A Collaborative Environment Allowing Clinical Investigations on Integrated Biomedical Databases

Matthias ASSEL[a], David van de VIJVER[b], Pieter LIBIN[c], Kristof THEYS[c], Daniel HAREZLAK[d], Breanndán Ó NUALLÁIN[e], Piotr NOWAKOWSKI[d], Marian BUBAK[d,e], Anne-Mieke VANDAMME[c], Stijn IMBRECHTS[c], Raphael SANGEDA[c], Tao JIANG[a], Dineke FRENTZ[b] and Peter SLOOT[e]

[a] *University of Stuttgart, High Performance Computing Centre, Germany*
[b] *Erasmus MC, University Medical Centre Rotterdam, Virology, The Netherlands*
[c] *Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium*
[d] *ACC CYFRONET AGH, Krakow, Poland*
[e] *Section Computational Science, University of Amsterdam, The Netherlands*

Abstract. In order to perform clinical investigations on integrated biomedical data sets and to predict virological and epidemiological outcome, medical experts require an IT-based collaborative environment that provides them a user-friendly space for building and executing their complex studies and workflows on largely available and high-quality data repositories. In this paper, the authors introduce such a novel collaborative working environment a so-called virtual laboratory for clinicians and medical researchers, which allows users to interactively access and browse several biomedical research databases and re-use relevant data sets within own designed experiments. Firstly, technical details on the integration of relevant data resources into the virtual laboratory infrastructure and specifically developed user interfaces are briefly explained. The second part describes research possibilities for medical scientists including potential application fields and benefits as using the virtual laboratory functionalities for a particular exemplary study.

Keywords. Virtual Laboratory, HIV Drug Resistance, Clinical Investigations, Collaborative Working Environment, Data Integration and Access, ViroLab, RegaDB

1. Introduction

Current scientific research is interdisciplinary with researchers of different fields meeting together to work cooperatively on defined projects in order to analyze, understand and reconstruct complex medical processes. An example of such an endeavor is the field of virology research, especially the part tackling anti-HIV treatment problems such as HIV drug resistance. This phenomenon is becoming an increasing problem worldwide, with combination therapy with antiretroviral drugs failing to completely suppress the virus in a considerable number of HIV-infected patients [1].

In order to determine such drug resistance as early and quickly as possible genetic information such as nucleic acid sequences but also treatment histories of patients are essential. Fortunately, large numbers of complex genetic sequences are increasingly becoming available [2] and HIV drug resistance is one of the few areas in medicine where genetic information is widely applied. Therefore, it is absolutely necessary to develop modern environments so-called virtual laboratories for scientists from different domains and institutes, which facilitate and improve the collaboration and analyses on the same data and information sets.

Such virtual laboratories should deliver a working environment that could combine efforts of computer scientists, healthcare professionals, and medical scientists, and should provide means for the first group of users to develop in-silico experiments and for the later ones to use previously prepared experiment plans for performing complex research or clinical studies. Thus, a set of dedicated tools needs to be provided in an integrated fashion as different types of users require specific approaches but they altogether should be accessible and usable in the same manner. Moreover, the laboratory has to be robust enough to overcome infrastructure failures, enabling adjustments and extensions, and finally, supporting multiple underlying technologies.

For these reasons the EU-funded project ViroLab[1] is designing and developing a virtual laboratory for healthcare professionals and especially for medical scientists primarily focusing on medical knowledge discovery and decision support for HIV drug resistance for daily clinical usage and research. It uses state-of-the-art Grid computing technologies and standards and consists of heterogeneous computing and networked sites that connect widely dispersed medical data resources.

Apart from ViroLab there are several research initiatives worldwide, which are looking at similar efforts to establish Grid infrastructures for biomedical research purposes. The US National Cancer Institute has founded a nationwide effort, called the cancer Biomedical Informatics Grid to develop a federation of interoperable biomedical information systems [3]. In Europe a handful of projects have created corresponding e-Infrastructures for sharing distributed computational resources in bioinformatics and enabling collaborative work in biomedical research, for example in infectious diseases [4] and immune diseases [5], as well as in cancer research [6].

In the remainder of this paper, we describe the novel approach of ViroLab's virtual laboratory with respect to the integration and secure access of distributed hospital databases as well as the development of dedicated graphical user interfaces for utilizing the resources and services appropriately. Afterwards, we are elaborating concrete research possibilities mainly from a medical scientist's perspective as using this virtual environment for a particular large-scale epidemiological study on HIV drug resistance.

2. The ViroLab Virtual Laboratory

The ViroLab Virtual Laboratory is an integrated set of tools and services for accessing and integrating distributed heterogeneous resources or services and, in general, facilitating research in the field of e-Science. Its main goal is to present a powerful, flexible and dynamic environment for experiment developers and end-users while preserving ease of use and reusability of the proposed solution, thus allowing transparent and secure access to corresponding underlying infrastructures. Primarily,

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[1] http://www.virolab.org

this virtual workspace is used by medical doctors to review actual HIV drug rankings and recent drug resistance interpretations or by scientists to conduct new experiments and simulations starting from pre-defined process flow templates, which allow an interactive and smooth selection of available bioinformatics tools to be combined into one explicit workflow for studying individual drug resistance susceptibility. In the following, we are focusing on two important aspects of the overall laboratory capabilities, namely data integration and user interfaces that allow the access to certain resources and services respectively. Further details on the general architecture and individual components can be found in [7].

2.1. Data Integration and Access

In the HIV world, clinicians and virologists manage a lot of sensitive data in local databases that could be used to perform collaborative research. There is currently an inhibition to such collaboration on two levels. Firstly, the data are sensitive and cannot be shared as such. Secondly, different database formats complicate the sharing of data. In addition, some of the analyses with such data require several bioinformatics tools, which may be available on the Internet or from a collaborator, and are too compute intensive or difficult to implement and run on a single computer. The ViroLab consortium encountered these issues when building a generic virtual laboratory, and recognized the RegaDB Viral Data and Analyses Management platform as a viable solution. RegaDB is a free and open source system, and was initially developed to store and manage data from HIV patients. Data is stored locally within the clinical environment of a hospital or institute rendering the data owner to be in full control to set up collaborations. RegaDB is designed to store epidemiological, clinical and virological data, in a way that is extensible to meet specific research needs. RegaDB supports, but is not limited to, patient attributes required for demographic research and different test results like viral load measurements. Treatment information can be specified using either commercial or generic drug names of the most recent anti-retroviral drugs (e.g. Retrovir vs. zidovudine (AZT)), combined with start and end data. RegaDB also integrates tools for sequence analysis, including automated codon-correct alignment of nucleotide sequences with detection of open reading frames, and correction of frame shift errors, genotyping and subtyping (Rega Subtyping Tool Collection), genotypic resistance interpretation systems specified in the Stanford ASI (including Rega, ANRS and HIVdb).

All five clinical and virological partners in the ViroLab consortium already had an anonymized research database available, which combined contains a significant amount of 7.672 patients and 5.383 viral isolates. All these databases were custom software implemented by the different institutes. To be able to integrate these anonymized databases into the RegaDB schema, scripts were implemented to parse the original databases and import the results. Although this typically is a tedious and error prone process, which requires a considerable amount of domain specific knowledge, RegaDB has an API available to simplify this process. During a later stage of the project, collaboration was set up with the EuResist[2] research project. To ensure a smooth transition between the two projects, the EuResist database was imported using the RegaDB import API. Through this collaboration the research dataset grew in size up to around 20.000 patients and 25.000 viral isolates.

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[2] http://www.euresist.org

Data access within the virtual laboratory basically consists of a developer interface, which is provided by the so-called Data Access Client (DAC) and a graphical user front-end integrated with the ViroLab web-based Portal. Both interfaces are connected to a set of backend services, the Data Access Services (DAS), that dynamically and securely aggregate biomedical data gathered from the distributed research databases which are hosted and managed by the hospitals themselves and primarily located within their demilitarized zone [8] in order to prevent any unauthorized access into their internal network facilities. While the DAS are implemented as a number of web services, any experiment executed and processed by the Gridspace Engine is communicating with these services through the DAC, which takes care of formulating the proper queries. Such queries can be either submitted to one of the RegaDB instances or concurrently to all accessible ones depending on the user's authorization status. DAS respectively DAC also allow the direct interaction with other relational databases as well as file or XML repositories. An experiment developer is provided with a simple API, which enables submission of queries using a dedicated data access object depending on the corresponding resource type. Security particularly user authentication and access control are supported following the integration of Shibboleth's basic security mechanisms (view next section). However, the DAS are responsible for securing the data transfer from and to any of the integrated RegaDB instances either by using common SSL connections or establishing an additional VPN tunnel if required.

In summary, the data access and integration infrastructure consists of a three-layered architectural concept following the modern principles of service-oriented infrastructures. Its main components and interfaces are depicted in the following figure.
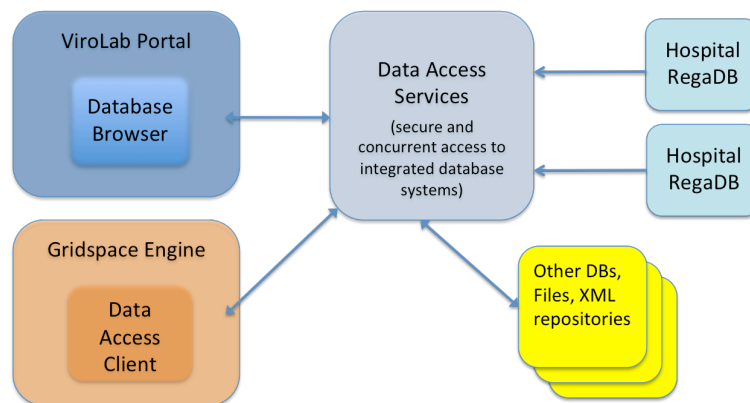
Figure 1. ViroLab's data access and integration concept

2.2. Security Aspects

In ViroLab, the security approach is based on a two-step authentication and authorization procedure where users initially authenticate themselves against their own local identity management system instead of deploying a centralized, system-wide identity provider. For this purpose, ViroLab makes use of the basic capabilities provided by the Shibboleth security framework [9] while using its features and services

for establishing a trusted federation among all members of the ViroLab consortium and thus, ensuring a secure and highly dynamic security infrastructure.

Since all data resource owners are more or less taking the final authorization decisions, access control to certain resources is implemented through self-managed access policies, which are based on a standardized and well-known policy language (XACML[3]) and processed by a dedicated component, a so-called Policy Decision Point (PDP). These policies can be created or changed on-demand by the respective resource administrator according to current purposes and will be immediately enforced by the infrastructure. As soon as a policy update is committed to the DAS, the services automatically and transparently re-authorize all current users. If the access for certain users has been e.g. denied for a particular resource, they are not able to perform further actions on that resource any longer. More details on specific implementation details and dedicated features or components of the overall security infrastructure can be found in [10].

2.3. User Interfaces within ViroLab

The main task of the ViroLab Experiment Planning Environment (EPE) is to assist the experiment developers in building new ViroLab-related applications [11]. To support the experiment creation a refinement cycle has been defined as a sequence of stages, which starts with a development phase and ends with a releasing phase. The EPE gathers tools for supporting each stage of this cycle into a single comprehensive Integrated Development Environment (IDE). Developing script-based experiments requires an advanced text editor that will correct errors made by the developer. It is also useful to get a quick access to various experiment elements (e.g. classes and method declarations) that describe the structure of the experiment. The EPE provides these tools in form of an Eclipse perspective. Since the entire virtual laboratory is concentrated on collaboration, a feature of great importance is the experiment sharing capability. There are two main reasons why the developer would like to share his/her work:

- The developer works in collaboration with other developers on a single experiment. In the case it is necessary to share the code of the application using a version control system which helps in managing changes made by different developers, e.g., to the same script file.
- Once the experiment is ready it should be published for the end users who are waiting for it. In most cases the first version of the experiment is not as good as it should be. Now users have the possibility to report a flaw in the experiment or to ask for a feature that should be added. After fixing flaws or developing new features, a new release should be made. For this kind of operations, a system for managing the published experiment versions called Experiment Repository was developed and EPE is fully integrated with this system [12].

The EPE is also integrated with the ViroLab runtime services [13]. This allows running prepared experiments at any time. This is necessary since the developer may check the current experiment behavior in order to validate it.

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[3] eXtensible Access Control Markup Language

Due to being based on the Eclipse RCP platform, the EPE can be extended without any limitation by adding new plugins to its core. Within the virtual laboratory, two plugins have been developed to demonstrate this concept:

- Grid Resource Registry browser allows developers to browse the ViroLab registry contents. Another feature is its code generation capability. By clicking on a chosen external computation element (like a remote service or a job submission mechanism) it is possible to generate a piece of code that takes care for invoking the remote capability on behalf of the experiment [14].
- Ontology Browser allows developers to browse the domain data ontology model that is stored in the common ontology store. The developer can also search for the grid operations related to the concepts contained in the ontology being viewed and they may use the abstract data model to quickly create queries to real data sources accessed by the experiment.

The Experiment Management Interface (EMI) is the main user interface tool (integrated with the ViroLab Portal based on the Gridsphere technology) for ViroLab users who would like to run experiments in order to achieve scientific results [11]. EMI (see figure 2(1)) is intended to provide a wide range of facilities, published through a lightweight web technology, to manage experiment execution and result handling. Three main aspects have been identified in the course of development.

- Browsing remote experiment repositories;
- Managing the experiment execution queue and particular results;
- Submitting feedback to experiment developers.

The first aspect is implemented as the repository widget which allows for browsing through published virtual experiments. EMI connects to an external experiment repository and loads a list of available experiments with detailed information (experiment versions, licenses and user feedback). This list is presented to the user. As already mentioned, each experiment has one or more versions. Each version has a separate window with important information, including author contact details, owning organization and the publication date. From here, the EMI user may:

- Execute the currently viewed version of a chosen experiment;
- View the experiment script (useful for validity checks and early problem spotting);
- View the license to learn what are the terms of use for the certain version;
- Report feedback by sending comments or filing an issue for the experiment author.

The experiment execution action is the most important of EMI capabilities. When an experiment is running the execution view is responsible for presenting the actual state of the experiment. It also maintains any interaction with the running experiment since the ViroLab interactive runtime allows for two-way synchronous user communication with the experiment. Since there could be many experiments running at the same time, the view shows all of them in a comprehensive list of items, where each item may be expanded to present the current execution log or the user input forms.

After an experiment finishes the user can see the final results. In case of a failure a description of the causes is also presented. If the experiment finishes successfully the results view is used to display the experiment results. Each result item shows a specific set of meta-data descriptors, like the owner of the result, the creation date, what

experiment (and in which version) produced the result and some free user annotation. Also, there is a link presented so the user may follow it to see the result payload (if the browser is able to visualize it: a text file, a graph etc.) or to download it to the local file system (for offline viewing). All the results are being kept in a secured, persistent store where they are permanently accessible by their owners. Of course, the owner may remove a result at any time if he wishes to.

In order to achieve a smooth frontend for dealing with remote data resources, a dedicated web-based application has been developed and integrated with the ViroLab Portal. It provides ViroLab end-users, as well as database administrators with an easily accessible and convenient facility for browsing databases and managing results. The portlet interacts with the DAS to access the dispersed biomedical databases. The basic interactions between the portlet and services are secured using encrypted messages. The Database Browser currently offers the following functionalities:

- Authorize ViroLab users transparently to access the appropriate databases by using the authorization module of the DAS that integrates with Shibboleth's service provider features.
- Browse accessible databases and search for desired data of patients, drugs, mutations etc. and their released schema definitions.
- Perform SQL queries to single or multiple databases concurrently. A special database stores previously used SQL queries per user in order to facilitate her working process the next time she wants to repeat any request.
- Grant functions for searching of precise data in results of performed queries, sorting data in different orders, as well as printing, saving data as xml, html or csv.

In ViroLab, a virtualized Decision Support System (DSS) and an interpretation tool are building the center of the virtual laboratory services. Examples of such interpretation tools are Retrogram, Rega algorithm, ANRS algorithm and HIVdb [15]. These algorithms estimate the drug sensitivity for available drugs by interpreting the genotype of a patient using mutational algorithms, developed by experts on the basis of scientific literature, taking into account the published data relating genotype to phenotype. In addition, the ranking is based on data from clinical studies on the relationship between the presence of particular mutations and clinical or virological outcome.

Providing end-users of such tools with an easy to use application, a dedicated portlet that integrates with the ViroLab Portal is being developed (refer to figure 2(2)). It offers a simple wizard-based sequence starting with the input of particular mutations and the selection of one or more algorithms for computing the actual interpretation. Having evaluated the given mutations being sent to a remote service, the front-end displays a well-structured overview of possible susceptibilities for certain drugs. These results can now be exported to different output formats in order to re-use them for example within a statistical analysis. Moreover, this application is currently being extended to provide direct references to high-quality publications, which shall substantiate the actual decision of the system.

UI for Experiment Execution (1)

**Web Tool for Treatment Advice –
The Drug Ranking System (2)**

Figure 2. ViroLab's dedicated user interfaces

3. Research Possibilities using the ViroLab Virtual Laboratory

ViroLab's virtual laboratory facilitates large-scale epidemiological studies on HIV drug resistance. In the following part of this paper, we describe why these large studies are needed to improve clinical care of patients living with HIV. This is complemented by a description of functionalities included in ViroLab, which facilitate such research.

3.1. Rationale for large-scale epidemiological Studies

During the past decade significant progress has been made in the treatment of HIV-infected patients. More than twenty antiretroviral drugs are available, divided over six classes. Patients should take a combination of at least two different classes of antiretroviral drugs to achieve complete suppression of the virus [15]. Use of such combination therapy has reduced mortality among HIV-infected patients [16]. But in a considerable proportion of patients the drugs fail to completely suppress the virus resulting in the rapid selection of drug-resistant HIV and loss of drug efficacy [17]. The

efficacy of these drugs for treatment of HIV has been shown in randomized clinical trials.

A well-known limitation of these trials is that they include patients that may not be representative for all individuals in clinical care. For example, individuals in an advanced stage of disease could be excluded as any unknown harmful effects may pose a too great risk for their frail health. But these patients may be treated preferentially with a new drug as resistance and/or toxicity may hamper their therapy with antiretrovirals already available. Previously unknown mutations associated with resistance to the new drug could therefore be identified in the virus of these patients.

Further adding to the complexity of this problem, is that new mutations are frequently being identified. For instance, a few years ago Nijhuis et al. found that mutations encoding for resistance to protease inhibitors can be found in the gag region of HIV and not only in the protease gene [18]. Mutations in the latter gene are the only ones used in HIV drug resistance interpretation systems for scoring resistance to protease inhibitors. All of these novel mutations are, however, frequently not occurring to a great extent. Thousands of patients are therefore required to study the impact of these mutations on the effectiveness of antiretroviral therapy.

Hence, thanks to ViroLab's large and high-quality databases, which have been integrated and made accessible within the virtual laboratory, these kinds of clinical studies can now be performed and to some extend repeated after a certain time.

3.2. Outline of a large-scale Study

We now describe a hypothetical example of a study with the aim of determining the impact of a novel mutation on the effectiveness of therapy (defined as having an undetectable viral load after a particular period of time). The study will compare two groups of patients starting a particular drug. The first group will carry a virus with the mutation of interest. The other group will be infected with HIV without this mutation. Performing such a study is complex.

The experiment starts by screening the databases of participating hospitals for relevant patients. In this example, these are patients that start a particular drug and for whom a genotype is available within a short period before start of that antiretroviral. Relevant demographic and clinical information of included patients must be collected, too. The extraction of interesting patients can be achieved for example with the aid of ViroLab's Database Browser application by directly browsing the integrated hospital databases and formulating the corresponding queries in order to gather potential data sets that can be stored for further processing or by using a pre-defined experiment script that integrates the DAC API.

Once the dataset for analysis has been defined, the respective genotypes require processing into a format, suitable from performing the analysis. A number of analysis tools are available for this purpose within the ViroLab project. Relevent steps are the codon-correct alignment against a reference sequence of choice, correction of frame-shifts, removal of unfit sequences and selection of the genomic region of interest. Different output formats, nucleotides or amino acids, are available. Determination of HIV subtype is possible by use of the Rega Subtyping Tool. All these tools are available as web services, thereby easily accessible to the research community and integrated with the virtual laboratory infrastructure. Additionally, a number of these tools are built-in services of RegaDB, thereby considerably simplifying the preprocessing procedure.

Antiretroviral drugs are always given in combination. Virological failure on combination therapy may be associated with resistance to one, two or all drugs in the combination. Typically, resistance to one drug will accelerate the development of resistance to other drugs, since the inhibition of virus replication is weakened, and therefore the virus may actively replicate during selective pressure of the remaining active drugs in the therapy. Detection of mutations and subsequent resistance interpretation are required in order to correct for the activity of the drugs, except the one under study, in the combination. Preprocessed sequences can be given as input to a resistance interpretation algorithm of your own choice through ASI. A resistance report is generated with information about activity of the drugs and the relevant resistance mutations. The tools are available as web services within ViroLab through the integrated DSS.

After the previous steps are finalized using the facilities of the virtual laboratory, the effectiveness can be assessed. For this purpose, we will determine how many patients reached an undetectable viral load after the defined period of time. Importantly, patients may have discontinued treatment before that time. These should be excluded.

The data are now ready for analysis. This brings us to the final steps. ViroLab supports for this purpose advanced regression techniques and allows the export of relevant data sets into common output formats or enables their graphical visualization. The proportions of patients with undectable viral loads will be compared between the groups with and without the mutation of interest. Multivariate techniques will be used to adjust for any confounding factors (activity of other drugs, viral load at start of therapy etc).

4. Conclusions

Collaborative interdisciplinary research is an important but crucial issue, particularly in the healthcare domain. It requires a challenging combination of two different worlds: Computer and medical science. However, both domains can essentially benefit from each other with respect to improve own research that is being advanced due to a fruitful cooperation.

In ViroLab, this vision was the driving force for building a novel virtual environment for e-Science in close and continuous collaborations between experts from the IT and medical area. Preliminary results as well as new research possibilities as presented in this paper provide a promising insight for future research and the next generation systems. Hence, using the ViroLab Virtual Laboratory as a prototype for further developments can certainly facilitate and improve medical diagnosis and treatment beyond the field of HIV drug resistance.

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