

EuResist

Integration of viral genomics with clinical data to predict response to anti-HIV treatment

The **EuResist** project aims to develop a European integrated system for the clinical management of antiretroviral drug resistance. The system will predict patient reactions to antiretroviral treatments for HIV, thus helping clinicians to select the most appropriate drugs and drug combinations for any given HIV genetic variant. To this end a huge European integrated data set will be created, linking three of the largest existing resistance databases: ARCA, AREVIR and Karolinska.

Objectives of the project

While combination antiretroviral treatment has made HIV a treatable condition, eradication of the infection has not yet been achieved. Treatment needs to be administered as a prolonged, possibly lifelong treatment. Long-term toxicity, difficulty in adhering to complex regimes, possible pharmacokinetics problems, and intrinsically limited potency are all factors favouring the selection of drug-resistant viral strains. The development of drug resistance is now a major cause for treatment failure.

EuResist aims to:

- integrate biomedical information from three large and expanding databases in different European countries collecting the required critical mass of historical and prospective data;
- develop and validate models for the effective prediction of responses to treatment based on HIV genotype and additional clinical information;
- make the prediction system available on the web for the optimisation of antiretroviral treatment.

“The EuResist integrated data set will be the largest in the world”

Project Description

The **EuResist** novel approach is based on using viral genotype data integrated with treatment response data from clinical practice to predict the resistances of a given HIV genotype. This strategy bypasses the genotype-phenotype correlation step and points directly to the most effective drugs and drug combinations on the basis of the available genotype data integrated with clinical data.

The **EuResist** integrated data set will be the largest in the world. It will result from the merging of three of the largest existing resistance databases: ARCA (I), AREVIR (D) and Karolinska one (S).

The **EuResist** integrated prediction system will use an array of predictors, each of them based on novel or state of the art method. The vastness of genetic and clinical data will lead to new approaches in the analysis of qualitative data:

1. Case Based Reasoning is a state-of-the-art method in Artificial Intelligence but has never been applied to HIV due to the lack of large data sets and difficulty to define an appropriate method.

2. Machine learning algorithms. The **EuResist** project will use hybrid algorithm merging the state-of-the-art generative and discriminative techniques (Bayesian networks) and support vector machine (SVM).

Scenario

A doctor connects via Internet to **EuResist** web page. He will input the HIV genotype data and possibly CD4 and HIV RNA levels as well as information on past exposure to antiretroviral. He could indicate the treatment regime he would like to use. The web server sends this data to the Prediction System that runs some sets of equations. It returns with an ordered list of the most effective drug combinations and also of the effectiveness of treatment using a single drug. If the user did input CD4 and HIV RNA values, the system will return the trajectory and variations between these two parameters. Depending on the amount of information input, and of the available driving data, a measure of the confidence of the output data will be provided.

3. Graph-theoretical methods. **EuResist** adopts a statistical approach to analyse the organisation of genetic material. Graph-theoretical methods will be used to reveal the organisational and functional structures of genetic material, possibly identifying new lines in medical treatment.

4. Evolutionary Models. Better understanding of viral evolution under the selective pressure exerted by specific drug combinations will form an important basis for the rational design of therapies and therapy sequencing. An improved understanding of the fitness landscape of HIV under HAART will be beneficial in an evolutionary model or as features for a statistical learning method.

5. Fuzzy Logic. The existing fuzzy logic based predictor will be enhanced by incorporating the new standard data and training into the large database.

The predictive System will be validated through a comparative study testing the prediction tools developed, together with the reference rules-based algorithms most commonly used for HIV genotype interpretation.

Expected Results & Impacts

The **EuResist** project, conceived to significantly improve the treatment of HIV patients in Europe will enhance the most sophisticated predictive models, by combining, in a unique and efficient way, the latest techniques or, promising techniques which have yet to be applied.

- Innovation aspects:
 - Expanded geographical representativeness of HIV variants.
 - Statistical and bioinformatics techniques used to develop the predictive engines.
- Expected advantages:

Expected advantages of the **EuResist** system include not only more effective care for patients but also decreased cost of therapy through reduced improper use of antiretroviral drugs and the resulting fall in the occurrence of infections combined with an improvement of the patient's immune status.

The project can also be considered as a pilot for HCV and HBV since a large antiviral treatment intervention have been started and the chronic nature of both of these viruses will lead to increased resistance to existing drugs. In Europe HBV and HCV are in fact more common than HIV.

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