Performance of a seizure warning algorithm based on the dynamics of intracranial EEG

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Abstract

During the past decade, several studies have demonstrated experimental evidence that temporal lobe seizures are preceded by changes in dynamical properties (both spatial and temporal) of electroencephalograph (EEG) signals. In this study, we evaluate a method, based on chaos theory and global optimization techniques, for detecting pre-seizure states by monitoring the spatio-temporal changes in the dynamics of the EEG signal. The method employs the estimation of the short-term maximum Lyapunov exponent (STLmax), a measure of the order (chaoticity) of a dynamical system, to quantify the EEG dynamics per electrode site. A global optimization technique is also employed to identify critical electrode sites that are involved in the seizure development. An important practical result of this study was the development of an automated seizure warning system (ASWS). The algorithm was tested in continuous, long-term EEG recordings, 3–14 days in duration, obtained from 10 patients with refractory temporal lobe epilepsy. In this analysis, for each patient, the EEG recordings were divided into training and testing...
datasets. We used the first portion of the data that contained half of the seizures to train the algorithm, where the algorithm achieved a sensitivity of 76.12% with an overall false prediction rate of 0.17 h$^{-1}$. With the optimal parameter setting obtained from the training phase, the prediction performance of the algorithm during the testing phase achieved a sensitivity of 68.75% with an overall false prediction rate of 0.15 h$^{-1}$. The results of this study confirm our previous observations from a smaller number of patients: the development of automated seizure warning devices for diagnostic and therapeutic purposes is feasible and practically useful.

Keywords: Intracranial EEG; Spatio-temporal dynamics; Automated seizure warning

1. Introduction

Although seizures traditionally have been considered to be unpredictable events, there is increasing evidence that seizure may, in fact, be predictable. Iasemidis et al. (1994) demonstrated that seizures occur in a time-dependent fashion, indicating that the underlying processes are deterministic. Intracranial electroencephalograph (EEG) signals recorded from patients with refractory temporal lobe epilepsy appear to have properties that are characteristic of chaotic systems since: (1) they are non-linear (Casdagli et al., 1996, 1997); (2) they have a non-integer (fractal) dimension (Grassberger and Procaccia, 1983; Babloyantz, 1988); (3) there is at least one positive Lyapunov exponent (Abarbanel et al., 1993; Iasemidis et al., 1990). Based on these observations, Iasemidis and Sackellares postulated that the dynamics underlying the occurrence of epileptic seizures were chaotic. Based on this premise, these investigators and their co-workers have used analytic tools developed for the study of non-linear chaotic systems to investigate the dynamics of the transitions into and out of the seizure (ictal) state.

These investigators found the short-term maximum Lyapunov exponent ($STL_{max}$) to be particularly useful for evaluating the dynamical behavior of the EEG signal over time. $STL_{max}$ is a measure of how rapidly (in bits per second) information is being created or destroyed, and it is an indicator of how chaotic (higher values) or ordered (lower values) the system is. From another perspective, monitoring the Lyapunov exponent of an EEG signal over time provides information regarding the stability of the dynamical state of the epileptic brain. $STL_{max}$ is noted as “short-term” because it is calculated iteratively for local time epochs of 10.24 s and does not assume stationarity of the analyzed signal within each epoch (for example, short-term bursts, like interictal spikes, do not bias the estimation of the $STL_{max}$—see Iasemidis and Sackellares, 1991). Profiles of $STL_{max}$ from intracranial EEG over time (temporal profiles) obtained from any single electrode did not show consistent temporal patterns during the transition from the interictal (period between seizures) to the ictal (during a seizure) state. This point was recently reported independently by Lai et al. (2003).

The most consistent feature of the dynamical transition from the interictal to the ictal state is the convergence in the value of the largest $STL_{max}$ calculated from EEG signals derived from critical electrode sites (Iasemidis et al., 1996). Iasemidis et al. (1996) and Sackellares et al. (2000) defined this spatio-temporal phenomenon as dynamical entrainment to emphasize the spatial convergence of the observed dynamics. The electrode sites showing a preictal convergence in $STL_{max}$ usually show divergence in $STL_{max}$ postictally (resetting).

Based on these findings, our research group has developed several automatic computer algorithms designed to predict seizures by detecting characteristic convergence in $STL_{max}$ values among critical electrode sites (Iasemidis et al., 2003; Yang et al., 2003; Sackellares et al., 2004). In addition to the estimation of $STL_{max}$ to quantify temporal properties of the brain dynamics, the essential features of these algorithms also involve an optimization technique to identify and select electrode sites for use in predicting an impending seizure. This selection is based on the behavior of the $STL_{max}$ profiles of all electrode sites before and after the preceding seizure. The prospective analysis of this method in the continuous long-term intracranial EEG recordings constitutes an automated seizure warning system (ASWS).

The current study was designed to evaluate the performance of one category of our algorithms, the non-adaptive ASWS algorithms (the other category being...
the adaptive ASPA algorithms, reported in Iasemidis et al., 2003), with respect to their sensitivity and false positive rate in seizure prediction for a larger patient population than what we reported before. Datasets from ten patients, in whom continuous long-term intracranial EEG recordings had been previously obtained for clinical purposes, were analyzed. Further, we performed two experiments to verify if the preictal transitions detected by the ASWS algorithm are truly related to physiological changes in the seizure development: (1) for the statistical validation of the observed temporal properties of the brain dynamics, we compared the prediction performance of ASWS with the ones from surrogate data. The surrogate data series consisted of identical EEG recordings as the original ones, with surrogate seizure times and preserved the length of the original inter-seizure intervals and (2) for the statistical validation of the spatial properties of the brain dynamics, we compared the prediction performances of ASWS with and without optimizing the electrode selection process. These two experiments will be explained in detail in Section 4.

The organization of the succeeding sections of this paper is as follows. The background, including quantification of the brain dynamics, statistical spatio-temporal properties and optimization, will be discussed in Section 2. The datasets used in this study and the procedure of the ASWS algorithm will be described in Section 3. The performance characteristics of the ASWS algorithm will be addressed in Section 4. Two experiments used to verify the sufficiency and utility of the algorithm will also be described in Section 4. Finally, conclusion and discussion will be addressed in Section 5.

2. Background

2.1. Quantification of the brain dynamics

Because of the non-stationary and non-linear characteristics of the EEG signal produced by the epileptic brain (Babloyantz and Destexhe, 1986), traditional signal-processing techniques have had limited utility. This limitation occurs because the EEG is generated by a multi-dimensional, non-linear system. Since the brain is a non-stationary system, algorithms used to measure brain dynamics must be modified to identify and to give appropriate weights to signal transients. To suitably measure the dynamics of EEG, Iasemidis (1991) and Iasemidis et al. (1990, 1991) adopted methods developed for measuring the maximum Lyapunov exponent $L_{\text{max}}$. This method generates a series of measures called the short-term Lyapunov, which provides local (in time and space) information regarding the dynamical stability of the brain. The STL estimates the local $L_{\text{max}}$ exponents within sequential short epochs (10.24 s) of EEG that may contain sharp outbursts of electrical activity (e.g., interictal spikes). We apply the STL$_{\text{max}}$ algorithm to EEG tracings from multiple intracranial electrode sites to compute multiple sets of STL$_{\text{max}}$ sequentially over time. Further details of the STL$_{\text{max}}$ algorithm are described elsewhere (Iasemidis, 1991; Iasemidis et al., 1990, 1991, 2000). With this method, the EEG signal from each electrode channel is treated as a one-dimensional time series. Using the method of delays (Packard et al., 1980; Takens, 1981), the time series is reconstructed into a seven-dimensional state space to capture the characteristics of the epileptic attractor (Babloyantz and Destexhe, 1986; Rapp et al., 1986; Iasemidis et al., 1988). The trajectories of the nearby points in the state space are used to calculate STL$_{\text{max}}$ (Wolf et al., 1985; Iasemidis et al., 1990). In essence, for each EEG epoch, the algorithm estimates the average rate of divergence or convergence of the orbits from a fiducial trajectory in the state space. The algorithm parameters were set so that sharp transients, such as spikes and spike-and-slow-wave complexes, present in the EEG signal, do not bias the estimation of STL$_{\text{max}}$. A large scale testing of the STL$_{\text{max}}$ algorithm demonstrated its robustness and repeatability (Iasemidis et al., 1990, 1991).

Fig. 1 shows the typical electrode placement used for our long-term EEG recordings. Figs. 2 and 3 depict short examples of EEG recordings during interictal and ictal periods, respectively. A 60 min plot of STL$_{\text{max}}$ of patient 3 obtained by analysis of the continuous EEG from a right hippocampal electrode (focal electrode) during the interictal period is shown in Fig. 4. For the same electrode site in the same patient, Fig. 5 shows STL$_{\text{max}}$ values during the interval 30 min before and after a seizure. In this figure, a typical pattern of STL$_{\text{max}}$ evolution from preictal to ictal to postictal states is demonstrated. There are intermittent drops in the already low values of STL$_{\text{max}}$ over the 30 min period before the seizure, and a sudden big drop in
Fig. 1. (A) Inferior transverse and (B) lateral views of the brain, illustrating approximate depth and subdural electrode placement for the performed intracranial EEG recordings. Subdural electrode strips are placed over the left orbital frontal (A_L), right orbital frontal (A_R), left subtemporal (B_L) and right subtemporal (B_R) cortex. Depth electrodes are placed in the left temporal depth (C_L) and right temporal depth (C_R) to record hippocampal activity.

STLmax during the ictal period. Postictally, there is a rapid rise in STLmax, exceeding preictal values.

By analyzing STLmax generated from multiple electrode sites, it is possible to investigate dynamical mechanisms underlying the development and resolution of epileptic seizures (Iasemidis et al., 1996). One of the most remarkable findings is the progressive convergence of STLmax profiles from certain electrode sites into a common value (a similar brain dynamical state) prior to seizures (Iasemidis et al., 1999, 2001). Fig. 6

Fig. 2. The 20 s EEG recording of the normal state of a typical epileptic seizure obtained from 32 electrodes in patient 3. Each horizontal trace represents the voltage recorded from the electrode site listed in the left column (see Fig. 1 for anatomical location of electrodes).
illustrates a 160 min plot of STLmax in patient 3, that shows the convergence of STLmax profiles during the preictal period. We have defined these characteristic spatio-temporal patterns (convergence in STLmax profiles) preceding seizures as signs of a preictal transition, and correspondingly the period within which these patterns are observed as a mathematically defined “preictal period”. In addition, studies by our group via STLmax profiles have shown that measures of the spatio-temporal dynamics of EEG demonstrate resetting of the brain after seizures’ onset (Shiau et al., 2000; Iasemidis et al., 2004), that is, postictal divergence of the preictally converged STL max profiles. In this study, we incorporated these findings to develop a prototype seizure warning algorithm.

2.2. Statistical quantification of spatio-temporal patterns

T-dIndex, the test statistic from the well-known paired t-test for comparisons of means of paired-dependent observations, was employed as a measure of statistical distance between pairs of STLmax profiles over a time window. The $T_{ij}$ index at time $t$ between the STLmax profiles of electrode sites $i$ and $j$ is then defined as:

$$T_{ij}^t = \frac{|\bar{D}_{ij}|}{\hat{\sigma}_{ij}(t) / \sqrt{N}}$$

where $|\bar{D}_{ij}|$ denotes the absolute value of the average of all paired-differences $D_{ij} = STL_{\text{max}}(i) - STL_{\text{max}}(j)$ within a moving window $w(t)$ defined as:

$$w(t) = 1 \text{ for } \lambda \in [t-N, t]$$
$$w(t) = 0 \text{ for } \lambda \notin [t-N, t]$$

where $N$ is the length of the moving window and $\hat{\sigma}_{ij}(t)$ is the sample standard deviation of the $(STL_{\text{max}}(i) - STL_{\text{max}}(j))$ within the moving window $w(t)$. Asymptotically, $T_{ij}$ index follows the $t$-distribution with $N-1$ degrees of freedom (shown in Iasemidis et al., 2004).
Fig. 4. Smoothed STL max profiles over 1 h derived from an EEG signal during the interictal state recorded at the epileptogenic site RTD2 in patient 3. The estimation of the $L_{\text{max}}$ values was made by dividing the signal into non-overlapping segments of $10.24\,\text{s}$ each, using $p=7$ and $\tau=20\,\text{ms}$ for the state space reconstruction. The smoothing was performed by a 10-point (1.6 min) moving average window over the originally generated STL max profiles.

Fig. 5. Smoothed STL max profiles over 1 h (30 min before and after the onset of the seizure) derived from an EEG signal during the preictal, ictal and postictal states recorded at the RTD2 site from patient 3. A seizure started and ended between the two vertical dashed lines. The smoothing was performed as in Fig. 4.
Fig. 6. Dynamical entrainment of a pair of brain sites between seizures 1 and 2 (patient 3). STLmax values at the normal site ROF4 (red color) progressively approach the ones at the epileptogenic site RTD2 (blue color).

Fig. 7. The $T$-index profile generated from the STLmax profiles in Fig. 6 (patient 3). The $\alpha = 0.05$ statistical significance level entrainment threshold is also shown (dashed horizontal line). Entrainment of the two sites occurs when $T$-Index values are within the depicted entrainment zone. The first crossing of the entrainment threshold from above occurs about 40 min prior to seizure 2.
In the estimation of the $T_{i,j}(t)$ indices from our data, we used $N=60$ (i.e., 60 differences of STLmax values per pair of electrode sites per moving window). Since each value in the STLmax profiles is derived from a 10.24 s EEG data segment, the length of the window $w_t$ used corresponds to approximately 10 min in real time units. Fig. 6 depicts the convergence of the STLmax profiles and Fig. 7 depicts the $T$-index calculated from the STLmax profiles in Fig. 6. A critical value $T_{0.005,59}$ from the $t$-distribution with $N−1$ (=59) degrees of freedom at significance level 0.01 is used to test the null hypothesis $H_0$ : "brain sites $i$ and $j$ acquire identical STLmax values within the time window $w_t(\lambda)$". To reject $H_0$, $T_{i,j}(t)$ should be greater than $2.662 (=T_{0.005,59})$.

2.3. Optimization: electrode site selection

The preictal transition is usually associated with convergence in STLmax profiles estimated from EEG signals at specific electrode sites, which may vary from seizure to seizure even in the same patient. The results from our previous studies suggested that electrode sites, which participated in the preictal transition preceding a given seizure, are most likely to participate in the preictal transition preceding the next seizure (Sackellares et al., 2000; Shiau et al., 2004; Chaovalitwongse et al., 2004, 2005). Thus, electrode pairs that are most convergent prior to and are divergent after the most recent seizure were monitored over time in an attempt to predict the next seizure (See Fig. 8). The development of the ASWS algorithm requires implementing a global optimization technique used to promptly identify the candidate electrode pairs, which otherwise can be computationally intense. However, the global optimization technique that we have developed overcomes this difficulty and accomplishes this step in real time. Motivated by the Ising model, we have used quadratic bivalent (zero-one) programming for the optimal selection of brain sites at periods prior to epileptic seizures (Pardalos and Rodgers, 1989, 1990). The objective function is to minimize the average $T$-index over all pairs of recording brain sites with a linear constraint for the number of critical electrode sites. The $T$-index matrix was estimated by the procedure described in the previous section. Furthermore, to ensure that the optimal group of critical sites shows the divergence in STLmax after the seizure, we included one more quadratic constraint. More specifically, this
optimization problem becomes quadratic integer 0–1 problem with quadratic constraint, given by:

\[
\begin{align*}
\text{minimize} & \quad (x^T Q x) \\
\text{subject to} & \quad \sum_{i=1}^{n} x_i = k \\
& \quad x^T A x > T_1 \times \left(\frac{k}{2}\right) \\
& \quad x \in \{0, 1\}^n
\end{align*}
\]

where \(n = 28–32\) is the total number of electrode sites and \(k\) is the number of sites to be selected. The elements of the matrix \(Q = (q_{ij})\) are \(T\)-index values of brain site pairs with respect to their STL max within a 10 min window prior to the seizure’s onset. The linear constraint for the number of critical electrode sites above was added in the optimization problem. In the quadratic constraint, the distance matrix \(A\) was generated from the \(T\)-indices from the 10 min epoch after the seizure’s end. This constraint ensures that the selected electrode sites also show disentrainment (divergence in STL max) after the seizure’s end, where \(\left(\frac{k}{2}\right)\) is the number of all considered pairs of sites in a group of \(k\) selected sites, and \(T_1\) is a fixed constant of the critical value of \(T\)-statistics with 59 degrees of freedom (previously defined in Section 2.2). In this case, \(k\) is one of the two parameters in the algorithm that need to be trained. The details of how to select the optimal parameter settings will be described in Section 3. The sites selected by the optimization method have provided two important insights. First, the sites participating in the preictal transition could thus be identified. These sites are different from seizure to seizure. Second, following the dynamical measures of the selected sites over time we could detect the preictal transition and might predict the upcoming epileptic seizure well before its onset.

Fig. 8 illustrates the comparison of the preictal transitions in \(T\)-index profiles generated from STL max of the optimal (critical) electrode sites obtained from the global optimization technique versus the one from other group of electrode sites over 2 h period between seizures 9 and 10 (patient 3). Obviously, the group of electrode sites selected from the optimization procedure shows more prominent preictal transition than the other randomly selected electrodes in a group. Statistical test of this observation is described and performed in the latter sections (Sections 3.5 and 4.3).

3. Materials and methods

3.1. Test dataset

The test dataset consists of continuous long-term (3–14 days) multi-channel intracranial EEG recordings from bilaterally, surgically implanted macroelectodes in the hippocampus, temporal and frontal lobe cortices of 10 epileptic patients with medically intractable temporal lobe epilepsy. The recordings were obtained as part of a pre-surgical clinical evaluation, using a Nicolet BMSI 4000 recording system with amplifiers of an input range of \(\pm 0.6\) mV and filters with a frequency range of 0.5–70 Hz. Prior to storage, the signals were sampled at 200 Hz using an analog to digital (A/D) converter with 10-bit quantization and stored on magnetic media for subsequent off-line analysis. Each recording included a total of 28–32 intracranial electrodes (eight subdural and six hippocampal depth electrodes for each cerebral hemisphere, and a strip of four additional electrodes if deemed necessary by the attending neurologist). These EEG recordings were viewed by two independent electroencephalographers to determine the number and the type of recorded seizures, seizure onset and end times, and seizure onset zones. A diagram of electrode locations is provided in Fig. 1.

The characteristics of the patients and the test recordings are outlined in Table 1.

3.2. Application to automated seizure warning system algorithm

The ASWS algorithm is outlined in Fig. 9. This algorithm involves the following steps.

3.2.1. Continuous STL max calculation

STL max values were iteratively calculated, on a continuous basis, from sequential non-overlapping 10.24 s EEG epochs obtained from each electrode site. The STL max method accomplishes a large data reduction (each 10.24 s EEG epoch becomes a single sample in the STL max profiles), and it is applied sequentially to each EEG channel, creating a new multi-channel time series that is utilized for subsequent analysis.
Table 1
Patients and EEG data statistics

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender</th>
<th>Onset region</th>
<th>Age (years)</th>
<th>Seizure types</th>
<th>Duration of EEG recording (days)</th>
<th>Number of seizures in recording</th>
<th>Range of inter-seizure interval (h)</th>
<th>Average inter-seizure interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>RH</td>
<td>45</td>
<td>CP, SC</td>
<td>3.63</td>
<td>9</td>
<td>0.52–47.93</td>
<td>8.69</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>RH, RF</td>
<td>60</td>
<td>CP, GTC, SC</td>
<td>11.98</td>
<td>7</td>
<td>2.66–78.77</td>
<td>20.32</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>RH</td>
<td>41</td>
<td>CP</td>
<td>9.06</td>
<td>24</td>
<td>0.30–14.49</td>
<td>3.62</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>RH</td>
<td>19</td>
<td>CP, SC</td>
<td>13.45</td>
<td>17</td>
<td>0.06–66.14</td>
<td>17.10</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>RH</td>
<td>33</td>
<td>CP, SC</td>
<td>12.24</td>
<td>18</td>
<td>0.84–77.24</td>
<td>15.30</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>RH</td>
<td>38</td>
<td>CP, SC</td>
<td>3.18</td>
<td>9</td>
<td>1.34–22.37</td>
<td>7.59</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>LH, RH</td>
<td>44</td>
<td>CP, SC</td>
<td>6.24</td>
<td>23</td>
<td>0.05–29.42</td>
<td>7.77</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>RH</td>
<td>29</td>
<td>CP, SC</td>
<td>6.07</td>
<td>19</td>
<td>0.32–70.70</td>
<td>6.61</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>LH, RH</td>
<td>37</td>
<td>CP, SC</td>
<td>11.80</td>
<td>20</td>
<td>0.01–68.28</td>
<td>12.54</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>LH, RH</td>
<td>37</td>
<td>CP, GTC</td>
<td>9.88</td>
<td>12</td>
<td>1.51–119.27</td>
<td>19.49</td>
</tr>
</tbody>
</table>

Total 87 45 (=2100 h) 158 0.01–119.27 10.86

Onset region: LH, left hippocampal; RH, right hippocampal; RF, right orbito-frontal. Seizure types: CP, complex partial; SC, subclinical; GTC, generalized tonic-clonic.

3.2.2. Optimization (selection of critical electrode sites)

Critical electrode sites are automatically identified by the algorithm after the occurrence of the first seizure in the record. They are updated after each subsequent electrographic seizure, which was indicated based upon visual inspection of the recordings by two independent board-certified electroencephalographers. In on-line prediction, a seizure onset detection algorithm is needed for complete, continuous automation of ASWS. In the optimization problem, we basically aimed to select electrode sites such that they are most entrained (most converged in STLmax profiles) prior to the seizure, conditional on their disentrainment (diverged in STLmax profiles) after the seizure end.

In the step of selecting the critical electrode sites, there are two parameters to be trained: number of sites (k) per group and number of groups (m) to be selected. Groups (m) are the subsets of the solutions to the optimization problems in m iterations. In this study, for each patient, we utilize the first half of the seizures to train k (values between 3 and 6) and m (values between 1 and 5). The optimal parameter setting was then determined by the ROC (receiver operating characteristic) curve, which is a method used to find the best trade-off of the seizure warning performance. The thus identified optimal parameter setting was then applied to the test seizure set in the same patient. The evaluation of the warning performance and details regarding how to estimate the ROC curve will be discussed later in Section 3.3.

3.2.3. Monitoring average T-index curves of the selected electrode groups

Once groups of critical electrode sites are chosen, the average T-index profile for each of these groups is continuously calculated from the STLmax profiles of the sites in the group, using sequential 10 min sliding windows. The average T-index values are continuously compared to a preset threshold value (Tth index), defined as the value below which the average difference of STLmax values in the corresponding time window is not significantly different from 0 (p > 0.01). When the average T-index of a group of selected sites becomes less than the Tth index, the group is considered to be entrained.

3.2.4. Warning of an impending seizure

The objective of the ASWS algorithm is to detect preictal transitions and generate seizure warnings. The onset of the preictal transition is defined as the point in time when at least one of the monitored groups of critical electrode sites is entrained. That is, the average T-index for that group of sites initially >5 (disentrained) drops to a value of 2.662 or less (entrained). These critical values were chosen based on statistical considerations because, when the T-index is greater than 5,
3.2.5. Reiteration

Following each successive seizure, groups of critical electrode sites are reselected, and the algorithm is repeated (back to step 1 in Fig. 9).

3.3. Evaluation of automated seizure warning system algorithm

To test this algorithm, we classify warnings into two classes, positive and negative, which can then be categorized into four subsets of warnings: true positives (TP), true negatives (TN), false positives (FP), false negatives (FN). A warning was considered to be true positive if a seizure occurred within 3 h after a preictal transition was detected. A 3 h period was chosen for purposes of this analysis, based upon the seizure warning intervals observed in preliminary studies of seizure predictability (Iasemidis et al., 2001). A warning was considered to be false positive if no seizure occurred in that 3 h prediction horizon. If a seizure occurred without a warning during the preceding 3 h, the algorithm was judged to have issued a false negative. A true negative happens when no seizure occurs and no warning is issued by the algorithm. In most practical applications, sensitivity and specificity are usually used to evaluate the performance of classifiers/predictors. Sensitivity measures the fraction of positive cases that are classified as positive. Specificity measures the fraction of negative cases classified as negative:

\[
\text{sensitivity} = \frac{TP}{TP + FN}
\]

\[
\text{specificity} = \frac{TN}{TN + FP}
\]

The sensitivity was defined as the total number of seizures being accurately predicted divided by the total number of seizures recorded. However, for on-line algorithm used to predict events (seizures), the specificity is hard to calculate because most of the time there is no events. Therefore, to evaluate our algorithm, we report the similar characteristic, false positive rate, which can be interpreted as 1-specificity. The false positive rate was defined as an average number of false predictions per hour (FPR). In medical community, sensitivity can be considered as a detection rate that one wants to maximize. In this case, we want to maximize the probability of detecting a preictal transition.
before an impending seizure. If the goal is to increase the sensitivity of warnings, we should try to increase the correct classifications of positive cases, TP, which is the number of seizures that are predicted. On the other hand, false positive rate can be considered as 1-specificity which one wants to minimize. In order to decrease the FPR, one should try to reduce the number of incorrect classifications, FP.

In the algorithm, we have two different parameter settings, which need to be optimized. In order to find the optimal parameter settings, we employed ROC curve analysis, which is used to indicate an appropriate trade-off that one can achieve between the false positive rate FPR (plotted on X-axis) and the true positive rate TPR (sensitivity, plotted on Y-axis). To test the ASWS algorithm on-line, we first trained the algorithm by dividing the dataset into training dataset and testing dataset. In each of the 10 test patients, we used the first half of seizures to train for the optimal parameter setting. With the optimal parameter setting obtained from the training phase, the algorithm was tested prospectively on the testing dataset. During the training phase, in order to find the most appropriate trade-off, we define the optimal parameter setting as the one closest to the ideal point in ROC curve (100% sensitivity and 0 false positive rate). A “prediction score” is used to measure the closeness to the ideal point, which represents the goodness of a prediction algorithm. The lower the prediction score, the better the prediction algorithm is. In fact, the prediction score is actually a distance from the performance point (sensitivity and false positive rate) of a predictor on the ROC curve to the ideal point (100% sensitivity and 0 false positive rate). The prediction score can be calculated as:

\[
prediction\ score = \sqrt{(1 - sensitivity)^2 + (FPR)^2}.
\]

3.4. Validation of the ASWS algorithm: temporal properties

To validate that the ASWS algorithm is capable of capturing the state transition to seizure based on temporal properties of the brain dynamics, we tested the ASWS algorithm on “surrogate seizure time” dataset (virtual seizure dataset). The virtual seizure dataset was generated by randomly shuffling the inter-seizure intervals, in which the temporal properties of the brain dynamics in the seizure development were negated. The shuffling process (permutations of the seizure intervals) is favored because the virtual seizure dataset will have the same mean and standard deviation of seizure occurrences as those of the real dataset, while the inter-seizure intervals are still preserved. Note, however, that this test is a very conservative one since we do not disallow the virtual seizure times to fall within the original seizure-prone periods. The purpose of this experiment is to demonstrate that the ASWS algorithm fails to predict the virtual seizures because the spatio-temporal properties of the preictal transition to virtual seizures do not exist. The ASWS algorithm was tested on 100 surrogate seizure time datasets. To provide a baseline (null) distribution for assessing the significance of the ASWS algorithm, the distribution (and average) of the prediction scores of the ASWS algorithm on the series of surrogate datasets were calculated too.

3.5. Validation of the ASWS algorithm: spatial properties

To evaluate the significance of the optimization process in the ASWS algorithm, we tested the ASWS algorithm without optimizing the electrode site selections. In other words, the non-optimized ASWS (NASWS) followed the procedure in Section 3.2 except that the groups of electrode sites used for monitoring the entrainment transitions were randomly selected. The NASWS algorithm was performed 100 times on the same dataset with randomly selected groups of sites (i.e. without the constraints of preictal entrainment and postictal disentrainment). As in the previous validation process, the performance characteristics and average prediction score of the NASWS algorithm were calculated to generate the null distribution of the prediction performance.

4. Results

In the ASWS algorithm, examples of the typical time evolution of the STLmax and the T-index for a group of critical electrode sites are illustrated in Figs. 10 and 11. The T-index values in Fig. 11 were derived from the STLmax profiles shown in Fig. 10. The aforementioned characteristics of the spatio-temporal dynamics of state transitions through the interictal, preictal, ictal and postictal states are observed in the given
Fig. 10. STL\textsubscript{max} values from five critical electrode sites calculated over the 2 h EEG recording between complex partial seizures 9 and 10 (patient 3). After occurrence of seizure 9, the five critical electrode sites were selected by the global optimization algorithm. STL\textsubscript{max} values for the selected sites are significantly different (disentrained) right after seizure 9. Prior to seizure 10, STL\textsubscript{max} values from these same sites converge to a common value (entrained). The sites become again disentrained after seizure 10.

Fig. 11. Average T-index profile from the STL\textsubscript{max} profiles shown in Fig. 10. When the average T-index drops from a value of 5 or above (upper threshold line) to a critical value of 2.662 (lower threshold line), statistically, it means that the average T-index for these sites is not significantly different than 0 (p < 0.01). At the first crossing of the lower threshold from above, the sites are considered to become dynamically entrained (being dynamically disentrained before), and a seizure warning is then generated by the algorithm. In this example, a seizure warning was generated approximately 60 min before seizure 10 (patient 3).
figures. In Fig. 10, plots of STLmax versus time, derived from EEG signals recorded from five critical electrode sites are shown. STLmax values of these sites are divergent after the first seizure (postictal disentrainment) in the series, but they converge to a common value prior to the next seizure (preictal entrainment). After the second seizure, they again diverge. This sequence of dynamical state transitions is repeated after each seizure. Preictal convergence and postictal divergence of STLmax profiles are reflected in the gradual reduction in the average T-index preictally and in a more rapid rise postictally, as shown in Fig. 11.

As mentioned previously, in this study, we tested the algorithm in two phases: training phase and testing phase. For each individual patient, the training was achieved by exploring a range of the parameter settings (number of electrodes per group and number of electrode groups) and estimating the ROC curve and the corresponding prediction score to identify the optimal parameter setting, that is the one with the lowest prediction score (see Fig. 12).

4.1. Performance of ASWS algorithm: real EEG data

The ASWS algorithm was tested on a dataset of 10 patients (see Table 1). The performance characteristics of the ASWS algorithm in the training and testing phases are summarized in Tables 2 and 3 respectively. With the optimal parameter settings, the prediction scores of the ASWS algorithm in the training and testing phases for individual patient and overall are summarized in Table 4. In the training phase, the algorithm achieved a sensitivity of 76.12% with an average false prediction rate of 0.17 h⁻¹, which is equivalent to a prediction score of 0.322 (see Table 4). This corresponds, on average, to a false warning every 6.7 h. The algorithm generated a mean true warning approximately 72 min before each seizure, while the average ratio of warning times to inter-seizure intervals is 0.317.

4.2. Performance of ASWS algorithm: surrogate seizure time data

The ASWS algorithm was tested on 100 surrogate seizure time datasets (see Section 3.4) for each of the 10 patients. For each individual patient, we used the same optimal parameter setting as in Section 4.1 in both training and testing phases. The performance characteristics and average prediction score of the ASWS algorithm in the training and testing phases for each patient and overall statistics are summarized in Table 5. In the training phase, the algorithm achieved an average sensitivity of 64.70% with an average false prediction rate of 0.278 h⁻¹, which is equivalent to a prediction score of 0.449. In the testing phase, the algorithm achieved a sensitivity of 59.99% with an average false prediction rate of 0.140 h⁻¹, which is equivalent to a prediction score of 0.437.

Note that the prediction score of the ASWS algorithm tested on the original dataset is significantly lower (better) than the average prediction score tested on the surrogate seizure time dataset (see Tables 3–5). Fig. 13 illustrates the distribution of prediction scores from 100 surrogate seizure time datasets in the testing phase, for patient 3. The prediction scores of the original dataset, as shown in the figures, are significantly lower than the prediction scores of the surrogate dataset, with p-values of 0.01. These results indicate that the preictal transitions detected by ASWS algorithm are specific to the actual preictal states.

4.3. Performance of ASWS algorithm versus NASWS algorithm: optimal versus non-optimal selections of electrode sites

The NASWS algorithm was tested with the randomly selection of groups of electrode sites for 100 iterations. For each individual patient, we use the same optimal parameter setting as in Section 4.1. The optimal parameter setting is chosen as the one with the best (lowest) prediction score (see text), that is, the one closest to the ideal score of 100% sensitivity and 0 false prediction rate.
optimal parameter setting as in Section 4.1 in both training and testing phases. The performance characteristics and average prediction score of the NASWS algorithm in the training and testing phases for each patient and overall statistics are summarized in Table 5. In the testing phase, the algorithm achieved a sensitivity of 59.10% with an average false prediction rate of 0.433 h⁻¹, which is equivalent to a prediction score of 0.471.

Note that the prediction score of the ASWS algorithm is significantly lower than the prediction score of the NASWS algorithm (see Tables 3–5). The distributions of prediction scores from 100 iterations of the NASWS algorithm tested on patient 3 in the testing phase is illustrated in Fig. 14. Again, the prediction score of the ASWS algorithm is significantly lower (better) than the prediction score of the NASWS with p-values of 0.02. These results indicate that the optimization process in the ASWS algorithm is helpful for capturing dynamical interactions in the spatial properties of preictal brain dynamics.

5. Discussion and conclusion

There is growing evidence that human epileptic seizures are preceded by physiological changes reflected in the dynamical characteristics of the EEG signals. Our group demonstrated spatio-temporal changes in \( \text{STL}_{\text{max}} \) values as seizures advance; how-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Parameters</th>
<th>Sensitivity</th>
<th>False prediction rate (false h⁻¹)</th>
<th>Average true warning time (min)</th>
<th>Average ratio: warning time to inter-seizure intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2/3 (66.67)</td>
<td>0.118</td>
<td>7/59.32</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2/3 (66.67)</td>
<td>0.065</td>
<td>1/115.38</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
<td>9/10 (90.00)</td>
<td>0.119</td>
<td>5/62.02</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5/7 (71.43)</td>
<td>0.181</td>
<td>10/213.47</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>5</td>
<td>5/8 (62.50)</td>
<td>0.212</td>
<td>15/165.09</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>2</td>
<td>4/4 (100.00)</td>
<td>0.090</td>
<td>2/22.22</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>5</td>
<td>8/9 (88.89)</td>
<td>0.190</td>
<td>15/78.95</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>2</td>
<td>6/7 (85.71)</td>
<td>0.105</td>
<td>9/55.71</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>2</td>
<td>7/10 (70.00)</td>
<td>0.155</td>
<td>23/48.39</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>5</td>
<td>3/6 (50.00)</td>
<td>0.220</td>
<td>30/177.27</td>
</tr>
</tbody>
</table>

All patients 11/51 (68.75) 0.173 175/1009.82 72.13 0.101

Values in parentheses are in percent.

Table 3
Performance characteristics of the ASWS algorithm on the testing EEG datasets with optimal parameter settings from Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sensitivity</th>
<th>False prediction rate (false h⁻¹)</th>
<th>Average true warning time (min)</th>
<th>Average ratio: warning times to inter-seizure intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2/3 (66.67)</td>
<td>0.109</td>
<td>2/30.00</td>
<td>15.5 ± 13.2</td>
</tr>
<tr>
<td>2</td>
<td>2/3 (66.67)</td>
<td>0.094</td>
<td>10/106.38</td>
<td>47.4 ± 14.3</td>
</tr>
<tr>
<td>3</td>
<td>8/9 (88.89)</td>
<td>0.074</td>
<td>3/40.54</td>
<td>87.5 ± 16.9</td>
</tr>
<tr>
<td>4</td>
<td>6/7 (71.43)</td>
<td>0.190</td>
<td>11/57.89</td>
<td>65.4 ± 19.3</td>
</tr>
<tr>
<td>5</td>
<td>2/8 (25.00)</td>
<td>0.189</td>
<td>18/95.24</td>
<td>78.6 ± 19.8</td>
</tr>
<tr>
<td>6</td>
<td>1/4 (25.00)</td>
<td>0.138</td>
<td>3/38.46</td>
<td>31.4 ± 10.0</td>
</tr>
<tr>
<td>7</td>
<td>6/8 (75.00)</td>
<td>0.184</td>
<td>12/86.36</td>
<td>78.6 ± 24.6</td>
</tr>
<tr>
<td>8</td>
<td>5/7 (71.43)</td>
<td>0.147</td>
<td>8/54.42</td>
<td>75.6 ± 13.4</td>
</tr>
<tr>
<td>9</td>
<td>5/9 (55.56)</td>
<td>0.178</td>
<td>16/99.89</td>
<td>50.1 ± 16.2</td>
</tr>
<tr>
<td>10</td>
<td>4/5 (80.00)</td>
<td>0.214</td>
<td>8/57.38</td>
<td>72.3 ± 16.6</td>
</tr>
</tbody>
</table>

All patients 44/64 (68.75) 0.154 92/596.5 72.07 0.317

Values in parentheses are in percent.
ever, changes in STLmax values from a single electrode (temporal properties) were not sufficiently enough to
detect preictal transitions. By exploring spatial proper-
ties of the brain dynamics, our group discovered pre-
ictal convergence of STLmax values (calculated from
intracranial or scalp electrode EEG recordings), which
occurs tens of minutes prior to seizures (Iasemidis
and Sackellares, 1991, 1999; Sackellares et al., 1999,
2000). Based on the observations in our previous
seizure predictability studies, this study investigated
the possibility of real time seizure prediction in patients
with focal epilepsy. The results confirm our hypothesis
that it is possible to predict an impending seizure well
in advance of its occurrence based on the “prospective”
analysis of dynamical characteristics in multi-channel
intracranial EEG recordings. By “prospective”, we
mean that the analysis at any point in time only acquire
the current or past information. Therefore, it might be
possible to incorporate ASWS with a timed therapeutic
intervention to prevent the occurrence of a seizure.
The method described in this paper makes the
prediction possible because, for the vast majority of
seizures, the spatio-temporal dynamical features of the
preictal transition were sufficiently similar to that of
the preceding seizure. This similarity makes it possi-
bile to identify electrode sites that will participate in
the next preictal transition. Seizures were predicted dur-
ing states of alertness and during sleep. Thus, preictal

### Table 4
Cumulative performance characteristics of the ASWS algorithm on real seizure time dataset with optimal parameter settings from Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>ASWA trained on real seizure points</th>
<th>Testing Overall score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>1</td>
<td>0.667</td>
<td>0.118</td>
</tr>
<tr>
<td>2</td>
<td>0.667</td>
<td>0.065</td>
</tr>
<tr>
<td>3</td>
<td>0.900</td>
<td>0.119</td>
</tr>
<tr>
<td>4</td>
<td>0.714</td>
<td>0.181</td>
</tr>
<tr>
<td>5</td>
<td>0.625</td>
<td>0.212</td>
</tr>
<tr>
<td>6</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>7</td>
<td>0.899</td>
<td>0.190</td>
</tr>
<tr>
<td>8</td>
<td>0.857</td>
<td>0.105</td>
</tr>
<tr>
<td>9</td>
<td>0.700</td>
<td>0.155</td>
</tr>
<tr>
<td>10</td>
<td>0.590</td>
<td>0.200</td>
</tr>
<tr>
<td>All patients</td>
<td>0.761</td>
<td>0.173</td>
</tr>
</tbody>
</table>

### Table 5
Cumulative performance characteristics of the ASWS algorithm on surrogate seizure time datasets and non-optimal electrode site selection on real seizure time dataset

<table>
<thead>
<tr>
<th>Patient</th>
<th>ASWA trained on shuffled seizure points</th>
<th>ASWA with non-optimal electrodes (randomly selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>1</td>
<td>0.540</td>
<td>0.108</td>
</tr>
<tr>
<td>2</td>
<td>0.473</td>
<td>0.128</td>
</tr>
<tr>
<td>3</td>
<td>0.672</td>
<td>0.134</td>
</tr>
<tr>
<td>4</td>
<td>0.489</td>
<td>0.139</td>
</tr>
<tr>
<td>5</td>
<td>0.707</td>
<td>0.103</td>
</tr>
<tr>
<td>6</td>
<td>0.545</td>
<td>0.074</td>
</tr>
<tr>
<td>7</td>
<td>0.546</td>
<td>0.040</td>
</tr>
<tr>
<td>8</td>
<td>0.558</td>
<td>0.139</td>
</tr>
<tr>
<td>9</td>
<td>0.573</td>
<td>0.163</td>
</tr>
<tr>
<td>10</td>
<td>0.763</td>
<td>0.211</td>
</tr>
<tr>
<td>All patients</td>
<td>0.599</td>
<td>0.140</td>
</tr>
</tbody>
</table>
Fig. 13. Distribution of the prediction score of ASWS in the testing dataset with shuffled seizure points (patient 3). The $p$-value of the prediction score of ASWS with the real seizure points in the same testing dataset is at 0.01 (red arrow).

Fig. 14. Distribution of the prediction score of NASWA in the testing dataset with real seizure points but with randomly selected critical brain sites for seizure prediction (patient 3). The $p$-value of the prediction score of ASWS (optimally selected critical brain sites), running on the same testing dataset, is at 0.02 (red arrow).
dynamics are sufficiently distinct to allow seizure prediction independent of the patient’s state of alertness. For practical applications, parameters can be adjusted to yield the best sensitivity–specificity performance for a given application. Parameters that affect the performance profile include: entrainment detection thresholds, number of electrode groups, number of electrode sites per group and the prediction horizon. A prediction horizon of 3 h used for this study because prior investigations indicate that approximately 99% of the preictal transition starts within 3 h prior to a seizure (Iasemidis et al., 2001). However, the prediction horizon can be adjusted for specific clinical applications. Increasing the prediction horizon will increase both sensitivity and specificity. Reduction of prediction horizon will reduce both sensitivity and specificity. Although evidence for the characteristic preictal transition was first reported by our group in 1991 (Iasemidis and Sackellares, 1991), further studies were required before a practical seizure prediction algorithm was feasible. Development of a seizure prediction algorithm was complicated by at least three factors: (1) the cortical sites participating in the preictal transition varied from seizure to seizure (optimization question); (2) the rate of transition varied from seizure to seizure (predictability question); (3) uniqueness of this type of spatio-temporal transition to the preictal period (specificity). These problems were overcome by use of global optimization procedures to select candidate electrode sites and by optimization of the rest of the algorithm’s parameters in continuous EEG recordings of several days in duration per patient. Using these techniques, we found that a preictal transition of 30–67 min in duration was retrospectively detectable in over 91% of the tested 58 temporal lobe seizures (Iasemidis et al., 1999, 2001). These predictability studies formed the basis of the automated prediction algorithm employed in the present study.

The results of this study indicate that a seizure warning algorithm designed to detect dynamical patterns of critical electrode sites is capable of providing a seizure warning 22.4–135.0 min prior to a seizure onset. This time interval is sufficient to allow a wide range of therapeutic interventions. However, the performance (sensitivity and false prediction rate) of the ASWS algorithm are still considerably inferior to that reported in our previous seizure predictability studies. This is because the electrode selection in those studies was done retrospectively (using the past and future information per recorded seizure, whereas herein only information from the previous seizure is used to predict the future seizures—prospective prediction). However, the ASWS can be further improved since we used the same optimal parameter settings to quantify the brain dynamics across all patients. It is reasonable to expect that a customized optimization per patient would produce better prediction results per patient, as we already have shown in Iasemidis et al. (2003).

Potential diagnostic applications include a seizure warning system coupled with long-term EEG monitoring in epilepsy monitoring units (EMU) in a hospital environment. Such a system could be used to warn the patient care staff of an impending seizure or trigger functional imaging devices that measure regional cerebral blood flow for epileptogenic focus localization. This algorithm could alternatively be incorporated into potential therapeutic applications, for example, digital signal processing chips for use in implantable devices to activate pharmacological or physiological interventions designed to abort an impending seizure. Future studies, employing novel experimental designs, will be required to investigate the therapeutic potential for implantable seizure warning devices.

Our group has also explored the application of the ASWS algorithm to patients with non-invasive scalp EEG recordings (Sackellares et al., 1999, 2003; Shiau et al., 2003). These ongoing investigations indicate that the preictal transition can be detected, using algorithms similar to those described in this manuscript, in EEG signals recorded from scalp electrodes. A detailed report on this work is currently in preparation.

The clinical utility of a seizure warning system depends upon both its false positive rate as well as its sensitivity. The system utilized in the present study produced false warnings at an average of 6.5 h, depending upon the parameter settings. Further investigations will be required to determine the cause of these false warnings. Several explanations are plausible. The value of STLmax is only one dynamical feature of the EEG signals. In theory, there is one Lyapunov exponent for each dimension of a system. STLmax is an estimate of only the largest Lyapunov exponent in a multidimensional system. Further analysis by the use of additional Lyapunov exponents (L) may make it possible to distinguish between a true preictal transition and other conditions in which, even though Lmax may...
converge, the rest of $I_n$ may not. Further investigation will be required to see whether other measures, or some combination of these measures, can provide a means to distinguish between true and false detections of the preictal state. Measures that characterize different aspects of the system dynamics, such as the correlation dimension, Kolmogorov-Saanà entropy, or other estimates of complexity exist. However, for some of these measures (e.g., correlation dimension), it is not always possible to obtain reliable estimates from experimental data (Theiler, 1986; Theiler and Rapp, 1996).

On the other hand, it is possible that the false warnings are not artifacts from the prediction method but they correctly detect a pre-ictal or seizure susceptibility state, in which physiological mechanisms intervene to reset the brain to a more normal dynamical state and postpone the occurrence of a subsequent seizure. In this case, careful examination of false warnings could be crucial in understanding the brain’s dynamical mechanisms under the epileptic condition and in the design of better predictors and actuators for its control (Iasemidis, 2003).

Acknowledgments

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