Legal approaches of the healthgrid technology

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CONTENT

1 FROM GRID TO HEALTHGRID: PROSPECTS AND REQUIREMENTS

1.1 RATIONALE

Evidence-based medicine requires medical decision making to be based on sound knowledge of the patient combined with peer-reviewed scientific evidence, rather than informed guesswork and personal skill. Furthermore, it is widely accepted that there is a pressing need to move away from manual management of patient information to digital records. Countries in the EU are investing heavily to establish electronic patient record systems. Technically the problem is one of standardisation and ensuring that systems are developed that interface through common 'languages' to enable the sharing of information. Technology to secure the information can also be complex and expensive to deploy. Moreover, access to many different sources of medical data, usually geographically distributed, and the availability of computer-based tools that can extract the knowledge from that data are key requirements for providing a standard healthcare provision of high quality.

Research projects in the integration of bio-medical knowledge, advances in imaging, development of new computational tools and the use of these technologies in diagnosis and treatment suggest that grid-based systems can make a significant contribution to this goal. Medical information is multimedial, large and distributed. The network structure of Healthcare provision centres and healthcare procedures are adequate for grid technologies. Mostly public but also private healthcare provision involves different centres which are in many cases connected at least at regional level. The benefits of improved access are raised to a new level, not merely enhanced by integration over a grid.

Grid technology has been identified as one of the key technologies to enable the 'European Research Area'. A major challenge is to take this technology out of the laboratory to the citizen, thus reaching far beyond eScience alone to eBusiness, eGovernment and eHealth. The benefits of grid technologies in areas involving long simulation processes covering a large set of experiments, have been clearly proven. For example, High Energy Physics (HEP) is one of the main application fields of grid technologies [**1**, **2**, **3**]. However, although explored in many projects, there are areas where the extension of the grid model is not trivial. Although grid technologies have clear potential for many applications (those demanding computing or storage power, dealing with geographically distributed information or requiring ubiquitous access), the take up of grid is slow. Reasons for this are the lack of adequate infrastructure, lack of users' confidence and, most frequently, the shortage of applications.

A Healthgrid should be an environment where data of medical interest can be stored, processed and made easily available to the different healthcare participants: physicians, healthcare centres and administrations, and of course citizens. If such an infrastructure were to offer all necessary guarantees in terms of security, respect for ethics and observance of regulations, it would allow the association of post-genomic information and medical data and open up the possibility for individualized healthcare.

While considering the deployment of life sciences applications, most present grid projects do not address the specific needs of an e-infrastructure for health, for instance the deployment of grid nodes in clinical centres and in healthcare administrations, the connection of individual physicians to the grid and the strict regulations ruling the access to personal data.

This white paper presents a survey of the Healthgrid technologies, describing the current status of grid and eHealth and analyzing mid-term developments and possibilities. There are numerous driving forces that are fostering the deployment and exploitation of the secure, pervasive, ubiquitous and transparent access to information and computing resources that grid technologies can provide.

Many technical problems arising in eHealth (standardization of data, federation of databases, content-based knowledge extraction, management of personal data…) can be solved with the use of grid technologies. However, there are many barriers that must be overcome. The paper considers the procedures from other grid disciplines such as High Energy Physics or numerical simulation and discusses the differences with respect Healthcare, with the intention of outlining a path forward towards the successful deployment of grid technologies for eHealth and ultimately the creation of a HealthGrid.

1.1.1 Structure of the Document and a Brief History

Over the last three to four years, a community of researchers working on Grid and High Performance Computing technologies started discussing the barriers and opportunities that grid technologies must face and exploit for the development of Health-related applications. This interest lead to the first Healthgrid conference, held in Lyon, France on January 16th-17th, 2003, with the focus of creating increased awareness about the possibilities and advantages linked to the deployment of grid technologies in health, ultimately targetting the creation of a European/international grid infrastructure for health.

The topics of this conference converged with the position of the eHealth division of the European Commission, whose mandate from the Lisbon Meeting was “To develop an intelligent environment that enables ubiquitous management of citizens’ health status, and to assist health professionals in coping with some major challenges, risk management and the integration into clinical practice of advances in health knowledge.” In this context "Health" involves not only clinical procedures but covers the whole range of information from molecular level (genetic and proteomic information) over cells and tissues, to the individual and finally the population level (social healthcare). Grid technology offers the opportunity to create a common working backbone for all different members of this large "Health family" and will hopefully lead to an increased awareness and interoperability among disciplines [20].

The first Healthgrid conference lead to the creation of the Healthgrid association, a non-profit research association legally located in France but formed from a wide community of European researchers and institutions sharing expertise in Health grids.

After the second Healthgrid conference , held in Clermont-Ferrand on January 29th-30th, 2004, the need for a “white paper” on the current status and prospective of Health grids was raised. 50 experts from different areas of grid technologies, eHealth applications and the medical world were invited to contribute to the preparation of this document.

The White Paper is structured into 9 chapters. This first chapter contains the objectives for the document and provides a view of the concepts, status and prospects for Health grid technologies. A revision of the status of the technology from both the scientific and industrial points of view is also given in this chapter. Impact and opportunities in business for the application of grid are described in depth in Chapter 2. Chapters 3 to 7 describe the specific issues related with the most promising and challenging applications in the health area (Medical Imaging and Medical Image Processing in Chapter 3, Therapy Planning and Computer Assisted Intervention in Chapter 4, Pharmaceutical and Rare Disease Research in Chapter 5, grids for Epidemiological studies in Chapter 6 and Genomic Medicine in Chapter 7). Finally, Chapters 8 and 9 raise the issues of the privacy of the information and legal and ethical issues, which are most important challenges in the adoption of grid technologies in Healthcare.

1.2 STRATEGIC ISSUES

1.2.1 Introduction to HealthGRIDs

1.2.1.1 The European Health Sector

eHealth deals with the use of Information and Communication Technologies (ICT) to develop an intelligent environment that enables ubiquitous management of citizens' health status, assists health professionals in coping with some major challenges or integrates the advances in health knowledge into clinical practice.

Many eHealth applications have been developed for dealing with information management and procedural challenges of current healthcare. eHealth is not only a good strategy for improving healthcare quality, but also a good business. The eHealth or Health Telematics sector is becoming the third industrial pillar of healthcare after the pharmaceutical and the medical imaging devices industries. It is estimated that the health expenditure on ICT systems and services would rise from 1% to 5% by 2010 [10], there are more than 1,500 health care sites on the Internet today and eHealth retailers predict revenues ranging from $22B to $348B (US) by the year 2004. Health care is the second most frequently searched topic on the Internet [11].

Service-based applications in eHealth are an important issue in general business. Application Service Provision (ASP) hosting, for example, makes it possible for service providers to specialize in installing and maintaining applications and services for their subscribing customers. ASP shifts the burden of hardware infrastructure to the providers and frees customers who only need an Internet browser to access the software. The general advantages of ASP, such as staff and resource specialization, broad marketability or scalable investment are complemented by the situation within the health sector: the Healthcare market is fragmented, as many people use proprietary systems; many processes are tedious and could be better streamlined; and healthcare organizations have comparatively old legacy computer systems and less ICT staff than other sectors. However, there are some disadvantages. The ownership of critical client functions is much more critical in the case of healthcare. Moreover, health records arise over long time-frames and require long-time storage and privacy of the information is an obligation by law. Furthermore, high service-level requirements are much more critical in healthcare, and medical information can require high bandwidth connections for achieving reasonable delay.

Electronic processing of medical data has opened many possibilities for improving medical tasks such as diagnosis, surgical planning or therapy, both in daily clinical practice and clinical research. However, several threads have appeared that can reduce the impact of HealthGRID technologies.

Security is the most important issue. Personal data (any piece of information in which its owner can be identified, either directly or in combination with information that is available or can be available) is confidential, so access to the information must be performed only by authorized and authenticated persons, and data must be encrypted to guarantee its confidentiality and integrity. Moreover, electronic archiving of personal data is strictly regulated by European and national laws. Pervasive Access and Fault Tolerance are other important aspects. Medical practice works around the clock, and thus requires "always-on" applications.

Medical information is huge and dispersed. Large resources are needed to store patient records comprising images, bio-signals, plain text, videos, photographs or other forms of computrised data. Moreover, healthcare provision structure is distributed and information is not consolidated among hospitals, primary care and casualty departments. Linking federated databases requires computing effort and complex structures. Medical Information is far from 'standard', since it is usually incompatible and standards are incomplete and not universally accepted. Moreover, even the use of a standard protocol does not imply that two pieces of information will be alike each other [Not sure

what's meant here…. perhaps: even the use of a standard protocol does not imply that independently derived data representing a specific piece of information will be identical ??] . Tuning and quality of equipment and expertise of the staff affects the final results.

Finally, linking databases with medical information is necessary, but not the final solution. Further processing of the information to extract knowledge is a must, since the dimension of medical information creates enormous difficulties for direct search. Data mining can provide the means to analyze relevant information and perform population-oriented health studies. Federating a database is not straightforward. Legal requirements on security must be undertaken, firewalls must be overcome, common ontology and metadata should be defined and Quality of Service and fault tolerance must be considered at global level.

Changes in medical procedures are slow. Medical staff will adopt newer technologies if the improvement for healthcare is proven, but self-confidence cannot be compromised. Medical ICT provides clear advantages but uptake is incremental.

The electronic processing of medical data is at different stages of evolution. Hospital Information Systems are widely used for patient hospitalisation management. Laboratory and Image Diagnosis departments have an important degree of electronic management of patient data. The adoption of these technologies in Primary Care is less advanced. However, the main challenge is the so-called Electronic Patient Record. The Electronic Patient Record comprises the coherent access and management of the complete patient information of an individual or a population. There is a great deal of effort alredy invested to achieve this aim, including on standardisation.

In the medium-term, it is reasonable to expect that most of the services in the healthcare will use computer-based resources to store, process and share patient information. Technologies are converging to a mature status and high-bandwidth communication networks are being deployed among healthcare centres throughout Europe Infrastructure in recently expanded EU countries may be several years behind, progression is expected to be quicker than in the rest of the EU countries). Thus, requirements for computer resources to be efficiently and securely processing and storing medical data will increase. A key enabling technology is the Grid.

1.2.1.2 Introduction to GRID

Grid computing aims at the provision of a global ICT infrastructure that will enable a coordinated, flexible, and secure sharing of diverse resources, including computers, applications, data, storage, networks, and scientific instruments across dynamic and geographically dispersed organizations and communities (Virtual Organizations or VO). Grid technologies promise to change the way organizations tackle complex problems by offering unprecedented opportunities for resource sharing and collaboration. Just as the World Wide Web transformed the way we exchange information, the grid concept takes parallel and distributed computing to the next level, providing a unified, resilient, and transparent infrastructure, available on demand, in order to solve increasingly complex problems.

Grids might be classified into Computational Grids, Data/Information/Knowledge Grids, and Collaborative Grids. The goal of a Computational Grid is to create a virtual supercomputer, which dynamically aggregates the power of a large number of individual computers in order to provide a platform for advanced high-performance and/or high-throughput applications that could not be tackled by a single system. Data Grids, on the other hand, focus on the sharing of vast quantities of data. Information and Knowledge Grids extend the capabilities of Data Grids by providing support for data categorization, information discovery, ontologies, and knowledge sharing and reuse. The Grid-enabled ASP approach (ASP for eHealth was discussed in Section1.2.1.1) can combine aspects from both of these types of Grids to provide appropriate services to users. Collaborative Grids establish a virtual

environment, which enables geographically dispersed individuals or groups of people to cooperate, as they pursue common goals. Collaborative Grid technologies also enable the realization of virtual laboratories or the remote control and management of equipment, sensors, and instruments.

From the original experiments investigating possibilities offered by broadband networks, Grid technologies have entered into a phase where production capabilities are available, e.g. NASA's Information Power Grid, CERN's DataGrid, or NSF's TeraGrid, to name a few. However, the vision of large scale resource sharing has not yet become a reality in many areas. This can be attributed mainly to the lack of commonly accepted standards, as well as to the diversity and fragmentation of available Grid middleware, tools and services. The Global Grid Forum (GGF), with participants from industry, research, and academia is the main body driving global standardization efforts for Grid services, protocols, and interfaces.

According to a recent survey of twenty European Grid projects, the most widely used middleware is the Globus toolkit followed by Unicore. Over the last two years, however, the Globus toolkit, which has been originally designed for the needs of HPC resource sharing in the academic community, has undergone a significant shift towards the adoption of a service-oriented paradigm, and the increasing support for and utilization of commercial Web Services technologies. The Open Grid Services Architecture (OGSA) was a first effort in bringing Grid technologies and Web Services together. The recent announcement of GGF to base the implementation of OGSA on the forthcoming Web Services Resource Framework (WSRF), currently standardized by OASIS, is a further significant step in this direction and will allow the utilization of standard Web Services technologies, which enjoy large scale industry support, for Grid computing.

Future developments of Grid technologies will be characterized by a full adoption of the service-oriented paradigm and Web Services technologies, a complete virtualization of resources and services, and the increased utilization of semantic information and ontologies (cf. Semantic Grid). Significant efforts will have to be undertaken in order to provide appropriate high-level tools and environments that hide the complexity and reduce the costs of Grid application development. The availability and adoption of advanced security standards, support for Quality of Service and the establishment of associated Grid business models and processes, will be pre-requisites for large scale adoption of grid technologies.

1.2.1.3 Healthgrids

Health grids are Grid infrastructures comprising applications, services or middleware components that deal with the specific problems arising in the processing of medical data. Resources in health grids are databases, computing power, medical expertise and even medical devices. Health grids are thus closely related to eHealth. Although the ultimate goal for eHealth in Europe would be the creation of a single Health Grid, i.e. a Grid comprising all eHealth resources, naturally including security and authorisation features to handle subsidiarity of independent nodes of the HeathGrid, the development path will mostly likely include a set of specific Health grids with progressive inter-grid interaction/interoperational capabilities.

The future [13] evolution of grid technologies addresses most precisely problems that are very sensitive to Healthcare. The majority of requirements of health ICT can be, or will be able to be, solved using grid technologies. Needs in ICT healthcare are oriented to improve individualized healthcare provision and analysis techniques in epidemiology. Needs in individualized healthcare are oriented to the integrated access to patient data, the availability of more advanced computer-aided diagnosis and the possibilities of personalized therapy. From the epidemiology point of view, relevant needs are on the extraction of knowledge from widespread databases and the availability of tools for easing the development of more effective medical treatments. Health grid applications are oriented to

both the individualised healthcare and the epidemiology analysis. Individualised healthcare is improved by the efficient and secure combination of the widespread personal clinical information and the availability of advanced services for diagnostic and therapy. The epidemiology Health grids combine the information from a wide population to extract the knowledge that can lead to the discovery of new correlations between symptoms, diseases, genetic features or any other clinical data.

The following issues are identified as key features of Health Grids:

- Health grids are more closely related to data, but many hospitals are reluctant to let the information flow outside the hospital bounds. For a large-scale deployment of Health grids, and thus for opening an attractive business, it is important to leverage security up to a trustworthy level of confidence that could release a generalized access to data from the outside (see also below). Although data storage is a responsibility for hospitals, many business opportunities can arise from data sharing and processing applications. Federation of databases requires computing effort and complex structures.
- Security in grid infrastructures is sufficient for research, but it must be improved in the future to ensure privacy of data. Encrypted transmission and storage is not sufficient, integrity of data and automatic pseudo-anonymisation must be ensured to guarantee that data is complete and reliable and privacy leakages can not appear due to unattended use of the resources.
- Robustness and Fault Tolerance of grids fits very well to the needs for ‘always on’ medical applications. Grid technologies can ease the access to replicated resources and information, just requiring the user to have a permanent Internet connection.
- Finally, flexibility is needed for the control of VOs at a large level. The management of resources should be more precise and dynamic, depending on many criteria such as urgency, users’ authorization or other administrative policies.

The current situation of grid exploitation in health is much more in the development field than on the side of the practitioners. Most of the grid applications for health follow the classic high-throughput approach. Simulation of numerical models for the behaviour of the organs obtained from patient’s data [14, 15], provide information for improving the knowledge of diseases or the design of medical devices. Patient-customised approaches can be found at research level in areas such as radiotheraphy, cranio-facial surgery or neurosurgery.

Other areas of application deal with large-sized information processing, such as medical imaging. Breast cancer imaging has been the focus of several successful grid projects [16, 17] and eHealth projects suitable to migrate to grid [18]. The efforts have been concentrated on federating and sharing the data and the implementation of semi-automatic processing tools that could improve the specificity and sensibility of breast cancer screening programs. Many efforts have been invested to reduce the information needed to be exchanged and to protect privacy of the information.

Person-centric grid for health approaches are also explored [19]. The main aim of this approach is to make the information available to the whole health community (patient, relatives, physicians, nursery...), considering access rights and language limitations.

Bioinformatics is the area where grid technologies are more straightforwardly introduced. Bioinformatics is the study of the contents and information flow in biological process and systems. The main challenge faced by bioinformatics is the development and maintenance of an infrastructure for the storage, access, transfer and simulation of biomedical information and processes. The maturity of genetics and proteomics opens a door to the problem for decoding the functions of genes, in order to relate them with the fundamental biologic problems. Structural genomics also requires the solution of the problem of efficiently determining the 3D structure of biological macro-molecules in order to

know its function better. Current efforts on biocomputation [19.A] are coherent with the aims of grid technologies. Efforts on the integration of clinical and genetic distributed information and the development of standard vocabularies ease sharing data and resources.

1.3 DEFICITS, OPPORTUNITIES AND REQUIREMENTS FOR INDUSTRY

1.3.1 The pharmaceutical Industry

The convergence of biotechnology and ICT are providing modern drug development mechanisms, but make pharmaceutical industry require enormous amounts of computing capacity for modelling interactions of drugs with receptors, and thus deciding which should be synthesized and tested. The increase on investments in modelling, discovery and testing enabled the development of new techniques providing more effective drugs.

Drugs that come to market by today are the results of several years of research. There is a need of accelerating the time to market for the new drugs, and this can be done by increasing the number of calculations processed for the docking analysis. There are models which with low calculations can discard ligands, and select those which worth a rigorous analysis. There are also constraints which may also be considered for creating more complex and predictive models of drug responses. These calculations need huge amounts of computing resources, and so it is needed to create a reliable environment for fast and large scale analysis.

The results of the tests and the virtual compounds produce a large amount of information which is hard to produce both in terms of time and cost. These results must be stored for further analysis and usage, creating the need mechanisms to share securely and privately the information among federated databases.

That sharing of results and virtual compounds is a field which may also be boosted, because notwithstanding the great amounts of data available and generated, there are no immediate ways for sharing and making full profit of them. The collaboration between scientists and researches from the industry will be crucial for the success of the pharmaceutical industry.

In fact, there is an overload of information, but there is a lack of interoperability between different applications and data sources. There are tools which neither can handle the results in an effective way nor can extract enough knowledge. This means that there is a lot of wasted information and unused results. The information is also being wasted in means that it could be shared with other scientists or enterprises, establishing other ways of commerce than drugs themselves.

The next step in drug development is to integrate phenotypes with genotypes and environmental factors, for making more personalized drugs and moving to an on-demand analysis, indeed, requires more resources and tools.

1.3.2 Medical Information Technologies Industry

Most important challenge in Medical Information Technologies is to reach the maximum degree of interoperability, seamless access and process of distributed electronic medical information. This challenge, based on the electronic patient record requires the interaction of industry, research and standardisation bodies.

These aims are not uniquely achievable by the integration of distributed databases. Firstly, not all the information is comparable, not only in terms of format, but also due to the different procedures, devices, human intervention or other factors. Federation of data must be performed even at semantic level, guaranteeing the interoperability. Secondly, much medical information is not currently processed electronically. Vital signs, perception tests, laboratory analysis are usually captured, even in

digital, but not stored for electronic processing. Interfaces for the equipment and formats for the storage are being agreed and standardised, but take-up is slow.

The integration of all the information will require increasing the resources for storage and processing, extending the possibilities of clinical institutions which surely will externalize computing services. Interoperability among devices will be a must. New services will be available on top of the networks as clinical aid applications, such as computer aided diagnosis, image processing, vital sign feature extraction, clinical output evaluation or even simulation.

1.4 DEFICITS, OPPORTUNITIES AND REQUIREMENTS FOR HEALTHCARE AND MEDICAL RESEARCH

1.4.1 Medical information processing

Over the past decade there have been several attempts to rethink the basic strategies and scope of Medical Informatics (MI) and Information Technologies in Biomedicine (ITB), while a debate about the nature, goals, and scientific character of MI continues. The ultimate goal of MI and ITB is to support the continuity of individualized health care spanning from prevention to rehabilitation. Research and development in MI and ITB has been supported by the European Union for the past 15 years. The results and impact of MI and ITB are slowly being recognized by researchers, health professionals, patients, and other participants in health care. However, integration of informatics and technology tools in clinical practice is progressing slower than expected, and the communication gap between clinicians and informaticians is still present.

The difficulties in widely implementing research results have been discussed extensively in recent years. Many factors could be mentioned related to both research and implementation difficulties, among which are the intrinsic difficulties of medicine, such as the complexity of information and organization, human factors, diverse cultures related financial and industrial issues, and others. Very often, specific algorithms have been developed, however applying efficiently to a very narrow range of specific cases, without extended validation. A wide MI and ITB platform, enabling interconnection and integration of resources, while supporting evidence-based medicine and validation of research results, would thus contribute to the acceptance of technological developments in the medical world. In the field of biomedical information processing and diagnosis, there is a huge amount of knowledge, however fragmented and spread in different and heterogeneous sources. A key point in MI and ITB is the management of medical information, and the efficient and quality certification of information and knowledge flow between all the players involved in the health delivery process. Previously obtained knowledge has to be captured and organized in a structured form in order to be retrieved in a context organized manner, thus contributing to educational and research purposes, and simultaneously feeding new healthcare diagnoses and the generation of new medical knowledge.

The basic strategies and scope of MI and ITB has also been reconsidered with regards to its relationship with Bioinformatics (BI). Both disciplines envision the development of novel diagnostic, therapeutic, and management tools, and products for patient care, having as an ultimate goal the continuity and individualization of health care as well as the unobtrusive and ubiquitous access to health services by the citizen. A combination of the expertise of MI and ITB in developing clinical applications and the focused principles that have guided BI could create a synergy between these areas of application, extending beyond merely applying the current activities of the MI to BI disciplines. Such an interaction between MI, ITB and BI leading to clinical applications combining both domains (e.g., collaborating in the area of functional genomics) could have a great influence on future health research. A potential for collaboration between the two disciplines could involve topics such as the understanding of molecular causes of diseases, the efficient disease management of chronically ill patients and the integration of clinical and genetic data. An interesting perspective is the combination

of the expertise in pervasive computing, facilitating the transmission and collection of biological data on a real-time basis outside a clinical setting, with the biomarkers and other ongoing findings of BI, resulting in a new phase for home care systems.

Concluding, there is an emerging need for exchange, synthesis and ethically-sound application of knowledge - within a complex system of interactions among researchers and users, in an interdisciplinary environment - to accelerate the capture of the benefits of research through improved health, more effective services and products, and a strengthened health care system. New services and ways of interaction and collaboration among diverse systems/actors have to be defined taking into account the capability of recording multi-channel data from a lot of micro and nano sensors, and the ability of the modern telecommunication systems to accommodate flow of multimedia information between the citizens wherever they are and the points of health services delivery. These requirements justify the applicability of GRID technologies, which provide the functional and architectural framework facilitating these extensions towards the aforementioned synergy concepts, and addressing the underlying ethical and privacy issues.

1.4.2 Medical computing

The research in the physics of the biomedical human processes has evolved very much recently. The consolidation of accurate and complete simulation tools for many engineering processes have contributed to the development of biomedical models of the structural dynamics, fluid dynamics, chemical processes or the electric potential propagation which describe with high degree of accuracy the physics of many organs and tissues.

Many examples can be found. Computational Fluid Dynamics (CFD) has been applied to the modelling and simulation of blood circulation in vascular models, mainly of aorta and heart area [2], and on the simulation of drug delivery in the respiratory system [15]. Simulation of electric potential propagation in cardiac tissues is of great interest for improving drug design, therapy in arrhythmia or the development of better pacemakers. Muscle-skeleton simulation is used in combination of crash test simulation codes to analyse risks of fractures in osteoporosis. Elastic deformation is applied on the simulation of surgery procedures, such as minimally invasive surgery or maxillo-facial surgery.

All these models are generally applied to restricted small areas or do not reach the desired accuracy due to the large memory requirements that fine meshing requires. Moreover, the complexity of human biomedical models lies on the high degree of coupling among the chemical, structural, magnetic and electric processes. This complexity requires the improvement of the biomedical models and the availability of an unprecedented huge amount of computing and memory resources.

Thus, the evolution towards the “virtual human” model is the long-term aim of biomedical computing. Tackling such problem requires the close cooperation of many entities, sharing computing resources, models and data. Accurate medical models are not freely available, and usually represent the most valuable capital of a research centres. Means for cooperating without compromising Intellectual Property Rights (IPR) are necessary.

Accurate and complex organ simulation is a challenge for the research, but an excellent opportunity for the medical industry, which can reduce strongly the economic, social and ethical costs of in-vivo simulation substituting it by ‘in-silico’ simulation.

1.4.3 Genomics

1.4.3.1 Technological status of Genomic Research

Biomedical research is currently facing a historical change in the perspectives and modality of gathering information about gene functions and biological processes. Genome-wide sequencing

projects have been completed for many organisms, including *Home Sapiens* [4] and *Mus Musculus* [5]. This reversed the conventional approach to biomedical discovery, in which understanding a certain biological function required identification (and sequencing) of one or more genes involved in that function: the current situation is that thousands of genes have been sequenced but still wait for any functional information to be assigned to them.

The fact that genes of unknown function represent over 70% of all genes, suggests that current comprehension of most biological and pathological processes is by far incomplete. As a consequence, new technological platforms that take advantage of the genome sequence information to explore gene function in a systematic way are evolving at an incredibly high pace. For example, the DNA microarray technology [6] currently enables mRNA expression analysis in parallel for several thousands of genes in a single microarray slide, so that the entire human transcriptome can be explored with just a couple of slides. Indeed, being expressed (at least at the RNA level) is an essential prerequisite for a gene to exert its function; therefore genes with restricted, tissue-specific expression are likely to play key roles in the biochemical and biological processes specifically occurring at the expression sites.

Application of the microarray technology to more translational research fields, such as cancer research, has unveiled its enormous potential as a diagnostic support to clinical management. Recent works have shown that it is possible to exploit gene expression profiling of tumour samples to define sets of genes (signatures) whose expression correlates, positively or negatively, with specific clinical features, such as metastasis-free survival in breast cancer [8], and response to therapy [7]. Other types of massive datasets currently generated in genomics projects include: protein expression levels, measured by proteomics screenings; protein-protein interaction datasets in various organisms; protein structure data; genomic sequencing of additional organisms, and comparative genomics; sequence polymorphisms in human populations, mutational analysis in human cancer and in hereditary diseases; loss-of function analysis in various organisms by small interfering RNA (siRNA)-based approaches [9].

1.4.3.2 Requirements

As a consequence of the above-mentioned genomic research activities, biomedical databases are continuously and exponentially increasing in number and size, together with bioinformatic tools that extract information from them.

The most common way biologists access genomic databases and analysis applications is anonymously via the web. Major research laboratories (e.g. NCBI in the USA and EBI in Europe) collect and regularly update information. These data can be analyzed using a web interface to a number of well-known applications (mainly data mining programs), that are CPU intensive and require large amounts of I/O.

As a matter of fact, this approach presents many drawbacks. Because of the great number of researchers involved in these activities, the usage of the web accessible computing resources is limited (for example, there are limits to the maximum number of simultaneous queries that a user can submit). Moreover, often the data analysis process requires the pipelining of the results through different applications. The retrieval of the results from a web-based application is an awkward and error prone task involving screen scraping. This is further complicated by the changes to the web interfaces. Even though the computing resources dedicated to the single researchers are limited, the concurrent access to the web applications leads to the congestion of the major resource centers.

As a consequence, biologists prefer to download the database files and to process them locally.

There are two major consequences: every single researcher has to track the database update process to keep his/her copy of the data up-to-date; the massive download of huge amounts of data worsen the performances of the web site and of the applications of the download center.

Another relevant aspect is the lack of a standardization of the published databases: cross-referencing of data is made difficult (if not impossible) by redundancies and incoherencies, there is neither standard query language, nor central management of data, and finally, different processing applications require different format of the same data.

This implies that different research centers maintain different copies of the same data and updates have to be propagated from a starting database to the others. As a consequence, performing a job simultaneously on different copies of the same data provided by different institutions might yield different results. As a consequence, the control on data quality and, accordingly, the confidence in the results obtained is poor.

A Grid infrastructure is expected to overcome many of the drawbacks of the existing web-based approaches to genomic data handling and mining, by offering new services. An important service is the transparent access to computing resources for CPU-intensive processes which is important due to the high computing demand of the biomedical problems. This high throughput computing infrastructure will enable the creation of services to support the most popular bioinformatics applications (BLAST, PATSER, Rosetta Resolver).

Another important task is the creation and management of shared, coherent relational databases to resolve incoherencies and inconsistencies in the actual databases and to provide the infrastructure to gather data coming from genomic experiments, providing the means to manage replicated copies of the data files and their coordinated updating.

Finally, database security (all aspects concerning data confidentiality), data transfer channel encryption and, last but not least, user authentication and authorization must be considered as a main requirement.

1.5 CONCLUSION:

1.5.1 General Key issues in Healthgrids

Considering health information in a broad sense, healthgrids involve managing information from the biomedical to the population level. Requirements for biomedical computing community are much different from requirements from healthcare users. However, there is a set of common key requirements that must be faced to ensure the success of heatlhgrids.

Improvement of security and privacy enhancing techniques is the main issue, biomedical information must be carefully managed to avoid privacy leakages. Failure on privacy in biomedical personal information causes an irreparable damage, since there is no way to come back to the previous situation. Secure transmission must be complemented with secure storage, higher security mechanisms that could avoid malicious users granting unauthorized access to part of the grid to be able to decrypt and visualize personal data. Automatic pseudo-anonymisation is necessary for a production stage.

There is a need for robust and secure production capabilities where resource consuming applications could be run. Research communities in biocomputing or biomodelling and simulation have a strong need for resources that can be provided through the Grid. Deploying testbeds for the shake of demonstrating the ‘proof of concept’ of grid technologies is not sufficient. Resources must be available for users to create the necessary trust for consolidating the grid culture.

Compliance with medical information standards is necessary for accessing large databases. There are many consolidated and emerging standards that must be taken into account. Complex and multimedia information such as images, signals, videos, etc. is clearly a target for Grid and is more sensitive to data formats.

Management of Distributed Databases and Data Mining capabilities are important tools for many biomedical applications in fields such epidemiology, drug design or even diagnosis. Expert systems services running on the Grid must be able to dig into large distributed databases extracting the knowledge that can lead to the early detection of new sources of diseases, risk populations, evolution of diseases or suitable proteins to fight against specific diseases. Addressing these healthcare issues require to deploy federation of databases, to develop tools to access distributed heterogeneous data, to develop semantic tools for information extraction while respecting security requirements.

These key issues are analysed from the industrial and the research points of view in the following sections.

1.5.2 Key issues in Grids for Industry

Health grids require a change of scale to operational (from laboratories to hospitals). It must make profit from the convergence between research and clinical applications. Seamlessly exchange of information and knowledge should be the horizon.

Grid technology is a ‘moving target’. The frenetic evolution of platforms and version introduces strong difficulties in the development of applications in a production stage. Researchers even find the evolution on standards and platforms hard to follow, and so does industry.

Main concern of industry is to define and exploit business models on the Grid. But industry needs more stability and standardisation on grid infrastructures before they can develop the business models. Moreover, business models of grids cannot be clearly identified until the technology is clearly available.

Indeed, current grid middleware lack from several components that are compulsory for business exploitation. Efforts need to be done on developing these layers and components, agreeing standards on all the components. It is necessary to foster the interoperability of different middleware and versions to preserve and leverage the value of the investment in porting applications.

Grid middleware lacks from reliable and complete accounting services that can clearly identify providers, consumers and resource usage in a scenario in which a wide range of heterogeneous resources, owned by different entities, are shared. Current efforts on robustness and fault tolerancy have positively increased the reliability and the production capabilities of middleware, which is a crucial point for exploitation in healthcare applications. Finally, security and privacy models of the grid are not enough for deploying applications that can be certified by end users and health authorities.

Reliable benchmarking must be performed to certificate that the components can perform with the quality of service and robustness requirements that healthcare applications have. Middleware certification is even more important in healthcare applications, which can have severe impact on patient morbidity and mortality and in which legal and ethical factors are implicated.

It is necessary to spread and ease the grid culture. Applications in the grid should be organised in the form of portals and user friendly single access points to hide the specific considerations of grid middleware and structure.

There are three scenarios in which health grid technologies can be successful from the industrial point.

Consolidation of resources: Resources in healthcare are distributed and poorly interconnected. Integral solutions for applications, data and resources at centre and region are needed. Distributed database technologies lacks from the interoperability of grids and on the capability of providing other resources rather than data. Temporal liaisons among centres for the achievement of larger goals will also require the federation of resources in the way grid provides.

Efficiency leveraging: Ideal applications from the business point of view are those requiring large peak resources followed of inactivity periods. However one important problem that grid exploitation has is the conflicts with the use of software licenses. Current software licenses usually prevent its use in grid environments in which the computers and the users are not clearly defined. New license models will appear with the development and new business models. Until then, successful applications should better focus on the exploitation of own or public license software.

Reduction of production costs in application where the return on investment is low but the social impact can be high. Joint public-private consortium can lead to the achievements of goals that are of main concern for large populations but of reduced economic profit. Neglected diseases, for example, have large impact on developing countries, which cannot pay for drugs that are thus not developed by the pharmaceutical industry. Providing resources for in-silico experimentation can lead to stimulate the discovery of easy-to-use, affordable, effective drugs for these diseases.

Before developing business-relevant applications, there is a clear need of a production infrastructure in which applications can be run. Many services can be implemented and tested and deployed for validation. Validation that any healthcare application requires for its exploitation can be performed on such a platform, although final exploitation can be performed on separate resources.

There is a long way to go before exploitation, and industry should assist and guide research on health grids in order to profit from reliable and interesting results. Europe is the best scenario for the deploying of healthcare applications, considering the infrastructure, potential users and technological level.

1.5.3 Key issues in GRIDs for the Healthcare and Medical Research

Grids are very promising in biomedical research. There are many possibilities for extending the scope of research with wider communities, more accurate tools and quicker results and there are also many new research opportunities opened by the availability of grid technologies.

The situation in healthcare and medical research are very different. Main target for Healthcare oriented grids is to access large amounts of data securely and efficiently. Medical research however deals with a wider set of issues. Computing resources, knowledge extraction from very large databases and means for solving grand-challenge problems are important concerns in different applications.

Biocomputing medical applications are one family of “killer applications” for biomedical grid research. The maturity of genetics and biomedical technologies conducts them closer to medicine, and grand-challenge computing problems of biocomputing are currently migrated to grid [19.A]. It is important to consider as a whole genes, proteins, cellular elements and its interactions. A European-wide biocomputing infrastructure (hardware, software and data resources) is needed. The definition of a standard ontology for characterizing all the features of proteins (names, structures, chemical parameters…) and possible interactions will enable to share the vast and dynamic protein information at a larger scale, being able to reduce the focus down to the individual.

Biomedical modelling and simulation is another important arena for grid applications. Biomedical models are highly coupled, involve complex physics and require intensive numeric computing. The evolution of models in fluid dynamics, mechanics, chemical interactions, electric potential is progressively and accurately characterizing the biological processes of tissues and organs.

Coupling the models is essential for achieving a realistic simulation that could feedback medical science and medical instrument technology. The long-term aim of the "virtual human being" can only be technologically feasible with very large computing resources. National e-science infrastructures cannot be sufficient for such a large goal.

Healthcare grids key issue is to be provided with the proper services for querying, storing and retrieving multimedia medical data from a data grid. Privacy Enhancing Techniques must be considered to allow medical data access from outside the borders of the medical database holders. Coordination1 with Electronic Patient Record initiatives is fundamental to avoid replication of effort and to ensure the applicability of the results. Connection to medical information systems such as Hospital Information Systems, Picture Archiving Computer Systems, Radiology, Laboratory and Primary Care Information Systems will be very important for accessing data, and the development of libraries of services will ease the process of building up medically-relevant applications

Last but not least, the grid is an important opportunity for the spreading of knowledge in developing countries. Sharing medical data, procedures, services and expertise to researchers in those countries were these tools are inexistent can improve healthcare delivery and improve medical expertise.

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2 CREATING A COMPELLING BUSINESS CASE FOR HEALTHGRID

2.1 WHY IS A COMPELLING BUSINESS CASE IMPORTANT FOR THE HEALTHGRID?

Although both healthcare in general, and the use of IT to support the development of effective treatment, delivery and management of healthcare, are top priorities in many countries, there are many competing areas of investment. The benefits of using even basic IT to provide high quality information and decision support to clinicians and patients are intuitively very significant. In other industries – airlines, automotive, banking, defence, manufacturing – IT has underpinned productivity, quality, security and improved product performance for many years. However, progress in even basic IT has been patchy and slow in the healthcare industry; there are few high quality, well documented business cases with results and very few for IT implementation at large scale. There are even fewer cases that demonstrate the benefits of dramatically new IT technologies (like GRID) or in innovative areas of healthcare such as genetics, imaging, or bioinformatics. Therefore in applying for funding and prioritisation of resources to continue to develop HealthGrid applications, it is vital that a clear and highly compelling business case is created that acts on all the benefits levers of healthcare.

2.1.1 The growing importance of IT in delivering efficient, high quality healthcare

The advent of HealthGrid applications, even at the research stage, coincides with a crucial period of investment and experimentation in IT for healthcare. The main drivers for this shift in the pace and levels of investment include:

- increased understanding of the impact of medical errors on patient safety and the resulting cost of care(* Insert Reference from US on Medical errors). IT's basic value proposition includes the ability to regulate processes and scale information "written" once to many uses and contexts;
- demand for healthcare outstripping resources at all levels, driven by an ageing population in most countries, living longer but with access to an increasingly sophisticated armoury of tests, surgical interventions, medications etc. IT has the power to both add to the armoury of clinical tools and reduce costs through efficient operation with reduced numbers of process steps, wasted activity (tests, prescribing unnecessarily etc.) and utilisation of disparate resources

The coincidence of growing capability in Grid technology with this increase in investment has its draw-backs. Firstly, there are many strategic and investment plans being made at local, regional and national levels that take no account of emerging technologies like GRID; even if the first truly useful HealthGrid applications will not be ready for several years, this is within the planning horizons and budgeting horizons of the Public Sector. Secondly, as IT is introduced into everyday healthcare, custom and practice is changing on how care is delivered. Such change in the clinical world is very significant – for instance rationalising the outpatient process to a single series of steps supported by sharing of electronic data, in all hospitals within a region, is a considerable change. Overlaying such serious changes with the completely new capabilities of Grid will simply add to the challenges. And in healthcare, change can take time to embed – a recent study in the USA showed an average 17 year delay in adopting widely proven practices in healthcare .

And are HealthGrid technologies being anticipated in the many eHealth strategies being created around Europe? In short the answer is "No". Very few senior health managers in Europe understand the potential or the practicalities of HealthGrid; in general they are certainly not embedding their strategies with even link points to take advantage of GRID in the future. The risk therefore is that it will be even harder than it should be to take advantage of HealthGrid capabilities over the next 5-10 years – unless the potential is understood quickly and strategies adapted accordingly.

2.1.2 Measuring success – Quality, Access, Cost

So as the business case for HealthGrid is so critical, how can it be articulated in terms that senior health managers can understand? One suggestion, based on the work of the European Commission eHealth Unit led by Prof Jean-Claude Healy, is to define the benefits across three categories, specifically the impact on:

- raising the ***quality*** of care. Here factors include the ability to make faster decisions or interventions; fewer medical errors; more informed decisions or diagnoses;
- improving the ***access*** of patients to care. Sources of benefit might include the extension of lengthy or complex tests and diagnoses to a massively increased number of patients through increased capacity; the provision of new tests or diagnoses that simply could not be made using traditional approaches (at reasonable cost);
- reducing the ***cost*** of care. A complex issue for HealthGrid since it is an emerging technology creating opportunities for new procedures and test for instance that may actually add to the short term budgets; however there may be sources of benefit from such short term investments against the long term reductions in cost of care as disease is identified earlier and prevented for instance.

It is important to recognise that rarely do these three factors appear independently – for instance it may be that improving the access to care via new tests also impacts the long term cost of treating either chronic diseases or immediate palliative care.

Casting the benefits of HealthGrid applications against these three factors has a great advantage in creating compelling business cases for senior health management – and politicians – because it allows them to see the benefit in the terms that they are managing day to day healthcare outcomes and budgets against. Creating such resonance is critical to gaining priority and share of resources / budgets.

2.2 WHY INVEST IN HEALTHGRID APPLICATIONS AND SERVICES?

Not only does the modern healthcare management team have many choices for investment of their time and money in traditional sources of patient care improvement – drugs; medical equipment; more nurses, doctors etc – but they also have a bewildering array of IT support that can be purchased. Picture Archiving, tele-medicine, home monitoring, Patient Administration Systems, the list is endless. So why, in such an already complex, packed marketplace, should the relatively new, often untried, GRID technologies be given any priority at all?

2.2.1 Critical opportunities for distributed computing approaches

Of course, not all Healthcare informatics problems will be remotely suitable for a GRID solution. There are "sweet spot" problems where the advantages of GRID approaches will out weigh

the potential drawbacks of a relatively untried and new technology. The characteristics of clinical problems that could have significant advantage from distributed computing-type solutions include:

- analyses that require dynamically assembled data-sets and investigation routines; for instance genetic-related investigations where the initial analysis may raise the need for further data sets to be added to give better, more representative results from analysis;
- processes of analysis and data assembly that cross organisational boundaries, where the ability to distribute both the data and analysis without recall to the normal "data process" flows is key. Again medical research, or in future patient-centric analyses, are probably two areas where the utility of the GRID will be highest;
- huge scale analysis, that requires a scalable infrastructure to deal with the potentially massive quantities of data both to be assembled and analysed. This leads us again to imaging and genetic analysis as potential opportunities;
- Dynamic grouping of Healthcare professionals for review / analysis of diagnosis or research results, such that different "expert teams" can be assembled without a formal organisation structure (indeed across organisation structures).

Therefore in summary there seems to be an advantage available from using GRID approaches where the clinical problem requires a scaleable, flexible infrastructure that can work across normal organisation and process boundaries. Further benefits may be realised through the pooling of resources, whether it be the sharing of training cases to enable smaller clinics to benefit from the knowledge available in larger hospitals, or the sharing of compute resource to reduce the local investment on IT. Feedback from clinicians on existing Grid health projects indicates a strong need to enhance collaboration on a daily basis between communities, removing their reliance on conferences to achieve this. Grid technology will make it possible to share advanced simulation applications that are characterized rather by their need for very high computational power as opposed to the manipulation of or access to huge data sets. Such applications are for example developed currently within the GEMSS project. The main advantage of Grid technology here is that there would be no need for installing powerful HPC platforms in hospitals, avoiding huge costs for specialized IT personnel and infrastructure.

The sections below discuss in more detail the impact of GRID technologies on access, quality and cost of care.

2.2.2 Impact on wider patient access to care

The key value that GRID approaches can bring to increasing patient access is to make possible new analyses of data, for individual patient care or group research that traditional computing approaches cannot provide. The principle features of problems that suit such approaches are those involving huge quantities of data requiring iterative, repetitive analyses – typically image diagnosis, genetic diagnosis are current problems with these features. Here the GRID approach could offer extended reach of "care" – by increasing the capacity of the healthcare system to make complex analyses that require cross-organisational skills or processes. The speed of such analyses should also be increased, offering the opportunity to use such complex analysis in more situations, especially those where time is an important factor – for instance in pre-operative planning (cardiology at one end of the scale, cosmetic surgery at the other).

2.2.3 Impact on raising the quality of care

Potentially, the Health GRID approaches could dramatically increase the quality of care for areas of research / care where it is used. This is because the application of GRID technology could allow better analysis of patient data – by dynamically assembling data sets for comparison; by using discoverable publishing to improve access to previously difficult to find data; by allowing self-describing data sets to be more freely used, therefore raising the quality of the resulting analysis. The areas where this could have greatest benefit may include rarer instances of disease diagnosis; complex image manipulation and even temporal comparisons of patient information to assist with determining change. 'Find one like it' analysis could be used to assist clinicians with determining likely outcome for cases.

2.2.4 Impact on reducing the cost of delivering care

Cost plays an ever more important factor in delivering healthcare, so any areas where HealthGRID approaches may provide a cost advantage will attract intense interest, and scrutiny of the comparable traditional approach. From all the discussions, it seems that the main, direct advantage that Health GRID could provide in its application is to create a high degree of utilisation of infrastructure and computing power, while still allowing a very flexible, scaleable infrastructure to be applied that could deal with dramatically varying demand. Indirect cost advantages would derive from two main categories - first is the maintenance and effort put into IT, which in a GRID solution should be, in theory at least, easier to manage since data is self discoverable, infrastructures managed in a more flexible way etc. Secondly, there are all the potential cost savings in the delivery of care stemming from the improved quality, increased access to care that GRID approaches offer.

2.3 BARRIERS TO ECONOMIC, RAPID IMPLEMENTATION

While there may be some very serious advantages to be had from applying HealthGRID technologies to suitable problems, there remain significant barriers to implementation. They can be summarised into 3 main areas:

2.3.1 Governance and accountability

On many levels, the HealthGRID does not match current governance models and tried and tested processes. As one example, research conducted using GRID approaches does not necessarily have the same degree of independent scrutiny and open accountability to which traditional research, reviewed by peers, is routinely subjected. In fact the very nature of dynamically assembled, self-discoverable data sets and analyses means that such scrutiny is probably impossible. Secondly, the entire area of trust (particularly in data) is critical to the wide-spread acceptance of GRID approaches in Health. This trust issue ranges from building diagnoses or clinical evidence on data collected, maintained and shared by organisations or individuals outside of the originator's span of control; to the acceptance of GRID applications being shared across organisations' infrastructures. Before there is widespread uptake of the HealthGRID, such governance issues must be addressed;

2.3.2 Quality of Service and speed

With any distributes system, where all pieces of the infrastructure (computing devices, data stores, networks) are not under a single span of control, then the issue of the availability of resources, and the maintenance / reliability of such resources, is critical. Add to this reliability issue the potential

contention for resources that massive data manipulation could experience, and the quality of service (guaranteed speed of response) could be frequently compromised. There are approaches for managing this problem, but most increase the cost or require heavy structured governance processes. There may be a limit for health applications, for real-time or mission critical speed of response – say 10 minutes as a default window, rather than 1 minute or 1 second;

2.3.3 Incomplete model & technologies

Much of the GRID technology has only been applied in research fields where human lives do not literally depend on it or the decisions made on its output. Before life-critical applications can be trusted, many more examples, pilots and controlled trials will be necessary. Whilst there have been significant advances in standards for the integration of healthcare systems (IHE), it is evident that further work is needed in order to take this to the dimension of 'the big joined-up healthcare' approach.

2.4 IN CONCLUSION

The HealthGRID is potentially a significant addition to the armoury of tools health professionals and researchers can use to increase the quality, access and reduce the cost of healthcare. However, significant progress is required on the Governance, Quality of Service and Operational models for GRID technology before it can become a widespread tool in daily use. Projects like GRIA and GEMSS are developing technology needed for deploying Grid applications in a business context, looking at appropriate business models, dynamic Quality of Service negotiation and the economic approaches to Grid computing.

Whilst this section has identified some of the benefits and also some of the barriers to be overcome in deploying such technology into a health environment, the vision for Grid computing to play an essential part of healthcare in the future clear. These barriers are also not un-surmountable but require a clear long term vision from the procurers of healthcare systems to ensure that these systems are developed and deployed in conjunction with those who will benefit from them.

3 MEDICAL IMAGING AND MEDICAL IMAGE PROCESSING

3.1 RATIONALE

Medical imaging has been one of science's greatest contributions to medicine. It has evolved over a century, from the earliest X-rays to the latest developments in functional MRI, to become one of the principal tools of the physician in diagnosis, therapy, and research. As with imaging in any other field, doctors have to apply very subtle knowledge and skill in interpreting the images they make. This can be improved by providing them with greater access to images and associated histories, with standards, with quality processes and with better and broader-based training.

3.2 ISSUES FOR MEDICAL IMAGING

3.2.1 3.2.1 Imaging in medicine

Medical diagnosis and intervention increasingly relies upon images, of which there is a growing range available to the clinician: X-ray (increasingly digital, though still overwhelmingly film-based), ultrasound, MRI, CT, PET scans etc. This trend will increase as high bandwidth systems for picture archiving and communications are installed in large numbers of hospitals (currently, primarily in large teaching hospitals). More than patient data, the medical images by far represent the major amount of information collected for medical data. However, medical images are not sufficient by themselves as they may need to be interpreted and analysed in the context of the patient's medical record (that is the metadata associated with the images).

Indeed, patient management (diagnosis, treatment, continuing care, post-treatment assessment) is rarely straightforward; but there are a number of factors that make patient management based on medical images particularly difficult. Medical data are naturally distributed over a number of acquisition sites. Data concerning one patient are not necessarily located in a single location nor accessible through a unified interface. Physicians most often have no way to access all the medical records across all of their patients. Patient images often represent very large quantities of data (such as 3-D images, time sequences, multiple imaging protocols), with complex structure (clinically and epidemiologically significant signs are subtle including patient age, diet, lifestyle and clinical history, image acquisition parameters, and anatomical/physiological variations). In many cases, no single imaging modality suffices, since there are many parameters that affect the appearance of an image and complementary information is captured by different physical acquisition systems.

Medical data are used in diagnosis, continuing care, and therapy planning. For diagnosis, medical images acquired in a medical centre are usually visualised and interpreted immediately after the acquisition by the radiologist before being sent (often on films) to a physician for second viewing. These two readings normally take place in different offices and possibly even in different sites. For therapy follow-up, even more clinicians may be involved as images acquired at different times may be acquired in different radiology centres and several physicians may need to read them. For therapy planning and assisted intervention, images also need to be accessible from the intervention room.

Picture Archiving and Communication Systems (PACS) deployed in hospitals today address some of the challenges related to medical data management. However they suffer many limitations:

- Often they are disconnected from the Hospital administrative Information System (HIS) or the Radiological Information System (RIS) carrying the medical records.

- They are often proprietary solutions of medical imaging companies and no open standards exist to ease communication between different PACS.
- They are usually limited to data management inside one health unit (one hospital or at best a federation of hospitals) and are not scalable on a national or international scale.

Manipulating medical data on a large scale also raises the problems of security and confidentiality of personal data. Grid technologies are expected to ease the design of distributed medical information systems in a secured environment. Although grids cannot by themselves resolve the problem of heterogeneity in data formats and communication protocols, they are expected to motivate the establishment of standards in this field.

3.2.2 From medical data acquisition to medical data storage and archiving

Although most recent medical imaging equipment produces digital images, the long term archiving of data is often performed on film only. Medical images represent enormous amounts of data: a single image can range from a few megabytes to one gigabyte or more. A medium sized radiology department is estimated to produce more than 10 terabytes of data per year. The total amount of digital images produced in Europe thus probably exceeds 1000 petabytes each year. The legal aspects concerning medical data archiving vary from country to country in the European Union but the actual trend is towards long term archiving of medical data (about 20 years for any data, up to 70 years for some specific data) and to make the patient the owner of its data.

To ease data storage and communications, the DICOM standard (Digital Image and Communication in Medicine) has been supported by several international bodies and industrial companies. DICOM covers both an image format and a transport protocol amongst other things. Most recent image acquisition and treatment devices implement the DICOM standard and that eases data exchanges between imagers, post-processing consoles, and archiving systems. The DICOM file format encompasses a format for image description and basic acquisition information (both patient related and acquisition related metadata). However, it does not include all features of RIS for data management and access, nor does it describe archiving strategies dedicated to PACS.

Medical data storage strategies can only be established when considering the access pattern that depends on the use of these data. The legal trend is for patients to have full read access to their medical records. The physicians obviously need access to the data of their own patients, however, any physician should not have access to all medical data owned by any patient. Other communities may in addition have restricted patient data access needs. For instance, researchers may need access to the core data although personal identification may not be needed in every case.

Grids provide a support for the distributed and mass storage of data. Several grid middlewares propose distributed and transparent file systems aggregating many storage resources to offer extensive storage capacity. Several aspects of grids that are still under investigation concern the implementation of data access control and security of data. Data access patterns may be quite complex in the medical domain as described above as several user communities need the access to medical data. While remaining internal to the hospitals, data security problems are rather easy to solve however enabling data exchanges between hospitals over wide area networks makes this matter much more complex. Medical data should always be considered as sensitive in general and identifying data should remain strictly confidential. In particular this means that data should only be accessible by authorised users (for sensitive data) or accredited users (for identifying data), often excluding service providers and system managers. Encryption (and thus anonymisation) of data on disk and during network transmission is therefore mandatory; the access to decryption keys being strictly controlled.

3.2.3 Challenges in building virtual datasets on grids

To enable analysis of medical images related personal and clinical information (*e.g.* age, gender, disease status) has to be identified. The number of parameters that affect the appearance of an image is so large that the database of images developed at any single site - no matter how large - is unlikely to contain a set of statistically sufficient exemplars in response to a query related to one of these domains:

- Screening programs: to study the distribution of some diseases at a pan-European scale and to correlate this information with common factors.
- Studies on rare diseases for which limited data is available on any single site.
- Assembling individualised datasets: when studying data from one patient or one particular population, one may need to assemble a comparative epidemiological dataset by selecting data with similar features at a pan-European scale (same gender, age, social category, etc).
- Alarm networks: to detect the spread of some pathologies over national boundaries.

Overcoming the problem of data distribution implies constructing a huge, multi-centre - federated - database, while overcoming statistical biases such as lifestyle and diet leads to a database that may transcend national boundaries. A distributed medical database could be used to assemble *virtual* datasets: *i.e.* datasets assembled on demand from various data sources belonging to different regions and countries for a specific purpose. For any medical condition, there would be huge gains in using virtual datasets so long as that (federated) database appears to the user as if it were installed in a single site (i.e. a single logical dataset). A rich and wide scale incremental medical knowledge database can thus be assembled: any new case associated to its diagnosis, metadata and image descriptors can immediately be made available to the whole community, and can help the diagnosis of any future case, whose attributes are similar. Such a geographically distributed (pan-European) database can be implemented using Grid technology, and the construction of a prototype would enable a study of the suitability of Grid technologies for distributed image analyses. A distributed database that reflects the spread of pathologies across the population would be an invaluable tool for the epidemiologist, while understanding of the variation in image acquisition protocols is essential to a radiologist or radiographer (radiological technician) in a medical image screening programme.

The medical image analysis community is not interested in the technicalities of the underlying computing technologies that support their activities. They require transparent access to collections of image data that may reside in a number of locations inside and outside their hospitals and in a number of different formats. It is crucial in deploying any software solution to this community that the complexities of those technologies that support virtual datasets are hidden from the users and that the essentials of their requirements are satisfied firstly ‘in the large’. Only then will the systems analysts and designers responsible for deploying the enabling technologies gain the commitment from that user community to develop the required infrastructure to satisfy the requirements ‘in the small’. The solution offered for virtual datasets must be sensitive to the over-riding issues of data protection and ownership (by individuals, by medic and hospitals), data security, medical anonymity and ease of access to the data.

Heterogeneity of image data is one headache in constructing Grid-based virtual databases of images. It will be necessary for any usable Grids medical image implementation to integrate multiple datasets be they database-resident or file-resident. To this end the requirement for discovery of and interaction with heterogeneous data schema needs to be resolved, potentially through the use of high-level meta-data abstractions (possibly using ontologies) of each different dataset. Careful consideration must be given to semantic heterogeneity too : different data systems may well refer to

the same data item with different names or different items with the same name. Identification of patients on a large scale is a critical problem too: usually, each hospital internally uses its own individual identification mechanism. The need for ensuring the patient's privacy makes it even more difficult.

The issue of handling annotation is one particular problem in building virtual datasets. Annotation can be added to image data in several forms: in radiologists drawing regions of interest on medical images (*e.g.* to denote areas for further study, computer assisted detection (CADe), biopsy etc), in radiologists writing medical notes alongside images, in technicians supplying written 'conditions' under which the image was recorded, and in annotation on sets of images, on a particular study or on actual patient records. Any virtual dataset would need to cater for these different levels of annotation and allow queries to be executed against the semi-structured and/or structured annotation. Clearly there is a need for standardisation in image annotation in the medical community (if possible) to enable query resolution.

Any successful medical data system must also provide links between image data and non-image data such as biopsies, medical treatment records and patient meta-data. Furthermore links between different forms of image (PET, CT, X-ray, mammograms) also need to be resolved as do the more general data issues such as privacy, security and appropriate role-based access.

3.2.4 Database indexing

One of the most important aspects in building large-scale virtual image datasets is the ability to perform queries in a transparent and efficient manner. The most standard way to formulate these queries is to express conditions on attributes associated to images. As noted before, these attributes can be DICOM metadata produced by the imagers, or human annotations stored by the medical staff. Another possibility for retrieving specific images is to use the content of the images themselves (at the pixel level) for expressing the request. For example, similarity measures based on mutual information or on correlation ratio coupled with geometrical transformations can be used to retrieve database images that are the most similar to a given query image. Nevertheless, these approaches are very intensive both in terms of computational power and data manipulations. An intermediate level between direct image access and requests using only metadata consists in querying image features. This kind of queries relies on the computation of indexes describing either global properties of images or local properties of individual image regions, salient objects or topological relations between these objects. These indexes can largely contribute to the acceleration of Content-Based Image Retrieval (CBIR) since standard database operators can be used, and the direct access to raw image data can (most of the time) be avoided.

Many related aspects appear when treating these indexes: the image processing community has proposed huge quantities of image indexing strategies, and new algorithms and methods are continuously being developed. However, the indexing of medical images has not retained the attention of researchers as much as the indexing of photographic images thus far and the selection of pertinent indexing methods, adapted to different kinds of images is a difficult and a very application-dependant task. There is therefore a real need for standardising the representation of these indexes, but also the description of algorithms used for their computation. Some of the key issues that have to be solved in a widely distributed image database environment are:

- The deployment on different geographical sites of indexing algorithms / libraries, and the management of new algorithms (or of algorithm version evolution).

- The indexing policy: which algorithms have to be applied, and which parameters are adapted for the different images? When is it necessary to (re)launch the indexing? What happens when new images/algorithms are integrated to the distributed environment?
- The "traceability" of indexes: it is crucial for having a pertinent query scheme to be able to know which algorithm, in which version, and with which parameters, was used to compute a set of indexes.
- In the case of complex processing, several stages can be chained : the data produced by a given algorithm can be used as input of an other stage of processing. The distributed system must include standardised ways to describe these dependencies and must be able to launch the necessary computations in the case of insertion of new data, or when a new algorithm is made available.

The possibility of handling the security of these indexes at different levels may be needed: in the same way that personal (nominative) data have to be anonymised for certain categories of users, the image data can itself require security, particularly when it permits patient identification (*e.g.* the 3D scanner of a face). However, indexes computed from these image data can be considered as public when they do not leave the possibility of patient identification. They can be of a great interest for research purposes, especially in the case of statistical or epidemiological studies.

3.3 ISSUES FOR MEDICAL IMAGE PROCESSING

3.3.1 Computerised medical image processing

Computerised medical image analysis algorithms have been developed for two decades or so. Beyond the simple need for visualising 3D datasets, the aim is to assist the clinicians in facing the amount of data by providing reliable and reproducible assistance to diagnosis and therapy. Indeed, the manual processing of 3D images is very fastidious and often error prone. Moreover, 3D medical image interpretation requires a mental reconstruction for physicians and is subject to large inter-operator variations.

Although image processing algorithms can provide accurate quantitative measurements (*e.g.* the measurement of the heart left ventricle ejection fraction from dynamic image sequences) or can accomplish some tasks that are not feasible by hand (*e.g.* accurate registration of multi-modal images), the reliability and the responsibility issues remain key showstoppers to their large scale development. Algorithm validation is often made difficult due to the lack of provable theory in order to compare with processing results and their development tends to be limited in scale.

Grid technologies will not only provide access to large amount of data for testing. It will also enable image processing communities to *share common datasets* for algorithm comparison and validation. They will offer an access to large processing power suited to processing full datasets in reasonable time, compatible with the needs for experiencing new algorithms. They will also ease *the sharing of algorithms* developed by different research groups thus encouraging comparative studies. For all these reasons, grid technologies are expected to boost the production of medical image analysis algorithms and to facilitate their quality improvement.

3.3.2 Compute intensive algorithms

Beside the need for processing very large databases that require enormous amounts of computing power, some medical image analysis algorithm are also very compute intensive. For instance many optimisation techniques are used for 3D reconstruction, image registration or image

segmentation. The algorithms selected for these tasks are often a trade-off between quality of the processing and computation time that has to remain short enough for clinical practice. Therefore, some algorithms that are known to produce better results are not used in practice due to a lack of computing power. Given that a sufficient amount of computing resources is available, parallelization is often a means to significantly speed-up these algorithms.

Another area of medical image processing with a need for computing power is stochastic algorithms. Markovian models for instance are commonly used for image texture analysis and segmentation. Their combinatorial nature makes them compute intensive even for 2D images and consequently, often hardly tractable for 3D images. Other statistics-based studies may require a significant amount of processing. For instance, Monte Carlo simulation requires re-execution of a simulation code with a large number of seeds. Bootstrapping in phylogenetics is another example of code re-execution. Optimisation techniques based on re-execution of an iterative algorithm starting with different initial conditions have also been proposed.

Validation of medical image processing algorithm remains a key stopper in the wide spreading of these techniques to the clinical world. Recently, new validation methods have been proposed to face the lack of *gold standard* or *ground truth* in medical applications. The so called *bronze standard* methods involve the execution and the cross-checking of results obtained by multiple algorithms on large datasets. Grids are naturally well suited to handle the load of such experiments as each algorithm can be executed independently on different computing resources. Performance evaluation and validation of an image analysis method for a particular clinical application inevitably relies on a representative database of cases that could be gathered on the grid as described above.

3.3.3 Image databases studies

We have introduced above the need for assembling large datasets by collecting data coming from different data sources that are geographically distributed. A couple of image analysis techniques have been developed that rely on atlases and average models. Building these models and atlases requires the processing of a representative dataset (the so-called *training* set). Typical processing on the training set includes data registration in a common frame and intensity equalisation. New images can then be analysed by comparison to the model or the atlas. They often need to be similarly registered and equalised onto the reference model.

3.3.3.1 Registration

Registration techniques have encountered considerable success in the medical image processing community not only as they permit the production of average models but also because they ease the comparison of image data coming from multiple sources. Registration may be intra-patient (when registering data coming from a same patient but acquired at different time and/or on different imagers) or inter-patient (when comparing data from different patients). It can be mono-modal (when registering images acquired using the same image modality) or multi-modal. The matching criteria used to perform optimisation depends on the kind of registration performed. But there is another categorisation of registration algorithm that has a largest impact on the optimisation procedure and its computational cost: one often differentiates between *rigid* and *non-rigid* registration algorithms.

Rigid registration algorithms concern the registration of intra-patient data: data images are considered to represent the same physical body (although it might appear quite differently in different acquisition modalities) and the registration procedure search for a rigid transformation (a composition of a translation and a rotation) to match the two images. Rigid transformations are described by 6 parameters only (3 degrees of freedom in translation and 3 degrees of freedom in rotation) and the associated optimisation process is usually reasonably tractable, unless processing very large dataset.

Common extensions to rigid registration include similarity registration (7 degrees of freedom, adding a scale factor) or affine registration (12 degrees of freedom, adding anisotropic scale factors and shear factors).

Non-rigid registration algorithms concerns the alignment of data acquired from different patients and representing similar but different shapes. Non-rigid registration is more complex than rigid registration as the transformation includes many more degrees of freedom (it is often a parametric transformation with variable degree of complexity or a dense transformation field). Therefore, non-rigid registration algorithms are much more costly (up to hours of computation time on today's workstations) and parallelization of some algorithms have been proposed. One of the key challenge to share non-rigid registration algorithms on a grid is the standardisation of the transformation format. Currently, transformation models as different as B-splines, NURBS, radial basis functions, or dense displacement fields are used to encode the deformation. A common framework will be needed to handle, compare and use all these models.

Image intensity correction techniques also often rely on optimisation procedures and therefore may fall in the compute intensive algorithms described in the previous section.

3.3.3.2 Atlases

Atlases have long been used in medicine for anatomy and physiology studies. For centuries, atlases have been produced manually by experts from their knowledge of the human body. Atlases attempt to provide a 'standard' description of the human body or parts of it. They are very dependent on the designer and have been incrementally refined with the progress of medicine. They tend to be general and hardly take into account infrequent parameters.

With the advent of digital images and image registration algorithms, the production of digital atlases has become possible. Digital atlases are assembled by registering large training sets in a common frame and averaging the registered images by different means. Digital atlases prove to be much more easy to produce than manual atlases. They have encountered a tremendous success and have lead to significant research progresses, especially in the domain of brain imaging. A common frame, the *Talairach space*, defined from characteristic features of the brain (such as the mid-sagital plane) is indeed widely accepted in the brain image processing community.

The production of atlases require the availability of training datasets large enough to be statistically representative of the population under study and of sufficient computation power for accomplishing the registration and intensity correction computations. Grids technologies promise to cover both aspects and should therefore boost the production of anatomical and functional atlases of the human body. Given a wide scale medical information system and considerable computing power, one can even imagine producing on-the-fly individualised atlases. For example a physician may want to study the brain of a 50 year-old male subject to multiple sclerosis; he could ask for the production of an atlas from a training set with matching criteria. Such an individualised atlas would prove to be much more specific and precise than a generic atlas. Digital atlases are expected to assist in improving patients' healthcare and clinicians' assistance.

3.3.3.3 Case study: Mammograms analysis for breast cancer screening

One current example of a large-scale medical image acquisition and processing application is the automated detection of malignant tumours in mammograms developed to support breast cancer screening programs that are starting in several European countries today. Screening programs at a national scale require the reading of a huge number of images (*e.g.* one mammogram for each woman older than 40 years every 2 years) thus considerably increasing the burden of image analysis on radiologists. Grid-enabled mammogram analysis projects aim to prove the viability of the grid by harnessing its power to enable radiologists from geographically dispersed hospitals to share

standardised mammograms, to compare diagnoses (with and without computer aided detection of tumours) and to perform sophisticated epidemiological studies across national boundaries. Research is currently being conducted into imaging workstation architectures, into information infrastructures to connect radiologists across a Grid, and into DICOM-compliant object models residing in multiple, distributed data stores, as well as into mammogram indexing, etc. There are a number of relevant technologies that are being harnessed together to provide a distributed infrastructure to support radiologists in their work. These include mammogram analysis algorithms, grid middleware implementations, and computer-aided detection software.

Through a deep and thorough analysis of the requirements of the user community (clinicians, radiological technicians, healthcare administrators etc) the breast screening programs have illustrated the need for simple but secure, anonymous access to standardised mammograms and their associated metadata. However they have only just scraped the surface in matching these user requirements. Data heterogeneity is one major issue in the storage and analysis of medical images – even in a single region of a single country never mind inter-regional or international data differences. The ability to process unstructured (*e.g.* radiologists annotations), semi-structured (patients' medical history) as well as rigidly structured patient data (metadata such as age, drug treatments, etc) is essential to enable the controlled execution of epidemiological studies or other query-based analyses.

3.3.4 Interactive image processing algorithms

3.3.4.1 Collaborative work

The grid technologies enable new collaborative work environments by facilitating fast data sharing and remote user interaction. Doctors can easily put medical data online that become accessible to their remote colleagues for discussion and second opinion, while remaining in a secured context. Additional benefits can be expected from collaborative applications that provide data processing in almost real time thus allowing experts to take advantage of image analysis algorithms to study the data subject to discussion.

3.3.4.2 User interaction

Another particularity of medical image processing algorithms is that some of them need to be executed interactively. There are two main reasons why a medical application might need to be interactive:

- To solve reliability problems: to ensure that the user gets full control of the algorithm output by interactive guidance.
- To solve legal responsibility issues: automatic processing of medical data often raises the problem of legal responsibility. A user-guided algorithm is not subject to this kind of criticism.

To ensure interactivity, an algorithm needs to be executed in a time short enough for the user to remain active in front of the screen (usually the whole process should not exceed a few minutes in the medical context). Grid infrastructures can provide the computing power needed to ensure that the execution time remains reasonable by allocating powerful computing resources for interactive jobs or by empowering parallel applications. However, porting interactive applications on a grid is made complex by the need to split the user interface (that displays the algorithm progress result on the user's screen) and the computing algorithm (that is remotely executed on the grid resources). Therefore, interactive applications have to be carefully designed in order to be ported onto Grids.

A typical user-guided interactive medical application is that of segmentation algorithms. Medical image segmentation is a complex problem for which there exists no general solution. Most

segmentation algorithms such as deformable models or voxel clustering algorithms are iterative. It is therefore possible to update the algorithm progress on the user screen periodically and to take into account some user input at each stage to guide the algorithm while it is progressing. Due to the lack of reliability of segmentation algorithms in general, user interaction can be a good way of controlling the output while releasing the user of a fastidious manual segmentation. Enabling segmentation algorithms on Grids permits the use of more complex models with an increased computation time while remaining compatible with interactive time constraints. Likewise, enabling interaction with grid-powered non-rigid registration algorithms would enable correction of mistakes created by local minima (especially in multi-subject brain registration) while retaining the accuracy of the automatic processing and a reasonable human computation time.

3.3.4.3 Real time constraints

If interactive algorithms require reduced computing times, there are real time algorithms that are even more demanding on computing power and network bandwidth. Real time algorithms include intervention simulation and augmented reality applications. Real time is not a precise notion as the maximal admissible delay between two updates depends on the kind of feedback desired. Visual feedback is known to be satisfying at 25 Hz. Haptic feedback may be much more demanding as a minimal frequency of 300 Hz is needed for realistic soft tissue haptic feedback and hard tissues such as bones may require much higher frequencies (in the order of thousands of Hertz). Given the complexity of some biomedical model of the human anatomy and physiology used for *e.g.* surgery simulation and planning, the computing requirements of these applications can be drastic. See section 4 for more details.

4 COMPUTATIONAL MODELS OF THE HUMAN BODY FOR THERAPY PLANNING AND COMPUTER ASSISTED INTERVENTIONS

4.1 RATIONALE

Beyond medical data acquisition and analysis, modelling of the human body enables specific medical treatments. The key distinguishing factor compared with image processing or image reconstruction in the same applications arena is the use of computational methods for predictive purposes – providing physically accurate (up to the possible modelling accuracy) information that is not included in medical images themselves. An example which clarifies the difference: by image analysis, one could investigate whether or not a prosthesis would fit for a given patient, even during movement (with some simple assumptions); with bio-mechanical modelling one could investigate the resulting forces on prosthesis and surrounding body parts, allowing predictive statements to be made on durability or perhaps event comfort/pain for the patient.

Enormous progress has been made in recent years (aided by the increases in performance of computing platforms) and numerical modelling is now able to provide realistic (and validated) predictions of very complex phenomena. However, there is a real need for the continued development of numerical modelling and simulation technology to address the future challenges of multi-scale, multi-physics problems that arise naturally and automatically in virtual human modelling.

Given the complexity and the computing cost of most human body models, grid technologies are a good candidate to face computation challenges arising in this area. Bio-modelling is used for simulation purposes and better understanding of the human body anatomy, physiology, and dynamics. In some areas, models and simulators have been developed for therapy planning. But the computation constraints limit the models granularity, the area of application, and the kind of intervention modelled. However, the increase in performance of computers and the optimisation of some models enabled real-time simulation and augmented reality with applications to computer assisted interventions where timing and accuracy become critical.

4.2 NUMERICAL SIMULATIONS OF THE HUMAN BODY

The release, some years ago, of the Visible Human (VH) dataset made it possible, for the first time, to access anatomical information without compromises. This produced a significant momentum in many areas. However, after some time it became clear that, while the dissection approach used in the VH project ensured extreme quality, it also lacked physiological information that other forms of data contain. These include *in vivo* data collection, multi-subject, gender, sex, and age variations, lack of connection with functional information, no pathology, etc. To put it simply, the Visible human is only representative of an anatomy of one individual, and he is dead. We do not know how he breathed, walked, swallowed, digested, and how the anatomy and the relative functional aspects vary from subject to subject. Many research projects have been carried out in Europe over the last few years to try to circumvent some of these limitations. A basic feature of the VH project, lacking in all these other projects, is completeness. The VH project relates ONLY to the normal anatomy of one human subject, and provides ALL the anatomical information for that subject. The other projects focused only on specific aspects. Because of the lack of the necessary critical mass, none has dared to search for completeness.

The Living Human Project (LHP) intends to develop a world-wide, distributed repository of anatomo-functional data and of simulation algorithms, fully integrated into a seamless simulation environment and directly accessible by any researcher in the world. The objective is patient-specific bio-numerics and image-processing (both for pre-processing and visualisation) for the complete

human body. It requires the integration of individual systems through hierarchical approaches at the algorithmic level. With the development of grids and large medical databases, one can expect the development of more specific or even individualised models. These models could be built from specific patient data and target specific pathologies or functions.

Many areas of development in numerical human modelling are already at the stage that they can be used by medical researchers as tools for investigation into cause of medical problems and treatment procedures. Research into cardio-vascular disease in particular is an area where HPC simulation software is widely used, for example to improve understanding of processes leading to illness or to failure of implants such as artificial heart-valves or stents. In general, medical researchers will be the first users of state-of-the-art developments in modelling technologies and simulation software. The Grid will give them access to large-scale computational resources, usually unavailable locally.

To build biophysics models, grid middlewares can provide an operational support over distributed systems and semantic tools to manage the information. The interest of the Grid approach is to provide services to medical or clinical users, removing any need for them to have to handle the details of the computing systems or simulation methods. Grid technologies are also required to provide high-bandwidth to large collections of coarse-grained, distributed, non-textual, multidimensional time-varying resources. Web services technologies are required to cope with the dynamic aspects of a digital library that provides, not only data, but also simulation services, collaborative work services, interactive visualisation services, etc.

Broadening the term “medical supplier” to include pharmaceutical industries, the acceptance of the potential benefits of using numerical simulation tools (*i.e.* actual use or willingness to investigate use) is already well established within the R&D divisions of companies. For large companies, Grid offers the possibility to deploy simulation software across their own distributed resources. There are also established SME’s supplying services and consultancy based on numerical simulation. Future Grid developments will allow them to enter into virtual organisations with their customers (including controlled access to data sources) and to have access to external computational resources when needed.

4.3 ISSUES FOR THERAPY PLANNING

Many human body models have been developed for therapy planning. Examples of numerical simulation used by health practitioners include radio-surgery/radio-therapy planning (see section 4.3.2), electromagnetic source localisation (an inverse procedure to identify areas of disorder within the brain based on external EEG/MEG measurements), reconstructive maxillo-facial surgery (see section 4.3.1), etc. Today, most developments are in the transition between research use and clinical use. Pilot studies performed by the technology/software developers in close collaboration with clinicians interested in cutting edge developments pave the way for research-to-clinical use transition. These tools can benefit from the use of more computationally intensive algorithms or methods that deliver increased accuracy (and in doing so, medical benefit). Grid can be used to provide access to appropriate computational services and deliver these to medical users. The HealthGrid requirements in such cases are for larger scale deployment studies allowing evaluation of a larger range of requirements, including local deployment aspects, and practical experience with production Grid use. The major challenges will be to ensure that services can be delivered into the user’s workplace in an appropriate, ergonomic manner and that security, policy and legal constraints related to the use of patient data are fulfilled.

4.3.1 Case study : surgical reconstruction

Surgical reconstruction is an area that could highly benefit from the computational resources provided by the grid. For instance, high performance interactive visualisation is particularly important to evaluate the cosmetic improvements in a surgical reconstruction of the face (*e.g.* cleft lip and palate repair for Pierre Robin syndrome in childrens). Another example is the use of a rigid external distraction system for midfacial distraction osteogenesis as a new method to correct for the underdevelopment of the midface. The treatment consists of a midfacial osteotomy (*bone cutting*) followed by a halo-based distraction (*pulling*) step. Currently, the method surpasses traditional orthognathic surgical approaches, but the surgeon's experience is currently the only mean of estimating the outcome of the treatment. Modelling the distraction process (with geometry based on CT data) may improve upon the current practice by allowing the surgeon to 'try out' several treatments *in silico* before selecting the most promising one.

Likewise, computer intensive numerical simulations may be used to optimize the functional improvements of a treatment. For instance, planning for the dental appliance best suited to the patients' oral morphological shape may be optimized with respect to the pronunciation using Computational Fluid Dynamics (CFD) analysis. To realise the prediction of the voice alteration after oral surgery or orthodontic treatment, a lot of morphological data of patients need to be stored and associated with the results of CFD analysis. The grid provides an easy way to gather morphological and simulation data.

By examination of the relationship between the morphological matter and the airflow produced by speaking, it is possible to predict the alteration of pronunciation after the oral surgery and the orthodontic treatment. The sound is calculated from the fluid vector field, which is called the Computational Aero Acoustical analysis (CAA analysis). This CAA analysis needs much more computational resource than CFD analysis, because a robust scheme is required to solve the equation of advection. Moreover, to visualise the tensor data, a much larger memory is needed. The key to solving these resource problems, is a distributed computational grid with an efficient resource manager as scheduler.

4.3.2 A GRID scenario for radiotherapy planning and treatment

Radiotherapy is one of the three major cancer treatment modalities. It has demonstrated its efficacy in curing cancer. It is also the most cost-effective modality. From a technology point of view, radiotherapy is a highly complex procedure, involving a variety of computational operations for data gathering, processing and control. The modularity of the treatment process and the need of large data sets from different sources and nature (physics, mathematics, bio-statistics, biology, and medicine) make it a privileged candidate for healthgrid applications.

In the face of budgetary constraints, it is a growing challenge for governments to guarantee to their citizens access to the most advanced health technologies that provide best quality of care but are dependant on major investments and highly specialised knowledge. In addition, the complexity of advanced radiotherapy is such that single institutes can no longer provide all the expertise for optimised treatment.

In an enlarged Europe with different traditions and histories, sharing data, expertise and computational resources will be a significant factor for a successful cost containment and improved access to a high overall quality of care in radiotherapy. It is an ideal tool for harmonising the cancer treatment throughout the continent as well as providing a common base for research collaboration.

The following picture describes the path of a patient undergoing radiotherapy. It displays the main phases of a treatment and their possible interface with different types of grid services.

4.3.2.1 Data mining in distributed databases

The variability in individual radiosensitivity is an important issue in radiotherapy. Presently patients are treated with standardised radiation doses. Gene profiling may enable an individualised adjustment of the dose so as to achieve tumour control in patients with a low radiosensitivity and avoid severe side effects in patients with above average sensitivity to radiation. To investigate whether radiosensitivity can be predicted and modulated, a virtual European tissue bank was created. It networks distributed tissue banks and their respective databases in which both the radiation treatments of the patients from whom the tissues were obtained and their effects are described. By retrieving from this shared infrastructure the gene profiles of tissues associated with overreaction to radiation, predictive assays might be developed that permit the individualisation of dose prescription.

In a first step a grid structure should allow research groups, each focusing on different molecular mechanisms, to access data in the distributed infrastructure for comparison studies. In a next step users should be able to submit the results of predictive tests for analysis to a shared software and expert platform for radiosensitivity grading.

A similar approach can be followed for other aspects of grid-supported clinical decision making such as the assessment a tumour's capacity for metastatic spread. For rapidly metastasising tumours, systemic (chemotherapy) treatment needs to be associated to the locally delivered radiotherapy to kill malignant cells that may already have migrated to other locations. New tests now under development, predicting on the basis of gene profiling which tumours are most likely to metastasise, can make 60% of the chemotherapy currently administered e.g. for breast cancer, redundant. However, it takes a highly specialised team to interpret the results of these tests correctly. Grid-supported consultation of libraries of gene profiles or, alternatively, tele-consulting services offer also in these case excellent perspectives.

4.3.2.2 Treatment planning and related imaging

Imaging for radiotherapy planning is subject to a shift in paradigm. Tissue electron density provided by CT scanning is still needed to calculate the dose delivered by photon and electron beams. To define the planning target volume (PTV) and organs-at-risk (OAR), new imaging modalities based on MR-imaging, MR-spectroscopy and PET are far superior and become a requirement for high-precision high-dose radiotherapy. In contrast to CT scanning, the latter imaging modalities are available only in reference centres for reasons of cost and expertise. To secure access for all patients to optimal imaging for radiotherapy planning, the coordinating centre could perform a grid-mediated selection of an imaging centre, and the resulting complementary image acquisitions could be sent back through the grid. To reproduce the patient positioning and perform the complementary imaging in treatment-relevant conditions, the patient-individual immobilisation devices could be physically sent to the imaging centre. Alternatively, a retrospective registration grid service (see Section 3.3.3.1) could be used to realign all the images in the relevant coordinate system.

Imaging and clinical examinations are the main sources of PTV and OAR definition. Geometrical definition of PTV still remains a tedious task for which no consensus regarding guidelines or criteria is available. Over the last decade substantial progress has been made to reduce inter- and intra-individual variation of PTV definition. Many tools have been developed for computer-aided definition of PTV and OAR including anatomical atlases that can be warped to the patient-individual anatomy (see Section 3.3.3.2), advanced image segmentation tools, databases with guidelines and examples, predictive assays. A grid could make such tools and their upgrades in due time available to all groups involved in PTV and OAR definition. Nodes on the grid that provide expert help for patient-related problems in defining PTV and OAR are needed.

4.3.2.3 Grid for Monte-Carlo dose computation

Accuracy of Monte Carlo (MC) dose computation is awesome, provided that the computing power is sufficient to allow for enough runs to reduce the statistical noise. In order to obtain an acceptable computational time for interactive use, parallel computing over a large number of CPUs has to be available. The GRID is a natural alternative to costly parallel computers. In this way, MC dose computations could become standard for radiotherapy quality assurance (QA), planning, and plan optimisation years before individual departments could afford a local investment that is capable to support MC.

Grid computing must be made accessible to medical physicists and physicians through a transparent and secure interface. As Monte Carlo simulations are performed using medical images (scanner and/or MR images showing the tumour location in the patient body), the security and integrity of the data has to be ensured, like for all other medical data.

Additional requirements needed for such deployment include the existence of a service level agreement between the departments and the grid providers by which the Grid level of performances in terms of security, stability and response time is guaranteed.

4.3.2.4 Grid for quality assurance

Each delivery centre manages the commissioning of its own treatment units and incorporates both mechanical-physical and dosimetric parameters, including uncertainty flags, into an identity card that is accessible through the grid. This identity card will allow treatment-planning providers and computation services to establish, refine or fit their computational model of the linear accelerator. The identity card also contains the reference data so that periodical quality assurance (QA) procedures could make sure that the machine performs accordingly. One might expect that the cooperation through the grid between QA providers and delivery centres will streamline the QA procedures and harmonise the identity cards over the different accelerator types.

The quality assurance of the treatment can also benefit from the grid, even if it is patient specific: once a treatment plan has been designed, some locations are selected to measure the dose level in a physical phantom that replaces the patient during the first treatment session. In parallel, the coordinating centre consults the grid for an independent dose computation service to compute the dose in the same set of points in the phantom. The comparison of the measured dose to the computed fractional dose is performed automatically at the delivery centre and will be submitted to the coordinating centre. In case of violation of tolerances, the treatment plan will be recomputed in patient and phantom by a second dose computation service in the grid. Alternatively, the coordinating centre may consult the grid for a virtual treatment at another delivery centre.

4.3.2.5 Grid for treatment delivery

The coordinating centre and the treatment delivery centre will usually be the same. However, for geographically remote areas a grid structure for treatment delivery may be useful. Modern treatment units are software controlled by control point files, made during the planning process, that define consecutive machine states and monitor unit counts to be delivered during a treatment session. As the identity and characteristics of the treatment unit are known by the planning unit, control point files can be generated and sent to the treatment unit irrespective of the geographical location of the planning and treatment units.

4.4 TOWARD REAL-TIME CONSTRAINTS

Therapy planning operations such as radiation dose computation or implant shape calculation may be computed off-line given that the results are returned in a reasonable time compatible with

clinical practice. However some applications such as surgery simulation are more demanding and require real-time computations. Real-time is a challenging problem for grid infrastructures today. Although grids can provide additional computing power, deporting computations on remote resources if often done at the cost of an initialisation pay-off that can be rather important (from minutes to hours in common batch oriented scheduling systems). To empower real-time applications, a grid middleware will need to ensure immediate execution of real-time code. Strong network requirements are also dictated by real-time constraints. Grid services dealing with jobs as sensitive as surgery simulation and computer assisted intervention should also take into account advance reservation of resources and emergency situations: the requested computation and networking resources must be allocated when the surgery starts and it should be possible to submit prioritised jobs in case of emergency with resource requisition if needed.

4.4.1 Issues for surgery simulation

Surgery simulation is the aim of many research activities today, as it is a promising tool both for surgery planning and training of surgeons. Realistic surgery simulation usually involves complex biophysical models of the human body. The building of a model for surgery simulation and its use in an interactive context have to be distinguished: building the model may require intensive and long term effort but its final formulation should enable very fast computation for the purpose of the simulation (deformation of organs, evolution of physiology, etc).

Finite Element Modelling (FEM) for instance is a well-established technique for modelling organs anatomy (through volume meshes) and the mechanical behaviour of the modelled tissues. Depending on the assumptions made on the mechanics of tissues the model may involve linear systems (*e.g.* elastic materials) or much more complex non-linear equations. A trade-off has to be found between realism and computation weight given the computation resources available.

Given the complexity of human body modelling, surgery simulators are often limited to a specific intervention procedure. Another constraint is the mechanical devices manipulated by the practitioner during the intervention: an endovascular intervention procedure or a laparoscopic surgery intervention are more easily simulated than open surgery since they require visual and haptic feedback devices with limited capabilities (visual feedback through micro-camera can be simulated on computer screens and specific haptic devices with limited degree of freedom such as laparoscopic tools can be designed). Development of open surgery simulation tools is also limited today by the state-of-the-art in 3D rendering and full degree of freedom devices. Even considering only limited intervention procedures, the computations involved may be very difficult to achieve in real time: visual feedback is known to require an update frequency of 25 Hz and realistic haptic feedback may require much higher frequencies (up to 300 Hz for soft tissues and thousands of Hz for rigid material such as bone).

A lot of progress in grid technologies regarding computing power and network bandwidth needed for real-time surgery simulation can be anticipated. The composition of various models (mechanics, visual rendering, device interactions, etc) is another area for grids to tackle that can enable more realistic and broader real-time simulation tools.

4.4.2 Issues for augmented reality and computer assisted intervention

The next stage in real-time modelling of biophysics is its coupling with interventional data in order to bring additional information that could not be observed during a medical intervention. For instance, augmented reality (AR) consists in superimposing on the scene that the practitioner perceives additional information coming from a computerised model, usually through visual devices. This enhanced perception proves to be useful in many types of interventions: it allows a neuro-surgeon to

visualise the brain tumour he has to remove projected on the head of the patient prior to, and during the intervention in order to guide its resection, a dentist to visualise the planned position and axis of the drilling to place an implant, or a radiologist to guide the placement of a needle for a biopsy or a radiofrequency ablation. In all these cases, augmented reality allows to reduce the invasiveness of the intervention.

Many currently existing augmented reality systems rely on simplified models where only a simple calibration step is required because this is computationally tractable. Indeed, more complex augmented reality applications need huge computing power for the pre-operative construction of patient-specific models and for the per-operative adaptation of these models to reality (registration, geometric deformations, etc). Going to the complete integration of a bio-physical model into a clinical AR system is a challenging task where the grid could be the key. However, this would imply very strong requirements on the security and dedication of the computer and network resources in order to ensure the reliability of the real-time system.

4.4.3 Issues for medical robotics

Another way to enhance the practitioner capabilities is to provide a computer assisted action, for instance though the use of robots. Even if the robot is passive (e.g. a robot-arm guided by a surgeon), it brings a large benefit such as minifying the human arm motion and filtering the hand tremor. Active robots may provide even more benefit, for instance by compensating for the heart motion to give the surgeon the illusion that he works on a static structure, etc. By decoupling perception (using augmented reality) from action (using robots), it has been possible to separate the surgeon from the patient, and remote surgery has proved to be possible through the use of high bandwidth dedicated networks. Even a cross-Atlantic tele- liver operation was performed a few years ago.

The main hurdle in medical robotics is the reliability of the system. Manipulating the controls through networks from a distant location definitely raises the problem of network performance and quality of service: the data flow is critical and a guaranteed bandwidth mandatory.

5 GRID ENABLED PHARMACEUTICAL R&D: PHARMAGRIDS

5.1 RATIONALE – PHARMAGRIDS

The Pharmaceutical R&D enterprise presents unique challenges for Information Technologists and Computer Scientists. The diversity and complexity of the information required to arrive at well-founded decisions based on both scientific and business criteria is remarkable and well-recognised in the industry. The decisions can form the basis for multi-year multi-person multi-millions of Euro investments and can create new scientific territory and intellectual property. Thus all aspects of managing, sharing and understanding this information is critical to the R&D process and subject to substantial investment and exploration of new informatics approaches.

Pharma R&D information includes: Chemical identity, structure, and kinetics; Biological sequence, structure and pathways; Genomic, Toxicological, Clinical trials patient data, and Pharmaco-economic and patent data to mention just a few that appear unique to the industry - in addition to the more widely familiar sources of critical organisational information such as project and financial management data and competitor intelligence information. This data takes some fairly unique forms as well, such as, optical and x-rays images, mathematical and 3-D models, billion character long encoded sequences, full text scientific reports, millions of records of prescriptions and physician encounter re-imbursements, not to mention more traditional RDMS repositories. These sources of information consist of internal proprietary, external commercial and open-source data – all often available in multiple formats and locations and occasionally conflicting – even for proprietary data inside an organisation.

These yield compelling technical challenges for information technologists and computer scientists. These problems range from knowledge-representation and integration, to distributed systems search and access control, to data mining and knowledge management, to real-time modelling and simulations, to algorithm development and computational complexity.

Managing access and sharing of such a spectrum of information across organisational barriers may not represent any new technical challenges compared to doing so simply within a multi-national Pharma company – though of course the risks may be perceived as greater.

GRID technology holds out the promise of more effective means to manage information and enhance knowledge-based processes in just the sort of environment that is well established in Pharma R&D. The potential has generated considerable interest and has led to the establishment of the PharmaGRID series of meetings [5.1] sponsored by the PRISM Forum. [5.2]. Early experiments have been very encouraging and form the basis of the following description of a PharmaGRID and inform our subsequent vision of a Rare Disease GRID and virtual organisation.

A pharmaceutical grid is a shared *in silico* resource to guarantee and preserve knowledge in the areas of discovery, development, manufacturing, marketing and sales of new drug therapies [5.3].

Pharma grids cover three dimensions:

- a resource that provides extremely large CPU power to perform computing intense tasks in a transparent way by means of an automated job submission and distribution facility
- a resource that provides transparent and secure access to storage and archiving of large amounts of data in an automated and self-organized mode
- a resource that connects, analyses and structures data and information in a transparent mode according to pre-defined rules (science or business process based)

Pharmaceutical grids open the perspective of cheaper and faster drug development. Today, average cost for developing a drug is estimated to $800 Million. Pharmaceutical grids should enable parallel processes in drug development, away from the traditional approach where target discovery, target validation, lead discovery, lead optimization and transition to development take on average 12 years. These parallel processes would take advantage of in silico science platforms for target identification and validation, compounds screening and optimization, clinical trials simulation for detection of deficiencies in drug absorption, distribution, metabolism and elimination (about 40% of drug failures).

For competitive and intellectual property protection reasons, pharmaceutical grids will predominantly be private enterprise-wide internal grids with strict control and standards. At least this will likely be the case in the near-term as more and more R&D organisations explore and become comfortable with this technology and its potential. Of course, we can argue that this will happen relatively quickly given the early reports of concrete and substantial ROIs for simple GRID applications in Pharma R&D.

However, the promise of the GRID to create effective virtual organisations based on efficient secure and trusted-collaborations will create the foundation for new forms of partnerships – amongst commercial, academic, government and international R&D organisations. Our proposed Rare Disease GRID will pilot such cross-Institution collaboration and help to define and seed this new territory.

5.2 USE CASE: PHARMACEUTICAL GRID FOR A RARE DISEASE VIRTUAL ORGANISATION

5.2.1 Introduction

There is presently a crisis in research and development for drugs for neglected diseases. Infectious diseases kill 14 million people each year, more than ninety percent of whom are in the developing world. Access to treatment for these diseases is problematic because the medicines are unaffordable, some have become ineffective due to resistance, and others are not appropriately adapted to specific local conditions and constraints. Despite the enormous burden of disease, drug discovery and development targeted at infectious and parasitic diseases in poor countries has virtually ground to a standstill, so that these diseases are de facto neglected. Of the 1393 new drugs approved between 1975 and 1999, less than 1% was specifically for tropical diseases. Only a small percentage of global expenditure on health research and development, estimated at US$50-60 billion annually, is devoted to the development of such medicines. [5.4] At the same time, the efficacy of existing treatments has fallen, due mainly to emerging drug resistance.

This is not to say that Rare Diseases are only a problem for the Developing World and those in the Developed World committed to helping ameliorate their impact. There are many thousands of rare diseases extant in the Developed World effecting children and adults only some of which are genetic or infectious, many debilitating some deadly. These represent grave personal tragedies and *in toto* substantial health and economic burdens even for the wealthiest nations. [5.5] And not insubstantial political activism recognised by government action and even legislation. Nor is it always true that there is no economic driving force for the development of therapeutic interventions for rare diseases. Sales of some orphan drugs have been reported to exceed hundreds of millions of US dollars. [5.6]

5.2.2 Issues

The unavailability of appropriate drugs to treat neglected diseases is among other factors a result of the lack of ongoing or well coordinated R&D into these diseases. While basic research often takes place in university or government labs, development is almost exclusively done by the

pharmaceutical and biotech industry, and the most significant gap is in the translation of basic research through to drug development from the public to the private sector. Another critical point is the launching of clinical trials for promising candidate drugs.

Producing more drugs for neglected diseases requires building a focussed, disease-specific R&D agenda including short-, mid- and long-term projects. It requires also a public-private partnership through efficient, secure and trusted collaborations that aim to improve access to drugs and stimulate discovery of easy-to-use, affordable, effective drugs.

The motivating perspective is to enhance the ability of both the pharmaceutical industry and academic and government research institutions to share diverse, complex and distributed info on Diseases of the Developing World for collaborative exploration and mutual benefit. The goal is to lower the barrier to such substantive interactions in order to increase the return on investment for the development of new drugs.

A PharmaGRID should create a virtual organisation and collaborative environment which will motivate and gather together:

- drug designers to identify new targets and drugs
- healthcare centres involved in clinical tests
- healthcare centres collecting patent information
- organizations involved in distributing existing treatments (healthcare administrations, non profit organizations,…)
- informatics technology developers
- computing and computer science centres
- biomedical laboratories searching for vaccines, working on the genomes of the virus and/or the parasite and/or the parasite vector

PharmaGRID will support such processes as:

- search of new drug targets through post-genomics requiring data management and computing
- massive docking to search for new drugs requiring high performance computing and data storage
- handling of clinical tests and patient data requiring data storage and management
- overseeing the distribution of the existing drugs requiring data storage and management
- trusted exchange of IP, possibly auction-mediated

A grid dedicated to research and development on a given disease should provide:

- resources for computationally intensive search for new targets and virtual docking
- resources for massive storage of post genomics and virtual docking data output
- grid portal access to post genomics and virtual docking data
- grid portal to access medical information (clinical tests, drug distribution,…)
- a collaboration environment for the participating partners. No one entity can have an impact on all R&D aspects involved in addressing one disease.

5.2.2.1 Concrete Structure of a GRID for Rare Diseases

A GRID for rare diseases has to tackle several problems which are not unique to pharmaceutical GRIDs but which have to be considered relevant for this type of research GRID. Several layers of a pharmaceutical GRID can be distinguished [see Figure 1]:

1. **The "Basic GRID Technology" layer**

This layer comprises the basic "GRID engine" for scheduling and brokering of resources. It will serve as the "common platform" to build on all other functionalities of the GRID.

2. **The "Virtual Organisation (VO)" layer**

A GRID for rare diseases is supposed to integrate users from different and heterogeneous organisations. Tasks to be dealt with in a GRID for rare diseases span from "drug design" to analysis and tracking of epidemiological data. It is more than likely that a GRID for rare diseases will have to administrate more than one virtual organisation. Access rights, security (encryption), trust building are issues to be addressed and solved on this layer.

3. **The "Distributed Data Access / Information Retrieval" layer**

Information retrieval and data integration is one of the big challenges in life science informatics. The problem of semantic inconsistence between biological and chemical databases is even more urging in the GRID context. Information retrieval and data integration yet unsolved problems in life science GRIDs. OGSA-DAI, for example, only covers the very basic level of data(base) access in a GRID and provides no means of semantic integration. Ontology-based mediation services for data integration might provide one road to go for a GRID for rare diseases; another option would be to make use of developments made in the course of other GRID projects (e.g. the distributed query processor (DQP) [5.7] or the federated version of SRS developed in the course of EU-project SIMDAT). [5.8]

4. **The "Integration of Application" layer**

Several applications useful for a GRID for rare diseases should be run in a distributed fashion. In part because they tend to be compute-intensive (such as virtual screening through high throughput docking) or because they require large data transfer if run on local machines (e.g. image analysis software). Integration of applications will require substantial meta-information on algorithms and input / output formats if tools are supposed to be interoperable in the GRID. Assembly of tools for virtual screening into complex workflows will only be possible if data formats are compatible and semantic relationship between objects shared or transferred in workflows are clear.

5. **The "Workflow" layer**

Pharmaceutical research on a GRID implies the partial representation of research and business processes in the form of complex workflows. One core element of a GRID for rare diseases is the virtual screening machine including, amongst other functionalities, a generator for focused virtual libraries, one or several high throughput docking softwares, different filters for pre- and post-processing of hits in the virtual screening procedure and software for the prediction of basic ADME parameters. The combination of the tools behind these functionalities in a workflow and the execution of this workflow in the GRID requires a formal description as provided e.g. by WPDL [5.9] or SWFL [5.10, 5.11]. A GRID for rare diseases could adopt workflow technology from one of the existing GRID projects in which workflow plays a central role (e.g. SIMDAT; workflow technology platform research group lead by Prof. Yike Guo or MyGRID led by Carole Goble). [5.12]

6. **The "Ontology / Knowledge Representation" layer**

Formalised knowledge representations (ontologies) will play a key role in any future pharmaceutical GRID. Whereas the life science sector has made substantial progress in the field of ontologies for gene function annotation (reference to GO), pharmaceutical discovery is not yet represented at a comparable quality and level of detail in a "pharma ontology". A GRID for rare diseases should have a decent activity on constructing an ontology for the disease under investigation, for genetic epidemiology aspects including the categorisation of clinical phenotypes. Moreover, a pharma ontology would have to bridge from biology to chemistry as it would have to formally describe a pharmaceutical target as well as the concept of a "in silico screening hit" and its development into a "lead compound" for experimental evaluation. As ontology construction is a task for a community of experts rather than work for one individual a consortium formed to work on a GRID for rare diseases would provide the ideal community to start construction of a pharma ontology.

7. The "Data and Knowledge Mining Services" layer

The GRID for rare diseases will also very much depend on services for statistical approaches to data mining (e.g. in the field of epidemiology) and learning and optimisation of *in silico* drug discovery approaches. Knowledge mining services will largely depend on the availability of a pharma ontology (see paragraph 6). As statistical models for (genetic) epidemiology vary across a broad range of possible approaches, meta-information on statistical approaches and methodology used for modelling will be crucial. If a GRID for rare diseases extends into aspects of health and infectious disease management as outlined above, modelling of disease spreading mechanisms and prediction of epidemic traits will be necessary. For this purpose, we will need to address the issue of interoperability of statistical models as well as the issue of comparability of predictions made on the basis of these statistical models.

5.3 CONCLUSION

A grid for a rare disease goes far beyond high throughput virtual screening by means of molecular docking. It requires the construction of a knowledge representation system for the organism / the disease under investigation as well as for the processes associated with R&D and interorganisational collaboration and exchange of Intellectual Property It appears as one of the most intriguing applications of grid technology in a short term provided Intellectual Property issues are properly addressed.

It is only one of many possible applications in the general arena of PharmaGRIDs, where the investment of GRID and Semantic Web technology has the potential of substantial return in cost reduction, new intellectual capital, innovative processes, new health interventions and powerful virtual organisations.

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6 GRIDS FOR EPIDEMIOLOGICAL STUDIES

6.1 RATIONALE

Conventional epidemiology requires extensive collections of data concerning populations, health and disease patterns, as well as environmental factors such as diet, climate and social conditions. A study may focus on a particular region or a particular outbreak, or it may take as its theme the epidemiology of a condition across a wide area. The range of data required will, therefore, vary with the type of study, but certain elements persist: a degree of trust in the data is essential, so its 'provenance' has to be assured and the standards of clinical practice under which it was obtained have to be above a certain threshold. Where the data has been gathered under different clinical regimes, it must be possible to establish their semantic equivalence, to ensure that aggregation or comparison of datasets is legitimate. Ethical issues may also arise if data collected in the first place in the course of individual health care is to be used for research.

The analysis of aggregated data requires the construction of complex models and the use of sophisticated statistical tools. This has necessitated collaboration between physicians and statisticians, and the rise of epidemiology as a discipline. The impact of genomic analysis will extend the kinds of variable under study and the range of expertise to be applied.

A useful illustration is provided by a current Swedish study into the effect of 'antibiotic pressure' – roughly, the volume of antibiotic prescriptions – on penicillin-resistant pneumococci. The phenomenon under study is the development of resistance in these bacteria as they occur in a population of children and their families, propagated primarily through contact at day nurseries and then displaying various patterns of spread beyond that. It is hypothesized that above a threshold level of antibiotic pressure, the spread of resistant bacteria is facilitated rather than hindered by dispensing antibiotics to the susceptible population. Preliminary results from this study suggest that patterns of urban and rural life (e.g. commuting to work) and social class-correlated attitudes to acceptance of medication may play a significant part in the propagation of resistant bacteria.

By way of contrast, we may consider a proposed study of breast cancer in Europe in a recent project which is seeking to aggregate relevant datasets from across the continent and so make possible a comparative study, including to some extent the effects of diet and lifestyle. Here the primary object of study is the mammograms of women with breast cancer and the correlation of particular features with various health factors.

The technology to allow federation of databases stored locally in hospitals has existed for some time. It is possible for these databases to be queried for epidemiological purposes while preserving patient anonymity. Such distributed queries may be managed and supervised by the hospitals with primary responsibility for the data, ensuring compliance with ethical and legal regulatory frameworks. None the less, the political difficulties inherent in the integration of information systems are well known and this has plainly not happened to the degree that it is possible despite major government efforts.

Grids supervene mere integration of databases. They can enforce the interoperability of tools and analysis services and they may also enforce common standards and semantic clarity about database content and tool input / output. Indeed, the grid-based federation of retrieval systems provides a significant alternative to federation of databases. Indeed, we may not see the latter for quite some time: federation of databases requires – in case the databases should be interoperable – clear semantics and standards based on conventions about semantics. Attempts to use semantics-based mediators have not been particularly successful so far.

Genetic epidemiology GRIDs for the identification of genes involved in complex diseases

Statistical studies: work on populations of patients. One example is the tracking of resistance to therapeutic agents. This is most notable in relation to antibiotic resistance in common bacteria in nosocomial and community settings

Drug assessment: drug impact evaluation through populations analysis

Pathology follow-up: pathologies evolution in longitudinal studies

Grids for humanitarian development: Grid technology opens new perspectives for preparation and follow-up of medical missions in developing countries as well as support to local medical centres in terms of tele-consulting, tele-diagnosis, patient follow-up and e-learning.

6.2 ISSUES FOR MEDICAL DATA MANAGEMENT

6.2.1 Need for data integration

Even though seamless integration of data sources constitutes an essential part of the general GRID vision the situation in the real world of medical data management clearly demonstrates how far we have to go from the current state to achieve this seamless integration. In contrast to bioinformatics, where at least two major systems for data integration are in use (ENTREZ at the NCBI and SRS at EBI), no such integration layer exists in the field of medical informatics. Based on the experience in the field of bio- and genome informatics it appears to be more than unlikely that standardisation initiatives will allow to promote tight integration of medical databases on the short run.

One road to go for the integration of medical data would be to adopt GRID strategies for data integration developed for bioinformatics. In SIMDAT, an Integrated Project funded in the course of the FP6 IST programme, federation of the data integration system SRS is one of the major R&D goals defined for this project. The advantage of this approach is twofold:

an existing and well established data integration system with a large user and developer community in both, academia and industry (more than 40 EMBnet nodes worldwide maintain SRS servers [reference EMBnet.org]) will be GRID enabled; avoiding the need for users to accommodate to new ways to e.g. query integrated databases.

federated SRS will be able to integrate non-federated databases and federate them at the level of data retrieval; thus circumventing the need to migrate established (local) databases to federated systems.

As mentioned above, an adoption strategy of the biomedical sector would align perfectly with existing funding strategies in FP6. Moreover, the cost and effort for establishing completely new databases in the field of clinical research / genetic epidemiology would be significantly limited, thus paving the way for smooth and rapid implementation of first demonstrators.

The proposed adoption of federated SRS as a data integration platform for medical (phenotype) data should not at all prevent a HealthGRID community in the field of genetic epidemiology from doing their homework on standards. Any type of interoperability requires a broad and common understanding of data types and applications. Even though federation of SRS will certainly help to overcome roadblocks such as local database systems, the integration of analysis tools in a GRID context will ultimately call for common understanding of semantics. Therefore, domain-specific meta-data will play a crucial role in GRIDs for genetic epidemiology (as much as in all other HealthGRID scenarios) to enable interoperability of analysis methods and comparability of data and results.

6.2.2 Data semantics in genetic epidemiology

Standardised semantics will be essential for genetic epidemiology. GRID enabled systems enforce even stronger efforts towards unified semantics as interoperability of data and analysis services rely almost completely on widely accepted naming of objects and processes. Although a significant portion of developments done in the context of the semantic web will be relevant and partially re-useable for biomedical GRIDs, domains such as genetic epidemiology will need dedicated initiatives for clarified semantics carried on by experts in the field. More specific: the standardised acquisition and recording of clinical phenotypes plays a pivotal role in genetic epidemiology. Unified naming of phenotypes and standardised acquisition and recording of clinical parameters have to be supported by a GRID for genetic epidemiology. One of the central services for in a GRID for genetic epidemiology studies therefore has to be a clinical annotation service for clinical phenotype descriptions. Such an annotation service has to be user – friendly, easy to use by non-computer-experts and it has to make use of widely accepted naming concepts in the domain of genetic epidemiology (if they exist at all). One possible solution to the problem of a GRID-based annotation service for clinical phenotypes would be an ontology-based annotation service which would allow navigation through controlled vocabularies and selection and linking of defined concepts to entries in existing databases for phenotype recording.

6.3 HETEROGENEOUS FORMATS OF MEDICAL IMAGES AND METADATA

6.3.1 Images, Standards and Medical Records

Images play a greater part in health care and medicine than ever before. Medical imaging modalities have proliferated with increasing sophistication in resolution, extraction, fusion, annotation and analysis. Some modalities have proved their worth in displaying anatomical structure; others are refining the possibilities of functional imaging. While the majority of images are taken with a view to diagnosis or to monitor the effects of treatment, some viewing modalities are extended to intervention, as in ultrasound-guided fine needle aspiration.

The question to what extent these images are part of the patient's medical record has largely been resolved in favour of the retention of images along with character-based and graphical data, from 'history' through admission/discharge notes and letters to pathology results. This raises a host of issues, concerning storage and presentation formats, communication protocols, and standards. We do not enlarge upon the wider picture here but illustrate some of the issues with an analysis of questions that arise in breast cancer screening.

6.3.2 Epidemiological Aspects of Breast Cancer Imaging

Breast cancer is arguably the most pressing threat to women's health. For example, in the UK, more than one in four female cancers occur in the breast and these account for 18% of deaths from cancer in women. Coupled with the statistic that about one in four deaths in general are due to cancer, this suggests that nearly 5% of female deaths are due to breast cancer. While risk of breast cancer to age 50 is 1 in 50, risk to age 70 increases to 1 in 15 and lifetime risk has been calculated as 1 in 9. The problem of breast cancer is best illustrated through comparison with lung cancer which also accounted for 18% of female cancer deaths in 1999. In recent years, almost three times as many women have been diagnosed with breast cancer as with lung cancer. However, the five year survival rate from lung cancer stands at 5%, while the breast cancer figure is 73%. This is testament to the effectiveness of modern treatments, provided breast cancer is diagnosed sufficiently early. [1] These statistics are echoed in other countries. The lifetime risk of breast cancer in the USA has been estimated as 1 in 8. Here also incidence has increased but mortality decreased in the past twenty years. [2] There is evidence that stress and diet may also be correlated with breast cancer, although the underlying

biochemistry is not fully understood. For example, twenty years ago breast cancer was almost unknown in Japan but its incidence now approaches Western levels. This may be associated with major changes that have occurred in Japan in this period, e.g. the increased consumption of high lipid foods and higher levels of stress with more women working. Finally, it may be noted that a very small number of men, for example, about 100 in the UK and 400 in the US, also die annually of breast cancer.

The statistics of breast cancer diagnosis and survival appear to be a powerful argument in favour of a universal screening programme. However, a number of issues of efficacy and cost effectiveness limit the scope of most screening programmes. The method of choice in breast cancer screening is mammography (breast X-ray), although self-examination and clinical palpation are also used; for precise location of lesions and 'staging' (establishing how advanced the disease is) ultrasound and MRI are also used. A significant difficulty lies in the typical composition of the female breast, which changes dramatically over the lifetime of a woman, with the most drastic change taking place around the menopause. In younger women, the breast consists of around 80% glandular tissue which is dense and largely X-ray opaque. The remaining 20% is mainly fat. In the years leading up to the menopause, this ratio is typically reversed. Thus in women under 50, signs of malignancy are far more difficult to discern in mammograms than they are in post-menopausal women. Consequently, most screening programmes, including the UK's, only apply to women over 50.

Given the decision to institute a screening programme, apart from deciding the subject age-group, another vital question is that of frequency of screening. Based on contemporary thinking and practice elsewhere in Europe, the UK programme was set up to screen every three years; however, by the time this was inaugurated, further research in Sweden suggested that screening should take place more often. Indeed, one of the problems the UK programme has faced has been the phenomenon of so-called 'interval cancers', cancers which develop substantially in the three-year interval between screens.

A further question which received a conservative answer in the UK was how many images of each breast should be taken. It is generally believed that two images of each breast are ideal: a cranio-caudal (CC) image, vertically downwards through the breast, and a medio-lateral oblique (MLO) image, at 45º from shoulder to opposite hip, taking in part of the pectoral muscle. However, in view of the resources needed to take and interpret four images, it was decided that two CC images should suffice.

Breast X-rays are rather challenging, both to take and to interpret. In mammography, the breast is compressed between two Lucite compression plates partly to immobilise it and partly to displace as much fat to the margins as possible. Carcinomas of different types attenuate X-rays of typical energies by about 5% more than functioning glandular tissue (parenchyma) and by up to twice as much as fatty tissue. Thus fat against parenchyma or tumour contrast very well, but it is very much harder to draw a clear distinction between signs of carcinoma and functioning tissue.

While clinically significant signs are subtle, many parameters also affect the appearance of an image. For mammograms, these include image acquisition parameters, such as degree of breast compression, tube voltage and beam intensity, and anatomical and physiological data, which show marked variation across the population, at different times in the menstrual cycle and throughout the course of a woman's life. The way diagnostic imaging systems are used and maintained by clinicians also varies between imaging centres and breast screening programmes. In order to study the epidemiology of breast cancer, it is necessary to understand this variability. This is also a prerequisite for the integration of Computer Aided Detection tools and quality control in the process.

Radiographers ('radiologic technicians' in the US) adhere to certain codes of professional practice, but are responsible for maintaining the X-ray equipment and have freedom to determine machine settings in the course of their work. This makes comparison of images as taken rather difficult. Occasionally this may be a problem for images of the same patient at different times, but it is rather more serious if comparability of images is to be used for diagnostic purposes or in a radiological training programme.

In the UK, a radiologist participating in the national screening programme may have as little as 40 seconds to study each pair of CC images taken of each woman screened. This is intensive and exacting work, so that viewing images for more than half an hour at a time may impair the radiologist's performance. This is likely to be a factor in an aspect of the screening programme which has drawn much public criticism, that both sensitivity (which gives a measure of false negatives) and specificity (which reflects false positives) have been unacceptably poor.

This has to be set against the reality that demand for screening services is increasing and the growing realisation that four images, two CC and two MLO, of each patient provide the radiologist with a better basis for diagnosis. The question arises, therefore, is it possible to improve the efficiency of diagnosis while at the same time increasing the screening frequency and the number of images? The supply of radiologists is limited, so another way to address the problem is to ask whether it is possible to support the radiologist with technology. [3]

6.3.3 Image-oriented epidemiology

Patient management (diagnosis, treatment, continuing care, post-treatment assessment) is rarely straightforward; but there are a number of factors that make patient management based on medical images particularly difficult. Often very large quantities of data, with complex structure, are involved (such as 3-D images, time sequences, multiple imaging protocols). In most cases, no single imaging modality suffices, since there are many parameters that affect the appearance of an image and because clinically and epidemiologically significant signs are subtle. Among the many relevant factors are patient age, diet, lifestyle and clinical history, image acquisition parameters, and anatomical and physiological variations. Thus any database of images developed at a single site – no matter how large – is unlikely to contain a large enough set of exemplars in response to any given query to be statistically significant. Overcoming this problem implies constructing a very large, federated database, while controlling for statistical biases such as lifestyle and diet almost certainly leads to a database that must transcend national boundaries. Realizing such a geographically distributed (pan-European) database necessitates so-called Grid technology [4], and the construction of a prototype would push emerging Grid technology to its limits.

This section outlines the advances made in the MammoGrid [5] project towards providing a collaborative Grid-based image analysis platform in which statistically significant sets of mammograms can be shared between clinicians across Europe. The applications to be implemented can be thought of as addressing three main problems:

- Image variability, due to differences in acquisition processes and to differences in the software packages (and underlying algorithms) used in their processing.
- Population variability, which causes regional differences affecting the various criteria used for the screening and treatment of breast cancer.
- Support for radiologists, in the form of tele-collaboration, second opinion, training, quality control of images and a growing evidence-base.

In practical terms, the project will:

- evaluate current Grids technologies and determine the requirements for Grid-compliance in a pan-European mammography database;
- implement a prototype MammoGrid database, using novel Grid-compliant and federated-database technologies that will provide improved access to distributed data;
- deploy versions of a standardization system (SMF – the Standard MammoGram Form [6]) that enables comparison of mammograms in terms of tissue properties independently of scanner settings, and to explore its place in the context of medical image formats; and
- use the annotated information and the images in the database to benchmark the performance of the prototype system.

The European dimension of the MammoGrid consortium, including hospitals in north and south Europe, provide the first opportunity for statistical studies of breast cancer to be conducted and analyses to be made on geographical, cultural, environmental and temporal influences on cancer development. MammoGrid should provide statistically significant numbers of exemplars even for rare conditions of cancer development and will therefore enable more diverse epidemiological studies than hitherto have been possible. The project will consequently pave the way for potential knowledge discovery in the diagnosis and understanding of breast cancer when the database is made available to medical professionals.

In addition, the development of an efficient information infrastructure requires data with integrity, quality and consistency. The project will meet these requirements by developing standard data formats and strict automated quality checks, which will lead to improved and normalised breast screening procedures. Such a secure, efficient and standardised storage of medical knowledge in an EU-wide federated database will also provide an ideal educational tool for training radiographers and radiologists. Standardisation on data formats will control the variation in the quality of images and diagnoses in European healthcare.

6.4 LARGE SCALE STUDIES

6.4.1 Building population-based datasets

A European GRID for Genetic Epidemiology would open completely new perspectives for gathering data on large populations and – as a consequence – would allow stratification of large cohorts for large scale European Genetic Epidemiology studies. Again we would like to stress that such stratification would have to be built on common standards for data acquisition and annotation of clinical parameters. One possible problem that we foresee in this context is that there are regional, legal and cultural differences that may obstruct the building of pan-European, population-based datasets. As a consequence, we propose to complement any type of HealthGRID activity that could possibly encounter problems of this type is supplemented and accompanied by research activities in the field of ethical, legal, and cultural aspects that might impact future HealthGRIDs.

The current situation in Europe is quite heterogeneous. Initiatives to build large population-based datasets have been started in Iceland [9], the UK [10], and in one Baltic state, Estland [11]. These national initiatives are driven by a different rational: whereas in Iceland it was a private-public partnership between DECODE genetics and the government of Iceland in the UK and in Estland the initiatives are based on governmental scientific research programmes. In how far commercial aspects will interfere with the goals of a pan-European initiative to build population-based datasets remains unclear, however, it is clear that large population-based datasets (and associated sample collections) are not only interesting for basic science but also for the pharmaceutical industry.

Even though we foresee problems as discussed above, the chances that come with large scale studies and pan-European population-based datasets will exceed the risks of potential abuse of genetic information by and large. Currently, genetic epidemiology studies suffer from low numbers of samples, inconsistent acquisition of bio-parameters and complex genetics. We expect a huge impact of GRID technology on the "limited number of samples" issue as a pan-European GRID for Genetic Epidemiology would substantially built on population-based datasets compiled in a coordinated action all over Europe.

6.4.2 Statistical studies

The statistical analysis of complex genetic diseases involving many genes and complex phenotypic parameters to describe "drug abuse" or "depressive behaviour" confronts us with the need for much higher numbers of samples to look at; it confronts us with the need to handle smaller numbers of patients that belong to the catchment area of (specialised) clinics and it

Built on population-based datasets statistical studies on the influence of allelic predisposition, behavioural aspects, nutrition habits, regional or national healthcare management and many other parameters will be possible. A central task for a GRID project for genetic epidemiology would be to enable and to promote interoperability of statistical analysis tools. Similar to initiatives e.g. in the field of systems biology an exchange service for statistical models based on a common understanding (and classification scheme?) of statistical approaches would be needed. A point to start with would be a "tool box" of statistical models including relevant meta-information on algorithms, modelling strategies and constrains, application scenarios and possible equivalence or variations of statistical models. As a GRID service this tools box would allow easy exchange of methods and improve interoperability of statistical models and data mining capabilities on the side of the users of the Genetic Epidemiology GRID.

6.4.3 Drug assessment

Large scale studies on the impact of the genetic "makeup" of patients for drugs effects in defined indication areas are certainly one of the major application scenarios for a GRID for genetic epidemiology. On the biological and pharmacological side, the determination of allelic frequencies of drug target genes in European population is one important application field for a genetic epidemiology GRID with large population-based datasets. A second application scenario concerns aspects of drug safety; again an aspect that is highly relevant for public health and the pharmaceutical industry. Adverse drug effects depend – amongst other factors – on cytochrome gene polymorphisms and one of the first large scale study done on a GRID for genetic epidemiology could be a project on cytochrome allelic variability in patients with e.g. resistance to a certain class of compounds.

A third application scenario could strive to unravel the genetic basis of drug insensitivity which is not based on allelic variation of acute response detoxification genes. As an example we might think of the insensitivity of a huge percentage of multiple sclerosis patients to treatment with Interferons. Another scenario would concern the insensitivity of a significant portion of the European population to treatment with glucocorticoids.

From the GRID research perspective, these studies require a tight integration of knowledge coming from heterogeneous disciplines, namely pharmacology and genetics. Currently, knowledge representations (ontologies) for pharmacology are missing by and large; we therefore expect that a GRID on genetic epidemiology that addresses aspects of drug action will have to include an activity on ontology construction for the domain of pharmacology. A "pharmacology – ontology" would also help to formalise and to standardise the description of clinical parameters measured in the course of large scale studies. As drug assessment comprises all aspects of pharmacodynamics, special attention will have to be paid to appropriate representation of dynamic processes (e.g. changes of drug serum

concentration over time); sharing of mathematical / statistical models for the analysis of drug effects and drug stability will be essential for pan-European studies.

6.4.4 Pathologies follow-up: pathologies evolution in longitudinal studies

The study of pathologies follow-up would include information related to regular hospital visits, home-care monitoring of signs and symptoms, recording of interventions and drug effects, environmental issues etc. for example in the study of chronic diseases such as cardiovascular diseases, asthma, diabetes, or sleep disorders. The main aim of clinical trials is to investigate new methods and medical knowledge for disease management. However, these studies are usually fragmented and non-uniform, thus, cannot result in common conclusions. One can see this issue from two standpoints: a) how pathology follow-up or the setup of clinical trials can be supported, and b) how the results of clinical trials can be better utilized in a manner that feeds medical knowledge and clinical practice.

The main obstacles that have to be overcome towards the evolution of pathologies into longitudinal studies, in order to provide enhanced medical knowledge and procedures, are:

Clinical protocols are not always standardized and widely accepted
Measurements, devices, computational overhead as well as data, may vary
Variability in populations participating in the clinical trials
Conception of diagnosis and treatment may also vary

Accordingly, the requirements arisen for effective longitudinal studies are:

Large studies leading to better statistics and understanding of mechanisms
Multi-center approaches that take into account environmental and other factors
Availability of evidence-based medicine
Sophisticated statistical analysis and modeling
Facilitate cooperation among healthcare professionals
End-up with protocols, data descriptions, measurement descriptions and models

Adoption of a GRID-based approach in developing pathology follow-up studies may provide the technological means to overcome some limitations related to the diversity and complexity of the currently available biomedical applications, in terms of:

Support and improvement of existing databases import/export facilities
Transparent access to data from the user viewpoint, without knowledge of the actual data location
Authorization policies allowing anonymous and private login for access to public and private databases
Provision for the privacy of medical information and fulfilment of legal requirements in terms of data encryption and protection of patient privacy
A wide range of analysis tools, and contribution to the comparison-benchmarking of software applications, as well as to the combination of methods supporting clinical practice
Access to tools and services that support the clinical trials, e.g., real-time processing tools, alerting tools for the clinicians, educational services for patients, etc.
Establishment of common protocols for homogenizing data originated from distributed and heterogeneous databases, based on common semantic mechanisms
Methods for fetching data based on similarity measures, for example, supporting diagnosis in ambiguous cases
Common calibration methods for measurements, thus, mechanisms dealing with measurements' variability and ensuring a common understanding of measurements and devices

In order for a HealthGrid platform to achieve such goals and contribute towards pathologies follow-up studies, interdisciplinary cooperation among clinicians, managers, decision makers and

informaticians is required, imposing the requirements for using GRID and defining such grid services that can be widely accepted and applied in clinical practice, while taking into consideration the local procedures and guidelines followed in healthcare delivery.

6.4.5 Homogenisation, interoperability and meta-analysis of large genetic epidemiology studies on complex diseases

The genetic basis of complex diseases provides a real challenge to any information system for genetic epidemiology and for a GRID for genetic epidemiology in particular. Complex diseases are characterized by the high number of parameters to be recorded and by a "intrinsic fuzzyness" of the conceptual definition of clinical phenotypes (e.g. "depression"). Genetic epidemiology studies in this field require much larger cohorts of patients to produce significant results.

From this analysis, the perspectives of a GRID for genetic epidemiology appear promising. A GRID for genetic epidemiology could have several effects:

- Homogenisation of the selection of clinical parameters to be measured for the analysis of the genetic basis of complex diseases
- Interoperability of data at both, the data acquisition level as well as the database and data management level through structured knowledge representations
- Broadening of the statistical basis through expansion of relevant cohorts from regional or national scale to pan-European scale
- Interoperability of statistical models and efforts to enrich meta-information on analysis tools, algorithms and modelling approaches

6.5 CASE STUDIES

6.5.1 Genetic epidemiology

Europe possesses a remarkable heterogeneity with respect to health parameters. Besides organisational issues (e.g. different healthcare systems and health policy) European health is very much dependent on local or regional parameters such as genetic predisposition and/or environmental (in particular nutritional) conditions. Genetic epidemiology studies try to establish links between genetic variation (polymorphisms / allelic variance) and individual risk that have an impact on the quality of life (including major diseases). There is extensive funding of genetic epidemiology studies in FP5 and FP6 in the course of genome research, in the context of nutrition research and in different health related projects.

Genetic epidemiology studies have a direct impact on decisions on health quality standards, disease management and risk assessment. Unfortunately, the prospects of Europe-wide genetic epidemiology studies have not yet been fully explored; even though significant effort has been undertaken in the course of national projects, data from different studies are not easily comparable and data access is very limited.

A GRID – based system for genetic epidemiology ("*GenEpi*GRID") will actually promote the development and / or adoption of standards in this field. It will also greatly improve interoperability of statistical analysis methods used for the analysis of genetic epidemiological data and it will probably allow for new ways to perform data mining approaches in a distributed (data) environment. The requirements of GRID – based systems for interoperability, clear semantics of data and applications,

secure data handling of medical data and administration of virtual organisations are extraordinarily high and we can expect that a *GenEpi*GRID - as a European reference activity - would have a strong effect on HealthGRIDs in general.

Based on the general considerations outlined above, a *GenEpi*GRID would have to address the following aspects:

- clear semantics for data acquisition methods
- standards for the selection and description of patient collectives
- standards for patient collective size and statistical power with respect to patient collective size
- an ontology for technologies used in genetic profiling (an ontology similar to the microarray ontology generated by the MGED consortium)
- an ontology for phenotype descriptions based on a relevant controlled vocabularies
- a dedicated, GRID enabled annotation service for genetic epidemiology
- data security aspects of biomedical data handling, in particular paying tribute to the different European regulations for the handling of patient data
- interoperability of data analysis methods, in particular a means for declaration of statistical methods used
- capturing of statistical rational applied to patient collective selection
- capturing of rational for candidate gene selection
- capturing of rational for the selection of chromosomal regions
- declaration and brokering of statistical analysis services
- GRID based statistical modelling and data mining
- GRID based evaluation of existing relevant literature (including electronic patient records) by means of automated information extraction methods (text mining).

As we realise from this list of topics to be addressed by a *GenEpi*GRID, clear and well structured semantics of concepts relevant for genetic epidemiology play a pivotal role for the success of such a reference project. This immediately raises the question, whether the community of genetic epidemiologists is prepared to “buy in” into a *GenEpi*GRID. Substantial effort on open standards, capturing and formalisation of statistical considerations relevant for patient collective selection and controlled vocabularies / ontologies is needed from the future users of a *GenEpi*GRID. The scientific benefit of such effort, however, would be paramount:

- Data from national as well as European genetic epidemiological studies would be comparable at different levels; ranging from sample acquisition and sample treatment protocols to the rational for patient stratification and suitable statistical analysis approaches
- Standards for the description of clinical parameters would be established; the semantic relationship between parameters would be clear and consequently comparability of genetic epidemiological studies based on conceptual equivalence at different levels would be possible
- Interoperability of statistical models and analysis methods would be greatly enhanced; rational capturing for statistical approaches would become a routine procedure

- Conclusions drawn from genetic-epidemiological studies could be re-analysed and re-tested with each new (equivalent) study run using the *GenEpi*GRID.
- Parameters influencing e.g. the prevalence for certain tumour types in certain regions within the EU could be identified with a much higher chance. Effects influencing genotype – phenotype – associations such as nutrition habits, behavioural differences, quality of health services and so forth could probably be quantified with much better significance.
- Variability of associations between genes and phenotypes could be assessed at the Pan-European level; which means that the genetic heterogeneity within Europe would open new perspectives to define "control groups" in statistical meta-analyses.

For a *GenEpi*GRID we foresee a key role for GRID services that refer to established controlled vocabularies and ontologies. These semantics based services will provide one key feature for future genetic epidemiology studies, in particular in studies that address complex diseases. A problem particular to this field is that it suffers from the complicated and very complex phenotype descriptions necessary to describe e.g. depression in terms of quantitative parameters. This problem is very serious; current discussion of future trends in genetic epidemiology of complex diseases already foresees that this field of science is running the risk to become too expensive to be continued in the way this science has been done in the past. [8] A *GenEpi*GRID will provide a first means to make data and tools interoperable at the European level; ultimately such dedicated GRID will help to limit the costs of genetic epidemiology research in the field of complex diseases. Following the argumentation of Merikangas and Risch, we would propose that complex diseases with the strongest evidence for genetic etiology, limited ability to modify exposure or risk factors, and high public health impact should have the highest priority for a European *GenEpi*GRID.

6.5.2 Case study : grid on nosocomial infections

Nosocomial infections are among the three most costly and deadly infectious diseases. The growth in these has continued unabated for nearly two decades, despite many measures – such as shorter hospital stays – which can reasonably be expected to have had an attenuating effect.

A major reason for this growth has been the emergence of antibiotic resistant bacteria. There are now bacterial strains which are resistant to all but one known antibiotic. It is widely argued that the only sustainable defense against this danger is greater vigilance, public education and a significant reduction in 'antibiotic pressure' in the community.

Greater vigilance and preparedness are also the only possible defenses against two other modern plagues: bioterrorism and various economically catastrophic animal diseases – in the United Kingdom, BSE and FMD being cases in point. Some of the ideas in this proposal intersect with proposals for dealing with these otherwise unrelated dangers.

There are many projects in Europe and elsewhere aimed at surveillance. In Europe, these range from the large scale EU-funded projects, such as the European Antimicrobial Resistance Surveillance System (EARSS) and the European Resistance Intervention Study (EURIS), to smaller partnerships between universities and commercial organizations.

Attention is also drawn to the American CDC's 1999 Public Health Action Plan to Combat Antimicrobial Resistance, launched with the aim to support and improve surveillance, prevention and control, research and product development. The executive summary of this report provides a convenient list of actions to be taken in combating antibiotic resistance.

There are several scientific and technical challenges in the design of a grid epidemiological information system. The typing, i.e. the identification, of bacterial strains is a problem for several

reasons, among which the multiplicity of typing methods and the difficulty in communication in the absence of a universal coding system are significant. Projects to define a common language often rely on one particular method, but there is a need to continue to accommodate new techniques which promise greater discrimination. It is argued that typing of bacterial strains, with the need to search for and reconcile fuzzy information across a large number of reference locations, is in itself a suitable grid problem.

However, the problem of infection is wider than the identification challenge. Any strategy to combat antibiotic resistance based on epidemiological insights will have to take account of the impact of such factors as levels of antibiotic prescription and of what is known about patterns of disease evolution. [7] In both these areas, provided information is gathered – e.g. about the volume of pharmacy-dispensed antibiotic prescriptions – the evidence base on which to determine best practice would itself continue to evolve and improve.

A grid collaboration in the epidemiological control of antibiotic resistant pathogens would require at least the following:

- partnership and integration of knowledge from projects such as EURIS and EARSS;
- a plausible solution to strain identification as an information problem;
- coordination of biomathematics efforts to identify and predict patterns of disease propagation.

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7 GRID IMPACT TO FACILITATE GENOMIC MEDICINE

7.1 TOWARDS GENOMIC MEDICINE

The full realisation of the *Genomic Medicine* concept, in which genomics and proteomics are used to empower health care, requires the integration of knowledge from worlds traditionally apart, specially biology and medicine. To effectively harness the wealth of information available in research centres and care facilities, a new framework of computer methods and tools must be in place, bridging medical and bio informatics.

7.1.1 Developments in Genomics affecting care delivery

The completion of the HGP is seen for medicine as a source of new knowledge to understand the relationships between the structure of human genes, environmental factors and physiopathological processes [1]. In the post-genomic era, the possibility of studying all the genes, all the proteins or a high number of mutations in human cells paves the way to new research possibilities not feasible until now to understand the molecular basis of complex diseases facilitating the development of new diagnostic and therapeutic solutions [2].

The term *Genomic medicine* would be valid for integrating molecular medicine and personalized medicine. *Molecular medicine* is defined as the discipline that aims to explain life and disease in terms of the presence and regulation of molecular entities. *Personalized medicine* applies genomic knowledge to identify the predisposition of a person to have a disease, to develop therapies adapted to genetic features of patients, that could be prescribed with guarantees of security and efficiency. Personalized medicine tries to know and clinically use individual genetic differences [3]. *Preventive Medicine* could be added here, in the sense of practising health interventions even before symptoms of the disease appear, bearing in mind the possibility to predict genotype-environmental interactions that could lead to disease associated phenotypes.

Research being carried out in genomics and proteomics will enable to better understand the molecular causes of disease and to discover how human genetic variation contributes or protects against suffering a disease. Genomic medicine will impact care provision in different ways:

- **Clinical diagnosis:** The high-performance new research devices (biochips) enable to monitor simultaneously a large number of parameters that can be used as diagnostic markers. Genetic analyses are used to identify a person who is likely to suffer a disease, as well as to confirm a suspected mutation in an individual or a family, identifying people with a high risk of contracting a disease before the associated symptoms appear [4]. Proteomics will also offer new markers of interest for patient monitoring [5].
- **Disease reclassification**: Comparison of different gene expression profiles between healthy cells and those that come from a diseased tissue, allows in some cases, the identification of different molecular shapes and the proposal of new classifications for the diseases, which will allow an improvement in their diagnoses and prognoses.
- **Pharmacogenetics and Pharmacogenomics**: Technological platforms proposed for successfully studying and applying individual variations on a molecular scale (*pharmacogenetics*) have been developed in the last years. New technologies that ease the understanding of the role of genes in

diseases are providing the industry with substantial opportunities of more powerful medicines, safer drugs and better vaccines (*pharmacogenomics*) [6].

- **Genetic epidemiology and Public Health:** The use of new genetic information technologies will make it possible to perform cost-effective screening (genetic tests) at the population level [7]. To transfer the genomic knowledge to the field of public health and epidemiology it will be important to develop efforts in associative genetics, genotype-phenotype population studies, programs for disseminating genetic information and training health workers.

7.1.2 The enabling role of IT

Though it is currently difficult to predict the health problems that a single gene or protein mutation can produce and how to translate that knowledge into new clinical procedures, it is clear that genes interact with many other genes and environmental factors. Only combined studies of gene interactions in humans and other animals and large epidemiological studies from many different populations can reveal the complex pathways of genetic diseases.

Current research on genomic medicine is producing enormous amounts of data, which requires computational resources to make it available worldwide and advanced computer tools to analyze it [8]. State of the art methods in bioinformatics include data banks available on the Internet, from which all the scientific community can benefit. Present informatics tools, however, seams to lack the necessary methods and features to effectively link genetic and clinical information and, moreover, existing genetic databases and their possible health applications [9].

Information management tools are necessary to convert the enormous amount of data that geneticists and molecular biologists can obtain at their labs in information that physicians and health workers can use. Information technology plays a key role in the translation of the knowledge between fields, enabling an unprecedented exchange of information, data storage and analysis. The challenge now is to find the appropriate technologies to transform biomedical outbreaks into shared knowledge, facilitating diagnostic and therapeutic solutions.

7.1.3 The necessary convergence of bio and medical informatics

Bioinformatics (BI), defined as the application of informatics in the processing of molecular information, and medical informatics (MI), defined as the application of informatics in the processing of health information, are beginning to interact and will have to get even closer in the future to fulfil the promise of genomic medicine.

The term Biomedical Informatics is increasingly being used in conferences and articles, indicating the space where both disciplines of MI and BI meet and interact. However, given the professional differences that have evolved over time, and the relatively small overlap of the MI and BI research communities, it is doubtful that such merging of the disciplines will happen easily or in the short term.

Genomic Medicine advancing requires a new integrative approach that merges the classical epidemiology, clinical research and genomic research. In such approach, all levels of information (from the molecule to the population, through the cell, the tissue, the organ and the patient) and the most appropriate techniques and methods would be used, some coming from bioinformatics, and others from medical informatics or even public health or epidemiological informatics (Figure 1).

The mapping of this holistic study of diseases into informatics tools will address the understanding and modelling of interactions among genetic, physiological and environmental factors

that contribute to health maintenance (*healthome-healthomics*), is spite of those that predispose or trigger the development of a disease (*diseasome-diseasomics*).

These novel informatics tools and approaches are the foundation to realize the genomic medicine's promises, a highly demanding vision, asking for a strong heart (pervasive computing power), strong brain (ability to model and associate biomedical concepts) and powerful arms (seamless resources networking and clustering).

Health information level	Classical health informatics applications	New genomic data and information	New health informatics applications
Population	Public Health & epidemiology databases Technology assessment, outcomes research	Genome epidemiology Genetic Screening	**Genome epidemiology databases and networks (CDC-HuGeNet)**
Disease	Disease classification systems Computerized clinical practice guidelines (CCPGs) Information systems in clinical trials	New classification of disease based on its molecular causes Genetic-based decision making Clinical trials in pharmacogenetics	**Decision-making support tools** Molecular classification of disease CCPGs including genetic tests and therapy follow-up based on genetic data Pharmacogenetics databases
Patient	Computerized patient health record (CPHR)	Genetic individual profiles (SNPs, mutations)	**Genetic data in the CPHR**
Tissue, organ	Pathology lab systems, medical image processing	Physiological genomics Genetic networks	**Tumour databanks** Disease models
Cell	Imaging in Cytogenetics, histology Microbiology lab information systems	Gene expression profiling Proteomics	**Molecular imaging** Information systems in pharmacogenomics (drug R&D)
Molecule	Biochemistry and genetic tests and laboratory information management systems	DNA and protein sequences Macromolecular structures	**Facilitating integrated and guided access to relevant genomic databases to health professionals**

Figure 1: Medical informatics and bioinformatics synergy to build broader views and raise opportunities in health informatics [10].

7.2 BIOMEDICAL INFORMATION INTEGRATION FOR HEALTH APPLICATIONS

Modern health care uses multidisciplinary data, originated from scattered systems, to attain better information to support diagnosis and therapy. Distributed on-line resources, especially those related to advances in genomics, combined with internal clinical information systems, are becoming increasingly important for care provision, health professionals' self-education, patient involvement in well-being management and life sciences research.

7.2.1 Modern information landscape for health: from genotype to phenotype

Progress on the understanding of genetic code, gene products and functions, is elucidating the mechanisms underlying diseases. As the HGP reaches conclusion, a major challenge to science is now to establish links from genotype into phenotype and environmental risks. This holistic view of a person's health condition is built upon the integration of different sources of knowledge, combining both clinical and genetic information. Biomedical information resources available to researches and practitioners include patient data and conditions, genome and sequences, protein sequence and structure, mutations, genetic diseases, genetic tests, terminology and coding systems, patient counselling resources, and more.

As an elucidative example of the knowledge pathway from "molecule to men", let us consider the study of a patient affected with Achondoplasia, a rare genetic disease. Figure 2 illustrates a possible protocol to guide a reasearch/practicioner on obtaining pertinent information on the disease, as follows:

- A professional would start by searching by **pathology** name. This search could be performed on the *OMIM* database, publicly available on the Internet.
- The pathology is due to a **mutation**, i.e., change in the nucleotide sequence of a DNA molecule (information available at *OMIM*) or to a **polymorphism or SNP** (information available at *dbSNPs*).
- SNPs are within a **nucleotide sequence** (*RefSeq*) which in turn is in a **gene** (*Genecards*). This gene has a a **chromosomal localization** (*LOCUSLINK*), an approved name (*HGNC*) and a **molecular function** found within Gene Ontology (*GO*).
- The gene codes for a **protein**, a **sequence** of amino acids (*SWISSPROT*).
- The sequence determines the **structure** of the **protein** (*PDB*). The protein is classified into **protein domains** (*InterPRO*) and have a **functional site** (*PROSITE*).
- Proteins have **enzymatic** properties (*ExPASY-ENZYME*) in **metabolic pathways** (*KEGG*).
- Drugs are **chemical compounds** (*Orphanet*) that are developed through **pharmacogenetic research** (PharmGKB) and validate in **clinical trials** (*Clinica Trials.gov*).
- Most of the entries described can directly link to bibliography in life sciences (*PubMed*).

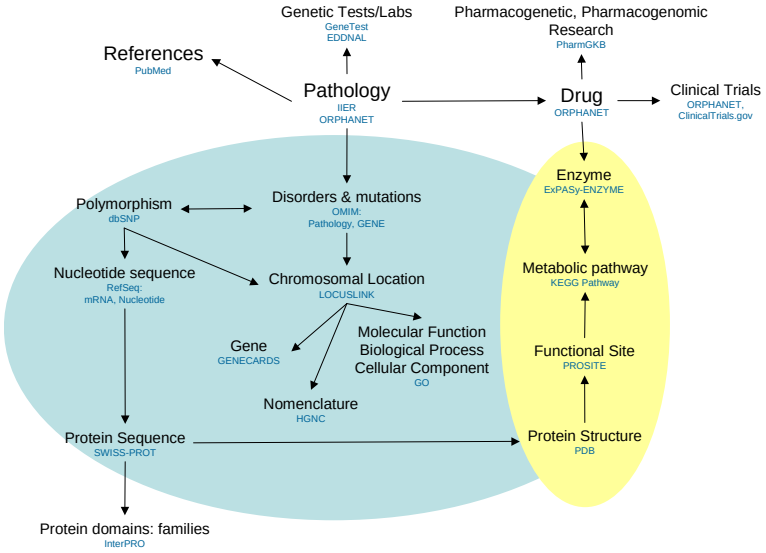

Figure 2: A conceptual framework for the study of genetic disorders.

7.2.2 Problems on bringing together genetic and medical information

Navigating between *phenotype* and *genotype* in clinical settings means that genetic assessment will be integrated in patient investigations. This vision requires the design and implementation of computer methods and tools to deliver effective platforms for seamless biomedical data association. The integration of biomedical knowledge resources brings up a new problem domain with some specific challenges to be addressed:

- There are many different sources of information spread over the Web; the relevant information needs to be modelled, discovered, accessed and retrieved.
- Data integration is difficult since databases can present a wide range of formats and different semantics. In addition, public information resources are often only available through web interfaces, not easily interrogated by computer applications.
- Coding and terminologies are not unified, sometimes being difficult to discern quality and link related concepts. Gene naming, for example, is far from being unified.
- Medical coding systems are not ready for managing the emerging genetic information.
- Intellectual property rights, privacy and confidentiality issues and protection of the ownership of valuable data may hinder the exchange of contents.
- Results are often published in natural language formats (scientific bibliography), requiring mining techniques to recover the knowledge in computer ready representations.

Generally put, the data available and being produced is both huge and massively distributed, requiring high-performance computer storage, processing power and networking infrastructures to be effectively communicated, managed and exploited.

7.2.3 Semantic integration of biomedical resources

The bioinformatics and biomedical fields are characterized by the presence of numerous and highly heterogeneous data sources, associated to a large number of applications and computing infrastructures. These resources are usually unrelated, though the contents they hold are strongly and semantically connected. Bringing together such knowledge is a complex task, since its difficult to overcome the underlying heterogeneity. Differences arise at multiple layers, starting with technical problems (establishing connectivity and interaction between computer systems) and ending with semantic issues (dealing with the automatic association of distributed concepts).

The semantic integration of these resources is one of the enabling factors to foster the deployment of novel biomedical applications involving research-oriented competence centres, specialized core facilities and laboratories (such as micro-chip array, mass spectrometry, etc.), and health centres where clinical guidelines are applied, such as hospitals. The main goals of semantic integration of biomedical resources are:

- allow a uniform access to biological, biomedical, bioinformatics, medical and clinical resources, especially data sources, such as bioinformatics data banks (e.g. Swiss-Prot, Protein Data Bank - PDB, etc.), Electronic Patient Record systems (EPR) [11], and other clinical and biomedical data;
- allowing the discovering and exploitation of intra and inter-data sources semantic relationships (e.g. a protein sequence in Swiss-Prot is related to a protein secondary structure in PDB, or a 3D shape of a protein in PDB can be bound to a drug compound of a ligand database).

The semantic integration of biomedical resources can benefit from existing standards, applying emerging knowledge management and modelling methodologies and technologies, such as Data and Text Mining, Document and Content management systems, ontologies, relational databases, semi-structured databases, UML and metadata management. The main services that compose semantic integration framework include:

- semantic modelling of different biomedical concepts and resources using ontologies (such as GeneOntology [12]) and metadata;
- semantic annotation of biomedical resources, to allow a continuous knowledge exchange between data sources and users (researchers, doctors, physicians, etc.);
- discovering, browsing and querying of biomedical resources, offered both to human users and to computer programs, driven by semantic concepts other than keywords;
- semantic modelling of medical documentation through different types of metadata: media-type dependent, content-descriptive, content classification, document composition, document history, document location.

Recent advanced in Grid technology are in line with semantic integration needs. Emerging Grid infrastructures include:

- Web Services, that allow the searching, calling and execution of distributed services, and could be used to implement some basic biomedical services and applications;
- Grid-based DBMSs and metadata management systems. In order to provide a secure, efficient, and automatic data source management in a Grid environment a new concept can be introduced: the Grid-DBMS [13].
- Support for Virtual Organization clusters through basic Grid services, such as security, and tools and platforms for cooperation.

Semantic integration involves both modelling and technical aspects. While the former allow for the deployment of high level semantic services and applications, the latter can enhance performance and efficiency on distributed and Grid environments.

7.3 DELIVERING GENOMIC MEDICINE IN THE GRID

Understanding the relations between genotype, phenotype and environmental parameters requires the use and integration of data for populations, diseases, patients, organs, and tissues along with genomics and post-genomics data. This means that highly heterogeneous competence centres will be engaged in research projects, sharing not only a goal, as their already existing computer resources. Care delivery will also be empowered by knowledge intensive tools, assisting the professional with integrated view of a patient's conditions. Grid-enabled infrastructures for life sciences and care provision can catalyze the use of (organizational and technological) common practices in a domain that is highly fragmented.

7.3.1 Biomedical Grids deliver secure distributed platforms for health applications

There are many research and development areas in informatics necessary to support the Genomic Medicine such as the development of models and digital simulations, molecular imaging, global scale data access and association, etc. The BIOINFOMED study [14] provides a comprehensive list of priorities. Grid technology is among these and can contribute to the development of some key areas by (1) supplying high computing power, (2) enabling seamless access and integration of complex and distributed data sources, and (3) establishing collaborative Virtual Organizations in order to enhance human-to-human interactions [15] [16].

Expected contributions of Grid technology to Genomic Medicine realization include:

1. ***Development of models and digital simulations of cells and diseases.*** 3-D models (of the body, cells, etc), combining anatomic and functional parameters, can be built to implement metabolic pathways and processes, linking structural information with cell assembly information. With the appropriate computer resources, gene sequences, functions, pathophysiological processes and clinical manifestations could be progressively integrated in a unified abstraction. This functional model could provide biomedical researchers and health educators and professionals with a reference for their routine work. These systems will be used in the assessment of the effects of a toxic agent or of the action that a given drug triggers in the cellular response against a disease. Grids are successfully being deployed to support demanding biomedical simulation (e.g.: [17]).
2. ***Providing tools to support physicians' training, and improve biomedical knowledge management.*** Most physicians have a narrow view and knowledge of genetics and genomics. E-learning tools may be decisive to introduce an easy and rapid shift to adopt new perspectives for their routine work and the introduction of genomic medicine, minimizing physician's anxiety or rejection. These collaborative e-learning tools will share computational resources such as data files, simulations, etc., being candidates to exploit the integration and share features of the Grid technology.
3. ***Molecular imaging.*** The new field of functional and molecular imaging arises from the combination of medical imaging technologies with genomic approaches. This area can increase the diagnostic arsenal by means of "in vivo" visualisation of cellular and genetic processes. Molecular imaging developments pursue quantitative and non-invasive studies of diseases at the molecular level. Grid can provide the processing power needed by this area.

4. ***Genetic epidemiology.*** Carrying out population studies in which the influence of environmental and genetic factors in the development of diseases will be studied. The information sources needed to perform such studies are spread in different and remote sites. Grid infrastructures can facilitate seamless access to all these resources.
5. ***Development of Pharmacogenomics.*** Drug design can be revolutionized through the use of new reasoning approach using gene sequence and protein structure function information rather than on a traditional trial-and-error method. A new generation of data models and repositories will be needed to handle the complex spectrum of information sources needed in these approaches (laboratory measures, clinical findings, human genetic variation, chemical compounds, metabolic pathways). Grid offers services that assist in the management of this diversity of information sources.
6. ***Developing tools that support clinical decision making***, combining multiple relevant information sources (genetic, clinical and environmental). In a genomic medicine framework, medical practitioners will access biological information and integrate it with data included in computerized patient records or departmental systems in large hospitals. Grid could help to integrate all the data used in decision-making and to build the computing power needed to run real time, complex interactive systems.
7. ***Integrating databases and knowledge between the clinical world and that of genomic research.*** Biomedical research is a collaborative science, in which multidisciplinary teams join skills and resources. Often, this research gathers multiple institutions and sets up virtual organizations, clinical trials being an exemplary case. Partners engaged in biomedical research need a computational infrastructure that meets this kind of collaboration and sharing of information systems, often previously existing and decentralized. In addition, progress in life sciences depend on the ability to development of common representations (ontologies, integrated vocabularies, etc.) to model and describe heterogeneous information. The challenge is to adapt existing systems or to develop new ones that allow the exchange and integration of data. Grid, enhanced with semantic integration services, can help not only to seamless share computer resources, as to integrate genetic data obtained in functional and comparative (individual) genomics into the clinical information systems.

7.3.2 Requirements and architectures of Biomedical Grids for heterogeneous knowledge integration

To be effectively adopted in bioinformatics and biomedicine domains, *next-generation Grids* need to face some emerging issues in genomic and post-genomic applications, such as (i) an overwhelming generation and availability of data, (ii) an increasing complexity of applications that more and more involves distributed data sources and points of computing and decision, and (iii) a large heterogeneity in the type of applications and the kind of users respectively running on and accessing to biomedical applications on Grids [18].

The way how data at different levels of Grid can be effectively acquired, represented, exchanged, integrated and converted into useful knowledge is an emerging research field known as "*Grid Intelligence*" [19]. In particular, ontologies and metadata are the basic elements through which Grid Intelligence services can be developed [20]. Using ontologies, Grids may offer semantic modelling of user's tasks/needs, available services, and data sources to support high level services and dynamic services finding and composition. Moreover, data mining and knowledge management techniques could enable novel services based on the semantics of stored data. *Semantic Grid* focuses on the systematic adoption of metadata and ontologies to describe Grid resources, to enhance and automate service discovery and negotiation, application composition, information extraction, and

knowledge discovery [21]. *Knowledge Grids* [22] offer high-level tools and techniques for the distributed mining and extraction of knowledge from data repositories available on the Grid, leveraging semantic descriptions of components and data, as provided by Semantic Grid, and offering knowledge discovery services.

Grid community has recognized as bioinformatics and post-genomic applications are both a challenge but especially an opportunity for distributed high performance computing and collaboration. The Life Science Grid Research Group, established under the Global Grid Forum where Grid standards are defined and agreed, aims to investigate how bioinformatics requirements can be fitted and satisfied by Grid services and standards, and what new services should Grids provide to bioinformatics applications. Many emerging Bioinformatics Grid projects are also appearing, such as the European EUROGRID project (www.eurogrid.org), the Bio-GRID work package (biogrid.icm.edu.pl) for biomolecular modeling, the Asia Pacific BioGRID (www.apbionet.org/apbiogrid/), the *myGrid* UK eScience project (mygrid.man.ac.uk).

To face the issues arising when bioinformatics meets medical informatics, more issues need to be faced, in particular the use of Grids to enhance medical practices and to allow collaboration between medical and research centers. In particular, *Biomedical Grids* must be able to produce, use and deploy knowledge as a basic element of advanced applications and will be mainly based on *Knowledge Grids* and *Semantic Grids* and, leveraging their high level services, will allow to deliver to the proper user, information, knowledge, medical guidelines, and results of research in a form applicable in the clinical activity. The Cancer Biomedical Informatics Grid (*caBIG*), a cancer-based biomedical informatics network developed by the National Cancer Institute (www.nci.nih.gov), goes along this direction. caBIG will connect cancer related data sources, tools, individuals, and organizations, and will help redefine how research is conducted, care is provided, and patients and participants interact with the biomedical research enterprise (cabig.nci.nih.gov/caBIG/overview/).

Biomedical Grids may help in storing, integrating, and analysing the data produced or used (e.g. provided by public databases) in the experiments and research activities. Moreover, they will support the modelling, designing and execution of workflow experiments (e.g. “in silico” experiments), by using standard modelling techniques such as UML, ontologies, and workflow languages. Main conceptual layers of Biomedical Grids include:

- *Data sources and modelling layer*. The data sources, comprising data produced during experiments (e.g. mass spectrometry, microArray, etc.), data provided by public databases (e.g. PDB, SwissProt), and data coming from the clinical practice, need to be modelled using well established and novel knowledge management methodologies, such as UML and ontologies. Data sources need to be integrated and federated to allow easy access to specific information or to data semantically correlated. Main tasks of this layer are: ontology-based modelling of biological/biomedical databases; modelling of distributed biomedical applications, such as in-silico experiments. The modelling should comprise all phases of experiments, such as sample preparation, data generation, data pre-processing and filtering, images analysis, bioinformatics analysis, bio-medical analysis, results visualization [23].
- *Applications composition and enactment layer*. Such layer allows to realize complex bioinformatics and biomedical applications (e.g. “in silico” experiments) as composition of basic (open source) bioinformatics tools, that will be executed on the Grid, exploiting the resources and data provided by research centres forming different Virtual Organizations. Useful software tools need to be classified in the modelling layer of the platform, with respect to technical aspects and use aspects. Key issues of this layer are: domain ontologies to model (open source) bioinformatics software components, and public available biological databases; ontology-based querying and browsing on domain ontologies for the search, selection, and location of bioinformatics and

biomedical resources (data and software components), to be used in the composition of applications; workflow-based modelling and scheduling of distributed applications on the Grid; extensive use of Open Source software components and components provided by the research centres.

- *Data analysis and knowledge extraction layer*. In this layer advanced data analysis tools, composed using the workflow technologies, allow the extraction of knowledge useful for prosecuting experiments. This layer should comprise a set of data analysis plug-in using different methodologies and approaches, for example: statistical analysis and data mining; survival analysis and other temporal data analysis; visualization of multidimensional data; classification of data, etc.

The *Data analysis and knowledge extraction layer* could leverage recent initiatives like Semantic and Knowledge Grids. As an example, the KNOWLEDGE GRID system is an environment for geographically distributed high-performance knowledge discovery applications on the Grid providing Grid-based knowledge discovery services [22]; the PROTEUS system extends the KNOWLEDGE GRID to face specific issues of bioinformatics and biomedical applications [24].

7.4 IMPACTS & FUTURE HEALTHCARE

Grid's are expected to change the way Information Technology participates in health research and care provision. In the following, we highlight key points of the emerging post-genomic scenario enabled by Grid infrastructures to bring together distributed, multidisciplinary knowledge.

7.4.1 A vision for the role of Grid in future health delivery and research

It is clear that some of the most important Biomedical informatics tools of the future will aim precisely at facilitating decision-making with regards to prevention, diagnosis and treatment thanks to the incorporation of genetic profiling into electronic healthcare records. Biomedical Informatics in the post-genomic era calls for the use of open and cooperative environments. Distributed, Grid-based collaboration infrastructures are one of the common emerging technologies being exploited by Medical Informatics and Bioinformatics.

From the Genomic Medicine point of view, the Grid is expected to facilitate:

- Computational genomics and proteomics in the identification of genes and proteins, automatic annotation and characterization of genetic individual variations.
- Relevant technologies to store large amounts of phenotype, genotype and proteotype data in relational databases.
- Elucidation of biochemical and genetic networks. Modeling and simulation of interactions, cellular processes from the perspectives of the system biology (*i.e.*, CellWare).
- Methodologies and computational power and tools to discover new relationships in such heterogeneous data in order to create a new and useful knowledge for healthcare process.
- Link gene expression patterns with disease models to uncover pathogenic pathways related with the patient's clinical condition, life-style, nutrition, and genetic disposition. Ubiquitous access to the whole history of health of a person, independently of the center where there has been gathered information of the clinical episodes.
- Support to the development of clinical tests.

- Provide personalized healthcare services following the genetic profile of each patient, epidemiological studies, heredity, statistical analysis results, and clinical observations.
- Enable customized drug synthesis and research on innovative drug targets based on combinatorial methods, maximizing the potential for new advances in the pharmaceutical industry.
- Provide e-health portals, orientated towards the resolution of problems by use of disperse applications.
- To access virtual laboratories of genomics information (*e.g.*: PROTEUS [24]).

7.4.2 Harnessing the benefits of a GRID-based approach

Grid-based integrative approaches enclose the potential for more effective large-scale collaboration, computing power availability and heterogeneous knowledge sources aggregation. These three dimensions are expected to contribute to the raise of Molecular Medicine in several ways:

- To obtain the maximum benefits of the genomics and biomedical information from the available data bases to use in health delivery and research.
- To facilitate the collaborative work between researchers and interaction between different scientific and professional communities.
- Development of *in silico* experiments to prove new hypotheses by using modeling and simulation.
- Advances in the education by means of the use of new technologies of visualization and remote collaboration in virtual environments.
- Availability of elaborated and extensible computing environments, orientated to biomedical problem solving.
- Scalability, openness and versatility of the systems to give response to new needs.
- Advances in standardization and interoperability of information.

7.4.3 The road ahead for Grid-enabled Genomic Medicine

Grid is an emerging technology, still in its infancy. The road ahead is uncertain, but it's possible to set up a very general roadmap for its implementation in the area of the Genomic Medicine domain. Some of the required steps include:

1. Developing the specific semantic grid-services required for a knowledge integration environment.
2. Deploying and testing of the first Grid middleware prototypes for the health sector (research and care provision).
3. Developing, deploying and testing of the first Grid Genomic Medicine-applications.
4. Fostering and promotion of the Grid-culture by means of the education and training of the physicians, scientists and the rest of the staff involved in the Genomic-Medicine sector.
5. Wide implantation of the Grid-culture and Grid-enabled sustained collaborations in the domain of the Genomic-Medicine.

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8 FROM GRID TO HEALTHGRID: CONFIDENTIALITY AND ETHICAL ISSUES

8.1 BACKGROUND: HEALTHCARE AND CONFIDENTIALITY

Healthcare today is increasingly supported by ICT. A point is reached where medicine, genomics and ICT are developing a symbiotic evolution [G96][M02]. Key area's such as evidence based medicine, genomics, proteomics, toxicogenomics, pharmacogenomics, medical simulations and imaging, ... require collection, storage and processing of vast amounts of data. These applications take the requirements on information technology to the next level.

GRID technology is a solution which finds its way in those domains that need full dynamic interoperability, computing power, massive data storage and data federation. The introduction of GRID technology to health research is thus unavoidable and imperative for further developments in e-Health.

Many other sciences have the same demand. Therefore a lot of experience with GRIDs in non-medical environments exist. Mainly the domain of High Energy Physics (HEP) has been the driving force behind the development of GRID technology [LCG]. Indeed a wide spectrum of tools and GRID middleware is available from these sources, and during the development of a HealthGRID, considerable effort should be dedicated to the exploitation of existing knowledge and technology in order to speed up this deployment. It is however clear, that some issues are not answered yet, and that the healthcare application domain introduces some demands of its own.

More in particular, in healthcare, sensitive personal data of patients is treated. This implies a need for strict confidentiality and enforced protection of privacy. These requirements where previously not dealt with in GRID technology. A logical consequence of the fact that in HEP, elementary particles need no privacy, as opposed to humans in a modern society.

(Bio-)Medical data usually has a very sensitive data and although generally used for the benefit of the community, this information is quite prone to abuse. There is an appropriate concern about the proper treatment of sensitive data. Incidents of abuse have been previously reported in the public media [L03], proving that the threat is genuine. It can be easily understood, that abuse of sensitive personal healthcare information can lead to considerable financial gain for malicious people, an important motive for crime. Imagine the impact on society, when banks, insurance companies, employers, ... could access healthcare data about their customers, revealing past, current and probable future (genomics) health condition. Indeed, abuse of medical data can effect all of us, as at some point in life practically everyone is confronted with loan, insurances and job applications.

8.2 ETHICS, LAW AND TECHNOLOGY

Today, it cannot be denied that privacy protection directly impacts personal well-being as well as society as a whole. Indeed, some go as far as to believe that failure to protect privacy might lead to our ruin [C03]. Privacy is in fact recognised as a fundamental human right, at least in Europe. Public authorities are sharply aware of these repercussions, and they are putting considerable effort into privacy protection legislation [EU95][EU02]. Because of the possibilities that are opened by modern GRID technology (such as trans-border processing of sensitive data), studies regarding legal constraints associated with a HealthGRID are of great importance. They are therefore discussed in a separate chapter of this white-paper (see further, chapter 9).

Furthermore, medical practice and research have always adhered to strict ethics. These domains are accustomed to supervision by (ethical) Institutional Review Boards which enforce such requirements as obtaining informed consent from patients [M01]. Scientists and technicians

developing GRID technology are usually not familiar with concerns about the proper treatment of information, healthcare professionals are. The privacy and legal issues raised by the HealthGRID are mainly caused by the transparent interchange and processing of sensitive Healthcare information, resulting from the aim of removing the line between local and remote resources with GRID technology. These problems are certainly not entirely new to Medical Informatics. It is therefore of utmost importance that experts from the BioMedical Informatics domain share their experience on security and privacy related issues in healthcare, in order to avoid that these become barriers for the realisation of the HealthGRID.

8.3 PRIVACY PROTECTION, SECURITY AND THE HEALTHGRID

8.3.1 GRID Security Technology

Since the very start, the GRID community has put a lot of effort into the design of security measures [W03]. **Authentication** and **authorisation** mechanisms are the main point of focus of these developments, as they are the most basic of security measures. Integration at the level of the lower middleware allows security mechanisms to be uniform (developer APIs) and interoperable [GLOBUS]. Implementation is often still in an early stage. It is important to realise that the further development of security technology is key to the acceptance of the HealthGRID concept.

Avoiding unauthorised access to sensitive data is a first level of protecting confidentiality. In healthcare state-of-the-art security solutions have always been used. An equal level of protection will be demanded from a GRID environment. Any HealthGRID initiative should therefore be aware of the latest security developments in the GRID community. Development of basic services, such as for example integration on a lower middleware level of fine grained access control (e.g. provided by CAS or VOMS GRID solutions), should be encouraged by the BMI society.

A specific HealthGrid initiative could offer the possibility to further test and develop these security mechanisms, beyond the point where classical GRID developers would stop because they believe that for their application sufficient measures are in place.

The security technology currently present in the GRID community might even offer a sufficient solution for the first and most obvious healthcare applications: computational problems in heatlhcare. Deployment of computational GRIDs in healthcare is a first logical step towards a true HealthGRID. The problems faced there are similar to the ones encountered in more classical GRID domains. Problems requiring intensive calculations such as image processing, modelling, simulations for surgery or radiotherapy, bioinformatics problems such as sequence alignment and protein folding, etc. can readily be addressed by existing technology. Several projects such as <include list of computational healthcare projects> have already proven this.

Contrary to many other area's of healthcare, confidentiality issues in such cases are usually of secondary importance. The nature of the application itself reduces the risk of disclosure of sensitive information. Computational challenges inherently segment the processed data and typically only deal with non-identifiable data related to complex computational models. Thus, the similarity with classical GRID applications persists also in the security domain, there is no real need for specialised "information security".

8.3.2 HealthGRID Security Requirements

HealthGRID does not intend to restrict to the use of GRID technology for distributed computing only. Eventually, HealthGRID should offer a generic platform for all e-Health actors. Sharing of large amounts of distributed heterogeneous (on various levels) data is therefore an

important point of attention. In that respect, data GRIDs share the vision of making progress through integration of several information sources with an important trend in e-Health: the integration of Medical Informatics (MI) and BioInformatics (BI) into BioMedical Informatics (BMI). Healthcare experts are convinced that the scientific opportunities that could be offered by the integration of medical information (such as EHRs) and genomic data (BI) are unprecedented [IBM04]. Quoting EU Officers S. Norager and Y. Paindaveine [HG]: "The vision is to create an environment where information at the 5 levels (molecule, cell, tissue, individual, population) can be associated to provide individualized healthcare.".

It is clear that the linkage of several distributed data sources bound to a single individual on a data GRID opens of up a range of privacy risks. The (virtual) federation of a large amount of personal medical data is not the only risk at hand. GRID technology will undoubtedly further stimulate the use of genomic data in research. However, this particular type of data has a number of specific characteristics related to privacy which are not found in any other type of (medical) information:

- Genetic data not only concerns individuals, but also their relatives. A person's consent to release his or her genetic information constitutes a de facto release of information about other individuals, i.e. his or her relatives. In the case of genomic medicine, there is a complex interaction between individual rights and collective requirements;
- Medical data deal with past and current health statuses of persons, whereas genetic information can also give indications about future health or disease conditions;
- An individual person's genotype is almost unique and stable, hence it can become the source of an increasing amount of information;
- The full extend of the information included in the genomic data is not known yet, hence it is difficult to assess the full extent of disclosure;
- Genomic data is easily wrongly interpreted by non-professionals, "susceptibility" to diseases can easily be mistaken with certainty of illness.

The above clearly indicates that the reconciliation of two seemingly conflicting objectives: on the one hand, the maximization of medical research productivity and efficiency in data handling; on the other, the protection of the human (privacy) rights; is the challenge at hand.

A couple of basic approaches to safeguarding confidentiality have been identified in the past in healthcare practice. The first approach focuses on the creators and maintainers of the information, prohibiting them from disclosing the information to inappropriate parties. Basically, this comes down to the deployment of classical security measures (a**ccess control, authorisation**). A HealthGRID initiative is ideal for the further development (and actual implementation) of GRID security technology, because of the strict requirements in healthcare. As mentioned earlier, security should be a specific point of attention when deploying GRIDs into healthcare, as GRID solution coming from other domains (such as physics) will never deal with the specific needs regarding the confidentiality of information which is not only an ethical but also a legal requirement in BMI. A first task within the HealthGRID context could thus be performing an in depth analysis of the new and specific risks and threats that arise.

An alternative and superior approach, often used in research initiatives, focuses on the use of Privacy Enhancing Techniques (PETs). PETs eliminate or minimize the collection of personally identifiable information.

8.3.3 Privacy Enhancing Technology

Technology which is specifically designed to safeguard privacy is generally referred to as Privacy Enhancing Techniques or Technologies (PETs). PETs can be described as (according to one author [B01]):

> *"A coherent system of ICT measures that protects privacy by eliminating or reducing personal data or by preventing unnecessary and/or undesired processing of personal data, all without losing the functionality of the information system."*

Privacy Enhancing Technologies are fairly new (the concept has only been around since the '90s), and have been extensively researched in both the USA and in Europe. Within the fifth and sixth framework, several projects – amongst them: PRIDEH, PRIDEH-GEN, PISA, PAMPAS, RAPID and PRIME, … – were (and are) focused on privacy protecting techniques, policies or closely related subjects, for a wide range of applications – such as anonymous communication (mailing, web surfing), anonymous transactions, etc.

In healthcare, PETs are mainly used for protection of the privacy of persons involved in medical data collection. The goal of these PETs is to guarantee anonymity of data subjects while making information available for clinical practice and research. The use of such techniques in healthcare has been demonstrated in several research projects [DC02] and solutions are already commercially deployed. Privacy protecting technology today is deployed in clinical trials, disease studies, for the exchange of research data, for the daily handling of sensitive data, etc. PETs such as anonymisation have even already reached the first steps that lead to standardisation (introduced as a working item in CEN/TC251).

Collection or exchange of identifiable personal medical data can be legally impossible or ethically unacceptable. Given the HealthGRID goal, privacy could thus form an impenetrable barrier for live-data applications. However, access to large amounts of useful, personal information can be unlocked though the use of privacy protection techniques (mainly de-identification methods). Deployment of Privacy Enhancing Technology in the GRID environment can thus be of great importance for the overall success of the HealthGRID initiative [DC04].

8.3.4 Grid Integration of PETs and Security

Security and privacy protection techniques are closely linked. Emphasis of the latter however lies on limiting the identifiable information content of the data rather than on merely restricting access to the data itself. Although the strict difference between the two is not always clear, Privacy Enhancing Technology and security technology should be regarded as complementary in the respect of safeguarding the confidentiality of personal information.

The question whether these specific security techniques and privacy protection measures should be integrated in the HealthGrid itself, is a valid one. It is beyond doubt that all HealthGRIDs need to take into account the stringent data protection requirements of the healthcare sector. However, these measures could be implemented completely separate from the GRID nature of an application. In such a case there is little difference with current "ad hoc" solutions (privacy aware health data collection unrelated to Grid technology).

On the other hand, the integration of specific privacy protection solutions into Grid services could offer considerable advantages. Integration is not only logical because of the close relationship with classical measures (which are largely part of the GRID middleware), but can also stimulate the use of privacy protecting technology leading to data protection "by default" in each healthcare related GRID application. Integration of PETs into the lower middleware level should probably be limited (in that context, see further, policy management). Lower middleware (such as Globus) aims at providing a

broad generic toolbox for GRID development. Specific BMI security and privacy means are not the primary objective of the middleware developers.

Just as several data integration initiatives, healthcare specific security and privacy solutions could be offered at an upper middleware level, combining the advantage of still being generic (at the disposal of a wide community), but not overloading the toolset for other areas of research which do not need such strict measures.

The main portion of privacy protection measures will, at least in the beginning, be situated at the application level. This does not imply that development falls beyond the scope of a HealthGRID initiative. On the contrary, next to the fact that stringent data protection is a prerequisite for healthcare IT, standardisation of PET technology can be encouraged by the development of specific GRID services. As an example, one can think of a policy driven pseudonymisation service, which allows centres to automatically de-identify their databases through a GRID service (guaranteeing use of the latest technology) before exchanging information with another site.

As developments and pilot projects progress, it will become clear which piece of technology should be implemented at what level. In fact, this task could be one of the objectives of a HealthGRID initiative.

8.3.5 HealthGRID Issues

In order to illustrate the need of specific research in a any HealthGRID initiative, some typical examples of problems caused by the strict requirement of the medical world are mentioned. The examples presented hereunder are fairly straightforward and thus have been identified before [GK02]. However they have not been adequately dealt with. With the introduction of a HealthGRID, the need for confidentiality and data protection is more real than ever.

The GRID promises access to heterogeneous resources, which means that in a HealthGRID environment remote resources will be storing and processing sensitive personal data. These resources should thus be trusted by the end-user. But how can one know? Who can be the judge of “trustworthiness” of a GRID resource? A simple and straightforward solution is to use “closed” systems, which means that any resource in the GRID is well known and specified in advance. This however conflict with the vision of dynamisms and the “ad hoc” nature of GRID technology.

Solutions should rather be searched in the area of policy advertising and negotiation. Resources should be able to inform a candidate user on how the data dealt with will be treated, which policies are applied, what PETs are used, who can have access to the data, etc. These methods are sometimes referred to as not being genuine Privacy Enhancing Techniques, as strictu-sensu they do not actually limit collection of personal identifiable data and do not give any guarantees about the actual processing. A resource can claim to adhere to strict rules, but in practice this can not be verified.

The first steps in the direction of policy management have already be taken by GRID developers. The development of standards such as WS-Privacy, WS-Policy and EPAL (Enterprise Privacy Authorisation Language) is an effort in the good direction. However, implementation till this day is rather limited, and the full possibilities of the technology will not be researched unless effort is spent here from the healthcare area (the main application domain). A HealthGRID would be the ideal environment where such PETs can be tested and further developed.

The above directly impacts typical GRID mechanisms such as data replication. Replication mechanisms automatically copy data on a resource in order to increase efficiency (e.g. to avoid transfer delays). With medical data, this might however not be allowed. The site on which the data will be replicated should at least be as trustworthy as the data source and should adhere the same strict

policies. A HealthGRID should be able to handle such cases autonomously in order not to loose its dynamic nature (and efficiency).

Another example is delegation. Delegation of rights is fundamental in a GRID environment, however in the medical world, this is far from obvious. If one passes on rights to others (resources), one becomes liable for actions performed on one's behalf. In a healthcare environment this has serious implications on liability. Restricted proxy certificates offer a path to a solution suitable for medical applications, but clearly need to be extended.

8.3.6 Challenges Ahead

The previous paragraphs indicate that policy management will be an important topic in HealthGRID. Both for security (e.g. authorisation policies) as for data protection (privacy policies). A difficult problem in this context is the one of policy enforcing and assuring that a certain policy is followed. Research within a HealthGRID initiative can certainly contribute in that area.

Equally important and closely related to this subject, is the implementation of **auditing mechanisms**. All actions in a medical context should be logged in a trustworthy way. Non-repudiation combined with a legal framework could help solve liability issues in healthcare.

Next to the areas of interest mentioned in this text, several other healthcare needs for GRID applications exist which could be developed at e.g. upper middleware level for the benefit of a large community within a HealthGRID context. Among those: encrypted storage for medical data (a far from obvious problem) and trustworthy federation of research databases – virtual federation of small "cells" of de-identified data (e.g. geographical area, hospital, …) can decrease the re-identification risk (by increasing the anonymity set). Finally a range of PETs which are well suited for distributed environments is emerging (Private Information Retrieval and Storage, privacy preserving data mining, processing of encrypted data, ...). However the road to an advanced generic privacy preserving framework for e-Health is still long and littered with technical difficulties which should be tackled one at a time.

8.4 CONCLUSIONS

e-Health encompasses the handling of sensitive personal data. This data is prone to abuse, failure to protect its confidentially can seriously reduce the quality of life of the data subjects. Protecting privacy and ensuring security while handling sensitive biomedical data, is a great challenge. The HealthGRID initiative aims at enhancing medical care and BMI research by providing dynamic access to heterogeneous resources, albeit storage and processing facilities or information and knowledge. This implies that the introduction of GRID technology in a healthcare environment raises some serious questions regarding the proper treatment of sensitive data.

It has been explained why current security technology does not fully meet the strict requirements demanded by several BMI applications. Healthcare GRID applications raise issues, which can only be dealt with by a combination of healthcare security experts and GRID developers.

Next to the deployment of state-of-the-art security technology and the design of appropriate policies, efforts should be put into healthcare specific security and privacy needs. Whether these should be implemented at middleware level, application level or as true GRID services, is something which will become clear along the way.

It is however a fact that GRID technology can only be successful in a biomedical environment if the ethical guidelines and legal requirements are adequately met by technological solutions which are continuously evaluated and updated as new needs arise.

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9 LEGAL APPROACHES OF THE HEALTHGRID TECHNOLOGY

9.1 INTRODUCTION

The introduction of GRID technology in the health care sector might seem insignificant and in any event without any legal relevance. It would only concern a new computing technology participating to the provision of healthcare services or to the completion of scientific research, mostly by providing huge computing and memory resources, possibly Internet based.

The first projects deal with medical imaging, medical tele-assistance, medical or pharmaceutical research, human genomic studies, creation of databases for therapeutic, scientific, statistical or epidemiological purposes.

However these projects are ruled by radically different legal contexts. Indeed, distinct legal rules govern the practice of medicine, scientific or pharmaceutical research, epidemiological studies, etc., even if those disciplines may contribute to medical progress.

Hence there is no unique answer to the determination of the legal framework in which HealthGRID technology may be implemented and used. In reality, the answers are multiple and depend on the context of each project as well as on the considered legal viewpoints (these may not necessarily be found in every project).

The apparent uniqueness of the GRID technology does not exist on a legal viewpoint.

HealthGRID technology must conform to the legal context specific to each project aiming at its implementation.

Nevertheless describing the different legal contexts in which HealthGRID technology might be implemented is not sufficient. The adequacy of the legal context with the characteristics of this technology should also be evaluated. In other words, one should question whether certain rules should not be adapted with respect to HealthGRID technology.

Here are some significant viewpoints to consider.

9.2 HEALTHGRID TECHNOLOGY'S STATUS

Technologies must frequently comply with precise technical norms in view of their legal utilisation. The same assertion is also valid for the health care sector.

It is therefore important to define the content of the technical norms relevant to each project.

In this matter, some technical norms have been harmonized on International or European level. With respect to this, it is useful to note that the European Committee for Standardization has issued a very interesting study entitled "*European Standardization of Health Informatics – Results of the mandated work by CEN/TC 252*" (CEN TC 251/N01-024 – 2001-06-17).

The European Union has also adopted several rules concerning medical devices :

- Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices;
- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices;
- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

It is hence required in each project to :

- determine the technical norms applicable to the HealthGRID technology in the considered project, depending on the national legal orders likely to rule it ;
- control the adequacy of these technical norms.

The Council of Europe states that the improvement of human life quality and the respect of human rights should prevail when dealing with new technologies. It namely recommends in this regard that the precise evaluation of any technology should as much as possible rely on the following criteria (cf. Recommendation (90) 8 of 29 mars 1990 on the impact of new technologies on health services, particularly primary health care) :

Validity of outputs,

Validity of data capture,

Ability to fit within the framework of primary health care,

Social acceptability,

Ethical acceptability,

Professional acceptability,

Reliability,

Capacity for continuous assessment,

Safety for providers, consumers and the environment,

Cost effectiveness compared to older technologies,

Availability of full information on the technology and experience in implementing it,

Protection of confidentiality,

Ability to be integrated smoothly into existing systems,

Availability of adequate resources.

This evaluation should consist of appropriate studies giving conclusive results, and should be carried out prior to the general introduction of any new technology.

9.3 STATUS OF THE PROCESSED PERSONAL DATA

Most of HealthGRID technology related projects imply personal data processing for therapeutic purposes or scientific research. Indeed :

- Providing HealthGRID based medical imaging services necessarily implies personal data processing;
- Medical tele-assistance assumes the transmission of personal data (images or any other data) via a telecommunication system to the tele-assistance performer,
- The use of HealthGRID technology in medical or scientific research aim at facilitating personal data processing,
- Human genomic studies presume that, at a specific moment, personal data should be retrieved and processed,

- The creation of HealthGRID databases implies *de facto* personal data processing.

However personal data processing is subject to numerous regulations. Indeed, these data are particularly sensitive and require subsequently high protection. Furthermore, because of the therapeutic or scientific stakes, personal data processing must be reliable, or it may lead to medical errors or erroneous scientific works.

On the international level many norms govern personal data processing (including the processing of personal data related to health).

Article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms is imperatively worth attention in that matter.

In the case M.S. v. Sweden of 27 August 1997 (74/1996/693/885) (§ 41), the European Court of Human Rights vigorously reminded that « (…) *the protection of personal data, particularly medical data, is of fundamental importance to a person's enjoyment of his or her right to respect for private and family life as guaranteed by Article 8 of the Convention. Respecting the confidentiality of health data is a vital principle in the legal systems of all the Contracting Parties to the Convention. It is crucial not only to respect the sense of privacy of a patient but also to preserve his or her confidence in the medical profession and in the health services in general. The domestic law must afford appropriate safeguards to prevent any such communication or disclosure of personal health data as may be inconsistent with the guarantees in Article 8 of the Convention. (Case Z. c Finlande of 25 February 1997, 1997-I, p. 347 , § 95).* »

Article 7 of the Charter of Fundamental Rights of the European Union similarly confirm everybody's right to privacy while Article 8 establishes the right to the protection of personal data.

The Council of Europe has issued important norms relative to personal data processing.

The Convention of the Council of Europe for the protection of individuals with regard to automatic processing of personal data (28 January 1981) (Treaty n° 108) represents in that matter a mandatory source for all Member States.

The Council of Europe has also adopted specific recommendations interesting personal data processing involved in projects implementing HealthGRID technology :

- Recommendation (83) 10 of the Committee of Ministers on the protection of personal data used for scientific research and statistics, adopted on 23 September 1983;
- Recommendation (90) 8 of 29 mars 1990 on the impact of new technologies on health services, particularly primary health care;
- Recommendation (97) 5 of the Committee of Ministers to Member States on the protection of medical data, adopted on 13 Feb. 1997;
- Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine : Convention on Human Rights and Biomedicine (Treaty n° 164) (4 April 1997);
- Recommendation (97) 18 concerning the protection of personal data collected and processed for statistical purposes, adopted on 30 September 1997;
- Recommendation n° R (99) 5 of the Committee of Members to Member States for the protection of privacy on the Internet – Guidelines for the protection of individuals with regard to the collection and processing of personal data on information highways, adopted on 23 February 1999;

- Recommendation 2/2001 on certain minimum requirements for collecting personal data on-line in the European Union, adopted on 17 May 2001.

The Council of Europe recommends that specific models designed to ensure confidentiality of patient information should be developed in relation to the application of information technology to health care systems (cf. R (90) 8 of 29 mars 1990, o.c., point 8 of the Guidelines).

In the extent of its attributions, the European Union has adopted special norms relative to personal data processing, namely :

- Resolution of the Council and of the Representatives of the Governments of the Member States, meeting within the Council, of 29 May 1986, concerning the adoption of a European emergency health card;
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications).

The European Group on Ethics has adopted an important opinion interesting the processing of personal data related to health (cf. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, Ethical issues of healthcare in the information society, n° 13, 30 July 1999).

The World Medical Association has issued several documents interesting for some HealthGrid projects :

- Declaration on the patient's rights (World Medical Association Declaration on the Rights of the Patient, adopted by the 34th World Medical Assembly Lisbon, Portugal, September/October 1981 and amended by the 47th General Assembly Bali, Indonesia, September 1995);
- Guidelines concerning the practice of Telemedicine (World Medical Association Statement on Accountability, Responsibilities and Ethical Guidelines in the Practice of Telemedicine, adopted by the 51st World Medical Assembly Tel Aviv, Israel, October 1999);
- Declaration on Ethical considerations regarding Health Data Bases (adopted by the WMA General Assembly, Washington 2002);
- Declaration on Ethical Principles for Medical Research involving Human Subjects (adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002).

National norms relative to personal data processing must comply with this international framework, although a certain margin is generally recognized to the Member States in view of their implementation. Besides this may cause a slight disparity in the national norms in this matter, adding to the existence of national norms for which no international rules exist and upon which Member States are free to decide.

In any case it is of prime interest to correctly qualify the operations realized on personal data when using HealthGRID technology and to define the role of each involved person (health care practitioners, service providers, patient, etc.).

From a technical viewpoint, the PET's technologies offer a very strong support to the security and the confidentiality of the processed personal data. They aim to reduce the processing of personal data and to suggest appropriate measures to secure data processing.

9.4 HEALTHGRID SERVICES' STATUS

Some projects aim at providing services to health care professionals or to scientists. These services must be qualified according to the norms applicable to Information Society services.

Information Society service is any service normally provided for remuneration, at a distance, by electronic means and at the individual request of a recipient of services.

- ***"At a distance"*** means that the service is provided without the parties being simultaneous present. Services provided in the physical presence of the provider and the recipient, even if they involve the use of electronic devices are not provided "at a distance" (e.g. medical examinations or treatment at a doctor's surgery using electronic equipment where the patient is physically present).
- ***"By electronic means"*** means that the service is sent initially and received at its destination by means of electronic equipment for the processing (including digital compression) and storage of data, and entirely transmitted, conveyed and received by wire, by radio, by optical means or by other electromagnetic means. Services that are not provided via electronic processing/inventory systems are not services provided "by electronic means" (e.g. telephone/telefax consultation of a doctor).
- ***"At the individual request of a recipient of services"*** means that the service is provided through the transmission of data on individual request.

Information Society services also includes services consisting of the transmission of information via a communication network, in providing access to a communication network, or in hosting information provided by a recipient of the service.

Activities which by their very nature cannot be carried out at a distance and by electronic means, such as medical advice requiring the physical examination of a patient are not information society services.

The taking up and pursuit of the activity of an information society service provider may not be made subject to prior authorization or any other requirement having equivalent effect (art. 4.1 of D 2000/31/EC of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market – Directive on Electronic Commerce).

The service provider must therefore comply with a number of special rules when offering Information Society Services.

This provision of services may result from a contractual relationship. The latter must be analyzed on an individual basis in each project. In case of an international situation when providing Information Society Services, one should preliminary examine what are the competent jurisdictions before defining the law applicable to the contractual obligations of the parties.

Several international instruments can be mentioned in this regard :

- Convention on the law applicable to contractual obligations opened for signature in Rome on 19 June 1980 (80/934/EEC);
- Directive 1999/93/EC of the European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures;
- Directive 2000/35/EC of the European Parliament and of the Council of 29 June 2000 on combating late payment in commercial transactions.

Consecutively the status of the HealthGRID services has to be defined.

9.5 END-USER'S STATUS

The use of HealthGRID technology by health care professionals raises special questions.

On one hand, is the end-user legally authorized to use the HealthGRID technology? Is the use of HealthGRID technology permitted in medical practice or in scientific research? The answer lays in the rules governing the professional activities of the end-user.

Concerning some projects, it is useful to remind that the European Union has adopted the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

On the other hand, in case of medical tele-expertise, medical tele-consultancy, or medical tele-assistance, involving healthcare practitioners from different Member States, the question is to know if the health care practitioner in charge of the patient is legally authorized to seek the assistance of a foreign healthcare practitioner, and, if positive, under which conditions.

Simultaneously this foreign healthcare practitioner should also investigate to know whether he is legally authorized to provide assistance to a healthcare practitioner located in another country.

Beyond the determination of the persons liable in case of medical accident or fault, one must define the status of the health care practitioner participating to the provision of health care in another Member State, and the status of the healthcare practitioner having asked his assistance. This problem is far beyond the simple question of medical qualification equivalency.

In the same way, the cooperation between health care practitioners inside a same Member State or from different Member States raises the very delicate question of the legal framework of this cooperation.

Hence the end-user's status has to be studied in each project.

9.6 PATIENT'S STATUS

Implicitly or explicitly all the HealthGRID projects aim to participate to the medical progress as well as in its preventive and curative aspects.

Hence the patient is well in the heart of the implementation of the HealthGRID technology.

This raises the question of the determination of the place of the patient in the provision of healthcare.

The Council of Europe is convinced of the interest of the active participation of the patient to his own treatment (cf. Recommendation R (80) 4).

The legal qualification of the parties involved in the processing of the patient's personal data, including the place of the patient, is likely to highlight some tensions underlying the medical relationship.

9.7 LIABILITY ISSUES

The question of the determination of the persons liable in case of medical accident or fault relative to the use of HealthGRID technology when providing health care to a patient, is crucial but delicate.

In case of an international situation, the question is far more complex. With respect to this, one should take into account several factors which are not necessarily likely to be under complete control.

The first element of uncertainty results from the determination of the possible jurisdictions likely to know the case.

With respect to this, the European Union has recently adopted the Council Regulation (EC) No 44/2001 of 22 December 2000 on jurisdiction and the recognition and enforcement of judgments in civil and commercial matters.

The determination of the jurisdiction will permit to determine the law applicable to the case.

The European Union has adopted some norms relative to the liability matter :

- European Convention on Products Liability in regard to Personal Injury and Death (Council of Europe, Treaty n° 91, adopted on 27 janvier 1977);
- European Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products.

It has to be reminded that the European Union has also adopted special rules interesting the resolution of disputes:

- Council Decision 2001/470/EC of 28 May 2001 establishing a European Judicial Network in civil and commercial matters. Its objectives are to improve effective judicial cooperation between the Member States and effective access to justice for persons engaging in cross-border litigation;
- Council Regulation (EC) No 1206/2001 of 28 May 2001 on cooperation between the courts of the Member States in the taking of evidence in civil or commercial matters.

A mention has to be made concerning alternative dispute resolution and on-line dispute resolution.

The liability of each person involved in the use of the HealthGRID technology should be investigated in each project.

9.8 IPR ISSUES

The creation and the use of HealthGRID technologies may raise important IPR questions.

Indeed, HealthGRID technologies are sometimes created like patchworks. This poses the question of the Intellectual Property Rights relative to the constitutive elements of the considered "patchwork".

The European Union has adopted several Directives concerning IPR issues :

- Council Directive 91/250/EEC of 14 May 1991 on the legal protection of computer programs;
- Council Directive 92/100/EEC of 19 November 1992 on rental right and lending right and on certain rights related to copyright in the field of intellectual property
- Council Directive 93/98/EEC of 29 October 1993 harmonizing the term of protection of copyright and certain related rights;
- Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases;
- Directive 2001/29/EC of the European Parliament and of the Council of 22 May 2001 on the harmonisation of certain aspects of copyright and related rights in the information society;

The IPR issues must be analyzed in each HealthGRID projects.

9.9 FUNDING ISSUES

The problem of the funding of the use of HealthGRID technology is essential. Indeed, some Member States are facing serious difficulties in the funding of their Social Security. The use of a new technology in the HealthCare sector might represent an adding cost. This new cost should be analyzed, evaluated and justified.

9.10 COMPETITION ISSUES

Usually projects aiming at implementing HealthGRID technology regroup several partners into consortium. Their behavior has to comply with competition law (Monopolistic positions, abuse of dominant position, concerted practices).

This points has to be seriously investigate.