A Grid-Enabled Toolkit for In Silico Oncology Simulations

Theodoros Athanaileas
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
thathan@esd.ntua.gr

Andreas Menychtas
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
a_menychtas@telecom.ntua.gr

Dimitra Dionysiou
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
dimdio@esd.ntua.gr

Georgios Stamatakos
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
gestam@central.ntua.gr

Dimitra Kaklamani
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
dkaklam@mail.ntua.gr

Theodora Varvarigou
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
dora@telecom.ntua.gr

Nikolaos Uzunoglu
School of Electrical and Computer Engineering, National Technical University of Athens
9 Heroon Polytechneiou Str.
15773, Zografou, Athens, Greece
nuzu@cc.ece.ntua.gr

ABSTRACT

In silico (on the computer) oncology is a multi-disciplinary field that focuses on the examination and modeling of biological mechanisms related to the phenomenon of cancer. *In silico* oncology simulation model may be used for evaluating and comparing different therapeutic schemes while at the same time considering different values of critical parameters which present substantial inter-patient variability. As the number of the involved parameters and of the considered radiotherapeutic schemes increases, the resulting exponential increase in computational requirements makes the use of a grid environment for the execution of the simulations both a necessity for the involved researchers and an opportunity to make *in silico* oncology applications available to a wider biomedical and research community. In this paper, we describe a toolkit that enables the execution of *in silico* oncology simulations on grid infrastructures. This toolkit is designed and developed as a web portal with advanced features that facilitates the execution of *in silico* oncology simulations in grid environments. Several scenarios of radiotherapy simulations have been performed on the EGEE grid and indicative simulation results, as well as execution times are presented.

SIMUTOOLS 2008, March 03-07, Marseille, France

DOI 10.4108/ICST.SIMUTOOLS2008.3042

Categories and Subject Descriptors

I.6.0 [SIMULATION AND MODELING]: *General, Simulation Support Systems.*

General Terms

Performance, Design, Experimentation.

Keywords

In silico oncology, grid computing, grid portal, parameter sweep simulations

1. INTRODUCTION

In silico (on the computer) oncology is an emerging interdisciplinary field aiming at mathematically describing and computationally simulating the multi-scale biological mechanisms that constitute the phenomenon of cancer and its response to therapeutic techniques. Within this framework, the *In Silico* Oncology Group, National Technical University of Athens, has already developed a four-dimensional simulation model of glioblastoma multiforme (GBM) [1] [2] response to radiotherapy. The simulation model may be used for evaluating and comparing

different radiotherapeutic schemes while testing several critical parameters which present inter-patient variability, thus revealing the relative merits of various radiotherapeutic schedules in a patient-specific manner. Towards this end, a number of simulations need to be performed with different input parameters and based on the individual characteristics of a tumour.

Parameter sweep applications (PSAs) are a class of applications that deal with the analysis of a specific simulation for a range of parameter values. Typically, this kind of applications is comprised of a large number of tasks, each of which performs a given simulation over a subset of parameter values. In the context of *in silico* oncology and radiotherapy simulation, a PSA is comprised of a set of *independent* tasks, which share some common files (executable code for a specific method of therapy and input files). Due to the fact that tasks are completely independent, the application is viable for efficient large scale execution on a computational grid, thus reducing dramatically the overall time demanded for its completion.

Grid computing has emerged in the last years as a technology for large-scale, flexible and coordinated resource sharing and in some cases with an orientation towards high performance computing [3]. Computational grids enable the sharing of a wide variety of geographically distributed resources across multiple organizations for solving large scale computational and data intensive problems.

In the work presented in this paper, a simulation environment for performing radiotherapy parameter sweep simulations on the grid infrastructure provided by the EGEE project [4] has been developed. The simulation environment builds on the gLite middleware [5] developed by EGEE and provides a web-based grid portal for enabling interactions with it in a simple and user-friendly way. In order to enable the execution of radiotherapy simulations on the grid, the legacy code has been suitably migrated to the operating system used on grid nodes and several scripts have been developed in order to automatically conduct parameter sweep radiotherapy simulations.

The application – portal is enhanced with added functionality in order to simplify the job submission process and automate the interaction with the grid services. In that way more users are able to access the computational resources while the administrators manage the application and monitor the operational status.

The remainder of the paper is as follows: Section 2 discusses related work. Section 3 concisely presents the radiotherapy simulator that has been originally implemented and discusses the grid-added value that the proposed implementation provides. Section 4 describes the architecture and implementation of the grid-enabled simulator and Section 5 presents results regarding certain parameter sweep simulations on the grid. Finally, Section 6 concludes the paper and presents directions for future work.

2. RELATED WORK

PSAs are a very common class of applications that are met in computational grids. Typically, they consist of a large set of independent tasks that run the same code over different input parameter values. High performance parametric modeling has been identified as a killer application for the grid [6]. Grid-Enabled PSAs have been recently developed in a number of scientific and engineering fields, like Bioinformatics [7], Particle Physics [8], Computational Fluid Dynamics (CFD), etc. The main challenge of porting PSAs to a grid environment is to provide efficient execution and scheduling mechanisms that have the ability to adapt to the dynamic and heterogeneous nature of grids. Relative issues have been discussed in [9] and [10].

However, the simulation application end users are not computer experts or familiar with grid technologies. Consequently the requirements for usability and user friendly interface are of major importance for the application and the web portal approach as a user interface is considered as the best option to fulfill them. More and more application services are offered to end users through web portals. In the domain of grid technologies, research on the web portals that offer grid services is a very challenging topic. For the EGEE grid infrastructure there are currently two portal implementations under development, the GENIUS Grid Portal [11] and the P-GRADE Portal [12]. These portals are available to the research community and include many advantages such as workflow construction and execution. However, these portal implementations include complicated processes for the job submission and given that they could not be easily extended and adopted in the application, a new, application specific, portal was designed and developed.

3. IN SILICO ONCOLOGY–GRID ADDED VALUE

3.1 Radiotherapy Simulation

The In Silico Oncology Group, NTUA, has adopted an essentially "top-down" modelling approach and developed a number of hybrid discrete Monte Carlo / cellular automata and continuous differential equation simulation models of tumour growth and response to therapeutic modalities. The aim is to better understand cancer and related phenomena and to optimize therapeutic interventions by performing In Silico (on the computer) experiments based on the individual data of the patient.

In order to evaluate and compare different therapeutic schemes, a simulation model of imageable GBM response to radiotherapy has been developed. The model is based on the clinical, imaging, histopathologic, and molecular data of the patient and numerous fundamental biological mechanisms are incorporated and explicitly described. The clinician delineates the tumour and its metabolic subregions on the available imaging data by using a dedicated computer tool.

A prototype system of quantizing cell clusters included within each geometrical cell of a discretizing mesh covering the anatomic area of interest lies at the heart of the simulation approach. During a simulation the geometrical mesh is scanned with a time step of an hour. The elementary cubic volume of the mesh is called "Geometrical Cell (GC)". In each time step, the updated state of a given GC is determined on the basis of a number of algorithms describing the behaviour of the cells constituting the tumor. More specifically, each GC of the mesh belonging to the tumor contains cells, which are distributed in a number of "classes" (compartments), each one characterized by the phase in which its cells are found (within or out of the cell cycle: G1, S, G2, M, G0, Necrosis, Apoptosis). Specially designed stochastic cellular automata describe tumor cell kinetics, by incorporating the following biological phenomena: cycling of proliferating cells through the subsequent phases of the cell cycle, spontaneous apoptosis, transition to a dormant (G0) phase due to inadequate supply with oxygen and nutrients, local reoxygenation and nutrient provision reestablishment, cell death through necrosis

due to prolonged oxygen and nutrients deprivation, radiotherapy-induced apoptotic or necrotic cell death.

Cell killing by irradiation is described by the Linear Quadratic or LQ Model, which is widely used in the pertinent literature: $S(D) = \exp[-(\alpha D + \beta D^2)]$, where S(D) is the surviving fraction after a (uniform) dose D (Gy) of radiation to a population of cells. The parameters α (Gy-1) and β (Gy-2) are called the radiosensitivity parameters of the LQ model.

Tumor expansion or shrinkage is simulated on the basis of the following algorithms: If the number of tumor cells contained within a given GC drops below a given threshold, then a procedure which attempts to "unload" the remaining cells in the neighboring GCs takes place. Cells are preferentially placed within the neighboring GCs with the maximum available free space. If the given GC becomes empty, it is assumed to disappear from the tumour, in which case an appropriate shift of a chain of GCs, intended to fill the "vacuum", leads to tumor shrinkage. This can happen after the killing of a number of cells by irradiation. On the other hand, if the number of alive and dead cells within a given GC exceeds a given threshold, then a similar procedure attempting to unload the excess cells in the surrounding GCs takes place. In case that the unloading procedure fails to sufficiently reduce the number of cells, then a new GC emerges. Its position relative to the "mother" GC is determined using a random number generator. An appropriate shifting of a chain of adjacent GCs leads to a differential expansion of the tumor.

For more information, the interested reader may refer to [1] and [2].

3.2 Grid-Added Value

Exploitation of grid technologies is imperative for *in silico* oncology for the following reasons:

- exponential increase of required computational resources when considering a more dense discretization of the space-time (4D) grid of the biological problem
- heterogeneity of required data (imaging, histopathologic, genetic) with different preprocessing requirements
- large number of involved patients

Exploitation of the vast resources provided by a grid may lead to a better understanding of the biological and clinical behavior of cancer and especially solid tumours. Furthermore, computer simulation may be employed in order to optimize treatment of cancer, by conducting a number of simulations for different therapeutic schemes based on the individual data of a patient. A restraining factor is that simulations need to be conducted in clinically accepted computational time. As the number of possible therapeutic schemes and consequently the number of simulations increases, the time required for evaluating and comparing the effects of the different schemes may become forbiddingly high. Exploiting grid computing is a very attractive solution, as the resources provided in a grid infrastructure may be efficiently used to reduce overall required execution time in a cost-effective and efficient manner.

In order for *in silico* oncology to be efficiently transferred to a grid infrastructure, certain aspects need to be addressed regarding its adaptation to the grid programming model.

- development of efficient grid workflows, taking into consideration the characteristics of the different simulation models
- mechanisms for automatic simulation submission and monitoring
- data management and result aggregation
- provide some basic QoS to the user (e.g. provide an optimal response time for various simulation models – always taking into consideration the characteristics of the model)

The architecture of the simulation environment, along with implementation details are presented in the following Section.

4. ARCHITECTURE–IMPLEMENTATION

In the work presented in this paper, an educational grid-enabled environment for *in silico* oncology has been developed, which may be used by doctors and researchers for evaluating and comparing the behaviour of different simulation codes (e.g. therapeutic schemes) and the ways they are affected by different input parameters. The grid-enabled environment has been developed for use on the EGEE grid infrastructure and thus builds on the gLite middleware, which has been developed by EGEE for providing the required grid functionality. In the following paragraphs, implementation details regarding the migration of the application to the grid environment of EGEE, as well as the overall architecture of the grid-enabled toolkit are presented.

4.1 Application Porting

The first step towards grid-enabling an application is to bring it to a form appropriate for execution on the grid. This involves adapting source code in order to be externally parameterizable and also creating the required scripts and description files which are used by the grid workload management system for job execution on the grid.

In order to grid-enable the execution of radiotherapy simulations, the following points were considered:

- The various simulation parameters for the original code of radiotherapy that was used in the work presented herein were hard-coded, which is obviously unsuitable for parameter sweep execution. The source code has been modified in order to be able to get input from standard parameter files, which are created at the user session and are transferred along with the executable code to the grid node for execution.
- Development of the required wrapper-scripts and helper programs for setting up and executing on the grid node the simulation that is submitted to the grid.
- Creation of Job Description Files that are used by the workload management system of the grid for job submission and for the job match-making process. A job description file describes various characteristics of the job to be submitted (such as executable name, input arguments, input and output files, etc) in a standard job description language. Obviously, each job in a parametric simulation corresponds to a different job description file and it is necessary to provide mechanisms for the automatic creation of these files according to user input. Figure 1 presents a sample job description file

according to the specifications of the gLite Job Description Language [13].

```
Executable = "setupAndExecuteInSilicoSimulation.sh";
Arguments = "2 1.2 20 0.05 0.05 96 Input96.raw";
StdOutput = "stdOut.out";
StdError = "stdErr.out";
InputSandbox = {"setupAndExecuteInSilicoSimulation.sh",
"inSilicoSrc.tar","inSilico.jar","Input96.raw"};
OutputSandbox = {"stdOut.out","stdErr.out","results.tar"};
RetryCount = 5;
Rank = (other.GlueCEStateWaitingJobs == 0 ? other.GlueCEStateFreeCPUs : -
other.GlueCEStateWaitingJobs);
```

Figure 1. Sample Job Description File

4.2 Grid Portal

The submission of simulation jobs in the grid infrastructure of EGEE requires the use of an intermediate server (UI - User Interface). This server includes all the essential software packages (e.g. gLite) so as to communicate with the grid resources (computational, storage and management). Through the UI the end users are able to bind these resources, submit new simulation jobs and monitor their status.

The *in silico* oncology simulation application targets specific user groups. These groups consist mainly of doctors and researchers; people that are not computer experts and are not familiar with grid technologies. There are several limitations of the EGEE infrastructure on this. The UI server requires a specific Linux distribution [14] that provides only Secure Shell (SSH) [15] access to end users. Consequently, the job submission and all the management actions are available through complicated Linux commands. The users should get familiar with a Linux environment and learn many gLite commands and their arguments even for the simplest job submission.

The important user requirement for usability was addressed with the design and the development of a web portal. Web portals are considered as cutting edge technology for user interfaces providing advanced services to the end users in a friendly and efficient way. The role of the portal in the application is of major importance since it offers grid services to the research community eliminating any usability issues. Additionally, the portal adds new features in the application beyond the core grid functionality, such as user management and usage statistics services.

4.2.1 Portal Architecture

The web portal was designed and developed following a multi-tier architectural approach. This approach defines different layers for the operations and functions of the application framework, simplifying the installation and the maintenance processes. The grid enabled In Silico oncology application belongs to the category of the applications that require enterprise functionality and usability at the same time. Multi-tier architectures have all the characteristics for building this kind of applications.

The application framework was developed in different layers providing several advantages. Initially it couples different technologies in a robust and effective way. The core grid services are developed independently from the user interface and consequently each layer can be maintained and extended without affecting the others. Additionally, each layer can be extended with new functionality and tools without changes in the other layers. Following this approach, the application has better quality and can be easily extended and customized to meet all the end user requirements.

The simulation application consists of four layers: the presentation (UI), the portal services, the gLite and the database. Figure 2 depicts the application architecture:

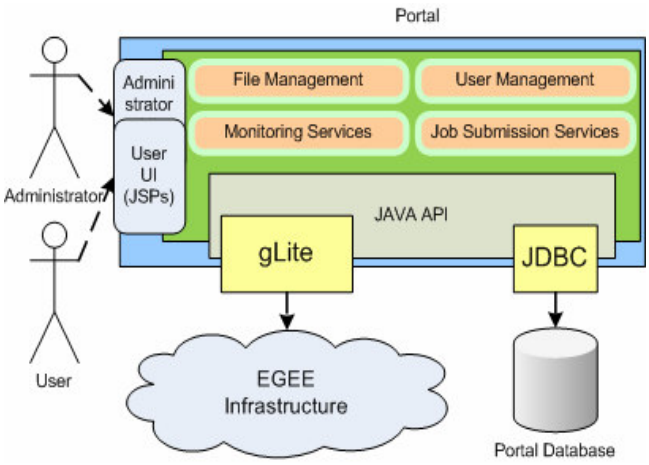

Figure 2. Application Architecture

The *presentation layer (User Interface)* includes all the functionality for the interaction with the end users. This layer was developed in order to simplify and visualize the grid processes for job submission and management. All the application functionality is presented to the users through web pages (JSPs) [16]. Each web page gets the user request, communicates with the respective services and presents back the result. In that way, the users are able to submit automatically *in silico* oncology simulations to EGEE grid infrastructure without requiring direct interaction with the complex grid processes. The presentation layer includes an administration area for a specific user group that manages the application and has access to historical and real time information regarding the application functions and the user actions.

The *portal services layer* includes all the functionality of the application and establishes the connection between the presentation and the gLite and database layers. The main services in this layer are the File and User Management and the Job Submission and Monitoring. All the services in this layer are implemented using the JAVA programming language creating an Application Programming Interface (API) that could be extended with more features or for creating other user interfaces. The presentation layer calls specific methods of the portal services to carry out the business processes. The user requests determine which services are called. Thereafter each service that handles the request communicates with the gLite layer, the database layer or both and creates the required input files such as the JDLs.

The *database layer* operates complementary to the services layer. This layer includes a Database and all the functionality for accessing it. The database keeps all the data regarding the application and user management. Additionally all the user actions, the simulation execution details and information about the grid resources are stored in the database. The administrators

have access to these data and exploit them for high level user and resource monitoring and management.

The *gLite layer* includes all the functionality for the communication with the grid services and resources. The methods of this layer call specific commands of the gLite middleware to map the grid environment operations to portal services. The development of this layer is the extension of the application porting process that was described in a previous section.

4.2.2 Job Submission Process

The multi-tier architecture and the web portal simplified the submission process for the *in silico* oncology simulations. As presented in the sequence diagram in Figure 3, the interaction between the user the core grid services is achieved through the portal services that handle the user requests.

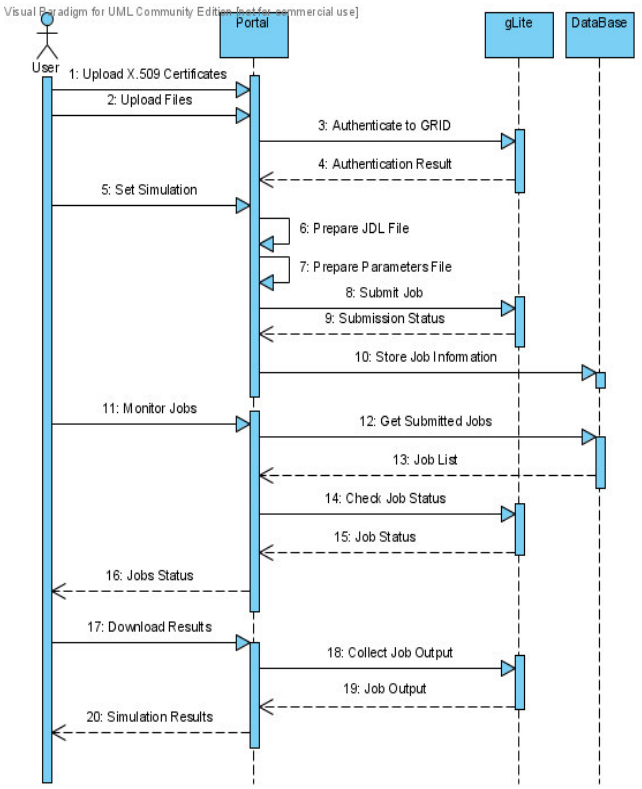

Figure 3. Job Submission Sequence

The job submission process is initiated with the input file upload to the portal. Each user has a specific data repository to store input and output simulation files. These files could be used for multiple simulations that may run concurrently. Thereafter the user selects the input files, the simulation algorithm, the simulation parameters and any other execution specific arguments such as the retry count. The portal creates the JDL and the parameters files based on the user request and submits the job to the EGEE infrastructure. The job details are recorded in the database and the users are able to get the active job list and check the status of each job. When the simulation jobs are finished the users are able to collect the results to the portal and finally download them locally through the web browser.

4.2.3 Web Portal Advantages

The web portals are the state of the art user interfaces for the network enabled applications. The *in silico* oncology grid portal has all the characteristics of an enterprise simulation toolkit. It includes all the core grid functionality, adds new features beyond grid, such as the user management and offers them through a user-friendly interface.

The portal has several advantages for the end users:

- *Usability*: The end users are able to access the simulation application and the grid services and resources through a web browser. In that way, all the difficulties of accessing the grid infrastructure and initiating the simulation process are eliminated.
- *Efficiency*: The graphical representation of the simulation and grid services through the portal automates the job submission and shifts the decision making from the end user to the portal mechanisms. The user does not edit complex files for the job submission since the portal gathers the required information from user forms and creates the required files. The user uploads the input files, fills the forms with the execution parameters and the simulation or the simulation sets are automatically submitted for execution.
- *Operating System independence*: Since the access to the application is realized through a web browser there is no need for a specific operating system neither any other prerequisite software, such as an SSH client.
- *Application extension*: The design and the development of the application as a web portal provide the advantage to add more features in the application that are directly adopted from the end users. For example a new scheduling algorithm could improve the efficiency of the simulation while the end user continues to use the application exactly the same way as before.

The web version of the simulation application can be easily accessed from an increased number of end users since it instantly enables access to the advanced computational resources of grid infrastructures through user friendly processes.

5. EXPERIMENTS-RESULTS

Indicative simulation results are shown in Figure 4 and Figure 5.

In Figure 4 the relative merits of various dose fractionation schemes commonly used for the treatment of solid tumours. The simulation results are in accordance with established clinical knowledge. They reveal that the accelerated fractionation and the accelerated hyperfractionation schemes seem to be particularly efficient in terms of tumour cell kill. They achieve maximum cell kill at specific instants compared to the other schedules. Nevertheless, their duration is smaller and as a result, if they fail in eradicating “all” tumour cells, tumour repopulation begins earlier. At the other extreme, hypofractionation is advantageous in terms of the duration of tumour control, but achieves less tumour cell kill. Of course, in clinical practice the choice of the appropriate radiotherapy schedule depends both on the expected tumour cell kill and the expected normal tissue complications.

Furthermore, the simulation model of imageable GBM response to radiotherapy has already been clinically validated to a substantial degree, by performing a series of simulations corresponding to the various arms of the RTOG study 83-02 [17].

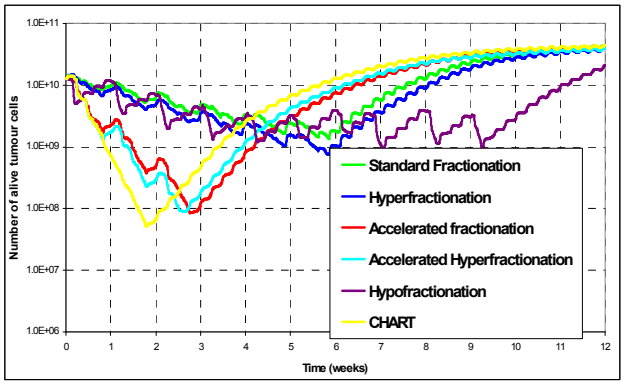

Figure 4. Comparing the relative merits of dose fractionation schemes commonly used for the radiation therapy of solid tumours.

For this purpose, a thorough study of the most critical parameters determining GBM response to radiotherapy has been performed, by considering the values of the parameters that have appeared in the literature for GBM. The parameters selected for the study were the α and β radiosensitivity parameters of the LQ model and the cell cycle duration (TC). According to accumulated clinical and experimental knowledge, these parameters are the most critical determinants of tumor response to radiotherapy. They reflect characteristics of a tumor that are determined largely by the underlying genetic profile of the tumor cells. Specifically, the study comprised a total of 462 radiotherapy simulations based on the 6 radiotherapeutic schemes of the RTOG 83-02 clinical study [17] and using 11 values of the cell cycle duration and 7 pair values of the radiosensitivity α and β parameters of the LQ model.

The simulation results are in agreement with the results of the RTOG 83-02 clinical study, as they reveal that for GBM radiotherapy the use of high-dose hyperfractionation schemes is advantageous in terms of clonogenic cell kill compared to low-dose hyperfractionation schemes or accelerated hyperfractionation schemes. This holds true for the whole range of parameter values that have been tested. An indicative case drawn from the whole series of simulations is presented in Figure 5.

The aforementioned simulations have been submitted for execution on the resources provided by the South Eastern Europe Virtual Organization (SEE-VO) [18] of the EGEE infrastructure. At the time the simulations were conducted, the SEE-VO provided 32 computing elements with various numbers of worker nodes and different capabilities. Each therapeutic scheme has been treated as a different parametric simulation. Each scheme consists of 77 combinations of input parameters and for each parameter combination a job has been created and submitted for execution to the grid, thus each scheme consists of 77 independent jobs submitted simultaneously to the grid.

Table I shows some statistics regarding execution times of the simulations. The Overall Schema Execution time is the time between the submission of the first job and the result retrieval of the last finished job. The Mean Job Execution Time is the average of the time that a job actually spends while *running*. Speedup is calculated as (Mean Job Execution Time) * (Number of Jobs)/ (Overall Schema Execution Time). The Overall Schema Execution Time is dependent on the load characteristics of the grid (e.g. queue waiting times) and thus the obtained speedup is variable.

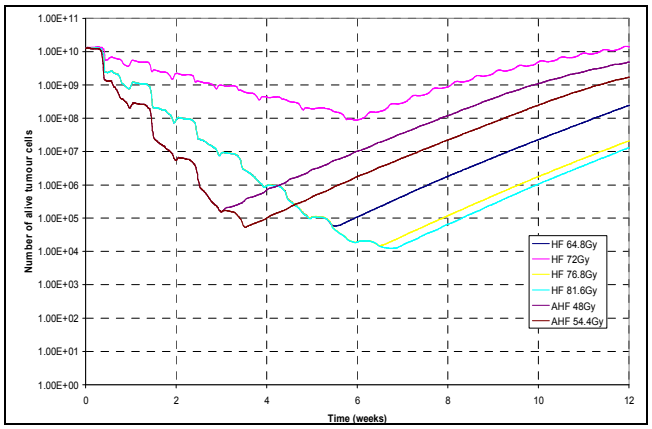

Figure 5. Indicative presentation of the number of alive tumour cells as a function of time from the start of the radiotherapy treatment for a hypothetical GBM tumour and the 6 radiotherapy schedules of the RTOG 83-02 clinical study (cell cycle duration TC=70h, LQ model parameters: α=0.31Gy-1, b=0.04Gy-2, HF:HyperFractionation, AHF: Accelerated Hyperfractionation. For each scheme the total dose is given).

Schema #	Mean Job Execution Time	Overall Schema Execution Time	Speedup
1	~32 mins	~58 mins	~42
2	~31 mins	~59 mins	~40
3	~34 mins	~59 mins	~44
4	~38 mins	~72 mins	~41
5	~36 mins	~66 mins	~42
6	~21 mins	~47 mins	~34

Table 1. Execution Times of Radiotherapy Parameter Sweep Simulations

Execution results indicate that by performing the parameter sweep simulations on the grid, a considerable speedup may be achieved. This is very important in the context of *in silico* oncology, since the computational requirements of the simulations become overwhelmingly large as the required detail of simulation grows and because of the large number of potentially involved patients. Grid computing is a very appealing solution in the context of *in silico* oncology, since the vast resources provided by a grid may be efficiently used for providing timely and accurate results.

6. CONCLUSIONS AND FUTURE WORK

In silico oncology is a multidisciplinary field that aims to model the multi-scale biological mechanisms that constitute the phenomenon of cancer and evaluate its response to therapeutic techniques by computer (In Silico) simulations. Due to the

exponential increase in the complexity of the simulation as the density of discretization of the 4D grid of the biological model increases and the heterogeneity of required data and their preprocessing needs, as well as the large number of potentially involved patients, the large scale execution capabilities and vast computational capacities offered by a grid may prove exceptionally beneficial.

In the work presented in this paper, a grid-enabled toolkit for *in silico* oncology Simulations has been developed. The toolkit builds on the gLite middleware and enables the execution of radiotherapy simulations on the grid infrastructure deployed by the EGEE project. Several mechanisms for automatically creating parameter sweep simulations have been implemented. The toolkit provides a web-based portal that acts as a user-friendly way for the non-grid expert doctor or researcher to access the resources of the grid.

Several parameter sweep simulations have been conducted using the toolkit. Exploitation of grid resources has made possible the simulation and comparison of different therapeutic schemas that would be extremely time consuming in case of execution on a conventional computer. Obtained results, which are in accordance to the clinical studies, have provided the required data for a thorough comparison of the simulated therapeutic schemas. Execution times prove that a considerable speedup may be achieved by using the grid and that the grid can also provide solutions in case that comparative results for therapeutic schemas are needed in real time.

In the future, we plan to port additional therapeutic methods (e.g. chemiotherapy) to the grid-enabled toolkit and use the grid in order to perform similar comparative simulations. Additionally, the simulation application will be extended in order to address the user requirements for Quality of Service (QoS). New mechanisms are under development to provide advanced job scheduling based on the user needs, the grid resources capabilities and the experience of the previous job executions.

7. ACKNOWLEDGMENTS

This work has been performed in the context of the research project “Development and adaptation of an *in silico* oncology application in grid environment” (GRID-APP). The project is funded by the General Secretariat for Research and Technology, Ministry of Development, Greece (75%) and the European Regional Participation Fund (25%).

8. REFERENCES

[1] Stamatakos G.S. et al.: In silico radiation oncology: combining novel simulation algorithms with current visualization techniques. IEEE Proceedings: Special Issue on “Bioinformatics: Advances and Chalenges 90 (2002) 1764-1777

[2] Dionysiou D.D. et al : A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation. J. theor. Biol. 230 (2004) 1-20.

[3] I. Foster, C. Kesselman, S. Tuecke. “The Anatomy of the Grid: Enabling Scalable Virtual Organizations.”, International Journal of Supercomputer Applications, vol. 15, No. 3, 2001, pp. 200-222.

[4] The EGEE Project, homepage: http://www.eu-egee.org/

[5] The gLite middleware, http://glite.web.cern.ch/glite/

[6] Abramson, D., Giddy, J., and Kotler, L., High Performance Parametric Modeling with Nimrod/G: Killer Application for the Global Grid?, IPDPS'2000, Mexico, IEEE CS Press, USA, 2000, pp. 520-528Dfg

[7] Giovanni Aloisio, Massimo Cafaro, Sandro Fiore, Maria Mirto: ProGenGrid: A Workflow Service Infrastructure for Composing and Executing Bioinformatics Grid Services. CBMS 2005: 555-560Dg

[8] B. Beeson, S. Melnikoff, S. Venugopal, and D. G. Barnes, A Portal for Grid-enabled Physics, Proceedings of the 2005 Australasian workshop on Grid computing and e-research, pp. 13-20

[9] H. Casanova, G. Obertelli, F. Berman, and R. Wolski. The AppLeS Parameter Sweep Template: User-level middleware for the grid. In Proceedings of the Super Computing Conference, pages 75–76, 2000.

[10] E. Huedo, R. S. Montero, and I. M. Llorente. Experiences on adaptive grid scheduling of parameter sweep applications. In 12th Euromicro Conference on Parallel, Distributed and Network-Based Processing (PDP’04), 2004.

[11] GENIUS Grid Portal: https://genius.ct.infn.it

[12] P-GRADE Portal: http://portal.p-grade.hu

[13] Job Description Language (JDL) Attributes Specification, https://edms.cern.ch/document/590869/1/

[14] Scientific Linux (SL): https://www.scientificlinux.org

[15] T. Ylonen, T. Kivinen, and M. Saarinen. SSH protocol architecture, November 1997.Multi-Tier architecture reference needed

[16] Java Server Pages (JSP): http://java.sun.com/products/jsp

[17] Werner-Wasik M. et al “Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas”, Cancer 77, 1535-1543, 1996

[18] The South-Eastern Europe Virtual Organization (SEE-VO), http://www.egee-see.org/see-vo.php?language=en