Bioprofiling over Grid for Personalised eHealthcare for AD

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Abstract. This paper is concerned with the exploitation of new information and communications technologies (computational intelligence algorithms and tools for biodata analysis, grid computing and web services, clinical user interfaces) to create a knowledge infrastructure to support personalised care for Alzheimer's disease (AD) - prevention, early detection, diagnosis, monitoring of progression and response to treatment. This revolves around the use of bioprofiles which is a personal 'fingerprint' that fuses together a person's current and past bio records and lifestyle. Analysis of an individual's bioprofile makes it possible to personalise care for AD. The paper is based on the work undertaken within the EU-funded project, BIOPATTERN. It provides highlights and insights into the requirements and challenges of personalised care for AD, the characteristic features and requirements of bioprofiles within the context of AD, techniques for the acquisition of useful parameters for inclusion in the bioprofile for AD, and a grid-based prototype system to demonstrate the concepts of bioprofiling for AD within the EU setting.

Keywords. grid, ehealthcare, Alzheimer's disease, bioprofile, diagnosis, cognitive decline, personalisation.

Introduction

This paper is concerned with the exploitation of new information and communications technologies (computational intelligence algorithms and tools for biodata analysis, grid computing and web services, clinical user interfaces) to provide a knowledge infrastructure to support personalised care for Alzheimer's disease (AD) - early detection, diagnosis, monitoring of progression and response to treatment, within the context of the EU.

AD is a progressive, degenerative brain disease that impairs cognitive functions [1-3]. With the increase in life expectancy, the number of people that will develop AD and other

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types of dementia is steadily rising and this is creating a considerable financial burden on the health and social services across the world. There is no cure for AD 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 important for sufferers and carers to get maximum benefit, in terms of increased period of quality of life. At present, the delay between actual onset of AD and clinical diagnosis using the current clinical criteria may be 3-5 years [2], and by then irreversible cell damage will have already occurred. Personalization of care is important because of the heterogeneity of the disease and this offers the potential to plan and optimize treatment for the individual.

A subproject within the EU-funded project, BIOPATTERN [4], is addressing the challenges of personalization of diagnosis and care for AD. BIOPATTERN introduced the concept of *bioprofile* which is a personal 'fingerprint' that fuses together a person's current and past medical history, biopatterns and prognosis.

From the perspective of AD, the long term goals are to develop, validate and integrate, seamlessly, AD-specific bioprofile tools and methods into national health care systems in Europe to allow clinicians, from anywhere and anytime, to routinely collect and analyse a citizen's bioprofile, and predict those who will develop AD, objectively diagnose AD early and accurately, quantify the severity of AD, plan treatment and monitor progression and response to treatment.

The paper provides highlights and insights into the following:

a) Requirements and challenges of personalised care for AD (including early detection, prediction of cognitive decline, monitoring of progression and response to treatment, planning of care and prevention of AD).
b) The characteristic features and requirements of bioprofiles within the context of AD
c) Techniques to enable the acquisition of useful parameters for inclusion in the bioprofile for AD.
d) The development of a grid-based prototype system to demonstrate the concepts of bioprofiling for AD and to understand the challenges of personalized care for AD within the EU setting.

1. Requirements and Challenges of Personalised eHealthcare for AD

1.1. The Need for Personalisation of Diagnosis and Care

Efforts are being made to develop new drugs and therapies to slow or even halt the progress of the disease, however there is, as yet, no cure. If these efforts are successful, the disease should be detected as early as possible for sufferers to get maximum benefit in terms of increased period of quality of life. According to recent brain imaging studies [2] the delay between actual onset of AD and clinical diagnosis using the current clinical criteria is 3-5 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 current clinical diagnosis is

that a significant amount of irreversible cell damage has already occurred by the time a diagnosis is made. For these reasons, the ability to predict cognitive decline and to detect the disease early are of utmost importance (prior to extensive and irreversible cell damage). Progress in this area therefore is preparatory to the development of neuroprotective treatments and may contribute directly to research in finding a cure for AD.

Personalisation of diagnosis and treatment is important because of the heterogeneity of the disease and differences in individual patients. For example, patients with mild cognitive impairment can follow significantly different clinical courses (some will go on to develop AD others will not, and patients with similar diagnosis may show different responses to treatment). Personalisation offers the potential to plan and optimise treatment and care by tailoring care to the needs of the individual [5].

1.2. Challenges of Personalisation

Thus, personalisation of care requires a reliable means and ability to:

- detect AD early
- predict cognitive decline
- monitor response to treatment
- plan care.

There is also a growing interest in finding ways to prevent AD (e.g. through identification and exploitation of risk factors).

1.2.1. Biomarkers for AD

To achieve the above, we need to find appropriate biomarkers of AD derived from biodata (e.g. genomics, neuroimaging and electrophysiology data).

Objective methods of assessing AD 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 may not always be available because of costs. 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. 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 patients. 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.

1.2.2. Creation an ICT-based Infrastructure to Support the Care for AD.

The benefits of personalisation can only be fully realised if healthcare and ICT resources are exploited (e.g. to provide access to relevant data, analysis algorithms, knowledge and expertise). Existing ICT technologies are inappropriate for this because of the difficulties in the use and management of heterogeneous IT resources at different centres and countries.

What is needed is an ICT knowledge infrastructure that integrates, seamlessly, AD-specific tools and methods into national health care systems in Europe to allow clinicians, from anywhere and anytime, to routinely collect and analyse a person's biorecords, and predict those who will develop AD, objectively diagnose AD early and accurately, quantify the severity of AD, plan treatment and monitor progression and response to treatment.

Potentially, grid can play an important role in this by allowing sharing of resources and expertise to improve the quality of care. A great of effort, resources and funding have been put into national, regional and international initiatives in developing healthgrid infrastructures, services and applications to support healthcare [7-11]. However, the challenge remains how to exploit grid technology for personalised care for AD.

2. Bioprofiles of AD

2.1. Biopatterns and Bioprofiles

The work on AD bioprofiling takes place within the BIOPATTERN project which was funded by the EU [4]. BIOPATTERN integrates the research efforts of 30 institutions from 11 countries across Europe to tackle and reduce fragmentation in the new field of biopattern and bioprofile analysis to underpin eHealthcare in the post genome era. It brings together leading researchers in medical informatics, bioinformatics and ICT from academia, the healthcare sector and industry in a new way, to harness expertise and information.

One of the results of this collaboration is a 20-year 'Roadmap' which will underpin the healthcare of the future. This revolves around the use of *biopatterns* and *bioprofiles.* A *biopattern* is the basic information (pattern) that provides clues about underlying clinical evidence for diagnosis and treatment of diseases. Typically, it is derived from specific data types, e.g. genomics information, imaging and vital life sign biosignals, such as the EEG. A bioprofile is a personal 'fingerprint' that fuses together a person's current and past medical history. Over time, snapshots of biopatterns can be used to identify trends. Thus, by combining data, analysis and predictions of disease susceptibility, healthcare can be personalised.

The Grand vision of the ambitious, groundbreaking project is to develop a pan-European, intelligent analysis of a citizen's bioprofile; to make analysis of this bioprofile remotely accessible to clinicians *and* patients, and to exploit it to combat major diseases by early diagnosis and treatments *specific* to each person.

BIOPATTERN proposes to provide novel computational intelligent techniques for biopattern analysis and a pan-European integrated, intelligent analysis of an individual's bioprofile. Information from distributed databases will be made available, securely, over the Internet to provide on-line algorithms, libraries and processing facilities for such analysis.

From healthcare perspectives, a bioprofile consists of a lifelong sequence of information (from "birth to death") which is of clinical relevance to an individual's health status, see Figure 1. Thus, a bioprofile goes well beyond the Electronic Health Record (EHR). In general, a bioprofile may include today's EHR as well as multimodal data, biomarkers, diagnosis, prognosis and other relevant information (e.g. lifestyle), whereas today's EHR is largely a record of a person's medical information, such as, medical history, and the outcome of examinations.

Over the past three years, we have developed advanced techniques for biopattern analysis to enable acquisition of useful parameters to include in the bioprofile, and prototype systems to demonstrate the concepts of bioprofiling to gain an insight into the barriers to the realisation of the grand vision in specific clinical areas (including Alzheimer's, early life, ovarian and breast cancer, and ocular melanoma), where a critical mass already exists. The prototype system includes the BIOPATTERN Grid [12, 13] and a grid-based framework for bioprofile analysis [14].

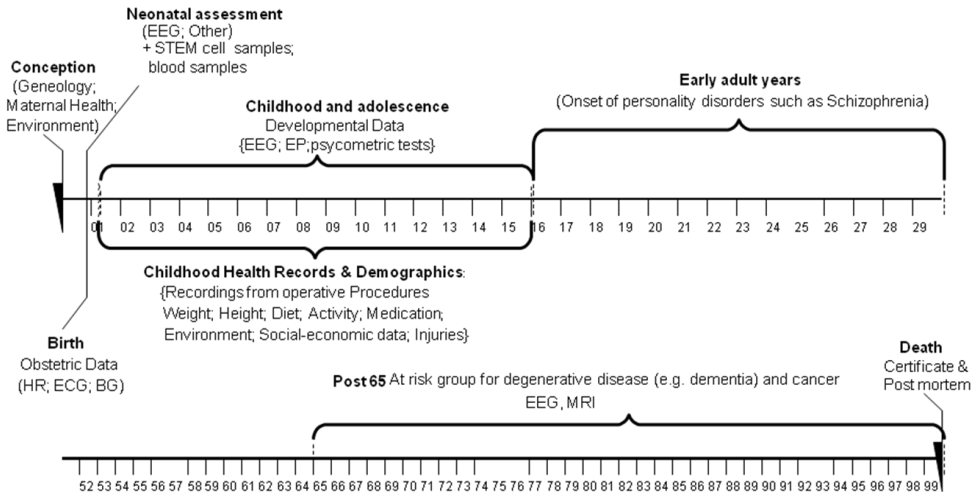

Figure 1. Concepts of bioprofiling from 'birth to death'

2.2. Acquisition of Biomarkers and Parameters to include in the Bioprofiles of AD

Finding suitable biomarkers of AD is crucial for successful bioprofiling as it provides the basis for early detection, monitoring of progression and response to treatment. This will help clinicians to predict cognitive decline, detect AD early, and predict response to treatment on an individual basis. It will enable them to plan, optimize and personalize therapy and monitor response to treatment.

Changes in certain biodata, such as the EEG and MRI, could be used to detect AD fairly early in the dementing process and the changes could be quantified as an index or marker.

Figure 2 illustrates the time-evolution of a hypothetical, subject-specific biomarker for AD. What we are looking for is a distinguishable change in the marker 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 biodata is used in the management and care of people with AD.

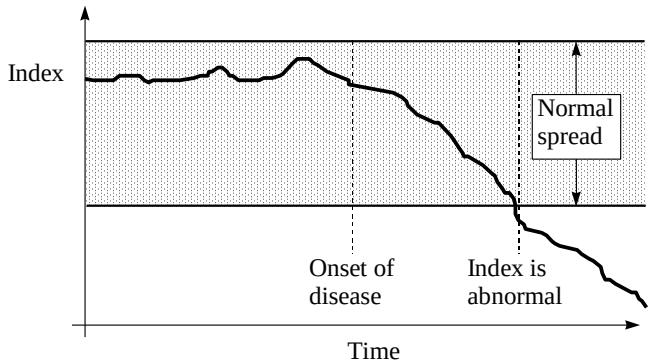

Figure 2. Variations of index over time

A great deal of efforts have gone into developing algorithms to extract biomarkers for subject-specific biopattern analysis from different types of biodata using a variety of techniques. Figure 3 illustrates the ideas that underlie the computation of EEG-based markers [15]. Some of the techniques are based on the assumption that the information processing activity in the brain is reflected in the electrical activity of the brain which is measured as EEG. Thus changes in the features of the EEG due to AD may be related to changes in the information content of the EEG. Our work has led to the development of

robust markers derived from non-linear analysis of the EEG [3, 15]. The markers can detect AD within the general at risk population with reasonable accuracy (specificity 99.9% and sensitivity 78%) [3]. This compares well with other studies, reported by the American Academy of Neurology which typically provide a sensitivity of 81% and specificity of 70%.

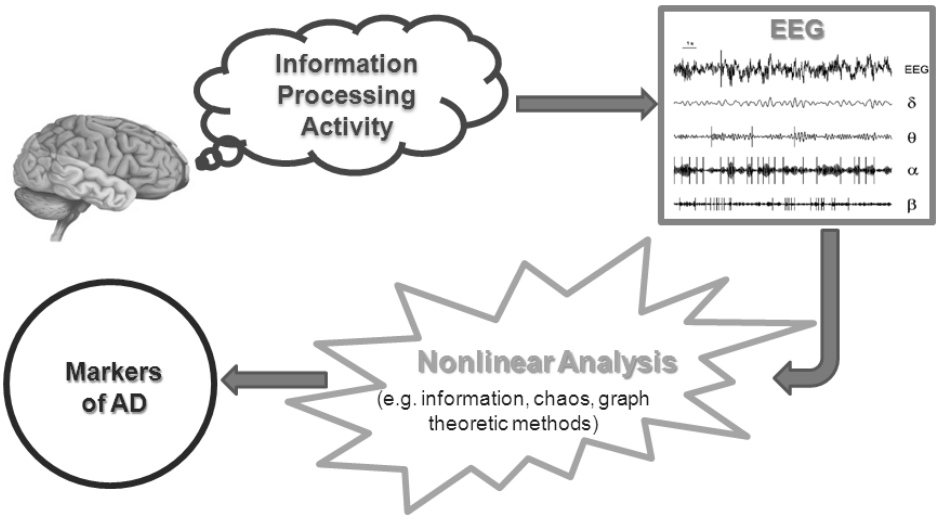

Figure 3. Nonlinear analysis of EEG to extract markers of AD

3. Grid-enabled framework for bioprofile analysis

As pointed out above, an important requirement for personalised e-healthcare for AD is to create an ICT knowledge infrastructure to integrate, seamlessly, AD-specific bioprofile tools and methods into national health care systems in Europe to allow clinicians, from anywhere and anytime, to routinely collect and analyse a citizen's bioprofile, and predict those who will develop AD, objectively diagnose AD early and accurately, quantify the severity of AD, plan treatment and monitor progression and response to treatment.

Why Grid? Conceptually, the collection and use of the bioprofile takes place from "birth to death" (see Figure 1). Thus, bioprofile databases will be geographically distributed and may be located in different countries and centres (Figure 4 illustrates this point using a hypothetical subject, Mike). The need to collaborate with partners across countries also requires sharing of resources (e.g. expertise, data and software/ algorithms).

Clearly, bioprofile databases will be huge and dynamic (because of the need to collect serial data - MRI, EEG, genomics, etc, and for regular update of data). In addition collection and use of bioprofiles requires:

- Online access to computational intelligent methods to process and analyse data, anytime and from anywhere.
- Online access to computational resources for intelligent analysis which is computationally intensive (e.g. for processing, analysis and interpretation of multi-model biomedical data; visualisation of large biomedical data sets, and integration and fusion of data).

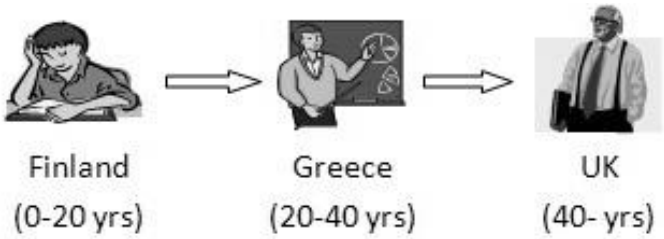

Figure 4. The figure illustrates the life journey of Mike, a fictitious individual, who at 60 is showing the earliest signs of dementia. Grid provides seamless access to computational resources and the distributed databases in different countries.

Existing ICT technologies are inappropriate for bioprofiling because of the difficulties in the use and management of heterogeneous IT resources at different bioprofile centres. Grid is particularly suited to this because it allows sharing of resources and expertise (e.g. to provide access to relevant data, analysis algorithms, knowledge and expertise).

We have developed a prototype test bed, the BIOPATTERN Grid, and used it to illustrate the concepts of bioprofiling and how grid computing could be used to support individualization of healthcare [12, 13]. A scenario that is used as vehicle in the development is the provision of support for early diagnosis and care for dementia. Appropriate biomarkers of dementia are computed continually during health checks and, over time, form part of the subject's bioprofile. For diagnosis, a clinician (anywhere in Europe) supplies the necessary information, an appropriate set of algorithms is then used to analyse the bioprofile to look for onset of disease. Grid provides seamless access to computational resources and the distributed databases in different countries. A library of software tools for extracting markers has been integrated into the BIOPATTERN Grid and is being continually extended and enhanced as more analysis tools are developed.

The architecture of the BIOPATTERN Grid is depicted in Figure 5. Figure 6 shows how five partners who contributed to the work are connected. We have also developed a framework for bioprofile analysis over grid to support individualised healthcare [14]. Bioprofile analysis is a critical part of bioprofiling. Without analysis, it will not be possible to extract relevant markers for diagnosis and to assess an individual's health status. The framework provides a basis for a "grid-based" solution to the challenge of bioprofiling.

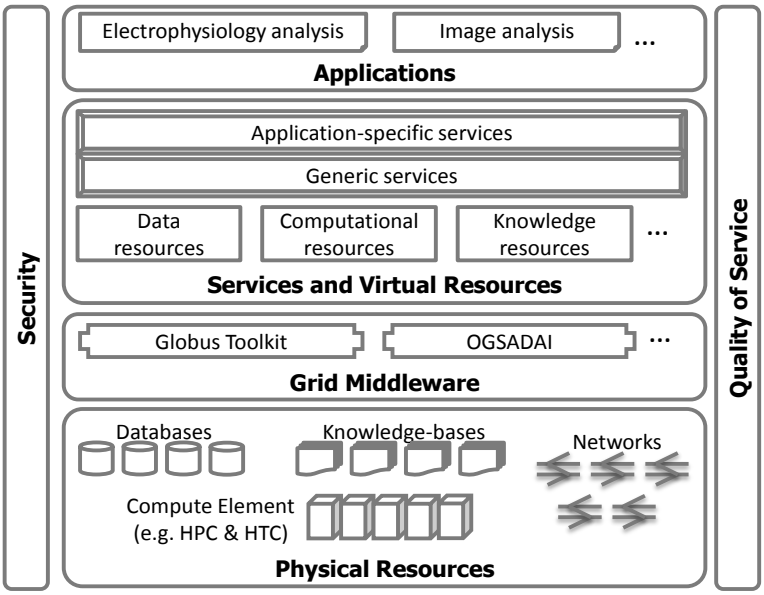

Figure 5. Architecture of the BIOPATTERN Grid

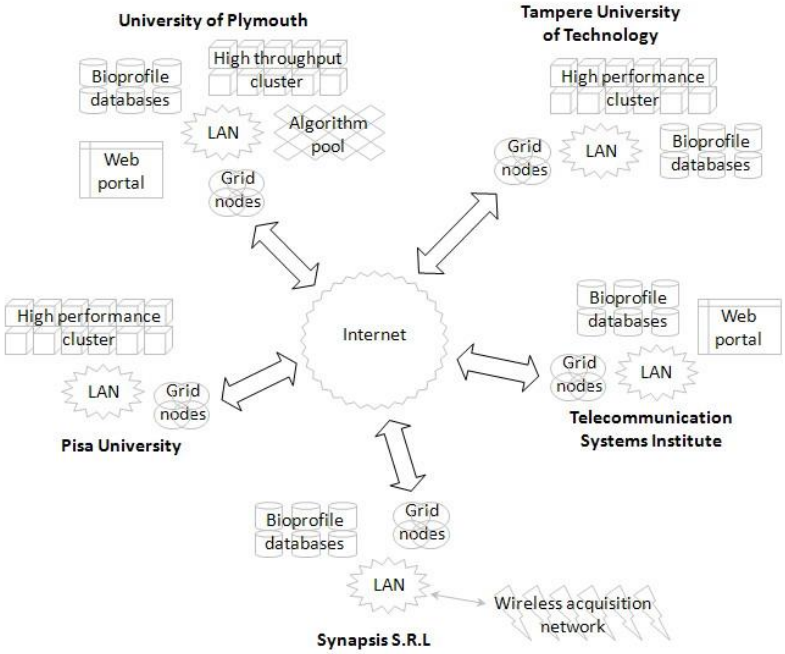

Figure 6. The prototype of the BIOPATTERN Grid

In addition to the framework for bioprofile analysis over grid and the grid test bed, we also developed a service model for bioprofile analysis over grid. An EEG analysis service model is used to demonstrate the utility and development of services to enable bioprofile analysis over grid. Figure 7 depicts example of screen shots from the use of test bed for EEG analysis.

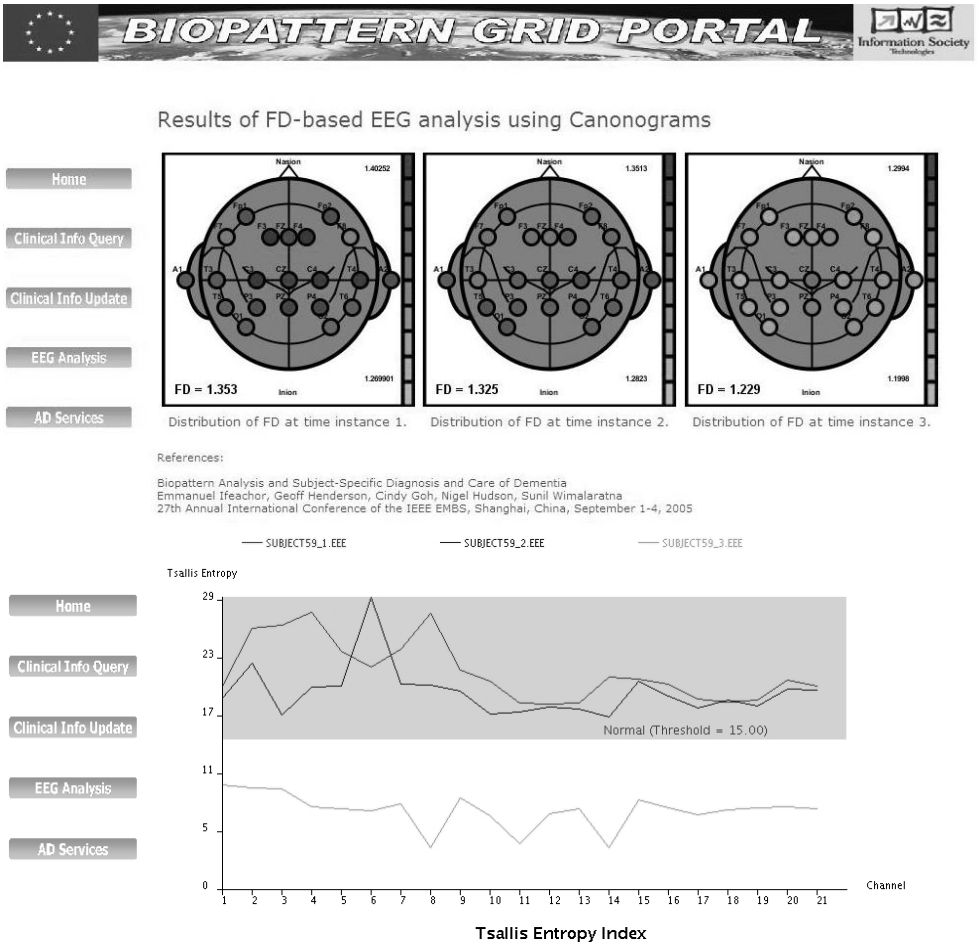

Figure 7. Screen shot of some results EEG analysis over Grid for AD assessment

4. Conclusions

We have developed a prototype grid-based system and a framework for bioprofile analysis and have used these to demonstrate the concepts of bioprofiling for personalised care for

AD. The system will be expanded to include more resources (e.g. online algorithms, computational resources and databases) and to link it with other larger grid systems to enhance its capability.

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