Efficacy of Differential Operators in Brain Electrophysiological Signal Processing: A Case Study in Epilepsy

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Abstract – Differential operator has long been used in image processing with great success to detect significant changes. In this paper we show that differentiation can enhance certain features of brain electrophysiological signals, contaminated with noise, artifacts and acquisition defects, leading to efficient detection of those changes. The main advantages of the method are simplicity of implementation and speed (linear time execution). We have tested the algorithm on 369 hours of non-seizure ECoG as well as 59 hours of seizure ECoG of 15 epileptic patients. It detected all but 6 seizures (91.525% accuracy) with an average delay of 8.18 seconds after the onset with a maximum false detection of 3 in 24 hours of non-seizure data. Eight novel statistical measures have been introduced to keep the number of false detections under check. To ascertain the reliability of the detection method an ROC curve analysis has been performed. The area under the ROC curve is 0.954, which indicates an excellent detection performance. The most important conclusion of this work is – irrespective of the spike or spike train detection method if the signal is differentiated prior to detection, the detection accuracy will increase.

Keywords – Differentiation, electrocorticoencephalogram (ECoG), automatic seizure detection, variance, receiver operator characteristics (ROC) curve.

I INTRODUCTION

Differentiation of a function represents its rate of change with respect to its argument. An image is represented as a spatial intensity function. Double differentiation (in the form of Laplacian operator) of the intensity function is widely used for edge detection in an image [1]. An edge can be characterized by an abrupt change in intensity indicating the boundary between two regions of an image [2]. Laplacian has been used to detect the gradient We have applied a similar logic in this paper to detect the boundary between a significant event and the back ground activity in the brain electrophysiological signals. An immediate application of which is automatic detection of seizure onset in the data of a continuously monitored epileptic patient. It has already been observed that double differentiation of human scalp EEG resulted in marked intensification of fast waves [3]. In fact taking 1.4 Hz as the threshold point it has been shown that the derivative of the EEG enhances the power associated with frequencies >1.4 Hz and at the same time diminishes the power associated with frequencies < 1.4 Hz. From the argument presented in [3] it is evident that the threshold should have been 1 Hz instead of 1.4. In this paper we will use this phenomenon as a high pass filter with cut off frequency 1 Hz, which is advantageous for eliminating movement artifacts [4].

Absolute value of first and second derivative of neonatal sleep EEG were used for feature extraction in order to automatically detect the sleep stages [5]. First and second derivative of EEG were also used to extract time domain features for automatic seizure detection in [6]. Normalized absolute value of first or second derivative (depending on the patient) has been used to amplify the seizure part of the depth EEG with respect to the background [7], which facilitated automatic seizure detection (see also [8]). This is in conformity with the use of the differential operator in signal processing in the measurement of small amounts of substances in the presence of large amounts of potentially interfering materials. In such applications it is common that the

actual signals are weak, noisy, and superimposed on large background signals [9] from which the actual signals need to be separated out. The biggest advantage of using a differential operator in this context is that it is linear and therefore suitable for online applications.

In this paper we will be studying the effect of differentiation on brain electrophysiological signals. Despite the great potentiality relatively little studies have been undertaken in this direction. One reason for this might be the smoothing effect of a differential operator. Differentiation smooth out the faint changes in generated potential due to events of interests. However in case of intense events like epileptic seizure the differential operator does not smooth out the seizure part, but rather enhances it as we will see in the next section. In the next section we will describe the complete method of seizure detection based on differentiation. In section 3 data acquisition will be discussed. Section 4 will contain the results of implementation of the methods on depth EEG or ECoG of fifteen epileptic patients. Detection performance study by ROC curve analysis will also be presented. We will use EEG and ECoG interchangeably throughout this paper. The last section contains concluding remarks.

II Mehod

A. Enhancement

We have followed the following algorithm for feature enhancement in a single channel brain electrophysiological signal x(t), where t is time.

1.
$$y(t) = G(x(t), f)$$
, where G is Gaussian (low pass) filter and f is the cutoff frequency;

2.
$$X(t) = \exp\left(\frac{1}{w}|D'y(t)|\right)$$
, D' is the derivative with respect to t and w is a normalization

constant (positive and large, in the present work w = 100000 throughout);

Due to the transformation $x \to X$ as described in 1 and 2, in case x is from the seizure focus in the brain of an epileptic patient, the seizure part of x gets enhanced considerably with respect to the background (which is suppressed to a good extent) in X. The reason is very simple. Let a, b and c are successive time points. If a spike occurs at b then statistically x(b) - x(a) and x(c) - x(b) both have high numerical value, which are two successive points in D'x. On the other hand if all the three points belong to normal background signal then x(b) - x(a) and x(c) - x(b) both will have small values (actually smaller than the average background signal amplitude). Thus D'x will enhance the spikes of x, but will suppress its background. The effectiveness of 1 and 2 varies across the patient population. For some patients the enhancement in the seizure part may be quite weak, for others it may be pretty sharp. In some cases it may even help non-experts to identify seizure by visual inspection.

B. High pass filter

Fourier expansion of X can be written as

$$X(t) = \frac{a_0}{2} + \sum_{n=1}^{\infty} (a_n^2 + b_n^2)^{1/2} \sin\left(\frac{2\pi nt}{p} + \alpha_n\right),\tag{1}$$

where a_n is Fourier coefficient associated with each frequency component n, p is the period of the signal and α_n is the phase associated with n given by $\alpha_n = \tan^{-1} \left(\frac{a_n}{b_n} \right)$ [11]. Although EEG is never periodic (non-stationary), but if its Fourier expansion is assumed to be valid then (1)

must have to be true for some p [12] (Chapter 11). Differentiating (1) we get

$$X'(t) = \left(\frac{2\pi}{p}\right) \sum_{n=1}^{\infty} n(a_n^2 + b_n^2)^{1/2} \cos\left(\frac{2\pi nt}{p} + \alpha_n\right),$$
(2)

where X' is the derivative of X. If right side of (1) is to converge to the left then $(a_n, b_n) \rightarrow (0,0)$ as $n \rightarrow \infty$. Also $p \gg 2\pi$. So components for small values of n tend to vanish. Therefore (2) acts as a high pass filter with respect to a phase shift of $\frac{\pi}{2}$ (a $\frac{\pi}{2}$ phase shift preserves many features of a signal including the spike trains). We can reasonably assume that it is a high pass filter with cutoff frequency n = 1 (also see ref. [3]).

C. Detection

It has been observed that the windowed variance is one of the most efficient methods to detect changes in signal due to epileptiform activities [10]. At the same time it is a linear method. We calculate $V_W(X(t),l,s)$, where V_W is the windowed variance operation with window length land sliding distance s. The windowed variance graph $Wvar(t) = V_W(X(t),l,s)$ has been shown in Fig. 1 with peak onset and offset clearly identified as local minimum before and after the seizure peak respectively. The seizure peak has been automatically identified as the maximum value of Wvar(t) in a one hour long snapshot of continuous stream ECoG data. Once a peak is identified as a seizure it is marked and never taken into consideration for further identification. The process continues to search for seizure peak after the last identified one. Please note that although the seizure peak identification is in real time, seizure onset detection is not in real time. We will see in section 4 that in almost all cases that have been studied the computer identified onset is very close to the epileptologist identified onset.

D. False detection

The more efficient a seizure detection method is the higher is the chances of false seizure detection in the non-seizure data. In order to eliminate false detection as far as possible we have introduced eight novel patient specific statistical criteria as following. To be qualified as a seizure the data must be identified as having seizure by each of the eight tests separately. Otherwise it will be classified as non-seizure.

- (a) Maximum windowed variance B = maximum(Wvar(t)) over one hour. For a given patient if B falls within certain interval (to be determined by sample seizure data of the patient) then it is a non-seizure. Otherwise it is a seizure.
- (b) Maximum windowed variance C of absolute value of y(t) in step 1. If C falls within certain interval (to be determined by sample seizure data of the patient) then it is a non-seizure. Otherwise it is a seizure.
- (c) |B mm(1)|, where mm(1) is the variance of X(t) in step 2 in the window next to the window of the maximum variance. If |B mm(1)| falls within certain interval (to be determined by sample seizure data of the patient) then it is a non-seizure. Otherwise it is a seizure.
- (d) mm(i) is the variance of X(t) at the *i* th window after the maximum window B. Number of windows to be considered after the maximum is stipulated (typically at 16). nl(1) is the position of the first of the windows with minimum variance among the stipulated number of windows. Let *M* is the position of *B* and N1 = M + window*n(1). Local minimum of X(t) within a window preceding *M* has been treated as the *onset* of seizure in this paper (the bottom right panel of Fig. 1) and local minimum of X(t) within a window following *M* is the *offset* (the bottom right panel of Fig. 1). In general this offset

is quite inaccurate and therefore we are not going to report the offset results in this paper. However it has important role in distinguishing between seizure and non-seizure peaks as we will see in (h) below. *E* is an array consisting of windowed variance of the filtered data starting from two windows before *M* up to *N*1. *x* is an array consisting of maximum values of *E*. *F* is another array consisting of values of *E* which are greater than or equal to $\frac{3}{4}$ max(*E*). And now we are in a position to say that ||mean(F) - x(1)|| is a quantity whose threshold distinguishes between seizure and non-seizure EEG as we will see in our experiments.

- (e) $\lfloor std(F) \rfloor$, where *std* stands for standard deviation, is a quantity whose patient specific threshold will distinguish between seizure and non-seizure spikes.
- (f) $DE = \exp\left(\frac{1}{v}|D''E|\right)$, where D'' denotes double differentiation and v is a positive normalization constant. *K* is an array consisting of values of *DE*, which are greater than or equal to $0.999 * \max(DE)$. Length of *K*, whose threshold distinguishes between seizure and non-seizure EEG.
- (g) For seizure EEG max(DE) must lie within a specified interval.
- (h) The difference between the seizure onset and offset points as described in (d) gives the width of a seizure peak or pillar. In case of some patients' data where there are too many noisy spikes this method will help eliminate non-seizure spikes from the signal, thereby making the detection more accurate (Fig. 2).

Each of the above operations executes in linear time. The whole method is extremely fast – takes less than 4 seconds for a one hour long snapshot of continuous stream data, with 15.625 second window length and 15.234 second overlap on an Intel Core 2 Duo Processor T8100

(2.1*GHz*/800*MHz* FSB, 3M L2 cache), Ubuntu machine with 4GB RAM. The implementation was in MATLAB (in C++ code the program is likely to run even faster). In a much slower Windows Vista based machine the operations didn't take more than 15 seconds. The MATLAB code implementing the above operations (except (h)) is available with [7].

III DATA ACQUISITION

To test the effectiveness of differential operator on brain electrophysiological signals we have chosen to run our algorithm on the publicly available ECoG data belonging to the Seizure Prediction Project of the Albert-Ludwig-Universitat Freiburg, Germany [13]. Together with the availability of the supplementary materials and the main MATLAB code [7] this should make our work largely reproducible. There are twenty one medically intractable focal epileptic patients' ECoG data. For each patient there are two to five hours of seizure data and twenty four to twenty six hours of non-seizure data. We have tested our algorithm on all of them. Only on fifteen of them it worked satisfactorily and in this paper we are going to report results on these fifteen cases only. Patient specific performance of the automatic seizure detection algorithms is well recognized [14], [15]. Since the patient data we have used here is an open source data, we will maintain the patient number, so that the future workers get a chance to compare with our findings.

The ECoG data were acquired using Neurofile NT digital video EEG system (It-med, Usingen, Germany) with 128 channels, 256 Hz sampling rate, and a 16 bit analog to digital converter. In all cases the ECoG from only six sites have been analyzed. Three of them from the focal areas and the other three from out side the focal areas (this is the configuration with which

the data was available to us). See Table 1 for the patient details. The patient population have earlier been studied in [16], [17], [18], where further details can be found.

IV RESULTS

A) Preprocessing

Gaussian low pass filter, with cut off frequency 100 Hz has been used to remove muscle contraction artifacts and noise (ECoG is much less noisy than scalp signal). Since differentiation has been applied, it worked as a high pass filter with cutoff frequency 1 Hz as shown in II(B) (see also ref. [3]). The phase shift keeps the seizure part intact. For each of the 15 patients we have tested the data of common reference montage as well as bipolar montage. In a patient specific way one gives better results over the other (Table II), and we have opted for the better in each case. The bipolar montage has been indicated as c1-c2, c2-c3, c3-c1, where c1 is channel 1 etc (only channels 1, 2 and 3 are associated with seizure focus).

B) Seizure detection

The detection algorithm was run on one hour snapshots of ECoG from the epileptic patients containing both seizure and non-seizure signatures (most of them didn't contain any seizure and the challenge was to avoid false detections on those data). Window length of 4000 time points (15.625 second) with 3900 (15.234 second) time points overlap (i.e., sliding by 100 points) has been used (256 points = 1 second). Seizure portions were identified by certified epileptologists at the place of origin of the data at each given time slot, but not for individual channels. The algorithm was implemented on each of c1, c2 and c3, or c1-c2, c2-c3 and c3-c1 to automatically detect the onset and the offset of a seizure (please see Table II). Onset of the seizure has been

taken to be the earliest point detected as the onset among all the three channels or the three channel pair subtractions, as the case may be. In this paper we have identified the offset for each channel or channel pair subtraction for only one purpose i.e., for determining the spike width (as shown in II(D), parameter (h)) in order to distinguish seizure spikes from the non-seizure spikes (the width may be not be accurate all the time, but it nicely serves our purpose of seizure non-seizure spike train distinction).

The single differentiation operation (SDO) has been applied on all patients. For the application of double differentiation operation (DDO) see ref. [7]. SDO works better with more noisy data. In the ECoG of patient 1 windowed variance could not detect seizures in the preprocessed signals. But after filtering with the SDO all the seizures could be detected by windowed variance. Out of total 59 seizures tested in 15 patients, 54 could be detected accurately (91.525% accuracy, which is comparable with [19]), with a total of 8 false detections in 369 hours of non-seizure data belonging to the 15 patients (Table II).

We do not have any non-seizure data for the Patient 2. Patient 4's data are heavily contaminated with chewing artifacts. We have kept the cutoff frequency of the Gaussian low pass filter for this patient at 50 Hz (this gives better detection than 100 Hz). For all other patients it has been 100 Hz. The fifth seizure ECoG of patient 4 required a very special preprocessing (suppression of all values ≥ 0.15 of the maximum value irregardless of sign) after which the seizure could be detected accurately. But this does not work for other seizures of the same patient. Therefore we will treat it as a failure to detection. For patient 5 there are 5 false detections if channel threshold is 2, but there are only 2 false detections if the channel threshold is 3 (Table II). This means if a seizure is detected it will have to be detected in not just 1 single focal channel but in 2 to (all) 3 focal channels (almost) at the same time. When, detection is

recognized only if it occurs almost simultaneously at 2 of the focal channels, we call the *channel threshold* 2. Similarly for channel threshold 3.

For some patients X(t) is full of non-seizure spikes. One way to detect the seizure spikes is to eliminate the non-seizure spikes. For this we have developed a *peak rejection method*. It has been observed that in patient specific signals Wvar(t) may have higher amplitude spike windows where windowed variance has higher value than the wider, but lower amplitude, seizure segment. On comparison, peak is rejected if it is a spike window having lower width than a subsequent much wider peak window. A wider peak window typically turns out to be a seizure window. Peak Rejection method has been applied only to the patients' data which are heavily corrupted with artifacts (Patient 6, 13 and 14).

Since the available seizure ECoG was rather scarce for each patient, thresholds were set at the time of detection. Then the effectiveness of the method was tested by the number of false positives on the 24 or more hour long seizure free signals. Performance measure has been given in terms of the area under the ROC curve in the next subsection. The average seizure detection time lag is 8.18 second after the epileptologist determined onset, which is 9.3 second in [15].

C) ROC Curve Analysis

To test the algorithm, we classify the automatic detections into two classes, positive and negative, which can then be categorized into four subclasses of detections: TP = true positive, TN = true negative, FP = false positive, and FN = false negative. A detection was considered if seizure has been detected (in one or more focal channels as the case may be) within 20 seconds of onset. Detection of a seizure on non-seizure signal (where all the 8 parameters of II(D) have failed to identify it as a non-seizure) has been classified as false positive. If a seizure didn't occur

and also it had not been detected then it is classified as true negative. If a seizure occurred yet it had not been detected then it is classified as false negative [20].

All this has been summarized in the receiver operator characteristic (ROC) curve that gives a performance measure of the algorithm. It has been plotted as true positive rate (TPR, plotted along the Y-axis) vs. false positive rate (FPR, plotted along the X-axis) (Fig. 4). TPR and FPR must be equal length vectors, with length equal to the number of patients. The *i* th entry of TPR and FPR, TPR(i) and FPR(i) respectively correspond the *i* th patient. FPR(i) = 1 - specificity

$$= 1 - \frac{TN(i)}{TN(i) + FP(i)}$$
 and $TPR(i) = \text{sensitivity} = \frac{TP(i)}{TP(i) + FN(i)}$, where $TN(i)$ is the true negative

value of the *i* th patient etc. For the purpose of the ROC curve plotting we have assigned 3 false detections to patient 2 in 24 hours (otherwise TPR and FPR will be unequal length vectors), which is the highest in the poll of patients under study (Table II). Always the least number of false positives have been chosen (with respect to channel thresholding). For a discussion on missing values conventions see ref. [21]. The area under the curve is $\approx 0.954 >> 0.5$, which indicates excellent identification accuracy. The ROC-curve computation is based on the data furnished in Table III. An ROC-curve is not supposed to be self-intersecting. To ensure this the values in FPR are first sorted out in increasing order (this is the way they appear in Fig. 4). Then the curve has been plotted with the corresponding TPR values.

CONCLUSION

In this paper it has been shown that the SDO works as an efficient filter for seizure in epileptic ECoG signals. SDO enhances the seizure part and suppresses the background so that automatic identification of seizure becomes easier. Also the time taken is linear. In other words, whichever method is employed to detect the seizure it is always advantageous to differentiate the signal prior to applying that method. SDO is capable in aiding detection even in presence of substantial noise (double derivative does not work as efficiently for a noisy signal [7]). In our present work excellent accuracy has been achieved in detecting seizures with a small number of false detections (Table II). The detection algorithm made up of differential operator, exponentiation, normalization and variance has turned out to be extremely fast. Eight parameters involving them have been identified whose patient specific threshold can distinguish between seizure and non-seizure signals for a given patient with impressively high detection and low false detection rate. The seizure onset detection time has substantially been improved compared to the previous work reported in [7]. Here we have achieved average onset detection delay of 8.18 seconds for 15 patients as against 20.45 seconds for four patients in [7].

The current method has shown promising success on ECoG, which is relatively noise free, but not artifact free (in fact some patient's data is heavily contaminated with artifacts). The SDO can greatly enhance the isolated spikes with respect to the background and therefore may be a potential tool for spike detection in single cell recordings. Since spike detection in electrophysiological data is of predominant importance in neuroscience [22], numerous statistical techniques have been developed for the detection tasks [23]. Our current work shows that differentiation of the signal can improve the outcome of the detection tasks. It can also suppress low frequency artifacts like those generated by body movements and eye blinks. The same is true for low intensity noise.

The algorithm is not specific to brain electrophysiological signals only. It can be applied to any one dimensional time domain signal to detect abrupt changes, which may be useful for other biomedical signals, such as, ECG processing.

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Fig. 1. Top panel is the windowed signal Wvar(t). Seizure pillar is distinctly visible, which has been magnified in the bottom left panel. Seizure onset and offset points are identified as local minimum before the peak and the local minimum after the peak. In all the graphs abscissa denotes time in second (256 points = 1 second) and ordinate amplitude.



Fig. 2. X(t) form of a one hour long seizure ECoG x(t). The seizure part appears distinctively as a short thick dense pillar above 6. A tall thin non-seizure peak appears between 3 and 4, which is to be eliminated by (h) in II(D). Abscissa gives time and ordinate amplitude.



Fig. 3. Automatic detection of seizure and its duration at a single channel for patient 1. Seizure part has been demarcated by parallel vertical lines in the plot of raw EEG at the bottom panel. In the second panel from the bottom the X(t) has been plotted, in which the seizure part is appearing as a distinct pillar like structure with respect to the back ground. The third panel from below plots DE (II(D), parameter (f)), whose distinct shape corresponds to seizure. The top panel plots mm, which determines a tentative duration of the seizure [7]. Automatic detection is from 74501 to 78501 time points, whereas the actual seizure occurred from 73382 to 78125 time points. 256 time points = 1 second. Reproduced from [7].



Fig. 4. The ROC curve of seizure detection. TPR = true positive rate and FPR = false positive rate (values are in Table III). Data points are denoted by '*'. There are multiple data on some points. Both X and Y axes are taken slightly greater than 1 for a better visualization of the curve. The area under the curve is ≈ 0.954 .

TABLE I

Patient	Sex	Age	Seizure	eizure H/NC Electrode Origin		# seizures	
			Туре				
1	F	15	SP,CP	NC	NC g,s Frontal		4
2	М	38	SP,CP,GTC	Н	D	Temporal	3
3	М	14	SP,CP	NC	g,s	Frontal	5
4	F	26	SP,CP,GTC	Н	d,g,s	Temporal	5
5	F	16	SP,CP,GTC	NC	g,s	Frontal	5
6	F	31	CP,GTC	Н	d,g,s	Temporo/Occipital	3
8	F	32	SP,CP	NC	g,s	Frontal	2
11	F	10	SP,CP,GTC	NC	g,s	Parietal	4
12	F	42	SP,CP,GTC	Н	d,g,s	Temporal	4
13	F	22	SP,CP,GTC	Н	d,s	Temporo/Occipital	2
14	F	41	CP,GTC	H and NC	d,s	Fronto/Temporal	4
15	М	31	SP,CP,GTC	H and NC	d,s	Temporal	4
17	М	28	SP,CP,GTC	NC	S	Temporal	5
19	F	28	SP,CP,GTC	NC	S	Frontal	4
20	М	33	SP,CP,GTC	NC	d,s	Temporo/Parietal	5

PATIENT DETAILS

SP = simple parietal, CP = complex parietal, GTC = generalized tonic-clonic, H = hippocampal,

NC = neocortical. Electrode: grid (g), strip (s), depth (d). Seizure frequency varies between 0.1 and 6.8 per day (Table I of [18]).

TABLE II

Patient number	Patient number Montage		# seizure	# seizure	# false positive	
		in hour	occurred	detected		
1	Unipolar	28	4	4	0	
2	Bipolar	3	3	3	N/A	
3	Unipolar	29	5	5	0	
4 (50 Hz)	Bipolar	29	5	4	0	
5	Bipolar	29	5	5	5(2), 2(3)	
6	Unipolar	27	3	2	0	
8	Unipolar	26	2	2	0	
11	Bipolar	28	4	3	0	
12	Bipolar	29	4	4	1	
13	Bipolar	26	2	1	3	
14	Bipolar	28	4	3	0	
15	Bipolar	28	4	3	3(2), 0(3)	
17	Unipolar	29	5	5	0	
19	Bipolar	28	4	3	0	
20	Unipolar	31	5	5	2(3)	

DETAIL OF THE PATIENT SPECIFIC RESULTS

For Patient 4, the cutoff frequency in the Gaussian filter is 50 Hz, for all other it is 100 Hz. For Patient 2, no non-seizure data is available. The number in bracket in the last column indicates channel threshold.

TABLE III

PATIENT-WISE FALSE POSITIVE RATE (FPR) AND TRUE POSITIVE RATE (TPR)

Patient	1	2	3	4	5	6	8	11	12	13	14	15	17	19	20
FPR	0	1/8	0	0	1/12	0	0	0	1/24	1/8	0	0	0	0	1/12
TPR	1	1	1	4/5	1	2/3	1	3/4	1	1/2	3/4	3/4	1	3/4	1