

# A SEMANTIC GRID SERVICES ARCHITECTURE IN SUPPORT OF EFFICIENT KNOWLEDGE DISCOVERY FROM MULTILEVEL CLINICAL AND GENOMIC DATASETS

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**Abstract:** This paper presents the architectural considerations of the Advancing Clinico-Genomic Trials on Cancer (ACGT) project aiming at delivering a European Biomedical Grid in support of efficient knowledge discovery in the context of post-genomic clinical trials on cancer. Our main research challenge in ACGT is the requirement to develop an infrastructure able to produce, use, and deploy knowledge as a basic element of advanced applications, which will mainly constitute a Biomedical Knowledge Grid. Our approach to offer semantic modelling of available services and data sources to support high level services and dynamic services for discovery and composition will be presented. In particular, ontologies and metadata are the basic elements through which Grid intelligence services can be developed, and the current achievements of the project in this domain will be discussed.

## 1 INTRODUCTION

Life sciences are currently at the centre of an informational revolution. Dramatic changes are being registered as a consequence of the

development of techniques and tools that allow the collection of biological information at an unprecedented level of detail and in extremely large quantities.

The nature and amount of the information now available open directions of research that were once in the realm of science fiction. Pharmacogenomics (Roses, 2000), diagnostics (Sotiriou, 2007) and drug target identification (Schuppe-Koistinen, 2007) are just a few of the many areas that have the potential to use this information to change dramatically the scientific landscape in the life sciences.

During this informational revolution, the data gathering capabilities have greatly surpassed the data analysis techniques. If we were to imagine the Holy Grail of life sciences, we might envision a technology that would allow us to fully understand the data at the speed at which it is collected. Ideally, we would like knowledge manipulation to become tomorrow the way goods manufacturing is today: highly automated, producing more goods, of higher quality and in more cost effective manner than manual production. It is our belief that, in a sense, knowledge manipulation is now reaching its pre-industrial age. The explosive growth in the number of new and powerful technologies within proteomics and functional genomics can now produce massive amounts of data but using it to manufacture highly processed pieces of knowledge still requires the involvement of skilled human experts to forge through small pieces of raw data one at a time. The ultimate challenge in coming years, we believe, will be to automate this knowledge discovery process.

This paper presents a short background section discussing the urgent needs faced by the biomedical informatics research community, and very briefly describes the clinical trials upon which the ACGT project is based for both gathering and eliciting requirements and also for validating the technological infrastructure designed. It continues with a presentation of the initial ACGT architecture defined, and presents its layers and key enabling services.

## 2 POST-GENOMIC CLINICAL TRIALS

In ACGT we focus in the domain of clinical trials on cancer. Cancer, being a complex multifactorial disease group that affects a significant proportion of the population worldwide, is a prime target for focused multidisciplinary efforts using currently available novel, high throughput and powerful technologies. Exciting new research on the molecular mechanisms that control cell growth and differentiation has resulted in a quantum leap in our

understanding of the fundamental nature of cancer cells.

While these opportunities exist, the lack of a common infrastructure has prevented clinical research institutions from being able to mine and analyze disparate, multi-level data sources. As a result, very few cross-site studies and multi-centric clinical trials are performed and in most cases it isn't possible to seamlessly integrate multi-level data.

It is well established that patient recruitment is often the time-limiting factor for clinical trials. As a result, clinical trials are gradually turning multi-centric to limit the time required for their execution (Sotiriou, 2007).

The ACGT project has been structured within such a context. It has selected two cancer domains and has defined three specific trials. These trials serve a dual purpose. Firstly, they are used for developing a range of post-genomic analytical scenarios for feeding the requirement analysis and elicitation phase of the project, and secondly they will be used for the validation of the functionality of the ACGT technologies.

The ACGT trials are in the domain of Breast Cancer and Wilm's Tumor (pediatric neuroblastoma). Specifically:

- The ACGT Test of Principle (TOP) study aims to identify biological markers associated with pathological complete response to anthracycline therapy (epirubicin), one of the most active drugs used in breast cancer treatment (Sotiriou, 2003).
- Wilms' tumour, although rare, is the most common primary renal malignancy in children and is associated with a number of congenital anomalies and documented syndromes (Graf, 2007).

In addition to these two clinical trials and on the basis of data collected for the purpose of their execution, and in-silico modelling and simulation experiment is also planned. The aim of this experiment is to provide clinicians with a decision support tool able to simulate, within defined reliability limits, the response of a solid tumour to therapeutic interventions based on the individual patient's multi-level data (Stamatikos, 2007).

### 2.1 Technical Challenges

ACGT's vision is to become a pan-European voluntary network connecting individuals and institutions and to enable the sharing of data and tools (see figure 1). In order to achieve its goals and objectives, ACGT is creating an infrastructure for

cancer research by using a virtual web of trusted and interconnected organizations and individuals to leverage the combined strengths of cancer centers and investigators and enable the sharing of biomedical cancer-related data and research tools in a way that the common needs of interdisciplinary research are met and tackled (Tsiknakis, 2006, Tsiknakis, 2007b).

Considering the current size of clinical trials (hundreds or thousands of patients) there is a clear need, both from the viewpoint of the fundamental research and from that of the treatment of individual patients, for a data analysis environment that allows the exploitation of this enormous pool of data generated.

As a result, a major part of the project is devoted to research and development in infrastructure components that are gradually been integrated into a workable demonstration platform upon which the selected (and those to be selected during the lifecycle of the project) clinical studies will be demonstrated and evaluated against user requirements defined at the onset of the project.

## 2.2. Scientific and Functional Requirements

The real and specific problem that underlies the ACGT concept is co-ordinated resource sharing and problem solving in dynamic, multi-institutional, pan-European virtual organisations. A set of individuals and/or organisations defined by such sharing relationships form what we call “an ACGT virtual organisation (VO)”. Simply stated, the participants in a multi-centric clinical trial form a VO, which exists for the duration of a trial or for any other period of time based on mutual agreements.

The task, therefore, of ACGT is to make data and tools securely available in this inter-enterprise environment where and when needed to all authorised users. As a result, the scientific and functional requirements for the ACGT platform can be summarised as follows:

- **Virtual Organisation Management:** support for the dynamic creation a VOs, defined as a group of individuals or institutions who share the computing and other resources of a "grid" for a common goal.
- **Data federation:** seamless navigation across and access to heterogeneous data sources, both private and public.
- **Data integration:** the capacity to pool data from heterogeneous sources in a scientifically,

semantically and mathematically consistent manner for further computation.

- **Shared services:** the development, sharing and integration of relevant and powerful data exploitation tools such as tools for bioinformatics analysis, data mining, modelling and simulation.

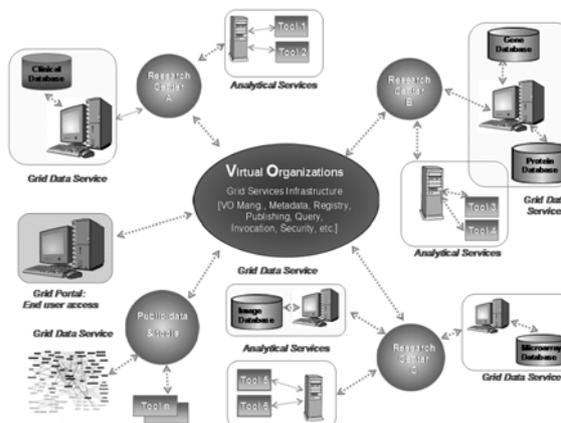


Figure 1: The vision of ACGT. Creating and managing Virtual Organisations on the Grid who are jointly participating in the execution of multicentric, post-genomic Clinical Trials.

The requirements elicitation process that has taken place in the project, based on input for a diverse range of users has resulted in the identification of the following key technical requirements.

- **Flexibility;** in other words modularity (supporting integration of new resources in a standardised way) and configurability (accommodating existing and emerging needs). This is required because (a) The a priori scientific and functional requirements are broad and diverse; (b) The data resources to be federated by the ACGT platform are characterised by deep heterogeneities in terms of source, ownership, availability, content, database design, data organisation, semantics and so on; and (c) the complexity of the underlying science, as well as the complexity of applicable knowledge representation schemas and applicable scientific algorithms;
- **Intuitive access to information;** From the user’s point of view, the ACGT knowledge management platform must provide relevant and simple access to information – both in terms of searching and navigation – and to services. In addition, it must provide a dynamically evolving set of validated data

exploration, analysis, simulation, and modelling services.

- **Security;** Finally, it must be consistent with the European ethical and legal framework, providing a high degree of trust and security to its users.

### 3 THE ACGT INITIAL ARCHITECTURE

In principle, the requirements for the ACGT platform can be met by designing a federated environment articulating independent tools, components and resources based on open architectural standards, which is customizable and capable of dynamic reconfiguration.

In order to fulfill the requirements imposed by scenarios identified in the ACGT project a heterogeneous, scalable and flexible environment is needed and the following technologies, which have gained momentum in the recent years, have been considered for adoption:

- Web Services technologies
- Grid technologies
- Semantic web technologies

Although initially separated, these technologies are currently converging in a complementary way.

Considering that the amount of data generated in the context of post-genomic clinical trials is expected to rise to several gigabytes of data per patient in a close future access to high-performance computing resources will be unavoidable. Hence, Grid computing (Foster, 2001) appears as a promising technology. Access and use of Grid-based resources is thus an integral part of the design of the infrastructure.

From the technical point of view, the requirements identified can be met using a distributed/federated, multi-layer, service oriented, and ontology driven architecture. The ACGT project decided to build on open software frameworks based on WS-Resource Framework (WSRF) and Open Grid Service Architecture (OGSA), the de facto standards in Grid computing.

Building on concepts and technologies from both the Grid and Web services communities, OGSA defines uniform exposed service semantics (the Grid service); defines standard mechanisms for creating, naming, and discovering transient service instances; provides location transparency and multiple protocol bindings for service instances; and supports

integration with underlying native platform facilities. These standards are implemented in the middleware selected, namely Globus Toolkit 4 (GT4 - <http://www.globus.org/>).

An overview of the ACGT system layered architecture is given in Fig. 2, which is shortly presented in the sequel.

A layered approach has been selected for providing different levels of abstraction and a classification of functionality into groups of homologous software entities (Tsiknakis, 2007a, Rueping, 2007). In this approach we consider the security services and components to be pervasive throughout ACGT so as to provide both for the user management, access rights management and enforcement, and trust bindings that are facilitated by the Grid and domain specific security requirements like pseudonymization and anonymization.

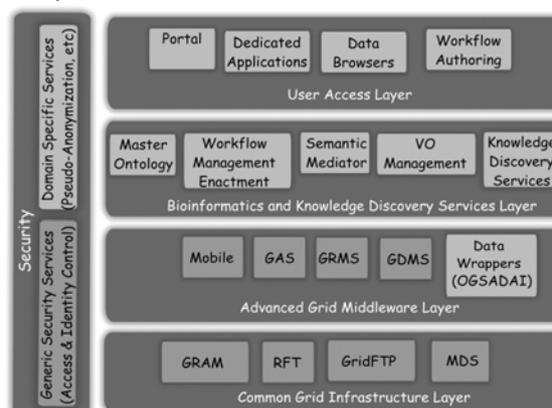


Figure 2: The ACGT layered architecture and its main services

In specifying the initial architecture of the ACGT technological platform, architectural specifications of other relevant projects have been thoroughly studied. Of particular relevance are the Cancer Biomedical Informatics Grid (caBIG - <https://cabig.nci.nih.gov/>) in the US and the CancerGrid (<http://www.cancergrid.eu/>) project in the UK.

#### 3.1 Heterogeneous Biomedical Databases integration

Distributed and heterogeneous databases, created in the context of multi-centric post-genomic clinical trials on cancer, need to be seamlessly accessible and transparently queried in the context of a user's discovery driven analytical tasks. A central

challenge, therefore, to which ACGT needs to respond, is the issue of semantic integration of heterogeneous biomedical databases.

The process of heterogeneous database integration may be defined as “*the creation of a single, uniform query interface to data that are collected and stored in multiple, heterogeneous databases.*” Several varieties of heterogeneous database integration are useful in biomedicine. The most important ones are:

- **Vertical integration.** The aggregation of semantically similar data from multiple heterogeneous sources. For example, a “virtual repository” that provides homogeneous access to clinical data that are stored and managed in databases across a regional health information network is reported in (Katehakis, 2007) and (Lesch, 1997).
- **Horizontal integration.** The composition of semantically complementary data from multiple heterogeneous sources. For example, systems that support complex queries across genomic, proteomic, and clinical information sources for molecular biologists are reported in (Stevens, 2000) and (Gupta, 2000).

The approach adopted in ACGT is based on the use of domain ontologies, acting as the global schema in a Local-as-View (LAV) integration methodology. Detailed presentation of the data integration architecture of the project and the tools and services utilized for this purpose is outside the scope of this paper. Such a detailed presentation of the data integration architecture can be found at (Anguita, 2007).

## 4 KNOWLEDGE DISCOVERY SERVICES

Once these multilevel clinical and genomic data are integrated, they can be mined to extract new knowledge that can be useful in topics such clinical diagnosis, therapy, prevention and, of course, the design of new studies (such as in the case of ACGT, clinico-genomic trials).

Knowledge discovery in clinico-genomic data presents a new array of challenges since it differs significantly from the original problems of data analysis that prompted the development of Grid technologies. The exploitation of semantics information in the description of data sources and data analysis tools is of high importance for the effective design and realization of knowledge

discovery processes. Semantics are usually made concrete by the adoption of metadata descriptions and relevant vocabularies, classifications, and ontologies. In ACGT these semantics descriptions are managed by the Grid infrastructure and therefore the knowledge discovery services build and operate on a Knowledge Grid platform (Cannataro, 2003).

### 4.1 Workflows

The Workflow Management Coalition (WFMC, <http://www.wfmc.org/>) defines a workflow as “The automation of a business process, in whole or part, during which documents, information or tasks are passed from one participant to another for action, according to a set of procedural rules”. In other words a workflow consists of all the steps and the orchestration of a set of activities that should be executed in order to deliver an output or achieve a larger and sophisticated goal. In essence a workflow can be abstracted as a composite service, i.e. a service that is composed by other services that are orchestrated in order to perform some higher level functionality.

The aim of the ACGT workflow environment is to assist the users in their scientific research by supporting the ad hoc composition of different data access and knowledge extraction and analytical services into complex workflows. This way the users can extend and enrich the functionality of the ACGT system by reusing existing ACGT compliant services and producing “added value” composite services. This reuse and composition of services is in some sense a programming task where the user actually writes a program to realize a scenario or to test a scientific hypothesis.

In order to support the ACGT users to build and design their workflows a visual workflow programming environment has been designed.

It is a web based workflow editor and designer that is integrated into the rest of ACGT system so as to take advantage of the Grid platform and the ACGT specific infrastructure and services. In particular, this workflow designer features a user friendly Graphical User Interface (GUI) that supports the efficient browsing and searching of the available ACGT services and their graphical interconnection and manipulation to construct complex scientific workflows. The choice of a graphical representation of the workflow and the support for ‘point-and-click’ handling of the workflow graph was made on the basis that this is more intuitive for the users and increases their productivity. Additional features that also take

advantage of the metadata descriptions of services include the validation in the design phase of the workflows in order to reduce or even eliminate the incorrect combination of processing units and the provision of a “service recommendation” functionality based on the data types and data formats of inputs and outputs, and are currently under development.

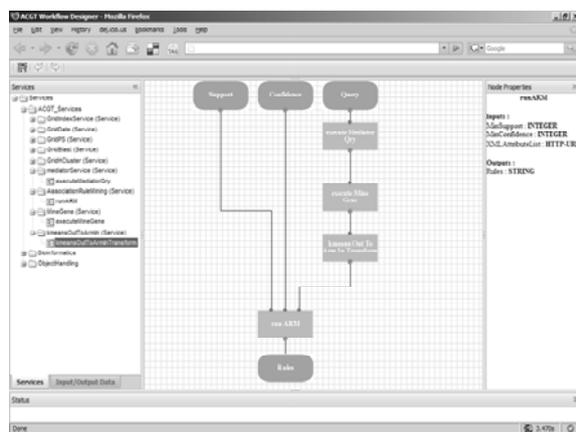


Figure 3: The AWESOME (Acgt Workflow Editor Supporting Online bioMedical invEstigations) Workflow editor developed in ACGT

The architecture of the workflow environment also includes a server side component for the actual execution (“enactment”) of workflows. Each workflow is deployed as a “higher order”, composite service and the Workflow Enactor is the Grid enabled component responsible for the invocation, monitoring, and management of running workflows. The standard workflow description language WS-BPEL ([http://www.oasis-open.org/committees/tc\\_home.php?wg\\_abbrev=wsbpel](http://www.oasis-open.org/committees/tc_home.php?wg_abbrev=wsbpel)) has been selected as the workflow description format and being a standard it enables the separation of the workflow designer from the workflow enactor and facilitates their communication and integration: the designer is a “rich internet application” running inside the users’ browsers that stores the workflows in WS-BPEL format into a workflow specific repository whereas the enactor is an ACGT service running into the ACGT Grid that “revitalizes” the persisted workflows as new services.

## 4.2 Data, Service and Workflow Metadata

Seamless integration of applications and services requires substantial meta-information on algorithms and input/output formats if tools are supposed to

interoperate. Furthermore, assembly of tools into complex “discovery workflows” will only be possible if data formats are compatible and semantic relationships between objects shared or transferred in workflows are clear. In achieving such requirements the use of meta-data is important. As a result, in ACGT we focus on the systematic adoption of metadata to describe Grid resources, to enhance and automate service discovery and negotiation, application composition, information extraction, and knowledge discovery (Wegener, 2007). Metadata is used in order to specify the concrete descriptions of things. These descriptions aim to give details about the nature, intent, behaviour, etc. of the described entity but they are also data that can be managed in the typical ways so this explains the frequently used definition: “metadata are data about data”.

Examples of this data are: research groups participating in a CT and publishing the data sets, data types that are being exposed, analytical tools that are published, the input data format required by these tools and the output data produced, and so forth. Some of the types of metadata that have been identified are:

- *Contact Info*: Contact info and other administrative data about a site participating in a CT who shares information on the grid.
- *Data Type*: The data type that a site is exposing and the context upon which this data was generated.
- *Data Collection Method*: This would include the name of the technique or the platform that was used to perform the analysis (e.g. Affymetrix), its model and software version, etc.
- *Ontological Category*: An ontological category describes a particular concept that the dataset exposes or a tool operates upon.

## 4.3 Analytical Services Metadata

Similarly the identified analytical services’ metadata descriptions fall into the following categories:

- the *task* performed by the service; that is the typology of the analytical data analysis process (e.g., feature/gene selection, sample/patient categorisation, survival analysis etc);
- the *steps* composing the task and the order in which the steps should be executed;
- the *method* used to perform an analytical/bioinformatics task;
- the *algorithm* implemented by the service;
- the *input data* on which the service works;
- the kind of *output* produced by the service;

Our ultimate challenge is to achieve the implementation of semantically aware Grid services.



legal system and dialect. Available technological (i.e. Web services) mechanisms for describing, discovering, accessing, and securing services provide a common alphabet, but a true lingua franca requires agreement on protocols, data formats, and ultimately semantics (d. Roure, 2003). In the ACGT project we are paying particular attention on these issues, and especially on the issue of semantics (see section on metadata).

## 6.2 Management

In a networked world, any useful service will become overloaded. Thus, we need to control who uses services and for what purposes. Particularly valuable services may become community resources requiring coordinated management. Grid architectures and software can play an important role in this regard and ACGT is focusing on exploiting these opportunities made available by Grid computing.

## 6.3 Quality control

As the number and variety of services grow and interdependencies among services increase, it becomes important to automate previously manual quality control processes—so that, for example, users can determine the provenance of a particular derived data product (Goble, 2004). The ability to associate metadata with data and services can be important, as can the ability to determine the identity of entities that assert metadata, so that consumers can make their own decisions concerning quality.

## 7 DISCUSSION AND CONCLUSIONS

In this paper, we consider a world where biomedical software modules and data can be detected and composed to define problem-dependent applications. We wish to provide an environment allowing clinical and biomedical researchers to search and compose bioinformatics and other analytical software tools for solving biomedical problems. We focus on semantic modelling of the requirements of such applications using ontologies.

The project has conceived an overall architecture for an integrating biomedical sciences platform. The infrastructure being developed uses a common set of services and service registrations for the entire

clinical trial on cancer community. We are currently focusing on the development of the core set of components up to a stage where they can effectively support *in silico* investigation. Initial prototypes have been useful in crystallizing requirements for semantics.

The project has set up cross-disciplinary task forces to propose guidelines concerning issues related to data sharing, for example legal, regulatory, ethical and intellectual property, and is developing enhanced standards for data protection in a web (grid) services environment.

In addition the project is developing

- standards and models for exposing web services (semantics), scientific services, and the properties of data sources, datasets, scientific objects, and data elements;
- new, domain-specific ontologies, built on established theoretical foundations and taking into account current initiatives, existing standard data representation models, and reference ontologies;
- innovative and powerful data exploitation tools, for example multi-scale modelling and simulation;
- standards for exposing the properties of local sources in a federated environment;
- a biomedical GRID infrastructure offering seamless mediation services for sharing data and data-processing methods and tools;
- advanced security tools including anonymisation and pseudonymisation of personal data according to European legal and ethical regulations;
- a Master Ontology on Cancer and use standard clinical and genomic ontologies and metadata for the semantic integration of heterogeneous databases;
- an ontology based Trial Builder for helping to easily set up new clinico-genomic trials, to collect clinical, research and administrative data, and to put researchers in the position to perform cross trial analysis;
- data-mining services in order to support and improve complex knowledge discovery processes;
- an easy to use workflow environment, so that biomedical researchers can easily design their “discovery workflows” and execute them securely on the grid.

A range of demonstrators, stemming from the user defined scenarios, together with these core set

of components are currently enabling us to both begin evaluating and gathering additional and more concrete requirements from our users. These will allow us to improve and refine the facilities of the ACGT services.

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