Detection of Seizure Precursors From Depth-EEG Using a Sign Periodogram Transform

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***Abstract*—Brief bursts of focal, low amplitude rhythmic activity have been observed on depth electroencephalogram (EEG) in the minutes before electrographic onset of seizures in human mesial temporal lobe epilepsy. We have found these periods to contain discrete, individualized synchronized activity in patient-specific frequency bands ranging from 20 to 40 Hz. We present a method for detecting and displaying these events using a periodogram of the sign-limited temporal derivative of the EEG signal, denoted joint sign periodogram event characterization transform (JSPECT). When applied to continuous 2-6 day depth-EEG recordings from ten patients with temporal lobe epilepsy, JSPECT demonstrated that these patient-specific EEG events reliably occurred 5-80 s prior to electrical onset of seizures in five patients with focal, unilateral seizure onsets. JSPECT did not reveal this type of activity prior to seizures in five other patients with bilateral, extratemporal or more diffuse seizure onsets on EEG. Patient-specific, localized rhythmic events may play an important role in seizure generation in temporal lobe epilepsy. The JSPECT method efficiently detects these events, and may be useful as part of an automated system for predicting electrical seizure onset in appropriate patients.**

***Index Terms*—Depth-EEG, epilepsy, nonparametric detection, onset prediction, signature event detection, visualization.**

NOMENCLATURE

n	Discrete time axis.
$x_{\mathrm{EEG}}[n]$	Original EEG data.
$x[n]$	Whitened joint sign periodogram event characterization transform (JSPECT) input.
$s[n]$	Sign-limited signal.
$J_m[k]$	JSPECT output.
N	Sliding window length.
M	Sliding window displacement.
$J_{f_{\mathrm{lo}}}^{f_{\mathrm{hi}}}[m]$	Maximum JSPECT amplitude.
$D[m]$	JSPECT signature detector.
f_{lo}	Lower cutoff frequency.
f_{hi}	Higher cutoff frequency.
O	Length of median operation.

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I. INTRODUCTION

TWENTY-FIVE PERCENT of the world's 50 million people with epilepsy have seizures that cannot be controlled by any available treatment. The need for new therapies, and the success of similar devices to treat cardiac arrhythmias, has spawned an explosion of research into algorithms for use in implantable therapeutic devices for epilepsy. Most of these algorithms focus on either detecting unequivocal EEG onset of seizures [1]–[3], or on quantitative methods for predicting seizures in the state-space, time, or frequency domains that may be difficult to relate to the neurophysiology of epilepsy [4]–[7]. Recently, Litt *et al.* presented evidence that mesial temporal lobe seizures are generated in a cascade of events, measured by depth EEG, that evolve over hours, leading to clinical seizure onset [8]. Among their observations in this "preictal cascade" were localized bursts of rhythmic, seizure-like activity whose rate of occurrence appeared to grow exponentially as seizures approached. The authors of this paper identified these localized discharges by manually reviewing days of EEG data, 10 s at a time. This approach is limited to detecting events of sufficient signal-to-noise ratio to be seen by the human eye, and by the potential for human error. Other investigators have reported these events prior to temporal lobe seizures, however, there are no reported studies using quantitative methods to elucidate the spatial and temporal characteristics of these low amplitude, high-frequency electrographic events. [9], [10].

In this paper, we quantitatively analyze low-amplitude, high-frequency activity appearing within seconds to minutes of electrical seizure onset before seizures in patients with temporal lobe epilepsy (see Fig. 1). We found these events to be composed of characteristic, individualized patterns in specific frequency bands, usually in the range of 20-40 Hz. In this paper, we present computationally efficient methods for detecting these "signature events" in the complex signal environment that often obscures their presence during clinical review. We also present a companion method for visualizing these events in time. We present an analysis of the temporal distribution of these electrographic events in prolonged, continuous depth-EEG recordings, spanning days, obtained from ten patients with mesial temporal lobe epilepsy undergoing evaluation for epilepsy surgery.

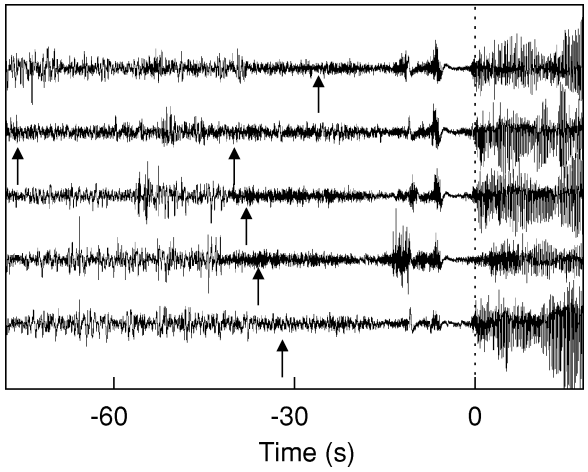

Fig. 1. Signature events. The plot shows the EEG of the same bipolar channel for five different seizures of a single patient. This passage just before the electrical seizure onset ($t = 0$ s) contains stereotyped, low-amplitude, high-frequency signature events (arrows indicate the detection times of these events with the JSPECT detection described in this paper). The second seizure is preceded by two signature events.

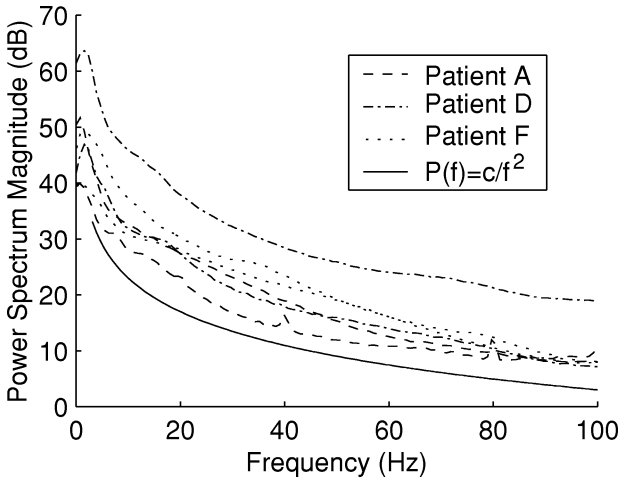

Fig. 2. PSD ranges of the EEG detection environment. The plot shows the PSD ranges of one hour EEG segments from the epileptic focus region, selected at least 4 h away from any seizure. We refer to these segments as "baselines," below. The PSDs of all study patients' EEGs were low-frequency-dominated (PSDs for three typical patients are shown in this figure). The form of the PSDs within single patients and across patients varies. However, the $1/f^2$ PSD is a first approximation for all the EEG PSD shapes. This approximation suggests a temporal derivative filter for whitening and decorrelating the detection environment. Of note are the large power dynamics of up to 10 dB within single patients and across patients.

The EEG is a nonstationary signal with a low-frequency-dominated spectrum [11]. In epilepsy, the EEG also contains epileptiform discharges (spikes), whose broad spectrum content can interfere with detecting events that are limited to a particular frequency band. These effects may be particularly prominent as seizures approach, or in the prolonged period of synchronization immediately after seizures [8], [12]. In addition, a wide variety of features in the normal EEG, such as changing amplitude and frequency content associated with state changes (e.g., awake, asleep, etc.), may obscure patterns of interest in the frequency domain.

Extreme low-frequency (ELF) communications and detecting signals embedded in underwater acoustic noise are two problem areas that share the challenges of detecting discrete electrical events in the intracranial EEG. Signal detection methods for those environments often use a nonlinear limiter function. This function can reduce sensitivity to spikes and improves detection performance. The simplest such limiter is the sign function. It is optimal for Laplacian independent, identically distributed additive noise (i.i.d.-noise). With Laplacian noise being the worst case, the sign detector also leads to robust detection performance in other harsh environments [13]–[16]. We have developed a method of applying the sign limiter function to the intracranial EEG in order to enhance detection of the signature preseizure events described above. We take the temporal derivative of the EEG signal to "whiten" the spectrum before input into the algorithms below.

Because the EEGs of interest to this type of study are usually 32–64 or more channels, digitized at a minimum of 200 Hz/channel, quantitative tools to study seizure generation, detection or prediction must be very computationally efficient. Long data epochs containing both preseizure and baseline data, preferably over days, must be processed in order to demonstrate the statistical validity of any seizure "predictors." These requirements were taken into account in developing the quantitative methods described below.

II. Theoretical Background

A. Characterization of EEG Detection Environment

It is important to consider the characteristics of the signal detection environment, in our case the EEG away from seizures, when developing an event detector. If modeled as a stochastic process, the EEG detection environment can be characterized by its power spectral density (PSD) and its probability density function (pdf). These tools can guide the signal detector design.

The independent identically distributed (i.i.d.) stochastic process assumption simplifies the detector design. A whitening prefilter stage can be used to decorrelate colored noise. As shown in Fig. 2, the PSDs of our EEG data were low-frequency dominated, suggesting that a first approximation for most EEG segments we recorded in this environment is a $1/f^2$ PSD. This suggests that the temporal derivative may be useful as a simple prefilter for our experimental data. By amplifying the power in the high-frequency bands by a factor f^2 the temporal derivative, even though not optimal, was a good approximation for decorrelating the wide range of PSD shapes in our EEG data. The computational efficiency of a simple temporal derivative filter is an additional advantage for large amounts of data and real time applications. We, therefore, applied a temporal derivative filter to all our EEG data as a first detector stage.

The pdf of the whitened environment determines the nonlinearity function of the detector. To guarantee robust detection, worst case distribution should be used to determine the nonlinearity [17]. In our case, the pdfs were nonstationary (see Fig. 3). The large pdf ranges within single patients and across patients inhibit a parametric description of the detection environment. Based on this difficulty, the JSPECT detector described in this paper is a nonparametric detector.

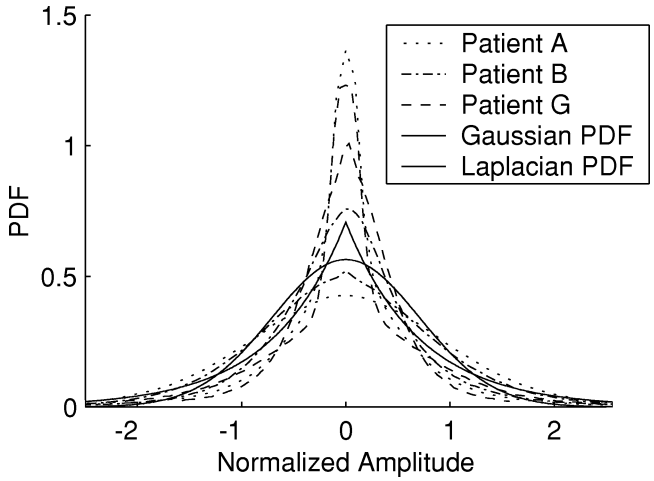

Fig. 3. Normalized pdf ranges of the temporally derived EEG detection environment. The Plot shows the pdf ranges of 1 h temporally derived EEG segments from the epileptic focus region at least 4 h away from any seizure onset or termination. The standard deviations of all pdf curves have been normalized to one. The pdfs are strongly varying within single patients and across patients. The pdf characteristics range from Gaussian to Laplacian and to even heavier tailed distributions. The pdfs are approximately symmetric.

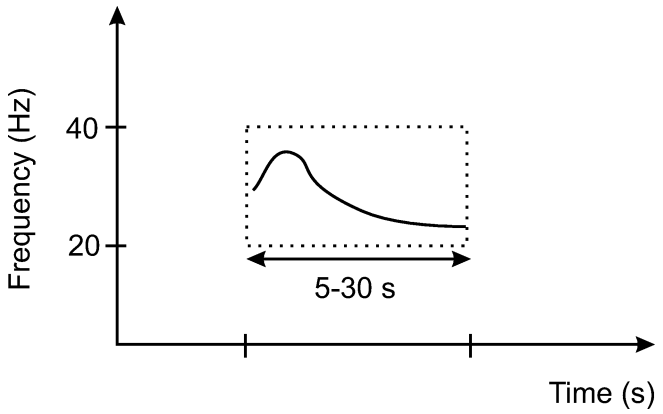

Fig. 4. Schematic frequency evolution of a signature event. For each patient, signature events demonstrate a characteristic frequency evolution (signature). The events were found to be predominantly in the 20-40 Hz range. Even though the shape of the signature events before each seizure remained similar for each patient, the offset frequencies and duration varied slightly between seizures.

B. Nonparametric Detection

D. H. Johnson describes the nonparametric detection as follows (cited from [17], shortened and partially paraphrased): "In situations when no nominal density can be reasonably assigned or when the possible extend of deviations from the nominal cannot be assessed, nonparametric detection theory can rise to the occasion [13], [14]. In this framework, little is assumed about the form of the noise density. Assume that model M_0 corresponds to the noise-only situation and M_1 to the presence of a signal. Moreover, assume that the noise density has zero median: any noise value is equally likely to be positive or negative. This assumption does not necessarily demand that the density be symmetric about the origin, but such densities do have zero median. Given these assumptions, the formalism of nonparametric model evaluation yields the sign test as the best decision rule. In the simplest model evaluation context, M_1 has constant, positive mean for each observation. However, Signal values are usually unequal and change sign; we must extend the sign test to this more realistic situation. Noting that the statistic of the sign test does not depend on the value of the mean but on its sign, the sign of each observation should be 'matched' with the sign of each signal value. A kind of matched filter results, where $sign(r[l])$ is match-filtered with $sign(s[l])$

$$\sum_{l=0}^{L-1} sign(r[l])\, sign(s[l]) \underset{M_0}{\overset{M_1}{\gtrless}} \gamma.$$

The sum counts the times when the signal and the observation signs matched.

The nonparametric detector expressed by the sign match-filter equation above has many attractive properties for array processing applications. First, the detector does not require knowledge of the amplitude of the signal. In addition, note that the false-alarm probability does *not* depend on the variance of the noise; the sign detector is, therefore, constant false-alarm rate (CFAR). Another property of the sign detector is its robustness: we have implicitly assumed that the noise values have *the* worst case probability density—the Laplacian. A more practical property is the one bit of precision required by the quantities used in the computation of the sufficient statistic: each observation is passed through an infinite clipper (a one-bit quantizer) and matched (binary operation) with a 1-bit representation of the signal. A less desirable property is the dependence of sign detector's performance on the signal waveform. A signal having a few dominant peak values may be less frequently detected than an equal energy one having a more constant envelope. Examples show that the loss in performance compared with a detector specially tailored to the signal and noise properties can be small (about 3 dB for sinusoidal signals)."

C. Characterization of Signature Events

Signature events were oscillations in the 20- to 40-Hz frequency band. The frequency evolved in a characteristic manner for each patient over 5–30 s (Fig. 4). Signature events were usually low in amplitude and often background EEG activity was reduced in amplitude during such periods. The absolute amplitude of the signature event is unimportant for the nonparametric detector described above because the detection only depends on the signs of the input. The frequency of the oscillations usually remained stationary over a 1-s window. We detected deterministic signature events using a periodogram of the sign-limited temporal derivative of the EEG signal.

III. Methods

A. JSPECT

The JSPECT detection is based on an i.i.d. environment model. To decorrelate the background samples, the temporal derivative is applied to the EEG as an approximative whitening filter

$$x[n] = x_{\mathrm{EEG}}[n] - x_{\mathrm{EEG}}[n-1]. \quad (1)$$

$$x_{EEG}[n] \rightarrow \boxed{\frac{d}{dt}} \rightarrow x[n] \rightarrow \boxed{\text{Sign}} \rightarrow \boxed{\text{N-FFT}^2} \Rightarrow J_m[k]$$

Fig. 5. JSPECT block-diagram.

The JSPECT of a discrete time sequence $x[n]$ is computed by taking the two-piece sign function

$$s[n] = \text{sign}(x[n]) = \begin{cases} 1, & \text{if } x[n] \geq 0 \\ -1, & \text{if } x[n] < 0 \end{cases} \quad (2)$$

of the input followed by the periodogram with a N-point fast Fourier transform (FFT) on a sliding window (see Fig. 5)

$$J_m[k] = \left| \frac{1}{N} \sum_{n=0}^{N-1} s[n+m-N] e^{-j2\pi kn/N} \right|^2 \quad m = 0,\ M,\ 2M,\ 3M,\ \ldots. \quad (3)$$

JSPECT resembles the first stage of the Rao detector for sinusoids of unknown amplitude and phase embedded in i.i.d. generalized Gaussian noise [16]. However, these assumptions do not hold for our application. As mentioned above, our EEG data had a strongly varying pdf. The worst case pdf, in our case the Laplacian, should be assumed to maintain good detection performance [13]. This results in a sign limiter function as an early detection stage. The quantitative amplitude of the signature events is known in our case but is not used because of this sign limiter function. Therefore, JSPECT and the Rao detector have similarities even though they are based on different models.

In addition to detection, JSPECT provides a visualization tool to characterize signature events. Fig. 6 shows a comparison between JSPECT and a classical power spectrogram, applied to the same 4-min data epoch (3 min prior to electrical seizure onset, (marked as time $= 0$), to 1 min after onset). The darkness of the output is linearly proportional to signal amplitude on both plots. On the plot of the JSPECT function, the preseizure signature event is easily seen at $t = -90$ s. This event is revealed with contrast enhancement on the classical spectrogram, but is much fainter without this enhancement, as it is overwhelmed by the spectrum of spikes and seizure onset. These plots demonstrate that JSPECT selectively filters out high amplitude events, which might obscure the signal, while preserving important characteristics of the signature events of interest.

A fundamental property of JSPECT is that it outputs a normalized energy spectrum. Looking at (2) we see that the energy in the observation window is $E_s = \sum_{n=0}^{N-1} s^2[n+m-N] = N$. Because of *Parseval's relation*, the total energy in the JSPECT is constant $E_J = \sum_k J_m[k] = E_s/N = 1$.

EEG data were sampled at 200 Hz, a window length of $N = 200$ points and a displacement of $M = 100$ points were used for processing. The corresponding frequency and time resolutions were 1 Hz and 0.5 s, respectively.

B. JSPECT Signature Detection

Distillation of JSPECT output into a single parameter is necessary for use in online detection of signature events. This is accomplished as follows. A simple feature can be derived from the JSPECT output for use in event detection

$$J_{f_{\text{lo}}}^{f_{\text{hi}}}[m] = \max(J_m[k])_{k=f_{\text{lo}}\cdots f_{\text{hi}}}. \quad (4)$$

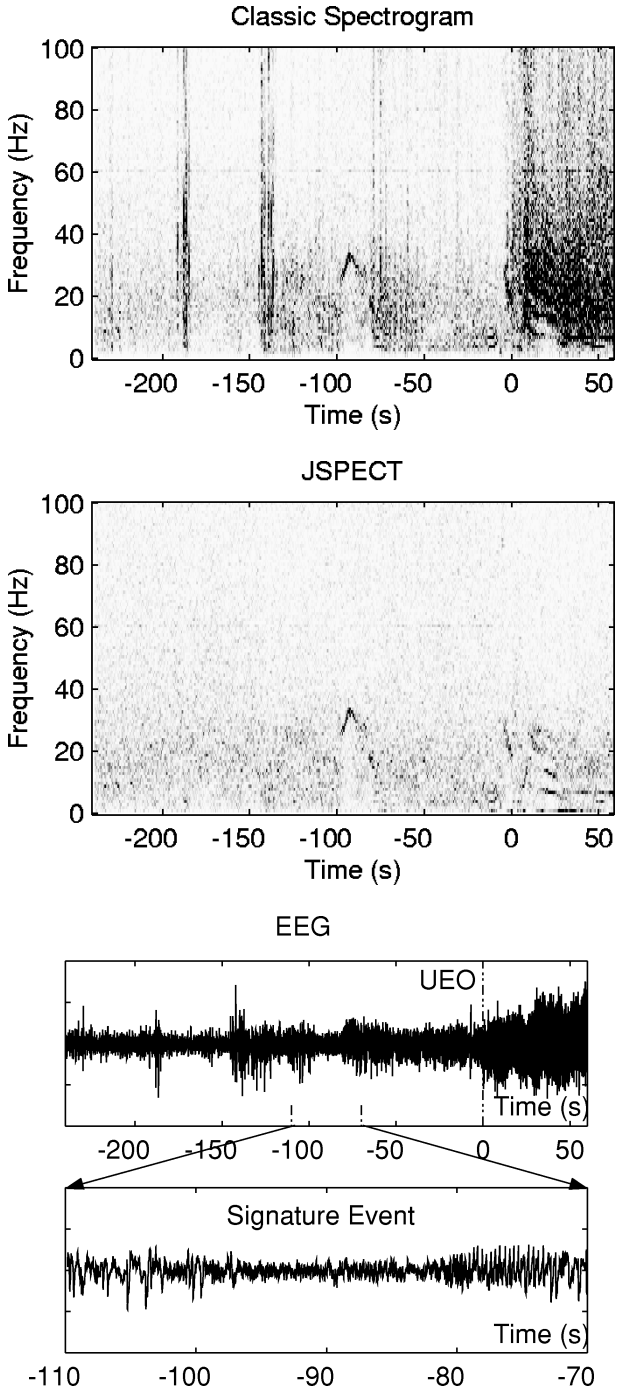

Fig. 6. JSPECT versus classic spectrogram applied to the same 5-min data epoch (4 min prior to electrical seizure onset at $t = 0$ to 1 min after onset). This comparison shows that JSPECT suppresses artifacts due to epileptiform discharges while preserving important signature information (hat shape at $t = -90$ s). The temporal derivative of the bipolar EEG signal has been analyzed. The UEO is marked as $t = 0$ s. The original EEG segment is also shown for comparison.

Then, the median across O consecutive values is computed

$$D[m] = \text{median}(J_{f_{\text{lo}}}^{f_{\text{hi}}}[m-i])_{i=0,\ M,\ 2M\ldots,\ (O-1)M}. \quad (5)$$

Looking at (2)–(5), we see that $D[m]$ is strictly causal, as it only depends on past values $x[m-1]$, $x[m-2]$, ... Therefore, a real-time implementation is straight forward.

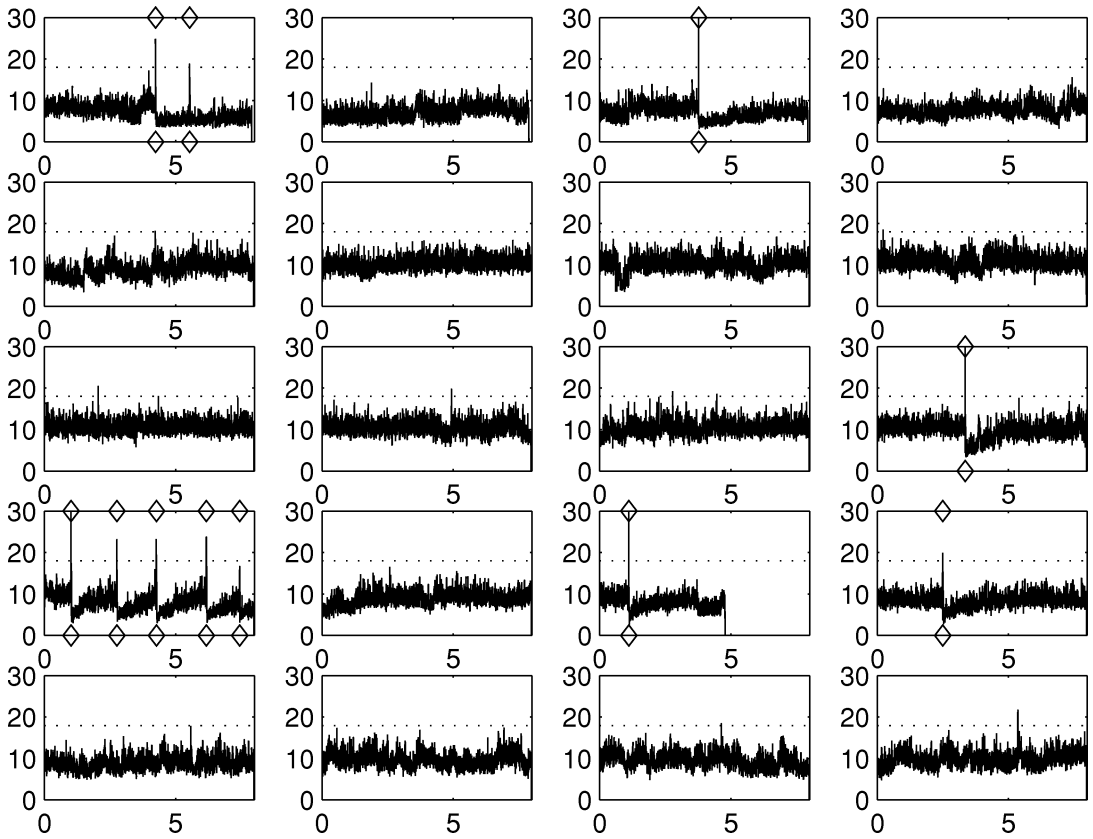

Fig. 7. JSPECT signature detection. The plot shows 160 h of processed single channel depth-EEG data from patient F. The y-axis is the JSPECT Signature Detection output value in arbitrary units. The x-axis is the time axis in hours. The consecutive subplots show the JSPECT Detection output of 20 data CDs. All CD contained 8 h of data except CD #15 which contained only 5 h of data. All signature detection peaks occurred approximately 20 s prior to the actual electrical seizures onsets, which have been marked with diamonds. The dotted line indicates a possible detection threshold allowing a maximum of one FN detection.

Trial evaluation of JSPECT output demonstrated that signature events were typically >5 s in duration. An analysis of different median lengths O was undertaken to determine the probability of false-positive (FP) waveform detections due to noise alone. The JSPECT detector, being nonparametric, has a CFAR which can be adjusted with the observation window length as described in Section II. Based on the tradeoff between detection delay and FP/false-negative (FN) probabilities, the median length was set to $O = 10$. This value was verified experimentally. Finding the optimal median length was not the focus of this study. In this algorithm, the median is only taken across ten values, so the usual computational intensiveness associated with the required sort operation was not a problem.

Fig. 7 shows the result of this algorithm applied to 160 h of continuous depth-EEG data from one single patient. By examining the *JSPECT Visualization*, (see Section III-C), the bipolar channel (voltage difference between two adjacent electrodes) nearest the epileptic focus region (spatial origin of a seizure) and the cutoff frequencies $f_{\rm lo}$ and $f_{\rm hi}$ were determined.

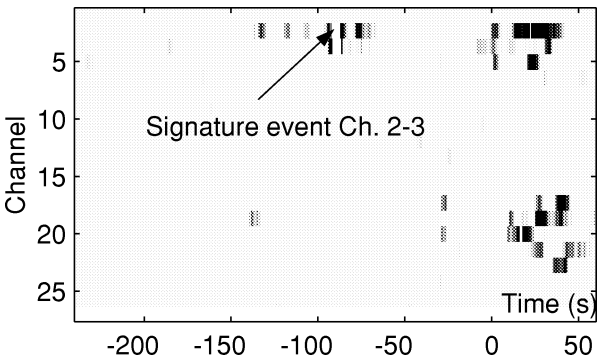

Fig. 8. JSPECT visualization of all channels. The complete patient records have been processed before visualization. The signature event indicates the important bipolar channel. It can be distinguished from the other events by its green color (corresponds to a frequency between 20-40 Hz), which cannot be seen on this black and white plot. Similar events could be found on the same channel before other seizures of this patient. A closer look at this channel in Fig. 9 reveals the detailed frequency evolution of this signature event. The EEG onset and propagation of the seizure to other channels can be seen after the electrical seizure onset ($t = 0$ s).

C. JSPECT Visualization

In order to determine the processing channel and to visualize the JSPECT output for long data segments, a condensed method for visually displaying results was developed.

Using the JSPECT followed by an adaptive frequency equalizer, the frequency corresponding to the maximum JSPECT amplitude is extracted and stored twice/second. A detection potential measurement is stored along with it in a Matlab file. The detection potential is equal to $D[m]$, using $f_{\rm lo} = 0$ Hz and $f_{\rm hi} = 100$ Hz, as described in Section III-B (5). With this method, data reduction by a factor of 50 is possible. We applied JSPECT Visualization to all the channels in the complete recordings.

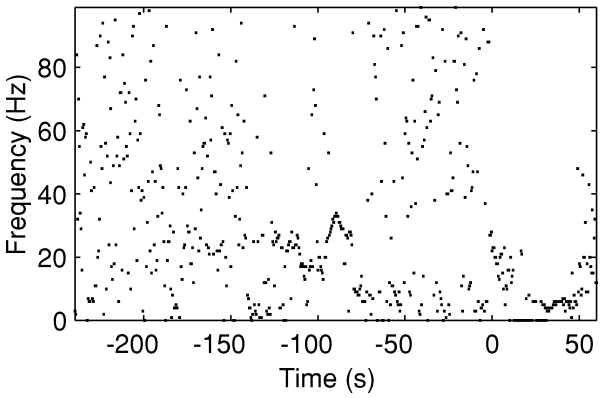

Fig. 9. JSPECT visualization of one channel. Even though only the maximum frequency is used for displaying, the signature event is visible ($t = -90$ s) as a hat shaped cluster of points in the 20- to 40-Hz frequency band. Its frequency evolution is observable as a curve of neighboring points being less than 10 Hz apart. In other patients, this curve shape was fuzzier but still within the 10-Hz range. An adaptive frequency equalizer was applied resulting in a uniform distribution for the background.

Using Matlab, all bipolar EEG channels are viewed simultaneously. The information is coded in the following way. The brightness of a pixel is made proportional to a sigmoid function applied to the detection potential. The color of the pixel is used to represent its frequency. Fig. 8 shows 28 bipolar EEG channels before electrical seizure onset. On this plot, the signature preseizure event is identified on channel 2-3. These events were found preceding all the seizures for this patient, localized to this same channel.

Once the channels of interest are identified, a single channel can be viewed on a time frequency plot. Fig. 9 shows such a plot of channel 2-3. The EEG detection environment results in randomly distributed points, in this figure. The signature event reveals itself as a cluster of points that stands out from the background.

D. Analysis of Human Data/Seizure Prediction Trial

We analyzed continuous 2-6 day EEG recordings from ten out of 13 consecutive patients with mesial temporal lobe epilepsy admitted to the Emory Epilepsy Monitoring Unit between January 1997 and May 1999, who underwent routine intracranial EEG monitoring during evaluation for resective epilepsy surgery. Three patients were excluded from this study for the following reasons. For two patients the whole EEG recordings were of poor quality and contained many artifacts because of detached reference electrodes. For one patient the EEG recordings contained only four seizures, which did not meet our selection criterion of minimal five seizures. After two years of follow-up, all of the patients whose data were analyzed were either seizure free or had rare seizures but a very significant improvement in their condition and quality of life.

Continuous intracranial EEG and video were collected using a digital, 64-channel, 12-bit Nicolet BMS-5000 epilepsy monitoring system and were stored on videotape. Referentially recorded EEG was downloaded from tape and archived to CD-ROM for processing. EEGs were digitized at 200 Hz and recorded after filtering through a bandpass of 0.1-100 Hz. All seizures occurred spontaneously, and were not provoked by any means other than gradually tapering each patient's antiepileptic medication, as per monitoring unit protocol, to encourage the occurrence of spontaneous seizures. Digitized EEG data were preprocessed only by using bipolar "montaging," an EEG technique in which signals from adjacent electrode contacts, each recording the potential difference between that contact and a common reference electrode, are subtracted to remove common mode signals and artifacts. dc changes can not be measured with bipolar montaging but in our case the dc information was not used for detection.

Patients whose data were evaluated in this study had the following clinical characteristics:

- Four patients had unilateral mesial (middle) temporal seizure onsets (A, B, D, G).
- One patient had unilateral seizure onsets from the lateral temporal neocortex (I).
- Two patients had independent bitemporal seizure onsets, with a brief diffuse decremental pattern as the earliest reproducible EEG change prior to seizure onset (C, E).
- Two patients had inferior frontal seizure onsets, one of which demonstrated simultaneous early involvement of the hippocampus on the same side (F, H).
- One patient had temporal epidural peg electrodes, which did not extend into the subdural space (J).

The following definitions were used for evaluation:

True positive detections of signature events were defined as those events which occurred within a 2-min window before unequivocal EEG onset of seizures [8]. FNs were defined as clinical seizures without a JSPECT detection peak above threshold in the 120-s window before EEG onset. FPs were defined as all peaks that rose above threshold outside the 120-s preonset window and in the absence of a clinical or subclinical seizure (SCS). The JSPECT method was developed using EEG data from patient A-E. Data from patients F-J were previously unseen by the JSPECT algorithm to avoid "training" of the method itself.

The following procedure was followed for each patient.

1) By examining the *JSPECT Visualization* of seizures in all bipolar channels, the channel demonstrating signature events was selected. With the computational efficiency of the algorithm all channels could have been used for detection, but to reduce false detections the algorithm was restricted to one channel identified by an expert reader in which electrodes were presumed to be closest to the region of seizure onset. This was defined as the channel in which the earliest signs of seizure onset were detected, or, if more than one channel met this criterion, the channel in which earliest EEG changes associated with seizure onset were maximal in amplitude. If no signature events prior to the electrical seizure onset could be found, the procedure was aborted. By signature events we mean characteristic waveforms on the EEG that reliably occurred within minutes prior to seizure onset with stereotyped temporal and spatial properties relative to seizure onset. Selection of channels for processing was verified by expert interpretation of depth-EEG studies by one of the authors (BL). In all cases in which signature events were identified by the JSPECT, the contacts in which these events were seen

TABLE I
JSPECT VISUALIZATION RESULTS

Pt.	Channel	f_{lo} (Hz)	f_{hi} (Hz)	Special
A	LAH	27	39	SCS
B	RIT	18	24	
C	none			bilateral
D	RIT	19	30	
E	none			bilateral
F	RIF	21	29	
G	RAH	23	31	SCS
H	none			
I	none			
J	none			

PT: patient. Channel. The anatomical location of the channel demonstrating the signature events is noted for each patient. None: no stereotyped signature event could be identified. LAH: left anterior hippocampus, RIT: right inferior/mesial temporal, RIF: right inferior frontal. RAH: right amygdala and anterior hippocampus (mesial temporal) $f_{\rm lo}$ and $f_{\rm hi}$: parameters were extracted by analyzing 2-3 seizures from each patient. Special: special properties of the patients. SCS: has subclinical seizures

(Table I) were found to be in the site of earliest EEG changes associated with seizures, as defined by Litt *et al.* [8].

2) By analyzing 2-3 randomly selected seizures, the parameters $f_{\rm lo}$ and $f_{\rm hi}$ were estimated to $f_{\rm lo} = \min - 1$ and $f_{\rm hi} = \max + 1$, respectively. Where $\min$ and $\max$ denote the lower and the upper frequency boundary of the signature events in the 2-3 selected seizures. All other seizures (at least half of the seizures for each subject) were set aside to validate the method.
3) *JSPECT signature detection* was applied to the entire set of continuous data in the previously chosen bipolar channel for the test patient. The parameters were set to $N = 200$, $M = 100$, $O = 10$, and to the previously estimated values for $f_{\rm lo}$ and $f_{\rm hi}$.
4) To evaluate signature event detection performance, a detection threshold was chosen to allow a maximum of one FN detection. All detections without a following clinical seizure were inspected by a board-certified reader (BL). These cases were split into detections with a following SCS and FP detections. The FP rate, or number of FPs/hour (FPH) was calculated. A complete ROC curve analysis was not performed, due to the small number of available seizures for each patient.
5) The time from detection of each signature event to EEG seizure onset was calculated by comparing event detection times with time of unequivocal electrical seizure onset (UEO) as marked by an expert EEG reader (BL).

The *JSPECT signature detection* method was implemented in C++. The custom written software *VirtualEEG* was used for computation and for reading the raw EEG data from CDs. The FFTW C-library [26] was used to compute the FFT.

IV. RESULTS

The evaluation procedure was applied on continuous EEG recordings from ten patients. Table I shows the EEG channels selected for analysis and the frequency bands delimiting signature events for each patient, as determined by JSPECT Visualization. Stereotyped signature events were found in five out of the ten study patients (see Table II).

TABLE II
JSPECT SIGNATURE DETECTION RESULTS

Pt.	L(h)	S	FN	SCS	FP	FPH
A	40	5	0	6	3	0.075
B	48	5	0	0	1	0.021
D	48	5	1	0	9	0.19
F	160	11	1	0	9	0.056
G	40	5	0	15	6	0.15

PT: patient number. L: duration of all the analyzed data. S: number of seizures. FN: number of false negatives. SCS: number of detections with a following subclinical seizure. FP: number of false positives. FPH: number of false positives/hour

Signature events reliably occurred in the 2 min prior to seizure onset on EEG. We demonstrate the statistical significance exemplary for patient F, who had the longest data record. We used a 2-min time window as a measure of association with events, similar to the way the "prediction horizon" is defined by Litt *et al.* [8]. Nine "false" detections occurred in absence of any seizure. For patient F, 160 h of data were recorded, which approximately corresponds to 160 h/2 min = 4800 segments. Ten detections occurred in the 11 2-min segments just before the UEO. The mean event detection rate with confidence intervals is $p_b = 0.0019 \pm 0.0016_{99\%} = [0.0003; 0.0035]_{99\%}$ for nonpreseizure segments and $p_s = 0.909 \pm 0.319_{99\%} = [0.59; 1.23]_{99\%}$ for 2 min before UEO preseizure segments. The confidence intervals do not overlap, therefore, the presence of signature events before seizures is significantly higher than elsewhere for patient F. Using the same procedure, we also found the signature event detection rate to be significantly higher $(>99\%)$ in the 2 min prior to UEO of seizures in patients A, B, D, F, and G. While JSPECT was trained on signature patterns from patients A-E, no information associating these patterns temporally with seizure onset was used in training, and this finding is not likely to be an artifact of study design.

The times between detection of signature events and EEG onsets are shown in Fig. 10.

V. DISCUSSION

This study suggests that nonparametric detection theory is a powerful tool for detecting signature events in the rough signal environment which surrounds the intracranial EEG. Historically, linear features have dominated the detection literature because of the broad acceptance of the Gaussian distribution [13]. JSPECT is a relatively simple feature from the nonparametric detector family that we have demonstrated to have utility in processing these biosignals. In future work, new features based on more sophisticated nonparametric detectors such as Wilcoxon Detector, Spearman Rho Detector or Kendal Tau Detector [13] should be tested on EEG data.

The temporal derivative stage in the algorithm raises the question about the physical EEG measurement setup from an electrical engineering point of view. Electrodes measure the voltage between two regions in the brain. Neuronal activity (predominantly post-synaptic potentials in this case) produces electric currents that flow between brain regions. If the two measuring regions are modeled as partially insulated regions (equivalent to a capacitor) with random current sources between them, the electrodes would measure the temporal integral of the neuronal

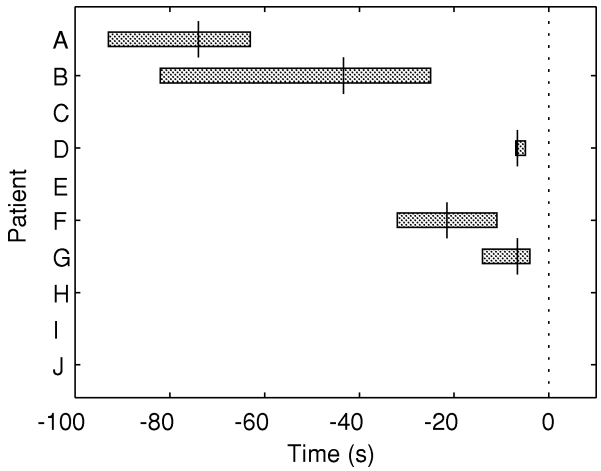

Fig. 10. Signature events: Time between detection of signature events and eeg onset for all patients. The range and mean detection times with respect to UEO of seizures is plotted for each patient. The UEO is marked as $t = 0$.

activity [25]. In this model, the temporal derivative of the measured EEG voltage may better represent the actual activity in the brain.

The signal analysis methodology and its application on clinical data presented in this paper are important for several reasons: First, they demonstrate a computationally efficient method for extracting, detecting and displaying patient-specific EEG events embedded in large volumes of EEG data; Second, they demonstrate that these events typically occur up to minutes prior to clinical seizures, in patients with unilateral mesial temporal lobe epilepsy. Finally, this paper suggests that unilateral temporal seizures of focal onset may be generated by different mechanisms than seizures of bilateral independent temporal and extra-temporal onset, as the seizure precursors detected by our method were only found prior to unilateral mesial temporal onset seizures and not on bilateral independent or extra-temporal onset seizures. Another, perhaps more plausible explanation for this finding is the possibility that EEG electrodes were not placed very close to the epileptic focus in the patients with bitemporal and extratemporal seizure onsets, perhaps evidenced by the more diffuse pattern of seizure onset on the intracranial EEG in several of these patients.

JSPECT was computationally efficient, processing data on a Pentium-II 266-MHz machine 300 times faster than real time. Though this is encouraging performance, the method will still require considerable optimization before being ready for implementation in low-power, 100 kHz implantable computing environments. Some challenges associated with applying this method in the clinical arena include automating the process of selecting a "focus channel" to be analyzed. In this paper, this choice was ultimately verified by an expert EEG reader (BL). In some patients, either with seizure patterns arising outside of the mesial temporal lobe, or where recording electrodes may be placed outside of the focus region, such patterns may not be recordable. Preliminary experiments showed that the performance of JSPECT was insensitive to the choice of the frequency band. A generic detector using a common frequency band (e.g., 16-100 Hz) would slightly increase the false-alarm rate, but might still perform well enough for a clinical implementation, depending upon the nature of alarm or therapeutic intervention to which it might be coupled.

Some signature events appeared to be more diffusely distributed than others, and their evolution over time appeared to vary. Events in higher frequency bands were better detected than those in lower frequency bands. This may be because of the fixed FFT window length, which could be avoided using alternative transforms (wavelet), or because lower frequency activity (0-15 Hz) is of higher power and fluctuates more in normal background EEG, particularly in relation to subject state of awareness (e.g., awake, asleep, etc.). This poorer performance at lower frequencies may potentially inhibit the use of JSPECT in patients with neocortical epileptic foci, which may initiate seizures at these lower frequencies [9], [18]. JSPECT was not applied successfully to patients with more diffuse or multifocal seizure onsets. A more careful evaluation of the method, and of the underlying neurophysiology in this patient group is warranted.

Of interest, several patients demonstrated 80-100 Hz activity in the seconds just before seizure onset, as revealed by JSPECT. Such activity has been described previously in intracranial recordings in patients with temporal lobe epilepsy [19]. This activity could not be explored in detail, given the limitations on recording bandwidth (Nyquist frequency of 100 Hz) of the routine clinical system used to obtain these recordings.

One of the most interesting questions raised by this paper is what generates the cellular activity responsible for the observed "signature events" picked up by our method; and what is their significance to the process of generating individual seizures? We hypothesized that individual seizures are generated in a cascade of electrophysiological events that may begin up to hours prior to seizure onset [8]. In one of these steps, in the minutes to seconds prior to seizure onset, rhythmic "chirp-like-events" have been observed. The method described in this paper provides an automated means for detecting these events. As part of this process, SCSs, and perhaps these more localized signature events, may play an important role in promoting localized synchronization which, under the right circumstances, may propagate into a clinical seizure. The signature events could identify the region whose synchronization might be critical to generating seizure onset, or identify the "point of no return," beyond which it is impossible to prevent seizure onset. These hypotheses are testable, and must be verified in appropriate clinical and animal research studies, which are far beyond the scope of this paper.

Of interest, the frequency modulation over time of the signature events detected by JSPECT, which often appeared in the form of "chirps," bears strong resemblance to patterns defining electrographic seizures, as defined by Reisinger *et al.* and Shiff *et al.* [20], [21]. With this in mind, it is possible that the signature events detected by JSPECT may be very small, localized seizures, which may play a role in synchronizing larger networks until enough tissue is recruited to propagate an event widely enough to cause clinical symptoms.

Of the ten patients tested, five demonstrated signature events that were associated strongly with electrical seizure onsets. The other five patients either had seizure onsets that were more diffuse or of different enough morphology that JSPECT was not able to detect them. Alternatively, it is possible that depth

electrodes were not positioned near the seizure-onset zone in these individuals. This would not be unusual, as our experience indicates that electrodes placed outside of the seizure focus region at a distance of more than 1-2 cm, in many cases, may be sufficiently far away to miss the earliest EEG changes associated with seizures [8], [22], [18], [23], [25]. It is also possible that activity in the frequency range on which we focused our efforts was not important to seizure generation in these patients. Event though JSPECT did not detect signature events in those five patients it could be valuable for early detection of unequivocal EEG onsets, which goes beyond the focus of this paper.

VI. Conclusion

Signature preseizure events, as detected by JSPECT, appear to have significant statistical association with electrical onset of seizures in individuals with unilateral onset mesial temporal lobe epilepsy. While the method detects EEG events that occur primarily between 5 and 80 s prior to electrographic seizure onset, it is more likely that these events are involved in the early stages of initiating seizures, before they begin to propagate, rather than as remote seizure precursors. Their presence prior to SCSs adds more credibility to their potential importance, though this must be taken into account when assessing their utility for triggering intervention to abort clinical events. This utility will likely depend upon side effects of the target intervention, and whether it will disrupt normal brain function. Higher FP rates are likely to be better tolerated if the intervention they trigger is relatively benign.

JSPECT produced FP alarm rates which are comparable to commonly used methods of seizure detection (e.g., [1]), though this limited study is not sufficient to compare JSPECT to other, more widely tested methods. At present, few studies of algorithms developed for identifying events associated with the "preictal cascade" have been published which analyze comparable volumes of clinical EEG data [8], [24], though the number of patients analyzed in this study was small. Further, more extensive studies will be required to assess the performance of the JSPECT in the broad range of patients with medically resistant epilepsy. This technique provides a rapid method for detecting physiological events that appear to be important in the last states of seizure generation. It is possible, with more validation of this method, that this technique could become part of a more comprehensive system for predicting epileptic seizures and triggering intervention to abort them prior to their clinical expression.

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