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The Eu*Resist* approach for predicting response to anti HIV-1 therapy

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6th European HIV Drug Resistance Workshop

26-28.03.08, Budapest, Hungary

BUDAPEST - HUNGARY
26 - 28 MARCH, 2008
Sixth EUROPEAN HIV DRUG RESISTANCE WORKSHOP
From basic science to clinical implications

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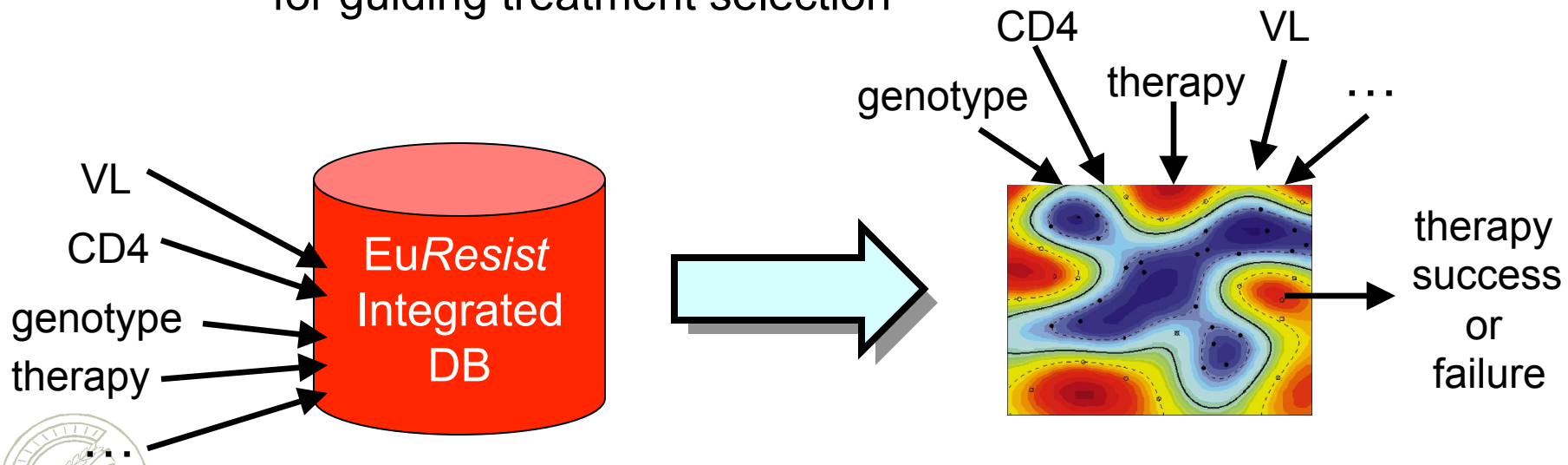
Aims of the Eu*Resist* project

1. Integration of clinical and virologic data from a large cohort of patients
2. Building a data-driven therapy response prediction system for guiding treatment selection



Data Integration

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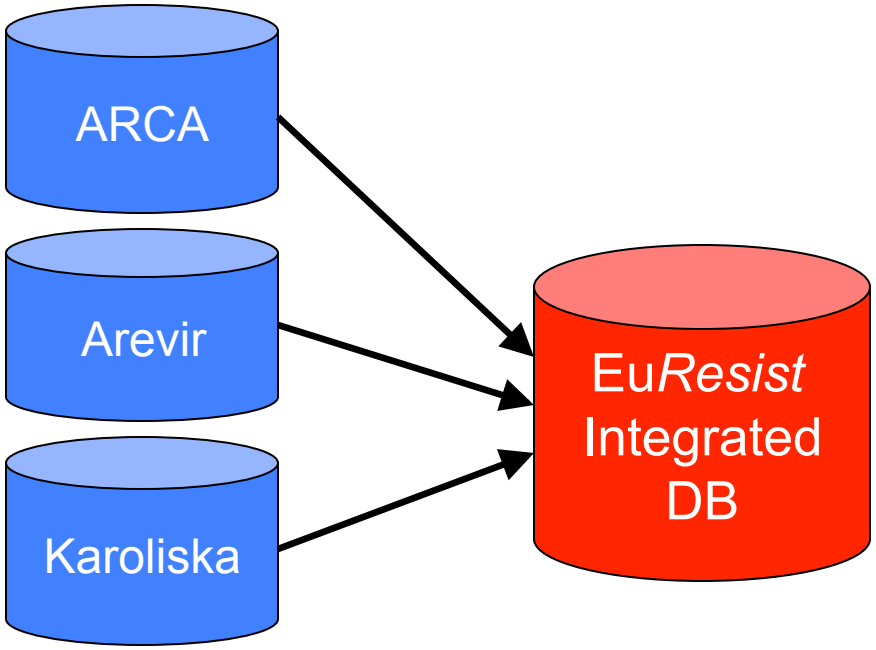
1. Integration of clinical and virologic data from a large cohort of patients



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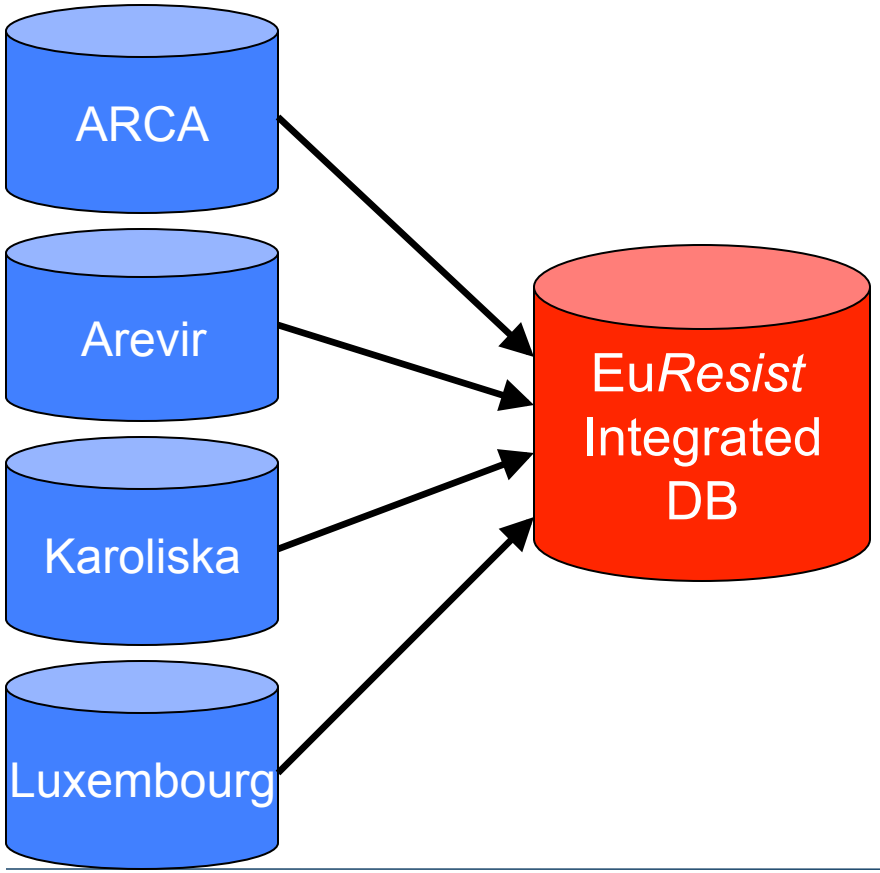

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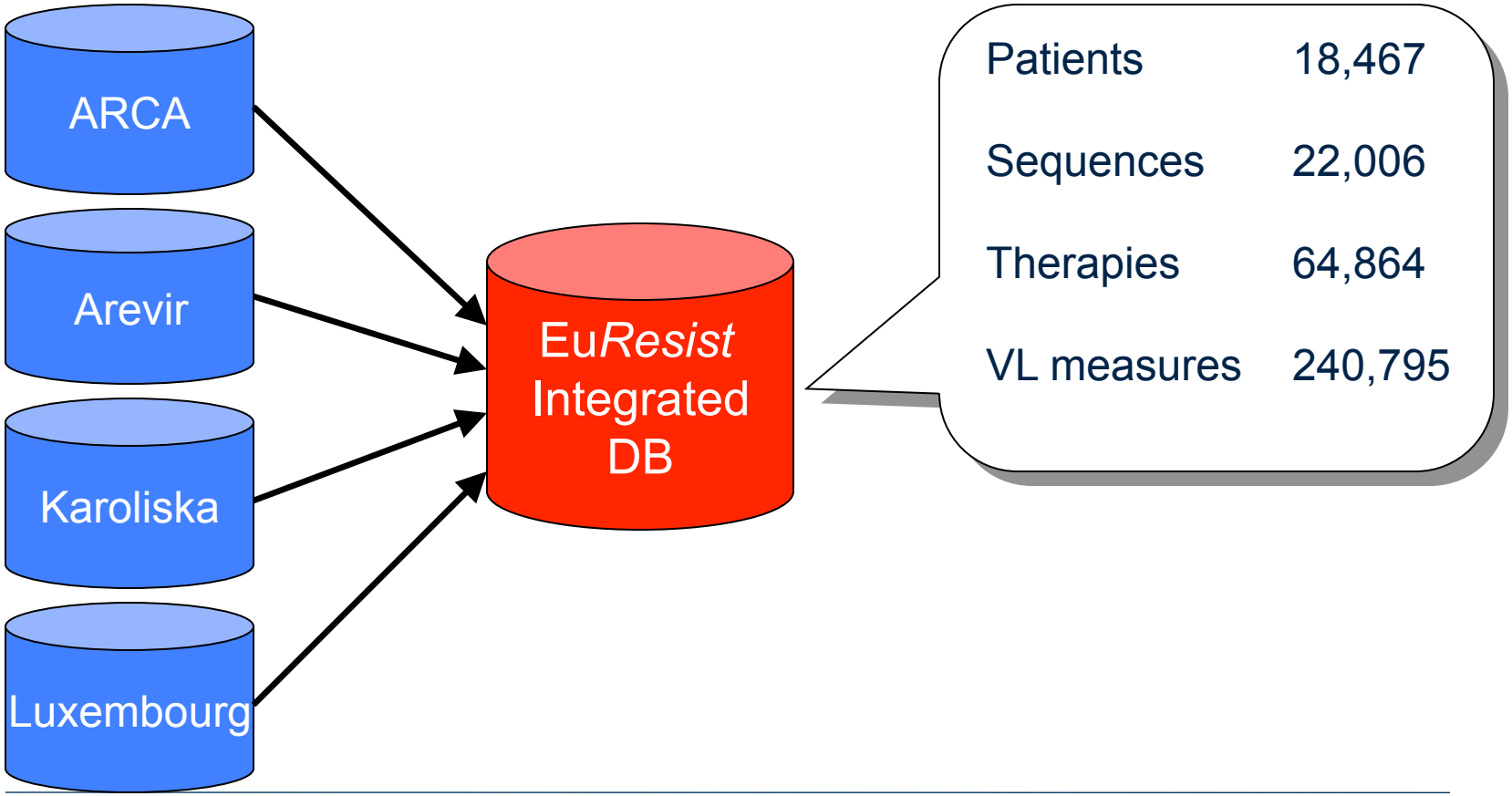
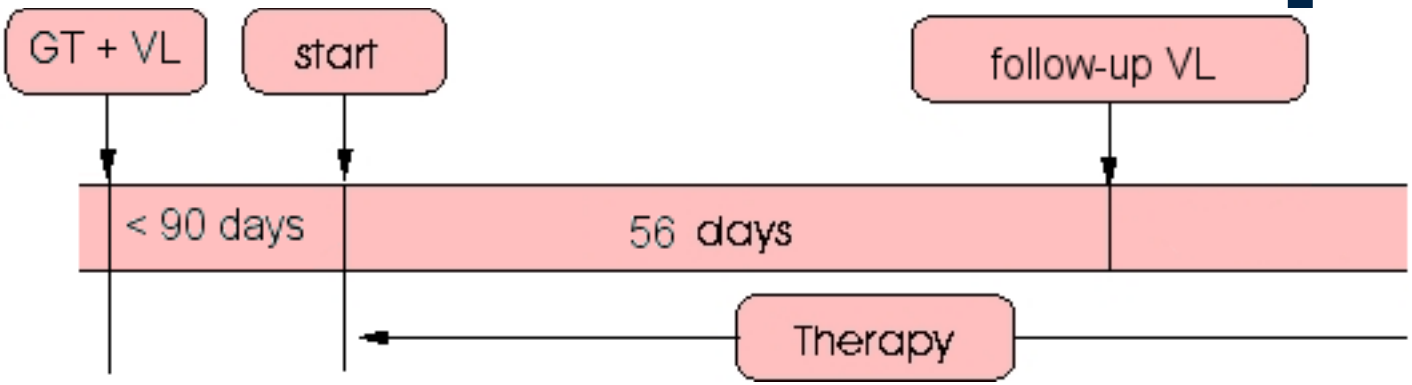
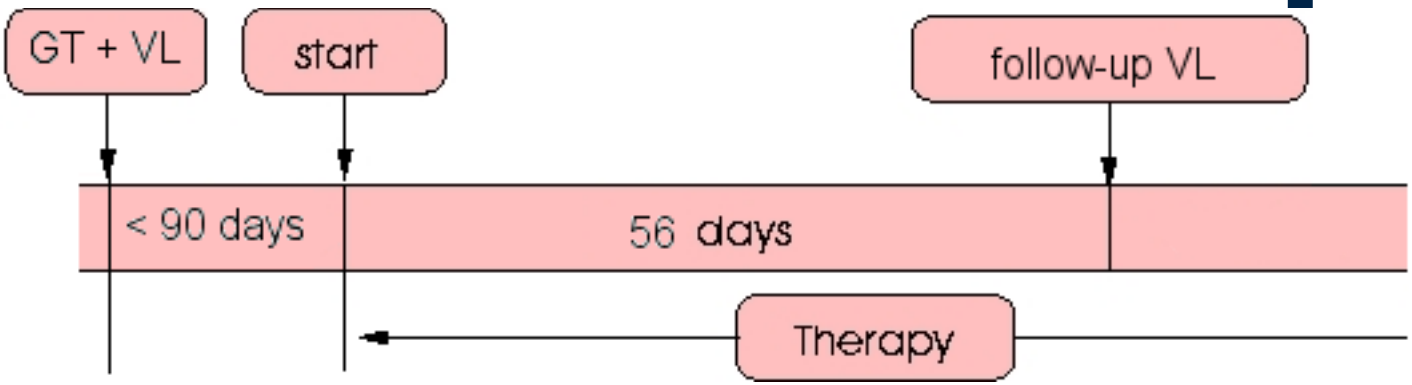


Definition of Therapy Success



- Genotype and baseline VL *at most* 90 days before therapy
- Follow-up VL at 8 [4 - 12] weeks of treatment
- Therapy successful if
  - Follow-up VL below 500 cp per ml
  - 100 fold reduction of VL

Definition of Therapy Success



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- Therapy successful if
  - Follow-up VL below 500 cp per ml
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3,023 therapies met the requirements

approx. 1/3 are labeled as *failures*

2,722 used for training & 301 used for validation

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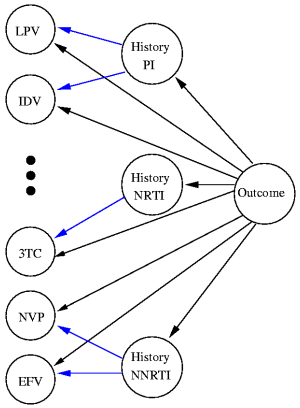
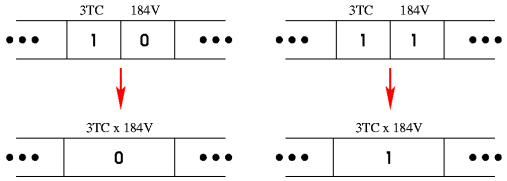
2. Building a data-driven therapy response prediction system for guiding treatment selection

- The Eu*Resist* prediction system consists of three core prediction engines using Logistic Regression
- They work with sequence information alone (*minimal*) …
- … and with additional measurements and information from previous treatments or genotypes (*maximal*)

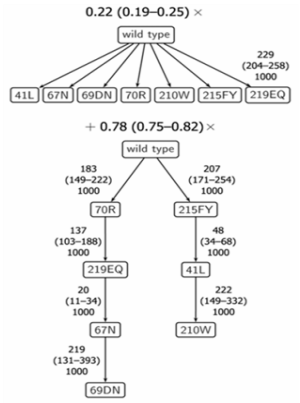
Generative Discriminative (GD) Engine



Mixed Effects (ME) Engine



Evolutionary (EV) Engine



Generative Discriminative (GD) Engine

- Bayesian Network (BN) trained on 20,000 therapies (without genotypic information)
- Middle layer of the BN uses
  - Indicators for drug classes (*minimal*)
  - Number of previously used drugs from that class (*maximal*)
- Success probability predicted by the BN is a new covariate for next prediction step
- Other features:
  - Indicators for drugs / mutations
  - Mutations in past genotypes (only maximal)
  - Number of past treatments (only maximal)
  - Baseline VL (only maximal)

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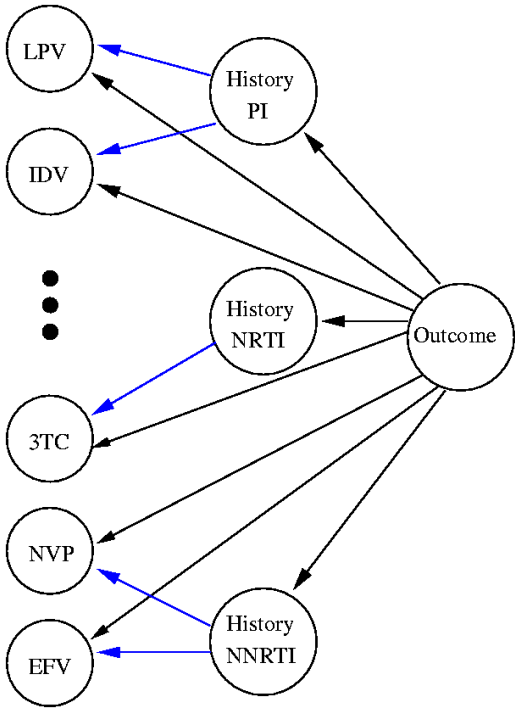

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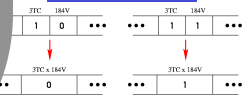

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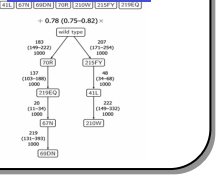

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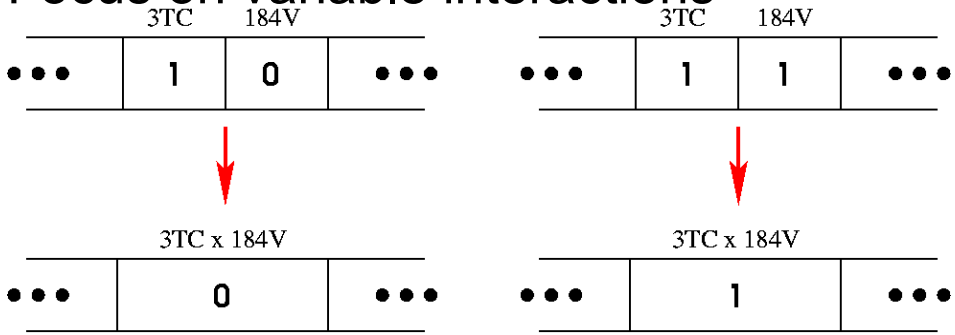
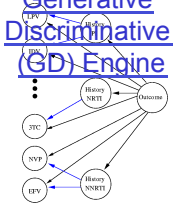
Mixed Effects (ME) Engine

- Focus on variable interactions

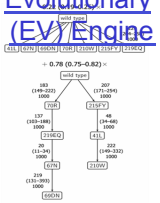


  - mutation x mutation
  - drug x drug (x drug)
  - mutation x drug (x drug)
- Further features are baseline VL, number of drugs in treatment, number of past treatments, vertical transmission, and NRTI experience
- Large number of covariates
- Model built for *maximal* feature set

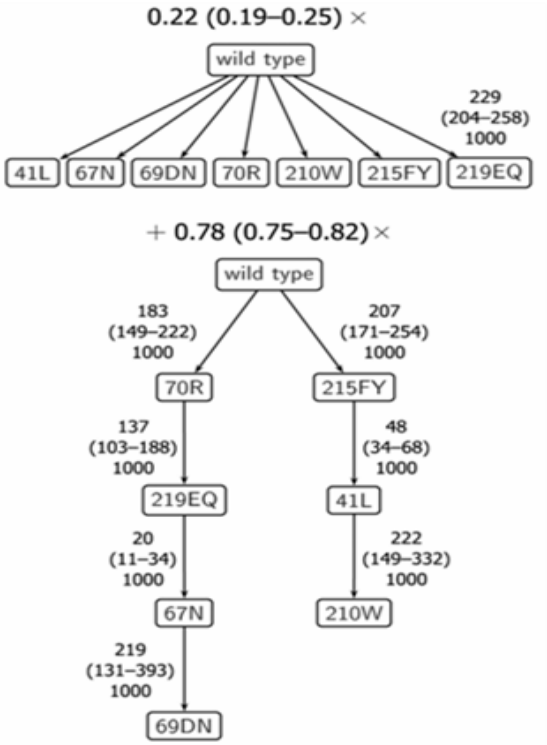
Generative Discriminative (GD) Engine

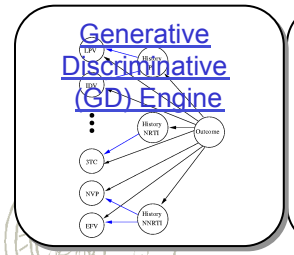


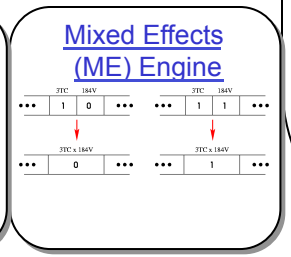
Evolutionary (EV) Engine



Prediction Engines







Evolutionary (EV) Engine

- Genetic barrier is computed for every compound in the regimen
- Probability of the virus not to escape from drug pressure by developing further mutations
- Further features are:
  - Indicators for drugs / mutations
  - Interactions between drugs, mutations, or mutations and drugs
  - Indicators for previously used drugs (maximal)
  - Interactions between drugs and previously used drugs (maximal)
  - baseline VL (maximal)

Results – single engines

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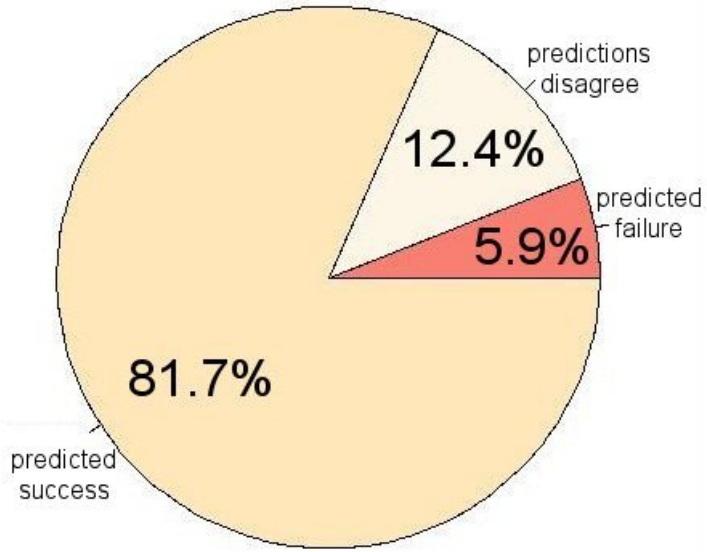
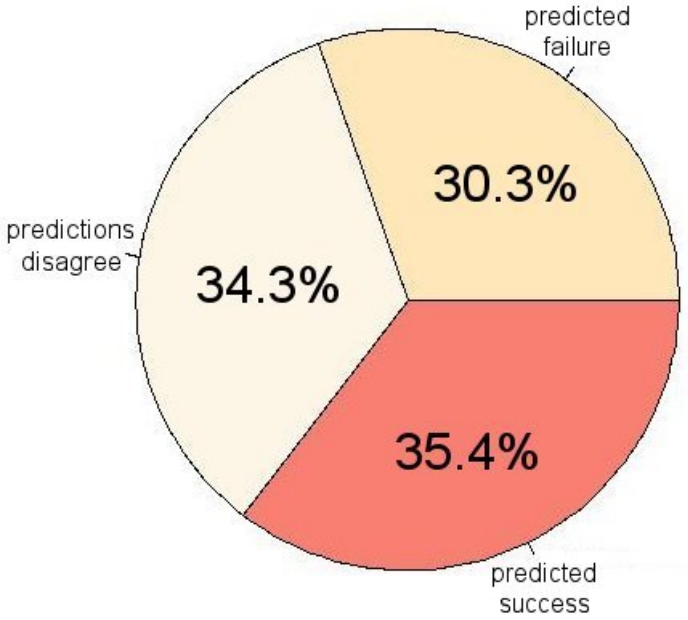
- Validation:
  - Predicted outcome for 301 cases

- Agreement among prediction engines …

…on cases labeled as success:



…on cases labeled as failure



Results – single engines

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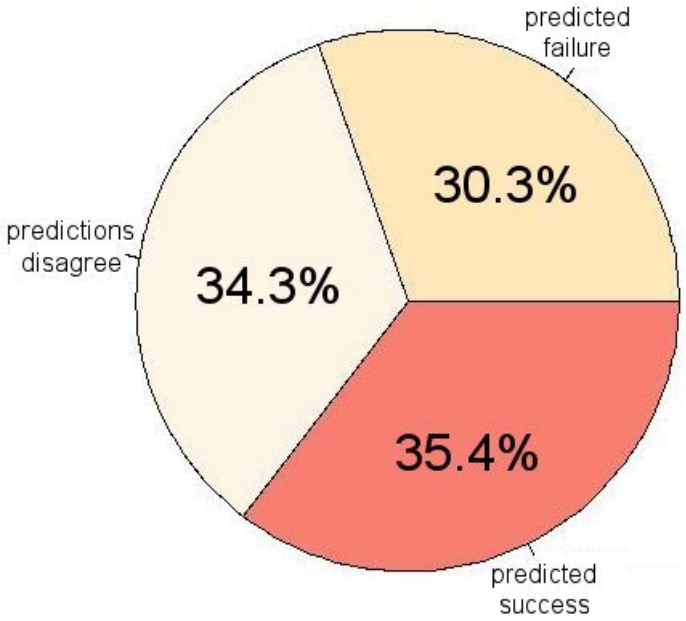
- Validation:
  - Predicted outcome for 301 cases
- Agreement among prediction engines …
- 35 cases are incorrectly predicted by all three engines
- Closer analysis showed that 16 had a VL measurement below 500 cp / ml once during treatment
- In remaining 64 cases this occurred only 13 times

p=0.011 (Fisher's Exact)

…on cases labeled as failure



Results – single engines

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- Validation:
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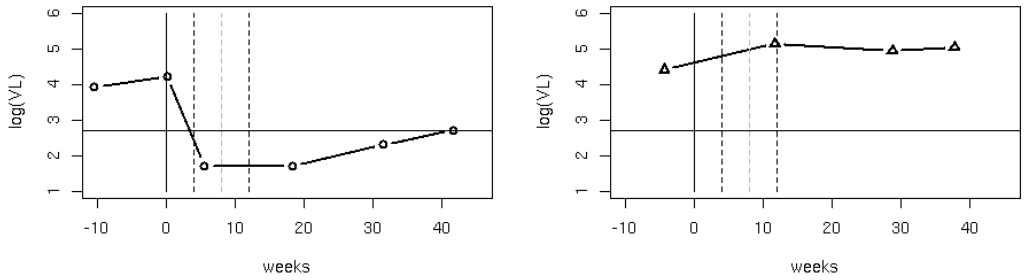
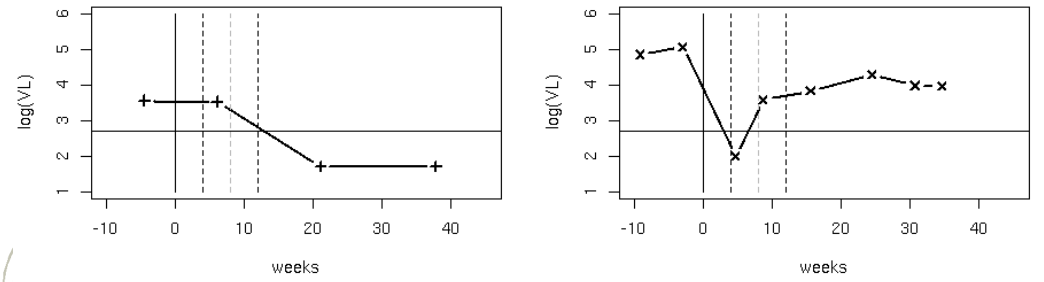


Labeled as failure



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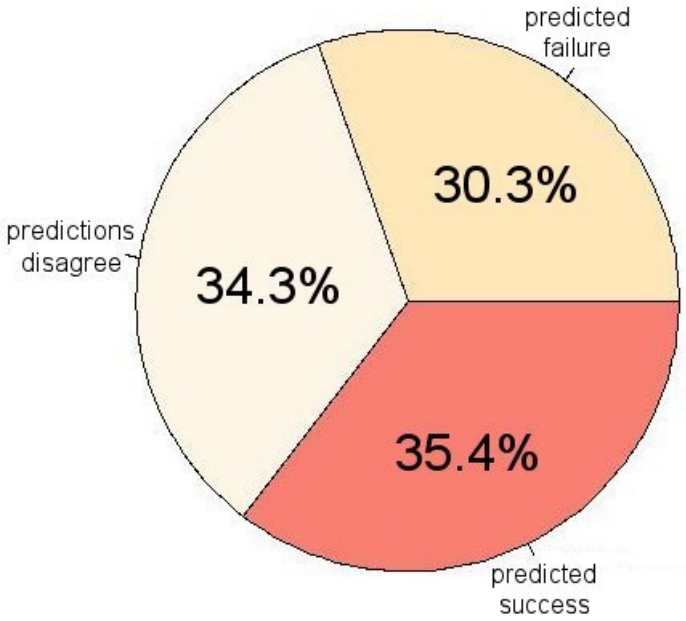

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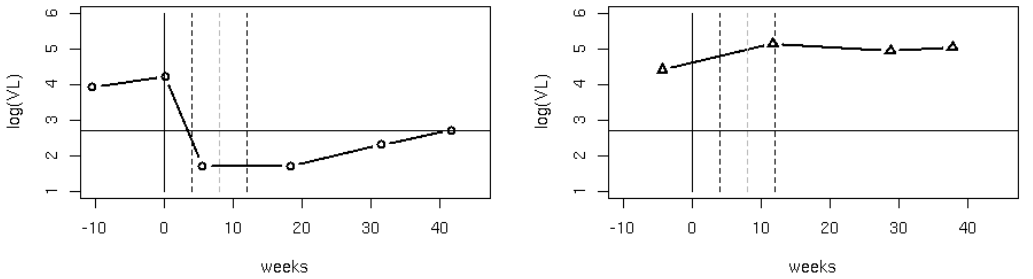
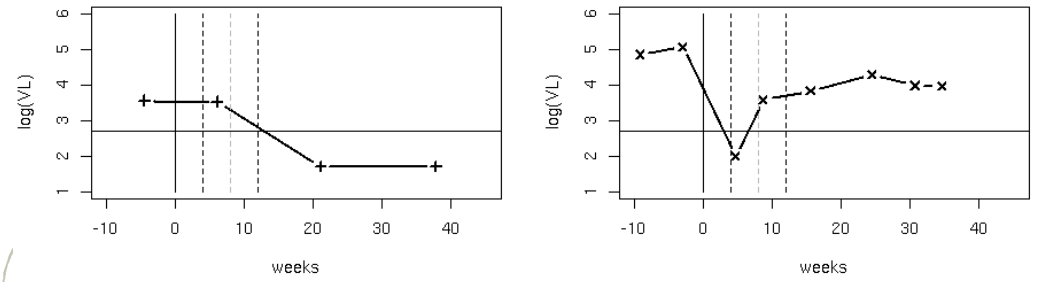


Often predicted as success



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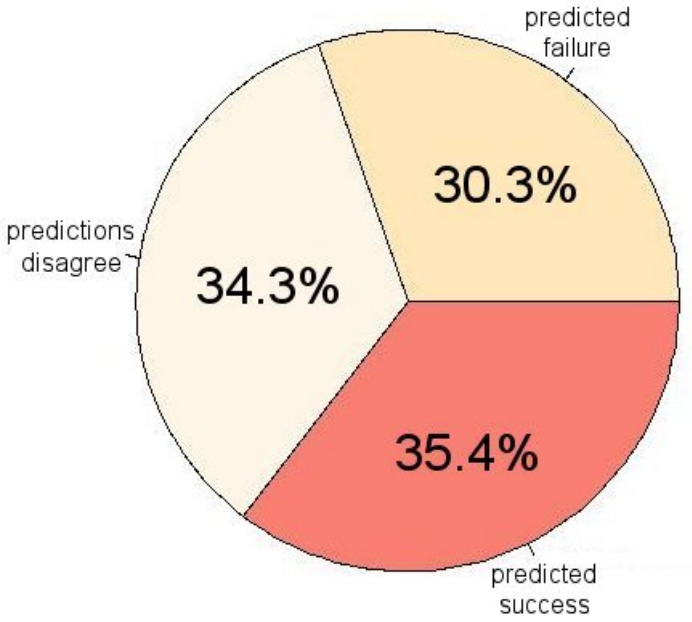

Results – combined engine

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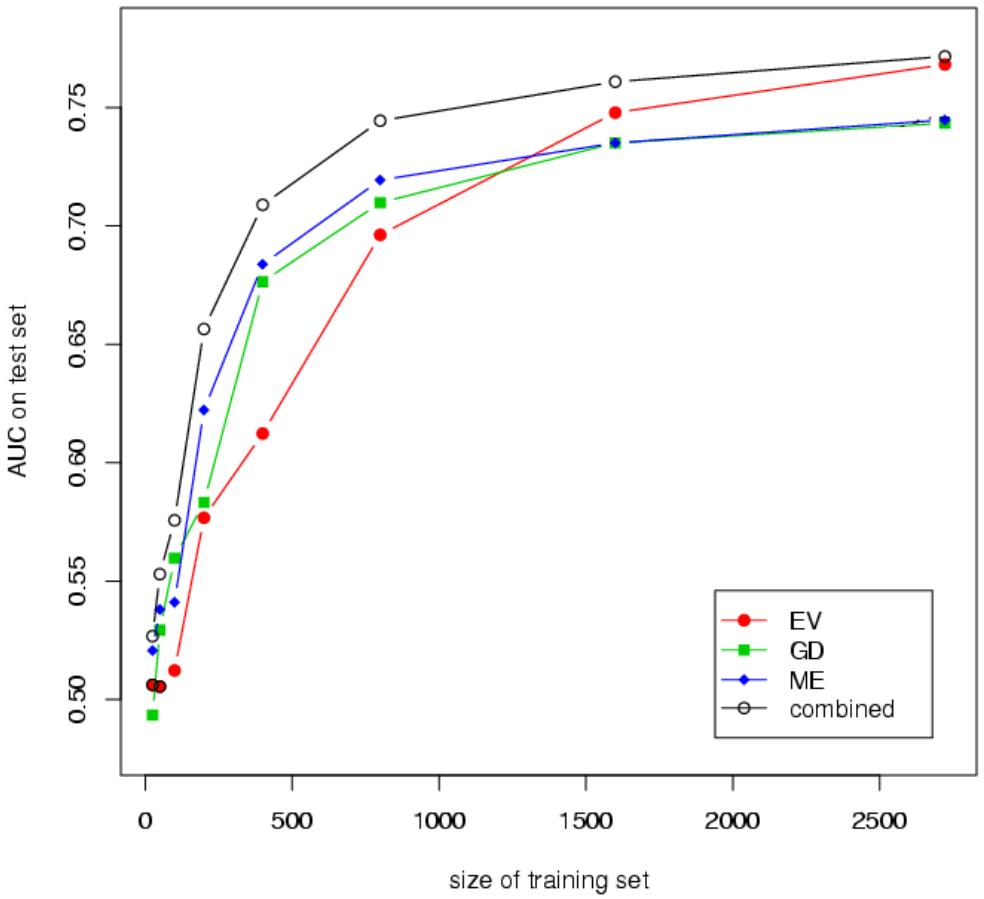
- Various methods for combining the prediction engines explored
- Computing the *mean* of the three predictions proved to be simple and efficient
- Variation of the training set size shows a better learning behavior of the combined engine



Results – combined engine

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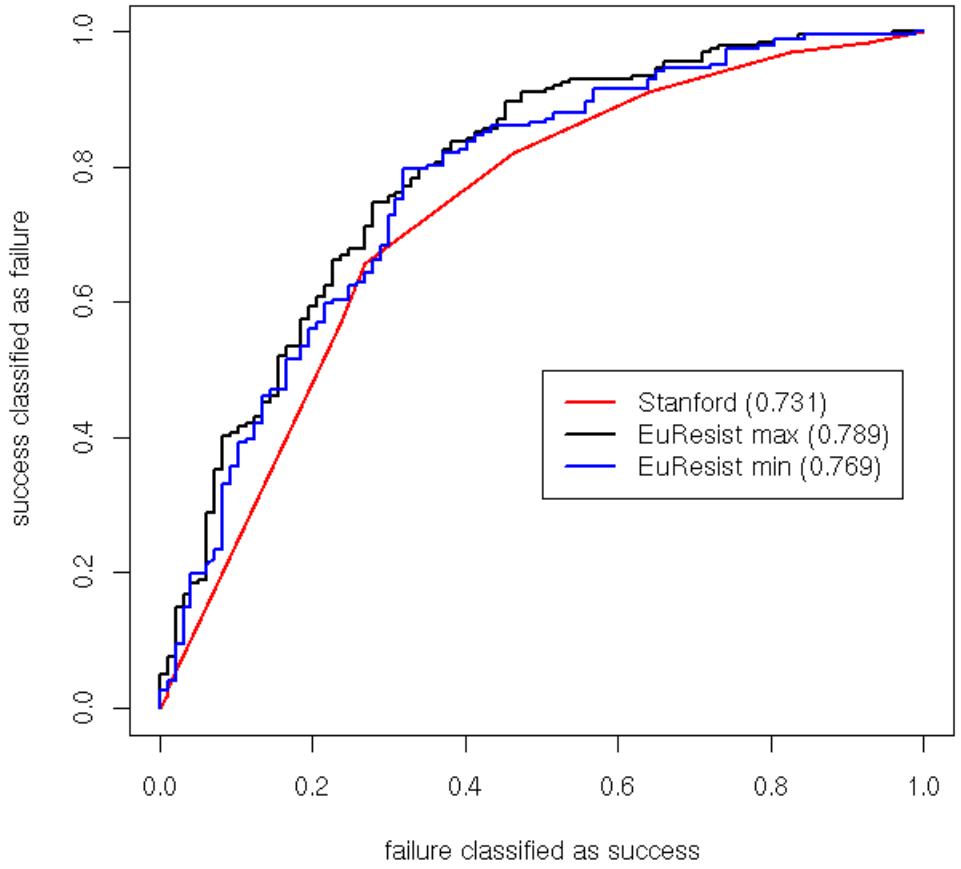
- Extended feature set outperforms the minimal feature set (p=0.048)
- Both feature sets outperform a GSS based prediction using the Stanford algorithm



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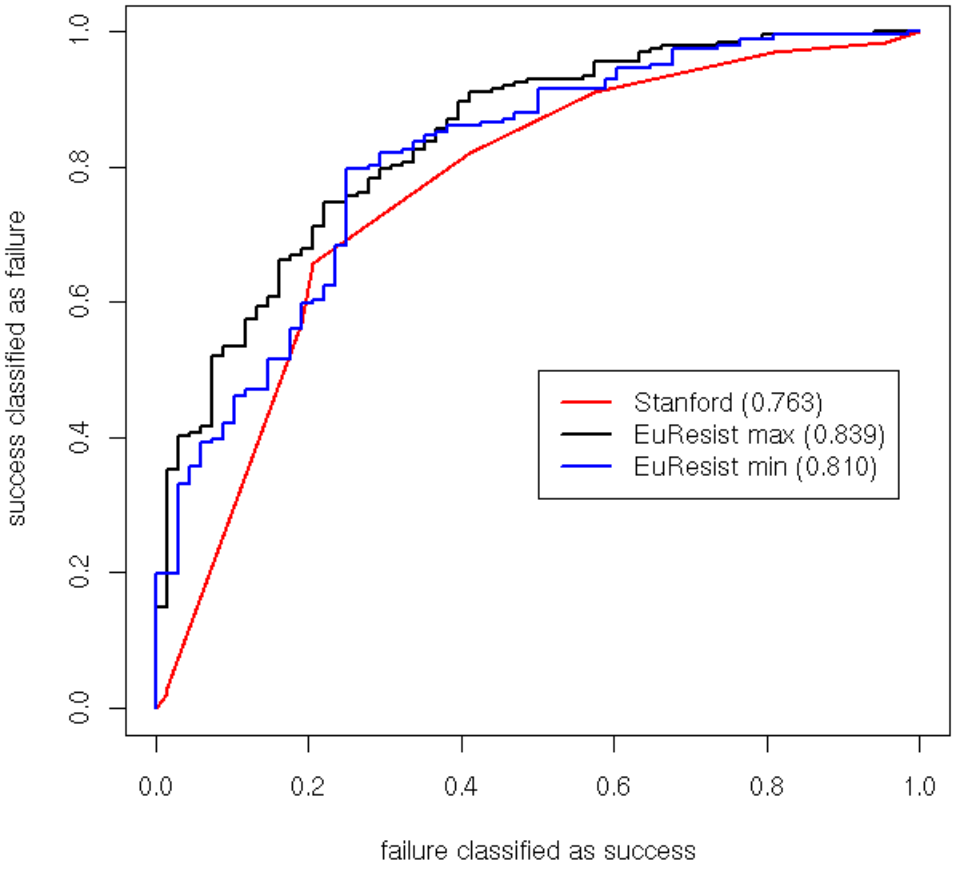
- Removal of failures with VL below 500 cp / ml once during treatment leads to an increased performance



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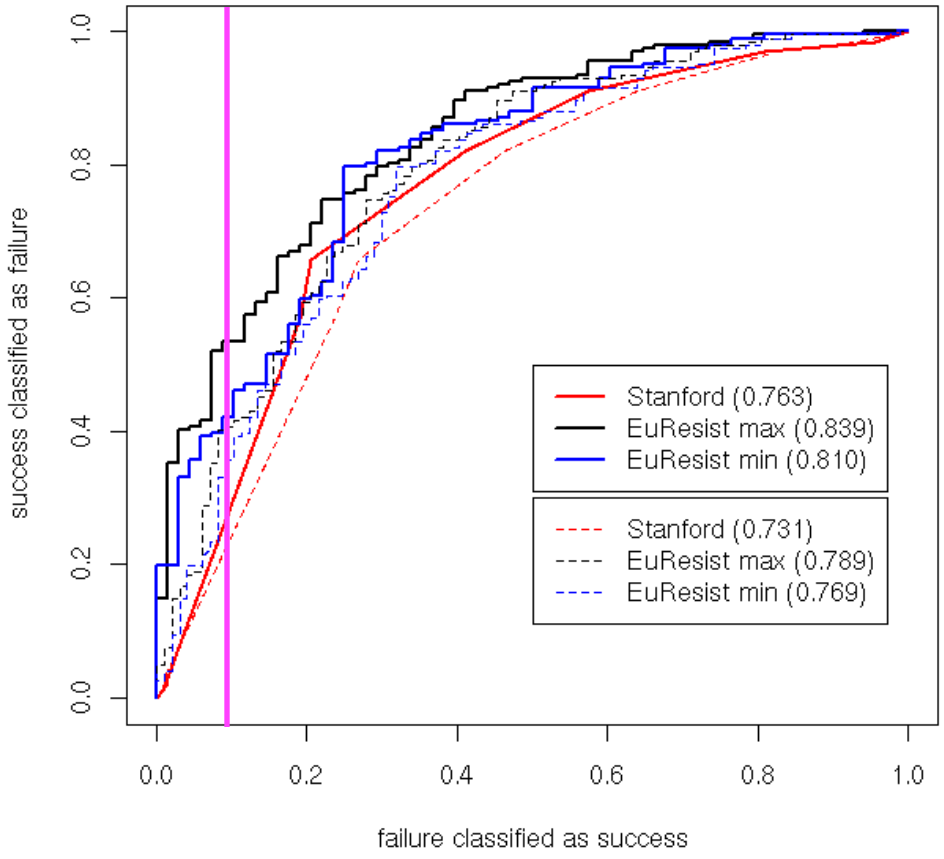
- Removal of failures with VL below 500 cp / ml once during treatment leads to an increased performance
- Gain is more pronounced for the Eu*Resist* engine than for the GSS based prediction



Conclusions

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- Additional features like information on past treatments and baseline VL significantly improve performance
- Combination of the three engines yields a further increase in performance and robustness
- A shortcoming in the current definition of success and failure could be detected
- Despite that shortcoming the combined engine could detect the trend correctly and the used performance measure underestimated the true performance
- The Eu*Resist* web service will be freely available at end of June 2008