PROSPECTS FOR ROUTINE DETECTION OF DEMENTIA USING THE FRACTAL DIMENSION OF THE HUMAN ELECTROENCEPHALOGRAM

G. T. Henderson[1], E. C. Ifeachor[1], H. S. K. Wimalaratna[2], E. M. Allen[3], N. R. Hudson[3]

[1]School of Electronic, Communication and Electrical Engineering, University of Plymouth, UK. [2]Radcliffe Infirmary Oxford/Princess Margaret Hospital, UK. [3]Department of Neurophysiology, Deriford Hospital, Plymouth, UK.

EARLY DIAGNOSIS OF DEMENTIA

Advances in nutrition, living conditions and healthcare in the developed world have led to an improved life expectancy; Raleigh (1). Unfortunately, this brings with it an increase in the number of people who will develop Alzheimer's Disease and other dementias because the number of people in the high risk age groups is now increasing; Hendrie (2). To offset this, efforts are being made to develop treatments such as the Acetylcholinesterase inhibitors (Tacrine, Donepezil and Exelon) which are claimed to slow the progress of the diseases; Kurz (3). However, unless a sufferer is diagnosed in the early stages the treatments cannot give the maximum benefit; Anand (4).

Current techniques such as Positron Emission Tomography (PET) that are used to diagnose and assess neurological disorders require specialist equipment and expert clinicians to interpret results. These methods, which are viable to confirm dementia or assess the nature of a neurological disorder, would be impractical as a method of detecting a small number of subjects with early dementia within the at-risk population because everyone within the at-risk group would need to be tested regularly. It is therefore desirable to develop a low cost method of assessment that can be carried out quickly by a non-specialist clinician, such as a General Practitioner.

To assess the required accuracy of the new system it is necessary to look at the effects of misdiagnosis. False negative diagnoses would be undesirable within the new method but would not make the situation any worse than at present. Similarly, false positive diagnoses would be undesirable but their effect would be an unnecessary referral to a specialist.

Potentially, analysis of the electrical activity of the brain (the Electroencephalogram or EEG), could provide the basis of an acceptable and affordable method for early detection of dementia; Ktonas (5). The EEG has long been used for diagnosis of neurological disorders and if it were possible to automate the process of interpretation this would provide the desired first line of screening.

It is well known that brain disorders are accompanied by changes in the EEG. The difficulty is that such changes in the EEG may not be specific. The challenge is to automate EEG analysis such that dementia can be accurately detected before there is noticeable mental decline. Ultimately, a system based on such an approach may be used by a General Practitioner during routine health checks of older patients.

The purpose of this paper is to report our initial study to demonstrate that subject specific variability of the Fractal Dimension of the Human Electroencephalogram is an important candidate method for the routine detection of dementia; Lipsitz and Goldberger (6).

SUBJECT SPECIFIC EEG ANALYSIS

A great deal of effort has been expended in the pursuit of automated EEG analysis but to date there has been a general lack of success (excepting Bispectral Analysis in Anaesthesia; Sebel *et al* (7)). We believe that one reason for this lack of success is that research has concentrated on group comparisons, that is, attempting to separate individuals into groups (Normal, Alzheimer's, Parkinson's, etc.) using indexes derived from isolated (snap-shot) EEGs. An alternative is subject specific analysis: comparing an EEG to those taken previously from the same subject and looking for trends in indexes that arise over time rather than comparing an EEG to what is generally normal within the population.

When an EEG is analysed one may extract indexes such as the alpha wave magnitude, Fractal Dimension and Bispectrum Index. Each of these indexes is subject to short, medium and long term variability. For subject specific analysis we require a distinguishable change that implies the onset of disease and a continuing change that gives a measure of disease progression or effect of treatment.

As an illustration, Figure 1 below shows changes in a hypothetical index from a subject who is initially normal and then enters a notable decline at the onset of disease. The index only becomes 'abnormal' some time after the onset of the disease when it falls outside the normal spread. This illustrates why a subject specific method that compares an EEG to those taken previously from the same subject has the potential to provide earlier detection of a disease than a method that compares an EEG to what is generally normal within the population.

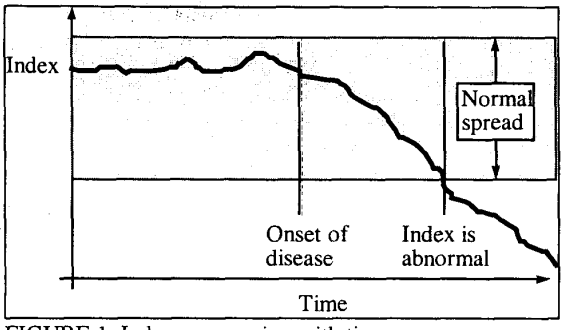

FIGURE 1. Index progression with time.

FRACTAL DIMENSION OF THE EEG

The Fractal Dimension index was used and developed in this paper as a vehicle to explore subject specificity. The reason for choosing the Fractal Dimension was that it had been reported to be successful in group comparison trials; Woyshville and Calabrese (8) and Wu et al (9). Until fractals were discovered the concept of dimension was equated to the number of independent coordinates necessary to specify a point within an object or set; this is the topological dimension, D_T. A precise, inductive definition is given below.

If the boundaries of arbitrarily small neighbourhoods of all points in a space are (n 1)-dimensional, then the space is n-dimensional. The empty set, and only the empty set, has dimension of minus 1.

This definition of the dimension of a space always gives an integer. A fractal set is characterised by a number of dimensions that is greater than the topological dimension and this dimension need not be integer.

Consider a smooth curve of length L, which has a topological dimension D_T of 1. The length of the curve may be estimated by covering it with $N(\delta)$ small line segments of length δ, so that L would be given by:

$$L = \lim_{\delta \to 0} \left(N(\delta)\ \delta \right) \quad \text{.....(1)}$$

Similarly, consider a shape with a topological dimension of 2, such as a circle, where the area may be estimated by covering it with small squares of side δ:

$$A = \lim_{\delta \to 0} \left(N(\delta)\ \delta^2 \right) \quad \text{.....(2)}$$

Thus, the measured quantity (length, area, etc.) may be found by covering the shape with small objects that have the same topological dimension. If these objects are covered by small objects of an inappropriate dimension then the result is either zero or infinite. For example if we use vanishingly small squares to cover a smooth curve then in the limit the 'area' will be zero. Also, if we cover a circle with small line segments then in the limit the 'length' will be infinite. We may write a generalised expression for the measured quantity M_d:

$$M_d = \lim_{\delta \to 0} \left(N(\delta)\ \delta^d \right) = \begin{cases} \infty & ,d < D \\ M_{d0} & ,d = D \\ 0 & ,d > D \end{cases} \quad \text{.....(3)}$$

The constant M_{d0} is the value of the measured quantity (length, area, etc.) when the step size d is of unit length. The Hausdorff-Besicovitch dimension D is of great significance for a fractal set. This "Fractal Dimension" is not normally an integer and obeys the inequality:

$$D_T < D \leq D_T + 1 \quad \text{.....(4)}$$

A coastline is an example of a natural approximation to a fractal. As one looks more closely more detail is seen and the length appears to be greater. If one steps around a land-sea boundary using N steps of length δ then N would be found to be a function of the step length, approximately given by:

$$L(\delta) = \delta N(\delta) = L_0 \delta^{D-1} \quad \text{.....(5)}$$

Here L is the apparent length of the coast, L_0 is a constant and D is the Fractal Dimension, which for Norway is about 1.5. This technique of using line segments to cover a Fractal with topological dimension of 1 is known as the Divider Dimension. An alternative is to cover the coastline with squares; this is the box dimension where the total area A is found to be related to the length of the square's side δ by:

$$A(\delta) = \delta^2 N(\delta) = A_0 \delta^{D-2} \quad \text{.....(6)}$$

The Fractal Dimension is a good candidate to be an indicator of possible dementia because it is a measure of signal complexity and it has been shown that the complexity of the EEG is less in demented subjects.

There is a complication when one considers computing the Fractal Dimension of the EEG which exists in an affine space. In an affine space 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; Mandlebrot (10).

In an early study (8) the Divider Dimension of the EEG was used to separate subjects with Alzheimer's Disease from a group of normal subjects. When this method was repeated on a single Alzheimer's subject and a single normal subject it was found that the arbitrary voltage/time scaling affected the results; a scaling of 0.6nV/s for example, gave Fractal Dimensions similar to

those reported (1.66 for a Normal subject and 1.28 for an Alzheimer's subject) but a higher scaling of 2.5nV/s gave very different results where the Normal subject had a lower Fractal dimension (1.21) than the Alzheimer's 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 have been reported in the literature which are suitable for estimating the Fractal Dimension of shapes in an affine space; Voss (11). The adapted box dimension and the dimension of the zero-set were chosen for this study. The adapted box dimension was chosen because it is similar to the box dimension often used in non-affine space. The dimension of the zero-set was used because it is an interesting and computationally efficient method.

To compute the adapted box dimension we divide the record of duration T into slices of length Δt and note the difference between the maximum and minimum during each slice (the extent). The mean extent $\varepsilon(\Delta t)$ is computed for a range of Δt and the dimension is computed by finding a best fit to the equation:

$$A(\Delta t) = T\,\varepsilon(\Delta t) = A_0 \Delta t^{2-D} \quad \text{.....(7)}$$

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 line formed by linear regression). The Topological Dimension of this set is zero. The Fractal Dimension of this zero-set is computed by covering it with N line segments of length Δt and finding the best fit to the equation:

$$L(\Delta t) = \Delta t\, N(\Delta t) = L_0 \Delta t^{1-D} \quad \text{.....(8)}$$

In this analysis the raw EEG data is divided into 1 second segments. Similar results are obtained for segment lengths between 0.5s and 2s. Below 0.5s the results become erratic because of the number of samples is becoming too small (the data is sampled at 256Hz). With segment lengths greater than 2s the results are affected by the non-stationary nature of the EEG.

To obtain a single result for a subject the estimated Fractal Dimension from each segment through the entire recording and across all 21 channels is plotted on a histogram and the highest point on the histogram (the mode) is taken as the composite measure of fractal dimension for that subject. This use of a histogram is intended to reduce the effects of artefacts and unusual activity on the final result.

The adapted box and zero-set dimension of the EEG were estimated in this way. A further 2 measures were produced by applying adapted box and zero-set dimension estimating techniques to the auto-correlation of the data; that is replacing the data segments with the discrete time analogue of the auto-correlation function:

$$R_s(t) = \int_{s\cdot\Delta t}^{(s+1)\cdot\Delta t} x(\tau)x(\tau+t)d\tau, \quad 0 \le t < \Delta t \quad \text{.....(9)}$$

Where s is the segment number and Δt is the segment duration (1s).

Data

Data for this study was obtained using the traditional 10-20 system in conjunction with a strict protocol; Jasper (12). A common montage was used in all recordings and the sampling rate was 256Hz.

EEGs were collected from 7 patients (3 Alzheimer's patients, 3 mixed type (Alzheimer's and multi-infarct dementia) patients and 1 multi-infarct dementia patient), 8 age matched controls (over 65 years of age), 1 young male and 1 young female. All of the age matched controls and the two young volunteers had normal EEGs (confirmed by a Consultant Clinical Neurophysiologist). One age matched control (known as 'vol1') has subsequently developed Alzheimer's disease; this record is of particular interest because it is potentially of a subject early in transition from 'normal' to Alzheimer's diseased. The young male (denoted by "X") and the young female (denoted by "Y") had their EEG recorded 3 times at intervals between 7 and 14 days. These recordings give an indication of the variability of a single subject's Fractal Dimension which may be compared with the variability between members of the set of normals.

The EEG recordings encompass various states: awake, hyperventilation, drowsy and alert with periods of eyes closed and open. The analysis described in this paper takes the whole recording including artefacts and has no *a priori* selection of elements 'suitable for analysis'. This approach leads to a prediction of the usefulness of the techniques as they would most conveniently be used in practice.

Results

It was found that the variation in Fractal Dimension over the scalp was too irregular to give significant results, but it is possible to say that there is an indication that the front of the scalp tends to have lower but more variable Fractal Dimension than the rear of the scalp. The data presented below are the Fractal Dimension of data aggregated from all channels over the scalp.

Table 1 shows the results from three recordings of each of the two young subjects (subjects X and Y). The variation from recording to recording of the same subject is the short term variability of the Fractal

Dimension. The estimated population standard deviation (S.D.) for a single subject for each measure is given in Table 2.

Table 3 shows the results for the age matched controls and the mean result for each of the young normals. It may be seen that for all the measures, except the zero-set dimension of raw data, the standard deviation (SD) of the results from the group of normals is larger than the variation for a single subject (Table 2).

The results for the demented subjects are shown in Table 4. The data shows that the adapted box dimension and zero-set dimension of the auto-correlation function are generally lower than normal when dementia is present. For these data the adapted box dimension of the auto-correlation function provides 100% separation between demented and normal subjects, but clearly the separation is small and there would undoubtedly be an overlap if more recordings were taken.

Finally we consider the results from the age matched control 'voll' who was at the time of recording confirmed by a clinician to be 'normal' but went on to develop Alzheimer's Disease. The results from 'voll' show that the adapted box dimension of the auto-correlation function and the dimension of the zero-set for the auto-correlation function are suspiciously low but not outside the range for normal subjects. Unfortunately in the absence of recordings before or after this recording it is not possible to say whether subject specific analysis would have detected the onset of this dementia.

These results described so far are reasonably good with some separation of demented from normal subjects, however, it is possible to achieve more by using the subject specific concept. Consider the zero-set dimension of the auto-correlation function for which the results from specific subjects vary over a number of weeks by only 0.01 (standard deviation) and the range of results from normal subjects (0.42 to 0.67, from Table 3) overlaps with the range from demented subjects (0.27 to 0.44, from Table 4). These results are summarised in Figure 2 which indicates that if we were to compare the fractal dimension from a subject to one take from the same subject some time earlier then we would be able to detect a subtle decrease and possibly the onset of dementia. Clearly this is only indicative and further work will be required to demonstrate that there is a measurable rate of decline in the early stages of dementia, that the stability of Fractal Dimension among normal subjects exists over longer periods and this stability is common among a substantial proportion of normal subjects.

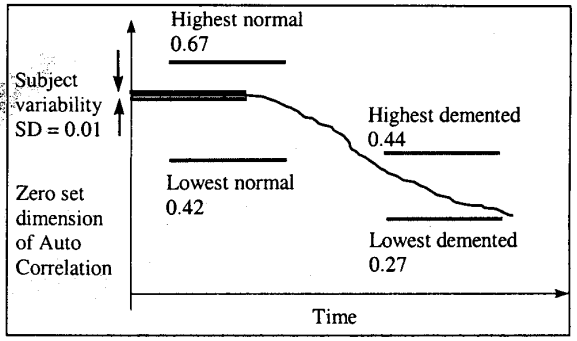

FIGURE 2. Subject Specific Variability

CONCLUSION

The results in this paper show that the adapted box dimension of the auto-correlation function and the dimension of the zero-set for the auto-correlation function are good candidates for use in subject specific detection of dementia. This is because the measured Fractal Dimension of the EEG is generally lower for a demented subject than for normal subjects and the variability of a single normal subject's Fractal Dimension is small in comparison to the variability between members of the set of normals.

The results indicate that this method may have the potential to achieve our goal of automated EEG analysis providing an opportunity to maximise the quality of life for patients by using modern treatments.

FURTHER WORK

There is a great deal of work to be done in developing the technique before it may be considered successful. Work will continue with more data being analysed to provide statistical significance (including serial recordings from Alzheimer's subjects who are in decline) and with indexes other than Fractal Dimension being tested such as Bicoherence.

Potentially, it may also be possible to extend the application for this method in the future to provide an inexpensive, simple and objective test for neurological decline that may be used by General Practitioners who are asked to certify that their patient is able to drive safely. Normally in this situation the GP has to come to a decision based on his subjective opinion whilst recognising the danger presented to the public by a driver with dementia and also recognising the negative effect on an older person if their independent mobility is reduced.

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TABLE 1: Comparison of fractal dimension measures from 2 young subjects.

Record	Raw EEG Data		Auto-correlation of EEG data	
	Adapted Box	Zero-set	Adapted Box	Zero-set
X1	1.564	0.563	1.350	0.536
X2	1.574	0.608	1.385	0.559
X3	1.559	0.564	1.223	0.555
Y1	1.521	0.577	1.273	0.411
Y2	1.519	0.561	1.284	0.425
Y3	1.513	0.558	1.269	0.423

TABLE 2: Variability of fractal dimension measures from 2 young subjects.

	Raw EEG Data		Auto-correlation of EEG data	
	Adapted Box	Zero-set	Adapted Box	Zero-set
S.D.	0.006	0.020	0.060	0.010

TABLE 3: Fractal dimension measures from controls and young normals.

Record	Raw EEG Data		Auto-correlation of EEG data	
	Adapted Box	Zero-set	Adapted Box	Zero-set
vol2	1.596	0.562	1.434	0.590
vol3	1.572	0.560	1.452	0.648
vol4	1.551	0.561	1.496	0.662
vol5	1.592	0.562	1.587	0.562
vol6	1.591	0.561	1.638	0.627
vol7	1.538	0.564	1.391	0.539
vol8	1.596	0.616	1.500	0.670
X	1.566	0.578	1.319	0.550
Y	1.518	0.559	1.275	0.420
Mean	1.569	0.569	1.475	0.585
S.D.	0.028	0.018	0.117	0.079

TABLE 4: Fractal dimension measures from demented subjects.

Record	Raw EEG Data		Auto-correlation of EEG data	
	Adapted Box	Zero-set	Adapted Box	Zero-set
AD1	1.560	0.565	1.134	0.323
AD2	1.520	0.560	1.181	0.368
AD3	1.512	0.554	1.183	0.331
MID1	1.483	0.496	1.219	0.384
MIX1	1.533	0.562	1.148	0.324
MIX2	1.442	0.497	1.118	0.270
MIX3	1.608	0.669	1.265	0.438

TABLE 5: Fractal dimension measures from a subject prior to dementia.

Record	Raw EEG Data		Auto-correlation of EEG data	
	Adapted Box	Zero-set	Adapted Box	Zero-set
vol1	1.547	0.564	1.325	0.516