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Do not blame the fitness!

Only slight impact of predicted replicative capacity for therapy response prediction

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EUROPEAN HIV DRUG RESISTANCE WORKSHOP

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Outline

1. Prediction of RC from genotype (RT and Pro)
2. Validation of predicted RC (pRC)
3. Relevance of pRC for inferring response to ART
4. Conclusion

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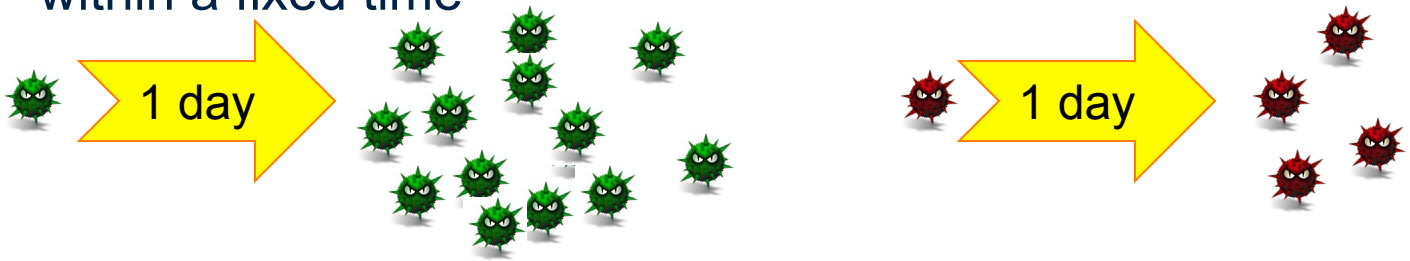
Viral fitness

- Here: replication capacity w/o presence of drugs
  - Measure number of newly assembled infectious particles within a fixed time



  - Only Protease and RT were studied, not the complete virus
- Is viral fitness useful for predicting response to ART?

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- To study effect of RC during ART
  - First build a model that predicts RC from genotype on datasets comprising genotype-RC pairs

…KVIGSVLIGPTPANIIGRSLM… 1.9
…KVVGTVLVGPTPANIIGRNLM… 13.0
…KVIGSVLVGHTPSNIIGRNMM… 88.7
…KVVGTVLIGPTPVNVIGRNLM… 2.5

  - For this study two datasets were available

1. Monogram (Mark R Segal et *al.* Stat. Appl. Genet. Mol. Biol. 2004)
2. Erlangen (Hauke Walter et *al.*)
   317 and 253 samples

Prediction of RC from genotype

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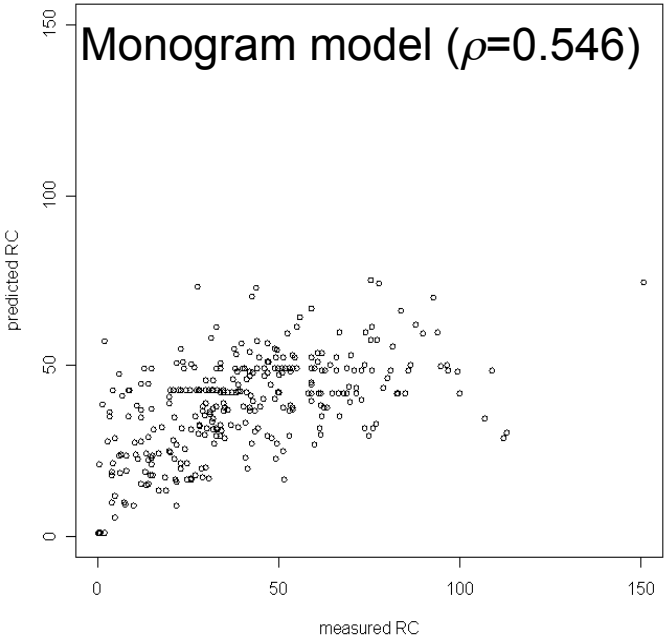
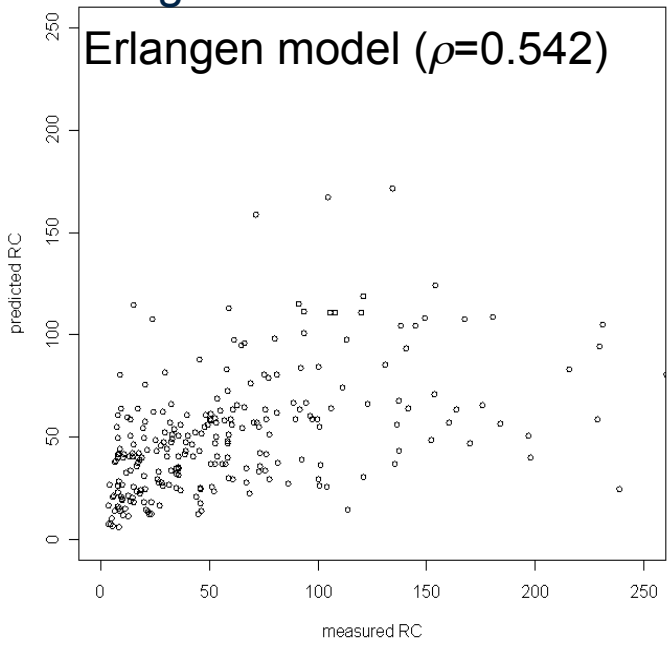
Training of a support vector machine (SVM) for each dataset

1. Linear SVM for selecting important mutations
2. Polynomial SVM for modeling synergetic effects between mutations

- Estimation of model performance (spearman correlation)
  - Leave one out cross-validation on training data





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Important mutations in the SVM models

rank	Monogram mutation	influence	Erlangen rank
1	RT M184V		19
2	PR K43T		568
3	RT A158S		126
4	PR Q92R		401
5	PR I64L		886
6	PR K55R		602
7	PR E34K		483
8	PR I47V		366
9	PR V32I		131
10	PR P39S		141

Erlangen mutation	influence	Monogram rank
RT Q207E		240
PR V82A		127
RT Y181C		150
RT T215Y		18
RT K20I		49
PR I13V		132
RT E122K		–
RT L74V		141
RT S162C		255
RT T39E		267

Validation of predicted RC

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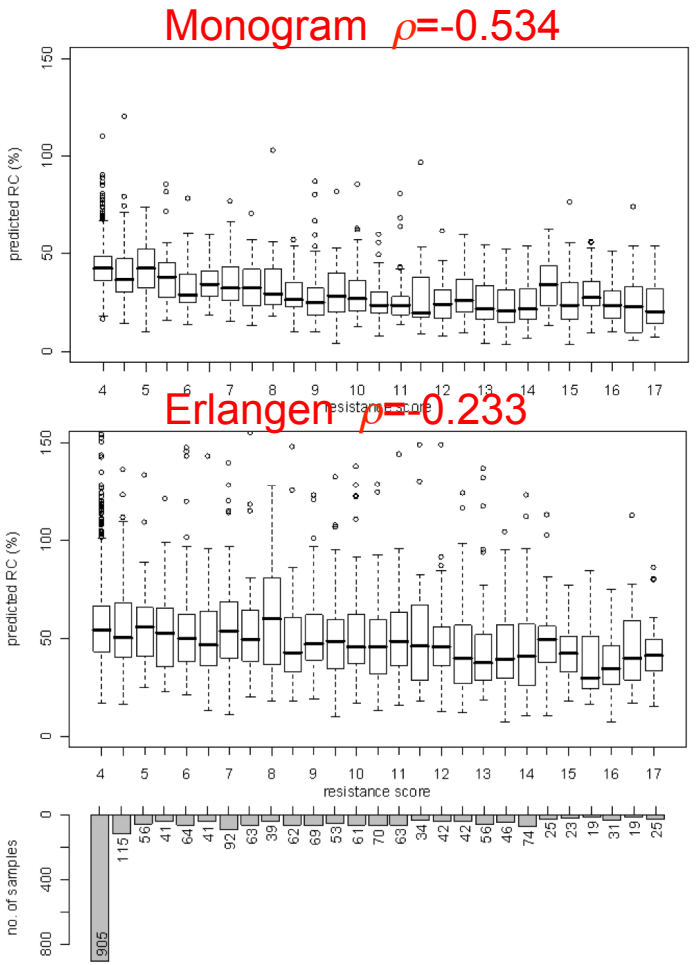
Correlation of pRC with drug resistance

- 2,913 sequences (RT and Pro) from EuResist Integrated Database
- Resistance against 17 antiretroviral drugs was computed with geno2pheno
- Continuous value of predicted Fold Change (FC) was discretized using clinical cutoffs of geno2pheno
- Resistance against drugs was added: cumulative resistance score (CRS)



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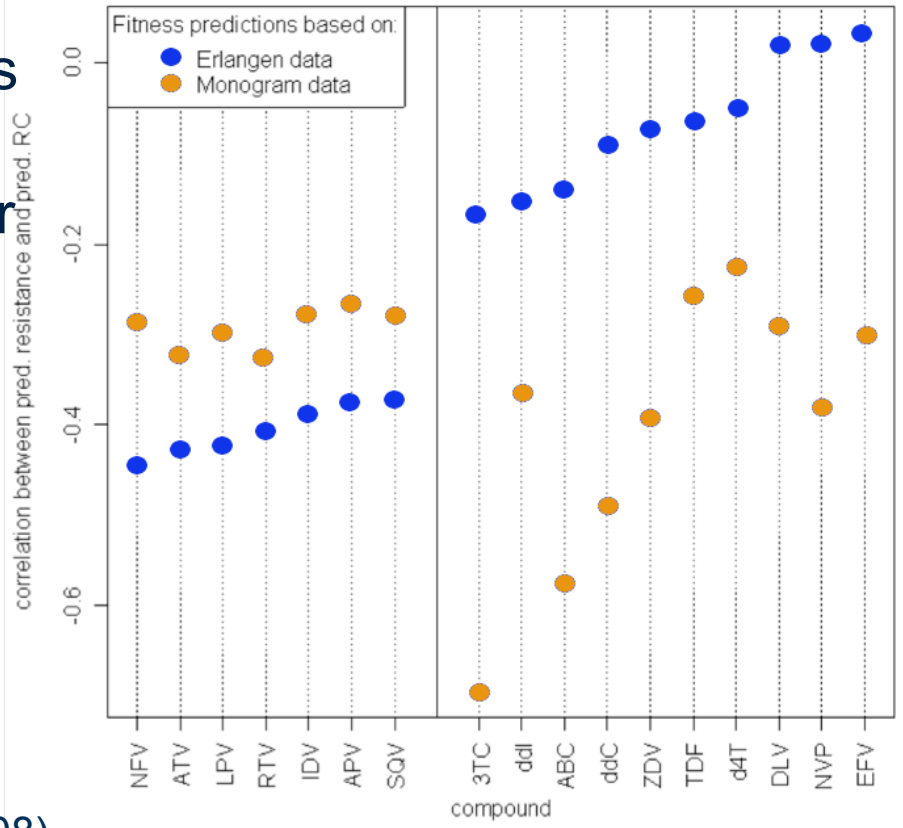
Correlation of pRC with drug resistance

- Same dataset, but single drugs
- For the Erlangen model a clear separation of drug classes is visible
- Pro sequences of Erlangen data were highly mutated
  - 61% > 0 mutations
  - 25% > 4 mutations
  - For Monogram: 28% and 3%!
    (Robert W Shafer et al. AIDS Rev.2008)



Validation of predicted RC

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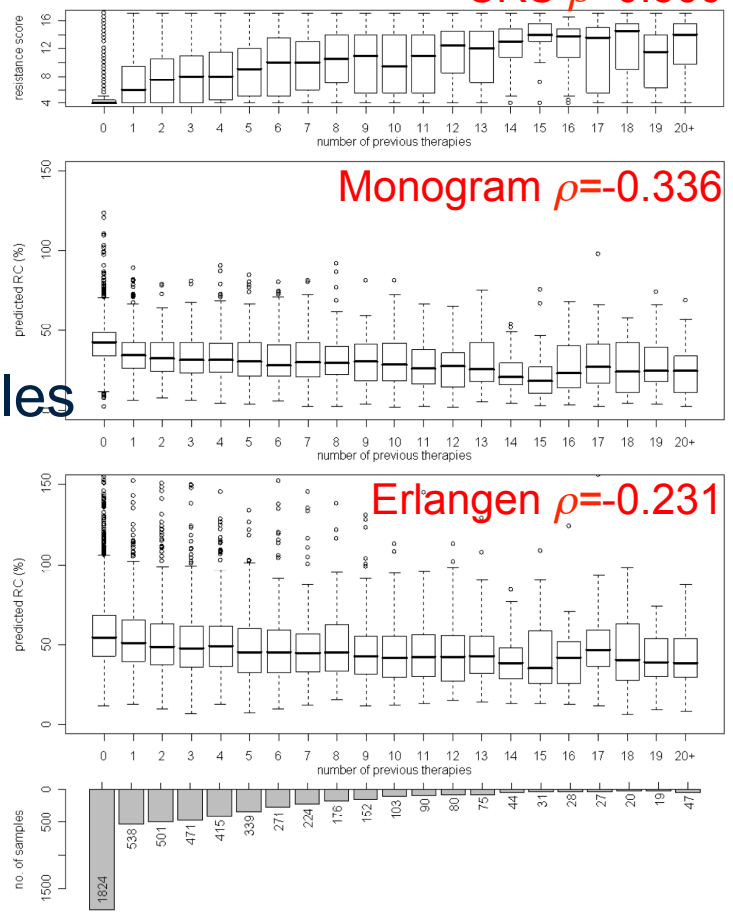
Correlation of pRC with treatment experience

- 5,475 Pro and RT sequences from 3,869 patients extracted from the EuResist DB
- CRS and pRC computed for all samples
- Correlated to number of treatment changes before genotyping
- Patients with >19 treatment changes formed one group
- Naïve patients formed largest group



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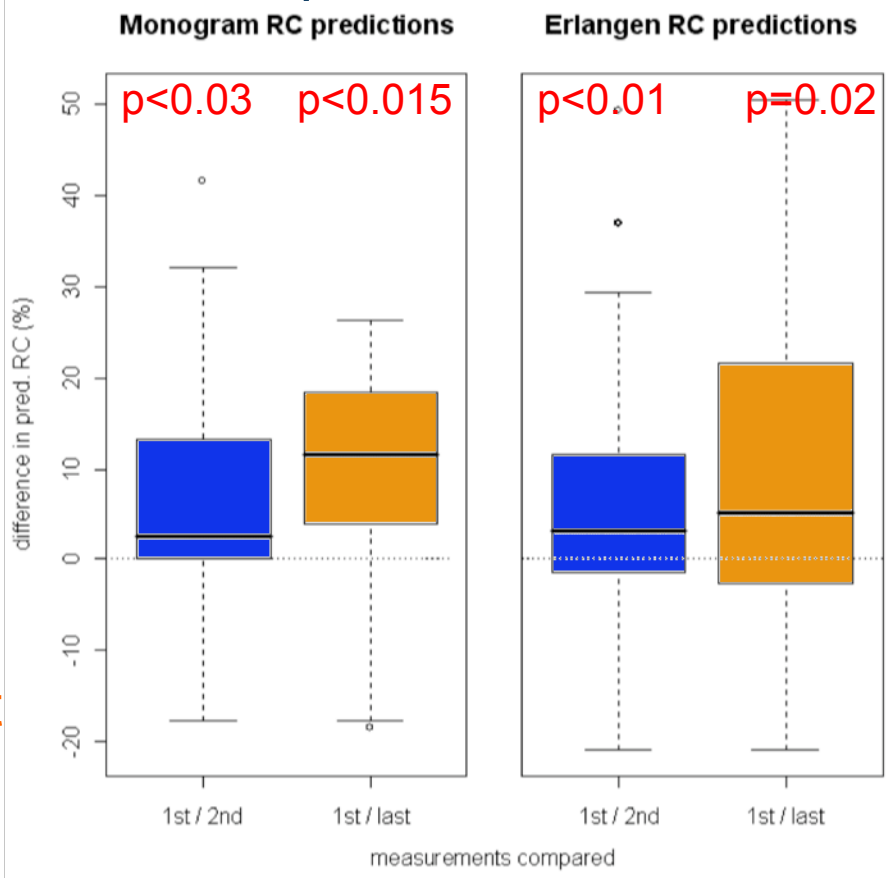
Development of pRC during treatment interruptions

- 162 sequences from 57 patients undergoing a treatment interruption
- Sequences were obtained at end of treatment and at max. 4 time points during the break
- Difference in pRC between baseline and first (n=56) or last (n=30) measure during the break



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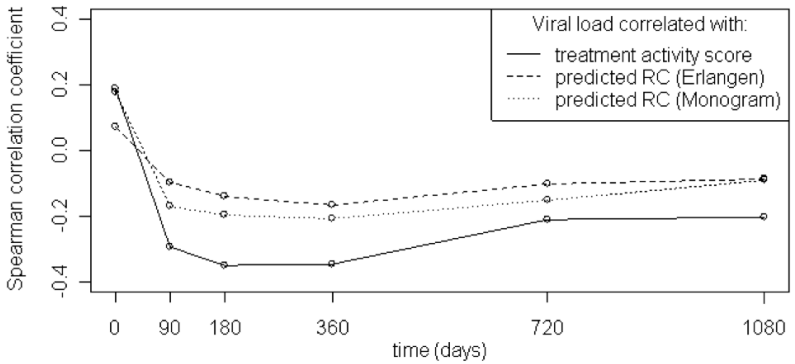
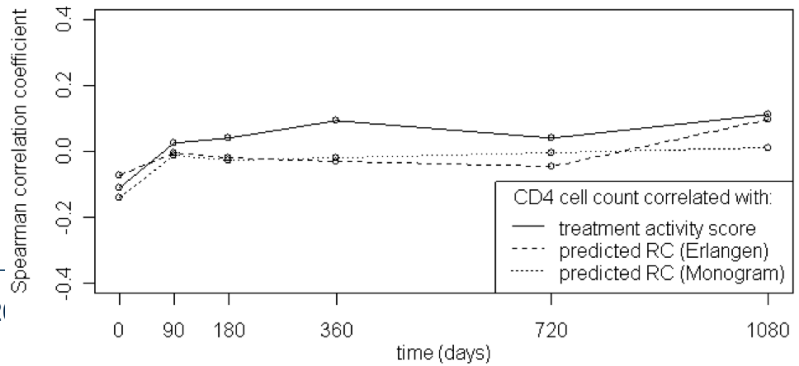
Extraction of TCEs from the EuResist database

measure \ time	baseline	90 days follow-up	180 days follow-up	360 days follow-up	720 days follow-up	1080 days follow-up
viral load	2913	2031	2047	1457	675	333
$CD4^+$ T-cell count	2376	1621	1613	1154	526	252

- Baseline genotype, VL, and CD4 within 90 days before treatment start
- Follow-up measures at different time points
- Correlation of treatment activity score (TAS; PSS) and pRC with measurements at different time points





Relevance of pRC for inferring response to ART

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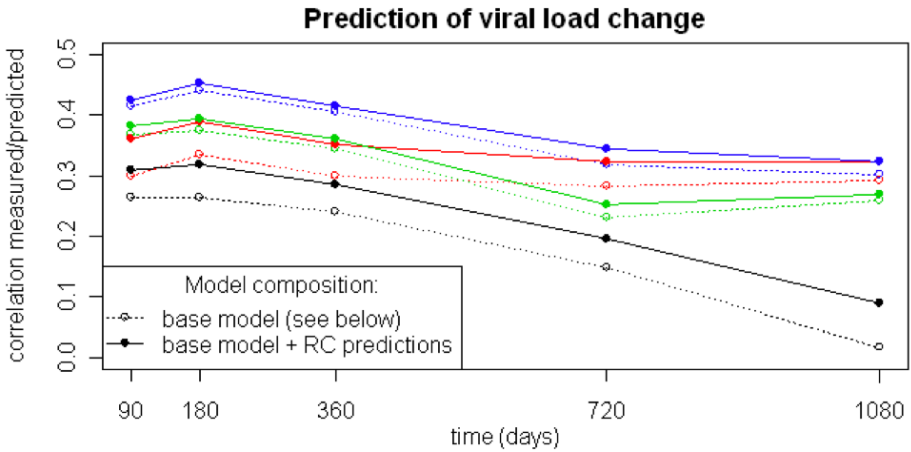
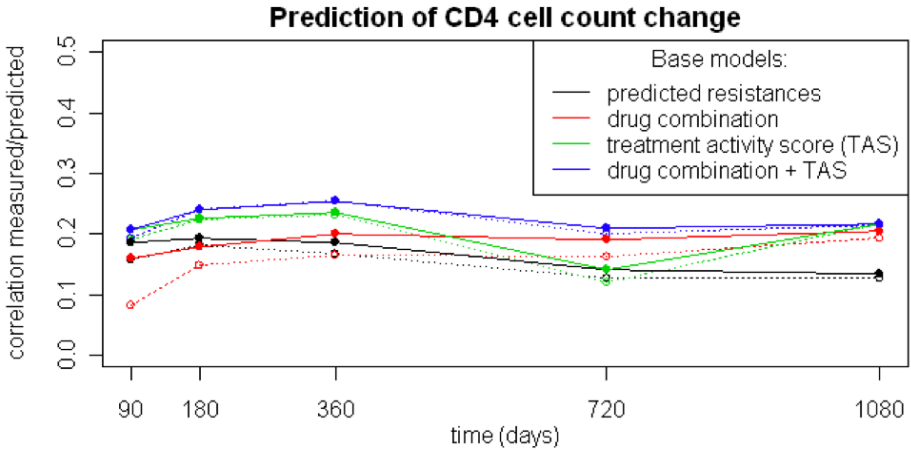
Predicting change in VL and CD4

- Linear regression model was trained using
  1. Predicted resistance to applied drugs
  2. TAS
  3. Drug combination
  4. Drug combination and TAS
- Models were built with and without pRC as covariate
- Performance was computed by 5x 5-fold cross-validation





Conclusions

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- Replication Capacity was predictable from genotype at moderate rates
  - Performance might be improvable with more more genotype-phenotype pairs
  - The pRC models selected different important mutations

- Pre-existing notions about RC were confirmed
  1. Inverse relation with drug resistance
  2. Relation to treatment experience
  3. Increase of RC during treatment interruptions

- Inclusion of pRC improved performance only moderately
  - No significant improvement over the best method

Resistance against applied antiretroviral drugs was dominant information for inferring response to ART

Do not blame the fitness!

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