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**Využití technologie GRID při zpracování medicínské
informace**

Utilization of GRID technology in processing of medical information

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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Abstrakt (česky)

Práce se soustředí na vybrané oblasti biomedicínského výzkumu, které mohou profitovat ze současných výpočetních infrastruktur vybudovaných ve vědecké komunitě v evropském a světovém prostoru. Teorie výpočtu, paralelismu a distribuovaného počítání je stručně uvedena s ohledem na počítání v gridech a cloudech. Byla studována oblast výměny medicínských snímků a Gridový PACS systém byl propojen s existujícími distribuovanými systémy pro sdílení DICOM snímků. Další studovanou doménou byla věda týkající se lidského hlasu. Vzdálený přístup k aplikaci pro analýzu hlasu v reálném čase byl představen zároveň s úpravou protokolů pro vzdálenou plochu pro přenos zvukových nahrávek. To přináší možnost využití stávajících aplikací na dálku specialisty na hlas.

Byl studován přístup tzv. systémové biologie v oblasti lidské fyziologie a patofyziologie. Bylo přispěno k metodologii modelování lidské fyziologie pro tvorbu komplexních modelů založených na akauzálním a objektově orientovaném modelovacím přístupu. Byly představeny metody pro studium parametrů pomocí technologie počítání v gridech a v cloudech. Proces identifikace parametrů středně komplexních modelů kardiovaskulárního systému a komplexního modelu lidské fyziologie lze významně zrychlit při použití cloud computingu a dobrých výsledků lze dosáhnout v rozumném čase. Tato metoda umožňuje aplikovat parametrické studie ve fyziologickém a biologickém výzkumu. Toto může zlepšit praktické použití matematických modelů a identifikaci parametrů ve zdravotní péči.

Klíčová slova: gridové počítání, počítání v cloudu, výpočetní fyziologie, odhad parametrů, výměna medicínských snímků, analýza hlasového signálu

Abstract

This thesis focuses on selected areas of biomedical research in order to benefit from current computational infrastructures established in scientific community in european and global area. The theory of computation, parallelism and distributed computing, with focus on grid computing and cloud computing, is briefly introduced. Exchange of medical images was studied and a seamless integration of grid-based PACS system was established with the current distributed system in order to share DICOM medical images. Voice science was studied and access to real-time voice analysis application via remote desktop technology was introduced using customized protocol to transfer sound recording. This brings a possibility to access current legacy application remotely by voice specialists.

The systems biology approach within domain of human physiology and pathophysiology was studied. Modeling methodology of human physiology was improved in order to build complex models based on acausal and object-oriented modeling techniques. Methods for conducting a parameter study (especially parameter estimation and parameter sweep) were introduced using grid computing and cloud computing technology. The identification of parameters gain substantial speedup by utilizing cloud computing deployment when performed on medium complex models of cardiovascular system and complex models of human physiology. This makes such kind of study applicable in order to perform identification of physiological system in reasonable time for physiological and biological research and good results are available in a reasonable time. This can improve practical usage of mathematical models in healthcare.

Keywords: grid computing, cloud computing, computational physiology, systems biology, parameter estimation, medical image exchange, voice signal analysis

List of Abbreviations

BOINC Berkeley Open Infrastructure for Network Computing, page 7

CPU Central Processing Unit, page 10

EGI European Grid Infrastructure, page 7

IaaS Infrastructure as a Service, page 8

NGI National Grid Initiative, page 7

WLCG Worldwide Large Hadron Collider Computing Grid, page 7

1. Introduction

Grid computing is usually defined as sharing computational and data storage resources across organizational boundaries. Grid computing in contrast to common distributed computing focus on large-scale resource sharing. The technology under grid computing provides access to a computational resources in a federated way, while preserving some rights of the owner. Requirements, standards and architecture, were proposed and published, e.g., by Foster et al. [1, 2] and such infrastructures are currently distinguished as "service" grids. It's non-trivial task to maintain scientific grid, thus specialists from the so-called national grid initiatives (NGI) maintains and cooperates with similar grid initiatives of other countries. In Europe these are coordinated, e.g., by European Grid Infrastructure (EGI). One of the largest project computed in these grid infrastructures are related to experiments of high-energy physics in order to process a large number of observed data in a reasonable time [3]. The Worldwide Large Hadron Collider Computing Grid (WLCG) was designed to store and process almost 30 PetaBytes of data per year in the period of 2009-2013 [4].

Another approach to grid computing is joining desktop computers from an individual user to form a voluntary or desktop grid. It was popularized by a project that tries to identify uncommon signals from space to search for extraterrestrial intelligence (SETI@Home)¹[5]. And general-purpose frameworks were built in order to facilitate the development of projects that use a similar philosophy of computing on desktop computers, e.g., BOINC [6] and others.

In recent years, the development of virtualization technologies has enhanced the availability of services that are provided by grid computing. It has additionally enabled an evolution of the so-called *cloud computing*, in which computing resources can be rapidly provisioned and released with minimal management effort or service provider interaction. This implicates important feature of cloud-computing – elasticity – ability to scale up and

¹<http://setiathome.ssl.berkeley.edu/>

down computing resources when required [7]. The cloud computing is provided in several models, however, currently the scientific infrastructures offer mainly Infrastructure as a Service (IaaS), which offers the whole virtual infrastructure including virtual machine and network accessible for user per request.

2. Hypothesis

Based on the development of technologies and the philosophy of providing them to end users, this thesis focuses on the multidisciplinary research related to grid computing, as well as to cloud computing. The hypothesis of this thesis is that the technologies that relate to grid computing and cloud computing may improve the processing of medical information in order to perform demanding tasks that are almost impossible or require onerous effort to achieve, using classical local or institutional resources.

The particular goals of this thesis were:

- To study the latest achievements in the field of exchanging medical images and possible improvements using the grid computing and cloud computing technology.
- To identify use cases in other fields of biomedicine which are suitable to utilizing the power of grid computing and cloud computing infrastructure.
- To develop and test the prototype application that utilizes grid or cloud technologies.

This thesis tries to discuss the hypothesis in different areas of biomedical research and its application which were identified during the work. (1) the exchange and processing of medical images, (2) the analysis of human voice and (3) the modeling and simulation of human physiology.

It tries to find answers to the following additional questions:

- *Is it beneficial to utilize grid computing and cloud computing technology for the processing of medical information and how do we do this?*
- *What are the limitations of processing medical information in grid or cloud?*
- *How can the grid computing and cloud computing influence the direction of biomedical research?* There was an idea that grid computing technology inspires the current architecture of distributed systems, e.g., exchanging medical images and influences the direction of information systems in hospitals.

3. Methods

From a computer science (informatics) point of view, it is assumed that the processing of medical information is, in general, a computational problem, which is understood as a task that can be solved by a computer. An algorithm is a set of operations that is used to accomplish tasks and solve problems. The important features of an algorithm are effectivity (what is the time complexity of the algorithm regarding the size of input data) and scalability (how far can an algorithm benefit from parallel computing). Grid computing and cloud computing brings a technology that enables parallel computing in a large amount of shared computers, servers or cluster of servers introduces large speedup of computation and can decrease the time of computation substantially. However, problems solvable by algorithms with exponential time complexity (e.g. NP-hard or NP-complete) can't be addressed by any large scale infrastructure [8]. Therefore, additional non-exact methods for such type of problems are used to obtain at least some solution including heuristic method (eliminate some steps or solution classes that seems to not go to optimal solution), randomization (pseudo random values are generated and statistical methods can be used to compute expected optimal value) and others.

3.1 Sharing Medical Images

The DICOM standard was used as a joint protocol to integrate grid-based system Globus MEDICUS [9] with current production system MEDIMED for sharing medical images among different hospitals [10], which is based on common distributed system with central cluster. Globus MEDICUS [9, 11] implements a DICOM Grid Interface Service (DGIS) and integrates the open-source PixelMed™ Java DICOM Toolkit¹ into a web service, communicating via the DICOM protocol. Furthermore, it forwards queries to the underlying services within Globus toolkit. The console application of the MEDIMED project can be interconnected via DICOM protocol with local PACS system and selected DICOM studies can be sent/retrieved to another institution connected to the MEDIMED project.

3.2 Voice Science

The software for parameterized Voice Range Profile (ParVRP) and Voice Range Profile in Real time (RealVoiceLab) was already developed and calibrated for selected types of microphones in an MS Windows platform by Fric et al. [12, 13]. Its implementation is carried out in an MATLAB environment, utilizing Signal Processing Toolbox². It is compiled with a MATLAB Compiler and distributed as an executable. To migrate this legacy application into distributed environment, the virtualization can be used with a protocol to control an application remotely. Remote Desktop Protocol (RDP) is a proprietary protocol that is used for desktop sharing. It was primarily developed in a Microsoft Windows platform, however, today, clients and servers exist for several other platforms. RDP itself contains the redirection of several services, e.g., audio, sound recording, drive access.

¹<http://www.pixelmed.com/> accessed February 2015

²<http://www.mathworks.com/products/signal/> accessed February 2015

3.3 Computational physiology

A mathematical formalization of the fundamental knowledge and relation among a biological system – a mathematical model - is used as a base abstraction in order to utilize the current discoveries of the genomics and proteomics. It is also used to formalize the knowledge and construct a "Physiome Model". By definition, a model is the simplification of a complex reality. Constructing the models and integrating them into a complex entity, which can be used for further purposes, is schematically illustrated in Figure 3.1.

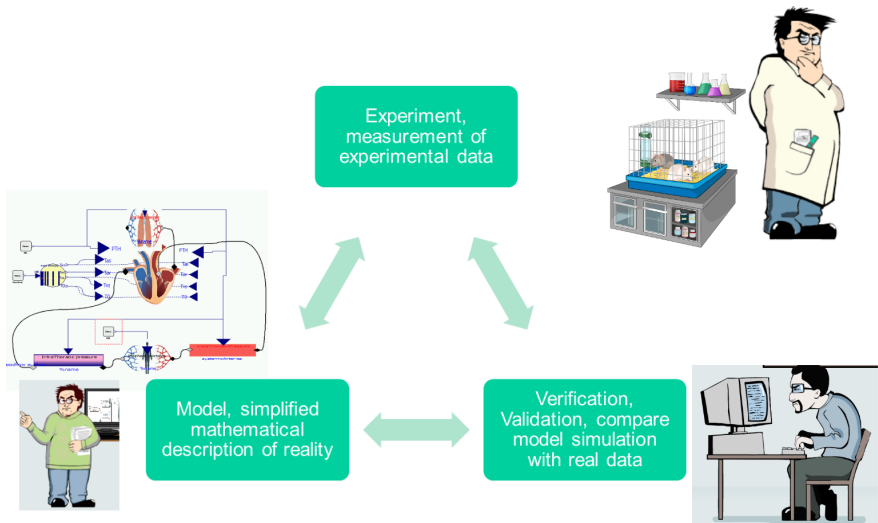


Figure 3.1: Schematic illustration of the scientific process. The experiments produce data that are interpreted and a hypothesis is formalized as a model. Validation compares the model simulation with the experiment, if the model satisfies the criteria – if it is in agreement with real experiments – then the validated model can be used for other purposes.

4. Results

In previous chapters, there were introduced different methods available for selected use cases in research in biology and medicine. As each of the use cases and available system was proposed on different operating system platform, different architecture and or different middleware the virtualization was utilized to build the virtual infrastructures for purposes of each project.

4.1 Medical Image Sharing

4.2 Remote Voice Analysis

4.3 Parameter Estimation

4.4 Parameter Sweep

5. Discussion

The presented solution, which is based on Globus MEDICUS, is, in general, a data warehouse, that stores one or more copies of DICOM images. However, federated files and metadata that are stored within home institutions, which only share network infrastructure to interchange the DICOM studies, seems to be a preferred and more acceptable solution by hospitals today, as published by Chervenak et al. [14]. The grid computing infrastructure seems to be suitable for research and educational purposes, but not generally acceptable for clinical use.

In the case of remote voice analysis, the remote access to an application via network protocol keeps the majority of user experience, as presented in section 4.2 and is a way how to migrate legacy application into the computing infrastructure and offer it as a service via network protocols and can be

instantiated per request.

In the case of the application for parameter estimation presented in section 4.3, the computation is sensitive on communication overhead. For simple models, local high performance computing (HPC) resources are most beneficial. For medium and highly complex models, the deployment of worker nodes into a cloud computing environment is worth considering. Another challenge is an optimal size of population for genetic algorithm so the algorithm will converge to some acceptable solution in a reasonable time, as Gotshall et al. proposed a method for determining the optimum population size for a given problem [15].

The parameter sweep problem is considered as embarrassingly parallel and highly suitable for high throughput computing (HTC), which is the main focus of current grid computing infrastructures.

When porting an application to a grid environment, one of the important decision to consider is the platform of the used system. The architecture, which involves computational nodes that are deployed in a cloud computing infrastructure is influenced by the fact that the model implementation is exported from a third party tool to the standard FMU library for the MS Windows platform, as mentioned in section ???. This determines the platform of the worker node and the virtualization - or, in the case of parameter estimation, cloud computing is utilized on a prepared platform with a MS Windows license. In the case of parameter sweep, a desktop grid computing BOINC worker and application for a MS Windows platform is only prepared for volunteers with the compatible system. To utilize the service grid infrastructure, an export of the model into a FMU library and implementation of the wrapper service must be done in the grid computing platform, which is usually a Linux based system. Another option is to use WINE¹ – a compatibility layer that is capable of running Windows applications on several POSIX-compliant operating systems, such as Linux, Mac OSX and BSD.

For smaller types of application and scientific community with their own

¹<https://www.winehq.org/> WINE. Accessed March 2015

tools, the question is, whether or not to invest on porting their tools to grid specific platform and parallel programming model. In the case of integrating with a service grid middleware or with desktop grid framework, expert knowledge is needed to configure and customize the system. This is the case for the sharing of medical images (section 4.1) and for parameter estimation and parameter sweep, which was tried with the desktop grid approach - BOINC framework (section 4.4).

Virtualization facilitates the integration effort, as presented in the case of remote analysis of the human voice (section 4.2) and in the case of deployment of worker nodes in a cloud computing environment for parameter estimation (section 4.3).

Based on previous results and ideas, the answer to the research questions can be formulated:

- *Is it beneficial to utilize grid computing and cloud computing technology for the processing of medical information and how?*

Grid computing and cloud computing can significantly speedup parameter study of medium and complex models in computational physiology. Such a speedup could influence its applicability in clinical use. For the case of sharing and processing medical images or analysis of voice signals, grid computing or cloud computing introduces technology that facilitates cooperation among a community of users from different geographically dispersed areas and facilitates the sharing of large data sets.

- *What are the limitations of processing medical information in grid or cloud?*

Limitation are given by the effort needed to integrate or port an application carry out computation or share data. The cost of porting an application to cloud computing is reduced by virtualization technology, rather than to a grid computing environment, which needs additional work in order to adapt the application for a grid computing platform and API.

The limitation are given by the theoretical features of algorithms too. Grid computing and cloud computing are not general solutions for hard problems (NP-complete problems). With connected with non-exact methods, a concurrent processing of many tasks may bring an acceptable non-exact solution.

- *How can the grid computing and cloud computing influence the direction of biomedical research?*

The fact that the computation or data are processed remotely is one of the paradigm shift. The data moves from files stored in some folder to elements or objects living somewhere on server or cloud which can be shared among researchers.

The research infrastructures, e.g. Integrated Structural Biology Infrastructure for Europe (INSTRUCT)², European Life Science Infrastructure for Biological Information (ELIXIR)³, European Biomedical Imaging Infrastructure (Euro-BioImaging)⁴ and others rely on grid-computing and cloud-computing infrastructures for science. The purpose of these initiatives is to understand high-level phenotypes from genomic, metabolomic, proteomic, imaging and other types of data. They also require multi-scale mathematical models and simulations, as noted e.g. by Hunter et al. [16] in his strategy for Virtual Physiological Human (VPH)⁵.

The integration with multidimensional models of geometrical, mechanical properties and the time-dependence of the compartment's data, which is taken from medical and biological repositories, can highly improve complex models of human physiology which are based mainly on lumped-parameter approach. E.g. Itu et al. achieved parameter identification on simplified windkessel model of hemodynamics in order to study aortic coarctation, which is based on pro-

²<https://www.structuralbiology.eu/> accessed March 2015

³<http://www.elixir-europe.org/> accessed March 2015

⁴<http://www.eurobioimaging.eu/> accessed March 2015

⁵<http://www.vph-institute.org/> accessed March 2015

cessing of MRI, and requires 6-8 minutes of computation time on a standard personal computer [17]. One of the challenge of systems biology approach, as identified by Kohl et al. [18], is to use multiparameter perturbation to identify the safe areas, e.g., for multitarget drug profile. The results presented in section 4.3 shows that the parameter study can be done on much more complex models in a reasonable time. The computation is able to become practical for clinical and further research towards patient-specific health care, in silico trials and drug discovery.

Based on the previous answers, another research question can be formulated for further research in the technology domain:

How can biomedical research influence the direction of grid-computing and cloud-computing development?

One area of discussion about this theme is how to preserve scientific data in long term in order to prevent loss of them [19, 20]. Another area of discussion is how to facilitate access to computational resources for large amounts of small scientific group, which have limited resources to port, integrate or customize their current tools and processes – to support the "long-tail" of science. The "long-tail" movement was first noted and described by Anderson [21] in the business domain. The long-tail term comes from a feature of statistical distribution, e.g., pareto distribution, where only a few (e.g., 20% – noted as head) elements have a high probability of some events (e.g., product being sold), while the rest (e.g., 80% – noted as tail) have a small probability. Thus, most businesses focus on hits (20% of products, the 80-20 rule). The expansion of the Internet and its related technologies have caused reduced sales, marketing and delivery costs for the products from the niche (80% of products) – long-tail. A strategy that focused on these kinds of products became profitable and successful, e.g., for companies such as Amazon or Apple.[21]. Cloud computing technologies seem to be customizable and may be an enabling technology to focus on long-tail science, as noted e.g. by Weinhardt et al. [22]. How to facilitate and decrease an effort to develop, customize and port domain-specific application to some distributed

computing model? This problem motivated, e.g., Anjum et al. to establish "platform as a service" (category of cloud computing service model) integrating several grid computing and cloud computing standards glueing via service oriented architecture approach [23]. Complementary approach is to support consultation, training and exchange in research software development toward the domain scientists, e.g., as presented by Crouch et al. regarding the Software Sustainable Institute within United Kingdom [24].

The provenance and reproducibility of scientific results implied a need to long-term preservation of scientific data, however, if it is left on individual researcher, there is loss of data, as analysed by Vines et al. or Heidorn [19, 20].

6. Conclusion

This thesis presents the infrastructure, which, thanks to virtualization technology, joined several domain-specific tools in the field of sharing and processing medical images, performing real-time voice analysis and simulating human physiology.

A seamless integration of grid-based PACS system was established with the current distributed system in order to share DICOM medical images. Access to real-time voice analysis application via remote desktop technology brings this type of service to any computer that can connect to the Internet. A system and portal to support the analysis and building of complex models of human physiology in the phase of parameter estimation and parameter sweep was introduced. Furthermore, additional computational nodes can be flexibly joined by starting the prepared virtual machines in cloud computing deployment.

The methodology of building complex models of human physiology was contributed with the use of acausal and object-oriented modeling techniques. Methods for conducting a parameter study were shown, as well as the parameter study of complex models that gain substantial speedup by utilizing cloud computing deployment, which makes such kinds of complex studies applicable in physiological and biological research.

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Publication of the author

Related to the thesis

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