**Proceedings of the 2005 IEEE**
**Engineering in Medicine and Biology 27th Annual Conference**
**Shanghai, China, September 1-4, 2005**

# Biopattern Analysis and Subject-Specific Diagnosis and Care of Dementia

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*Abstract* – **Worldwide, the number of people that develop Alzheimer's disease and other types of dementia is rapidly rising and will create a considerable financial burden on the health and social services. The availability of new drugs that may slow or even halt the disease progression makes accurate early detection crucial. Objective methods are needed to support clinical diagnosis and care for patients; to quantify severity, monitor progression and response to new treatments. Electrophysiological markers have an important role to play in the objective assessment and care for dementia. The EEG provides a measure of brain dysfunction and EEG changes could be detected fairly early in the dementing process. Subject-specific EEG analysis offers the possibility of using objective methods to assess and care for dementia on an individual basis. The main objectives of this paper are: (i) to introduce the concepts of subject-specific EEG analysis as a basis for improving diagnosis and care for dementia; and (ii) present two novel methods for deriving suitable subject-specific electrophysiological markers – analysis of fractal dimension and zero crossing interval density of the EEG. We present findings that indicate that the methods are potentially good candidates for the development of individualized, low-cost, easy to administer and reasonably accurate methods for detecting dementia within the growing at risk population.**

*Keywords*—EEG, dementia, Alzheimer's disease, fractal dimension, zero crossing distribution, biopattern, bioprofile.

## I. INTRODUCTION

Dementia is a progressive, degenerative brain disease that impairs cognitive functions [1]. With the increase in life expectancy, the number of people that will develop Alzheimer's disease (AD) and other types of dementia is steadily rising and this will create a considerable financial burden on the health and social services across the world [2,3].

There is no cure for dementia at present, but the availability of new drugs that may slow or even halt the progression of the illness makes earlier and more accurate detection of critical importance for sufferers and carers to get maximum benefit [4]. Current diagnosis involve clinical assessment by specialists (e.g. neurologists) and neuropsychological tests which are subjective. Objective methods are needed to support clinical diagnosis and care for patients such as to quantify severity, progression and response to treatment. This is important given that it may take 3-5 years to meet the current clinical criteria for diagnosis dementia [5].

Objective methods of assessing dementia include those based on imaging and electrophysiological techniques. Neuroimaging techniques such as Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) are useful in identifying structural abnormalities, but are limited in identifying patients with AD. Single Photon Emission Computer Tomography (SPECT) scans are widely available and are sometimes helpful in identifying multi-infarct dementia (MID), but could be useful only in advanced stages rather than early dementias. Positron Emission Tomography (PET) are sensitive in diagnosing early dementias, but require specialized procedures and are expensive and hence are not appropriate for widespread screening or early detection of dementias.

Electrophysiological methods (e.g. based on electroencephalogram (EEG) and event-related potential (ERP)) offer a potentially important approach to improve diagnosis. EEG is very useful in detecting organic abnormality of the brain function [6]. In addition to its non-invasiveness, it is widely available and could be develop as an affordable method of assessment which can be carried out rapidly and widely in the high-risk age group that will develop dementia. EEG changes could be detected fairly early in the dementing process and the changes could be quantified as an index or marker which could then be use to:

- Measure progression of the disease and to monitor response to treatment. Hence, it could be used to evaluate the effectiveness of treatment in individual patient. No such objective tool exists at present.
- Provide a basis for an affordable tool for screening high-risk patients even before they develop clinical symptoms.
- Perform patient-specific way for follow ups, e.g. 'patient A' showing a 'degree of dementia X', may be different from 'patient B' showing a 'degree of dementia Y'. Thus, subject-specific EEG analysis could be important in being able to identify patient specific features, i.e. a "finger print" of a person's EEG.

The EEG is a useful means of making an objective measure of the degree of dysfunction. However, although neurophysiologists could offer an excellent opinion of an EEG using their knowledge of the clinical conditions and experience in reading EEGs, traditional methods of analysis of the EEG are subjective. It is necessary to automate the analysis and to quantify EEG changes to obtain the appropriate electrophysiological indices or markers for dementia.

Several potential electrophysiological markers such as ERP-based markers, sleep EEG markers, waking EEG markers exist. However, there are a number of important outstanding methodological issues that need to be resolved. These include the need to develop robust analysis algorithms for obtaining the markers, the need for a large cohort to evaluate their performance and the need for subject-specific EEG analysis as opposed to group comparison.

The main objectives of this paper are: (i) to introduce the concepts of subject-specific EEG analysis as a basis for

improving diagnosis and care for dementia, and to (ii) present some methods that may be used to derive suitable subject-specific electrophysiological markers.

The work described in this paper is part of an EU project, BIOPATTERN, which aims at developing a pan-European, intelligent model for analyzing a citizen's bioprofile to combat major diseases such as dementia. A *biopattern* is the information (pattern) that provides clues about underlying clinical evidence for diagnosis and treatment of diseases. It can be derived from specific data types such as the EEG. A *bioprofile* is a personal 'fingerprint' that fuses together a person's current and past medical history, biopatterns and prognosis. It combines data, analysis and predications of possible susceptibility to diseases. Bioprofile is aimed at individualization of healthcare such as disease prevention, diagnosis and treatment.

## II. SUBJECT SPECIFIC EEG ANALYSIS

Subject-specific EEG analysis offers the possibility of using objective methods to assess and care for dementia on an individual basis. It moves away from normal group-based comparison by comparing a biorecord (say an EEG/ERP) to those taken previously from the same subject and looking for trends in the markers over time rather than comparing a marker to what is generally normal within the population. The markers will serve as a form of a 'bioprofile' for the individual and would allow clinicians to understand how the person is progressing relative to previous results. The key motivation for this idea stems from the fact that the features of the biodata associated with dementia are subject-specific over time.

Figure 1 illustrates the time-evolution of a hypothetical, subject-specific biomarker for dementia. What we are looking for is a distinguishable change in the markers that implies the onset of dementia and a continuing change that gives a measure of disease progression or effect of treatment. The challenge is to find a reliable biomarker or set of biomarkers that can be used for different aspects of dementia – early detection of onset of dementia and monitoring the disease progression, over time, on an individual basis. If appropriate biomarkers can be found, a study of the evolution of these would not only enable the clinician and carer to differentiate between normal and demented subjects, but also to find out the type, degree, progression and the best treatment option for the patient on an individual basis. This would represent a major leap forward in the way electrophysiology is used in the management and care of people with dementia.

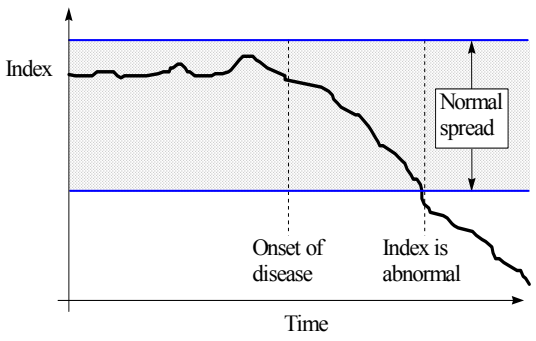


Fig. 1. Variations of index over time

## III. METHODS FOR COMPUTING MARKERS FOR SUBJECT SPECIFIC EEG ANALYSIS

Here, we will concentrate on two methods, used for the computation of electrophysiological markers - fractal and zero-crossing interval density.

### *A. Detection of dementia by analysis of the fractal dimension of the EEG.*

Fractal-based methods have been used, with some success, to analyze the EEG to differentiate between subjects with AD from a group of normal subjects [7]. In this paper, FD-based subject-specific EEG analysis is used, where an EEG taken from the same subject is compared to those taken previously and looking for trends in the FD indices that arise over time.

One approach for computing the FD is the zero-set [8]. To do this, we first form the set of instances when the EEG record intersects with a suitable straight line (we have used the 0 V reference). The FD is then found by covering the set of instances with $N$ line segments of length $\Delta t$ and finding the best fit to:

$$L(\Delta t) = \Delta t N(\Delta t) \approx L_0 \Delta t^{1-D} \quad (1)$$

The data used to develop the method consists of 7 patients (3 AD, 3 mixed type - Alzheimer's and Vascular dementia - and 1 Vascular dementia (VD)) and 8 age-matched controls (over 65 years of age) [9]. One age-matched control (vol1), who has subsequently developed AD represents a potential subject early in transition from 'normal' to AD. This is an important record as it can show the detection ability of the methods prior to subject exhibiting any clear symptoms.

The results of a study of changes in the FD are summarized in Figure 2. It was found that the FD of the auto-correlation of EEG data is generally lower for subjects with dementia than for normal subjects. The studies showed that an appropriate FD measure can achieve 67% sensitivity to probable AD (as confirmed by a clinical neurophysiologist from the EEG) with a specificity of 99.9%. Further work is required to validate the results in both normal and patient subjects.

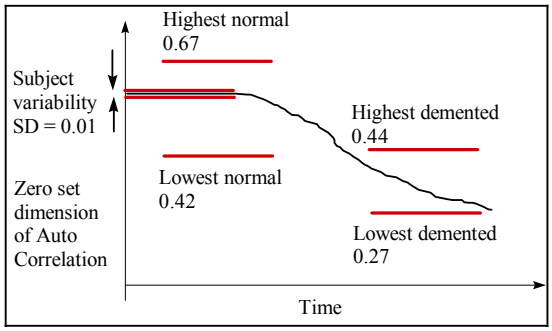


Fig. 2. Subject-Specific Variability

The results suggest that for a Normal distribution, if one were to demand a specificity of 99.9%, then FD less than 0.6697 would indicate abnormality. In the case of AD and VD (or mixed), this would imply a sensitivity of 99.5% and 97.2% respectively. Based on this, the FD of 'vol1' would have been flagged as slightly abnormal before it was detected by a clinician. Furthermore, these results show that the zero-set dimension has a significant effect ($p<0.0001$) on the developmental data in terms of its ability to capture the EEG changes in normal and subjects with dementia. In order to test the method more rigorously, a separate data set (assessment data set) was used.

The assessment data consist of new EEG recordings, which encompassed various states: awake, drowsy and alert with periods of eyes closed and open, taken from 24 normal records, 17 probable AD and 5 probable VD [9]. It should be pointed out that some of the subjects in this data set were not referred for dementia diagnosis, but for investigations such as seizures. In particular, the probable AD subjects were not previously diagnosed and were therefore in the early stages of exhibiting symptoms. Using the student's t-test, the difference between normal and subjects with dementia is confirmed ($p<10^{-11}$). The results showed that the method can be use to determine AD with a sensitivity of 67%. Although, this appears to be inferior to the 99.5% sensitivity obtained from the development data set, the parameters used here have not been fine-tuned to obtain optimal results as in the previous case.

Investigations into whether changes in a single subject's EEG is less than the changes across the population of normals were conducted by having repeated EEG recordings for a group of four normals. Two of the normals had their EEG recorded three times at intervals between seven and 14 days and a further two subjects had two EEGs taken with a three week interval. All the recordings were analyzed as before. This supplementary experiment showed that the changes in a single subject's FD (over intervals of weeks) is approximately 0.016. This may be compared to the standard deviation of FDs of 0.029 for normals. Further results are required for the subject-specific analysis to quantify the benefits of the extension to the method.

The studies carried out so far has been based on the assumption that the EEG is a fractal and that it is this fractal nature which causes the method to work. It is possible to test this assumption by inserting an additional step into the zero-set method by first taking the Fourier transform of the raw data and construct surrogate data that has the same spectrum but randomized phase. If the fractal nature of the EEG contributes to the success of the method, then the effectiveness of the method will be reduced by this phase randomization. The results obtained indicates that for a specificity of 99.9%, the sensitivities are 94.3% for the development data and 74.5% for the assessment data. When compared to earlier results obtained without phase randomization, it is apparent that the fractal nature of the EEG (should it exist at all) is not a contributory factor to the success of the method. The results also show that all of the information required to distinguish between normal and AD lies within the spectrum of the EEG (excluding phase).

*B. Zero Crossing Interval Density*

The zero crossing interval density method shares similar features with the zero-set dimension and was developed to exploit the findings of the previous section. The zero-crossing interval is defined as the time interval between a positive to negative voltage transition to the next positive to negative voltage transition. Based on this, a list of zero crossing intervals can be extracted from a single channel EEG record and the Probability Density Function (PDF) of these data can be plotted. Figure 3 and 4 shows the zero crossing interval PDFs from Parietal-Occipital channel pairs for normal and subjects with dementia from the development data set respectively. It is clear that the PDFs exhibit noticeable differences. When different regions of the scalp are examined, the PDFs obtained from the temporal, parietal and occipital regions of the scalp, showed the most difference in PDFs for normal subjects and those with dementia. This mirrors the findings in FD. In the frontal region, the results are less ordered and this is probably because this area is prone to ocular and other muscular artifacts.

It should be noted that the 50 Hz mains interference artifacts were removed using a simple, second order, digital notch filter. Thus, the zero crossing distribution method has an advantage because it ignores spectral content during artifacts as there are very few zero crossings in this period.

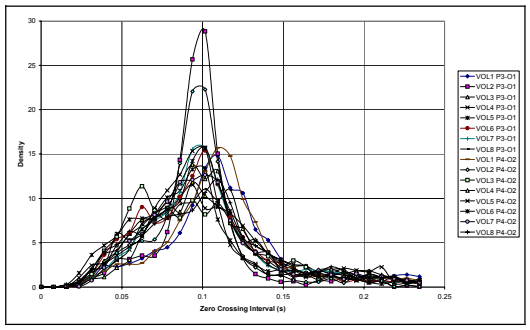


Fig. 3. Zero-crossing interval PDF for normal subjects.

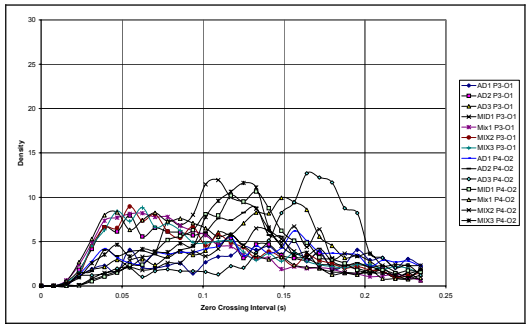


Fig. 4. Zero-crossing interval PDF for subjects with dementia.

Furthermore, the method provided better separation as compared to FD of the EEG. Based on the assumption

that the distribution is Gaussian, the results obtained showed that if one were to demand a specificity of 99.9%, the sensitivity to AD is 78.8%.

## IV. CONCLUSIONS AND THE FUTURE

In this paper, it has been shown that the zero-set method can be used to accurately compute the FD of the EEG for the detection of AD within the general at risk population. A promising extension to the method (which still requires more work to quantify any additional benefit) is also suggested, using subject-specific methods. The results obtained from the PDF of zero crossing intervals indicate that it is potentially a good candidate to fulfill the need for an individualized, low-cost, easy to administer and reasonably accurate method (sensitivity of 78.8% and specificity of 99.9%) for detecting dementia within the growing at risk population. These results are comparable to those reported by the American Academy of Neurology, with typical sensitivity of 81% and specificity of 70% [5].

It is noteworthy that the EEG recordings used to assess the performance of this method did not have any pre-selected features that are 'suitable for analysis' and all difficult elements of the EEG such as artifacts are included. This gives a good prediction of the usefulness of the technique, as it would be used in practice. Furthermore, the method is able to separate subjects with probable AD who were not previously diagnosed and were therefore in the early stages of exhibiting symptoms.

With the advent of new drugs that can slow the progression of dementias, methods for early detection could help give extra years of quality life for many patients in the growing at risk age group who will develop dementia. Nonetheless, it is important to recognize that if they were to be widely adopted then there would be knowledge, data and computational infrastructure requirements to allow for patients' history of EEG data to follow them wherever they were. In the near future, this should be possible with the outcomes of eHealth initiatives such as BIOPATTERN [11].

Electrophysiological markers have an important role to play in the assessment and care for dementia. However, it is likely that a combination/integration of relevant biomarkers from different biomedical sources (e.g. genomics, proteomics, electrophysiology, biochemical and neuro-imaging), together with clinical assessment, will be needed to achieve accurate and earliest possible diagnosis and care for dementia because of the biological heterogeneity of the disease and peculiarities of individual patients. Although research into the genomics/proteomics markers for dementia are still at an early stage [12], it should provide an insight into the characteristics of this complex disease at the molecular level, including its genetic epidemiology, multifactorial risk factors, pathogenic mechanisms associated with with genetic networks, and in the development of new drugs to personalize care and treatment [13].


## ACKNOWLEDGMENT

The authors would like to acknowledge the assistance and significant support given by Dr. Elaine Allen in the early stages of this research. We would also like to thank Biologic for making it possible to read their proprietary EEG data file format. The part financial support by the EU under BIOPATTERN project is acknowledged.


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