy patients. In our case, we are studying continuous data where we are searching to show all differences between data studied.

Next, in our case, the idea is to use a mean-based algorithm because the variation of both features (ApEn and NRRi) especially the NRRi varies around the average for normal patients. Next, we only have two groups of data and neither of them follow the normal distribution (gaussian distribution), so we need to use a non-parametric algorithm where we end up with the Mann-Whitney algorithm. In fact, the Mann-Whitney U test will be used to compare differences between these two independent groups which tests our hypothesis that these two groups are extracted from a same population (p). Besides. Mann-Whitney U test can be applied even on a small number of data between 5–20 values and larger group of data (> 20). In counter, the performance of the Mann Whitney algorithm increase with more input data [27].

As can be seen in the Figs. 10, 11, 12, 13 there's a significant difference between the feature NRRi distribution taken from epileptic and healthy patients. The NNRi value range is ranged from 80 to 160 but for the epileptic patients is ranged from less than 100 up to more than 250. Moreover, for the healthy patients, the value's distribution is spread outcompared to the epileptic distribution which is concentrated in value intervals [125–150]. In the same way, as it can be seen in Figs. 10, 11, a huge difference can be seen when comparing the histogram distribution of the ApEn feature of epileptic and healthy subjects where the healthy distribution is more spread outcompared to the epileptic distribution. Moreover, the epileptic distribution is more concentrated around the value 0.8 compared to the healthy distribution where the concentration of the values is more spread outin the range of [0.6–0.9].

To more prove the difference between both data. The Mann-Whitney algorithm was used. In fact, the statistical P value given by the Mann-Whitney algorithm for both features taken from both kind of subjects (epileptic and healthy) is less than null hypothesis 0.05 which mean that both distributions are not from the same category, especially for the NRRI features distribution.

In fact, further research needs to address the limitations of the proposed work, which includes only a small number of subjects in the study. Moreover, all patients from the Siena scalp database suffer from IAS seizures with only one patient with WIAS seizure and only one patient with bilateral seizure. For that reason, no investigations can be made on the effects of the seizure's type on the ECG signal in the pre-ictal period. In addition, it would be more important to study pre-ictal and inter-ictal periods of ECG acquisitions taken under the same conditions to have more accurate results and contributions not from three separated databases. In addition, having the clinical details about patients' medical history, more information about the patient's condition, and video monitoring can lead to better explications about the changes in the ECG signal and be 100% confident of the contributions made by the proposed methodology. In addition, with more ECG acquisitions, another study can be made to compare the effect of the epileptic seizures on the pre-ictal state of acquisitions taken from both children and adults. Nevertheless, another investigation could be done on the effect of the epileptic seizures in the pre-ictal period based on the use of other frequency-domain features and non-linear features analysis based on the chaos theory to more understand the effect of the epileptic seizure on the ECG signal. Furthermore, the HRV-based epileptic seizures prediction approach could be proposed in order to quantify the results of our work and the works that proved the effectiveness of epileptic seizures on the ECG signal.

4 Conclusion

In this study, we proposed two new approaches to ensure the quantification of the significant changes in the pre-ictal period based on the use of the threshold technique on the STD curves. Moreover, the STD curves were computed using the time-domain analysis feature NRRi and the non-linear feature ApEn to reflect the high increase and the irregularity of the ECG signal before the epileptic seizures. Using the manual threshold approach on the IAS seizures taken from the Siena scalp EEG database, we achieved a sensitivity of 100%, specificity of 95%, and an accuracy of 96.4% whereas using the acquisition from the Post-Ictal database we achieved a sensitivity of 100%, specificity of 91% and an accuracy of 94%. and using the acquisitions from the local database, we achieved a sensitivity of 100%, a specificity of 97%, and an accuracy of 97.5%. Furthermore, the proposed approach predicted 58.7%, 57.2, 40% of the seizures before the onset by more than 10 min for the data taken from post-ictal, local and Siena database, respectively. Using the automatic threshold technique, we were able to achieve a sensitivity, specificity, and accuracy of 85%, 81%, 82% using the local database respectively, whereas using the acquisitions take from the Siena Scalp EEG database, we achieved a sensitivity of 75%, specificity of 85% and an accuracy of 82%. Besides, using the post-ictal database, we achieved a sensitivity of 90%, a specificity of 83% and an accuracy of 85%. In future work, additional ECG acquisitions will be collected and used to improve the performance of the proposed approaches and to give more credibility to the results obtained.

Declarations

Data availability

The datasets Siena Scalp EEG and Post-Ictal Heart Rate Oscillations in Partial Epilepsy analysed during the current study are available in the Physionet Platform [28], [16]. The local database analysed during the current study is available in the Functional Brain Tractography Project [29].

Declaration of competing interest

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.

Author contribution

M. BEN MBAREK., A. BEN ABDALLAH I., and M. CARRÈRE conceptualized the proposed idea. M. BEN MBAREK., I. ASSALI., S.HAMDI., A. BEN ABDALLAH, M. CARRÈRE, M.H. BEDOUI Checked the analytical methods. M. BEN MBAREK. O. DAVID and M. AISSI did the data Curation. M. BEN MBAREK. and M. CARRÈRE, I. ASSALI. analyzed the data. M. BEN MBAREK and M. CARRÈRE carried out the computations. M. BEN MBAREK., I. ASSALI., S.HAMDI., A. BEN ABDALLAH, M. CARRÈRE and M.H. BEDOUI contributed to the evaluation of the results. M. BEN MBAREK., A. BEN ABDALLAH, M. CARRÈRE and M.H BEDOUI wrote the manuscript in cooperation with the other authors. All authors discussed the results, contributed to the final manuscript, and have approved the final article.

References

1. P. Du, J. Dai, J. Li, and Q. Mal, “Nonlinear Granger causality and its application in the analysis of epileptic EEG and ECG signal,” Dec. 2015, pp. 1773–1776. doi: 10.2991/icmse-15.2015.320.
2. S. Behbahani, N. J. Dabanloo, A. M. Nasrabadi, C. A. Teixeira, and A. Dourado, “A new algorithm for detection of epileptic seizures based on HRV signal,” J. Exp. Theor. Artif. Intell., vol. 26, no. 2, pp. 251–265, Apr. 2014, doi: 10.1080/0952813X.2013.861874.
3. J. J. Falco-Walter, I. E. Scheffer, and R. S. Fisher, “The new definition and classification of seizures and epilepsy,” Epilepsy Res., vol. 139, pp. 73–79, Jan. 2018, doi: 10.1016/j.eplepsyres.2017.11.015.
4. H. Choubey and A. Pandey, “A combination of statistical parameters for the detection of epilepsy and EEG classification using ANN and KNN classifier,” *Signal Image Video Process.*, vol. 15, no. 3, pp. 475–483, Apr. 2021, doi: 10.1007/s11760-020-01767-4.
5. T. Sun *et al.*, “Analysis of Epilepsy EEG and ECG Correlation Based on IRC Algorithm,” in 2018 *International Conference on Information Systems and Computer Aided Education (ICISCAE)*, Jul. 2018, pp. 398–401. doi: 10.1109/ICISCAE.2018.8666912.
6. J. I. Sirven, “Epilepsy: A Spectrum Disorder,” Cold Spring Harb. Perspect. Med., vol. 5, no. 9, Sep. 2015, doi: 10.1101/cshperspect.a022848.
7. P. Kwan and M. J. Brodie, “Emerging drugs for epilepsy,” *Expert Opin. Emerg. Drugs*, vol. 12, no. 3, pp. 407–422, Sep. 2007, doi: 10.1517/14728214.12.3.407.
8. J. Jeppesen, S. Beniczky, A. Fuglsang-Frederiksen, P. Sidenius, and Y. Jasemian, “Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: a pilot study,” Technol. Health Care Off. J. Eur. Soc. Eng. Med., vol. 18, no. 6, pp. 417–426, 2010, doi: 10.3233/THC-2010-0606.
9. O. M. Doyle, B. R. Greene, W. Marnane, G. Lightbody, and G. B. Boylan, “Characterisation of heart rate changes and their correlation with EEG during neonatal seizures,” in 2008 *30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Aug. 2008, pp. 4984–4987. doi: 10.1109/IEMBS.2008.4650333.
10. A. B. Das, M. I. H. Bhuiyan, and S. M. S. Alam, “Classification of EEG signals using normal inverse Gaussian parameters in the dual-tree complex wavelet transform domain for seizure detection,” Signal Image Video Process., vol. 10, no. 2, pp. 259–266, Feb. 2016, doi: 10.1007/s11760-014-0736-2.
11. M. A. Lopez-Gordo, D. Sanchez-Morillo, and F. P. Valle, “Dry EEG Electrodes,” *Sensors*, vol. 14, no. 7, Art. no. 7, Jul. 2014, doi: 10.3390/s140712847.
12. G. Gargiulo *et al.*, “A new EEG recording system for passive dry electrodes,” Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol., vol. 121, no. 5, pp. 686–693, May 2010, doi: 10.1016/j.clinph.2009.12.025.
13. O. Devinsky, “Effects of Seizures on Autonomic and Cardiovascular Function,” Epilepsy Curr., vol. 4, no. 2, pp. 43–46, Mar. 2004, doi: 10.1111/j.1535-7597.2004.42001.x.
14. A. Leal *et al.*, “Heart rate variability analysis for the identification of the preictal interval in patients with drug-resistant epilepsy,” Sci. Rep., vol. 11, p. 5987, Mar. 2021, doi: 10.1038/s41598-021-85350-y.

15. M. K. Moridani and H. Farhadi, “Heart rate variability as a biomarker for epilepsy seizure prediction,” Bratisl. Lek. Listy, vol. 118, no. 1, pp. 3–8, 2017, doi: 10.4149/BLL_2017_001.
16. I. C. Al-Aweel *et al.*, “Post-Ictal Heart Rate Oscillations in Partial Epilepsy: Data and Analysis.” physionet.org, 1998. doi: 10.13026/C2QC72.
17. G. Shamim, Y. U. Khan, M. Sarfraz, and O. Farooq, “Epileptic seizure detection using heart rate variability,” in 2016 *International Conference on Signal Processing and Communication (ICSC)*, Dec. 2016, pp. 250–254. doi: 10.1109/ICSPCom.2016.7980585.
18. S. Behbahani, N. J. Dabanloo, A. M. Nasrabadi, and A. Dourado, “Prediction of epileptic seizures based on heart rate variability,” *Technol. Health Care Off. J. Eur. Soc. Eng. Med.*, vol. 24, no. 6, pp. 795–810, Nov. 2016, doi: 10.3233/THC-161225.
19. J. Pavei *et al.*, “Early Seizure Detection Based on Cardiac Autonomic Regulation Dynamics,” Front. Physiol., vol. 8, p. 765, 2017, doi: 10.3389/fphys.2017.00765.
20. P. Detti, G. Vatti, and G. Zabalo Manrique de Lara, “EEG Synchronization Analysis for Seizure Prediction: A Study on Data of Noninvasive Recordings,” *Processes*, vol. 8, no. 7, Art. no. 7, Jul. 2020, doi: 10.3390/pr8070846.
21. O. David, A. Woźniak, L. Minotti, and P. Kahane, “Preictal short-term plasticity induced by intracerebral 1 Hz stimulation.,” NeuroImage, vol. 39, no. 4, pp. 1633–46, Feb. 2008, doi: 10.1016/j.neuroimage.2007.11.005.
22. M. Elgendi, M. Jonkman, and F. De Boer, “Frequency bands effects on QRS detection: 3rd International Conference on Bio-inspired Systems and Signal Processing, BIOSIGNALS 2010,” *BIOSIGNALS 2010 - Proc. 3rd Int. Conf. Bio-Inpsired Syst. Signal Process.*, vol. 1, pp. 428–431, 2010.
23. S. M. Pincus, I. M. Gladstone, and R. A. Ehrenkranz, “A regularity statistic for medical data analysis,” *J. Clin. Monit.*, vol. 7, no. 4, pp. 335–345, Oct. 1991, doi: 10.1007/BF01619355.
24. F. Vanderlei, L. C. M. Vanderlei, L. C. de Abreu, and D. Garner, “Entropic Analysis of HRV in Obese Children,” *Int. Arch. Med.*, vol. 8, Sep. 2015, doi: 10.3823/1799.
25. J. S. Richman and J. R. Moorman, “Physiological time-series analysis using approximate entropy and sample entropy,” *Am. J. Physiol.-Heart Circ. Physiol.*, vol. 278, no. 6, pp. H2039–H2049, Jun. 2000, doi: 10.1152/ajpheart.2000.278.6.H2039.
26. D. Lee, J. In, and S. Lee, “Standard deviation and standard error of the mean,” *Korean J. Anesthesiol.*, vol. 68, pp. 220–3, Jun. 2015, doi: 10.4097/kjae.2015.68.3.220.
27. N. Nachar, “The Mann-Whitney U: A Test for Assessing Whether Two Independent Samples Come from the Same Distribution,” Tutor. Quant. Methods Psychol., vol. 4, Mar. 2008, doi: 10.20982/tqmp.04.1.p013.
28. Detti, Paolo, “Siena Scalp EEG Database.” PhysioNet. doi: 10.13026/5D4A-J060.
29. “Functional Brain Tractography Project – funded by the European Research Council.” https://f-tract.eu/ (accessed Oct. 26, 2022).

Figures

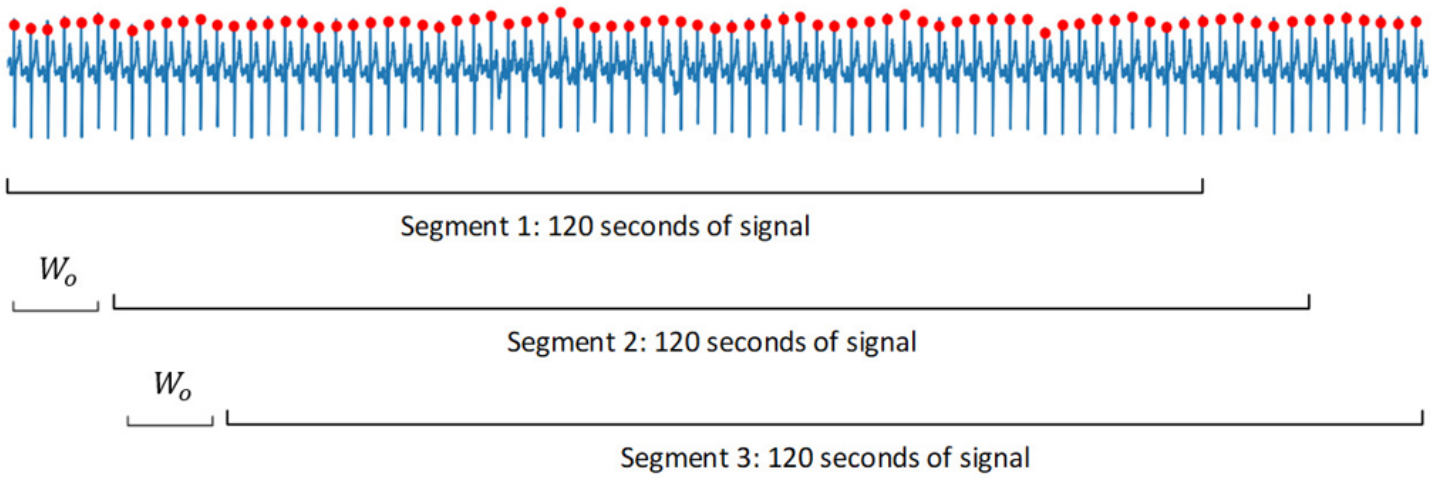

Figure 1

Sliding window of 120 seconds with overlapping of 10 seconds

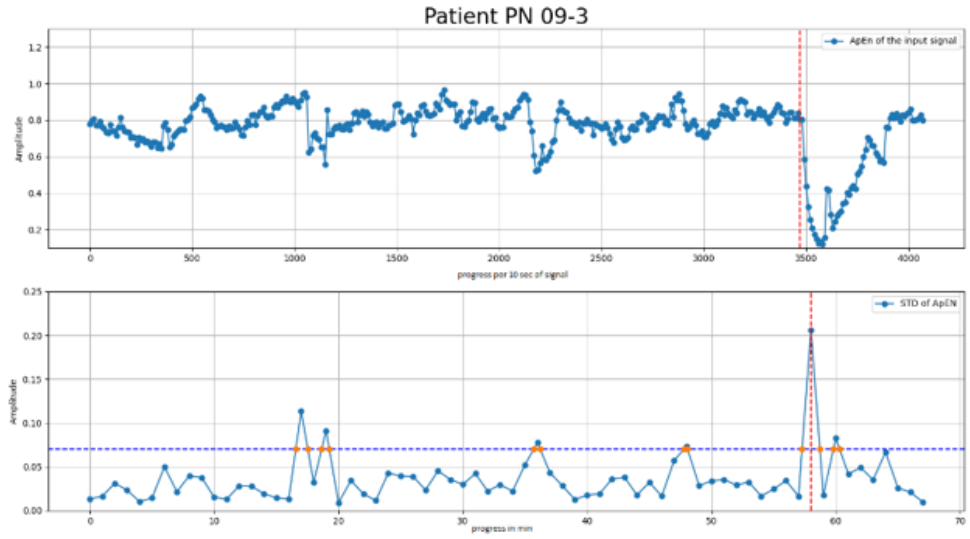

Figure 2

The result of computing the ApEn from the RRi and the result of computing the STD-ApEN from the ApEN results

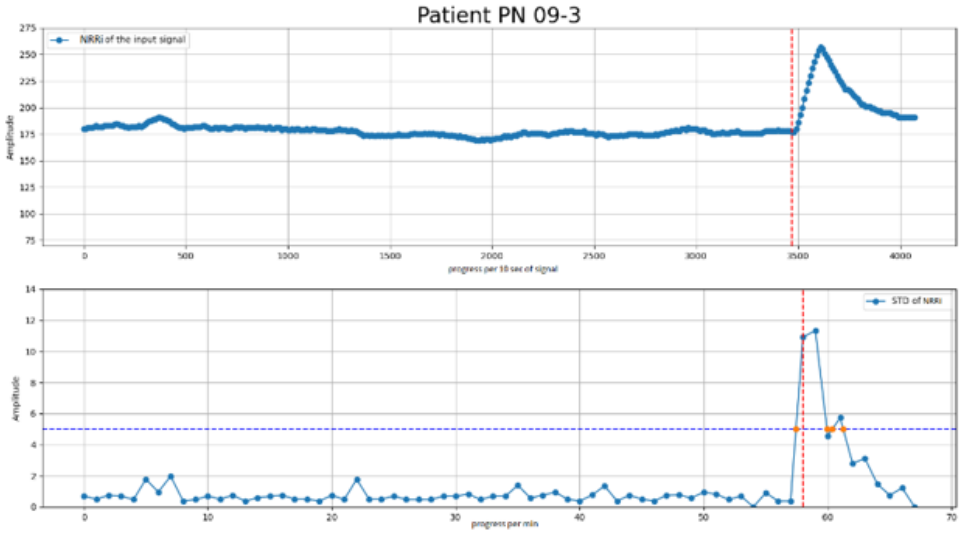

Figure 3

The result of computing the NRRi from the RRi and the result of computing the STD- NRRi from the NRRi results

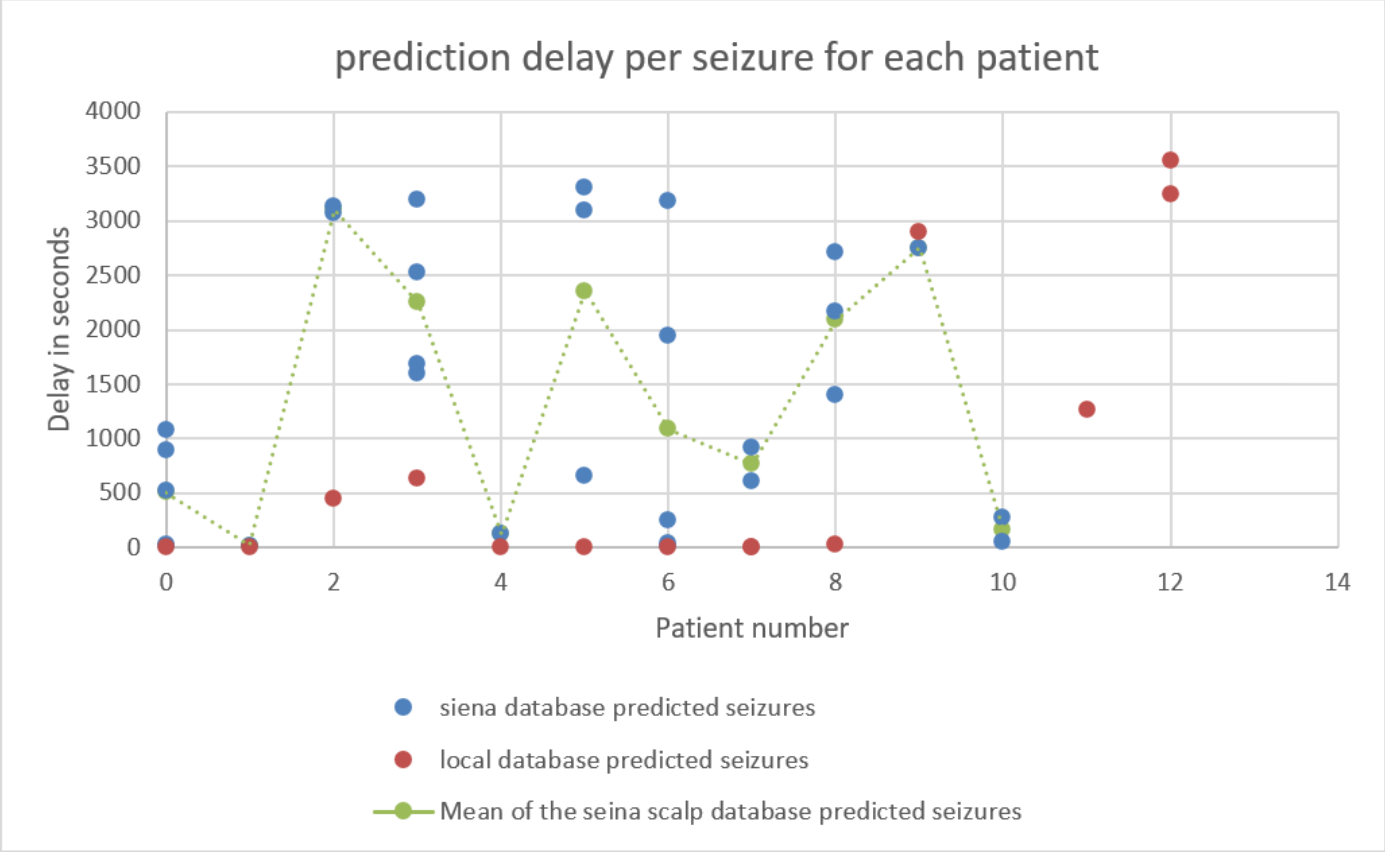

Figure 4

Presentation of the prediction delay for the Siena database and the local database

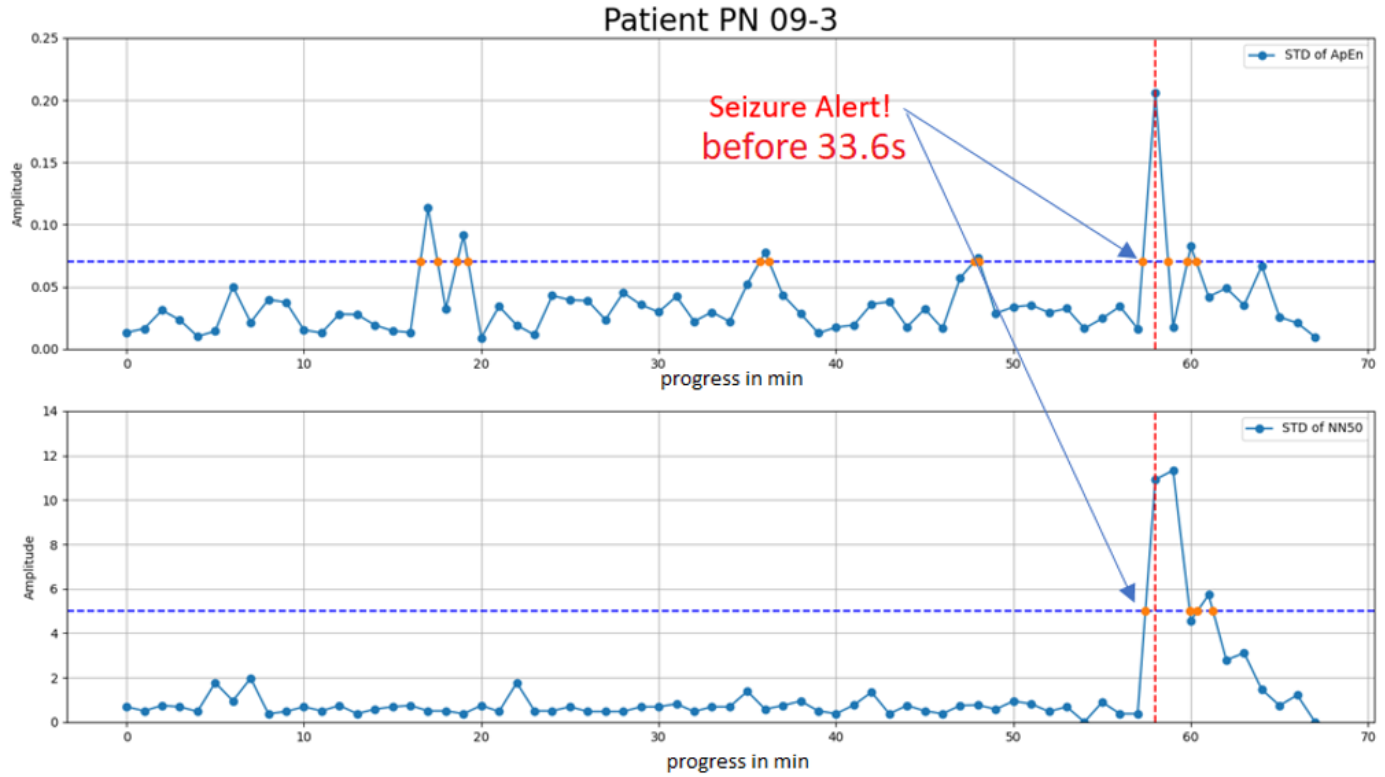

Figure 5

The result of applying the proposed STD approach on Patient PN09-3

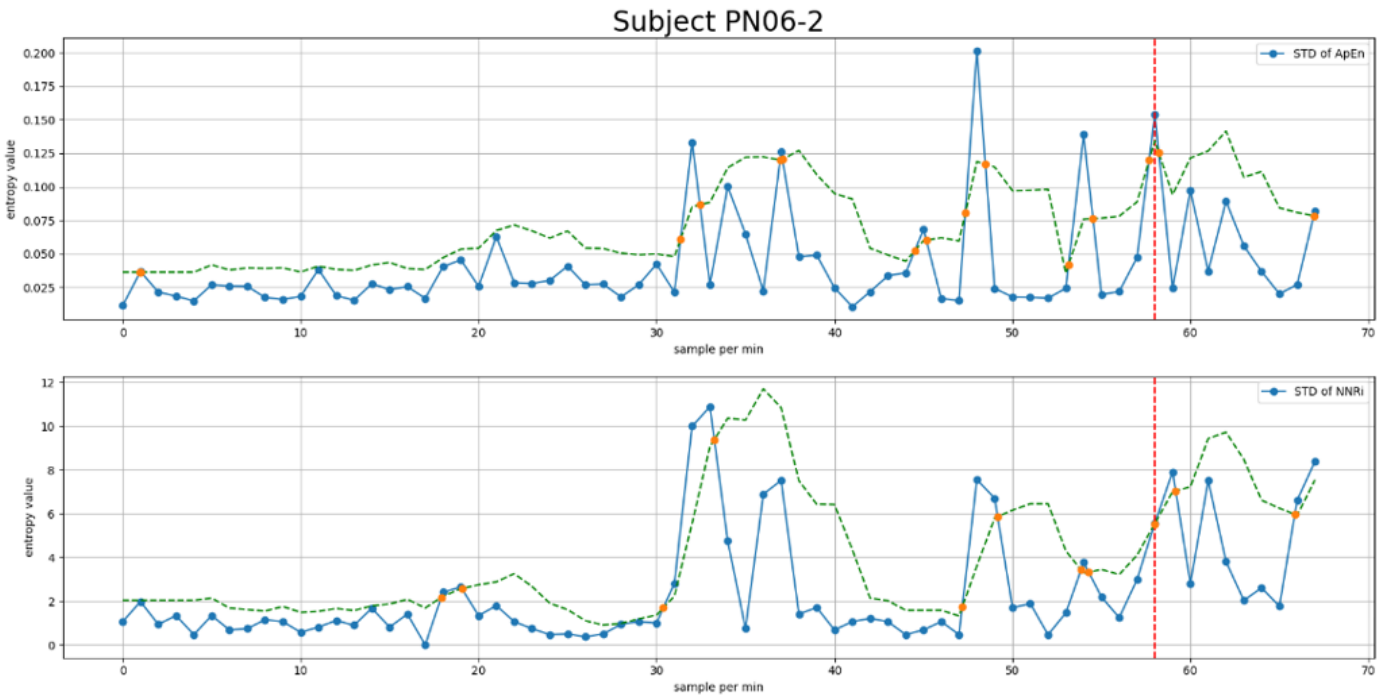

Figure 6

An example of applying the automatic threshold prediction approach on the acquisition PN06-2

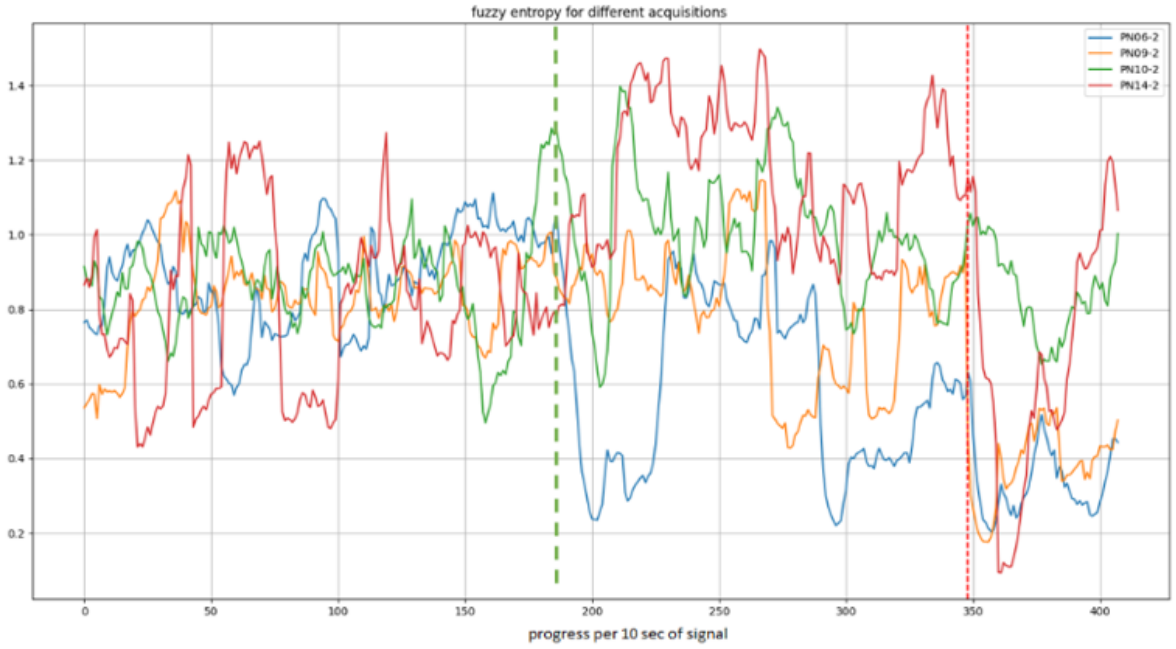

Figure 7

Fuzzy entropy curves of four different patients in the pre-ictal period (1h before the seizure)

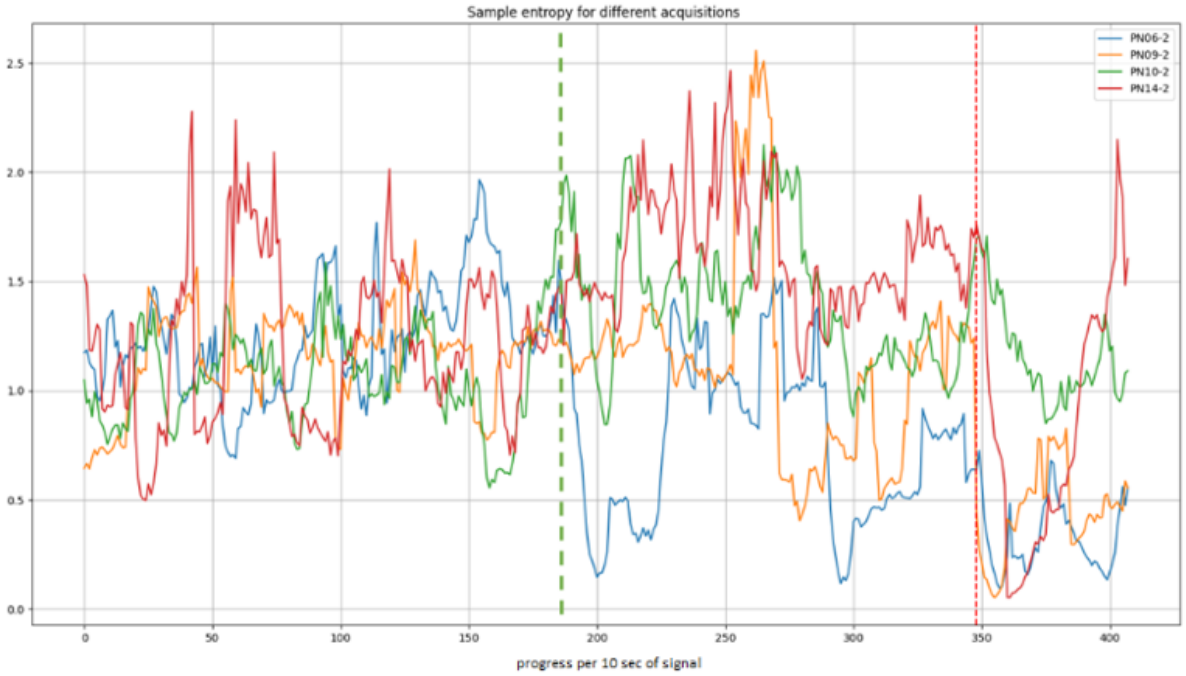

Figure 8

Sample entropy curves of four different patients in the pre-ictal period (1h before the seizure)

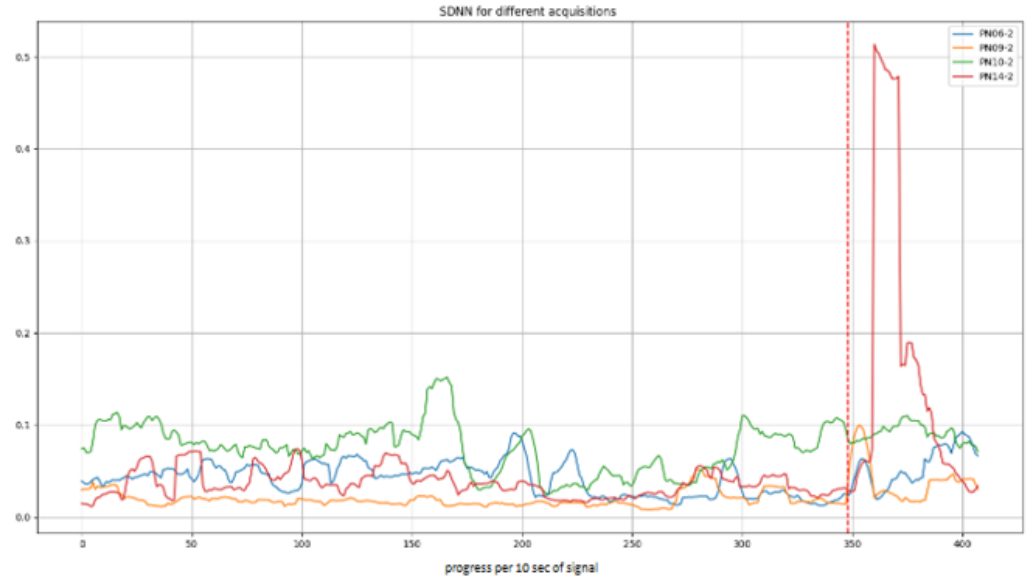

Figure 9

Extraction of time-domain analysis features SDNN using the four acquisitions studied

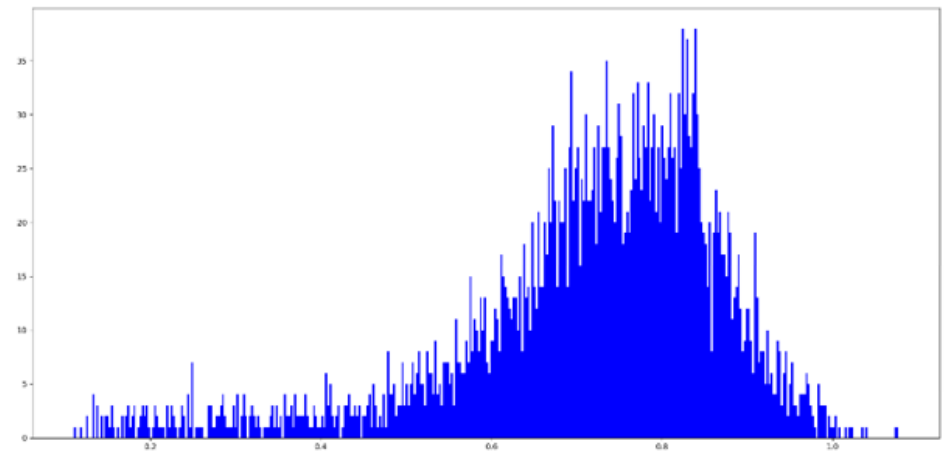

Figure 10

The histogram of the ApEn entropy for the healthy patients

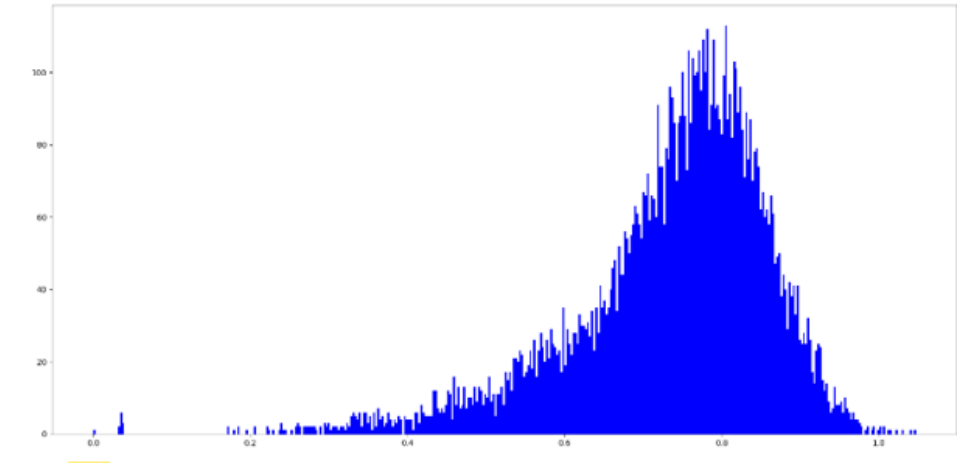

Figure 11

The histogram of the ApEn entropy for the epileptic patients

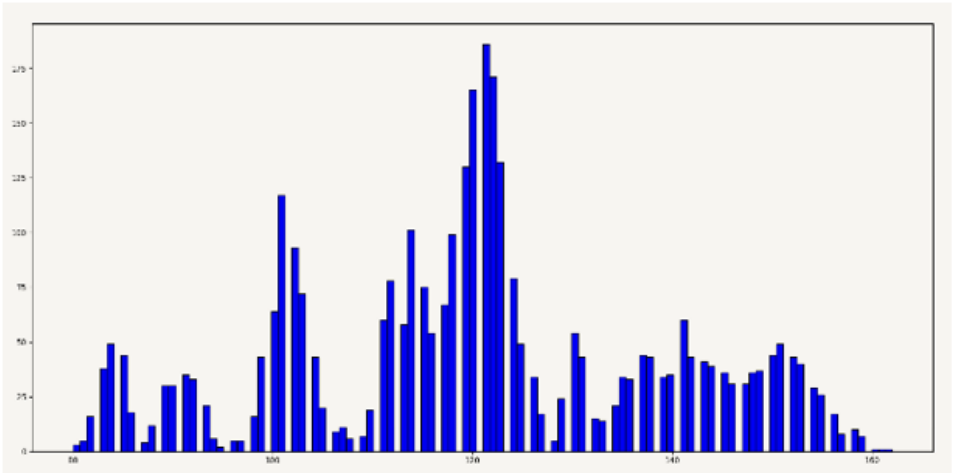

Figure 12

The histogram of the NRRi feature for the healthy patients

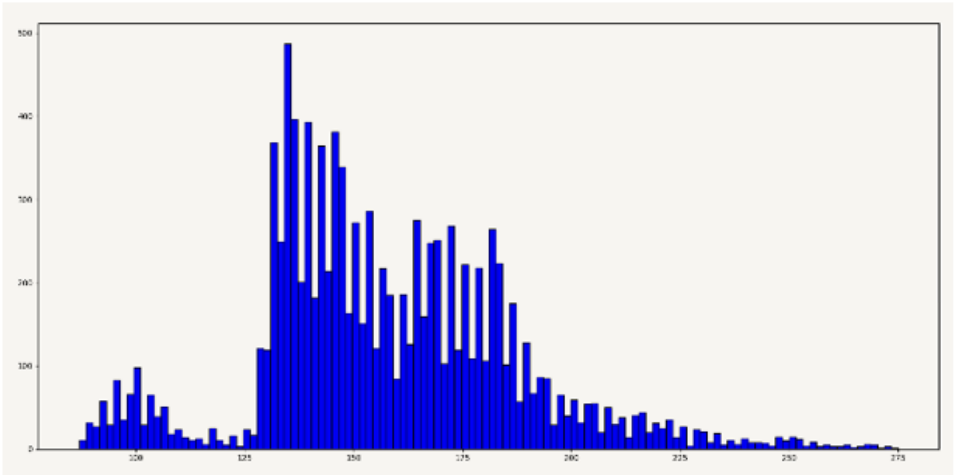

Figure 13

The histogram of the NRRi feature for the epileptic patients