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SCIENTIFIC PAPER

Optimal selection of SOP and SPH using fuzzy inference system for on-line epileptic seizure prediction based on EEG phase synchronization

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Abstract

Living conditions of patients with refractory epilepsy will be significantly improved by a successful prediction of epileptic seizures. A proper warning impending seizure system should be resulted not only in high accuracy and low false positive alarms but also in suitable prediction time. In this study, the mean phase coherence index was used as a reliable indicator for identifying the pre-ictal period of 21-patient Freiburg dataset. In order to predict the seizures on-line, an adaptive Neuro-fuzzy model named ENFM (evolving Neuro-fuzzy model) was used to classify the extracted features. The ENFM was trained by a new class labeling method based on the temporal properties of a prediction characterized by two time intervals, seizure prediction horizon (SPH) and seizure occurrence period (SOP), which are subsequently applied in evaluation method. It is evident that increasing the SPH duration can be more beneficial to patients in preventing irreparable consequences of the seizure, as well as providing adequate time to deal with the seizure. In addition, a reduction in SOP duration can reduce the patient's stress in SOP interval. These two theories motivated us to design Mamdani fuzzy inference system considering sensitivity and FPR of the prediction result in order to find optimal SOP and SPH for each patient. 10-patient dataset assigned for optimizing the fuzzy system, while the rest of data was used to test the model. The results showed that mean SOP by 6 min and mean SPH by 27 min provided the best outcome, so that last seizure as well as about 15-h inter-ictal period of each patient were predicted on-line without false negative alarms, yielding on average 100% sensitivity, 0.13 per hour FPR, 86.95% precision and 92.5% accuracy.

Keywords On-line seizure prediction · Mamdani fuzzy inference system · Neuro-fuzzy model · Phase synchronization · Seizure prediction horizon · Seizure occurrence period

Introduction

Epilepsy is considered as one of the most common neurological disorders affecting the 1% of the world population which is abnormally and spontaneously resulted from excessive electrical discharge in the cerebral cortex [1]. For epilepsy patients who are not able to control the seizure completely, it strikes suddenly in an unanticipated way that shows one of the most disabling aspects of the illness. Except for the risk of critical injury, there is often a feeling of helplessness that strongly affects the regular daily life of the patients. Hence, if a robust method is capable of accurately predicting the seizure onset, epilepsy patients' life quality and therapeutic possibilities can be significantly improved [2].

Detection of pre-ictal period is considered as overall basis for predicting epileptic seizures. Significant changes in EEG dynamics are reported to be between a few minutes to

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several hours prior to the seizure onset that remain an open question in epilepsy research [3–7]. The advent of high-capacity storage caused the epileptic seizure centers to store complete data for pre-operative monitoring. The purpose of these centers was to test and compare the methods presented on the data set. Most of the seizure prediction results indicate relatively poor performance of univariate measures when they were applied to the long-term database, whereas better results were obtained based on multivariate (bivariate) measures [1, 2, 8, 9]. The multivariate measurement of time series involves the simultaneous recording of more than one observation over time to evaluate the relationship between different components of a system [10]. Based on the hypothesis suggested that seizures are generated by unusual synchronization of neurons, many researchers are tried to predict the seizure onset by characterizing the interaction of different brain areas [11]. They have used bivariate measures in order to predict seizures, such as nonlinear interdependence, phase synchronization, and the cross correlation [12, 13]. Nevertheless, combining the univariate and bivariate nonlinear measures may improve the performance to predict partial seizures in patients with focal neocortical and hippocampal epilepsy [14].

Lack of a widely accepted methodology to evaluate and compare seizure prediction algorithms is considered as one of the main seizure prediction challenges. Although "seizure prediction characteristic" approach has been introduced to evaluate seizure prediction performance, this method is suitable for off-line evaluations [15]. In this approach, a time interval after an alarm, the seizure prediction horizon (SPH) (Fig. 1), is required to administer therapeutic intervention or seizure warning devices effectively. Drugs or other treatment strategies can be applied or the patient behaves cautiously within this time interval. In addition, we expect that the seizure should be occurred following the prediction horizon. However, due to chaotic natures of EEG, seizure onset usually does not occur immediately after the SPH. A new time interval seizure occurrence period (SOP) has been introduced to account for the impossibility of a perfect prediction and to allow a temporal uncertainty in the occurrence of prediction seizures. In addition to accurate prediction defined by the occurrence of a seizure within the SOP, two points must be considered. First, the SPH should be high enough to provide the patient with adequate time to prepare or prevent the occurrence of the seizure after warning alarm. Second, the SOP should be low enough to reduce the waiting time in order to decrease the patient's stress [9, 16].

In this study, the interaction of different brain regions in specific frequency bands has been quantized using long-term intracranial EEG data, through a phase synchronous index as a bivariate measure, and then an adaptive Neuro fuzzy model was used for classification and prediction. A similar method "seizure prediction characteristic" has been used to evaluate the output of model, as in this study, the classifier is trained based on the two time indices SOP and SPH, which are subsequently used in the evaluation approach. The output of model was evaluated by various SOP and SPH values followed by finding optimum SOP and SPH by a set of predetermined rules using the Mamdani fuzzy inference system. In the following; Sect. 2, after introducing data and preprocessing stage, proposed methodology including EEG frequency decomposition, phase synchronization index, optimal features selection, adaptive epileptic seizure prediction, post-processing process, model evaluation and optimal SOP and SPH selection approach are described. In Sect. 3, the results of the implementation and performance of the seizure prediction are presented and the final discussion and conclusion are given in Sects. 4 and 5, respectively.

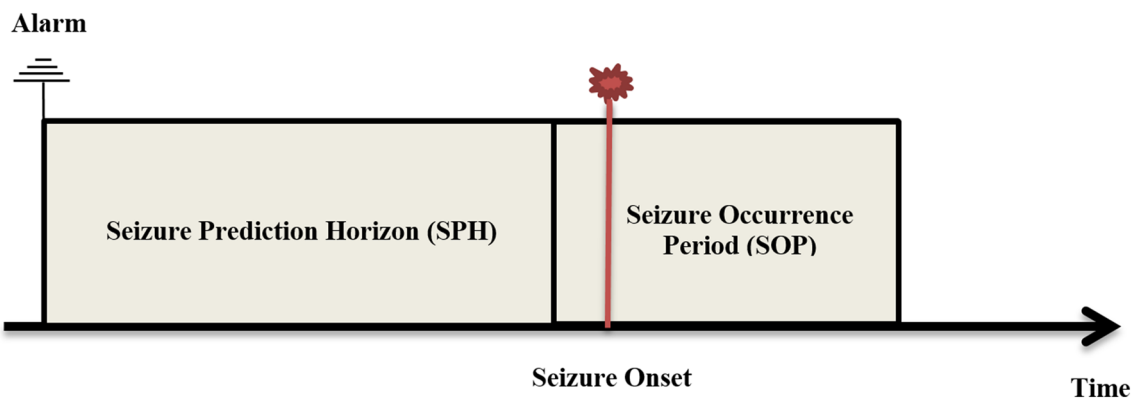

Fig. 1 The schematic of the SOP and SPH intervals

Methods

Data and preprocessing

We evaluated our seizure prediction method on the publicly EEG database recorded at the Epilepsy Center of University Hospital of Freiburg, Germany. The dataset contains invasive long-term EEG data, recorded using a Neurofile NT digital-video EEG system with 128 channels, a sampling rate of 256 Hz, and a 16-bit analogue-to-digital converter [17]. Their clinical characteristics have been summarized in Table 1. In the source dataset, a confirmed neurologist selected only 6 channels of EEG dataset which three electrodes (1–3) were chosen over focal areas and three electrodes (4–6) over non focal areas. The EEG recordings for each patient contain separate pre-ictal and inter-ictal datasets, the former including epileptic seizures and at least 50 min pre-ictal samples for each seizure and latter includes almost 24 h of EEG recording without seizure activity. Before extracting features from EEG, we used a sliding window with 20% overlap which consists of 4096 samples (equals to 16 s). In the preprocessing stage, then a FIR low pass filter with cutoff frequency of 70 Hz, and order of 18 was used to eliminate the high signal frequencies.

Decomposition of EEG frequency bands

It is necessary to calculate the instantaneous phase of signals in order to get the phase differences of the pair channels of signals. Phase information can be computed by various methods, such as Fourier transform and Wavelet transform, these methods have a trade-off between the frequency resolution and the temporal resolution [18]. The Hilbert transform is a well-known method for calculating the instantaneous phase of any signal assuming the signal contains only one frequency component. This method cannot directly be applied to a complex signal, i.e. EEG containing multiple frequencies at any time, as the past application of the Hilbert transform was restricted to single frequency signal [19, 20]. A new method called the Hilbert-Huang transform (HHT) was introduced to solve this problem based on the combination of empirical mode decomposition (EMD) and Hilbert transform [21]. Decomposition of EEG to frequency bands based on Hilbert–Huang transform will be composed in three steps [19, 21, 22]:

1. Decompose the signal into a number of intrinsic mode functions (IMF) using EMD. In practice, it can be shown that this decomposition process is complete, adaptive and local. Figure 2 depicted the IMFs of single channel EEG signal, as the first IMF contains the highest frequency contents but last IMF incorporates the lowest frequency contents of the signal.

Table 1 Patient characteristics (*SP* simple partial, *CP* complex partial, *GTC* generalized tonic–clonic, *H* hippocampal, *NC* neocortical)

Patient no.	Sex	Age	Seizure type	Seizure origin	# Seizures	Inter-ictal (h)
1	f	15	SP, CP	NC	5	24
2	m	38	SP, CP, GTC	H	3	24
3	m	14	SP, CP	NC	5	24
4	f	26	SP, CP, GTC	H	5	24
5	f	16	SP, CP, GTC	NC	5	24
6	f	31	CP, GTC	H	3	25
7	f	42	SP, CP, GTC	H	3	24
8	f	32	SP, CP	NC	2	24
9	m	44	CP, GTC	NC	5	24
10	m	47	SP, CP, GTC	H	5	24
11	f	10	SP, CP, GTC	NC	4	24
12	f	42	SP, CP, GTC	H	4	25
13	f	22	SP, CP, GTC	H	2	24
14	f	41	CP, GTC	H and NC	4	24
15	m	31	SP, CP, GTC	H and NC	4	24
16	f	50	SP, CP, GTC	H	5	24
17	m	28	SP, CP, GTC	NC	5	24
18	f	25	SP, CP	NC	5	25
19	f	28	SP, CP, GTC	NC	4	24
20	m	33	SP, CP, GTC	NC	5	26
21	m	13	SP, CP	NC	5	24

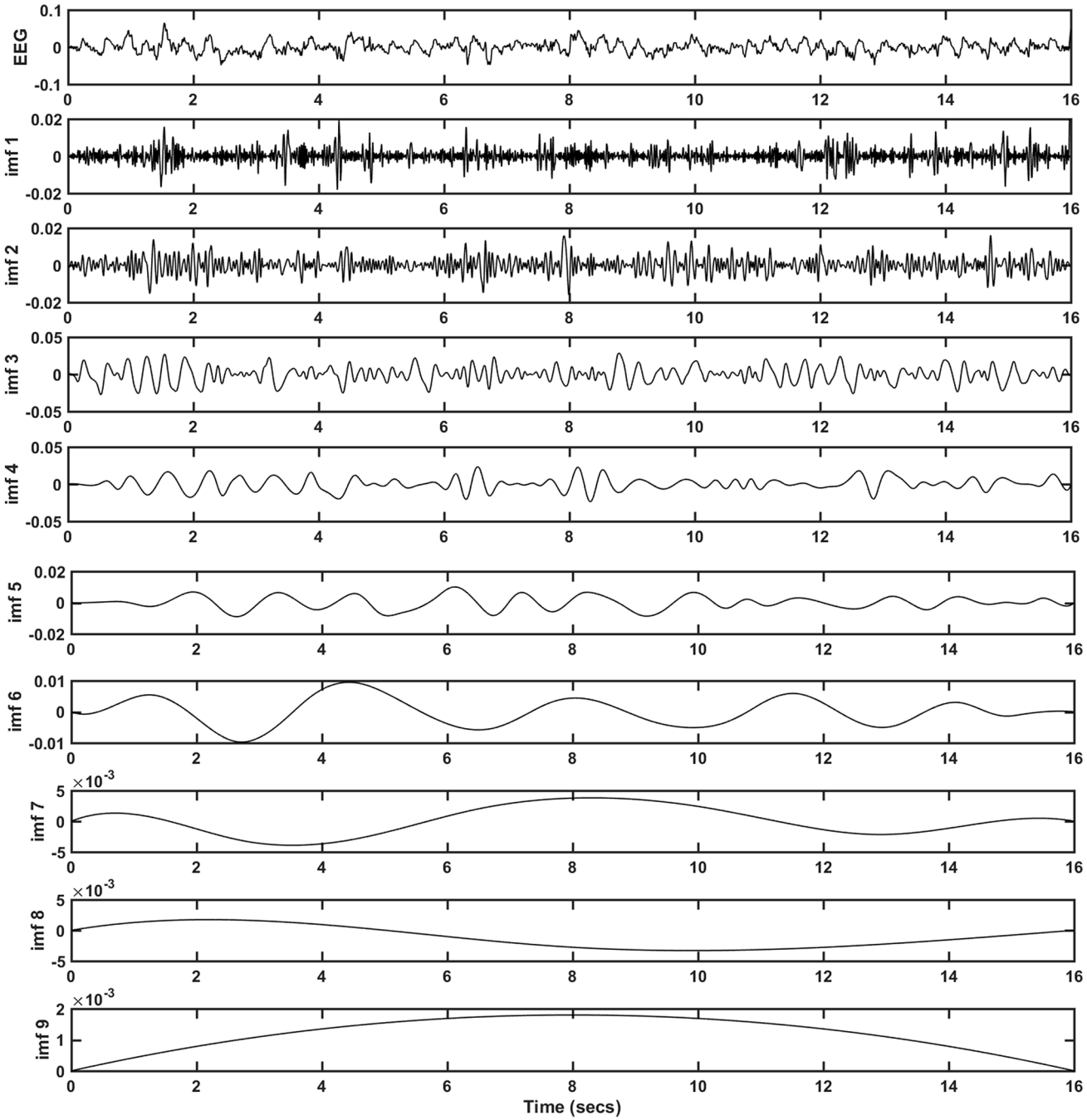

Fig. 2 Decomposition of the 16-s (equal to window time) normalized filtered EEG of fifth channel recorded from patient 1 into 9 components (IMFs) using EMD algorithm

2. Apply the Hilbert transform to each IMF to compute the instantaneous frequency at each sample time. As shown in Fig. 2, the EEG signal includes 9 IMFs. Hence, there are 9 frequency components in each sample time.
3. For locating delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13), beta (13–30) and gamma (30–70) frequency bands, in each sample, calculates the sum of IMF whose frequencies are assigned to the one of the frequency bands. To better illustrate the characteristics of EEG frequency bands, power spectrum of obtained delta, theta, alpha, beta and gamma are shown in Fig. 3.

Phase synchronization calculation

To describe the interactions of different brain regions, the mean phase coherence has been used as a measure of phase

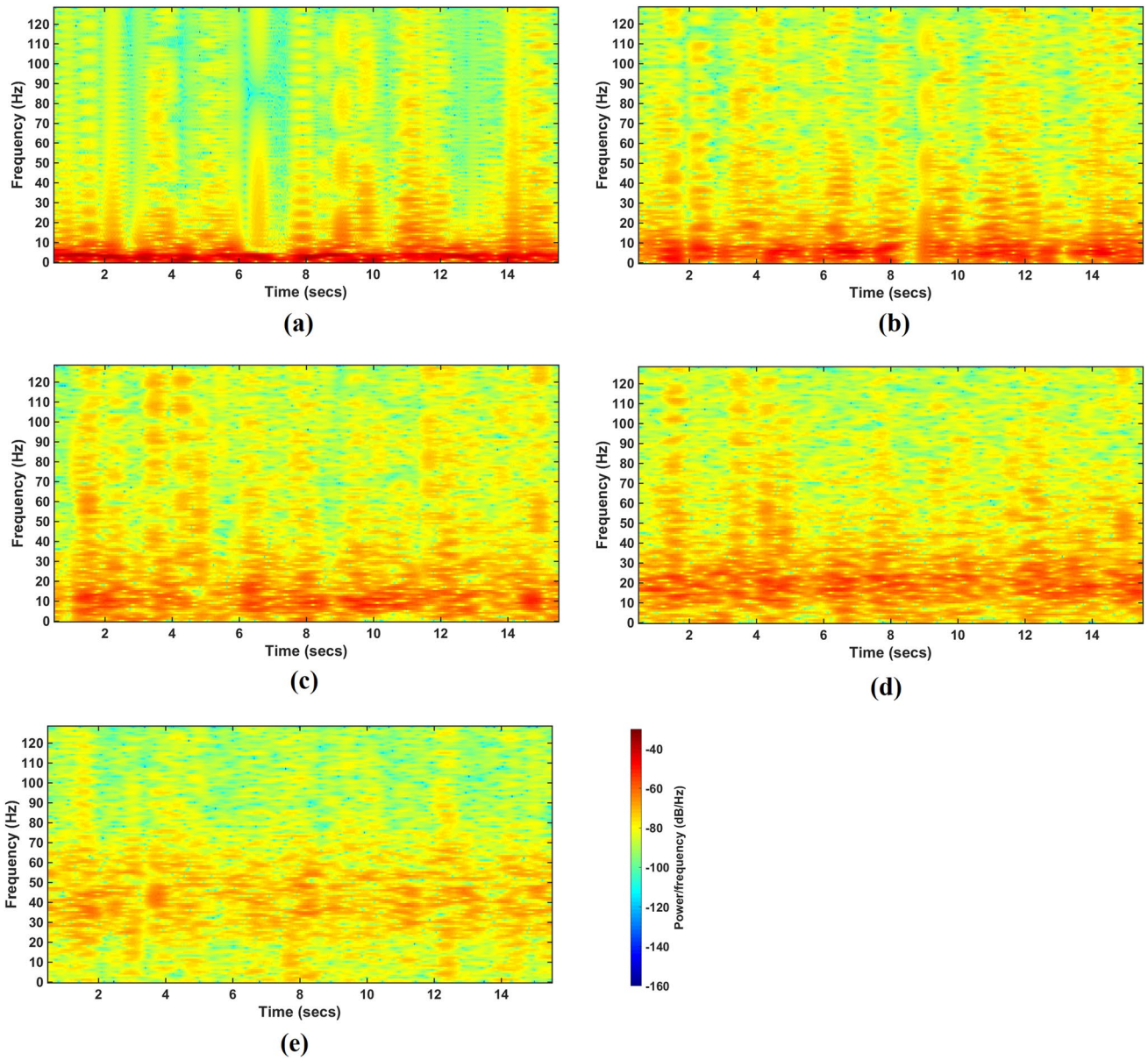

Fig. 3 Power spectrum of EEG frequency bands obtained from HHT algorithm. **a** delta (0.5–4 Hz) **b** theta (4–8 Hz) **c** alpha (8–13 Hz) **d** beta (13–30 Hz) and **e** gamma (30–70 Hz)

synchronization in the proposed method. It characterizes the variations of phase difference between two separate oscillating systems [9, 11]. The relative phase of such two such systems is computed as following:

$$\varphi_{n,m}^{1,2}(\mathrm{t}) = \left|\mathrm{n}\phi_1(\mathrm{t}) - \mathrm{m}\phi_2(\mathrm{t})\right| \tag{1}$$

where m and n are integers and state that the frequency lock occurs at the specific phases of two oscillating systems $\phi_1(\mathrm{t})$ and $\phi_2(\mathrm{t})$ denoting instantaneous phase of the oscillators computed by Hilbert transform [23]. Mean phase coherence of two recording channels 1 and 2 based on the relative phase with a ratio of n:m = 1:1 and a sampling rate of $\frac{1}{\Delta \mathrm{t}}$, is defined as:

$$\mathrm{R}_{1,2} = \left|\frac{1}{\mathrm{N}}\sum_{\mathrm{j}=0}^{\mathrm{N}-1} e^{-j\varphi_{1,1}^{1,2}(j\Delta t)}\right| \tag{2}$$

For every possible combination of different EEG recording channels i and j, the mean phase coherence value related to every pair of frequency bands f was computed for each consecutive window. As in this research, there are 6 channels and 5 frequency bands so 75 different values $R_{i,j}^{f}$ were extracted from each window.

$$\text{Features} = \begin{bmatrix} R^{\delta}_{1,2}, R^{\vartheta}_{1,2}, R^{\alpha}_{1,2}, R^{\beta}_{1,2}, R^{\gamma}_{1,2} \\ R^{\delta}_{1,3}, R^{\vartheta}_{1,3}, R^{\alpha}_{1,3}, R^{\beta}_{1,3}, R^{\gamma}_{1,3} \\ \vdots \\ R^{\delta}_{5,6}, R^{\vartheta}_{5,6}, R^{\alpha}_{5,6}, R^{\beta}_{5,6}, R^{\gamma}_{5,6} \end{bmatrix}_{15\times5} \quad (3)$$

Selecting the optimal features

Most of studies claimed that considerable dynamic changes of interaction between brain areas are always appeared on some specific brain regions prior to the occurrence of the seizure [9]. It is believed that among the 75 values of features in (3), they should be properly selected in order to predict epileptic seizures accurately otherwise the calculations become more complex and the possibility of the false alarms increases significantly. One solution is choosing features representing the least correlation between pre-ictal and inter-ictal samples. To this end, the correlation coefficients between features of inter-ictal samples and features of pre-ictal samples are calculated by Spearman's correlation coefficient test before a p value is computed for each coefficient in order to test the null hypothesis that there is relationship between two categories. Ultimately, features showing no significant relationship ($p < 0.01$) are selected as optimal features.

On-line classification

The evolving neuro fuzzy model for on-line prediction

Unlike on-line approaches, off-line ones are not appropriate for predicting long-term data due to high computational cost. In this study, we took the advantage of evolving neuro-fuzzy model (ENFM) for seizure prediction based on recursive fuzzy clustering developed by Soleimani et al. [24]. The Gath–Geva (GG) clustering as the basis for recursive fuzzy clustering was used in the ENFM structure, since GG has some advantages over other fuzzy clustering (e.g., k-means algorithm, Gustafson Kessel clustering) in terms of creating clusters in different shapes and sizes [25, 26]. The ENFM structure is analogous to Takagi–Sugeno fuzzy models and it has ability to adapt to changes in system behavior by adding new neurons (fuzzy rules) or merging similar existing neurons. Contrary to simple GG algorithm, cluster parameters (e.g., cluster center and covariance matrices) of ENFM are updated using adaptive equations. For more details, refer to Appendix 1.

On-line training and labeling

The basis of prediction is that the interval from the time prior to seizure onset is continuously alerted to the patient. The length of this interval is equal to the predictive time (P). The block diagram in Fig. 4 shows the on-line training algorithm. Every consecutive window is labeled based on the occurrence of a seizure $p_{\max}$ minutes later (1 for "seizure", and 0 for "no seizure"), yielding a sequence $F[n]$ of features related to n*th* temporal window with corresponding labels $C[n]$. Since in on-line training the duration of pre-ictal and inter-ictal is unknown, every such windows are labeled 0 ($C[n] = 0$), representing inter-ictal period, unless the seizure to be occurred in a specific duration. In such case, with regard to the two time characteristics specified in the evaluation method, features ($F[n]$) for as long as $p_{\max} - p_{\min}$ (SOP) to $p_{\min}$ (SPH) prior to seizure onset are labeled + 1 ($C[n] = 1$), while others are assigned 0 (see Fig. 5). Thus, there is a $p_{\max}$ (SOP + SPH) delay between the training data and the test input sample, so that the ENFM is trained at the n*th* window based on the input $F[n - p_{\max}]$ and the output $C[n - p_{\max}]$. As shown in Fig. 5, for every alarm that rises in the color window ($p_{\max} - p_{\min}$), the seizure onset will occur within the SOP span following SPH interval, while alarms

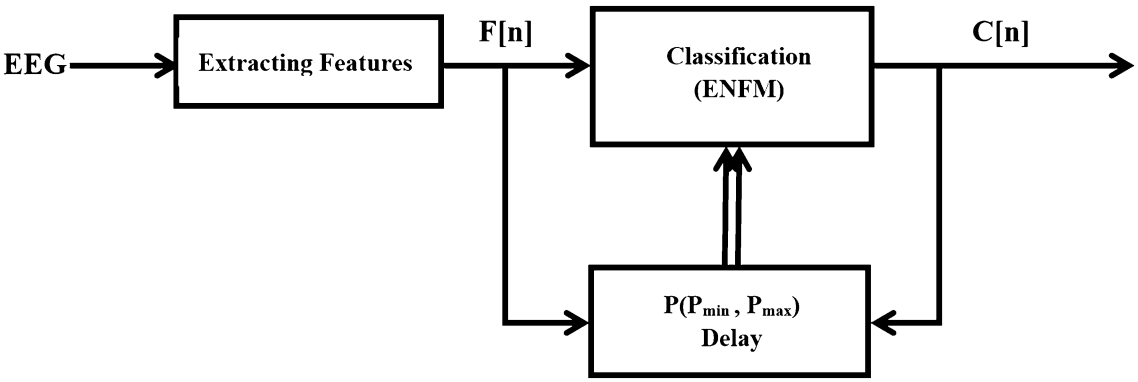

Fig. 4 After feature extraction, the ENFM predicts seizure occurrence period (SOP) *pmin* minutes ahead (SPH). The model is trained at n*th* window based on feature *F[n-pmax]* and class label *C[n-pmax]*

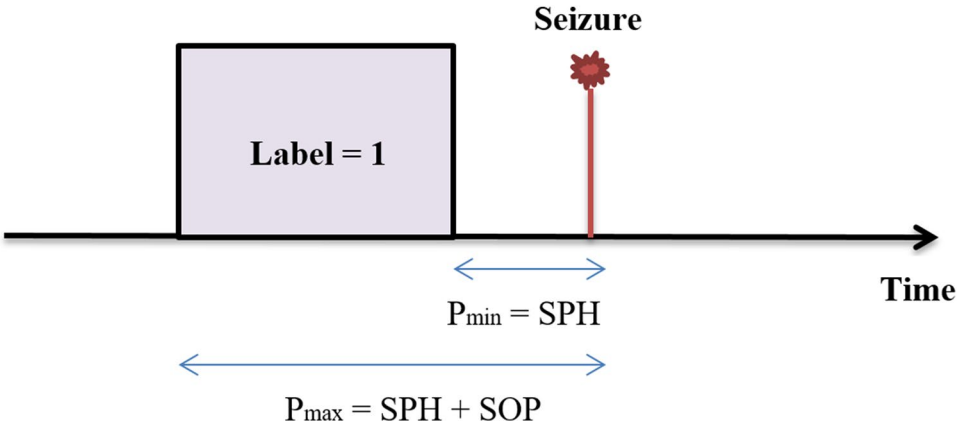

Fig. 5 Labeling the ENFM output in on-line training when the seizure starts

that take place outside the color window are all considered as false positive prediction. Therefore, the model is expected to be properly trained for each SOP and SPH.

Post-processing

The number of false predictions should be controlled of which too many cannot be accepted, e.g., for a seizure warning device due to the loss of patients' confidence. Here a simple algorithm is proposed to minimize false prediction. Although raw ENFM output is between 0 and + 1, it is possible to set absolute value of 0 or + 1 for each output sample. We achieved this by moving average filter (MA filter) with different length of time window. In this algorithm, the proposed model detects the SOP after the SPH before calculating the mean of raw outputs in specific time window. If mean value of each window consecutively increased four-times, then the alarm rises and it will stay on, until the mean value consecutively decreased two-times afterward. This algorithm which is useful in on-line processes makes output sensitise to slope of amplitudes changes rather than amplitudes itself.

Optimal SOP and SPH selection

As learning of the ENFM is based on SOP and SPH length, these two intervals should be properly selected. Three terms are critical in determining these values. First, a proper seizure prediction requires high Sensitivity but low FPR [27]. Second, increasing SPH can be more beneficial to patients to retreat to the safe place or to intervene early. Third, decreasing SOP would reduce the patients' stress and it leads to minimize physiological disadvantages caused by potential side effects of drugs or long term electric stimulation of focal brain structures.

These three terms can be helpful to find unique SOP and SPH among different intervals. To achieve that, we used Mamdani fuzzy inference system, which is a nonlinear mapping that derives its output based on fuzzy reasoning [28]. Firstly, according to three terms mentioned earlier predefined rules are specified as follow:

1. If SOP is low and SPH is high and Sensitivity is high and FPR is low then, Result will be Excellent.
2. If SOP is low and SPH is low and Sensitivity is high and FPR is low then, Result will be Good.
3. If SOP is high and SPH is high and Sensitivity is high and FPR is low then, Result will be Good.
4. If SOP is high and SPH is low and Sensitivity is high and FPR is low then, Result will be Acceptable.
5. If Sensitivity is low or FPR is high then, Result will be Poor.

Next, we need to define membership functions of fuzzy system. According to (4) and (5), four Gaussian-type membership functions were wielded for four input variables $x = \{x_1, x_2, x_3, x_4\}$ (Sensitivity (x_1), FPR (x_2), SOP (x_3) and SPH (x_4)). Each membership function consists of two Gaussian fuzzy sets, low (L) and high (H) corresponding membership values $\mu_L(x)$ and $\mu_H(x)$ which defined as

$$\mu_L(x_j) = \exp\left[-\left(\frac{(x_j - c_L(j))}{\delta_L(j)}\right)^2\right], \quad j = 1,2,3,4 \tag{4}$$

$$\mu_H(x_j) = \exp\left[-\left(\frac{(x_j - c_H(j))}{\delta_H(j)}\right)^2\right], \quad j = 1,2,3,4 \tag{5}$$

where c_L and c_H denote center of the low and high Gaussian fuzzy sets and δ_L and δ_H denote variance of the low and high Gaussian fuzzy sets. On the other hand, four triangular functions have been used as output variable membership function (Result). Since the output of the fuzzy system belongs only

to one of the four categories (Excellent, Good, Acceptable, Poor), no overlap is considered between membership functions. The output range of the result variable is defined from 0 up to 40. Thus, Poor, Acceptable, Good and Excellent groups are ranged equally from 0 up to 10, 10 up to 20, 20 up to 30 and 30 up to 40, respectively.

The fuzzy inputs are applied to the antecedents of the fuzzy rules. Firing strength of each rule has been calculated through the min operator as a t-norm operation for evaluating conjunction of the 1–4 rules, similarly, max operator as a t-conorm operation for evaluating disjunction of the fifth rule. The implementation of the inference rules is done using the compositional rule of inference. Then, the final output is calculated by defuzzification using Centre of Gravity (CoG) method by aggregation of the 5 individual output fuzzy sets [29].

Finally, a fuzzy output was attributed for each set of SOP-SPH. Specific SOP and SPH corresponded to the highest fuzzy output, will be the best SOP and best SPH.

Model evaluation

Assessment of prediction result

The evaluation of seizure prediction model is possible by two most common measures: sensitivity and specificity, which the latter is defined in the form of false positive rate (FPR). To obtain these two metrics, the prediction outcome should be categorized into one of the following four subsets:

1. If $C[n] = 1$ and at least one seizure occurs within the SOP duration following the SPH interval, then it is the true positive result (TP).
2. If $C[n] = 1$ and any seizure does not occur within the SOP duration following the SPH interval, then it is a false positive result (FP).
3. If $C[n] = 0$ and any seizure does not occur within the SOP duration following the SPH interval, then it is true negative result (TN).
4. If $C[n] = 0$ and at least one seizure occurs within the SOP duration following the SPH interval, then it is false negative result (FN).

Assessment of prediction performance

It is believed that, in contrast to batched learning we cannot divide the entire dataset into two separable segments: in-sample and out-sample in on-line learning classification, because each time a test sample given to the classifier sequentially that sample turned to train sample after a fix delay, which in this case the delay is $p_{\max}$ for ENFM as is mentioned in Sect. 2.5.2. Thus, it is expected that, initially, the ENFM cannot make accurate prediction and it requires amount of sufficient time for learning the pattern of pre-ictal and inter-ictal. Accordingly, instead of defining training data and test data, we defined non-evaluative segment and evaluative segment, which the former was not considered for model assessment and it contains approximately half of the total dataset for each patient (10-hour inter-ictal samples as well as pre-ictal samples of the first 3 or 4 seizures) and the latter, which contains remaining 14-hour inter-ictal samples as well as pre-ictal samples of the last seizure, was considered for assessment. An illustration of such segments is given on Fig. 6.

Note that the duration of inter-ictal and pre-ictal must be known for choosing optimal features in (3), that it contradicts with on-line learning mode. To overcome this problem, non-evaluative segment was assigned for optimal feature selection assuming that inter-ictal and pre-ictal periods are known (i.e. the duration of pre-ictal is at least 50 min per seizure). On the other hand, we supposed pre-ictal and inter-ictal periods of evaluative segment are unknown considering for on-line prediction based on selected optimal features in non-evaluative segment.

In Sect. 2.7, parameters of Gaussian membership functions (4) and (5) have a huge impact on fuzzy output. Subsequently, they affect the accuracy of assessment. Choosing proper parameters is crucial in Mamdani fuzzy inference system. However, due to lack of true positive alarm in non-evaluative segment, it is difficult to find, yet optimization of fuzzy system required a separate data for learning parameters ($c_L, c_H, \delta_L, \delta_H$). We defined such data as a fuzzy training data consisting of sensitivity and FPR of evaluative segment of 10 patients for various range of SOP and SPH, while other results of 11-patient evaluative segment, which is called fuzzy test data, was evaluated based on optimum parameters of Gaussian membership functions.

Results

Computational settings

According to Appendix 1, in addition to cluster center and covariance matrices, two constant threshold called th_1 and th_2 controlling the number of neurons (clusters) were introduced in ENFM structure. The former, which determined the novelty of new data point, performed adding neuron, while the latter controlled it using merging the similar clusters. This study did not focus on determining the values of th_1 and th_2, as Soleimani et.al. has already achieved them. Therefore, we sufficed to their results as th_1 and th_2 were set 0.15 and 0.5, respectively.

In order to test the concept of on-line learning, the ictal dataset was set to a long-term inter-ictal dataset. Then, the

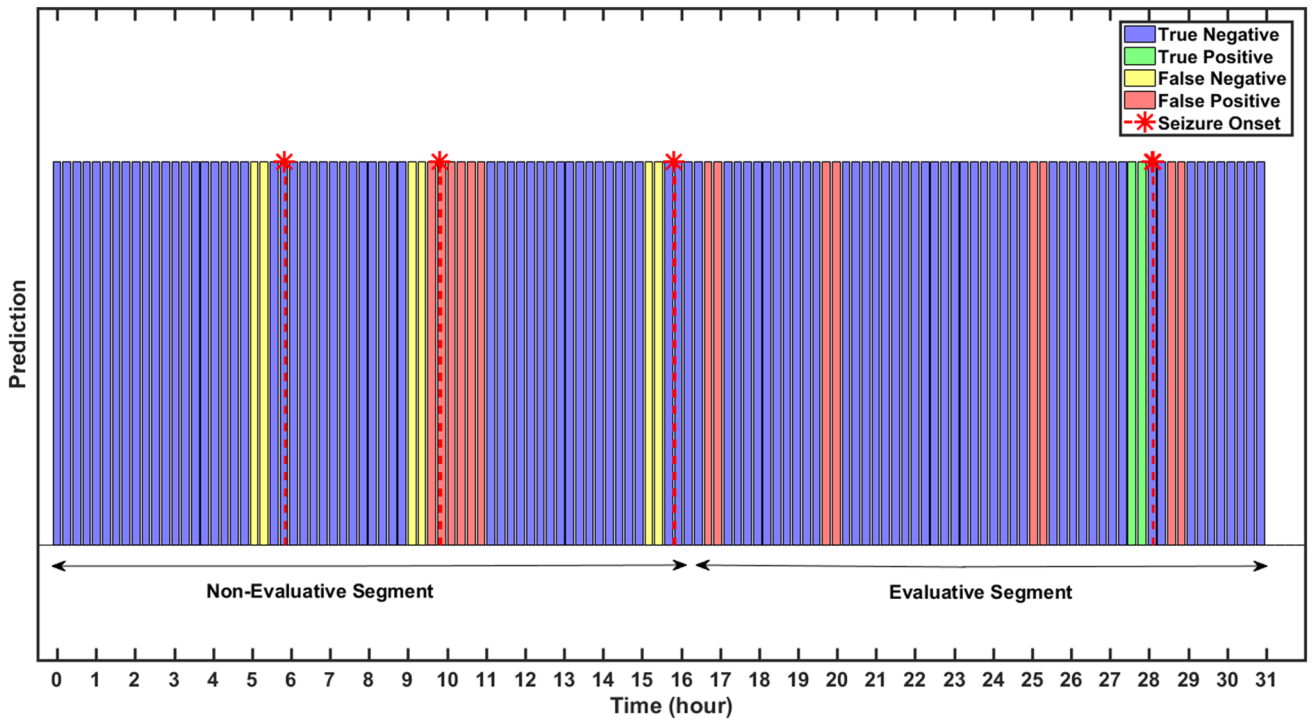

Fig. 6 Detail of the performance of the on-line prediction obtained from the all EEG samples of patient 1. Assessment results of the first half of the data did not report as predictor requires considerable time to learn the pattern of pre-ictal and inter-ictal samples as well as selecting optimal features, but the rest of the data including the pre-ictal of the last seizure is devoted for evaluation

non-evaluative and evaluative segments the length of which were about 15 h were determined for each patient. Nevertheless, depending on the duration of pre-ictal dataset and number of seizure, the length of both segments could be changed. The illustration of rearranging data as well as seizure prediction outcome of patient 1 taking into account 10 min SOP and 20 min SPH are shown in Fig. 6. Each output also represents of 15 min as same as MA filter order. The statistic results for this specific patient is 0.1 per hour FPR with no TP in non-evaluative segment and 0.14 per hour FPR without any FN in evaluative segment. In total, the 25% sensitivity and 0.14 per hour FPR were achieved for patient 1.

Since we developed a patient-specific seizure predictor, the ENFM has been applied individually for each patient with different SOPs and SPHs (5, 10, 15, 20, 25, 30 min for both durations), so that SOP and SPH were varied from 5 to 30 min for entire patients except for patients 11 and 15. In those cases, SOP and SPH were changed from 10 to 60 min.

Analyses of fuzzy system parameters

As mentioned in Sect. 2.8.2, best prediction result can be achieved only by setting optimum values of c_L, c_H, δ_L and δ_H. Since there are four fuzzy system inputs, four different values have been defined for each of them. Note that all optimum c_L, c_H, which are further discussed in Sect. 4.2, are obtained based on the clinical knowledge. For calculating δ_L and δ_H, firstly, the fuzzy system parameters were set by default values ($c_L(1) = c_L(2) = 0, \delta_L(1) = 0, c_H(1) = 100, \delta_H(1) = 25, \delta_L(2) = 0.13, c_H(2) = 1, \delta_H(2) = 0.3, c_L(3) = c_L(4) = 5, \delta_L(3) = \delta_L(4) = \delta_H(3) = \delta_H(4) = 7, c_H(3) = c_H(4) = 30$). Secondly, the fuzzy system was designed based on the default parameters. Then, all sensitivities, FPRs, SOPs and SPHs obtained from fuzzy training data are given to fuzzy system which subsequently provides the highest possible fuzzy outcome (Result) for each patient as well as best sensitivity, FPR, SOP and SPH. Following taking average from obtained values, the same process repeated for different δ_L and δ_H, as it can be seen from Fig. 7, the variation of mean best sensitivity, mean best FPR, mean best SOP and mean best SPH accounted for different $\delta_L(j)$ and $\delta_H(j)$ ($j = 1{:}4$). Note that all variables were normalized so we can observe the variations with the same scale. We then analyzed the data by looking for δ_L and δ_H that lead to the highest Result. Although this approach seems logic, fuzzy system does not always provide best sensitivity, best FPR, best SOP or best SPH, because the model is fitted by the default parameters. As a result, the fuzzy system cannot be optimized. Since there were not a specific δ_L or δ_H leading to the highest sensitivity and SPH as well as the lowest FPR and SOP at the same value, instead of considering best Result, we had

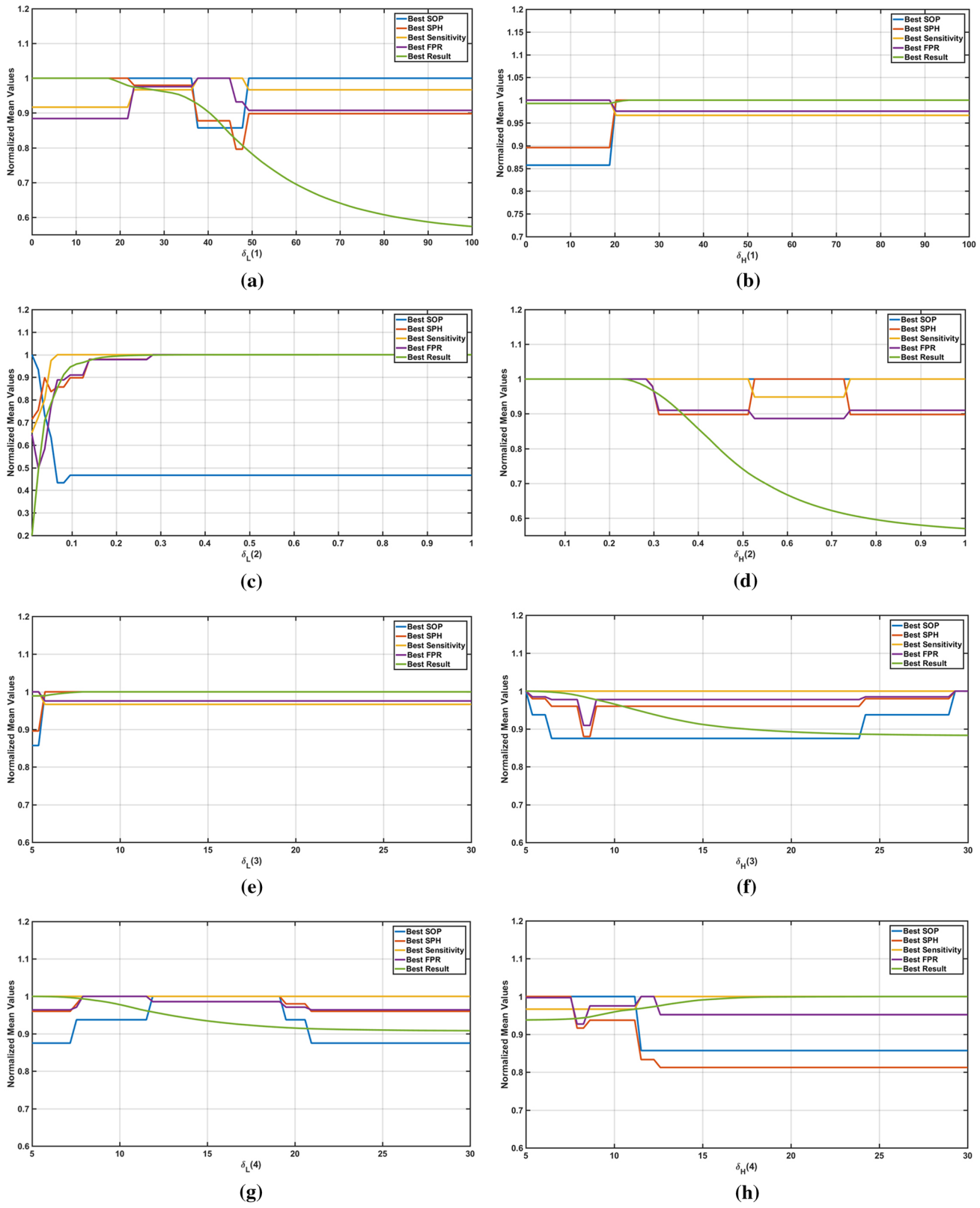

Fig. 7 Showing the variation of best Result (fuzzy system outcome), best sensitivity, best FPR, best SOP and best SPH chosen by fuzzy system for various choice of variance of all Gaussian membership functions: **a** low fuzzy set of input 1 **b** high fuzzy set of input 1 **c** low fuzzy set of input 2 **d** high fuzzy set of input 2 **e** low fuzzy set of input 3 **f** high fuzzy set of input 3 **g** low fuzzy set of input 4 **h** high fuzzy set of input 4

prioritized each of them, so that sensitivity outweighed FPR, while FPR outweighed both SPH and SOP. Alternatively stated, it is irrational that seizure predictor accurately predicted the TN at the cost of missing the TP. In Fig. 7a, for example, sensitivity peaked at 48, while FPR reached a normalized value by 0.95 at the same value, so we obtained $\delta_L(1) = 48$. On the other hand, in Fig. 7f, it can be seen that sensitivity reached maximum and both FPR and SOP bottomed out at value of 8, so we set $\delta_H(3) = 8$, but at cost of decreasing SPH duration. Eventually, the optimum parameters of fuzzy system were obtained based on similar analyses, so that input fuzzy membership functions were established according to optimum values of Table 2. In addition, the illustration of designed membership functions can be seen in Fig. 8.

Performance of the seizure predictor

Having designed optimum fuzzy system, we evaluated the fuzzy test data. The summary of prediction result for fuzzy training data and fuzzy test data are shown in Tables 3 and 4, respectively. All results were categorized whether into time characteristic results or statistic results. On average, optimal SOP by 6 min and optimal SPH by 18 min as well as 100% sensitivity and 0.12 per hour FPR were obtained for the fuzzy training data. Interestingly, similar results were achieved for fuzzy test data with no FN along with best SOP by 6 min, best SPH by 27 min and 0.13 per hour FPR, however increasing mean of optimal SPH is derived from patients 11 and 15 with best SPH by 60.

According to time characteristic results of Tables 3 and 4, we also reported the best SOP and best SPH in another way with defining the interval of [SPH SPH + SOP] indicating the seizure activity expected to be occurred following the alarm raised successfully. It is clear that all the prediction times, which are defined as an interval between the first true positive alarm and seizure onset, are within the [SPH SPH + SOP]. This can be also deduced from Fig. 9 that reveals the outputs of seizure prediction model in evaluative segment of fuzzy test data, so that duration between the first TP of each patient and seizure onset is equal to corresponded prediction time reported in Table 4. As shown in Fig. 9, in order to compensate the imbalance of pre-ictal and inter-ictal samples, the length of evaluative segments was changed for each patient. This variation cause difference in total number of predictor outputs for each patient. To control it, we set different MA filter's orders, as they are reported in Table 4.

In Table 5, the performance of the proposed approach was compared with some of the recent studies evaluated with the seizure prediction characteristic method. The values of SOP, SPH, sensitivity and FPR reported in those studies were given as inputs to the designed fuzzy inference system. Generally, SOP and SPH were considered to be 5 up to 30 min, whereas it can be seen that some of studies found the SOP and SPH out of this range. Thus, we extended the range of input variables (SOP and SPH) from 0 up to 60 min without changing the pattern of membership functions just for evaluating those studies. Finally, fuzzy system outcomes confirm the superiority of the proposed method over other studies.

Further analyses were implemented by surveying number of features for each patient. Following feature selection described in Sect. 2.7, we achieved the mean number of features by 9.71 in total. In addition, a test statistic was performed to notice that whether any different relationship between number of features and fuzzy system outcome is likely to be due to chance or not. The result showed that no significant relationship existed with respect to 0.05 significance level ($p = 0.6$). Details are shown in Fig. 10.

Table 2 Optimal values of fuzzy system parameters

Mamdani parameter setting	Optimum values	Mamdani parameter setting	Optimum values
$c_L(1)$	0	$\delta_L(1)$	48
$c_H(1)$	100	$\delta_H(1)$	10
$c_L(2)$	0	$\delta_L(2)$	0.08
$c_H(2)$	1	$\delta_H(2)$	0.35
$c_L(3)$	5	$\delta_L(3)$	6
$c_H(3)$	30	$\delta_H(3)$	8
$c_L(4)$	5	$\delta_L(4)$	6
$c_H(4)$	30	$\delta_H(4)$	8

Confining the SOP and SPH

Among the different SOPs and SPHs, not all of them eventuate desired results. Recognizing the proper range of SOP and SPH can be effective in reducing the size of fuzzy system inputs, so that fuzzy system particularly focused on finding the best SOP and SPH in a limited time zone. For example, fuzzy system output of 4 patients for each pair of SOP and SPH are displayed in Fig. 11 It is clear that the certain time zone represents appropriate Result (Acceptable, Good, Excellent), so we can therefore estimate the suitable duration of SOP and SPH. We also did the same analysis for other patients as if the approximate suitable ranges of SOP and SPH are shown in Fig. 12 As a result, the SOP from 5 to 18 min and SPH from 11 to 25 min were obtained on average.

Performance metrics

Despite of strong imbalance between inter-ictal and pre-ictal samples, sensitivity and FPR are still valid measures, because sensitivity evaluates the predictor only based

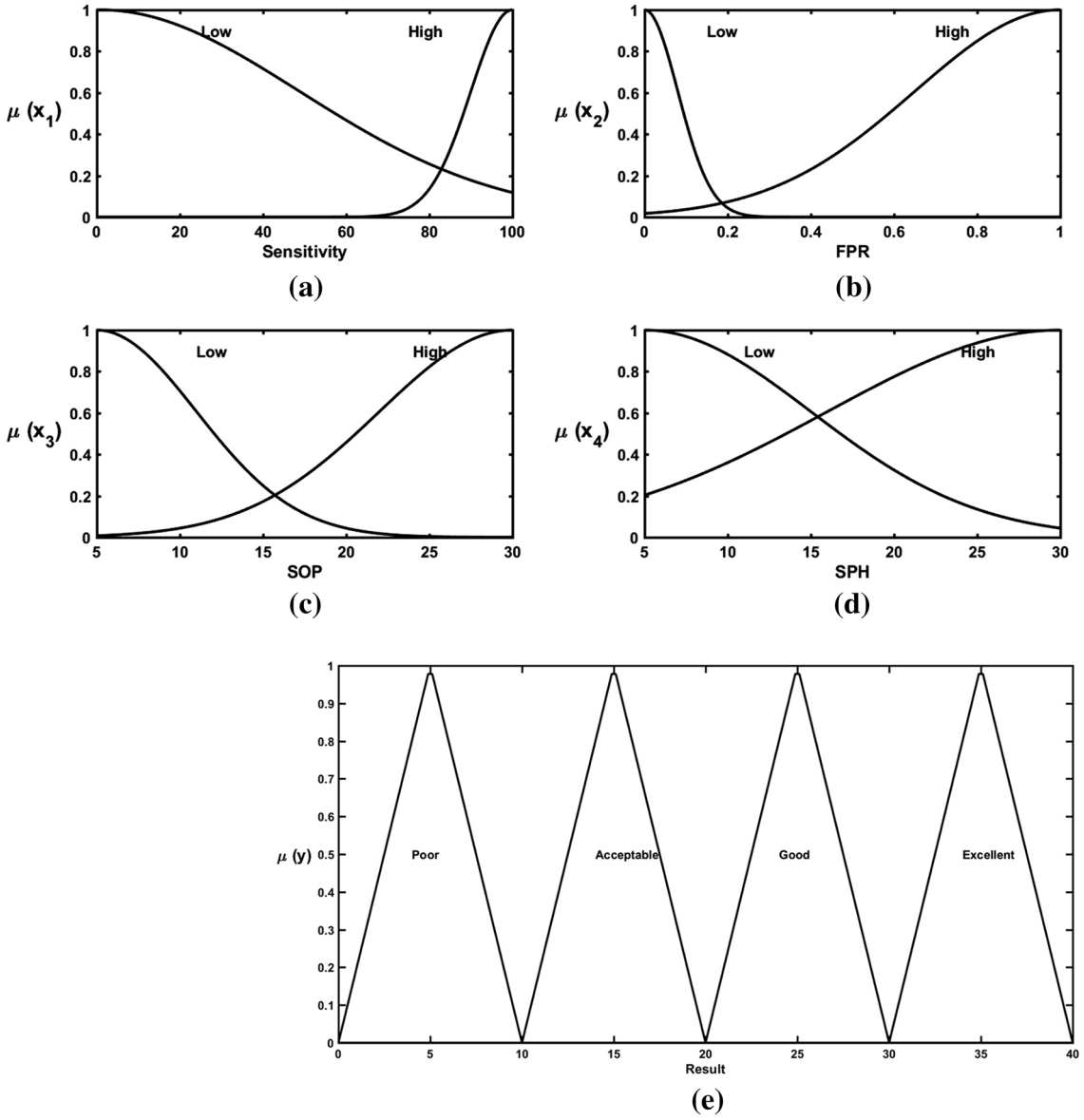

Fig. 8 Schematic of optimum membership functions of inputs and output of the fuzzy system. **a** input 1. sensitivity **b** input 2. FPR **c** input 3. SOP **d** input 4. SPH **e** output. Result

on pre-ictal samples, and FPR evaluates only based on inter-ictal samples, but this is not true for other statistical measures such precision and accuracy. A better interpretation can be explained by confusion matrix as it was computed with respect to TP, TN, FP and FN obtained from results of total fuzzy test data (see Fig. 13). The imbalance between non-seizure class including 806 predictor output and seizure class comprising only 20 predictor outputs is evident. However, the problem of misclassified class is being solved by normalizing the developed confusion matrix with respect to size of each class. As can be seen in Fig. 13b, all the elements were changed to a same scale. Now we can calculate precision and accuracy considering normalized confusion matrix, as if mean value of recall, FPR, precision and accuracy are summarized in Table 6.

Discussion

Importance of finding suitable SOP and SPH

This study attempts to solve the challenge in selecting SOP and SPH, which varies for each patient and the type of epilepsy. Statistically, high value of sensitivity and low value of FPR obtained by different SOP and SPH represent good result. Clinically they may not good, though, because there

Table 3 Prediction results on fuzzy train data

Patient	Time characteristic result					Statistic result		
	Best SOP (min)	Best SPH (min)	Expected seizure onset	Prediction time (min)	Time window of MA filter	Sensitivity (%)	FPR (per h)	Fuzzy outcome
1	10	30	[30 40]	32	15	100	0.12	Good (25.19)
2	5	5	[5 10]	8	10	100	0.17	Good (20.15)
3	5	30	[30 35]	30	15	100	0.08	Good (28.33)
4	10	15	[15 25]	24	15	100	0.09	Good (26.35)
5	5	10	[10 15]	13	15	100	0.1	Good (25.87)
6	5	25	[25 30]	28	15	100	0.09	Good (27.32)
7	5	30	[30 35]	33	10	100	0.05	Good (28.97)
8	5	5	[5 10]	7	5	100	0.18	Acceptable (18.21)
9	5	5	[5 10]	8	15	100	0.22	Acceptable (12.23)
10	5	20	[20 25]	25	15	100	0.1	Good (26.67)
Average	6	18				100	0.12	Good (23.92)

Table 4 Prediction results on fuzzy test data

Patient	Time characteristic result					Statistic result		
	Best SOP (min)	Best SPH (min)	Expected seizure onset	Prediction time (min)	Time window of MA filter	Sensitivity (%)	FPR (per h)	Fuzzy outcome
11	10	60	[60 70]	61	5	100	0.17	Good (21.02)
12	5	20	[20 25]	22	15	100	0.19	Acceptable (17.64)
13	5	25	[25 30]	27	5	100	0.15	Good (22.78)
14	5	20	[20 25]	22	15	100	0.09	Good (27.07)
15	10	60	[60 70]	65	10	100	0.18	Acceptable (19.51)
16	5	15	[15 20]	18	10	100	0.15	Good (23.36)
17	5	20	[20 25]	25	15	100	0.13	Good (25.04)
18	5	15	[15 20]	16	15	100	0.07	Good (26.87)
19	5	15	[15 20]	19	5	100	0.12	Good (25.66)
20	5	15	[15 20]	17	10	100	0.16	Good (22.22)
21	10	30	[30 40]	32	15	100	0.09	Good (27.16)
Average	6	27				100	0.13	Good (23.48)

are literally certain prerequisites that must be followed and met before making decision on prediction result. By considering several rules, we used Mamdani fuzzy inference logic to determine the optimal SPH and SOP duration for each patient, so that the medical attention can be promptly given to the patient improving the quality of life and reducing the stress and anxiety for each patient. Ultimately, the proposed method must accurately predict SPH and reduce the duration of SOP as close to true seizure occurrence as possible.

According to Tables 3 and 4, the Good fuzzy output for most patients indicated that the inputs of fuzzy system corresponded to desired conditions such as low SOP, high SPH, high sensitivity and low FPR. Particularly, patient 7 among the all patients had the lowest optimal SOP and FPR along with the highest optimal SPH and sensitivity, consequently, output of fuzzy system reached the highest value by 28.33. On the other hand, it can be seen that patients 8, 9, 12 and 15 got Acceptable result. The reason for lower value of Result is mainly because FPR related to those patients were lower than others, while sensitivity stayed the same at 100%. Apart from that not only the best SOP and the best SPH were detected but also we simply specified the approximate suitable SOP and SPH for each patient in a more extensive range with the help of fuzzy system output without considering values of FPR and sensitivity. As we expected the result showed higher range of suitable SPH compare to range of suitable SOP (see Fig. 12).

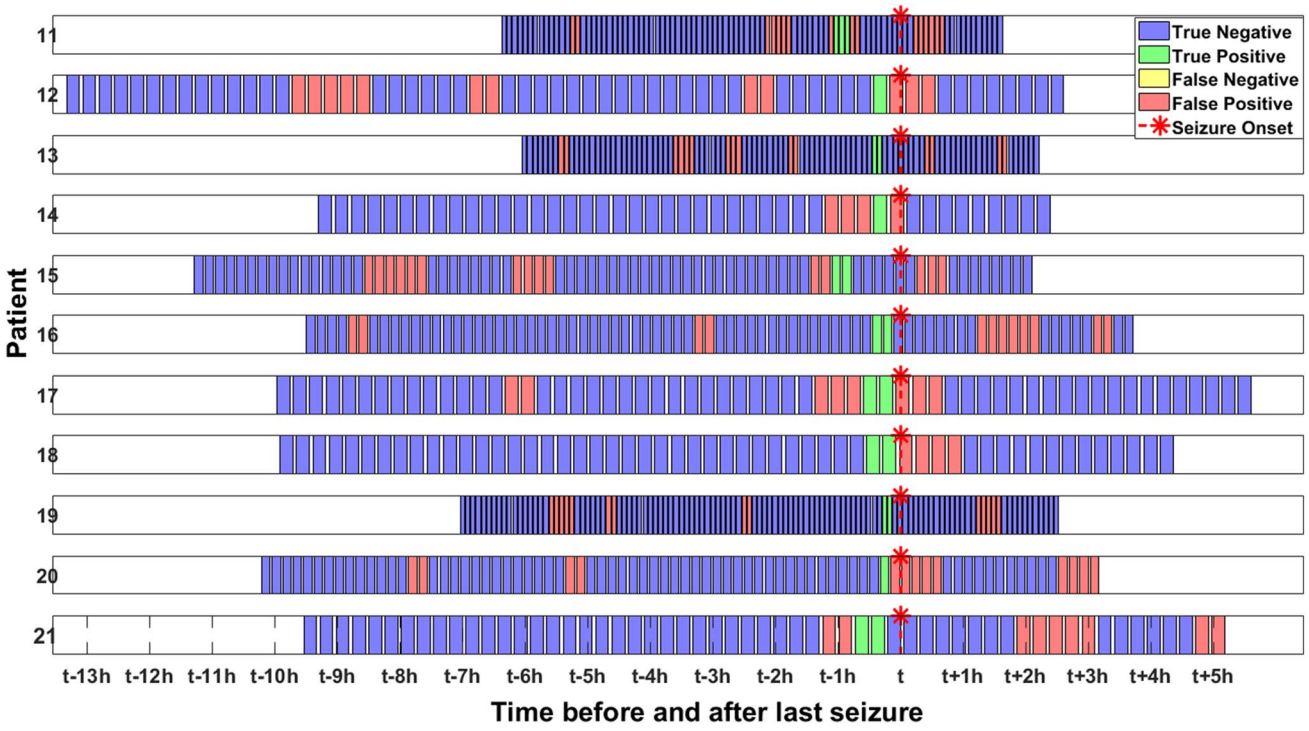

Fig. 9 Illustrating the predictor performance on evaluative segment of fuzzy test data

Table 5 Comparison of our approach with other approaches evaluated on Freiburg EEG database

Authors	Year	Measure	SOP	SPH	Sensitivity (%)	FPR	Fuzzy group (score)
Winterhalderet	2006	Phase synchronization	30 min	10 min	60	0.15	Poor (5.04)
Shao-Hang Hung	2010	Wavelet-correlation di- mension	18 s	60 min	86.96	0.25	Poor (6.88)
Shufang Li	2013	Spike rate	50 min	10 s	72.70	0.1	Poor (7.17)
Yang Zheng	2014	Phase synchronization	30 min	10 min	85	0.15	Acceptable (14.3)
Yanli Zhang	2014	Higuchi fractal dimension	30 min	2 min	86.95	0.2	Poor (9.82)
Ardalan Aarabi	2017	Nonlinear features	50 min	10 s	92.90	0.09	Acceptable (10.49)
Our approach	2019	Phase synchronization	6 min	27 min	100	0.13	Good (23.48)

Effect of fuzzy system parameters on prediction

This study proved that outcome of fuzzy model entirely depended on fuzzy membership functions controlled by centers and variances described in Sect. 3.1.1. Gaussian functions' center actually limited the input range, which were explicitly defined for sensitivity with $c_L(1) = 0$ and $c_H(1) = 100$, and for FPR with $c_L(2) = 0$ and $c_H(2) = 1$. The only problem is the range of SOP (x_3) and SPH (x_4). One could argue that they could be obtained by considering patients' safety and citing to other studies. For example, as the patient needs an early seizure warning of 3 to 5 min, we then set the minimum SPH of 5 min ($c_L(4) = 5$) [6, 30, 31]. When the seizure prediction method works well, a much smaller SOP may be eligible (for example, for a seizure warning device) [6]. Therefore, the minimum SOP period is also set to 5 min ($c_L(3) = 5$). In addition, half an hour SOP is also reasonable, if the treatment effect lasts for this period, in which maximum SOP is set to 30 min ($c_H(3) = 30$). For example, this is usually expected for

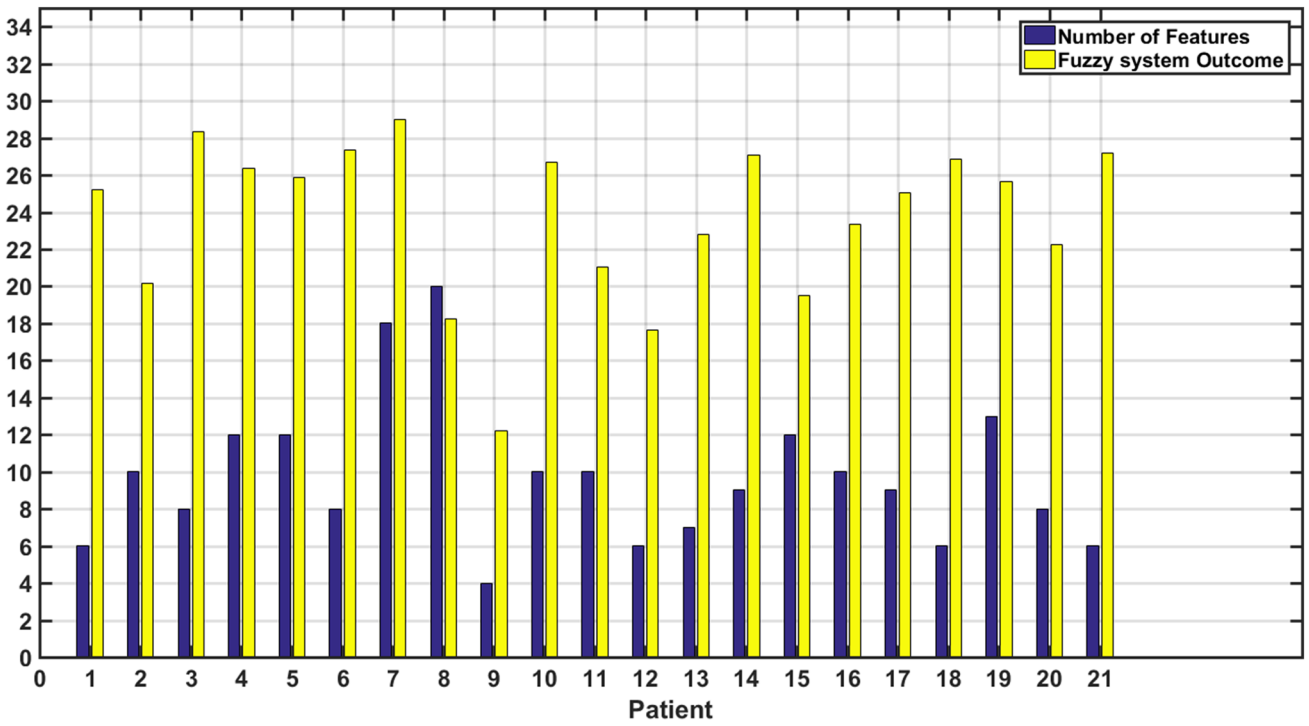

Fig. 10 Comparing the number of features with the fuzzy system outcome for each patient

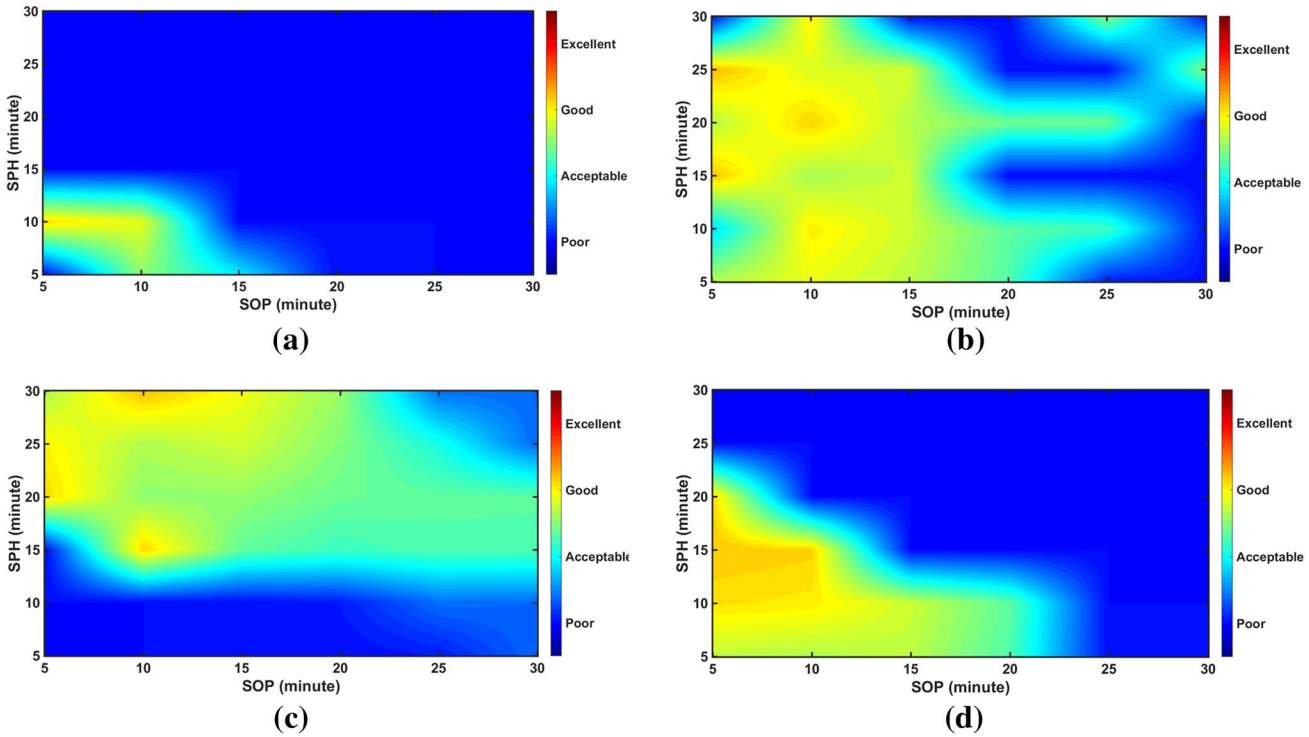

Fig. 11 Fuzzy system outcomes for different set of SOP and SPH over four patients. **a** patient 5 (best SOP = 5, best SPH = 10), **b** patient 6 (best SOP = 5, best SPH = 25), **c** patient 21 (best SOP = 10, best SPH = 30), **d** patient 18 (best SOP = 5, best SPH = 15)

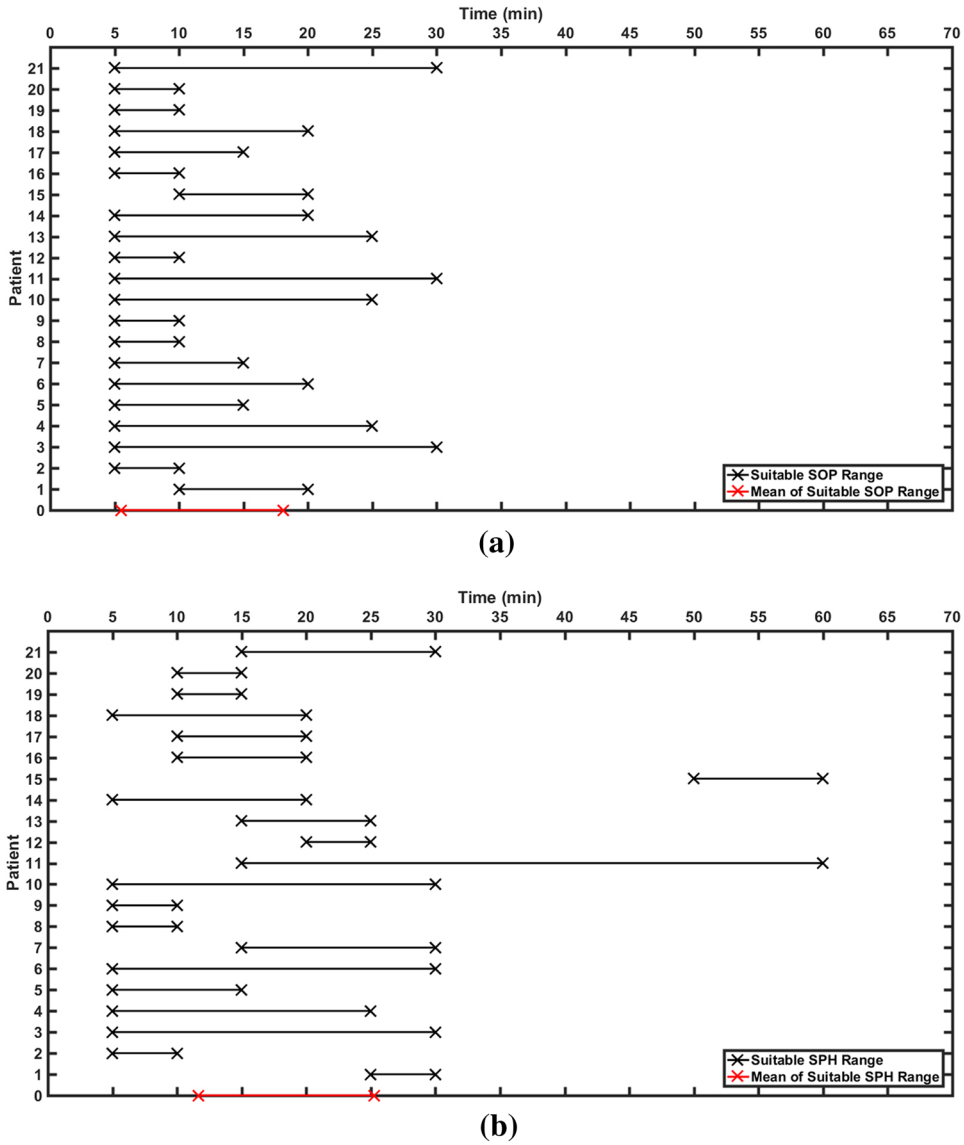

Fig. 12 Estimated suitable ranges of **a** SOP and **b** SPH for each patient

antiepileptic drugs (AEDs) [6]. Finally, unlike Aarabi et al., Baghdadi et al., Arthurs et al. and Zhang et al., it is strongly argued that maximum SPH should be extended as possible in order to provide enough time for possible strategies to prevent the irreparable consequences of seizure, for example, a patient who is driving on a highway or swimming in a pool requires more time to escape from such dangerous situations when the impending seizure is likely to occurred [14, 22, 30, 32]. As a result, maximum SPH is set to 30 min ($c_H(4) = 30$), which seems an adequate time for patient to behave more efficiently.

Further analysis showed that good result could be achieved through the specific variances of input membership function, so we can conclude that center and variance of input fuzzy membership functions play a significant role in selecting SOP and SPH. On the other hand, achieving perfect results in both fuzzy training dataset and fuzzy test dataset indicated that the designed fuzzy system has the ability in providing with satisfying result from the unseen data.

Overcoming high number of features

In spite of the fact the source EEG channels decreased from 128 to 6 channels, bivariate measures gave rise 75 features of mean phase coherence for each 16 s time window. These high dimensional features are not practical in on-line prediction, but this number declined to maximum 20 features for patient 8 and minimum 4 features for patient 9 per window indicating the proposed selection method coped with the high number of features. However,

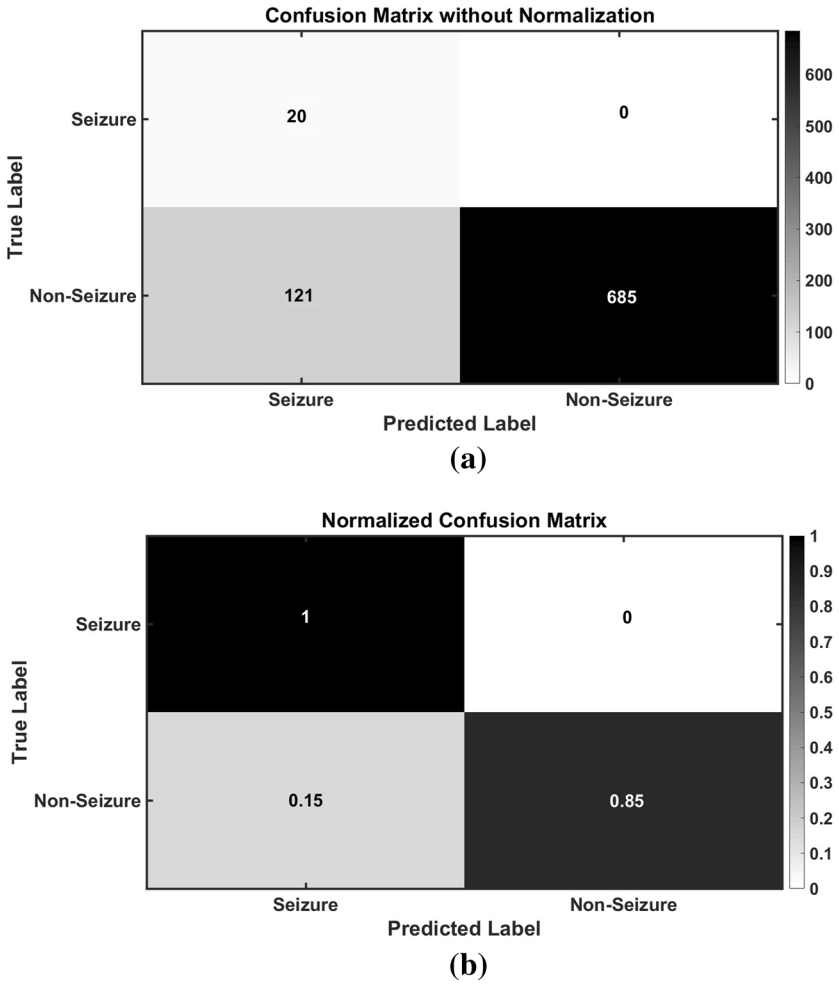

Fig. 13 Confusion matrices provided by the results of seizure prediction over fuzzy test data. **a** without normalization and **b** with normalization

Table 6 Averaged results of prediction on two-type data: fuzzy train data and fuzzy test data

Statistical measure	Fuzzy train data	Fuzzy test data
Sensitivity	100	100
FPR	0.12	0.13
Precision	87.85	86.95
Accuracy	93.08	92.5

result also showed that prediction performance did not depend on the number of features.

Improving the efficiency of ENFM

ENFM, which incorporates a recursive fuzzy clustering, is a powerful nonlinear neural network that was proposed by Soleimani et al. [24]. Although this classifier was designed for on-line application and especially for seizure prediction, it is not compatible with long term EEG databases to predict seizure activities, since they contain very few pre-ictal samples whereas most of samples are inter-ictal. Hence, classifier may gradually loose the capable of detecting pre-ictal patterns following a long inter-ictal patterns. Soleimani et al. suggested that in order to compensate the unbalanced classes, method of surrogate data should be used to generate new pre-ictal samples by perturbing the available data points. However, in addition to questioning validity of the prediction performance, this approach leads to perturbing the phase of the Fourier transform of the real data points, and pre-ictal period cannot be properly identified by mean phase coherence. Here we overcame this problem by introducing two delays ($p_{\max}, p_{\min}$) into the feedback training of ENFM instead of defining a fix delay (P), so that SOP and SPH were applied to train the ENFM without adding artificial samples to the actual data (see Fig. 4).

Comparisons to other seizure prediction methods

The proposed fuzzy system not only is capable of finding best SOP and SPH per case but also can be applied for evaluating the prediction performance. So this privilege gave us an opportunity to consider the results of other studies. According to Table 5, our method got higher fuzzy output

than the others. The major reason for this superiority is that the fuzzy system outcome strongly depends on sensitivity and FPR. For example, SOP by 18 s and SPH by 60 min are perfect choices for Hung et al., but, the evaluation does not justify 0.25 of FPR [33]. Likewise, Li et al. and Winterhalderet et al. got poor outcome mainly because of low sensitivity (72.7 and 60%) [5, 27]. On the other hand, Yang Zheng et al. and Aarabi et al. achieved rather good sensitivity and FPR, as a result higher fuzzy outcome they got [9, 14].

Conclusion

In this study, a new patient-specific model has been presented for on-line prediction of epileptic seizures. To this end, the interaction of different brain regions was obtained through the phase synchronization of the EEG channels pairs in specific frequency domains. The mean phase coherence was applied to distinguish between pre-ictal and inter-ictal period. Optimal features were then extracted by the Spearman's correlation coefficient test to minimize complexity of the calculation. Finally, a recursive extension of Gath-Geva clustering algorithm called ENFM (evolving neuro-fuzzy model) was applied to predict epileptic seizures. In addition, a novel evaluation method based on Mamdani fuzzy inference system is proposed to select optimal SOP and SPH for each patient. This optimization algorithm can also be used to evaluate other research achievements, as result showed the superiority of the proposed method over other studies. The results also showed that for the mean SOP by 6 min and mean SPH by 27 min, which seem reasonable durations for security of epileptic patients, sensitivity, FPR, precision and accuracy were obtained by 100%, 0.13 per hour, 86.95% and 92.5%, respectively.

Finally, in the context of present neuroscience knowledge, the length of pre-ictal period is unclear and varies from seizure to other seizure [3]. This variation may affect the results when a constant SOP and SPH were considered for the whole EEG. The future work therefore will be devoted to designing an adaptive SOP and SPH optimization algorithm to improve the performance of this epileptic seizure prediction model. In summary, this approach can be used for home care applications for which a seizure warning system can be designed that predicts safe time zone and warning time zone with high accuracy.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies performed on human or animals participants by any of the authors.

Informed consent For this type of study formal consent is not required.

Appendix

Brief introduction of evolving neuro-fuzzy model (ENFM)

Basically, ENFM is a single-layer neural network that output of each neuron is weighed by a membership value which is obtained by recursive Gath-Geva clustering (RGG). Suppose that $\bar{x}$ is the input vector and ω_i is the weight vector of the ith neuron. The output of each neuron is calculated as

$$\bar{x} = \left[1, x_1, x_2, \ldots, x_n\right]^T,$$

$$\omega_i = \left[\omega_{i_0}, \omega_{i_1}, \ldots, \omega_{i_n}\right]^T,$$

$$y_i = \omega_i^T \bar{x} \tag{6}$$

where n is the number of input variables. Note that the weight vector is computed recursively by least squares algorithm (RLS). If we say u_i is the membership value of each neuron with the total of C neurons, then the output of the ENFM is computed as

$$\hat{y} = \sum_{i=1}^{C} u_i y_i \tag{7}$$

Generally, in RGG clustering the following objective function must be minimized:

$$J = \sum_{i=1}^{C} \sum_{j=1}^{Q} u_{ij}^2 d_{ij} \tag{8}$$

The membership value and distance of the jth data point to the ith cluster (u_{ij}, d_{ij}) with respect to the prior probability of the ith cluster (K_i), are estimated as:

$$d_{ij} = \frac{\sqrt{det\left(\sum_i\right)}}{K_i} \exp\left(\frac{1}{2}\left(x_j - \mu_i\right)^T \sum_i^{-1} \left(x_j - \mu_i\right)\right) \tag{9}$$

$$u_{ij} = \frac{\left(1/d_{ij}\right)}{\sum_{i=1}^{C}\left(1/d_{ij}\right)} \tag{10}$$

$$K_i = \frac{\sum_{j=1}^{Q} u_{ij}^2}{\sum_{i=1}^{C}\sum_{j=1}^{Q} u_{ij}^2} \tag{11}$$

where μ_i and $\sum_i$ are the mean and covariance of the ith cluster. These two parameters calculated through the iterative equations with respect to new data point (x) and its membership value to the ith cluster. Updating μ_i and $\sum_i$ are given as

$$\mu_i^+ = \mu_i^- + \frac{x - \mu_i^-}{N_i^+} u_i^2 \tag{12}$$

$$\sum_i^+ = \frac{N_i^-}{N_i^+}\left(\sum_i^- + \frac{u_i^2}{N_i^+}\left(x - \mu_i^-\right)\left(x - \mu_i^-\right)^T\right) \tag{13}$$

$$N_i^+ = N_i^- + u_i^2 \tag{14}$$

where superscripts + and – denote current and past values, respectively. Equation (14) shows that the sum of membership values related to the ith cluster, also computed recursively. Every time $\tilde{x}$ given to the model, a novelty value is calculated for each cluster as defined

$$M_i = \exp\left(-\frac{1}{2}\left(\tilde{x} - \mu_i\right)^T \sum_i^{-1} \left(\tilde{x} - \mu_i\right)\right) \tag{15}$$

If the maximum novelty value is less than a threshold called *th1*, another cluster is added with center of $\tilde{x}$ and diagonal matrix as covariance of new cluster.

Furthermore, in order to control the number of clusters, a merging criteria between mth cluster and nth cluster is computed as

$$S_{mn} = \exp\left(-\frac{1}{2}\left(\mu_n - \mu_m\right)^T \sum_m^{-1} \left(\mu_n - \mu_m\right)\right) \tag{16}$$

To find similar clusters, S_{mn} and S_{nm} must be obtained. If they are more than a threshold value *th2*, mth cluster and nth cluster will be merged, and the parameters of new cluster estimated as follows:

$$N_k = N_m + N_n \tag{17}$$

$$\mu_k = \frac{N_m\mu_m + N_n\mu_n}{N_m + N_n} \tag{18}$$

$$\sum_k = \frac{1}{\left(N_m + N_n\right)^3}\left[\begin{array}{l}\left(N_m^3 + 2N_m^2N_n + N_mN_n^2\right)\sum_m \\ +\left(N_n^3 + 2N_n^2N_m + N_nN_m^2\right)\sum_n \\ +\left(N_n^2N_m + N_nN_m^2\right)\left(\mu_n - \mu_m\right)\left(\mu_n - \mu_m\right)^T\end{array}\right] \tag{19}$$

References

1. Litt B, Lehnertz K (2002) Seizure prediction and the preseizure period. Curr Opin Neurol 15:173–177
2. Mormann F, Andrzejak G, Elger CE, Lehnertz K (2007) Seizure prediction: the long and winding road. Brain 130:314–333
3. Bandarabadi M, Rasekhi J, Teixeira CA, Karami MA, Dourado A (2015) On the proper selection of preictal period for seizure prediction. Epilepsy Behav 46:158–166
4. Cheng-Yi C, Chang N, Chen T, Chen H, Chen L (2011) Seizure prediction based on classification of EEG synchronization patterns with on-line retraining and post-processing scheme. In: Annual international conference of the IEEE, Engineering in Medicine and Biology Society, EMBC, pp 7564–7569
5. Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Schulze-Bonhage A, Timmer J (2006) Testing statistical significance of multivariate time series methods for epileptic seizure prediction. Chaos 16:013108
6. Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Schulze-Bonhage A, Timmer J (2006) Do false predictions of seizures depend on the state of vigilance? A report from two seizure-prediction methods and proposed remedies. Epilepsia 47:2058–2070
7. Wang S, Chaovalitwongse W, Wong S (2013) Online seizure prediction using an adaptive learning approach. IEEE Trans Knowl Data Eng 25:2854–2866
8. McSharry PE, Smith LA, Tarassenko L (2003) Prediction of epileptic seizures: are nonlinear methods relevant? Nat Med 9:241–242
9. Zheng Y, Wang G, Li K, Bao G, Wang J (2014) Epileptic seizure prediction using phase synchronization based on bivariate empirical mode decomposition. Clin Neurophysiol 125:1104–1111
10. Carney PR, Myers S, Geyer JD (2011) Seizure prediction: methods. Epilepsy Behav 22:94–101
11. Mormann F, Lehnertz K, David P, Elger CE (2002) Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D 144:358–369
12. Arnhold J, Grassberger P, Lehnertz K, Elger CE (1999) A robust method for detecting interdependencies: application to intracranially recorded EEG. Physica D 134:419–430
13. Mormann F, Kreuz T, Andrzejak G, David P, Lehnertz K, Elger CE (2003) Epileptic seizures are preceded by a decrease in synchronization. Epilepsy Res 53:173–185
14. Aarabi A, He B (2017) Seizure prediction in patients with focal hippocampal epilepsy. Clin Neurophysiol 128:1299–1307
15. Winterhalder M, Maiwald T, Voss HU, Aschenbrenner-Scheible R, Timmer J, Schulze-Bonhage A (2003) The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. Epilepsy Behav 4:318–325
16. Wang L, Wang Ch, Fu F, Yu X, Guo H, Xu C, Jing X, Zhang H, Dong X (2011) Temporal lobe seizure prediction based on a complex Gaussian wavelet. Clin Neurophysiol 122:656–663
17. Freiburg EEG Database, Epilepsy Center of the University Hospital of Freiburg (2010). https://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database
18. Mallat S (ed) (2009) A wavelet tour of signal processing, 3rd edn. Academic Press, San Diego
19. Sharbaty H, Martin J, Jammes B, Esteve D (2006) Alpha and theta wave localisation using Hilbert–Huang transform: empirical study of the accuracy. In: 2nd international conference on information & communication technologies, pp 1159–1164
20. Losonczi L, Bako L, Marton LF (2012) Hilbert–Huang transform used for EEG signal analysis. In: The international

conference interdisciplinarity in engineering INTER-ENG, pp 361–369
21. Huang NE, Shen Z, Long SR, Wu MLC (1998) The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis. Proc R Soc Lond Ser A 454: 903–995
22. Baghdadi G, Nasrabadi AM (2012) EEG phase synchronization during hypnosis induction. J Med Eng Technol Eng Technol 36:222–229
23. Rosenblum M, Pikovsky A, Kurths J, Schafer C, Tass P. (2001) Chapter 9 Phase synchronization: from theory to data analysis. In: Moss F, Gielen S (eds) Handbook of biological physics, vol 4, pp 279–321. Elsevier, Amsterdam
24. Soleimani-B H, Lucas C, Araabi B, Schwabe L (2012) Adaptive prediction of epileptic seizures from intracranial recordings. Biomed Signal Process Control 7:456–464
25. Gath I, Geva AB (1989) Unsupervised optimal fuzzy clustering. IEEE Trans Pattern Anal Mach Intell 11:773–781
26. Soleimani BH, Lucas C, Araabi B (2010) Recursive Gath–Geva clustering as a basis for evolving neuro-fuzzy modeling. In: International conference on fuzzy systems.
27. Shufang L, Zhou Weidong, Qi Y, Yinxia L (2013) Seizure prediction using spike rate of intracranial EEG. IEEE Trans Neural Syst Rehabil Eng 21:880–886
28. Jang SR, Sun CT, Mizutani E, eds (1997) Neuro-fuzzy and soft computing, 1st edn. Prentice Hall, Upper Saddle River, NJ
29. Leekwijck WV, Kerre EE (1999) Defuzzification: criteria and classification. Fuzzy Sets Syst 108(2):159–178
30. Arthurs S, Zaveri HP, Frei MG, Osorio I (2010) Patient and caregiver perspectives on seizure prediction. Epilepsy Behav 19:474–477
31. Gadhoumi K, Lina JM, Gotman J (2013) Seizure prediction in patients with mesial temporal lobe epilepsy using EEG measures of state similarity. Clin Neurophysiol 124:1745–1754
32. Zhang Y, Zhou W, Yuan Q, Wu Q (2014) A low computation cost method for seizure prediction. Epilepsy Res 108:1357–1366
33. Shao-Hang H, Chih-Feng C, Shu-Kai W, Bor-Shyh L, Chin-Teng L (2010) VLSI implementation for epileptic seizure prediction system based on wavelet and chaos theory. In: IEEE region 10 conference, TENCON, pp 364–368