Validation of geno2pheno and THEO on a large independent clinical dataset

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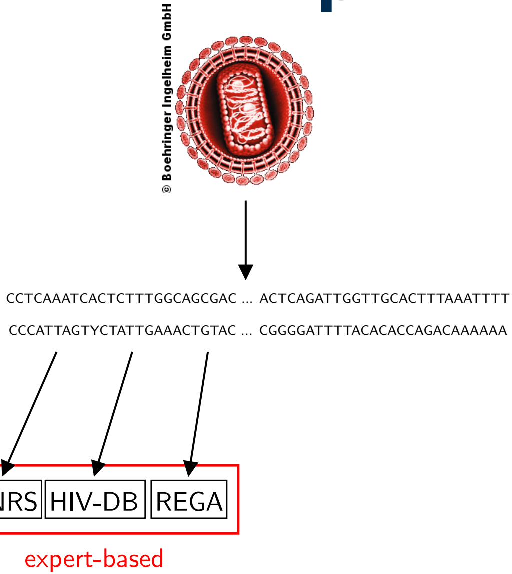
Background

- Genotyping is "standard of care"
- Various methods provide help to genotype interpretation
- Expert-based algorithms
  - ANRS V2006.07
  - HIV-DB
  - Rega V6.4.1
  - ...



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CCTCAAATCACTCTTTGGCAGCGAC ... ACTCAGATTGGTTGCACTTTAAATTTT

CCCATTAGTYCTATTGAAACTGTAC ... CGGGGATTTTACACACCAGACAAAAAA

expert-based

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  - …
- Data-driven algorithms
  - geno2pheno
  - THEO
- Data-driven methods have to be validated on clinical data


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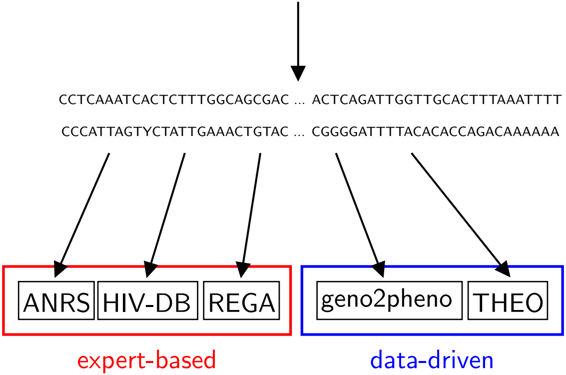
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ANRS | HIV-DB | REGA

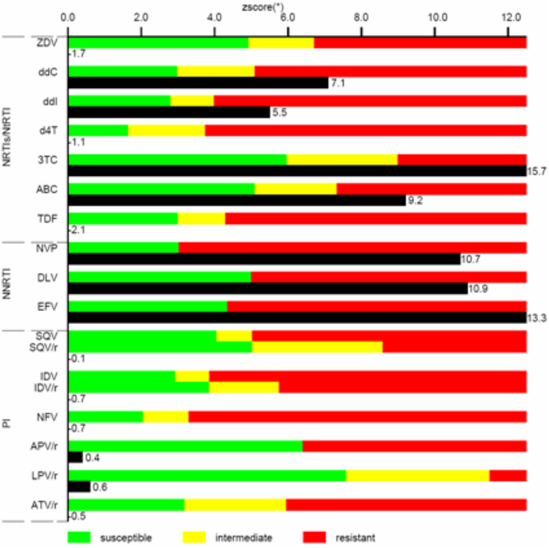
geno2pheno | THEO

expert-based

data-driven

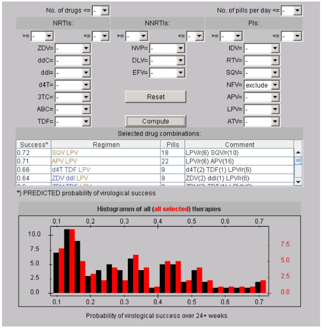
Background - geno2pheno

- geno2pheno$_{\text{[resistance]}}$ predicts phenotypic resistance from genotype
- Trained on ≈ 800 genotype-phenotype pairs per drug
- Expert derived clinical cut-offs
- www.geno2pheno.org
- Details:
  Presentation of H. Walter



Background - THEO

- THErapy Optimizer (THEO) predicts *in vivo* response to combination therapies
- Trained on data from the Stanford HIV Drug Resistance Database and from two Northern California clinic populations
- Computes genetic barrier to drug resistance for every drug in regimen
- Part of the geno2pheno web-service
- *Antiviral Therapy 2007* (**12**) p 169-178:



No. of drugs <= -
No. of pills per day <= -

NRTIs: >= - <= -
NNRTIs: >= - <= -
PIs: >= - <= -

ZDV= -
ddC= -
ddI= -
d4T= -
3TC= -
ABC= -
TDF= -
NVP= -
DLV= -
EFV= -
IDV= -
RTV= -
SQV= -
NFV= exclude
APV= -
LPV= -
ATV= -

Selected drug combinations:

Success*	Regimen	Pills	Comment
0.72	SQV LPV	18	LPV/r(6) SQV/r(10)
0.71	APV LPV	22	LPV/r(6) APV(16)
0.66	d4T TDF LPV	9	d4T(2) TDF(1) LPV/r(6)
0.64	ZDV ddI LPV	9	ZDV(2) ddI(1) LPV/r(6)

*) PREDICTED probability of virological success

Improved prediction of response to antiretroviral combination therapy using the genetic barrier to drug resistance

André Altmann[1], Niko Beerenwinkel[2], Tobias Sing[1], Igor Savenkov[1], Martin Däumer[3], Rolf Kaiser[3], Soo-Yon Rhee[4], W Jeffrey Fessel[5], Robert W Shafer[4] and Thomas Lengauer[1]*

Background - THEO

CCTCAAATCACTCTTTGGCAGCGAC ...

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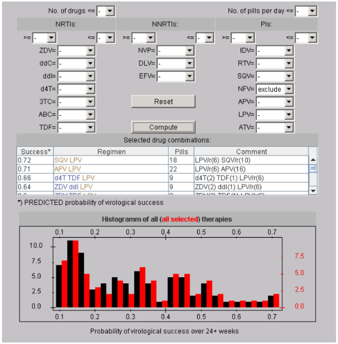
+

d4T TDF LPV

APV LPV

ZDV ddI LPV

SQV LPV



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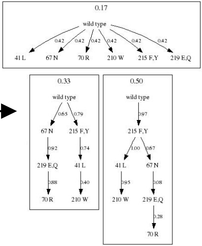
Histogramm of all (all selected) therapies

Probability of virological success over 24+ weeks

0.72	SQV LPV
0.71	APV LPV
0.66	d4T TDF LPV
0.64	ZDV ddI LPV



statistical learning

Methods - Data

- Database: EuResist
  Integration of viral genomics with clinical data
  to predict response to anti-HIV treatment
  - ARCA
  - Arevir
  - Karolinska
- Two views to extract data:
  - classic: typical treatment situation
  - alternative: less requirements ⇒ generates more data
- See also:
  - Presentation of M. Zazzi
  - Poster Eu*Resist*: #56

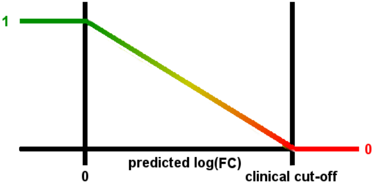
Methods - Treatment scores

Computation of treatment scores:

- Expert-based methods:
  - calculate rating for single drugs
  - sum of single drugscores used

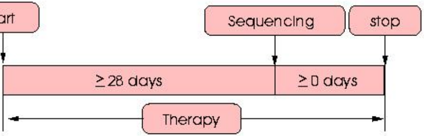
resistant ⇒ 0.0
intermediate ⇒ 0.5
susceptible ⇒ 1.0

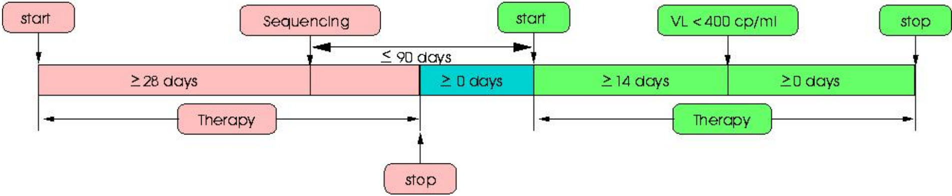
- geno2pheno:
  - calculate fold-change (FC) in IC_{50}
  - normalize using linear interpolation
  - sum of single drugscores used



- THEO directly generates scores for a combination therapy!

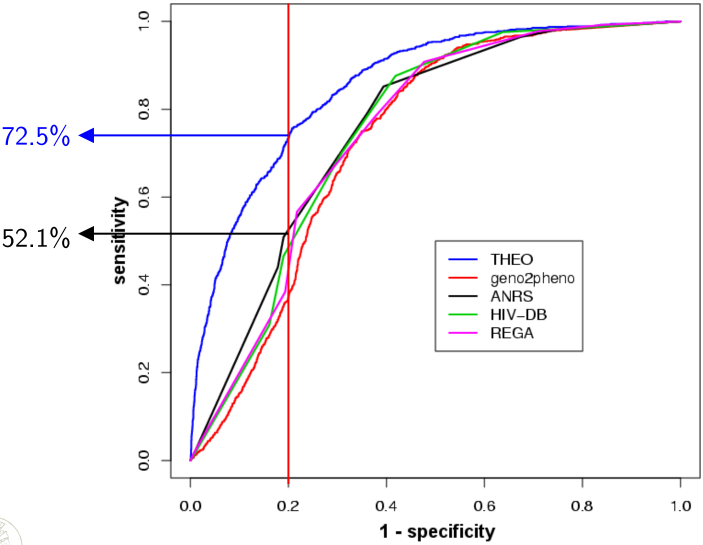
Results - “alternative” Standard Datum





- 5224 treatment-sequence pairs (Eu*Resist* database)
  - 904 successes
  - 4320 failures

Results - “alternative” Standard Datum

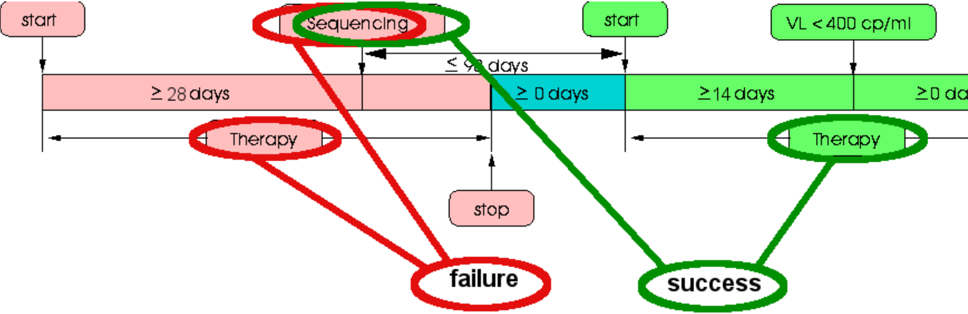


ROC reminder:

Y-Axis: proportion of successes classified as successes

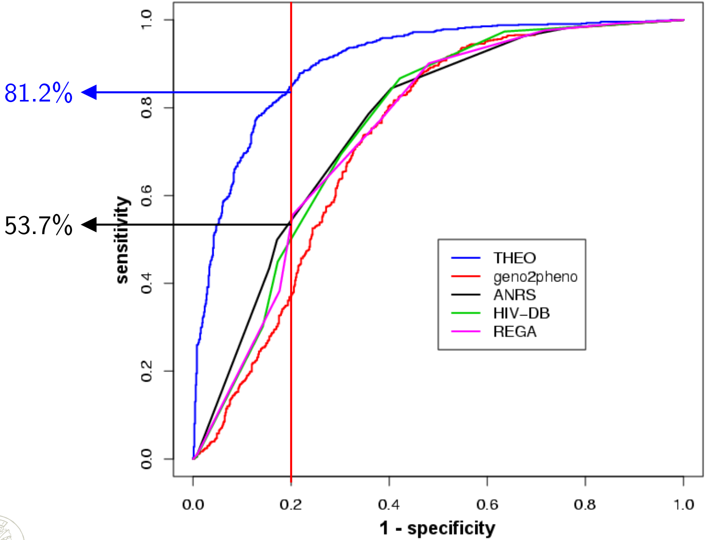
X-Axis: proportion of failures classified as successes

Results - Balanced subset

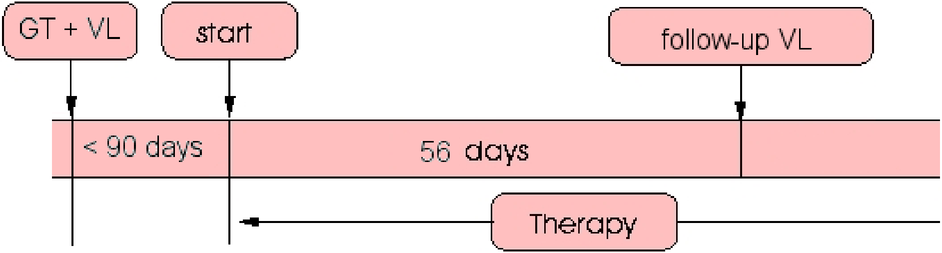


- 1518 treatment-sequence pairs (Eu*Resist* database)
  - 759 sequences
  - 2 therapies per sequence: one failure & one success (same patient)
- perfect dataset to compare algorithms

Results - Balanced subset



Results - “classic” Standard Datum

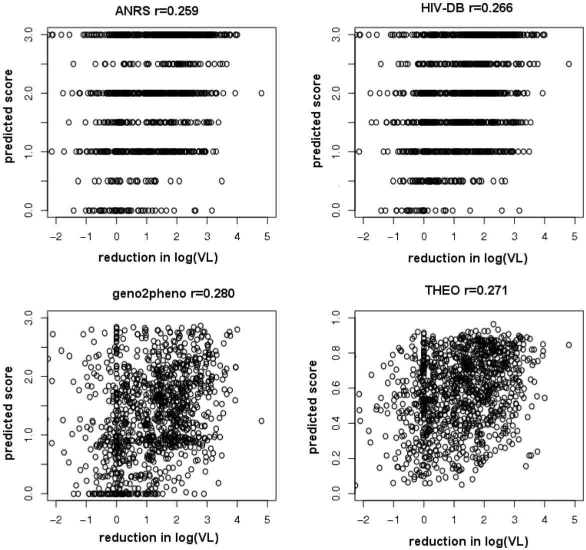


- Focus on *initial response* under *typical treatment* situation
- Success: undetectable (400 cp/ml) or VL reduction of two log
- 1064 treatment-sequence pairs

  ⇒ 614 successes and 450 failures
- Two different tasks:
  - Classification
  - Prediction of $\Delta \log(VL)$

Results - Correlation

- Method score vs. $\Delta \log(VL)$
- Important information missing:
  $\Rightarrow$ baseline viral load



Results - Correlation

- Method score vs. $\Delta \log(VL)$
- Important information missing:
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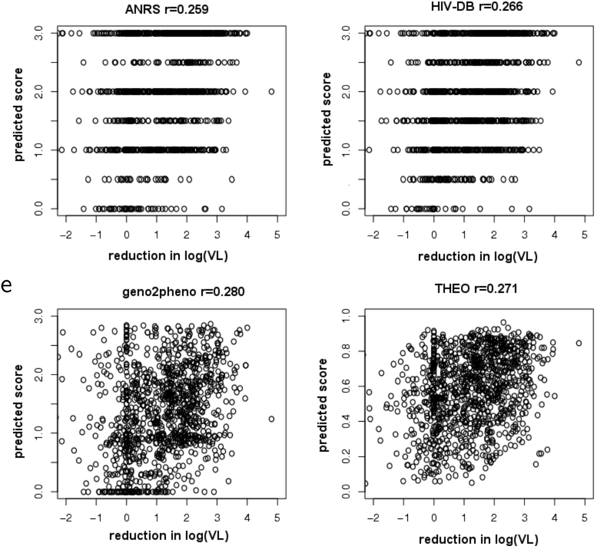
- Predict $\Delta \log(VL)$ with simple linear model:

$$\Delta \log(VL) = x_1 * VL + x_2 * \text{score}$$



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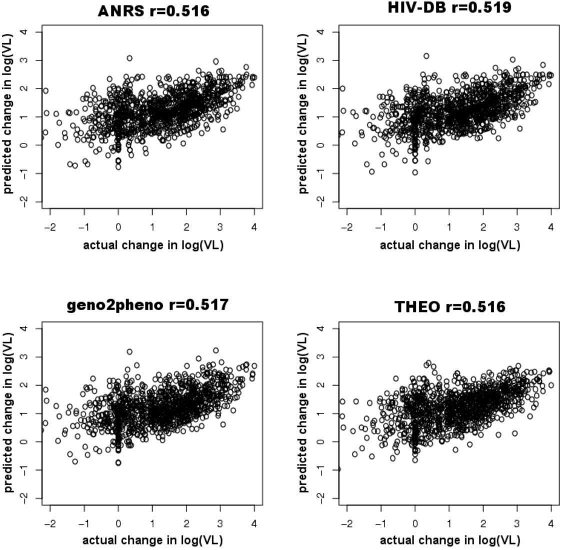

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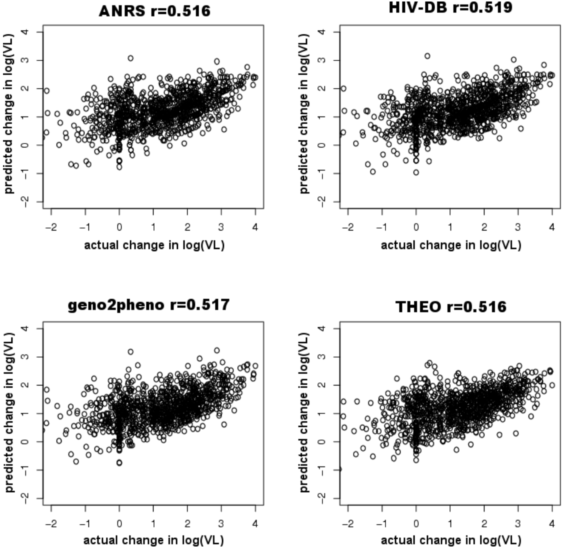
- THEO allows to include log(VL) as an additional feature into the statistical model



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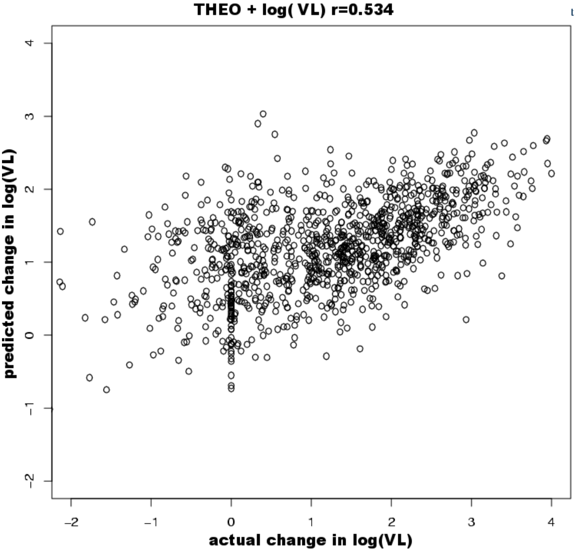
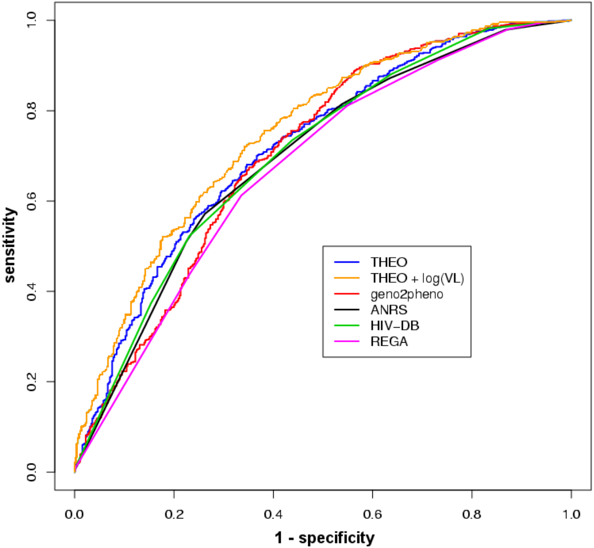


$$\boxed{\Delta \log(VL) = 0.58 * \log(VL) + 1.77 * THEO \; - 2.22}$$

Results - Classification

- Back to classification
- Methods perform equally well
- Slight advantage for THEO+log(VL)
- significantly better than ANRS ($p = 0.04883$) REGA ($p = 0.01953$) HIV-DB ($p = 0.04883$)
- pair-wise rank sum test



Conclusions

- PSS guided treatment selection works as well as GSS guided treatment selection
- No difference between methods in *typical treatment* situation
- Completely data-driven approach outperforms GSS/PSS in classification task
- THEO shows ≈ 20%-points improvement in sensitivity at same specificity (80%)
- On balanced subset ≈ 28%-points improvement
- THEO is part of the geno2pheno service and freely available for research purposes at www.geno2pheno.org

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