Forewarning of Epileptic Events from Scalp EEG

Lee M. Hively, J. Todd McDonald, Nancy B. Munro, and Emily Cornelius

***Abstract* -- This paper addresses epileptic event forewarning. One novel contribution is the use of graph theoretic measures of condition change from time-delay-embedding states. Another novel contribution is better forewarning of the epileptic events from two channels of scalp EEG, with a total true rate of 58/60 (sensitivity = 39/40, specificity = 19/20). Challenges include statistical validation in terms of true positives and true negatives; actionable forewarning in terms of time before the event; detection of the event to reset the forewarning algorithm; and implementation in a practical device.**

I. INTRODUCTION

Epilepsy afflicts nearly three million people in the US, with two-thirds controllable with drugs, which have bad side effects (e.g., sleepiness, fuzzy thinking). Epilepsy surgery can cure 7-8%, while risking cognitive impairments. No therapy is effective for intractable epilepsy (25%). Seizure disorders are typically associated with multiple hospitalizations, incurring high medical costs. Reliable forewarning would allow the patient to stop hazardous activity, lie down in a quiet place, undergo the seizure, and then return to normal activity. Reliable forewarning also allows a new paradigm of constant monitoring, rather than continuous medication. Other timely preventive steps include taking medication to preclude the impending seizure for those responsive to anti-seizure drugs, requesting emergency responders, and/or alerting caregivers or one's physician. Reliable event forewarning could also be used in add-on software in epilepsy monitoring units and for drug discovery.

Patients can predict their seizures hours before an event at a level above chance via trigger factors or mood state [1], [2], [3]. Research toward automation of seizure prediction has been pursued since the 1970's [4]. International Workshops on Seizure Prediction are being held: Bonn, Germany in 2002 [5]; Washington, DC in 2006; Friedberg, Germany in 2007 [6]; Kansas City, USA in 2009 [7]; and Dresden, Germany in 2011 (http://iwsp5.org/). This research suggests that prediction of seizures (and other biomedical events) may be possible, but is a grand-challenge-class problem.

This paper is organized, as follows. Section II discusses the specific challenges in forewarning Section III describes the analysis approach to address the challenges. Section IV provides discussion, while Section V gives the conclusions.

II. CHALLENGES

Mormann *et al.* [8] suggest that a preictal state may occur from minutes to hours before a seizure, depending to the analysis technique. This finding implies that condition change can be used for forewarning. Mormann *et al.* [9] recently proposed guidelines for the methodological quality of studies of seizure forewarning, focusing on pre-ictal state identification in blinded, prospective, randomized clinical trials. Mormann [10] provides additional details on seizure prediction. A 2011 research summary [11] found that no algorithm provides better-than-chance seizure prediction in statistical tests. This last finding presents a huge challenge to the research community. This paper addresses these challenges one-by-one, namely: statistical validation, timely prediction, event detection, and practical implementation.

Statistical validation of forewarning requires measures of success. One measure is the number of true positives (*TP*) for known event datasets (*Ev*), to yield the true positive rate (sensitivity) of *TP*/*Ev*. A second measure is the number of true negatives (*TN*) for known non-event datasets (*NEv*). The true negative rate is *TN*/*NEv* (specificity). The goal is a sensitivity and specificity of unity. Consequently, minimizing the distance from ideal (*D* = prediction distance) is an appropriate objective function for any event type:

$$D = \{[1 - (TP/Ev)]^2 + [1 - (TN/NEv)^2\}^{1/2}. \qquad (1)$$

Excessive false positives (inverse of a true negative) will cause real alarms to be ignored, and needlessly expend caregiver resources. False negatives (inverse of a true positive) provide no forewarning of seizure events.

The goal is enough forewarning to stop or mitigate an event. Patients and caregivers [12] suggested 1-6 hours for safety, planning the day, and "driving myself to the hospital." Non-parent caregivers preferred 25 minutes to 1 hour for travel to the patient's location. Others gave 3-5 minutes, because longer forewarning was seen as more stressful to the patient. A recommendation from the International Workshop on

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Seizure Prediction classifies an indication of <10 seconds prior to the event as "early detection" [13]. An alternative would be an estimate of the time until the event.

A third challenge is reliable event detection, which is distinct from seizure prediction. Reliable detection (ideal = 100%) is needed to properly reset a forewarning algorithm. Indeed, failure to detect an event means that no reset is done. False indication of a non-event would result in restarting the forewarning analysis, when no such reset is appropriate. No seizure detection algorithm reaches the ideal.

The fourth challenge is a practical implementation. A vital feature involves long-term, low-noise acquisition of brain wave (electroencephalogram – EEG) data. Sub-dural or intra-cranial electrodes are invasive and non-ambulatory, with risks of infection and surgical damage. Another feature is a portable, low-cost device, allowing wireless notification of emergency responders with automated identification of the patients' location. Smart-phones are ubiquitous for end-user applications, as a low-cost, commercial device with enough computing power for real-time analysis. Smart-phones allow automated calls to emergency responders or caregivers, and include a global-positioning unit that facilitates response to the patient's exact location.

A fifth challenge is that event forewarning should not depend on certain variables (e.g. patient's age, sex, event onset time, medications, ambulatory setting, event sub-type, activity). Moreover, forewarning should anticipate multiple real events in a continuous stream of EEG, while providing no indication during inter-ictal periods. Practical forewarning should be obtainable from one (or a few) data channel(s).

III. FOREWARNING ANALYSIS

We use one channel of *scalp* EEG as a measure of the noisy synchronous dynamics in cortical neurons over an area of roughly 6 cm^2. These data were uniformly sampled in time, t_i, at 250 Hz, giving N time-serial points in analysis window (cutset), $e_i = e(t_i)$. Data acquisition was under standard human-studies protocols from 41 temporal- lobe-epilepsy patients (ages from 4 to 57 years; 36 datasets from females, and 24 datasets from males). The datasets range in length from 1.4 to 8.2 hours (average = 4.4 hours). Data characterization included patient activity. Forty datasets had seizures, and twenty had no event [14].

One novel improvement of the present work is *better* forewarning, using *two scalp* EEG electrodes. Previous work [15] identified this location at the right, frontal area (F8 - FP2) of the scalp, in the 10-20 system. In contrast, earlier work obtained channel-consistent forewarning across nineteen EEG channels [16]. The garbage-in-garbage-out syndrome is avoided by rejecting inadequate data [17].

A novel zero-phase, quadratic filter enables analysis of scalp EEG by removing electrical activity from eye blinks and other muscular artifacts, which otherwise obscure the event forewarning. This novel filter retains the nonlinear amplitude and phase information [18]. The filter uses a moving window of $2w + 1$ points of e_i-data, which are fitted to a parabola in a least-square sense, yielding $N - 2w$ points of artifact data, f_i. The residual (artifact-filtered) signal has essentially no low-frequency artifacts, $g_i = e_i - f_i$.

A novel trade-off is required between coarseness in the data to exclude noise, and precision in the data to accurately follow the dynamics. Thus, the artifact-filtered data (g_i) are symbolized into S discrete values, s_i, which are uniformly distributed between the maximum (g_x) and minimum (g_n) in the first base case cutset. Uniform symbols are generated by the form: $0 \le s_i = \mathrm{INT}[S\,(g_i - g_n)/(g_x - g_n)] \le S - 1$. Here, INT converts a decimal number to the closest lower integer.

Takens' theorem [19] gives a smooth, non-intersecting dynamical reconstruction in a sufficiently high dimensional space by a time-delay embedding. The symbolized data are converted into unique dynamical states by the time-delay-embedding vector, y_i:

$$y_i = [s_i, s_{i+L}, \ldots, s_{i+(d-1)L}]. \quad (2)$$

Takens' theorem says that the y_i-states are diffeomorphic to the underlying dynamics, as a way to capture topology (connectivity and directivity). The time-delay lag is L, which must not be too small (making s_i and s_{i+L} indistinguishable) or too large (making s_i and s_{i+L} independent by long-time unpredictability). The embedding dimension is d, which must be sufficiently large to capture the dynamics, but not too large to avoid over-fitting.

Time-delay states from Eq. (2) are nodes. The process flow, $y_i \rightarrow y_{i+M}$, forms state-to-state links. The set of nodes and links provide a formal, diagrammatic construction, called a "graph." This representation gives topologically-invariant measures that are independent of any unique labeling of individual nodes and links [20].

Another novel improvement uses graph-invariant measures between cutsets: (1) nodes in graph A but not in B; (2) nodes in B but not in A; (3) links in A but not in B; and (4) links in B but not in A. These measures sum the absolute value of differences, which are better than traditional nonlinear measures that use a difference of averages. Each measure is normalized to the number of nodes (links) in A (for A not in B) or in B (for B not in A). These features, V, are used to classify the EEG as giving forewarning or not. The analysis obtains a vector of mean dissimilarities, $\underline{V}$, and matching standard deviations, σ, by comparison among the $B(B-1)/2$ combinations of the B base-case graphs. Subsequent test-case graphs are then compared to each of the B base-case graphs to get an average dissimilarity vector, v. Forewarning indication is several successive instances (K) above a threshold (U_T) for each of J features, $U(V) = |v - \underline{V}|/\sigma$.

The training analysis minimizes the prediction distance, D_N (or the smallest forewarning time, if no improvement occurs in D_N). There are 13 training parameters, namely {*B*, *d*, *J*, *K*, *L*, *M*, *N*, *S*, U_T, *w*}; U_T is a vector corresponding to the *J* features. Random and exhaustive searches are used because the prediction distance has very irregular, fractal features, as shown in Figure 1. Figure 2 shows a typical receiver-operating space. Figure 3 shows a typical distribution of forewarning times. The results are a significant improvement over the previous work [15] toward addressing the challenge of lowering the rate of false positives and false negatives. Earlier work showed detection of several successive seizure events in the same dataset (e.g., Figure 8 of [14]), toward addressing the challenge of reliable event detection.

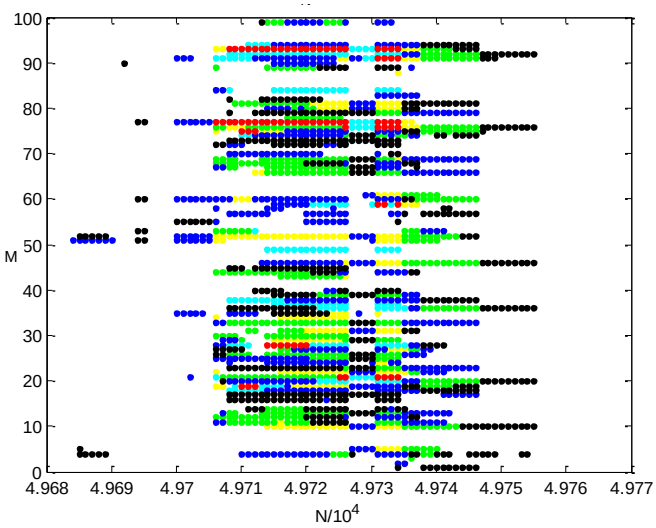

Figure 1. Minimum prediction distance (D_N) versus *N* and *M* (other parameters: *d*=7, *S*=3, *L*=56, *w*=29, *B*=12). The colors correspond to the following values of D_N: red (0.0559); yellow (0.0707); green (0.0901); cyan (0.1031); blue (0.1118); black (0.1250); and white (≥0.1346).

IV. DISCUSSION

Our premise is that the right-frontal region acts as a filter for pre-ictal condition change, as a phase transition in the brain dynamics [21] that can be induced by noise [22]. Pittau *et al.* [23] reviewed the recent technical literature on sound-induced (musicogenic) seizures, which activate the fronto-temporo-occipital area. Inversely, soothing music (e.g., Mozart's double piano sonata K448) decreases the intensity and frequency of epileptic seizures [24].

These results are encouraging, despite several limitations, which are discussed next. (1) We analyzed 60 datasets, 40 with epileptic events and 20 without events. Much more data (hundreds of datasets) are needed for strong statistical validation. (2) All 60 datasets are used as a training set, limiting the statistical strength of the results. However, the alternative involves dividing these 60 into 30 training and 30 test sets (for example), giving less adequate statistics. We have 142 uncharacterized datasets, which will be used as test

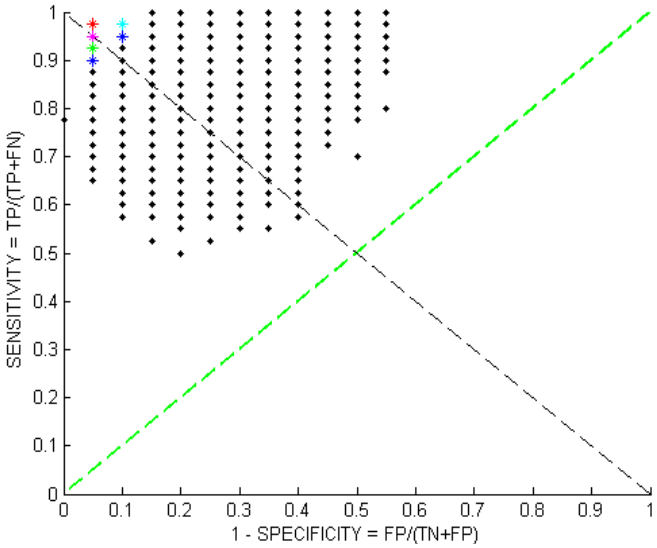

Figure 2. Receiver-operating space (TP=39/40, TN=19/20). The colors show D_N values: red (0.0559); magenta (0.0707); green (0.0901); cyan (0.1031); blue (0.1118); black (≥0.13).

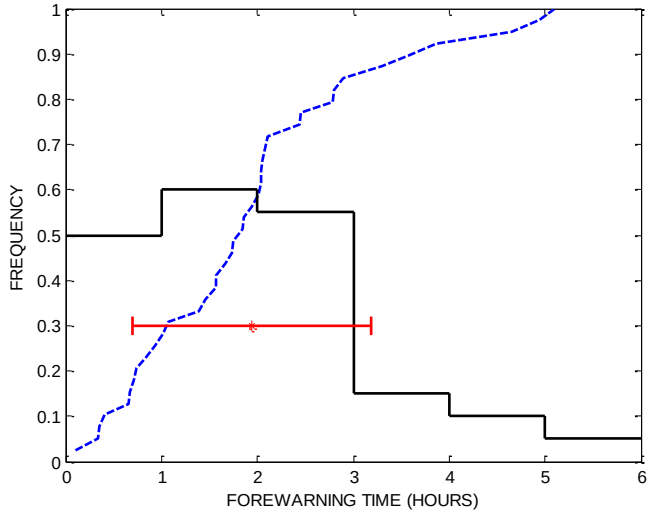

Figure 3. Distribution of forewarning times, T_{FW}. Solid black line is the occurrence frequency (arbitrary units) in 1-hour bins. The dashed blue line is the cumulative distribution of T_{FW} versus time. The red H-bar with the star in the middle indicates the mean value of T_{FW} (1.9 hours) and the sample standard deviation. Parameter values for this example are: *B*=12, *d*=7, *J*≥2, *K*=15, *L*=56, *M*=77, *N*=49716, *S*=3, U_T={0.3638, 0.0049,-0.1780, 0.0107}, *w*=29.

data after their characterization. (3) These data are from controlled clinical settings, rather than an uncontrolled (real-world) environment. (4) The results depend on careful adjustment of training parameters. (5) Only physician-selected portions of the EEG are available, rather than the full monitoring period. (6) The present approach uses retrospective analysis of archival data on a desktop computer. Real-world forewarning requires analyst-independent, prospective analysis of real-time data on a portable device. Prospective data were unavailable for this

analysis. (7) The results give forewarning times of 5.1 hours or less. A time-to-event estimate is needed. (8) All EEG involved temporal lobe epilepsy; other kinds of epilepsy need to be included. (9) A prospective analysis of long-term continuous data is the acid test for any predictive approach, and has not been done. Clearly, much work remains to address these issues.

V. CONCLUSIONS

This work improves epilepsy forewarning by analysis of topological invariants, as guaranteed by Takens' theorem [19] in a sufficiently high-dimensional space. The discrete, time-delay embedding states, y_i, are nodes with the state-to-state links forming a "graph." Graph theorems [20] guarantee measures that depend only on the graph structure. The results of this analysis are an accuracy of 58/60 (97%) with a sensitivity of 39/40 (97.5%) and a specificity of 19/20 (95%) from one (right frontal) bipolar channel. Since the theorems are data independent, this forewarning method also works for other biomedical and equipment examples [25].

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