Bioprofiling over Grid for eHealthcare

L. SUN [a], P. HU [a], C. GOH [a], B. HAMADICHAREF [a], E. IFEACHOR [a,1], I.BARBOUNAKIS [b], M. ZERVAKIS [b], N. NURMINEN [c], A. VARRI [c], R. FONTANELLI [d] , S. Di BONA [d], D. GUERRI [d], S. La MANNA[d], K. CERBIONI [e], E. PALANCA[e] and A. STARITA[e]

[a]School of Computing, Communications and Electronics, University of Plymouth, UK
[b]Telecommunication System Institute, Technical University of Crete, Greece
[c]Institute of Signal Processing, Tampere University of Technology, Finland
[d]Synapsis S.r.l. in Computer Science, Italy
[e]Computer Science Department, University of Pisa, Italy

Abstract. A trend in modern medicine is towards individualization of healthcare and, potentially, grid computing can play an important role in this by allowing sharing of resources and expertise to improve the quality of care. In this paper, we present a new test bed, the BIOPATTERN Grid, which aims to fulfil this role in the long term. The main objectives in this paper are 1) to report the development of the BIOPATTERN Grid, for biopattern analysis and bioprofiling in support of individualization of healthcare. The BIOPATTERN Grid is designed to facilitate secure and seamless sharing of geographically distributed bioprofile databases and to support the analysis of bioprofiles to combat major diseases such as brain diseases and cancer within a major EU project, BIOPATTERN (www.biopattern.org); 2) to illustrate how the BIOPATTERN Grid could be used for biopattern analysis and bioprofiling for early detection of dementia and for brain injury assessment on an individual basis. We highlight important issues that would arise from the mobility of citizens in the EU, such as those associated with access to medical data, ethical and security; and 3) to describe two grid services which aim to integrate BIOPATTERN Grid with existing grid projects on crawling service and remote data acquisition which is necessary to underpin the use of the test bed for biopattern analysis and bioprofiling.

Keywords. HealthGrid, Healthcare, Grid computing, Crawling service, Remote data acquisition, Dementia, Brain Injury, Bioprofiling, Biopattern analysis.

1. Introduction

There is a growing interest in the application of grid computing to healthcare to support data-, computation- and/or knowledge-intensive tasks in areas such as diagnosis, prognosis, disease prediction and drug discovery. Often, this involves the acquisition, analysis and visualisation of biomedical data (medical informatics + bioinformatics). Examples of healthcare applications include distributed mammography data retrieval and processing (e.g. the MammoGrid [1] and eDiaMoND [2] projects), and multi-centre neuro-imaging (e.g. BIRN [3]). There is a trend in modern medicine towards

[1] Corresponding Author: Professor Emmanuel Ifeachor, School of Computing, Communications and Electronics, University of Plymouth, Plymouth PL4 8AA, UK; E-mail: E.Ifeachor@plymouth.ac.uk.

individualization of healthcare and, potentially, grid computing can also play a role in this by allowing sharing of resources and expertise to improve the quality of care. In this paper, we report efforts to exploit grid computing to support individualization of healthcare to combat major diseases such as brain diseases within a major EU-funded, Network of Excellence (NoE) project, BIOPATTERN (www.biopattern.org). The Grand Vision of the project is to develop a pan-European, coherent and intelligent analysis of a citizen's bioprofile; to make the analysis of this bioprofile remotely accessible to patients and clinicians; and to exploit bioprofiles to combat major diseases such as cancer and brain diseases. 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 and proteomic information and biosignals, such as the electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI). 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 predictions of possible susceptibility to diseases. It will drive individualization of care. The project aims to make information from distributed databases available in a secure way over the Internet, and provide on-line algorithms, libraries and processing facilities, e.g. for intelligent remote diagnosis and consultation. Potentially, grid-enabled network can facilitate the seamless sharing and pervasive access to such distributed databases and for online bioprofile analysis and diagnosis.

The main objectives in this paper are 1) to report the development of a new Grid test bed, the BIOPATTERN Grid, for biopattern analysis and bioprofiling in support of individualization of healthcare. The BIOPATTERN Grid is designed to facilitate secure and seamless sharing of geographically distributed bioprofile databases and to support analysis of biopatterns and bioprofiles to combat major diseases such as brain diseases and cancer; 2) to illustrate how the BIOPATTERN Grid could be used for bioprofiling for early detection of dementia and for brain injury assessment on an individual basis. We highlight important issues that would arise from the mobility of citizens in the EU, such as those associated with access to medical data, ethical and security; 3) to describe some of the important services that are required to underpin the use of the test bed for biopattern analysis and bioprofiling, including *crawling* and *data acquisition.*

The remainder of the paper is organised as follows. In Section 2, the BIOPATTERN Grid architecture and prototype are described. In Section 3, two applications of the BIOPATTERN Grid in brain diseases (for dementia and brain injuries) are presented. In Section 4, two specific grid services - crawling and remote data acquisition services are discussed. Section 5 concludes the paper.

2. BIOPATTERN Grid Architecture and Prototype

2.1. BIOPATTERN Grid Architecture

The architecture of BIOPATTERN Grid is divided in four layers as shown in Figure 1. The Grid Portal serves as an interface between an end user (e.g. a clinician or a researcher) and the BIOPATTERN Grid. At the client side, an end-user accesses the Grid Portal via a web browser. After user authentication (login/password), the end user can then make use of the services provided by the BIOPATTERN Grid. The Grid

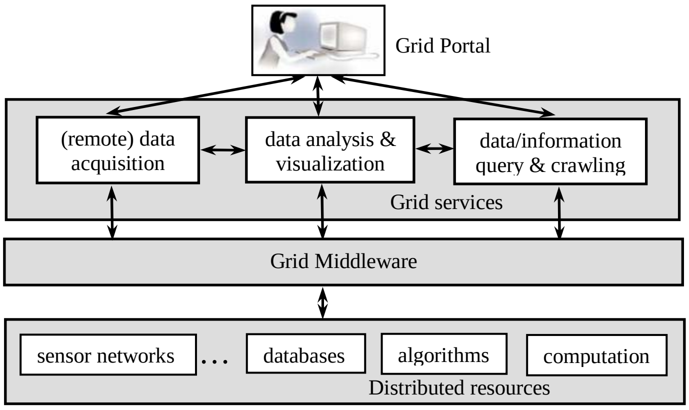

Figure 1. BIOPATTERN Grid Architecture

Portal sits in a web server with relevant components (e.g. databases and classes) and establishes connections between an end-user and the lower layer grid services.

The grid services layer provides services for data acquisition, data analysis & visualization, and data/information query and crawling. For data acquisition, a patient's clinical data, electrophysiological data (e.g. EEG), imaging data (e.g. MRI) and bioinformatics data (including biochemical and genomic data) can be either uploaded via a Grid Portal or transferred from remote data acquisition networks. The data is stored in distributed databases. For data analysis, different biodata analysis algorithms are stored in distributed algorithms pools. The analysis algorithms may be used to generate biomarkers to quantify disease severity and to support medical decision-making. The results of the analysis are displayed in a user-friendly manner via the Portal. The computational requirements for biodata analysis using complicated algorithms are met by High Performance Computing (HPC) or High Throughput Computing (HTC) resources. The data/information query services enable the user, for example, to query existing patient's information or to search medical information with the help of a crawling service.

The Grid middleware provides grid functionalities for security (authentication /authorization), resource management (e.g. resource allocation and job manager), information service (monitoring and discovery system for resource availability), data management (GridFTP and replica management) and data services support (e.g. Open Grid Service Architecture Data Access and Integration (OGSADAI)). The Globus Toolkit 4 (GT4) [4] is chosen to implement Grid middleware functions. Condor is used for job queuing, job scheduling and to provide high throughput computing. The bottom layer, the grid resource layer, contains computational resources, data resources (e.g. relational databases), and knowledge resources (e.g. software codes for computational intelligence algorithms) and networks (e.g. sensor networks for data acquisition).

2.2. BIOPATTERN Grid Prototype

The prototype BIOPATTERN Grid aims to provide a platform for clinicians and researchers within the BIOPATTERN Consortium to share information in distributed bioprofile databases and computational resources to facilitate the analysis, diagnosis and care for brain diseases and cancer. Currently, the prototype connects five sites –the

University of Plymouth (UOP), UK; the Telecommunication System Institute (TSI), Technical University of Crete, Greece; the University of Pisa (UNIPI), Italy; Synapsis S.r.l. (Synapsis), Italy, and Tampere University of Technology (TUT), Finland (see Figure 2). Each site may hold bioprofile databases, Grid nodes, Condor pool, high performance cluster, algorithms pool, Grid portal, or an interface to remote data acquisition networks. At present, the bioprofile databases contain basic patient's clinical information, EEG data (awake EEG at resting state) for dementia, and EEG data (MVEP) for brain injuries. The data are distributed into bioprofile databases at TUT, TSI, and/or UOP. The pool of algorithms, which is located at the UOP site, includes analysis algorithms for brain diseases, such as the Fractal Dimension (FD) and Independent Component Analysis (ICA) algorithms. In addition, UoP provides Grid nodes with Globus, a condor pool with 50 nodes and a web server to host the Grid Portal. Between UOP, TSI and TUT, we have developed two applications on the BIOPATTERN Grid for Brain diseases (for dementia and brain injury) (see Section 3). UNIPI and Synapsis are connected to the BIOPATTERN Grid via a Grid Node based on GT4. At UNIPI, the crawling services will be adapted to the BIOPATTERN Grid. Synapsis will provide an interface to the (remote) wireless acquisition network for automated remote data acquisition (see Section 4).

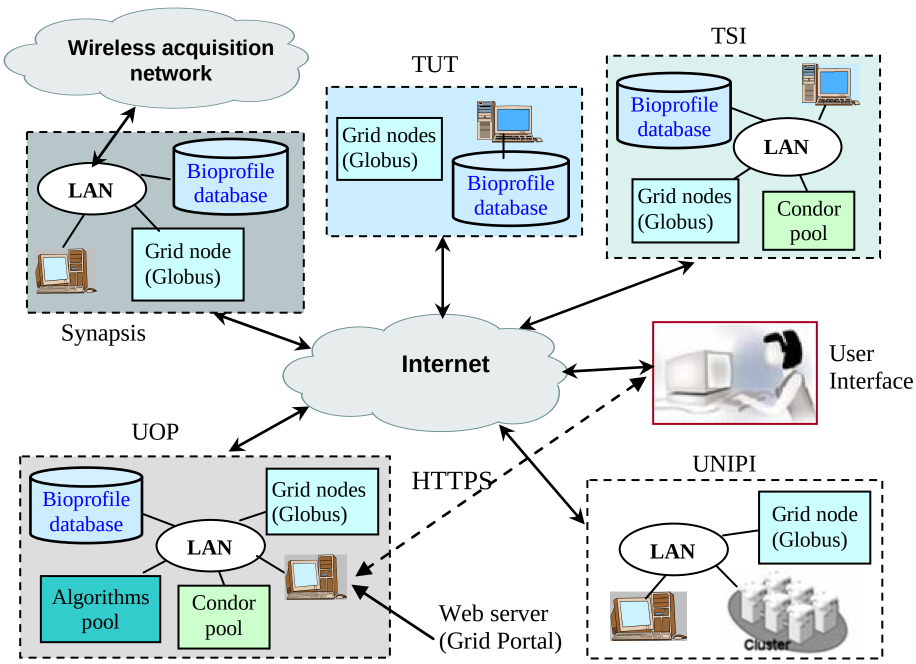

Figure 2. BIOPATTERN Grid Prototype

3. The use of the BIOPATTERN Grid to assess brain diseases

3.1. Bioprofiling over Grid for Early Detection of Dementia

Dementia is a neurodegenerative cognitive disorder that affects mainly elderly people [5]. At present, several acetyl cholinesterase inhibitors could be administered for dementia of the Alzheimer's type, but for maximum benefits early diagnosis is important. Currently several objective methods are available that may support early diagnosis of dementia. Amongst others, the EEG which measures electrical activities of the brain offers the potential for an acceptable and affordable method in the routine screening of dementia in the early stages. Using current clinical criteria, delay between the actual onset and clinical diagnosis of dementia is typically 3 to 5 years. A limitation of current objective methods is that diagnosis is largely based on group comparisons, i.e. attempting to separate individuals into groups (Normal, AD, Parkinson's, etc.). An alternative to this is individualized care through subject-specific biodata analysis. Such an approach would allow us, for example, to compute biomarkers which over time would represent the subjects 'bioprofile' for dementia, and to look for trends in the 'bioprofile' that arise over time to detect possible on-set of dementia [6].

Figure 3 illustrates the life of a fictitious individual called Mike who was born in France and lived in several countries before retiring to the U.K. At the age of 65, Mike is diagnosed with probable AD. To provide accurate diagnosis, his GP in UK requires his past and present medical information (bioprofiles) which could be located in databases in several different countries (e.g. UK and Italy). Additionally, information stored in the databases would be very large as these are Mike's lifetime medical records such as EEG, MRI, clinical information, etc. Furthermore, analysis of the data would usually entail the use of complex algorithms which could take several hours to complete and could be held at various centers. Using the grid, to provide seamless access to geographically distributed data and high computational resources for complex analysis and data storage, more accurate and efficient diagnosis can be achieved.

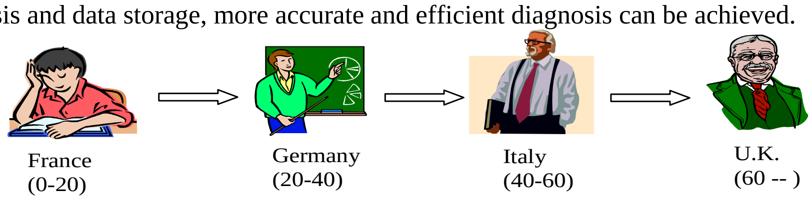

Figure 3. Mike's Life Itinerary

To illustrate the concept of Bioprofiling over Grid for early detection of dementia, a hypothetical patient pool consisting of 400 subjects, each with three EEG recordings was created. These data are hypothetical representation of recordings taken at three time instances akin to longitudinal studies carried out in reality. Each dataset consists of 21 channels of recording and is 1.3Mbytes. The recording duration is 4 minutes and the sampling rate is 128 Hz. The datasets are distributed to TSI, TUT and UOP sites. The FD analysis algorithm is used to compute the FD of each dataset.

Through the portal, a GP can select a patient, e.g. Mike, and the algorithm is used to perform the analysis. Upon submission, Mike's information, including his previous medical records which are at TSI and TUT is retrieved and analyzed. Results are then returned to the user in near-real-time. These can be visualized using, for example, the

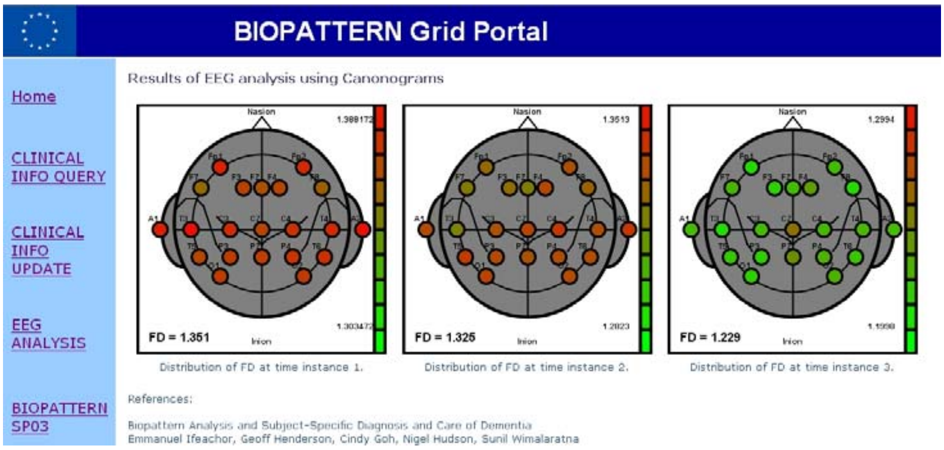

Figure 4. Canonograms Showing the Distribution of FD Values from EEG Analysis for Patient 'Mike'

canonograms (see Figure 4) where changes in the EEGs indicating Mike's conditions are shown. The canonograms (from left to right) show the FD value (or index) of the Mike's EEG taken at time instances of 1 (data at TSI), 2 (data at TUT) and 3 (data at UoP) respectively. The FD value for the left canonogram indicates Mike in a normal condition with high brain activity, whereas the FD value for the right canonogram indicates Mike in a probable Alzheimer Disease with low brain activity. The middle one shows the stage in between. The changes (or trends) in the FD values provide some indication on the disease progression. This can help clinicians to detect dementia at an early stage, to monitor its progression and response to treatment.

3.2. The use of the BIOPATTERN Grid to analyze MVEP for brain injuries

An important goal in this study is to generate electrophysiological markers which can be used to assess brain injuries on an individual basis by analysing evoked potentials (EPs) buried in raw EEG recordings. The idea is to use ICA methods to reveal single trial evoked potential activity of clinical interest and discard irrelevant components (e.g. those due to background EEG and artefacts). The generation of evoked potentials involve two phases – an encoding phase, during which each subject is asked to memorize 10 simple pictures each presented for 2 seconds. This is followed by a retrieval phase during which 20 pictures – 10 from the previous phase and 10 new - were presented and subjects were asked to indicate whether they have seen each image before or not. This bi-phase process is repeated three times. Finally 20 pictures from the two phases are presented to the subjects. There were a total of 30 trials per subject in the encoding phase. Figure 5 illustrates the overall structure of the ICA-LORETA (LOw Resolution Electromagnetic TomogrAphy) method [9][10] that is used to analyse the EEG and EPs. The extended version of the Infomax ICA algorithm was used [7] and ICA was applied on concatenated single trial recordings for each patient [8]. Then, the components that contributed strongly to the EP, judged from the average of all trials, are selected. Extracting components containing event-related activity simplifies the problem of source localization and allows more accurate estimation of the brain regions involved in task. We have used the spherical infinite homogenous conductor model [9]. To validate our conclusions, the methodology will need to be tested on a large number of cases. Such a scenario makes analysis in a conventional

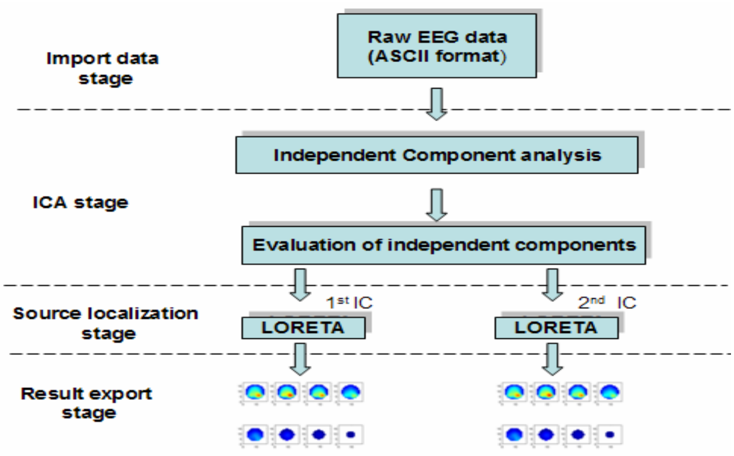

Figure 5. Schematic Representation of EEG Analysis

computer platform unrealistic. Thus, Grid computing seems to be the alternative solution to the provision of the required computing resources through a Virtual Organization. Data for such analysis are likely to be collected and stored at different centres. The plan is to store these in grid-enabled databases to facilitate remote access and to speed up analysis.

We have integrated an ICA-LORETA algorithm into the Grid algorithm pool (located at UOP). Via the Grid Portal, the algorithm can be selected to analyze the MVEP for brain injuries. This is implemented as Matlab scripts compiled and using the Matlab run-time library over the Grid nodes. Figure 6 shows an example of results of such analysis via the portal, with topography maps (only for the two first ICA components) of one normal patient (top) and one patient (bottom). The head model, which is shown, is assumed to be an 8cm sphere and is represented with 8 slices (the lower slice is the left and the higher is the right).

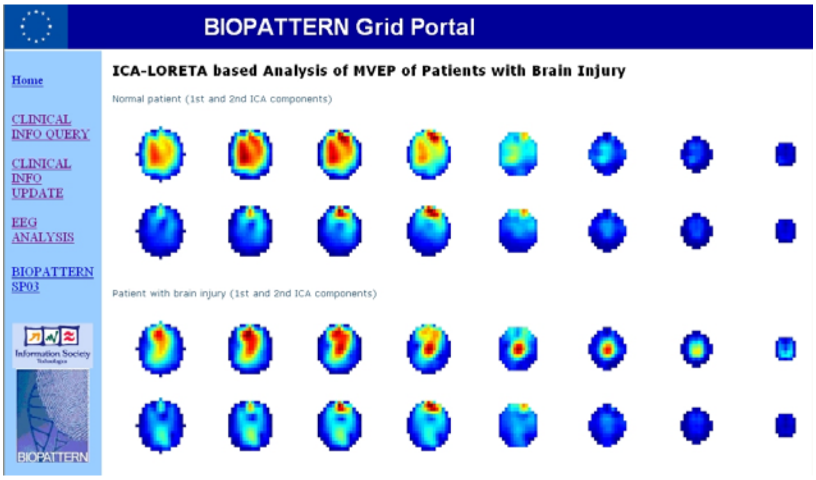

Figure 6. Topography Maps of Normal Subjects and Patients with Brain Injury

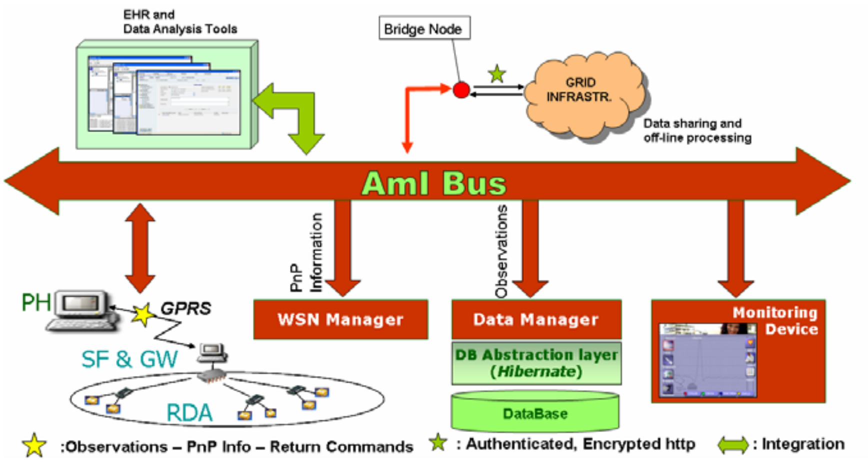

Figure 7. Architectural Overview of the AmI-GRID Platform

4. Services for the BIOPATTERN Grid

4.1. Remote Data Acquisition Services for BIOPATTERN Grid

An important service for the BIOPATTERN Grid is remote, automated data acquisition. The work described here is aimed at integrating the BIOPATTERN Grid and the AmI-GRID platform. The Ami-GRID, a complementary activity within the NoE, aims to provide a framework for automated data acquisition, management and exchange based on the Ambient Intelligence paradigm. The challenge is to effectively share and process medical data by exploiting the resources and the capabilities of both the AmI system and the GRID based infrastructure. The AmI system is composed of an integrated platform able to collect data acquired by Remote Data Acquisition systems (RDA), and to distribute data to registered devices (e.g. storage devices, analysis tools, etc.). The system allows not only automated acquisition and monitoring, but also storage of data in medical RDA environments and integration of related clinical information into the EHR (Electronic Health Record). The advantages of this heterogeneous platform are manifolds:

a) To acquire real-time data from patients that can be automatically monitored and processed by software tools specifically developed for this purpose;
b) To integrate data acquired from heterogeneous sources into a dedicated EHR;
c) To perform additional *on-line* and *off-line* processing on the information available (the GRID infrastructure guarantees the ubiquitous access, security, transparency, robustness, authentication, tracing, etc.).

As shown in Figure 7, the AmI system consists of environments permeated with non-invasive wireless sensors networks (WSN) implementing an intelligent RDA system, and a set of Monitoring Devices that are connected through a particular communication infrastructure which has a bus like topology: the AmI Bus. After a device has been connected to the bus, it will be able to publish an addressing scheme that enables all other devices to communicate with it. The devices can be subdivided

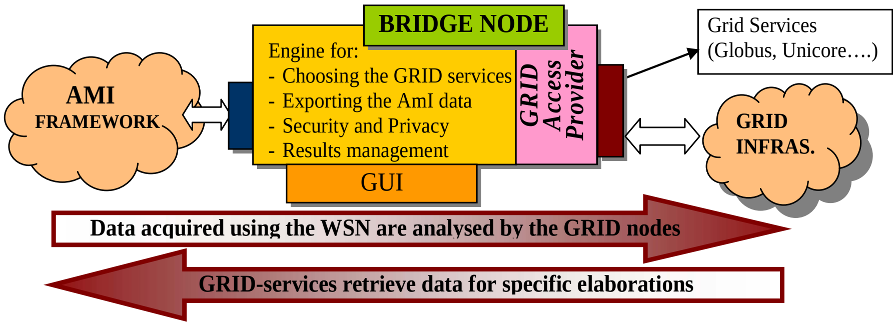

Figure 8. Architectural Overview of the *Bridge Node*

into Manager Devices and Client Devices. The Client devices are used to enable human operators to access the functionalities offered by the AmI system (e.g. monitoring devices responsible to notify alarms and to display the data produced by the RDA). The Manager Devices are in charge for managing AmI resources and processes (e.g. the Wireless Sensor Network Manager responsible to manage the addition, update and removal of wireless RDA elements). This view allows evolution from a database-centric perspective to a totally distributed architecture which provides abstraction, automatic composition, scalability and evolution (for more details see [11]).

The connection between the AmI platform and the BIOPATTERN GRID guarantees the sharing of the acquired data among a wide community of users, as well as the possibility to automatically process the new data by using a large spectrum of technologies. This way, it is possible for the GRID nodes to have a detailed view of both the AmI platform status and the available data, and possibly also to interact with the RDA system by using the adequate services provided by the platform itself. The interaction between the AmI platform and the GRID infrastructure is mediated by a *Bridge Node* responsible for the interaction with the GRID network, i.e. for requesting specific services on the acquired data (e.g. processing algorithms or simply storing services) and to provide the functionalities offered by the framework to the GRID community. This node will be also being responsible for issues such as security and privacy of data acquired through the RDA, thus allowing e.g. the anonymisation of personal information. The architecture of the *Bridge Node* is shown in Figure 8.

The workflow of this system can be seen from two different points of view: The AmI platform acquires data using the RDA system and exploits the services of the GRID infrastructure to perform analysis on the data; A node of the GRID infrastructure needs to find clinical data stored in the database of the AmI framework for specific elaborations (KDD, epidemiological studies etc). In the first case the Bridge Node is responsible for the interaction with the GRID middleware, and for the location and exploitation of the required services. In the second case, the AmI platform represents a special repository of data from which a large amount of information can be obtained (integration with EHR). In this case the GRID Middleware needs to interact with the AmI framework in order to verify the availability of data for the desired elaborations.

As discussed in Section 3, individualization of care through subject-specific analysis would significantly advance the early detection of brain disorders. In this context, the AmI framework will significantly enhance the possibility to personalise the diagnosis on the specific case by implementing a special environment in which patients can be monitored continuously over long periods, with the measured parameters measured tailored to individual subjects according to their “bioprofile”.

4.2. Crawling Services for BIOPATTERN Grid

A Distributed Focused Crawling surfs the Web and gathers documents on a specific topic. It can be used like a search engine to obtain more information faster, by narrowing its crawl to specific subjects. For a particular topic, the focused crawler results contain many more relevant specific documents than the collection returned by a generic search engine. An important advantage of a Web Crawling System deployed on a GRID stems from the fact that such a service would be offered to individuals that are entitled to access the highly distributed computational power of a GRID, eliminating the need of a central authority/repository such as a unique search engine. On the other hand it is foreseeable that individuals would employ a GRID crawler differently from general purpose search engines, using it to maintain a bookmark of resources on a persistent and topic-specific interest, rather than to answer sporadic queries. In the future, we expect that HPC Grid applications which exploit more complex parallelism patterns will be required to sustain an agreed QoS. To obtain this goal, applications will require to change dynamically the set of resources used for their execution; this requires a new generation of application launchers with the ability to interact with the application and the underlying Grid resources.

The Distributed Focused Crawling Service may be considered part of this scenario. It has been implemented using ASSIST, a HPC programming environment that provides language constructs to express adaptable and reconfigurable components [12]. The ASSIST programming environment provides a set of integrated tools to address the complexity of Grid-aware application development. Its aim is to offer to Grid programmers a component-oriented programming model, in order to support and enforce reuse of already developed code in other applications, as well as to enable full interoperability with existing software, both parallel and sequential, either available in source or in object form. The adopted system architecture model is Distributed and Object-Oriented, using as programming model a Multi-Tier implementation approach. The main core of the system is the second tier (Figure 9), it gets as input the query string data provided by the user and sets off a GRID distributed crawling search on the Web. The result of this search is a set of links relevant to the user’s query that are stored in the Cache module (representing the third tier of the architecture).

The computationally demanding part (e.g. graph algorithms) is implemented in C++ using the ASSIST framework and tools to distribute the elaboration in a high performance environment: when new resources are required in the Web exploration phase, the distributed modules can each query asynchronously a (potentially large) number of web services that either perform a fresh acquisition or retrieve a stored copy of the document. The Distributed Focused Crawling Service has been deployed and tested on a Fedora Core 1 cluster consists of 34 nodes connected via Gigabit Ethernet and tuned for high performance. For the Web exploration phase a variable number of web services, based on Axis 1.3, have been placed on the network. Axis is a reliable and stable open-source implementation of the SOAP protocol and it is the base on which to implement Java Web Services. The Distributed Focused Crawling Service has been developed under the Grid.it Project 2003-2005 [13], and its deployment on the BIOPATTERN GRID will provide a HPC application in order to assist the medical community to increase efficiency, accuracy and speed up of the information retrieval

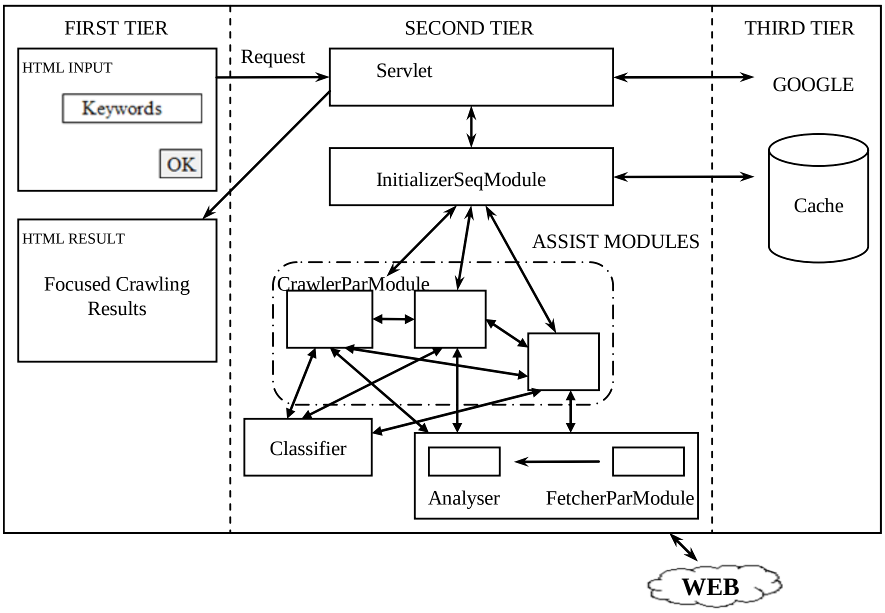

Figure 9. Architecture of the Crawling System

process [14]. Due to architectural issues (i.e. the parallel modules share memory usage), it is not possible to distribute the computation directly on the BIOPATTERN GRID nodes (UoP, TSI, Pisa, TUT and Syapsis) because the integration of the ASSIST framework on Globus Toolkit 4 is still under development by the Grid.it team.

The first step of the deployment will involve the transformation of the application into a Grid Service available through the Grid portal. In the first instance, the Grid Service will be localized in Pisa node (Figure 2) to exploit the connection with the clusters to execute the modules and provide the results. Subsequently other instances could be placed on other BIOPATTERN Grid nodes with compatible computational resources.

5. Conclusions

The BIOPATTERN Grid aims to provide a Grid-enabled network within the BIOPATTERN Consortium to facilitate secure and seamless sharing of bioprofile databases and to support the acquisition and analysis of bioprofiles to combat major diseases on an individual basis. This is an ongoing project and the results presented here are preliminary. In future, the Grid prototype will be extended to include more resources (e.g. more grid nodes, clinical data, algorithms and computing resources) and more applications and services. Due to the nature of healthcare, the BIOPATTERN Grid will need to address several issues before it can move from research prototype to actual clinical tool. These include regulatory, ethical, privacy and security, and quality of service issues. However, this should not prevent us from looking into the future possibilities of ehealthcare with Grid computing.

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