Development and Assessment of Methods for Detecting Dementia Using the Human Electroencephalogram

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***Abstract*—This paper makes an outline case for the need for a low-cost, easy to administer method for detecting dementia within the growing at risk population. It proposes two methods for electroencephalogram (EEG) analysis for detecting dementia that could fulfil such a need. The paper describes a fractal dimension-based method for analyzing the EEG waveforms of subjects with dementia and reports on an assessment which demonstrates that an appropriate fractal dimension measure could achieve 67% sensitivity to probable Alzheimer's disease (as suggested by clinical psychometric testing and EEG findings) with a specificity of 99.9%. An alternative method based on the probability density function of the zero-crossing intervals is shown to achieve 78% sensitivity to probable Alzheimer's disease and an estimated sensitivity to probable Vascular (or mixed) dementia of 35% (as suggested by clinical psychometric testing and EEG findings) with a specificity of 99.9%. This compares well with other studies, reported by the American Academy of Neurology, which typically provide a sensitivity of 81% and specificity of 70%. The EEG recordings used to assess these methods included artefacts and had no *a priori* selection of elements "suitable for analysis." This approach gives a good prediction of the usefulness of the methods, as they would be used in practice. A total of 39 patients (30 probable Alzheimer's Disease, six Vascular Dementia and three mixed dementia) and 42 healthy volunteers were involved in the study. However, although results from the preliminary evaluation of the methods are promising, there is a need for a more extensive study to validate the methods using EEGs from a larger and more varied patient cohorts with neuroimaging results, to exclude other causes and cognitive scores to correlate results with severity of cognitive status.**

***Index Terms*—Alzheimer's disease, dementia, EEG, fractal dimension, sensitivity, specificity, zero-crossing intervals.**

I. Introduction

IMPROVED life expectancy [1] has led to a significant increase in the number of people in the high-risk age groups that will develop Alzheimer's disease (AD) and other dementias [2]. Efforts are being made to develop treatments such as the Acetylcholinesterase inhibitors (Galantamine, Donepezil, and Rivastigmine) which are said to slow the progress of the disease [3], however, there is, as yet, no cure. If these efforts are successful, there are benefits in detecting the disease as early as possible [4]. According to a study of cortical atrophy [5] the delay between actual onset and clinical diagnosis of AD using the current clinical criteria, is three to five years. It is, therefore, possible that poor treatment effect reported in some studies could be because of delay in initiating treatment. The main problem with clinical diagnosis and other diagnostic methods including Magnetic Resonance Imaging is that a significant amount of irreversible cell damage has already occurred by the time a diagnosis is made. Thus, current research efforts mainly focus on early detection of dementia in the high-risk population (prior to extensive and irreversible cell damage). Progress in this area, therefore, is preparatory to the development of neuroprotective treatments and may contribute to research in finding a cure for AD.

Preliminary diagnosis of dementia is normally by a general practitioner (GP) on the basis of clinical history of memory impairment and sometimes using established techniques such as Mini-Mental State Examination (MMSE). This usually happens after there has been a significant decline of the patient's cognitive function. Electroencephalogram (EEG)-based measures are used to support clinical diagnosis and suggest treatable co-morbidity. Neuro-imaging techniques could be used to diagnose and assess neurological disorders including dementias, but they require expensive specialist equipments and expert clinicians to interpret results and are clearly inappropriate as a method of detecting individual subjects with early dementia within the large at-risk population.

Therefore, it is desirable to develop a novel method of assessment which can be carried out quickly by a nonspecialist clinician without special training or understanding of EEG. The result of a positive indication of dementia from such a method would be to refer the patient for further tests. The result of a false positive would cause an unnecessary, noninvasive follow-up session and a false negative would be no worse than the status quo. Thus, the method is required to be low-cost, easy to administer (similar to the bed-side EKG test) and accurate enough to provide sufficient benefit to justify the cost. However, although the EEG is an important clinical tool, it is a complex, nonstationary signal which is affected by the subject's condition (e.g., age, wakefulness, and disease), external stimuli (e.g., light, sound and sensation) and artefacts (e.g., due to

Manuscript received April 12, 2005; revised January 29, 2006. This work was supported in part by the European Union under the BIOPATTERN project, through the Network of Excellence Project FP6-2002-IST-1 No 508803. *Asterisk indicates corresponding author.*

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muscle activity, poor electrode contact, and eye movement). Artefacts are a major challenge in EEG analysis in general, but more so in automated EEG analysis because the experienced human interpreter can recognize and disregard them relatively easily whereas this is difficult for automated systems. Many automated artefact rejection methods have been proposed [6], but the state of the art is not sufficiently advanced to be relied upon. Therefore, the methods presented in this paper were chosen partly for their perceived insensitivity to artefacts. The EEG is normally presented for "human" clinical interpretation on a computer screen or paper strip with little preprocessing. Automated analysis of the EEG may add objectivity and provide the desired first line of screening for dementia. However, although a great deal of effort has been expended in the pursuit of automated EEG analysis [7], [8] there are few successful automated methods used in clinical practice. A notable exception is, perhaps, Bispectral analysis [9], [10].

It is acknowledged that even if there was an acceptable automated analysis tool for EEG, given current practice and the need for nonspecialists to learn about EEG, the first use of EEG-based methods for early detection of dementia is likely to be as an adjunct to clinical assessment. Our long term aim, however, is to develop an objective method with simplified user-friendly interface that could be used by non specialists to detect earliest possible EEG changes in dementia. Combined with patient specific EEG analysis, such a method would be valuable in monitoring progress and response to a specific treatment plan. Potentially, it would also be valuable in major clinical centers as part of future multimodal diagnostic tools, e.g., to support early diagnosis of AD more accurately and the assessment of cognitive decline in subjects with mild cognitive impairment (MCI), the preclinical stage of AD [11], in other to identify those that will progress to AD so that therapy can be initiated early. The methods could form the basis for generating EEG markers that would be used in combination with other markers to predict cognitive decline in MCI subjects.

The specific objectives in this paper are: 1) to make an outline case for the need for a low-cost, easy to administer and reasonably accurate method for detecting dementia within the growing at risk population; 2) to develop and assess two EEG-based methods for detecting dementia that could fulfil the above need. An important aspect of the methods is that they do not involve *a priori* selection of only elements of data that are "suitable for analysis." They involve the use of whole EEG records and the inclusion of all the difficult elements of the EEG (artefacts etc.) which gives a good prediction of their usefulness in practice. If the significance of the methods are confirmed and they were adopted and the practical difficulties of using EEG were addressed, they could advise a GP whether the patient should be referred to a hospital for further tests.

The EEGs of subjects with dementia are characterized by a slowing of activities (e.g., a decrease in high frequency activities and an increase in low frequency activities), and previous studies have shown that there is a link between the slowing of the EEG activities and the severity of cognitive decline [12]. However, despite this and significant effort over a long period, no spectral-based measure had been good enough to use in general clinical practice. We believe that this is because the Fourier transform-based methods give a poor picture of the lower frequencies when, because of signal stationarity, short segments must be analyzed. Therefore, in this study it was decided to take a different approach.

The first method we developed is based on fractal dimension (FD) analysis of the EEG waveform. FD is a nonlinear measure commonly used in nonlinear dynamical analysis to quantify the complexity of the underlying system and typically involves time delay embedding techniques [12]–[14]. In this context, this measure is often referred to as the correlation dimension or dimensional complexity [13], [14]. It is thought to reflect the number of degrees of freedom involved in the process that generated the EEG waveform and, thus, the complexity of the underlying cortical dynamical processes. Previous studies have found that the EEGs of subjects with AD have lower values of correlation dimension than age-matched normal subjects [14], [15]. However, FD is only meaningful when used as a relative measure of complexity to quantify irregular behavior of the brain and not as an absolute measure [15]. Fractal dimension values are sensitive to the parameters of the algorithm used (e.g., the embedding dimension, time delay, and data length) and the physiological and patho-physiological implications of changes in the fractal dimension are still unclear [15]. In this paper, we will examine an alternative approach and apply fractal analysis to the EEG waveform itself [16]–[18]. This quantifies the waveform shape complexity, does not require embedding process and is computationally fast and robust [19], [20]. However, it is important to note that FD in this case is a measure of the structural details of the waveform itself rather than a measure of the complexity of the underlying system. In addition, our method does not involve *a priori* selection of sections of the EEG "suitable for analysis," but uses whole records.

The second method we have developed is based on analysis of the probability density function (PDF) of the zero-crossing intervals (ZCI) of the EEG. Zero-crossing analysis has been successfully applied to EEG analysis before [21] and was shown to be robust in the characterization of sleep spindles. However, to our knowledge it has not been applied to EEG of AD before. As will be discussed later, zero-crossing analysis approach shares similar properties with fractal analysis and both gave more accurate results than conventional spectral analysis. It is thought that this is due in part to the fact that they are less sensitive to artefacts.

The remainder of the paper is organized as follows. In Section II, we present the development and assessment of the FD-based method for analyzing the EEGs of dementia. In Section III, we present the development and assessment of the second method which is based on the analysis of the PDFs of ZCIs of the EEG. In Section IV, we conclude the paper.

II. The Fractal Dimension of the EEG

A. Introduction

In this paper, we have applied fractal analysis to the EEG waveform itself [7], [16], [18] to quantify the waveform shape complexity. One way to measure the FD of a shape with topological dimension of one (e.g., a time series), is the divider dimension: if one steps around the boundary using N steps of length δ then L, the apparent length, is given by: $L(\delta) = N(\delta)\delta \approx L_0\delta^{1D}$, where L is a constant, and D is the FD.

Using a range of values for δ and measuring the corresponding values for length $L(\delta)$ a least squares (or similar) method can be used to estimate D. An alternative method to assess the fractal properties of a waveform is the Detrending Fluctuation Analysis (DFA) [22]. DFA has been used to analyse the fractal structures of the EEG [23] and to study the correlation properties of fetal heartbeat [24].

An important issue in FD analysis is that the EEG lies in affine space where there is a defined origin but different directions have different units, meanings and properties. The EEG has two dimensions; voltage, which is normally plotted on the vertical axis and time, which is normally plotted on the horizontal axis. Voltage has units of volts, it is an expression of a potential difference (in the electrical sense) between two points and the same voltage may be repeated many times within a recording. Time, in contrast, has units of seconds, represents the interval since a reference to the measurement point and there may only be one instance of any value of time within the record. This has important implications for measuring the FD of the EEG because the axes have incompatible units and there is no natural scaling between them (distance along the time axis cannot be compared with distance along the voltage axis) and as such δ and computed D may not be meaningful [4].

In studies of the fractal dimension of the EEG [25], [26] the Divider Dimension of the EEG was used to separate subjects with AD from a group of normal subjects. When this method was repeated on a single AD subject and a single normal subject it was found that the arbitrary voltage/time scaling affected the results; a scaling of 0.6 nV/s for example, gave FDs similar to those reported (1.66 and 1.28 for a normal and an AD subject, respectively) but a higher scaling of 2.5 nV/s gave very different results where the normal subject had a lower FD (1.21) than the AD subject (1.61). This problem is a direct consequence of applying the divider dimension to the EEG, which exists in an affine space.

A number of methods may be used to estimate the FD of shapes in an affine space [26]. In this paper, we have used the dimension of zero-set approach rather than other methods, such as the adapted box method, because it gave better results. To compute the dimension of the zero-set, we form the set of instances when the record intersects with a suitable straight line (we have used the zero volt reference). It is estimated by covering the set with $N(\Delta t)$ line segments of a chosen length, Δt (see Fig. 1). The total length of all the line segments is $L(\Delta t) = \Delta t \cdot N(\Delta t)$ which is calculated for a range of segment lengths $30\ \mathrm{ms} \leq \Delta t \leq 500\ \mathrm{ms}$. An estimate of the dimension D that satisfies the equation in a least squares sense, where L_0 is a constant and D is the dimension, is then determined. This is obtained from the log of this function, such that $\log(L(\Delta t)) \approx \log(L_0) + (1 - D) \cdot \log(\Delta t)$ and estimating the slope $(1 - D)$ using linear regression.

B. Method Development

With a range of fractal methods and parameters available to choose, it was important to settle on a single method with fixed parameters before an assessment was conducted; otherwise it could be said that the assessment was not a fair test and that

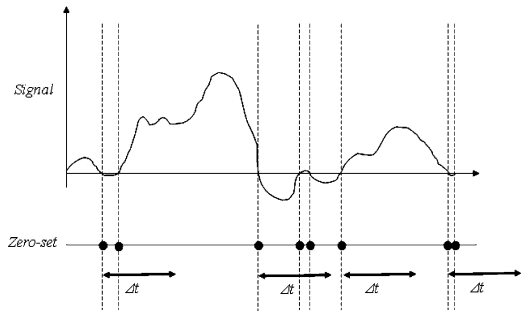

Fig. 1. Sketch of the zero sets of a signal.

parameterization favorably skewed the measured specificity and sensitivity. The parameters that needed to be fixed were; the range of lengths used in the zero-set dimension, the frequency band limiting applied, montage, et cetera.

The data used in the development of this method were recorded for a previously reported study [27]. The EEGs were collected from seven patients (three AD patients, three mixed type, i.e., AD and Vascular Dementia (VaD) patients and one VaD patient) and eight age-matched controls (over 65 years of age). The EEG recordings encompass various states: awake, drowsy, and alert with periods of eyes closed and open. They were obtained using the traditional 10–20 system in a Common Reference montage which was later converted to Common Average and Bipolar montages in software. The sampling rate was 256 Hz. These data were obtained using a strict protocol from Derriford Hospital, Plymouth, U.K. and had been collected using normal hospital practices. All patients were referred to the EEG department in the hospital from a specialist memory clinic. It is the clinical practice at the memory clinic that all patients undergo a battery of psychometric tests (MMSE [28], The Rey Auditory Verbal Learning Test [29], Benton Visual Retention Test [30], and memory recall tests [31]) before referral. The results from the psychometric tests are scored and interpreted by a specialist psychologist and all clinical and psychometric findings discussed at a mutlidisciplinary team meeting following the clinic. Each patient is then referred to the hospital for EEG assessment by the memory clinic with a working diagnosis (e.g., probable AD, depending on the outcome of the clinical and psychometric assessments). All age-matched controls were healthy volunteers and had normal EEGs (confirmed by a Consultant Clinical Neurophysiologist). One age-matched control (known as "Vol1") subsequently developed AD; this record is of particular interest because it is potentially of a subject early in transition from "normal" to AD. The classification of subjects with dementia is based on the working diagnosis provided by the specialist memory clinic and EEG findings. Magnetic resonance imaging (MRI) data was not recorded because this facility was not available at the hospital at the time.

For all records, to avoid the possibility of inadvertently or unconsciously selecting data particularly suitable for analysis a predetermined protocol was applied. For each record, data from the period 60 s to 300 s was used. This avoids electrical artefacts, which commonly occur at the beginning of a record, and gives a standard four minutes of data to analyze. This segment

of data including artefacts was analyzed with no *a priori* selection of elements "suitable for analysis." This approach leads to a prediction of the usefulness of the technique, as it would most conveniently be used in practice.

For all data the recorded sampling rate was 256 Hz reduced to 128 Hz for analysis by averaging sets of two consecutive samples because of the limitations of the machine in use at the hospital at the time. However, as the chosen bandwidth was 25 Hz (see below), there was no loss of accuracy. This was confirmed by numerical experiments, which demonstrated that there was no discernable difference in results from a number of uncompressed and corresponding compressed records.

The data and methods were honed to ensure the best performance and this was found to occur under the following conditions.

- *Montage:* Bipolar montage (which exclude the frontal signals); T3-T5, T4-T6, T5-O1, T6-O2, C3-P3, C4-P4, P3-O1, P4-O2, and Cz-Pz. Using the minimum FD across the channel pairs.
- *Band limiting (1 Hz to 25 Hz):* Applied by taking the fast Fourier transform and reconstructing the signal from just the required components. The upper limit of 25 Hz was chosen as a compromise between including higher frequency components which would improve the estimation of fractal dimension and excluding artefacts such as scalp muscle activity. The value of 25 Hz was found by experimentation on the Development Data Set to provide the best separation of normals and subjects with dementia. The lower limit of 1 Hz was set by the segment length.
- *Segment length:* The raw EEG data were divided into one second segments and the estimated FD from each segment through the entire duration of the recording is plotted on a histogram. The histogram comprised 128 bins to represent values between zero and one. Numerical experiments were conducted to demonstrate that 128 was a sufficient number of bins; increasing the number of bins beyond 128 did not affect the result. This was due to the interpolating effect of the method used to extract a single fractal dimension value from the histogram (see below). The results obtained are almost invariant for segment lengths between 0.5 s and 2 s. Below 0.5 s the results become erratic because of the number of samples is becoming too small compared to the sampling rate employed. With segment lengths greater than 2 s the results are affected by the nonstationary nature of the EEG [7].
- *Taking the FD from the histogram:* the mode of the histogram was taken as the composite measure of FD for that recording. Fig. 2 shows the histograms of the zero-set dimension for a normal and an AD subject, respectively. The strict mode was not used because of a theoretical anomaly if two peaks of equal size occur and because the mode provides no interpolation if there are two similarly sized peaks. The equation used was: $FD_{\text{index}} = \sum_{i=1}^{N} D_i^n FD_i / \sum_{i=1}^{N} D_i^n$. Where D_i is the histogram height (density) at FD estimate FD_i and n is a control constant. When $n = 1$, the estimate becomes the mean and when n tends to infinity the estimate tends to the mode. For our experiment $n = 4$ was chosen, but using strict mode made very little difference.

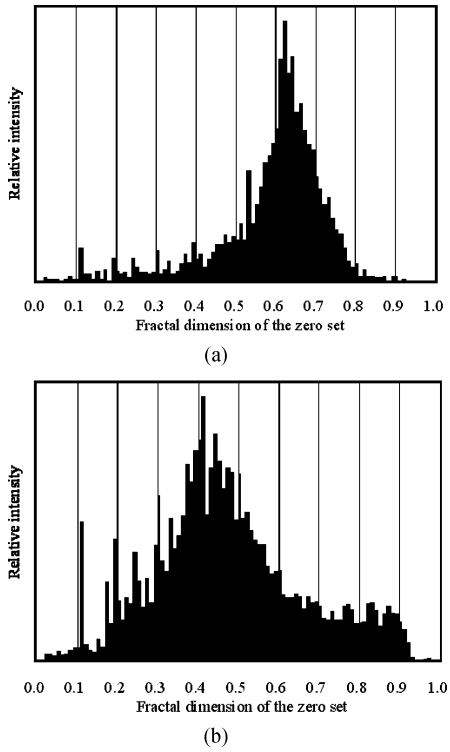

Fig. 2. Histogram of the zero-set dimension of a normal and a AD subject. (a) Normal subject. (b) AD subject.

The results under these conditions are shown in Table I. From these results and assuming a Normal distribution to the results it is possible to estimate the efficacy of the method in detecting dementia. For the FD of the zero-set; if one were to demand a specificity of 99.9% then a result would be considered abnormal if it were less than 0.67. This implies a sensitivity to AD of 99.5% and a sensitivity to VaD (or mixed) of 97.2%. Furthermore, the normal subject who went on to develop AD (Vol1) would have been flagged as abnormal before it was detected by a clinician. It can also be shown using a student's t-test that there is a statistically significant difference between the means of the two group for both methods ($p < 0.0002$). Although these results appear to be good, they were the result of honing many parameters. Therefore, it was necessary to test the method on completely separate, statistically significant data sets (Assessment Data Sets A and B, see below).

C. Assessment of Method

Two data sets were used to assess the method. The first data set (Assessment Data Set A) consists of 24 normal records, 17 probable AD and five probable VaD and were obtained in the same manner as the development data set, details are given in Section II-B. This data set did not reuse any of the development data set. These data were obtained using the modified Maudsley system which is similar to the traditional 10–20 system. The age and gender statistics for the assessment subjects, given in Table II, show that the groups are not perfectly age matched, however, it will be shown that this does not have a major effect.

The EEG data were analyzed in the same way as they were during the method development and the results (Table III) show that there is a significant difference between the normal and

TABLE I
FD OF THE ZERO-SET FOR DEVELOPMENT DATA SET

Descriptions	Subjects	Fractal Dimension of Zero-set
Normal who went onto develop AD	VOL1	0.65
Normal	VOL2	0.70
	VOL3	0.70
	VOL4	0.68
	VOL5	0.71
	VOL6	0.69
	VOL7	0.69
	VOL8	0.69
Mean Normal		0.695
Std Dev		0.008
Probable AD	AD1	0.55
	AD2	0.61
	AD3	0.53
Vascular and Mixed Dementia	MID1	0.59
	MIX1	0.61
	MIX2	0.54
	MIX3	0.63
Mean AD		0.593
Std Dev AD		0.040

TABLE II
AGE AND GENDER STATISTICS OF ASSESSMENT DATA SET A

Descriptions	Normal	AD	VaD
Number of subjects	24	17	5
Mean age	69.4	77.6	80.6
SD of ages	11.5	10.0	4.4
Maximum age	84	93	86
Minimum age	40	50	74
Percentage male	42%	53%	80%

probable AD subjects ($p < 10^{-9}$ using student's t-test). The effect of age on the significance of the results was assessed by studying the FD as a function of age for the 3 groups (see Fig. 3) and there is no discernable trend of FD with age.

The results for the development and Assessment Data Set A (Tables I and III) are markedly different in one aspect only and that is the standard deviation of results from normal subjects. It is suspected that this is because of the statistical uncertainty in estimating standard deviations of small data sets and because the protocol used in the development data set was more strict.

Assuming a Gaussian distribution and a required specificity of 99.9%, the sensitivity is predicted to be 67.0%. It is not surprising that this is not as good as the previously quoted 99.5% from the Development Data Set because none of the parameters were adjusted to hone the result.

The assessments above were based on patient cohorts where neuro-imaging studies were not carried out and for which access to the neuro-psychological scores was not possible because the patients were from a different district, although full cognitive tests were carried out. To further evaluate the method, we have used a second assessment data set (Assessment Data Set B), which had available all clinical data including MMSE scores for both AD and healthy controls and the subjects had undergone neuro-imaging studies. These data has been obtained from a different centre in a different country.

TABLE III
FD OF THE ZERO-SET FOR ASSESSMENT DATA SET A

Descriptions	Normal	AD	VaD
Results	0.64	0.57	0.62
	0.65	0.57	0.64
	0.72	0.62	0.58
	0.68	0.55	0.67
	0.67	0.58	0.60
	0.64	0.52	
	0.67	0.58	
	0.64	0.56	
	0.66	0.61	
	0.67	0.50	
	0.69	0.52	
	0.70	0.63	
	0.70	0.59	
	0.71	0.51	
	0.65	0.50	
	0.71	0.60	
	0.74	0.65	
	0.65		
	0.72		
	0.66		
	0.68		
Mean	0.679	0.568	0.621
Std Dev	0.029	0.046	0.033
Number of Samples	24	17	5

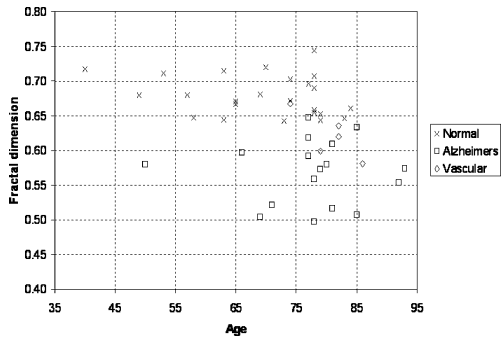

Fig. 3. Graph of FD against age for the 3 subjects groups.

The data were collected from 10 AD patients and 10 normal healthy old subjects as controls. Local institutional ethics committees approved the study and all experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board. Probable AD was diagnosed according to NINCDS-ADRDA [32] and DSM IV criteria. The patients underwent general medical, neurological and psychiatric assessments. They were also rated with a number of standardized diagnostic and severity instruments that included MMSE [33], Clinical Dementia Rating Scale (CDRS) [34], Geriatric Depression Scale (GDS) [35], Hachinski Ischemic Scale (HIS) [36], and Instrumental Activities of Daily Living scale (IADL) [37]. Neuroimaging diagnostic procedures (computed tomography or MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias, in order to have a homogenous mild AD patient sample. Exclusion criteria

TABLE IV
SUMMARY OF INFORMATION ABOUT ASSESSMENT DATA SET B

Control Subjects (10 cases)					
Subject	Gender	Age (yrs)	Education (yrs)	MMSE	Diagnosis
Nold01	F	85	5	30	Nold
Nold02	M	77	13	30	Nold
Nold03	M	78	5	28.7	Nold
Nold04	F	71	8	28.4	Nold
Nold05	M	72	5	29.3	Nold
Nold06	M	83	13	29.1	Nold
Nold07	F	78	5	28.7	Nold
Nold08	F	78	5	28.7	Nold
Nold09	F	79	5	29	Nold
Nold10	M	79	18	30	Nold
Mean	5M/5F	78.0	8.2	29.2	-
Std Dev	-	4.24	4.76	0.61	-
AD Subjects (10 cases)					
Subject	Gender	Age (yrs)	Education (yrs)	MMSE	Diagnosis
AD01	F	78	2	21	AD
AD02	M	77	9	27	AD
AD03	F	78	5	21.7	AD
AD04	M	83	13	23.1	AD
AD05	F	78	5	18.7	AD
AD06	F	72	5	23.3	AD
AD07	F	77	5	21.7	AD
AD08	M	80	13	22.1	AD
AD09	M	74	18	25.7	AD
AD10	M	86	8	23.8	AD
Mean	5M/5F	78.3	8.3	22.8	-
Std Dev	-	4.03	4.97	2.37	-

included, in particular, any evidence of 1) frontotemporal dementia, 2) VaD (i.e., VaD was also diagnosed according to NINDS-AIREN criteria; [38], 3) extra-pyramidal syndromes, 4) reversible dementias (including pseudodementia of depression), and 5) fluctuations in cognitive performance (suggestive of a possible Lewy body dementia). The normal control subjects were recruited mainly among patients' spouses. All Nold subjects underwent physical and neurological examinations as well as cognitive screening (including MMSE). Subjects affected by chronic systemic illnesses (i.e., diabetes mellitus or organ failure) were excluded, as were subjects receiving psychoactive drugs. Subjects with a history of present or previous neurological or psychiatric disease were also excluded. All Nold subjects had a GDS score lower than 14. Details of the subjects are summarized in Table IV.

The results of using the FD-based method on the second data set (Assessment Data Set B) are summarized in Table V and in Fig. 4. An examination of Fig. 4 suggests that the results from the new data supports our earlier findings in all cases with the exception of two cases – AD1 and Nold1. A review of the EEGs suggest that the data for Nold1 look atypical. There were significant slow waves at the rear of the scalp and the record seems to have discontinuities at 1 s boundaries. This may have had an effect on the results. From these results and assuming a Gaussian distribution and using the same threshold as the development data set (0.67), the sensitivity of the method to AD is approximately 90%. However, this would result in specificity of approximately 40% since only 4 out of 10 normals lie above this

TABLE V
FD OF THE ZERO-SET FOR ASSESSMENT DATA SET B ($p < 0.00125$)

Descriptions	Normal	AD
Results	0.37	0.68
	0.65	0.50
	0.64	0.46
	0.71	0.63
	0.70	0.44
	0.62	0.59
	0.69	0.50
	0.67	0.48
	0.61	0.41
	0.63	0.43
Mean	0.63	0.51
SD	0.10	0.09
Number of Samples	10	10

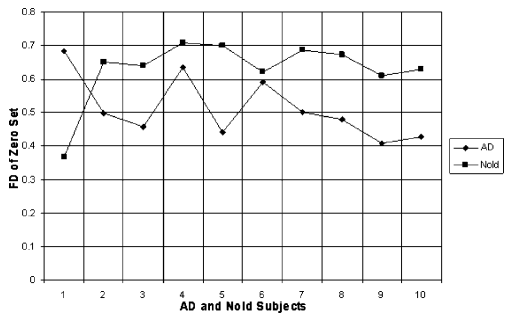

Fig. 4. FD of the zero-set for Assessment Data Set B.

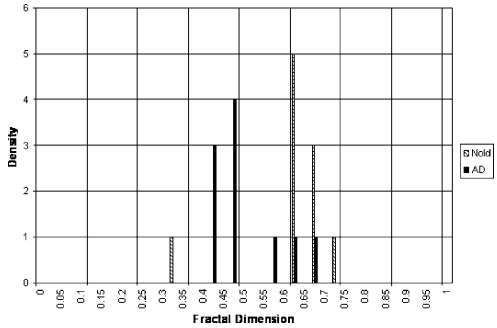

Fig. 5. Distribution of FD of zero-set of Assessment Data Set B.

threshold. Nonetheless, it is apparent from Fig. 5 that there is little overlap in the distribution of the FD between the Nold and AD groups. If we were to set the threshold at 0.6, we would obtain a figure of approximately 80% for both sensitivity and specificity. This is a more valid result given the clear separation between the two groups shown in Figs. 4 and 5 and in fact supports the concept that the FD should be used as a relative measure and not as an absolute value.

III. ZERO-CROSSING INTERVAL DENSITY

A. Introduction

The second method is based on the analysis of the distribution of ZCIs. The ZCI is defined, in this context, as the time interval between a positive to negative voltage transition to the next positive to negative voltage transition. If one examines an

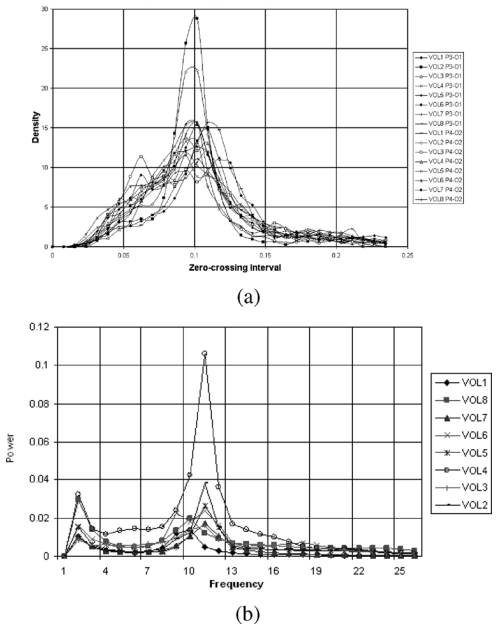

Fig. 6. ZCIs for PDF and power spectra of normal subjects. (a) ZCIs. (b) Power Spectra.

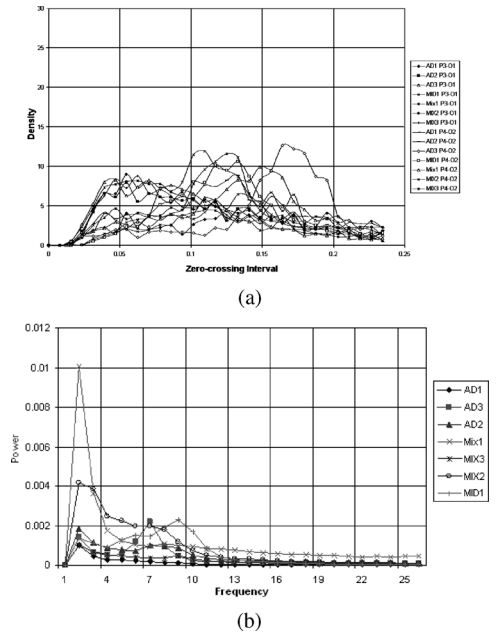

Fig. 7. ZCIs for PDF and power spectra for subjects with dementia. (a) ZCIs. (b) Power Spectra.

EEG record from a single channel, a list of zero-crossing intervals may be extracted and the PDF of these data may be plotted. For example, the PDFs of the ZCIs from parietal-occipital channel pairs for normal subjects from the development data set is shown in Fig. 6(a). Similar data for the subjects with dementia is shown in Fig. 7(a). The power spectra of the normal subjects and subjects with dementia are also shown in Figs. 6(b) and 7(b), respectively. The results appear to indicate that there is an increase in slow activities in subjects with dementia (Fig. 7) as compared to normal subjects (Fig. 6).

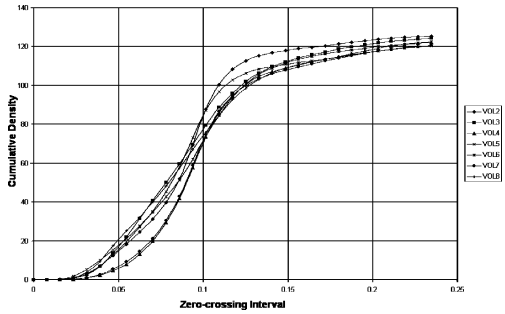

Fig. 8. CDF of the ZCI for normal subjects.

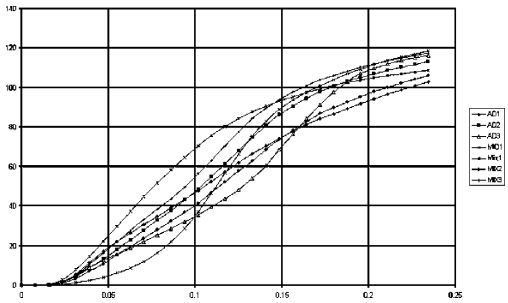

Fig. 9. CDF of the ZCI for subjects with dementia.

Figs. 6 and 7 show a noticeable difference between normal subjects and subjects with dementia. By examining different regions of the scalp, it was found that plots obtained from normal subjects are characteristically different from subjects with dementia in the temporal, parietal and occipital regions. This is consistent with the findings for FD. In the frontal region, the results are less ordered and this is probably because this area is more prone to ocular and other muscular artefacts. It should also be noted that 50-Hz mains interference artefacts were removed using a simple, second-order, digital notch filter.

Zero-crossing and FD of the zero-set analysis share similar features and produce measures that quantify the structural details of the waveform in the time domain. Working in the time domain provides greater differentiation between similar, but different, lower frequency components than would be observable by conducting a fast Fourier transform on a data set which is nonstationary. The FD of the zero-set is based on finding a set of instances when the waveform intersects with the time axis (i.e., at the zero crossings). It can be seen from Fig. 1 that FD of a waveform is directly related to the PDF of ZCIs. Results show that longer ZCIs (lower frequencies) tend to give a lower FD.

B. Cumulative Density of Zero-Crossing Interval

The first metrics investigated, to evaluate their ability to numerically differentiate the normal and demented subjects, were cumulative-based metrics. If we plot the cumulative density distribution, for bipolar channels at the rear of the scalp, for normals (Fig. 8) and subjects with dementia (Fig. 9) then it is clear that the normals have a higher density at lower time intervals. For this reason, we evaluated a range of the percentile points of the cumulative distribution as a potential metric. The best was the 85th percentile and these results are shown in Table VI.

TABLE VI
85TH PERCENTILE OF THE CDF

Descriptions	Normal	AD	VaD and Mixed
Results	0.70	0.55	0.59
	0.70	0.61	0.62
	0.68	0.53	0.54
	0.71		0.63
	0.69		
	0.69		
	0.69		
Mean	0.695	0.561	0.593
Std Dev	0.008	0.042	0.040
Number of samples	7	3	4

TABLE VII
MEAN ZCIS OVER REAR OF SCALP

Descriptions	Normal	AD	VaD and Mixed
Mean	98ms	121ms	52ms
Std Dev	4.6ms	9.0ms	8.31ms
Number of samples	8	3	4
Sensitivity (for a Specificity of 99.9%)		82.2%	9.6%

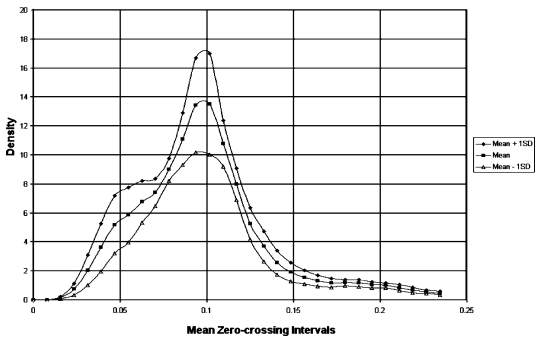

Fig. 10. Reference zero-crossing PDF for normal subjects.

From these results and assuming a Gaussian distribution it is possible to determine the sensitivity of the method to AD and VaD (with a required specificity of 99.9%) are 50.8% and 39.8%, respectively.

C. Mean Zero-Crossing Interval

The second metric investigated was the mean zero-crossing interval and these results are shown in Table VII.

From these results and assuming a Gaussian distribution it is possible to determine the Sensitivity of the method to probable AD and VaD (with a required Specificity of 99.9%) are 82.2% and 53.4%, respectively.

D. Correlation to Normal Zero-Crossing Interval Distribution

The features of the PDFs of the ZCIs [Figs. 6(a) and 7(a)] are complex and it appears that the important features are the positions and shapes of peaks that are characteristic of a normal PDF. It was decided to estimate what is normal (with a tolerance) and then compare each subject to it. The mean and standard deviation of the PDF for the set of normals, at each interval was assessed and plotted in Fig. 10.

Each record from the development data set was compared to this reference curve and the distance from it, at each point, was expressed in standard deviations. The *rms* of these standard deviations was taken as the error from the complete record. This comparison was encouraging, but the significance is compromised because they are self-referential. It is not surprising that the normals used to create the standard curve are closest to it. For this reason it is important to repeat this test on the assessment data set (i.e., Assessment Data Set A), while using the standard normal curve from the development data as the reference. This runs contrary to the general rule of reserving the assessment data set for testing the best of these novel methods and, hence avoiding the charge of simply testing enough methods that one was bound to be successful eventually. However, in this instance it was felt that nothing else would provide a sensible measure of the method's efficacy. These results are shown in Table VIII.

TABLE VIII
COMPARISON OF RESULTS FROM DEVELOPMENT AND ASSESSMENT DATA SET A

Descriptions	Development Data Set	Assessment Data Set A
Mean result from normal subjects	2.25	2.25
Standard deviation from normal subjects	0.14	0.88
Limit to achieve 99.9% Specificity	1.36	4.98
Mean result for AD subjects	6.23	5.03
Standard deviation of AD subjects	2.64	2.23
Estimated Sensitivity to AD	96.8%	51.0%
Mean result for VaD subjects	4.13	3.44
Standard deviation of VaD	1.60	1.18
Estimated Sensitivity to VaD	95.8%	9.6%

From these results, it may be seen that the sensitivities to AD and (particularly) VaD using Assessment Data Set A (51% and 9.6%, respectively) are significantly lower than similar results using the development data (96.8% and 95.8% respectively). This is because the difference between the normals in the Assessment Data Set A and the Development Data Set is large—but not as large as the difference to any of the groups of subjects with dementia. It is felt that this method is unlikely to provide a reliable, sensitive metric to detect dementia. However, it may be worth repeating this experiment in the future with a larger set of development and assessment data taken with the same recording protocol.

E. Alpha/Theta Ratio Based on Zero-Crossing Interval

Of the linear, spectrum techniques reported in the literature [39], the Alpha/Theta ratio is one of the most successful in numerically differentiating the normal and demented subjects. In this method, the ratio of the signal power in the alpha (8–12 Hz) band to the sum of the signal powers in the alpha and theta (4–8 Hz) bands is used to predict dementia. Inspired by this we decided to use the same ratio, but replace signal power with density of zero-crossings. See Table IX.

Thus, this metric appears (on the development data set) capable of differentiating control subjects from subjects with dementia with a wide band between the two groups. The estimated sensitivities to AD and VaD for a specificity of 99.9% are 98.7% and 89.2%, respectively.

TABLE IX
ALPHA/THETA RATIO FROM THE ZCIS OF DEVELOPMENT DATA SET

Descriptions	Normal	AD	VaD and Mixed
Mean	0.815	0.448	0.569
Std Dev	0.042	0.108	0.095
Number of samples	7	3	4

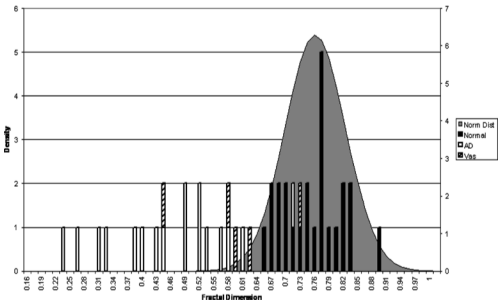

Fig. 11. Distribution of Alpha/Theta ratio of Assessment Data Set A.

TABLE X
COMPARISON OF METHODS

Methods	Estimated Sensitivity to AD	Estimated Sensitivity to VaD
85% Cumulative density position	50.8%	39.8%
Mean zero-crossing interval	82.2%	53.4%
Difference from reference normal curve	96.8%	95.8%
Repeat of difference from reference normal curve using evaluation data	51.0%	9.6%
Alpha/Theta ratio based on zero-crossing interval	98.7%	89.2%

TABLE XI
ALPHA/THETA RATIO FROM ASSESSMENT DATA SET A

Descriptions	Normal	AD	VaD
Number of samples	24	17	5
Mean	0.761	0.466	0.604
SD	0.063	0.130	0.103

F. Assessment of Method

All of the prospective methods based on the ZCIs were compared (Table X) to see which should be tested using the two assessment data sets. The Alpha/Theta ratio metric based on the ZCIs was chosen as it showed the most promise. The results of this method applied to Assessment Data Set A are shown in Table XI and an illustration of the distribution of the results is given in Fig. 11.

The effect of age on the significance of the results was assessed by studying the results as a function of age for the three groups (see Fig. 12) and there is no discernable trend with age. These results show that, if one were to demand a specificity of 99.9%, then a result would be considered abnormal if it were less than 0.565. This gives an estimated sensitivity to AD of 77.8% and an estimated sensitivity to VaD (or mixed) dementia of 35.2%.

As with the FD of the zero-set, the Alpha/Theta ratio based on the ZCIs was evaluated using Assessment Data Set B. The

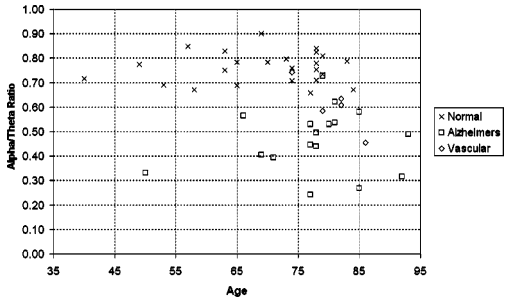

Fig. 12. Graph for Alpha/Theta ratio against age for the 3 subject groups.

TABLE XII
ALPHA/THETA RATIO ASSESSMENT DATA SET B

Descriptions	Normal	AD
Number of samples	10	10
Mean	0.701	0.456
SD	0.165	0.174

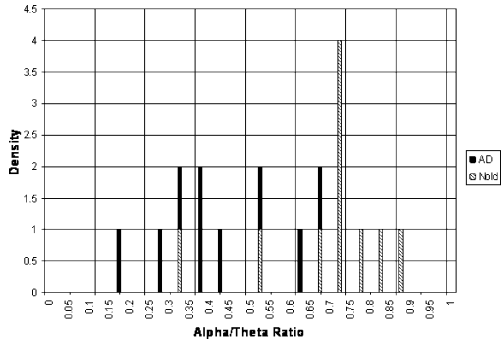

Fig. 13. Distribution of Alpha/Theta ratio for Assessment Data Set B.

TABLE XIII
ALPHA/THETA RATIO FROM PSD OF ASSESSMENT DATA SET A

Descriptions	Normal	AD	VaD
Number of samples	24	17	5
Mean	0.712	0.523	0.604
SD	0.061	0.076	0.065

results are summarized in Table XII and Fig. 13. Based on the results obtained, if one were to demand a specificity of 99.9%, then any result below 0.294 would be considered abnormal. This gives an estimated sensitivity to AD of approximately 90%.

G. Alpha/Theta Ratio Based on Power Spectral Density

Having produced an Alpha/Theta ratio metric based on the ZCIs it was important to test the equivalent Alpha/Theta ratio from the power spectral density (PSD) to determine whether similar results could have been produced this way. Results from a PSD-based Alpha/Theta ratio (Assessment Data Set A) are given in Table XIII.

These results show that, if one were to demand a specificity of 99.9%, then a result would be considered abnormal if it were less than 0.52. This gives an estimated sensitivity to AD of 50.3% (compared with 77.8% for Alpha/Theta ratio based on ZCIs) and an estimated sensitivity to VaD (or mixed) dementia of 10.7% (compared with 35.2% for Alpha/Theta ratio based on ZCIs). Hence, an Alpha/Theta ratio generated from the ZCIs has

better performance than the same generated from the PSD. The reason for this difference, we believe, is related to the treatment of artefacts. It should be recalled that the entire recording from each subject was used without any preselection of segments that we wish to analyze. Therefore, the zero-crossing distribution method has an advantage because spectral content during low frequency artefacts is ignored because there will be very few zero-crossings in this period and those that do exist will typically have intervals much larger than those associated with alpha or theta activity.

IV. Conclusion

This paper has shown that the zero-set FD of the EEG may be used to detect AD within the general at risk population (specificity 99.9%, sensitivity 67%). An alternative method based on the PDF of ZCIs provides even better separation (specificity 99.9%, sensitivity 78.8%). This compares well with other studies, reported by the American Academy of Neurology which typically provide a sensitivity of 81% and specificity of 70% [40]. The FD and zero-crossing methods are both time domain approaches, share similar features, and it is interesting that they give more accurate results than conventional spectral analysis. It is thought that this is due in part to the fact that they are less sensitive to artefacts. The results show that of the two methods, the simpler zero-crossing analysis performed better than the FD analysis. This suggests that there may be a need to investigate and develop the fractal analysis based method further. The robustness of the zero-crossing approach has already been demonstrated in the analysis of EEGs in sleep studies [21].

The EEG recordings used to assess these methods had no *a priori* selection of elements "suitable for analysis." This approach leads to the inclusion of all the difficult elements of the EEG (artefacts, etc.) and, therefore, gives a good prediction of the usefulness of the technique in practice. It is noteworthy that the probable AD subjects had not previously been diagnosed (prior to the assessment at the memory clinic which led to their referral to the EEG department) and were, therefore, in the early stages of exhibiting symptoms.

This paper has shown that the two methods (fractal analysis of the EEG waveform and the Alpha/Theta ratio based on the analysis of the PDF of the ZCIs), are good candidates to fulfill the need for a low-cost, easy to administer and reasonably accurate method for detecting dementia within the growing at risk population.

However, much of the results were based on patient cohorts which did not have neuroimaging studies carried out to exclude other causes and access to cognitive scores was not possible. Although a preliminary evaluation of the methods with a new set of data (10 AD 10 healthy age-matched controls) from another study in a different centre which included neuro-imaging and cognitive examinations supports the above findings, there is a need for a more extensive study to validate the methods using EEGs from large and varied patient cohorts with neuro-imaging results, e.g., from MRI, to exclude other causes, and cognitive scores, to correlate results with severity of cognitive status. The full significance of the results can only be fully assessed after such a study.

If the significance of the methods are confirmed and the methods were adopted and the practical difficulties were addressed, they could advise a GP whether the patient should be referred to a hospital for further tests. It would also be possible to transfer the recordings made in the consulting room via the Internet to a clinical neurophysiologist for an opinion and, thus avoiding the need for the patient to attend a hospital in the first instance. It is, however, important to recognize that if this method were widely adopted then there would be infrastructure requirements to allow a patient's history of EEG data to follow them. In the near future, this should become somewhat more achievable with eHealth programs such as BIOPATTERN [41] pressing forward the development of database, internet and computational technologies in pursuit of better health care.

Acknowledgment

G. Henderson would like to thank Dr. E. Allen for her assistance and support in the early days of this research and Biologic for making it possible to read their proprietary EEG data file format.

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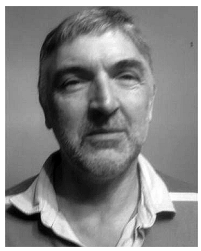
He is a Professor of Intelligent Electronics Systems and Head of Signal Processing & Multimedia Communications at the University of Plymouth, former chair of the Institution of Electrical Engineers (IEE) Professional Network on Healthcare Technologies. He was Head of School of Electronic, Communication, and Electrical Engineering from 1995 to 1999. He has published extensively in the areas of signal processing and computational intelligence, including co-authoring *Digital Signal Processing – A Practical Approach* (Prentice-Hall, 2002), and co-editing five books including *Artificial Neural Networks for Biomedicine* (Springer-Verlag, 2000).

Prof. Ifeachor has received several external awards for his work including two awards from the IEE—the IEE Dr. V. K. Zworykin Premium in 1997 and 1998.



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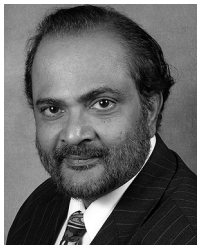

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