
Innovations
A Collaborative Decision Support System in Viral Disease Treatment
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ViroLab: A Collaborative Decision Support System in Viral Disease Treatment

"Our vision is to provide researchers and medical doctors with a virtual laboratory for infectious diseases, which we call ViroLab, to enable easy access to distributed simulations as well as sharing, processing and analyzing virological, immunological, clinical and experimental data"

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Background

During the past ten years significant progress has been made in the treatment of viral disease infected patients. For instance, around 20 antiretroviral drugs are now available for treatment of HIV, divided into five classes, with patients taking a combination of usually three drugs from at least two different classes of antiretroviral drugs in order to achieve complete suppression of the virus[1]. In a considerable proportion of (pre treated) patients however, complete suppression of viral replication is not reached, resulting in the rapid selection of drug-resistant viruses and loss of drug effectiveness. Resistance can be achieved by a multitude of combinations of mutations, and frequent cross-resistance exists between drugs from the same class, complicating the clinician's decision process. Such a decision process requires translating information on virus mutations to in vitro changes in drug sensitivity or to in vivo clinical responses to specific regimens. A straightforward relational approach is not possible, there are too many mutational patterns to perform all in vitro drug susceptibility experiments, and there is too much genetic variation and too many confounding factors driving clinical therapy response resulting in lack of 'clinical experience' for the specific virus genetic information of the patient at hand. A number of genotypic resistance interpretation tools that assist clinicians and virologists in choosing effective therapeutic alternatives have been developed in recent years. However, there is significant interpretation discordance among the available systems for interpreting, e.g., HIV-1 genotypic resistance[2]. There is an urgent need for a joint effort to develop, validate, publish standardized rules as well as definition criteria for genotypic resistance interpretation, and to provide accessible tools for interpretation that help improve the clinical usefulness of genotypic assay results. The application of artificial intelligence and computational techniques applied to biomedicine has resulted in the development of computer-based decision support systems (DSSs).

Recent developments in distributed computing further allow the virtualization of massive data, computational, and software resources that complex DSSs require. Our vision is to provide researchers and medical doctors with a virtual laboratory for infectious diseases, which we call ViroLab[3], to enable easy access to distributed simulations as well as sharing, processing and analyzing virological, immunological, clinical and experimental data. Currently, HIV/AIDS phycisians, virologists, pharmacists etc. browse journals, pick results, compile them for discussion, and derive rules for ranking and making decisions. ViroLab advances the state of the art by offering clinicians a distributed virtual laboratory securely accessible from their hospitals and institutes distributed all over Europe, for all the members of the virtual organization.

Advanced environment

ViroLab is based on a Grid-based virtual laboratory for infectious diseases that facilitates medical knowledge discovery, providing the medical doctors with a decision support system to rank drugs targeted at patients. Its infrastructure provides virologists with an advanced environment to study trends on an individual, population and epidemiological level. That is, by virtualizing the hardware, computing infrastructure, and databases, the virtual laboratory offers a user-friendly environment, as seen in Figure 1.

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Peter Sloot, PhD, has disclosed that he has not received grants or research support from any commercial entities

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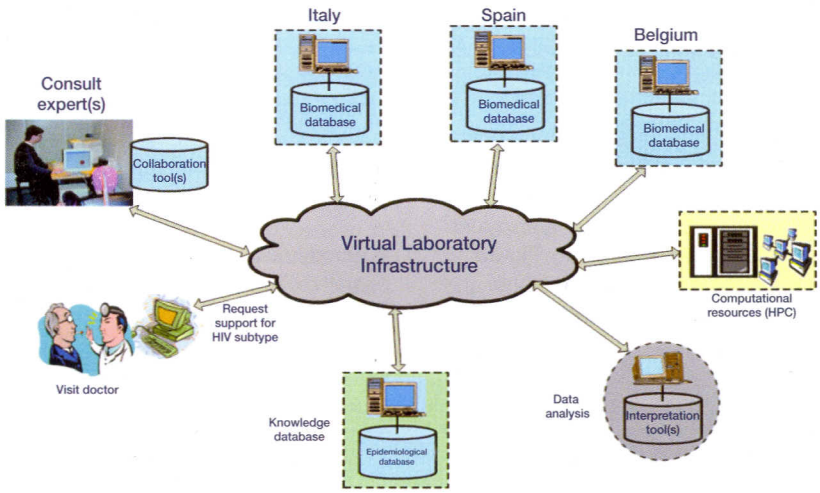

Figure 1: Simplified view of the Virolab Virtual laboratory.[4].

ViroLab also offers tailored workflow templates to harness and automate such diverse tasks as data archiving, data integration, data mining and analysis, modelling and simulation, integrating the biomedical information from viruses (proteins and mutations), patients (e.g. viral load) and literature (drug resistance experiments), resulting in a distributed decision support system for drug ranking. In ViroLab we put a virtualized DSS and an interpretation tool at the center of the distributed virtual laboratory, details can be found in[3, 4]. Examples of such interpretation tools are Retrogram, Rega algorithm, ANRS algorithm and HIVdb[5]. 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. ViroLab includes advanced tools for (bio)-statistical analysis, visualization as well as modelling and simulation that enable prediction of the temporal virological and immunological response of viruses with complex mutation patterns for drug therapy as is shown in Figure 2.

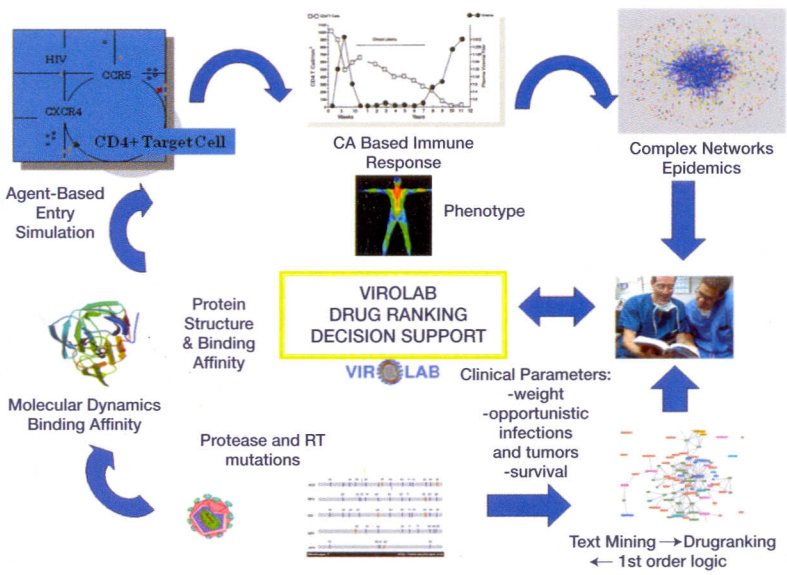

Figure 2: Simplified workflow using the Virtual laboratory. The various components indicate how patient information is used to (from bottom left): Calculate the binding affinity of inhibitors to Reverse Transcriptase and to Protease; Calculation of the co-receptor tropism for the entry process; Simulation of the HIV dynamics and immune response; Estimation of transmission of drug-resistance through complex networks and Literature based drug ranking.

Results

'Progress in natural sciences comes from taking things apart; progress in computer science comes from bringing things together.'[6]

In ViroLab, we need statistical and immunological models to study the dynamics of the HIV populations and molecular dynamics models to study drug affinities, in addition to rule-based and parameter-based decision support as is shown in Figure 2. These approaches render the highly dimensional and complex data more amenable, more details can be found in[3,7].

HIVdynamics Simulation

A mesoscopic model to study the evolution of HIV infection and the onset of AIDS is used in ViroLab. The model takes into account the global features of the immune response to any pathogen, the fast mutation rate of the HIV, and a fair amount of spatial localization, which occur in the lymph nodes. Ordinary (or partial) differential equation models are insufficient for describing the extreme time scales involved in HIV infection (days and decades), as well as the implicit spatial heterogeneity. We developed a non-uniform Cellular Automata model to study the dynamics of drug therapy of HIV infection, which simulates four-phases (acute, chronic, drug treatment response and onset of AIDS). Three different drug therapies (mono-therapy, combined drug therapy and highly active antiretroviral therapy) can also be studied in this model. Our model for prediction of the temporal behaviour of the immune system to drug therapy qualitatively corresponds to clinical data[8]. The influence of patient specific mutations on the drug binding affinities can be calculated through high performance Molecular Dynamics Simulation. In a recent paper we showed results for the prediction of binding free energies for Saquinavir-bound HIV-1 Proteases[9].

BioStatistics and data mining

The bio-statistical analysis of the HIV-1 genotype datasets aims to identify patterns of mutations (or naturally occurring polymorphisms) associated with resistance to antiviral drugs and to predict the degree of in-vitro or in-vivo sensitivity to available drugs from an HIV-1 genetic sequence. The statistical challenges in doing such analyses arise from the high dimensionality of these data[10]. Direct application of the well-known mathematical approaches to analysis of HIV-1 genotype results in a lot of problems. The problem stems from the fact that in HIV genetic analysis, the main scope of interest is the so-called relevant mutations, a set of mutations associated specifically with the drug resistance. These mutations might exist in different positions over the amino-acid chains. Moreover, the sheer complexity of the disease and data require the development of the reliable statistical technique for its analysis and modelling. A possible approach is through Bayesian Network Learning[11,12], a datamining technique allowing graphical mapping of conditional dependencies in genetic sequences. Such a technique could take into account epistatic interactions between mutations from which an in silico model can be built, representing the in vivo fitness of the virus under drug selective pressure[13].

Resistance Transmission in Sexual Networks

In Virolab we have developed a Complex Network based model that allows us to study the transmission of resistance in sexual networks[14]. By inferring network parameters from e.g. the Centre of Disease Control we are able to study the dynamics of infection in a (dynamically changing) population through the construction of so-called complex networks, as an alternative to PDE based SIR models, see[14] for more details.

Discussion and Future Work

With the increasing availability of genetic information and extensive patient records the time has come to study diseases from the genetic level all the way up to medical responses. What is more, the long-standing challenges of individual-based, targeted treatments come within reach. What is necessary is to provide integrating technology to the medical doctors and researchers bridging the gaps in multi-scale models, data fusion and cross-disciplinary collaboration.
Indeed, one of the main issues for near future work is collaboration enhancement. Collaboration technology aims to enhance the productivity and effectiveness of multi-disciplinary biomedical research. To this effect, Grid technology offers the possibility of leveraging computing tools into distributed collaborative environments, or collaboratories.

In this ongoing research, interesting results have already been obtained, showing the viability and the extensibility of the approach taken[e.g. 3,4,7,8,9,11,12,13,14.]
The system we described is still under development with new functionalities added frequently through extensive usability studies in a series of hospitals across Europe.

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Full article

The full article and other articles describing the ViroLab virtual laboratory, are available at www.virolab.org

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