Phenotypic deconvolution: the next frontier in pharma

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July 2, 2015

About me and Open Analytics NV

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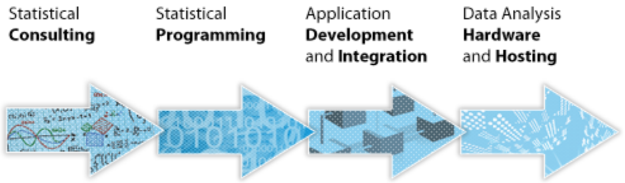


Statistical **Consulting**

Statistical **Programming**

Application **Development** and **Integration**

Data Analysis **Hardware** and **Hosting**

Architect

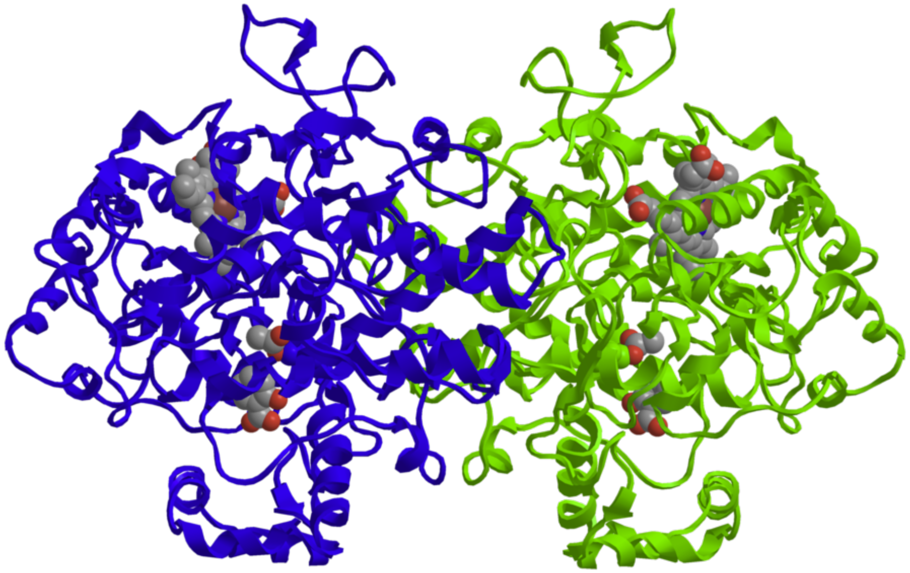
A data scientist's best friend

http://www.openanalytics.eu/architect

Pharma, the simple story

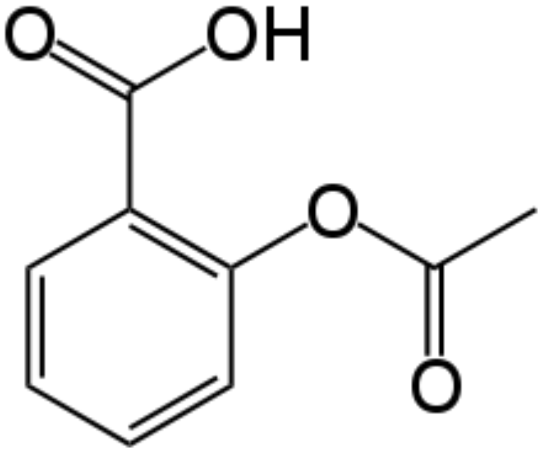
Protein target

- Focus on isolated disease related targets



Compound

- Screening for lead compounds
- Further optimization (chemical modification)
- Blockbuster drug



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Pharma, the true story

High failure rates in clinical trials

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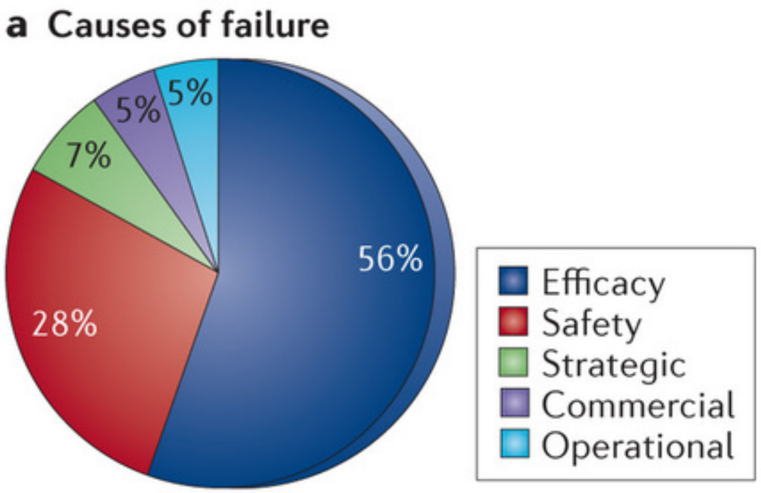
ARMS
INFORUM

Pharma, the true story

High failure rates in clinical trials

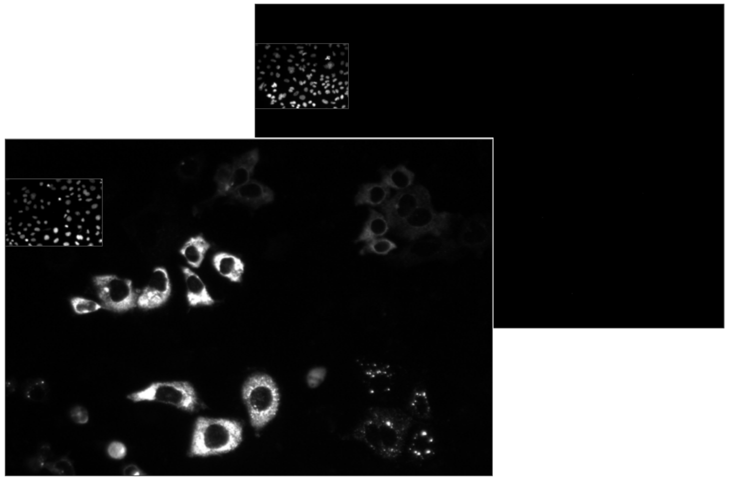
- Phase II success rates below 20%
- 84% of clinical trials fail due to efficacy and safety issues



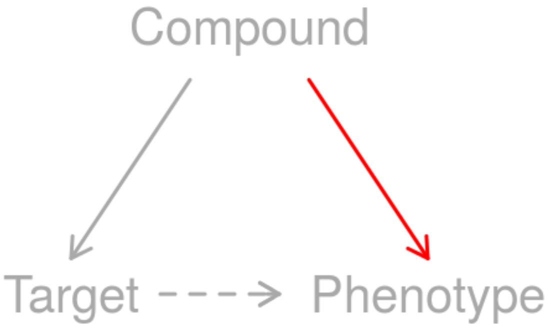
Arrowsmith, J. & Miller, P. Nat Rev Drug Discov, 2013

Phenotypic assays

- Attempt to reduce failure rates
- Compounds activity measured in different type of assay
  - Disease-relevant, multi-target, cellular context
  - Instead of classic assay: isolated target



Phenotypic high-content imaging assay

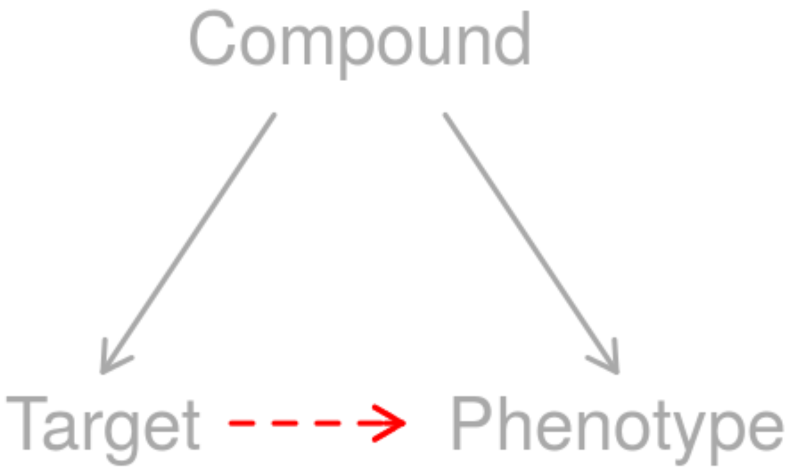


Compound

Target ---> Phenotype

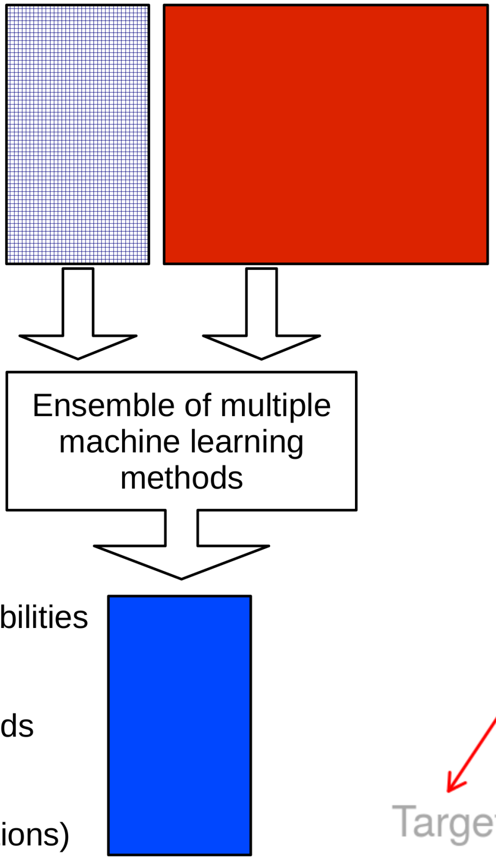
Phenotypic target identification

- Unknown mode of action in phenotypic assay
  - Required for further drug development
- Task: Identify targets that can best explain compound activity in phenotypic assay



Train data: Activity

Sparse (2%) matrix
1.5M compounds
x
2k targets
(x 5 concentrations)



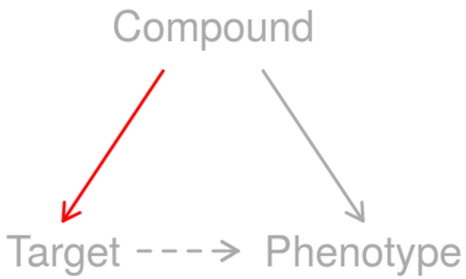
Features:
Molecular fingerprints

1.5M compounds
x
18 M substructures

Ensemble of multiple machine learning methods

Output: Probabilities

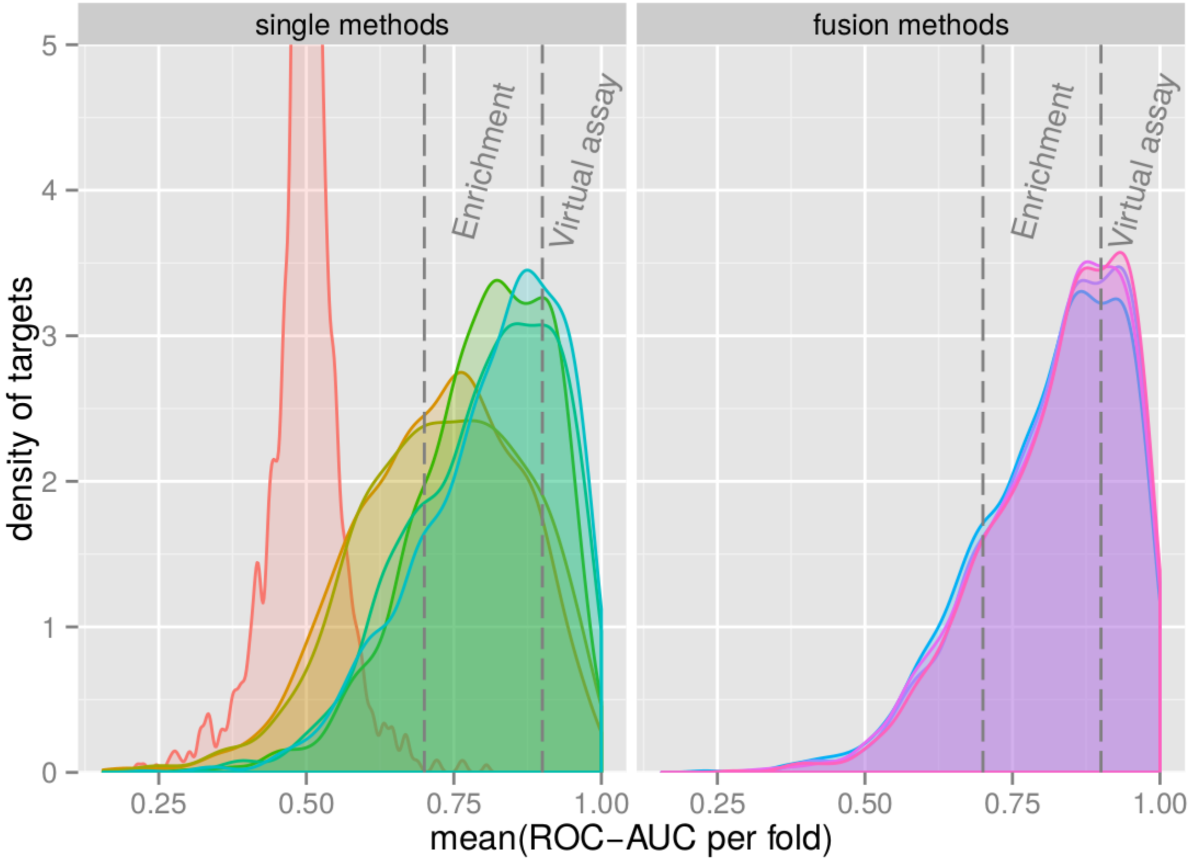
Dense matrix
1.5M compounds
x
2k targets
(x 5 concentrations)



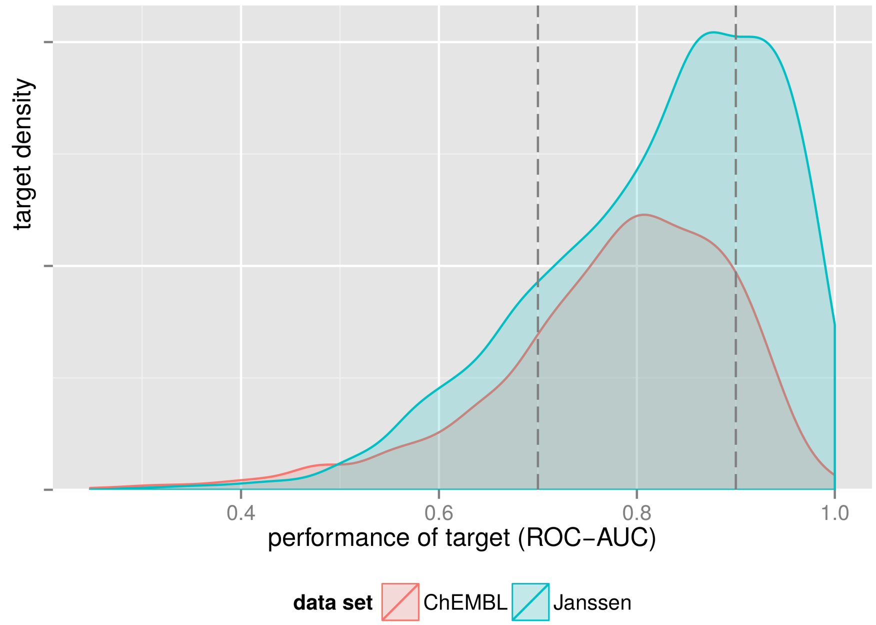
Compound

Target ---> Phenotype

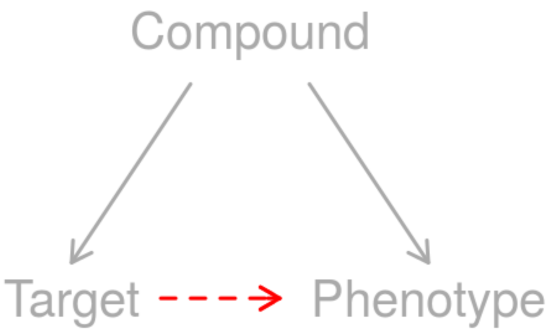
Ensemble of best classifiers



- Literature in chemogenomics field: only public data
- We use public + internal + commercial data
  - More (and better quality) train data
  - Better prediction quality
- Not all available methods were up to the task



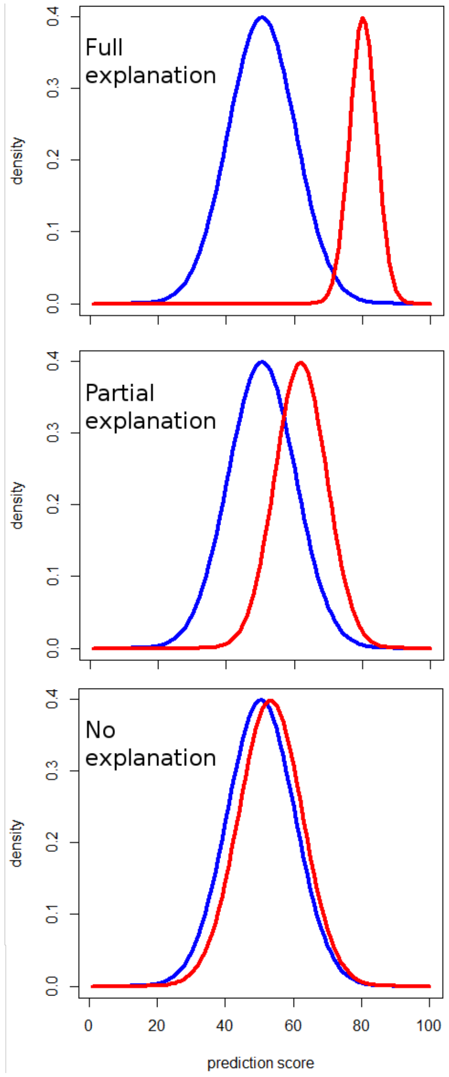
- How well does a target explain the phenotype?
  - ROC-AUC
- How well do multiple targets explain the phenotype?
  - Elastic net logistic regression (glmnet)
  - Random Forest (Boruta)



Compound

Target

Phenotype



Next steps

- Scientific:
  - Ongoing improvements of methods
  - Repeat benchmark with additional sampling
  - Publication(s)
- Operational:
  - Application in various disease areas
  - Now: experimental follow up
  - Iterative cycle of wet lab experiments and modeling

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Acknowledgements

Contributors

- University of Linz
  - Sepp Hochreiter
- University of Leuven
  - Yves Moreau
- IMEC
  - Roel Wuyts
- Arcadia
- Intel Corporation NV
- Janssen Pharmaceutica
  - R&D Discovery Sciences, Computational Sciences
- Open Analytics

Sponsors

- ChemBioBrige IWT
- Exascience IWT

Tak for din opmærksomhed!

Bonus material

Under the hood…

- **C++** (heavy work on "large matrix")
  - **Boost**
  - **TBB**
  - **JCompoundMapper**
- **Spark** on **YARN** (distributed runs for nested cross-validation)
- **R** (everything else, including analysis and postprocessing)
  - Faster, simpler and more elegant code : **data.table**
  - Target identification : **glmnet**, **Boruta**, **randomForest**
  - Reporting : **rmarkdown**