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Physica D 194 (2004) 357–368
PHYSICA D
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Comparison of three nonlinear seizure prediction methods by means of the seizure prediction characteristic

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Received 13 May 2003; accepted 23 February 2004
Communicated by E. Kostelich

Abstract

Epilepsy is characterized by the spontaneous and unforeseeable occurrence of seizures, during which the perception or behavior of patients is disturbed. The predictability of these seizures would render novel therapeutic approaches possible. Several prediction methods have claimed to be able to predict seizures based on EEG recordings minutes in advance. However, the term seizure prediction is not unequivocally defined, different criteria to assess prediction methods exist, and only little attention has been paid to issues of sensitivity and false prediction rate. We introduce an assessment criterion called the *seizure prediction characteristic* that incorporates the assessment of sensitivity and false prediction rate. Within this framework, three nonlinear seizure prediction methods were evaluated on a large EEG data pool of 21 patients. Altogether, 582 h intracranial EEG data and 88 seizures were examined. With a rate of 1–3.6 false predictions per day, the "dynamical similarity index" achieves a sensitivity between 21 and 42%, which was the best result of the three methods. Sensitivity was between 18 and 31% for the extended, prospective version of the "accumulated energy" and between 13 and 30% for the "effective correlation dimension". These results still are not sufficient for clinical applications.

PACS: 05.10.−a; 05.45.Tp; 87.19.La; 89.20.−a

Keywords: Seizure prediction; Sensitivity; False prediction rate; Seizure prediction characteristic; Comparison; Epilepsy

1. Introduction

"It's the variability that really makes it so stressful. You never know when it is going to be chaos again and you'll have one. Just because this morning is terrific doesn't mean tonight is going to be terrific, either behavior-wise, medication-wise, or any other-wise. So it is the unpredictability of it that is really nerve-racking to live with." [1]

Like the parent of a child suffering from the Lennox-Gastaut syndrome, many epilepsy patients have to cope with the incessant uncertainty of sudden seizures. Hence, in 1996, the primary research priorities of the American Epilepsy Society read "seizure prediction, early recognition, and blockage of seizures" [2].

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doi:10.1016/j.physd.2004.02.013

Table 1
Achievements of seizure prediction methods developed to date

Year	Authors	#Patient	#Seizure	Interictal (h)	MPT (min)	Sensitivity (%)	FP/h	Method
1998	Osorio et al. [24]	13	125	34	0.25	92	0	Based on frequency analysis
1998	Martinerie et al. [18]	11	19	0	2.64	89	–	Correlation density
1998	Lehnertz and Elger [10]	16	16	5.2–34.7	11.5	94	0	Effective correlation dimension
1999	Le Van Quyen et al. [13]	13	23	0	5.75	83	–	Similarity index
2000	Le Van Quyen et al. [14]	9	17	0	4.45	94	–	Similarity index
2001	Iasemidis et al. [7]	5	58	0	49.1	91	–	Lyapunov exponent
2001	Le Van Quyen et al. [16]	23	26	0	7	96	–	Similarity index (surface EEG)
2001	Lehnertz et al. [11]	59	95	≥115	19	47	0	Effective correlation dimension
2001	Jerger et al. [8]	4	12	0	1–3	–	–	Seven different prediction methods
2002	De Clercq et al. [5]	12	12	0	–	0	–	Sim. ind., corr. dim. (surface EEG)
2002	Schindler et al. [26]	7	15	<144	4–330	100	>0.014	LIFU (surface EEG)
2002	Navarro et al. [23]	11	41	12–60	7.54	83	0.3	Similarity index
2003	Mormann et al. [20]	10	14	15	86/102	86	0	Phase coherence, lin. cross corr.
2003	Mormann et al. [21]	18	32	49	4–221	81	0	Synchronization decrease

Listed are the number of patients and seizures investigated, the total duration of interictal EEG data for calculation of the false prediction rate, the mean prediction time (MPT), sensitivity, and the rate of false predictions per hour. All but three studies were done with intracranial EEG data. False prediction rates of 0 FP/h mean that no false prediction occurred for the investigated EEG data.

Up to now, several investigations based on nonlinear time series analysis have been carried out on intracranial and surface EEG data with promising results [3–20,22–26]. Table 1 summarizes the achievements of seizure prediction methods developed to date. For a review, see [27,28].

The clinical utility of a seizure prediction method would be to predict the occurrence of an upcoming seizure and trigger an external intervention system to control the seizure. An intervention system could be in the form of an electrical stimulation of the vagus nerve or the administration of a potent anticonvulsive agent directly into the epileptic focus [17,29,30]. Besides, a simple warning could help the patient avoid dangerous situations, like swimming or climbing a staircase.

Fig. 1 provides an example of how a seizure prediction method works. A mathematical algorithm extracts a "feature" from the EEG recording. Once this feature crosses a specific threshold level, an alarm is triggered. A comparison of interictal periods far away from any seizure and pre-ictal periods resulting in seizure onset leads to the choice of a suitable threshold value. In this case, lower threshold values correspond to higher sensitivity, since more seizures can be predicted correctly. Consequently, more false predictions occur during the interictal epochs. The tight dependency between sensitivity and the false prediction rate holds for every prediction method.

In this paper, we address three shortcomings that need to be resolved for further development of seizure prediction methods:

(1) Different assessment criteria of seizure prediction methods exist, and the term "seizure prediction" is not unequivocally defined.
(2) Generally, little attention has been paid to the dependency between the sensitivity and the false prediction rate. For example, the performance of half of the prediction methods summarized in Table 1 is characterized only by the sensitivity, without calculation of the false prediction rate.
(3) All prediction methods have been developed and tested on different EEG data pools, making it difficult to compare their performance.

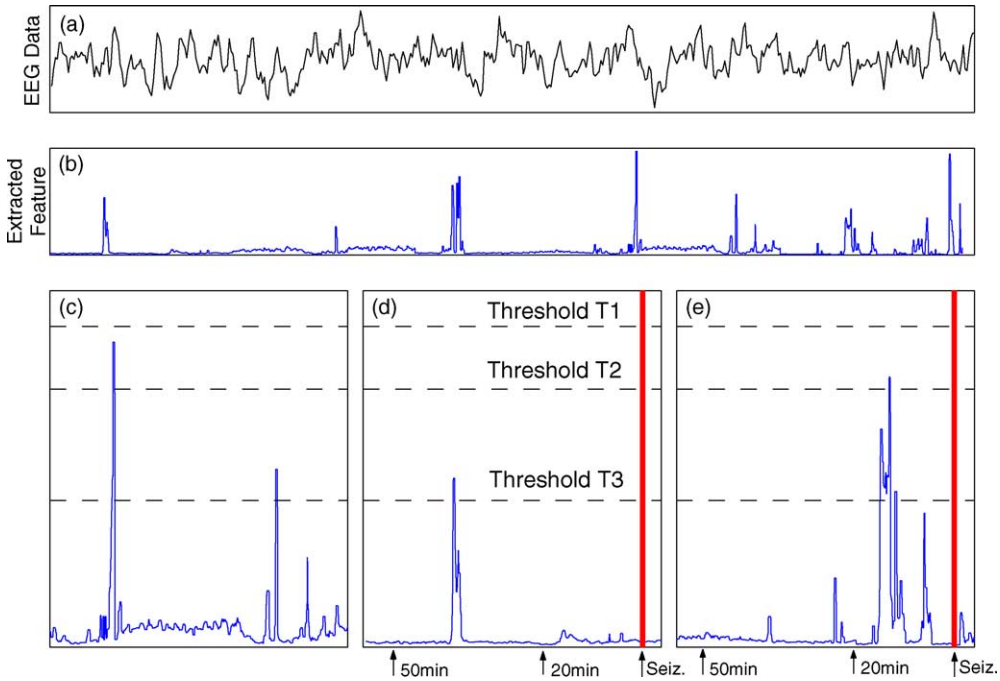

Fig. 1. Dependency between sensitivity and false prediction rate. The upper and middle panels display an example for EEG data (a) and an extracted feature (b) used by the seizure prediction method "increments of the accumulated energy". Below, 1-h interictal (c) and 2-h pre-ictal epochs are shown ((d) and (e)). Vertical lines mark seizure onsets. Upward crossing of a threshold (dashed line) triggers an alarm. Three different thresholds illustrate the dependency between sensitivity and false prediction rate. For T_1, no alarm occurs either during pre-ictal or interictal epochs, meaning zero sensitivity and zero false predictions. Threshold T_2 leads to the correct prediction of the second seizure in (e) in a time interval 20 min before the seizure onset, at the expense of one false prediction during the interictal epoch in (c). Decreasing the threshold to T_3 to predict the first seizure in (d) produces another false alarm. Evaluation of a prediction method should require the simultaneous assessment of both sensitivity and false prediction rate.

Osorio et al. suggested in 1998 that prediction methods should be evaluated by both sensitivity *and* false prediction rate [24]. We have extended this approach and have developed an assessment criterion that we call the *seizure prediction characteristic* [31]. It takes into account statistical and clinical considerations and enables one to assess and compare different seizure prediction methods.

To evaluate seizure prediction methods on the same EEG data, Jerger et al. in 2001 employed seven prediction methods on intracranial EEG data from four children [8]. Though no clear performance order could be established, prediction times between 1 and 3 min were reproduced. However, only pre-ictal phases of 5 min duration and no interictal EEG data were examined.

In this study, we assess and compare three nonlinear prediction methods by means of the seizure prediction characteristic: the *effective correlation dimension* [9–11], the *dynamical similarity index'* [13,14,16], and an extended, prospective version of the *accumulated energy*, which achieved promising results in a retrospective setting [17]. Altogether, 88 seizures from 21 patients and 582 h of intracranial EEG data were examined. This data pool is still growing and will be publicly available in the near future to serve as an open source for the development and comparison of prediction methods.

The paper is structured as follows: part 2 focuses on the terminology and assessment criterion, part 3 on the EEG data pool, and part 4 on the applied prediction methods. Their performance is

presented in part 5, which is followed by the conclusion.

2. The seizure prediction characteristic

2.1. Terminology

A seizure prediction method has to forecast an impending epileptic seizure by raising an alarm in advance of the seizure onset. A perfect prediction method indicates the exact point in time when a seizure occurs. This ideal behavior is not expected for current prediction methods that analyze EEG data. The uncertainty can be considered by use of the *seizure occurrence period*, SOP, which is defined as a time period during which the seizure is to be expected (Fig. 2). In addition, to permit a therapeutic intervention, a minimum window of time between the alarm raised by the prediction method and the beginning of SOP is essential. This window of time is called the *seizure prediction horizon*, SPH. Taking into account the two time periods SPH and SOP, a correct prediction is defined as follows: after the alarm signal, during SPH, no seizure has occurred yet. During SOP, a seizure occurs. The exact time of seizure onset may vary within SOP, thereby reflecting the uncertainty of the prediction. Seizures outside of any SOP are not predicted by the system and therefore are classified as false negatives. Alarm signals without a seizure during SOP are false predictions.

Two measures describe a prediction method performance for given SPH and SOP:

- sensitivity, defined as the fraction of correctly predicted seizures within the total seizures;
- false prediction rate, the number of false predictions per time interval.

As discussed above, these measures are not independent.

2.2. Clinical considerations

Single false predictions are unavoidable in a realistic setting. Measurements in large complex systems like the human brain are subject to fluctuations that are likely to produce false alarms if the investigated time interval is long enough. Should false alarms occur, the patient prepares for a seizure in vain. In the case of electrical stimulations or administration of drugs, unnecessary side effects may occur. If the number of false predictions per time interval is too large, then patients will disregard future alarms or will suffer from psychological stresses; the side effects of repeated interventions will accumulate and may lead to a neurophysiological impairment. Depending on the patient and the chosen intervention system, a maximum false prediction rate, FPR_{max}, must be defined that is acceptable from a clinical point of view.

The average seizure incidence may be a basis through which reasonable values for FPR_{max} can be chosen. Bauer and Burr [32] evaluated the seizure diaries of 63 patients who were resistant to anticonvulsant treatment. Based on nearly 9 years of documentation and about 313 seizures per patient on average, the mean seizure rate was 3 per month.

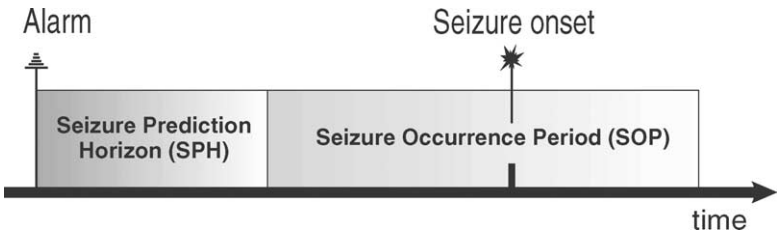

Fig. 2. Definition of a correct prediction. The seizure does not occur before the end of the seizure prediction horizon (SPH). This time interval is followed by the seizure occurrence period, during which the seizure occurs, but the exact point of time is unknown. Seizures outside of any SOP are not predicted and therefore are considered false negatives. Alarm signals without a seizure in the following seizure occurrence period are false predictions.

Reduction of anti-epileptic drugs, e.g., during presurgical monitoring, leads to increased seizure frequencies. Haut et al. [33] investigated seizure clustering for 91 patients with medically intractable epilepsy who underwent monitoring for presurgical evaluation. The average maximal number of seizures in a 24 h period during monitoring increased to 3.6 seizures per day compared to the low number under normal conditions. Higher values of $\mathrm{FPR}_{\max}$ are questionable with respect to possible clinical applications. Even if all seizures can be predicted correctly, at least 50% of all alarms would be false alarms for patients during monitoring. This percentage increases to 97% for epileptic patients under normal conditions.

Similar constraints exist for SPH and SOP, depending on the patient and the intervention system. Anticonvulsive drugs, for instance, do not take effect immediately, as they must pass through the blood-brain barrier before reaching the target neurons. Here, a minimum seizure prediction horizon, $\mathrm{SPH}_{\min}$, is required. Electrical stimulation is supposed to be fast-acting and may require only a few seconds. If the patient is only warned, $\mathrm{SPH}_{\min}$ increases to tens of seconds—enough time for the patient to leave a dangerous situation.

Because the exact point of time for seizure onset is unknown, the effect of any intervention should last for the whole seizure occurrence period. If the SOP lasts too long, then additional administration of anticonvulsive drugs or longer electrical stimulation may be required. In the case of a warning system, the patients' psychological stress increases with longer SOP, because a seizure is expected at any moment during this time interval. Thus, an SOP that is too long would increase the patient's anxiety. The physiological and psychological stress determines an upper bound for SOP, the maximum seizure occurrence period $\mathrm{SOP}_{\max}$.

2.3. Statistical considerations

To be regarded as a prediction method, the performance of a seizure prediction method has to be superior to a prediction in a random, periodic, or other nonspecific manner, independent of any prior information. Fig. 3 displays how seizures can be predicted correctly by chance. In general, the parameters of a

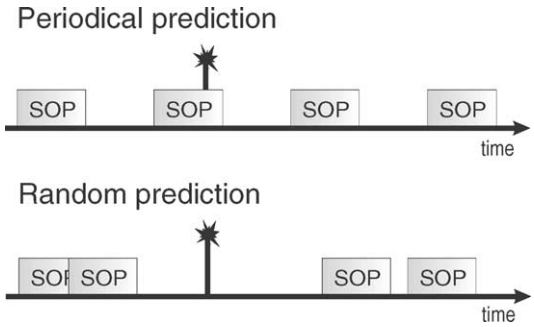

Fig. 3. Unspecific prediction methods. Upper panel: A periodical prediction method raises alarms after a certain period of time. For example, with SOP = 30 min and $\mathrm{FPR}_{\max}$ = 1 FP/h, the sensitivity is 50%. Lower panel: A random prediction method raises alarms by chance. Since seizure occurrence periods can overlap, the sensitivity is a bit worse than for the periodical prediction method. Nonetheless, both methods converge to a sensitivity of 100% for false prediction rates that are too high or for seizure occurrence periods that are too long.

seizure prediction method will be adjusted to increase sensitivity until the false prediction rate equals the upper bound $\mathrm{FPR}_{\max}$. Then, during a small interictal time interval I, the probability for an alarm is $p = \mathrm{FPR}_{\max} I$. Observing a longer time interval, W, the probability for at least one alarm can be calculated as follows:

$$p(\text{no alarm in } I) = 1 - \mathrm{FPR}_{\max} I,$$

$$p(\text{no alarm in } W) = (1 - \mathrm{FPR}_{\max} I)^{W/I},$$

$$p(\text{at least one alarm in } W) = 1 - (1 - \mathrm{FPR}_{\max} I)^{W/I},$$

$$p(\text{at least one alarm in } W \gg I) \approx 1 - \mathrm{e}^{-\mathrm{FPR}_{\max} W}.$$

With $W = \mathrm{SOP}$, this is exactly the sensitivity S of a random prediction method, because it is the probability of at least one alarm during the seizure occurrence period.

A periodical prediction method raises alarms regularly after a certain period of time. If, during interictal phases, the false prediction rate equals $\mathrm{FPR}_{\max}$, then the probability and, therefore, the sensitivity S for an alarm during the seizure occurrence period SOP is

$$S = \min\{\mathrm{FPR}_{\max} \mathrm{SOP}, 100\%\}.$$

For large values of SOP or $\mathrm{FPR}_{\max}$, both the random and the periodical prediction method achieve high

sensitivities that approach 100%. This happens independently of the value for the seizure prediction horizon. For a maximum false prediction rate of 1.0 false predictions per hour (FP/h) and a seizure occurrence period of 50 min, the random prediction method achieves a sensitivity of 57% and the periodical prediction method a sensitivity of 83%. Hence, for maximum false prediction rates that are too high or for seizure occurrence periods that are too long, the performance of any specific seizure prediction method cannot be distinguished from the results of these unspecific prediction methods.

2.4. Assessment criterion: the seizure prediction characteristic

The values for $\mathrm{FPR}_{\max}$, $\mathrm{SPH}_{\min}$, and $\mathrm{SOP}_{\max}$ depend on a particular clinical application, i.e., a patient and an intervention system. This is generally unknown during the development of a seizure prediction method. Therefore, the method's sensitivity S should not be calculated for a fixed setting but instead for a reasonable range of values for $\mathrm{FPR}_{\max}$, SPH, and SOP, leading to the seizure prediction characteristic

$$S = S(\mathrm{FPR}_{\max}, \mathrm{SPH}, \mathrm{SOP}).$$

This approach enables the assessment and comparison of seizure prediction methods independently of any particular clinical application. As a minimum requirement, a prediction method should be superior to unspecific methods like the random or periodical ones by achieving a significant higher seizure prediction characteristic.

The calculation of the seizure prediction characteristic to evaluate a prediction method comprises five steps:

(1) Specification of the number of maximum tolerated false predictions during the interictal periods $\mathrm{FPR}_{\max}$, SPH, and SOP.
(2) Adjustment of parameters of the prediction method, for example, the value of a threshold, until the false prediction rate equals $\mathrm{FPR}_{\max}$ for every single patient. Interictal data sets of at least $1/\mathrm{FPR}_{\max}$ duration for each patient are required for this procedure.
(3) Calculation of sensitivity S using the pre-ictal data sets of each patient.
(4) Averaging the values of sensitivity for all patients.
(5) Repetition of these steps for a reasonable range of values for $\mathrm{FPR}_{\max}$, SPH, and SOP.

Eventually the seizure prediction characteristic $S(\mathrm{FPR}_{\max},\mathrm{SPH},\mathrm{SOP})$ can be estimated.

3. EEG data and patient characteristics

In this study, EEG data from 21 patients were investigated, with a total of 88 seizures, 509 h of interictal, and 73 h of pre-ictal or ictal EEG data. The interictal periods were at least 1 h distant to any seizure. For 13 patients, 24 h of contiguous interictal recordings were available. In the remaining cases, no seizure-free day occurred during monitoring. Here, a small number of interictal periods covering a whole day was combined to obtain 24 h of interictal data. Between two and five seizures (mean 4.2) per patient were examined, each with a seizure-free pre-ictal phase of 50 min.

All patients suffered from pharmaco-refractory focal epilepsy and underwent presurgical epilepsy monitoring with invasive electrodes. Depth electrodes were implanted stereotactically, and subdural electrodes, via burr holes or open craniotomy. Further details for data acquisition and patient characteristics are given in Table 2. For each patient, a certified epileptologist selected three in-focus and three out-of-focus electrodes, which were referenced to an electrode displaying a minimal amount of epileptic activity.

The EEG data were recorded with a Neurofile NT digital-video EEG system with 128 channels, a sampling rate of 256 or 512 Hz, and a 16-bit A/D converter. A bandpass filter between 0.5 and 120 Hz (resp. 80 Hz for the effective correlation dimension) was applied. Possible line noise was eliminated with a 50-Hz notch filter.

Table 2
Patient characteristics

Patient	Sex	Age	Seizure type	H/NC	Electrodes	Outcome	#Seizures	Interictal (h)
1	f	15	SP, CP	NC	g,s	III	5	24
2	m	38	SP, CP,GTC	H	d	IV	3	24
3	m	14	SP, CP	NC	g,s	I	5	24
4	f	26	SP, CP,GTC	H	d,g,s	No surgery	5	24
5	f	16	SP, CP,GTC	NC	g,s	I	5	24
6	f	31	CP, GTC	H	d,g,s	I	3	24
7	f	42	SP, CP, GTC	H	d	I	3	25
8	f	32	SP, CP	NC	g,s	II	2	24
9	m	44	CP, GTC	NC	g,s	II	5	24
10	m	47	SP, CP, GTC	H	d	IV	5	24
11	f	10	SP, CP, GTC	NC	g,s	II	4	24
12	f	42	SP, CP, GTC	H	d,g,s	IV	4	25
13	f	22	SP, CP, GTC	H	d,s	II	2	24
14	f	41	CP, GTC	H and NC	d,s	I	4	24
15	m	31	SP, CP, GTC	H and NC	d,s	II	4	24
16	f	50	SP, CP, GTC	H	d,s	I	5	24
17	m	28	SP, CP, GTC	NC	s	I	5	24
18	f	25	SP, CP	NC	s	No surgery	5	25
19	f	28	SP, CP, GTC	NC	s	I	4	24
20	m	33	SP, CP, GTC	NC	d,s	I	5	26
21	m	13	SP, CP	NC	s	I	5	24

Seizure types and location: simple partial (SP), complex partial (CP), generalized tonic-clonic (GTC), hippocampal (H), neocortical (NC). Electrodes: grid (g), strip (s), depth (d). Outcome according to Engel classification: (I) free of seizures, (II) 90% seizure reduction, (III) 75% seizure reduction, and (IV) less seizure reduction to a worsening of the patient's condition [34]. Between two and five seizures (mean 4.2) and at least 24 h of interictal EEG data for every patient were analyzed.

4. Seizure prediction methods

4.1. Dynamical similarity index

We implemented the dynamical similarity algorithm according to [13,14]. The basic idea is to compare the dynamic of a sliding window S_t to a fixed reference window S_{ref} of a seizure-free period. The main steps of the calculation may be summarized as follows.

New time series I_n, $n \in \mathbb{N}$, are constructed by computing time intervals between two positive zero-crossings of the EEG signal. Delay embedding with dimension $m = 16$ and delay $\tau = 1$ leads to $A_n = (I_n, I_{n-\tau}, \ldots, I_{n-((m-1)\tau)})$. A singular value decomposition for the trajectory matrix $\mathbf{A}(S_{\mathrm{ref}})$ of the reference window is applied. The reference lasts 300 s and is far away from any seizure. The projection of $\mathbf{A}(S_t)$ for the sliding window and $\mathbf{A}(S_{\mathrm{ref}})$ onto the principal axis of the reference window yields $\mathbf{X}(S_t)$ and $\mathbf{X}(S_{\mathrm{ref}})$, respectively. A random selection (see [13]) $\mathbf{Y}(S_{\mathrm{ref}})$ of $\mathbf{X}(S_{\mathrm{ref}})$ in the phase space is compared with $\mathbf{X}(S_t)$ via the cross-correlation integral:

$$C(S_{\mathrm{ref}}, S_t) = \frac{1}{N_{\mathrm{ref}} N_t} \sum_{i=1}^{N_{\mathrm{ref}}} \sum_{j=1}^{N_t} \Theta(r - \|Y_i(S_{\mathrm{ref}}) - X_j(S_t)\|),$$

with the Heaviside step function Θ, the euclidian norm $\|\cdot\|$, and the number of points in the phase space of the reference N_{ref} and of the sliding window, N_t. The distance r is defined as the 30th percentile of the cumulative neighborhood distribution of the reference window. Finally, the dynamical similarity index $\gamma(S_t)$ is given by

$$\gamma(S_t) = \frac{C(S_{\mathrm{ref}}, S_t)}{\sqrt{C(S_{\mathrm{ref}}, S_{\mathrm{ref}}) C(S_t, S_t)}}.$$

A threshold crossing with the constraint of a minimum crossing time of 150 s was used as alarm signal. The threshold was varied.

4.2. Effective correlation dimension

Based on the correlation dimension D_2 [35,36], which is an estimator for the fractal dimension of the attractor of a deterministic dynamical system, Lehnertz and Elger introduced the *effective correlation dimension*, D_2^{eff}, as a means to predict epileptic seizures [9]. *Dimension drops* are evaluated [11], characterized by the time interval and maximal deviation by which D_2^{eff} drops under a threshold.

For the effective correlation dimension, the EEG time series are embedded for different dimensions up to $m = 25$, leading to $\vec{x}_m(t)$. The correlation sum

$$C_m(r) = \frac{1}{N(N-1)} \sum_{i \neq j} \Theta(r - \|\vec{x}_m(i) - \vec{x}_m(j)\|)$$

is calculated for a range of the radius r with the Heaviside step function Θ and the maximum norm $\|\cdot\|$. The correlation dimension is defined as

$$D_2 = \lim_{r \to 0} \frac{\mathrm{d}\log C_m(r)}{\mathrm{d}\log(r)}.$$

The limit requires a proper scaling region, which is not necessarily given for measured data. Lehnertz and Elger use an operational method, leading to the so-called *effective correlation dimension*, D_2^{eff}. This measure is applied to EEG data using a sliding window technique.

The average of D_2^{eff} during interictal periods serves as the threshold. For every drop below this threshold, the time t_{drop} until the next threshold crossing and the maximum deviation d_{drop} from the threshold value are measured. Originally, t_{drop} and d_{drop} of pre-ictal periods had to extend the maximum dropping parameters in interictal periods and precede the seizure onset directly to be counted as predictive drops. This approach leads to no false alarms, but only one of the 88 investigated seizures was preceded by a predictive drop [37]. This could be due to the long interictal data sets used in this study. Therefore, we took the dropping parameters as variables that are varied to determine the seizure prediction characteristic.

4.3. Increments of accumulated energy

Litt et al. investigated the ability of the *accumulated energy* algorithm to distinguish pre-ictal from interictal periods of 50 min duration [17]. About 90% of the pre-ictal and 88% of the interictal periods were classified correctly. Unfortunately, this method requires knowledge of the seizure onset, which is not given in a prospective analysis. Since the results were very promising, we investigated the performance of an extended, prospective version, the *increments of the accumulated energy*.

The accumulated energy $\mathrm{AE}(k)$ is based on the "average energy":

$$E_k = \frac{1}{N} \sum_{i=1}^{N} x_{i(k)}^2 \quad \text{for time window } k \in \mathbb{N}$$

calculated for a time window of 1.25 s in length. Two consecutive time windows are shifted by 0.45 s, and $x_{i(k)}$ is the electrode potential of sample i in window k. Finally, the accumulated energy and the increments of the accumulated energy are defined as

$$\mathrm{AE}_m = \frac{1}{10} \sum_{k=10m-9}^{10m} E_k + \mathrm{AE}_{m-1},$$

$$m = 1, 2, \ldots, \quad \mathrm{AE}_0 = 0,$$

$$\mathrm{iAE}_m = \frac{1}{10} \sum_{k=10m-9}^{10m} E_k = \mathrm{AE}_m - \mathrm{AE}_{m-1}.$$

A higher slope of AE corresponds to higher increments iAE. Using a median filter over 90 s ensures that only permanent changes in these increments lead to different values of the iAE. The threshold crossing of iAE was used as the alarm signal and the threshold value was varied.

5. Results

Since the seizure prediction characteristic depends on three different parameters, it is necessary to fix at least one of them to present the result in two dimensions. The assessment and comparison of the three

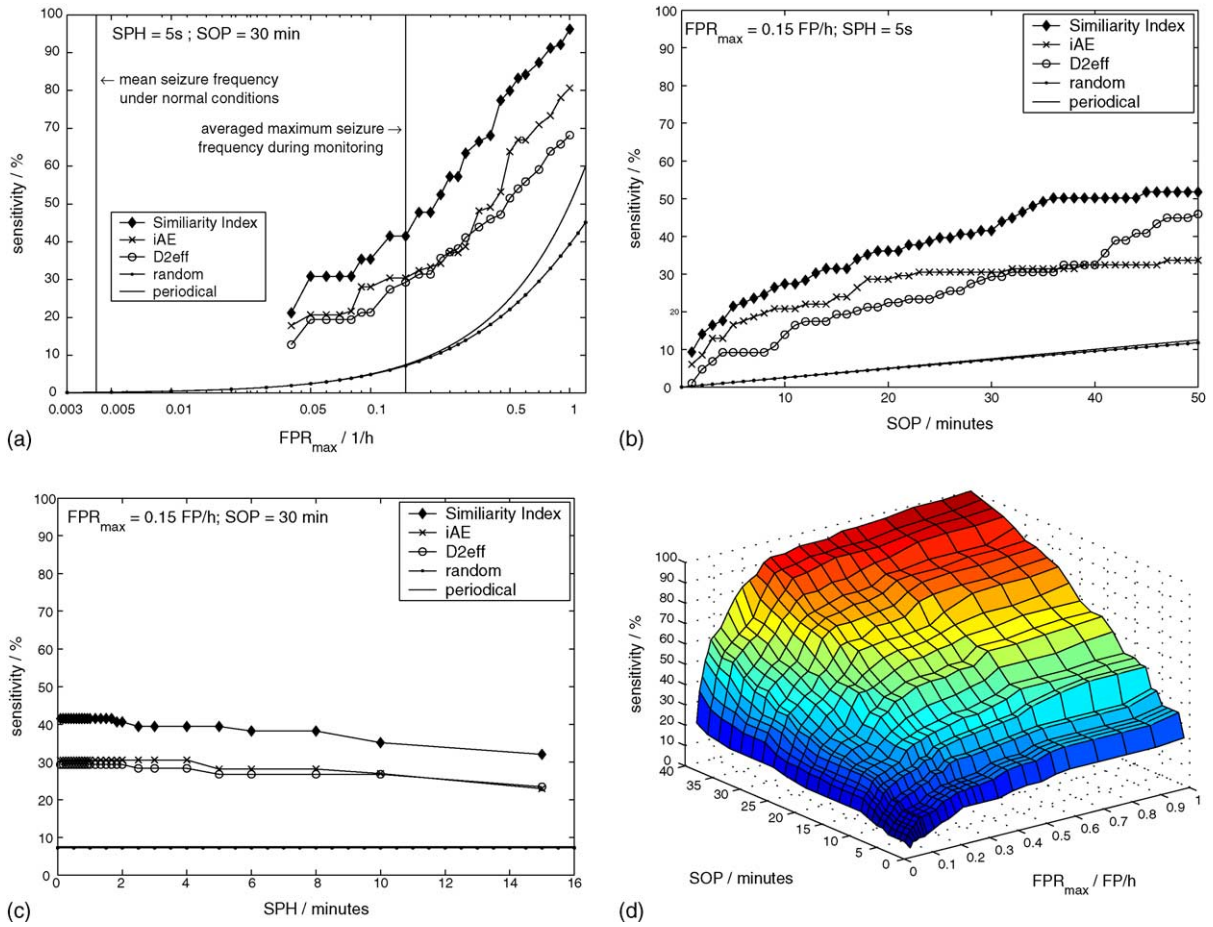

Fig. 4. Seizure prediction characteristic $S(\mathrm{FPR}_{\max}, \mathrm{SPH}, \mathrm{SOP})$ of three specific and two unspecific prediction methods. (a) Dependence of the sensitivity S on the maximum false prediction rate ($\mathrm{FPR}_{\max}$) for a fixed seizure prediction horizon of 5 s and seizure occurrence period of 30 min. (b) Dependence on SOP for $\mathrm{FPR}_{\max} = 0.15$ FP/h and SPH = 5 s. (c) Dependence on SPH for $\mathrm{FPR}_{\max} = 0.15$ FP/h and SOP = 30 min. (d) Dependence on SOP and $\mathrm{FPR}_{\max}$ for SPH = 5 s for the dynamical similarity index. See text for details.

prediction methods is presented by the seizure prediction characteristic depending on (1) $\mathrm{FPR}_{\max}$; (2) SOP; and (3) SPH. The prediction methods are compared to each other and to the unspecific methods (the periodical and random alarm systems). Finally, the dependence of the sensitivity S on two measures, $\mathrm{FPR}_{\max}$ and SOP, is shown for the dynamical similarity index.

5.1. *Sensitivity depending on* $FPR_{\max}$

The dependence of the sensitivity S on $\mathrm{FPR}_{\max}$ is shown in Fig. 4(a) for the dynamical similarity index (diamonds), the increments of accumulated energy (crosses), and the effective correlation dimension algorithm (circles).

The seizure prediction horizon was fixed to 5 s, corresponding to a fast intervention, and the seizure occurrence period to 30 min. The vertical lines mark the mean seizure frequency under normal conditions (left) and the averaged maximum seizure frequency during presurgical monitoring (right).

The logarithmically scaled maximum false prediction rate $\mathrm{FPR}_{\max}$ covers three regions. Values around $\mathrm{FPR}_{\max} = 0.004$ FP/h correspond to the mean seizure frequency of pharmacoresistant focal epilepsy patients under normal conditions with a mean of three seizures

per month. For this range, contiguous EEG data of several days up to weeks are required to evaluate the seizure prediction characteristic. Our data pool, comprising 24 h of EEG data for every patient, enables the evaluation of at least one false alarm per day, i.e., 0.042 FP/h.

The middle region ranges from one false alarm per day up to the averaged maximum seizure frequency of 3.6 per day during monitoring (0.15 FP/h). Here, the false prediction rate is 35 times higher than the seizure frequency under normal conditions. The sensitivity ranges from 21.2 to 41.5% for the dynamical similarity index, 12.8 to 29.3% for the effective correlation dimension, and 17.9 to 30.5% for the increments of the accumulated energy.

For higher maximum false prediction rates up to $\mathrm{FPR}_{\max} = 1$ FP/h, the sensitivity rapidly increases and reaches values close to 100% for the similarity index. Consequently, the percentage of false predictions of the alarm signals increases as well: at least 50% of the predictions are false predictions on a day of monitoring with a maximal number of seizures. Compared to the mean seizure frequency under normal conditions, this fraction amounts to at least 98%. Hence, values of $\mathrm{FPR}_{\max}$ that are higher than the averaged maximum seizure frequency during monitoring are questionable.

All three prediction methods achieve better results than the unspecific methods.

5.2. Sensitivity depending on SOP

In Fig. 4(b), the sensitivity S is plotted as a function of SOP for fixed values of $\mathrm{FPR}_{\max} = 0.15$ FP/h and $\mathrm{SPH} = 5$ s.

The dynamical similarity index again achieves the best result for the whole parameter range. The sensitivity of the increments of accumulated energy is greater than for the effective correlation dimension for SOP smaller than 37 min. For larger values of SOP, D_2^{eff} achieves a better performance than iAE.

For SOP values greater than 36 min, the sensitivity of the dynamical similarity index increases more slowly than the unspecific prediction methods. This increase can be interpreted simply as a statistical property: larger seizure occurrence periods allow more unspecific and therefore false alarms to be evaluated as correct predictions. The same effect is observable for the increments of the accumulated energy for SOP larger than 20 min. In contrast, the strong increase in sensitivity for the effective correlation dimension indicates the processing of more specific information.

5.3. Sensitivity depending on SPH

Only a small dependence of sensitivity on SPH could be observed (Fig. 4(c)). For $\mathrm{FPR}_{\max}$ of again 0.15 FP/h and SOP of 30 min, all prediction methods have a constant sensitivity for SPH shorter than 2 min. Hence, most intervention systems should have enough time to take effect.

5.4. Sensitivity depending on $\mathrm{FPR}_{\max}$ and SOP

Fixing only one parameter, in this case SPH, to 5 s, a three-dimensional plot displays the behavior of the seizure prediction characteristic depending on $\mathrm{FPR}_{\max}$ and SOP for the similarity index (Fig. 4(d)). For certain combinations of $\mathrm{FPR}_{\max}$ and SOP, high sensitivity values up to 100% can be achieved. The clinician has to decide with the individual patient whether the corresponding $\mathrm{FPR}_{\max}$, SOP, and SPH are acceptable.

6. Conclusions

We suggest the application of the seizure prediction characteristic as a function of sensitivity and the maximum false prediction rate $\mathrm{FPR}_{\max}$, the seizure prediction horizon SPH, and seizure occurrence period SOP, to determine the performance of a seizure prediction method. In this way, it is possible to assess and compare prediction methods and to choose a suitable method for a particular patient and type of intervention.

For a range of $\mathrm{FPR}_{\max}$ between 1 and 3.6 per day, SPH shorter than 2 min and SOP up to 30 min, the dynamical similarity index achieves a sensitivity between 21 and 42%, which was the best result of the three evaluated prediction methods. The sensitivity of the increments of the accumulated energy lie between

18 and 31%, and for the dimension drops of the effective correlation dimension, between 13 and 30%.

Higher values of FPR_{max} are questionable with respect to clinical applications. Even with a sensitivity of 100%, at least 50% of all alarms would be false alarms for patients during monitoring. Epileptic patients under normal conditions with three seizures per month would have to endure 97% false alarms.

The results of the investigated nonlinear prediction methods are significantly better than the performance of unspecific methods, like the random or periodical prediction. This indicates the existence of specific "predictive" information in pre-ictal epochs and that the investigated methods are sensitive to this information. However, the resulting seizure prediction characteristics are so far not sufficient for clinical applications.

Acknowledgements

We wish to acknowledge the support of Dr. Klaus Lehnertz, Epilepsy Center, Bonn. In particular, providing reference data was helpful to validate the algorithm "effective correlation dimension". Special thanks are due to Ms. Carolin Gierschner for her support regarding EEG data acquisition, storage, and transfer, and to Mr. Sherwin K. Sy for proofreading of the manuscript.

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