Alternative Metrics for Virtual Screening

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Nicholls A (2008) What do we know and when do we know it?
J Comput Aided Mol Des 22:239–255

Truchon J-F, Bayly CI (2007) Evaluating virtual screening methods: good and bad metrics for the ‘‘early recognition’’ problem.

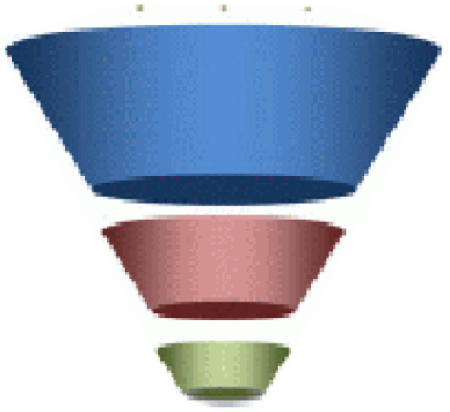
J Chem Inf Model 47:488–508

Agenda

- Virtual screening
- Existing quality measures
- Problems of measurement metrics
- Cost structure of virtual screening

What is Virtual Screening?

$5x10^6$ vendor library



Drug-like, mimetic, modeled, universal sets of compounds

Property space

Virtual screening

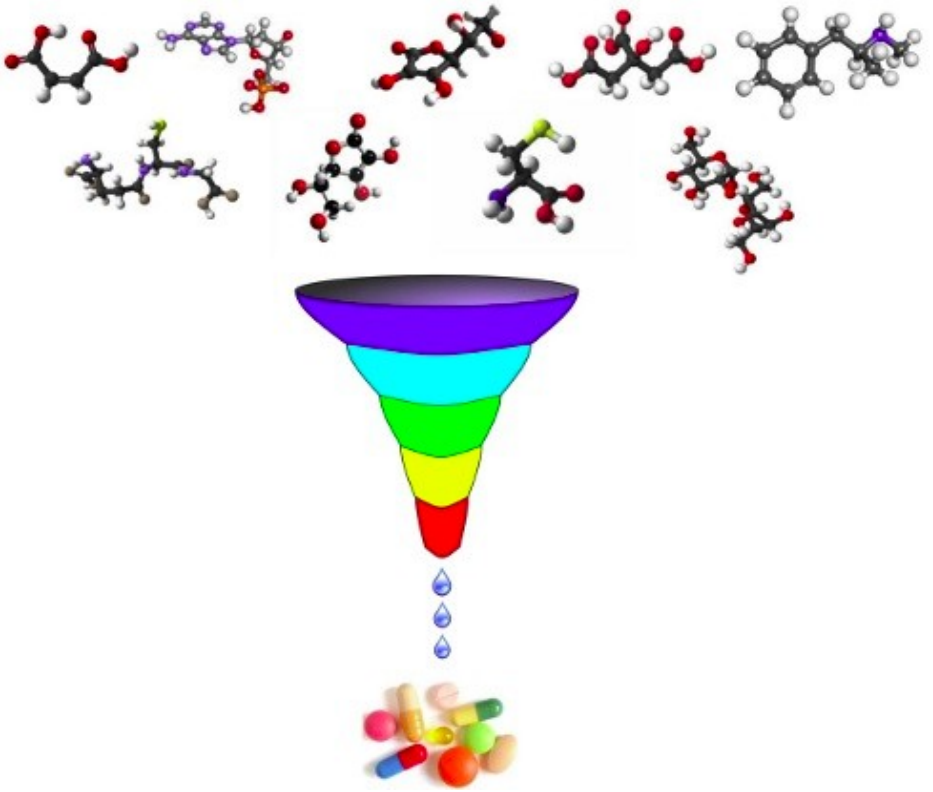
Focused library for physical screening

Computational technique to search libraries of small molecules in order to identify structures which are most likely to bind to a drug target

adapted from Krisztina Dobi Combination of 2D/3D Ligand-Based Similarity Search in Rapid Virtual Screening from Multimillion Compound Repositories.

What is Virtual Screening?

- Library of small molecules
- Protein receptor or enzyme
- Computational technique
- Evaluation metrics

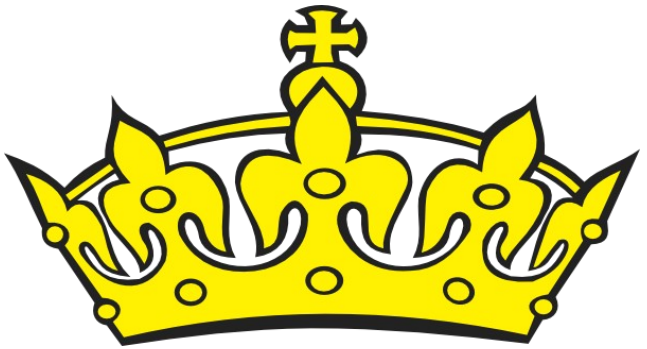


picture from Structural Bioinformatics Team Division of Structural and Synthetic Biology Center for Life Science Technologies 230-0045, Japan

What is expected from Virtual Screening?

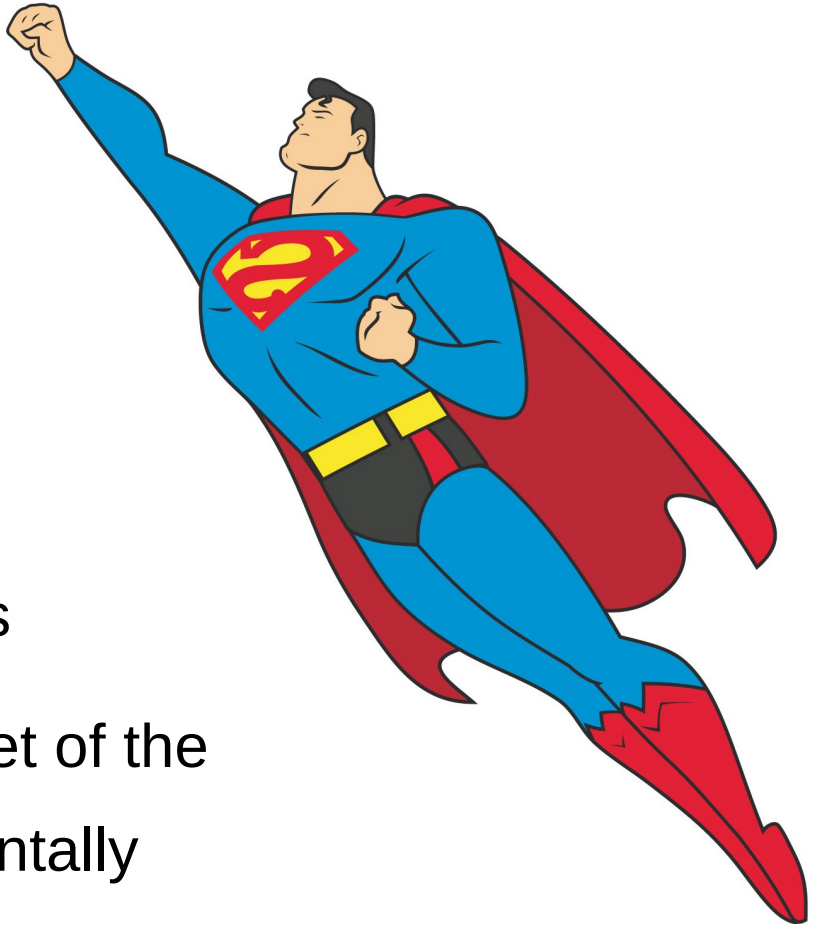
1. Approach works

2. Very small set of compounds will be tested experimentally



What is expected from Virtual Screening?

Early recognition



- Ranks actives very early
- Works with larger set of compounds
- Makes it possible that very small set of the compounds will be tested experimentally

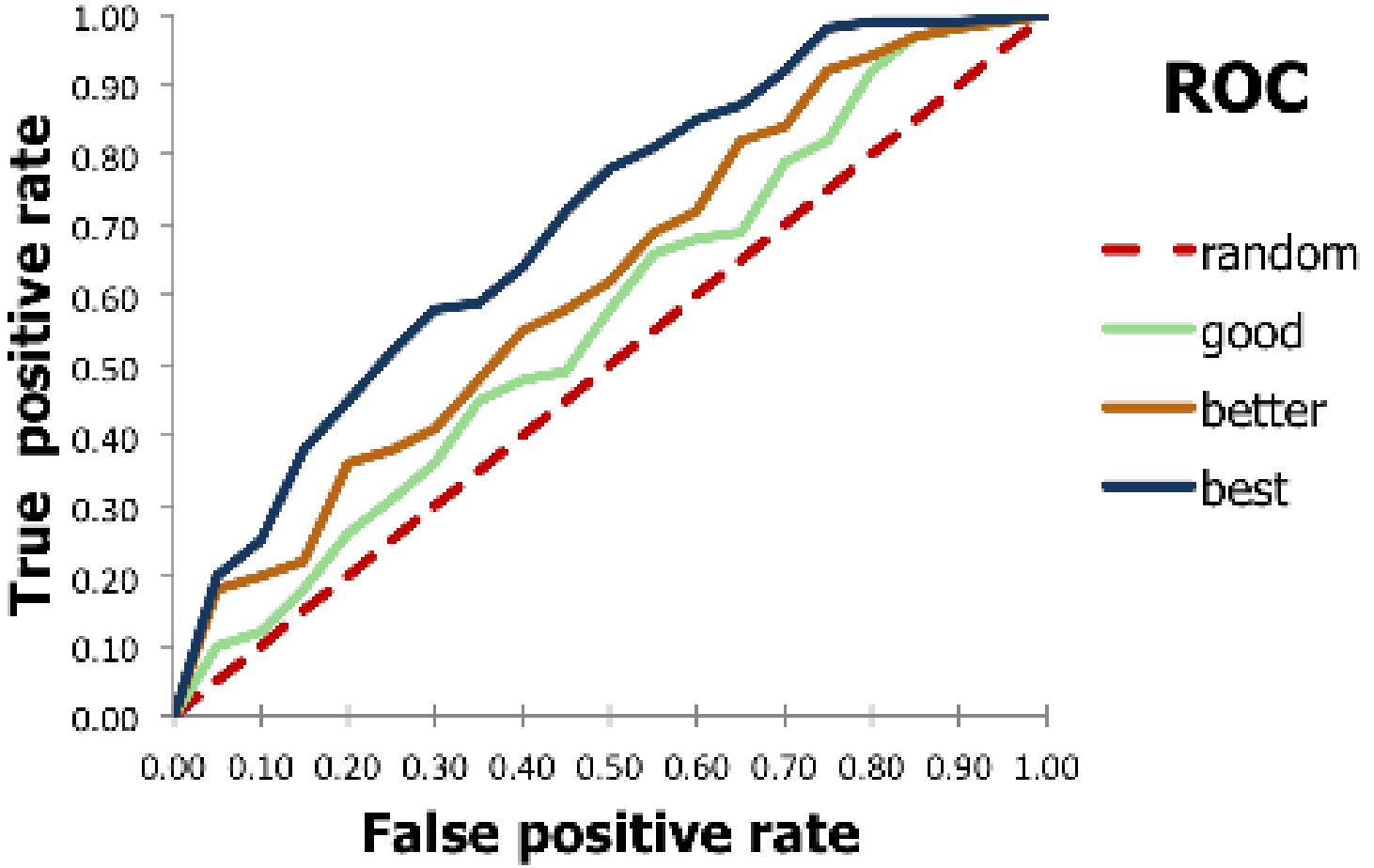
What is expected from Virtual Screening?

What about point 1 (Approach works) ?

Traditional Measures

- Area under Receiver Operating Characteristic
- Area under Accumulation Curve
- Enrichment Factor

Receiver operating characteristic (ROC)



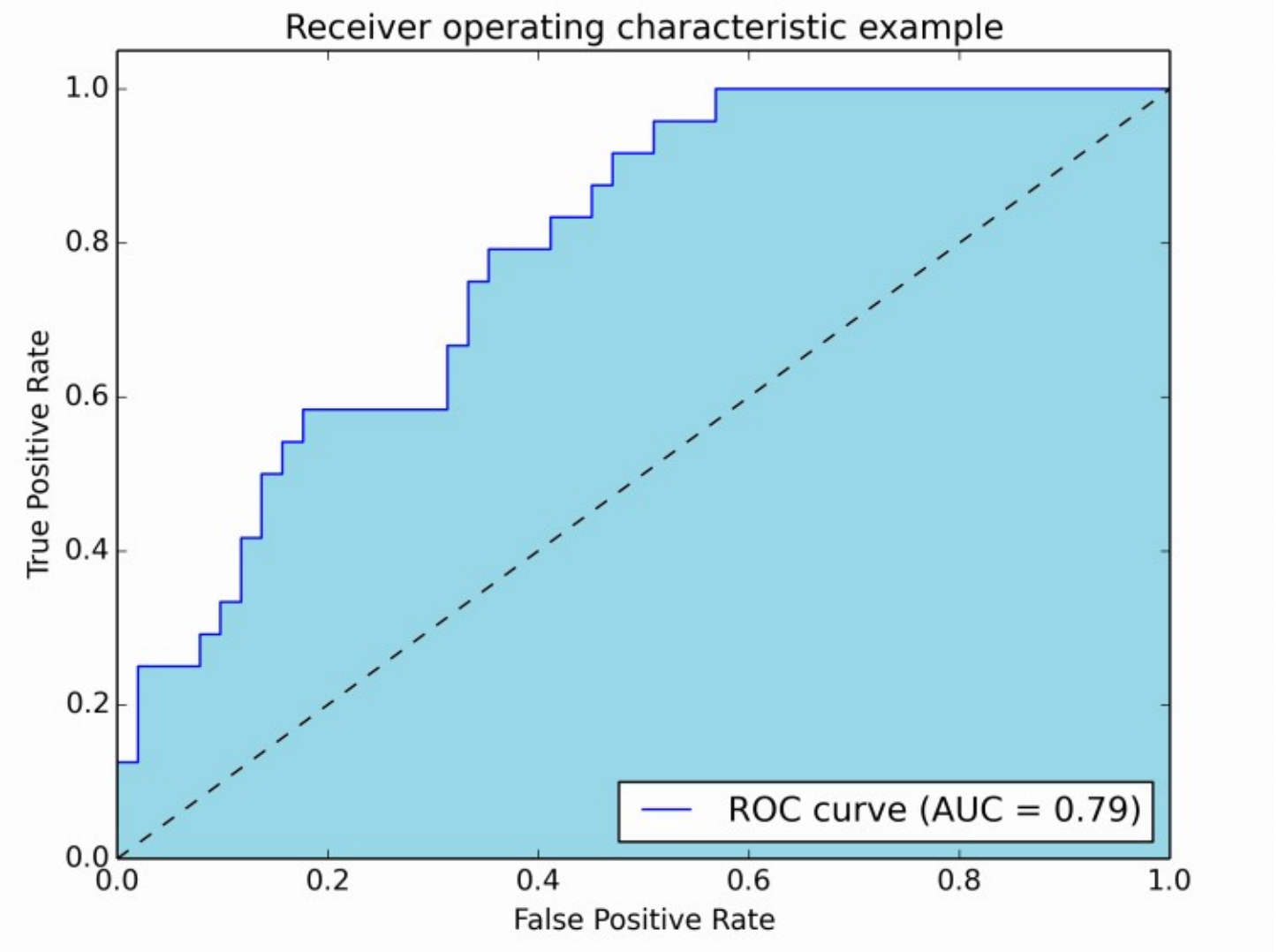
Receiver operating characteristic (ROC)

- **TP** – true positive
- **TN** – true negative
- **FP** – false positive
- **FN** – false negative

$$TPR = TP / \left(TP + FN \right)$$

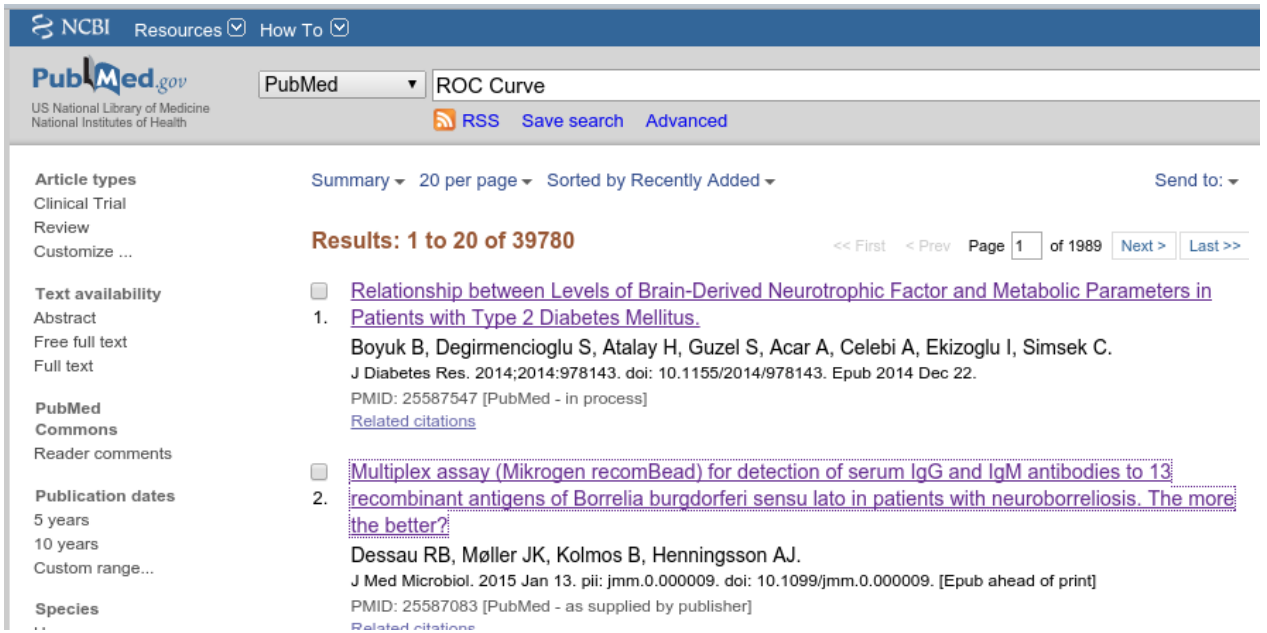
$$FPR = FP / \left(FP + TN \right)$$

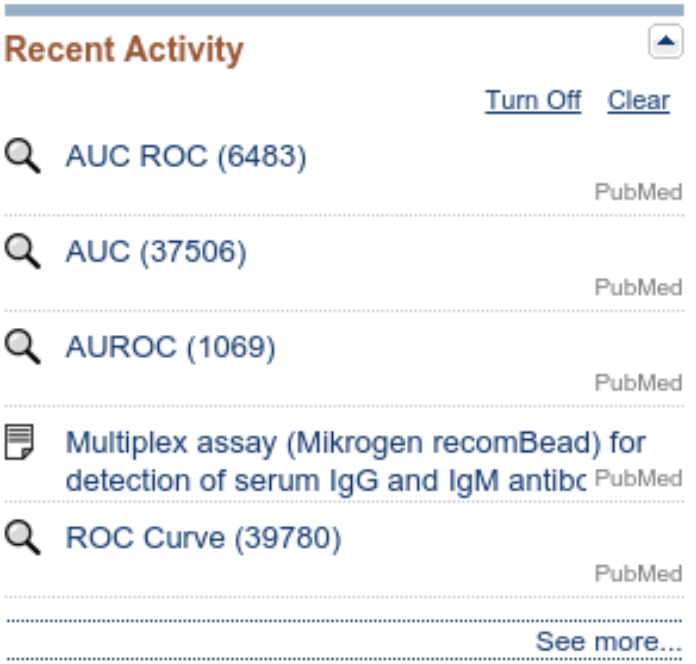
Area under ROC



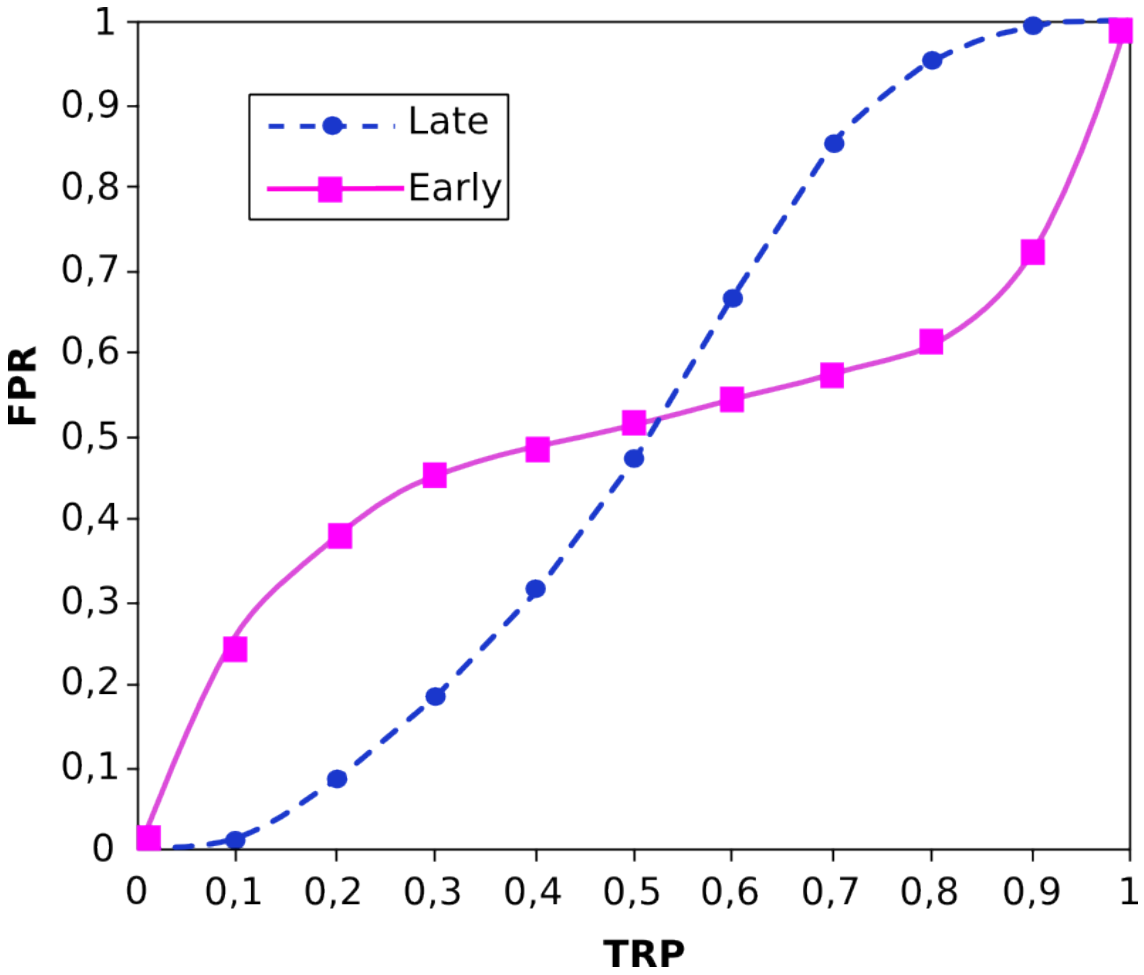
picture from scikit-learn.org, Example of Area under Receiver Operating Characteristic.

Area under ROC





Why is AUC not enough?



Area under ROC = 0.5

Alternatives

- Robust Initial Enhancement (RIE)
  - developed by Sheridan

- Boltzmann-Enhanced Discrimination of ROC (BEDROC)
  - developed by Truchon

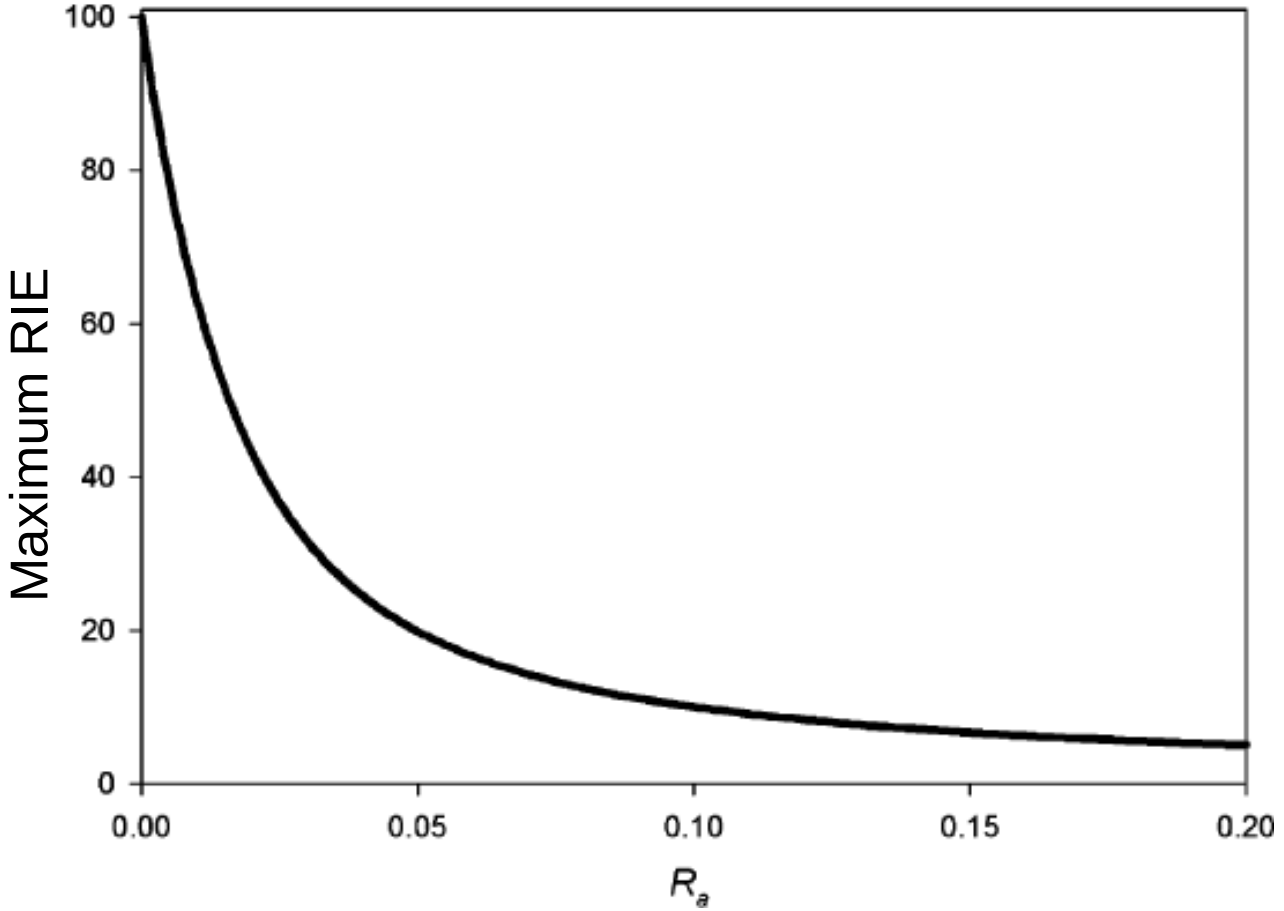
Robust Initial Enhancement (RIE)

$$RIE = \frac{\sum_{i=1}^{n} e^{\frac{-\alpha r_i}{N}}}{\left\langle \sum_{i=1}^{n} e^{\frac{-\alpha r_i}{N}} \right\rangle_r}$$

Metric using a continuously decreasing exponential weight as a function of rank

- r_i - is a rank of the *i*-th active
- N - is a number of elements
- n - is a number of actives
- α - is a exponential factor
- angle brackets means averaging
- subscript r means that it is over a uniform distribution.

Robust Initial Enhancement (RIE)



RIE maximum as a function of the ratio of actives R_a with α=100.

picture from Truchon J-F, Bayly CI (2007) Evaluating virtual screening methods: good and bad metrics for the ‘‘early recognition’’ problem.

Boltzmann-Enhanced Discrimination of ROC (BedROC)

$$BEDROC = \frac{RIE - RIE_{min}}{RIE_{max} - RIE_{min}}$$

Values from 0 to 1

RIE and BedROC Properties

RIE

- Gives early rankings more weight
- Weight depends on their position in the list
- Exponential factor
- Sensitive to the total number of inactives

- Normalized by RIE of a random distribution of actives

BedROC

- Gives early rankings more weight
- Weight depends on their position in the list
- Exponential factor
- Sensitive to the total number of inactives

- Normalization by the maximum dynamic range
- Values from 0.0 to 1.0

Are they perfect?

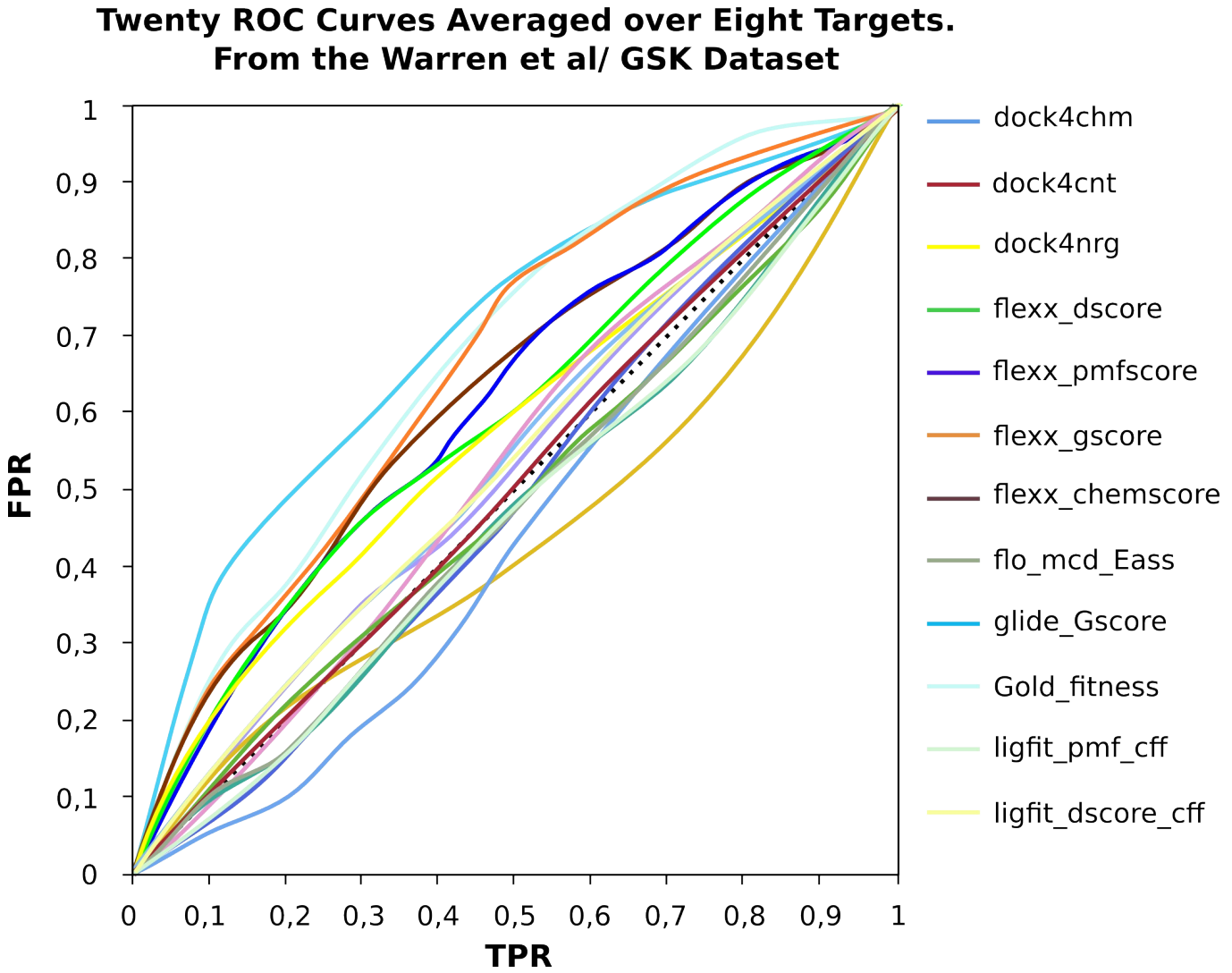
RIE

- Have RIE values a absolute meaning?
- Are RIE values interpretable?
- How good is the RIE value 5.35?

BedROC

- Have BedROC values an absolute meaning?
- BedROC scales the values from 0 to 1, how understandable is that?
- Can you compare BedROC values with different alpha-factors ?

Are they better as AUC?

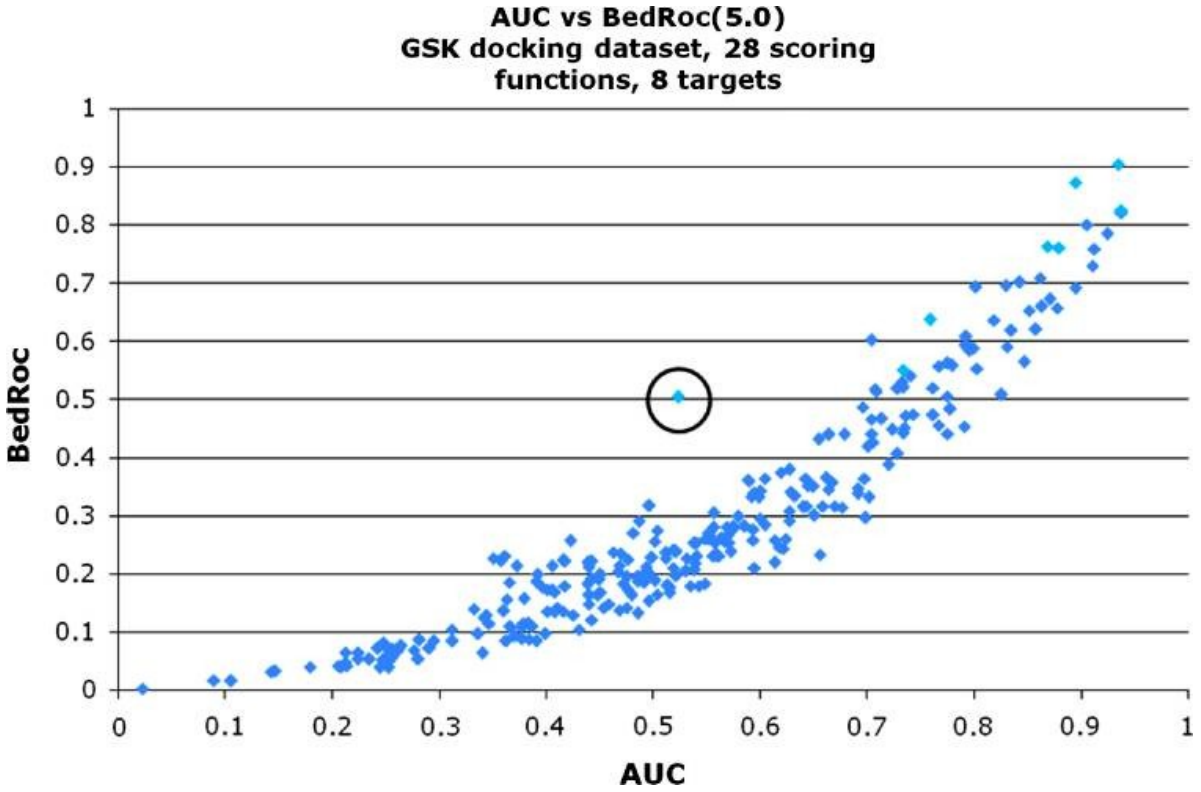


No biphasic nature.

Why there is no biphasic nature?

- The individual curves are not biphasic.
- The averaging dilutes this characteristic.

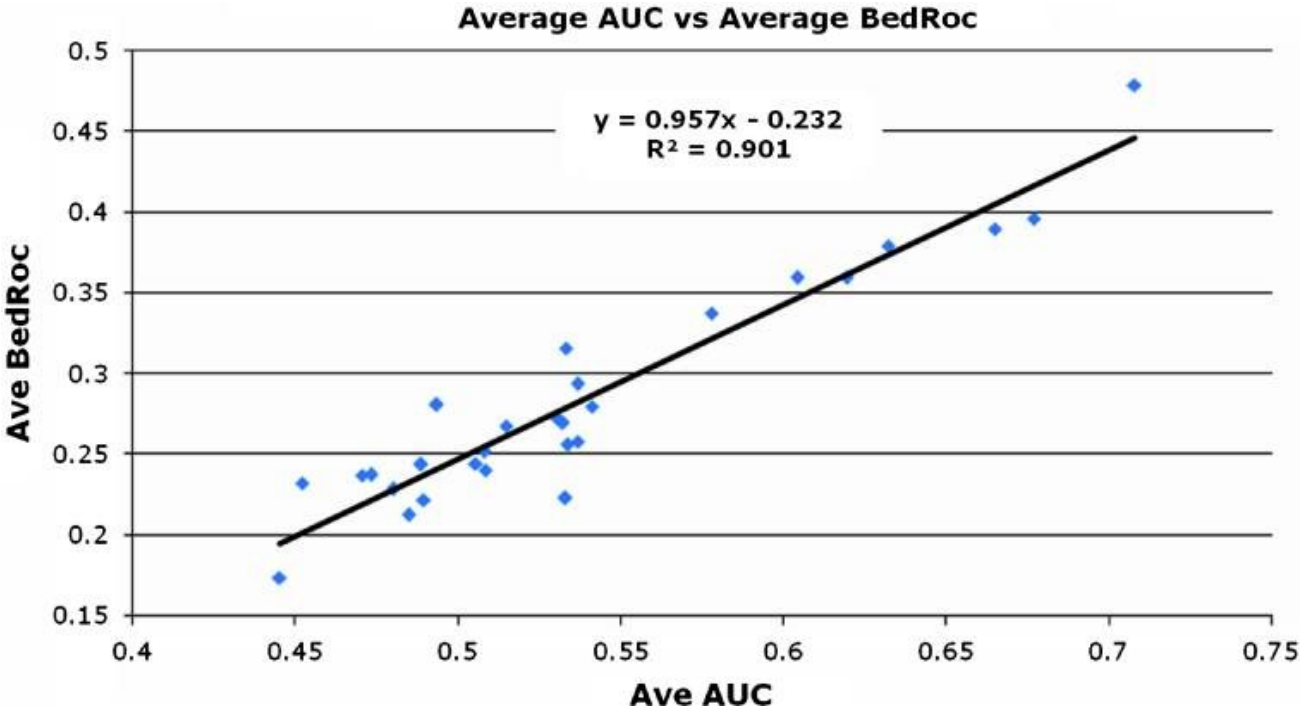
270 Virtual Screenings



- Low AUC
- High BedROC

No evidence for biphasic behavior

Average biphasic behavior?



The better the AUC value is, the better the BedROC value is (strongly correlated).

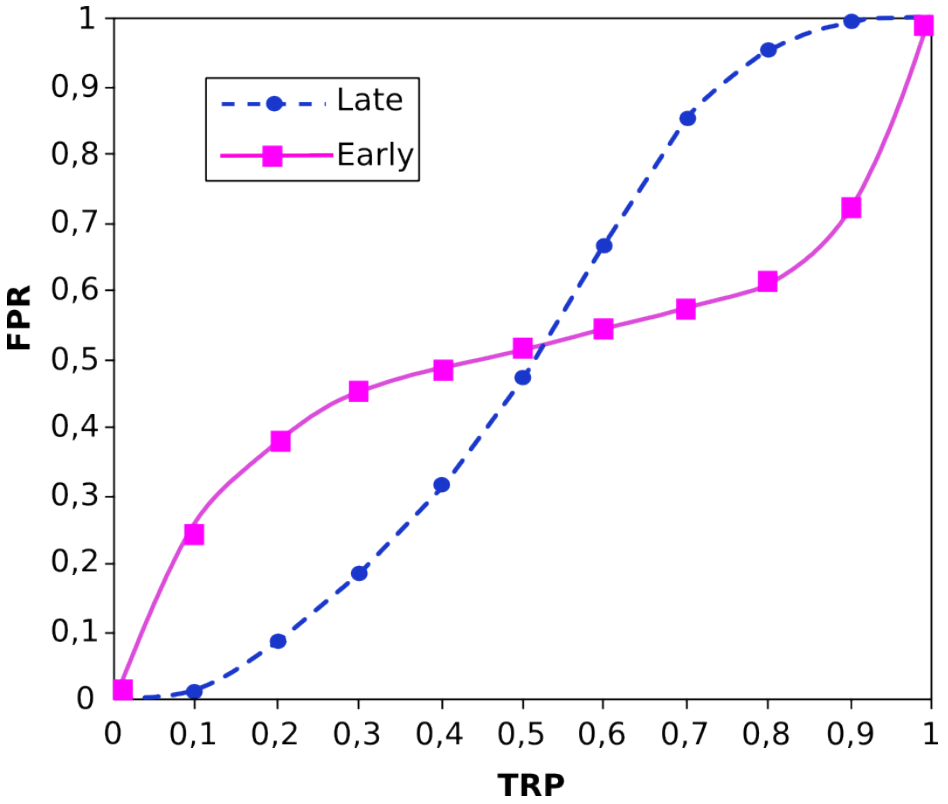
What does this mean?

- No evidence for biphasic nature
- The better the AUC value is, the better the BedROC value is
- In average case RIE and BedROC are not better than AUC

Is there something better?

- Practice-orientated
- Easy to understand

Gives an answer why the solid curve represents a better method than the dashed curve



Is there something better?

Cost structure of Virtual Screening

- Easy to understand
  - also for outsider
- Industry oriented

What is a cost structure of Virtual Screening?

- True positive values
- False positive values
- False negative values
- True negative values

What is a cost structure of Virtual Screening?

True positive values = successful diagnosis

- Fast results
- Saves time
- Saves money

What is a cost structure of Virtual Screening?

False positive values = false diagnosis

- Costly tests
- Waste of time
- Waste of money

What is a cost structure of Virtual Screening?

False negative values = more severe condition develops

- May cost a lot
- Waste of time
- Waste of money

What is a cost structure of Virtual Screening?

True negative values – no false diagnosis

- Saves money
- Saves time

What is a cost structure of Virtual Screening?

To transform ROC into real costs we need:

- Expected number of actives and inactives
- Or the ratio of the two

Cost structure of Virtual Screening

- True positives = 8.0
- True negatives = 0.02
- False positives = -0.16
- False negatives = -2.0

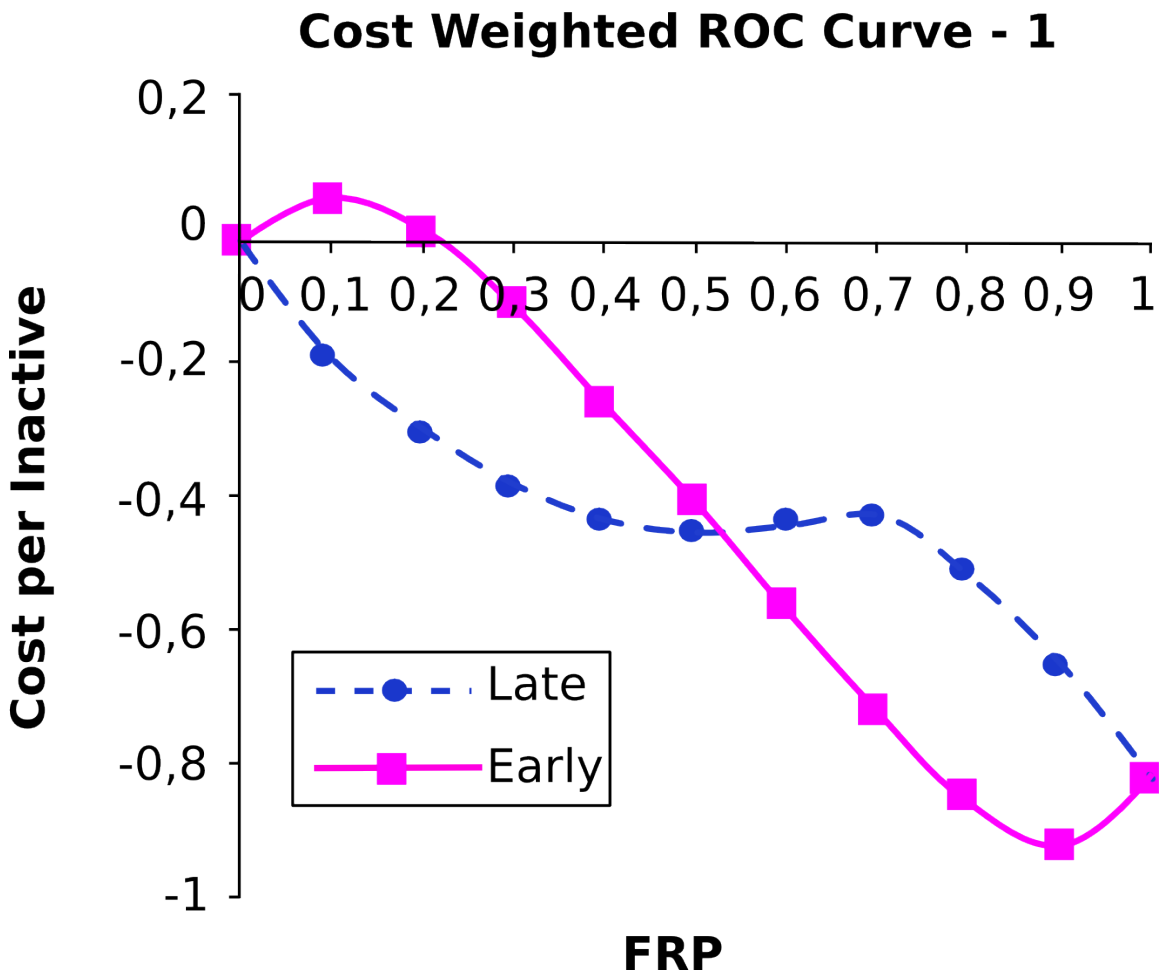
$$Cost(t) = TPR \times N_a \times (8.0) + (1 - TPR) \times N_a \times (-2.0) + FPR \times N_i \times (-0.16) + (1 - FPR) \times N_i \times (0.02)$$

Cost structure of Virtual Screening

$$N_a/N_i = 1/100$$

$$Cost(t)/N_i = 0.10 \times TPR - 0.18 \times FPR$$

Cost weighted versions of ROC



- TP = 8.0
- FN = −2.0
- FP = −0.16
- TN = 0.02

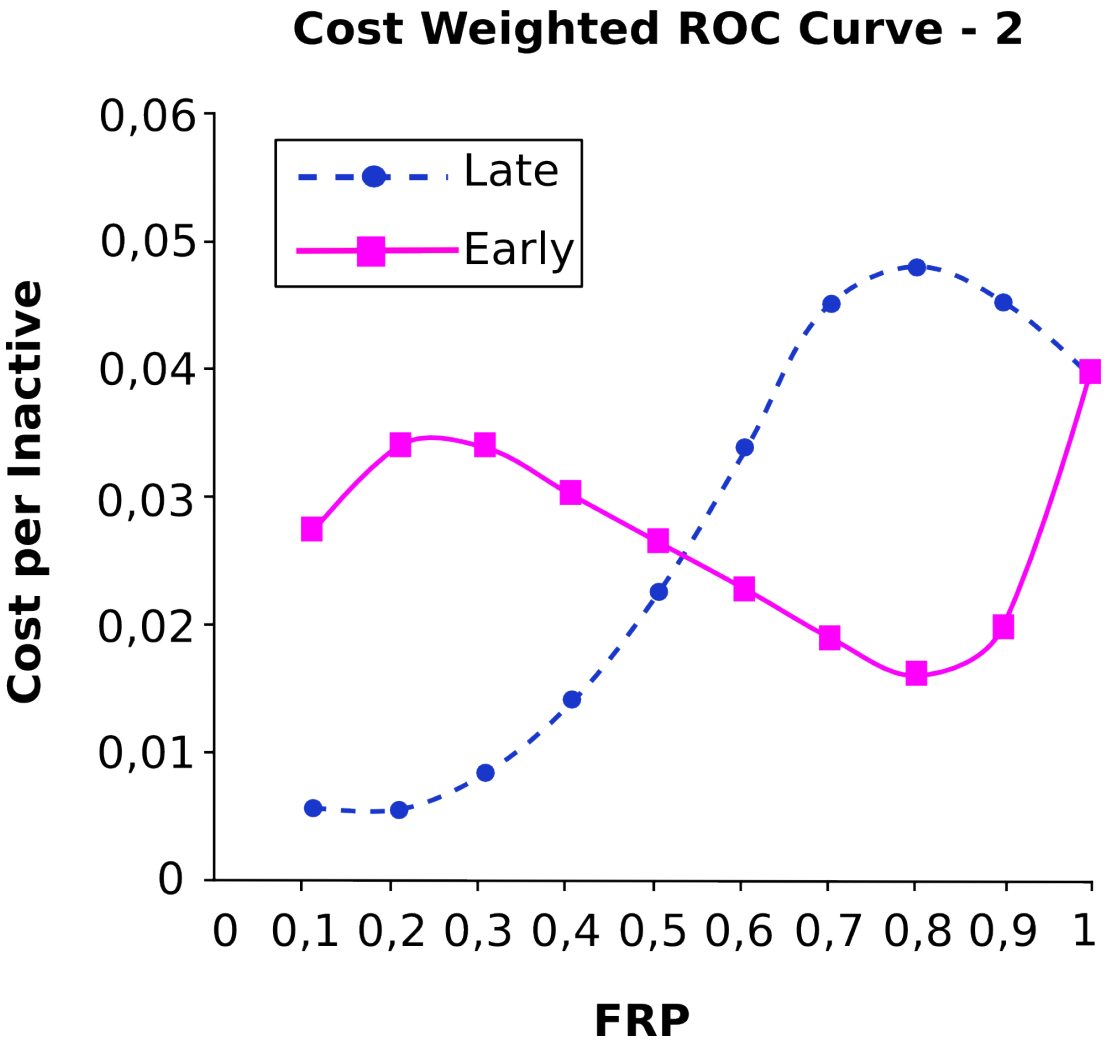
$$Cost(t)/N_i = 0.1 \times TPR - 0.18 \times FPR$$

What does this mean?

Early recognition is better as late recognition

Late recognition ist never cost effective

Reducing the cost of a FP by 75%



- TP = 8.0
- FN = −2.0
- FP = −0.04
- TN = 0.03

$$Cost(t)/N_i = 0.1 \times TPR - 0.07 \times FPR + 0.01$$

What does this mean?

By reducing the cost of a false positive by 75% late recognition is also cost effective.

Assumptions

- These examples are obviously only illustrative.
- Early recognition is important only because of an assumed cost structure.

Summary

- Virtual screening is an important part of a drug-discovery
- Metrics for Virtual Screening are the common problem
- Cost structure of Virtual Screening might be a solution
- This is an open field for research