# Performing Fast and Accurate Virtual High-Throughput Screening

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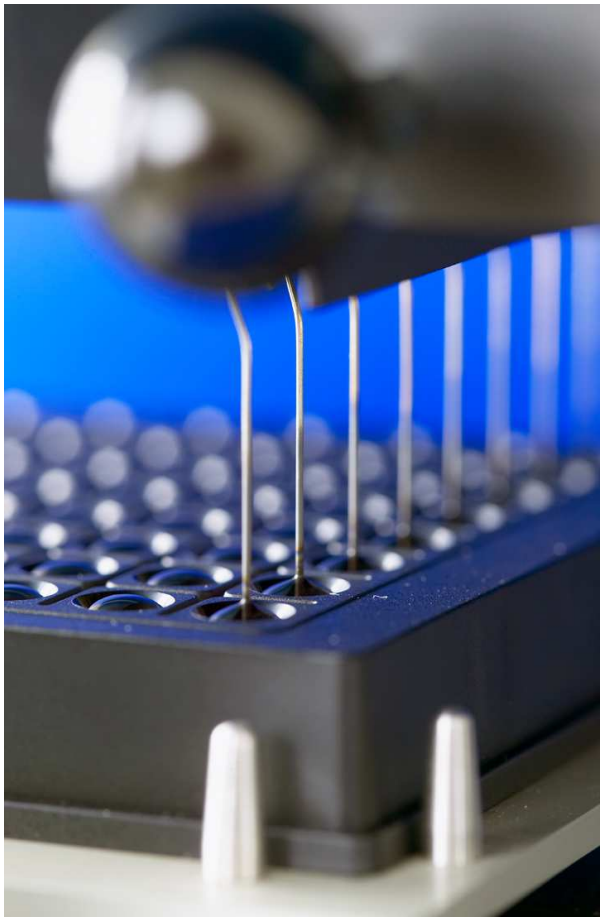
# High-Throughput Screening

- Assay a large library of potential drugs against their target
- Very costly

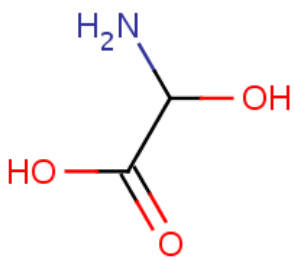


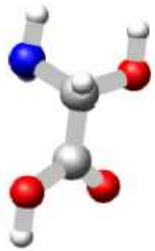
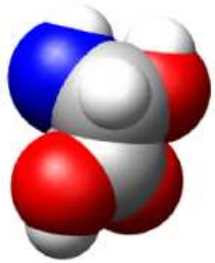
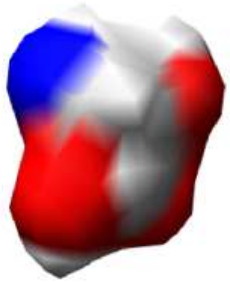
# Virtual High-Throughput Screening

- Cost-effective, in silico complement of experimental HTS
- Predict the activity of new compounds

# Representing Chemicals *in silico*

- Finding molecular descriptors that encapsulate the necessary information is hard
- Expert knowledge may be incomplete
- We need a representation that is *"complete"* enough.



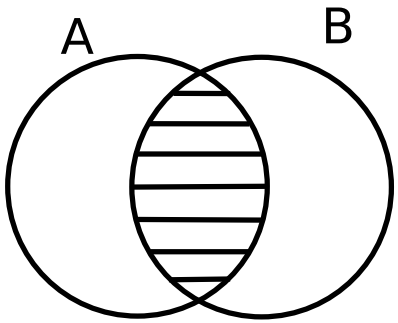




# Feature Vectors based on Structural Information

- Define *feature vectors* that record the presence/absence (or number of occurrences) of particular substructures in a given structure
- $$\phi(A) = (\phi_s(A))_{s \text{ substructure}}$$

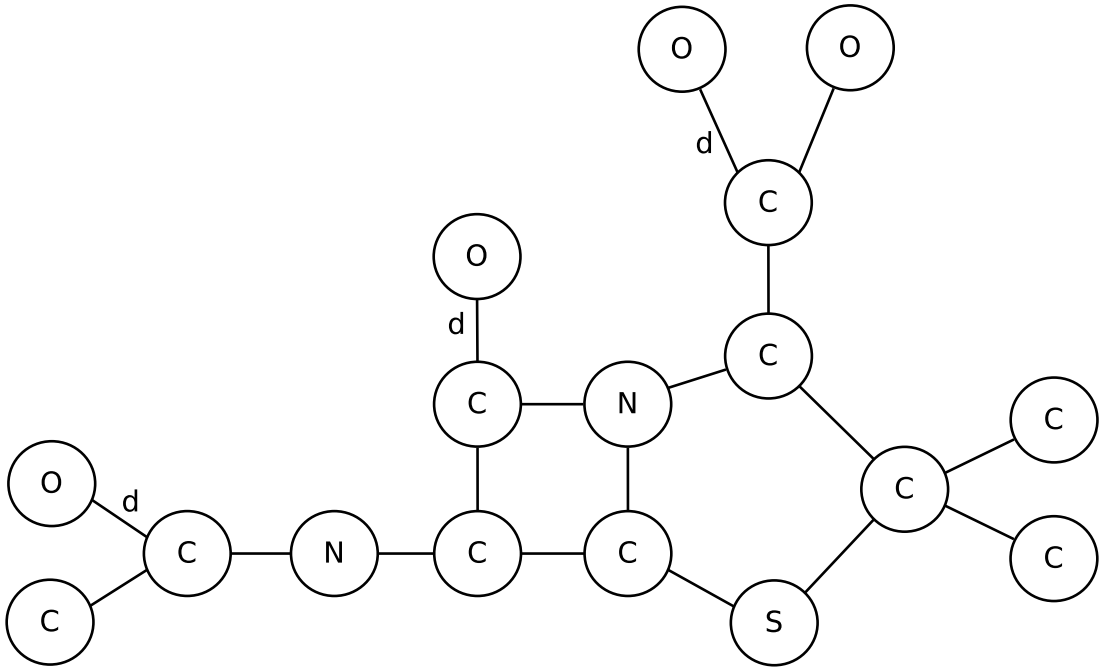
  where
  $$\phi_s(A) = \begin{cases} 1 & \text{if } s \text{ occurs in } A \\ 0 & \text{otherwise} \end{cases}$$
- Extension of traditional chemical fingerprints

# Tanimoto and MinMax Similarities




- Tanimoto (binary setting): $k(A,B) = \frac{A \cap B}{A \cup B}$
- MinMax (counts setting): $\frac{\sum_{i=1}^{N} \min(A_i, B_i)}{\sum_{i=1}^{N} \max(A_i, B_i)}$
- Kernel $\rightarrow$ SVMs

# Molecular Graph



# Two-Dimensional Substructures

- Labeled sub-paths (walks)

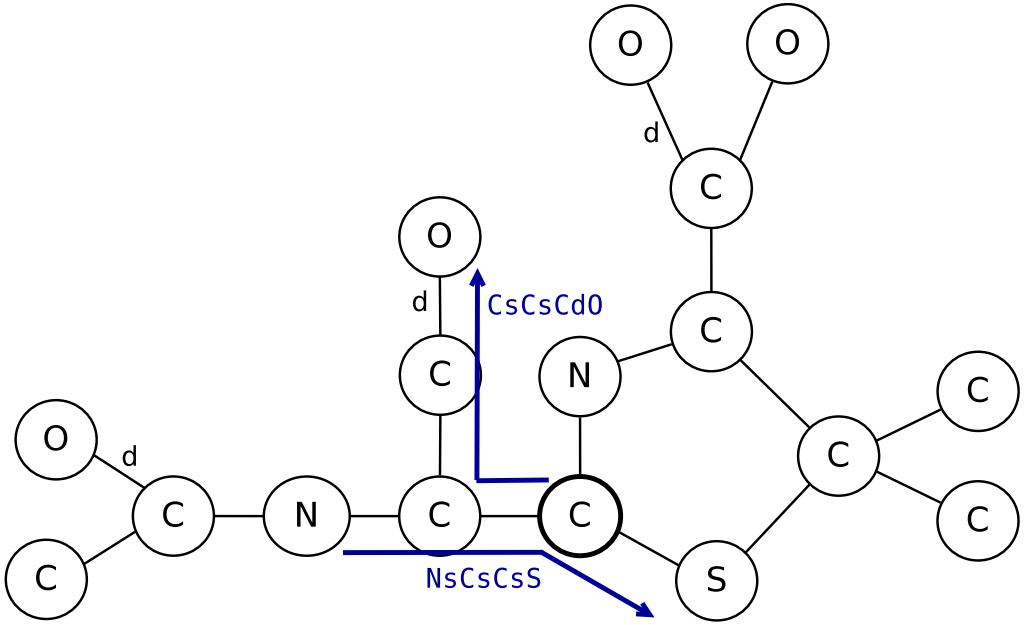



Figure: Some sub-paths of depth 3

# Two-Dimensional Substructures II

- Labeled sub-trees - Extended-Connectivity (or Circular) features

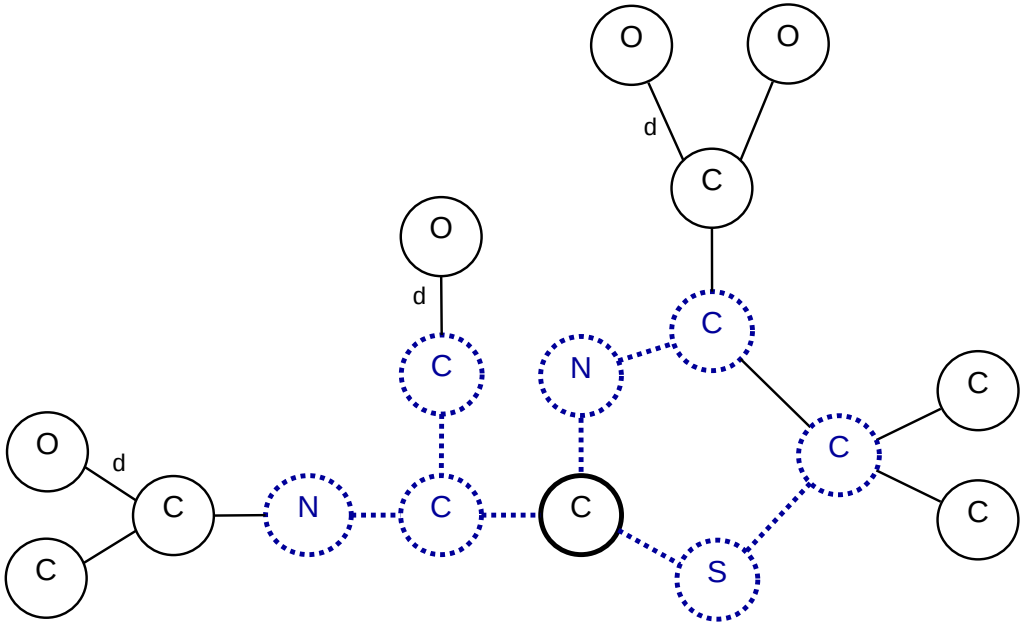
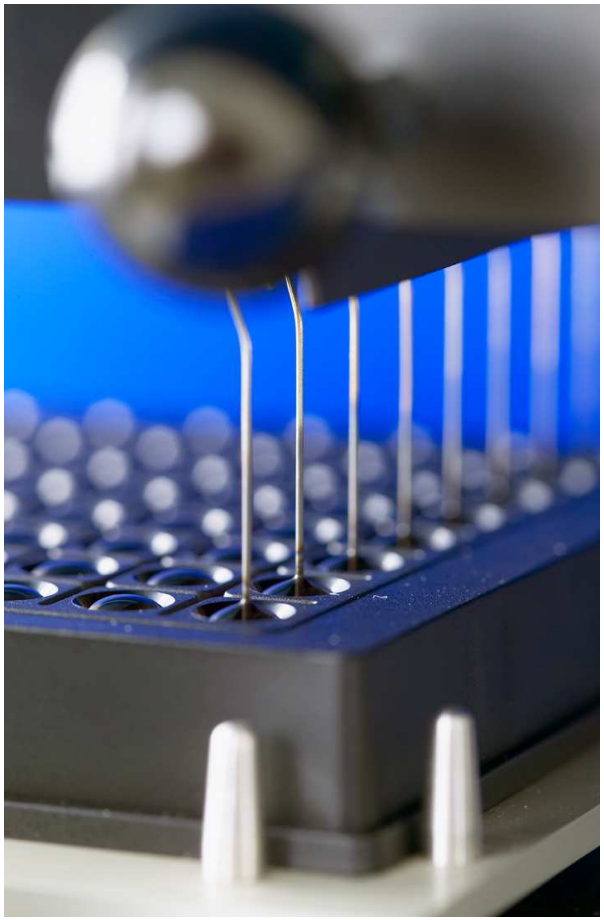



Figure: Example of a circular substructure of depth 2

# High-Throughput Screening

Back to vHTS...



# State-of-the-art

- Max-Sim

$$f(X) = max_{A_i \in \mathcal{A}} k(X, A_i)$$

- kNN

$$f(X) = \frac{|\mathcal{A} \cap \mathcal{N}(X)|}{k}$$

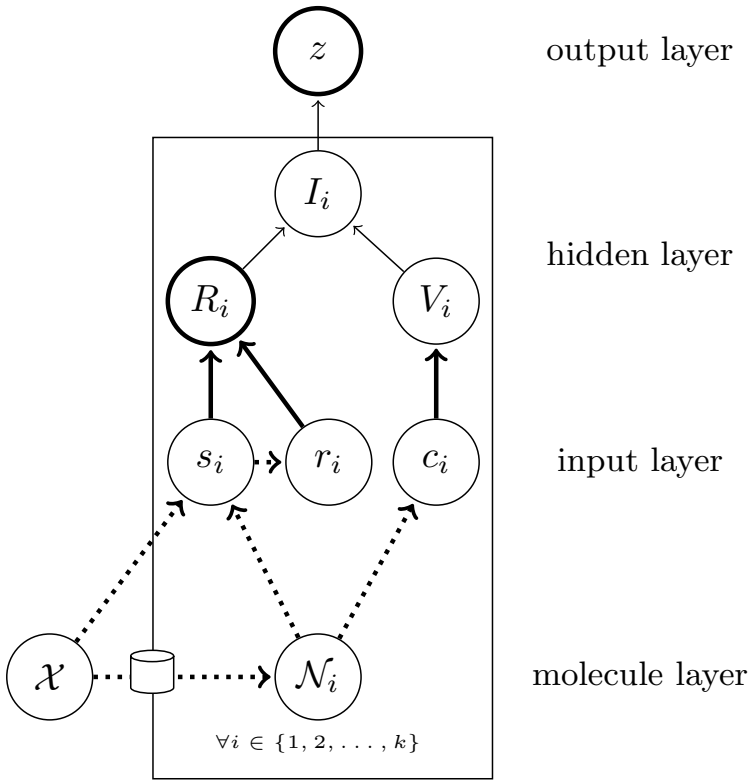
- SVM

$$f(X) = \sum_{i=1}^{n} a_i k(X, X_i) + b$$

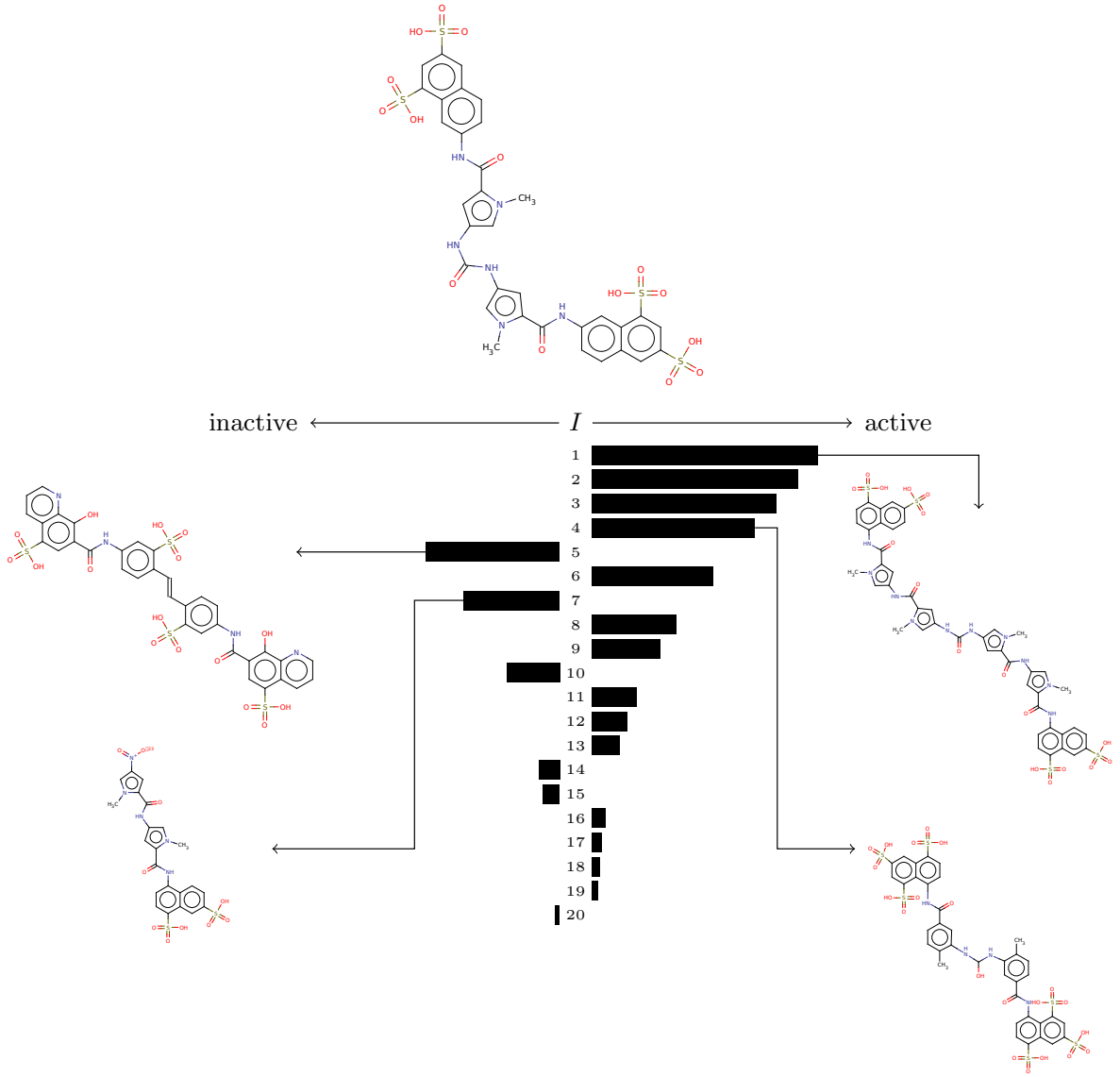
# The Influence Relevance Voter

(Joint work with Josh Swamidass)

- k-Nearest Neighbors
- Neural network on top
- Similarity: MinMax on 2D structural fingerprints



# Interpretability



# Benchmarked Performance

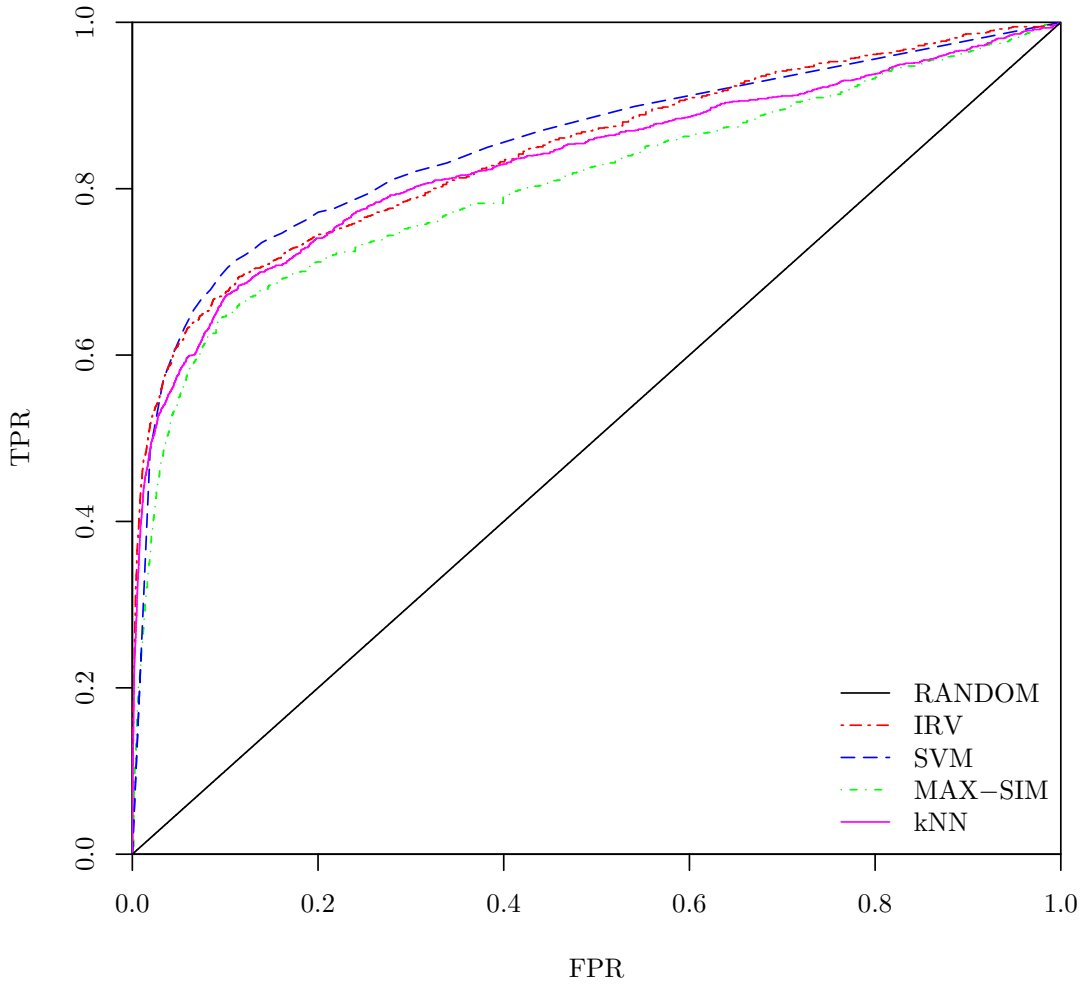
HIV data (IJCNN07 Challenge):

- train: 4,229 compounds (149 actives)
- test: 38,449 compounds (1,354 actives)

| | BER | AUC |
|---|---|---|
| IJCNN07 | 0.283 | 0.771 |
| SVM | 0.269 | 0.764 |
| IRV | 0.271 | 0.762 |
| kNN | 0.276 | 0.747 |
| MAXSIM | 0.283 | 0.739 |

# Early Recognition (HIV)

## ROC Curves



# Early Recognition

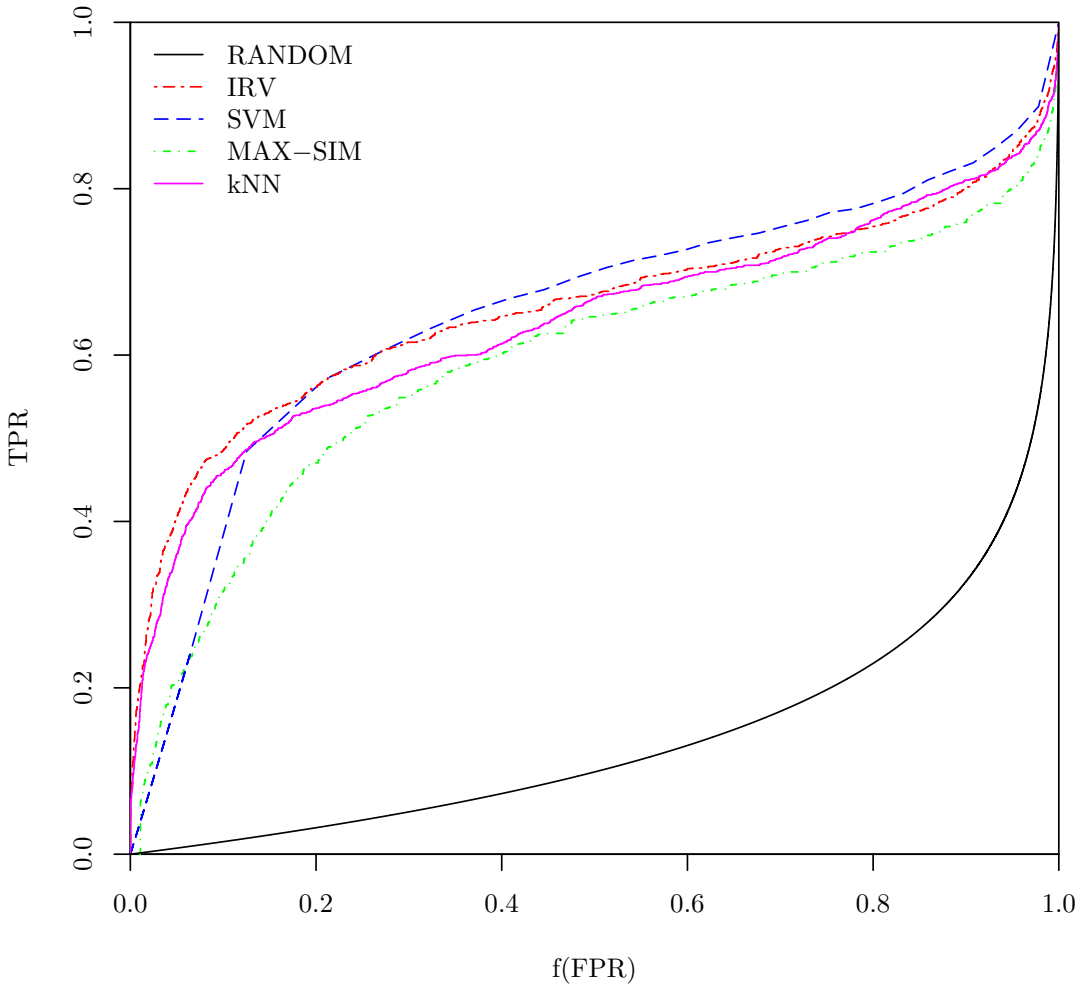
- Rank active compounds early
- $\rightarrow$ Magnify corresponding portion of the curve
  $f : [0, 1] \rightarrow [0, 1]$, continuous, concave down

$$\frac{1 - e^{-\alpha x}}{1 - e^{-\alpha}} \qquad x^{1/(\alpha+1)} \qquad \frac{log(1 + \alpha x)}{log(1 + \alpha)}$$

- $\rightarrow$ Concentrated ROC (CROC) curves

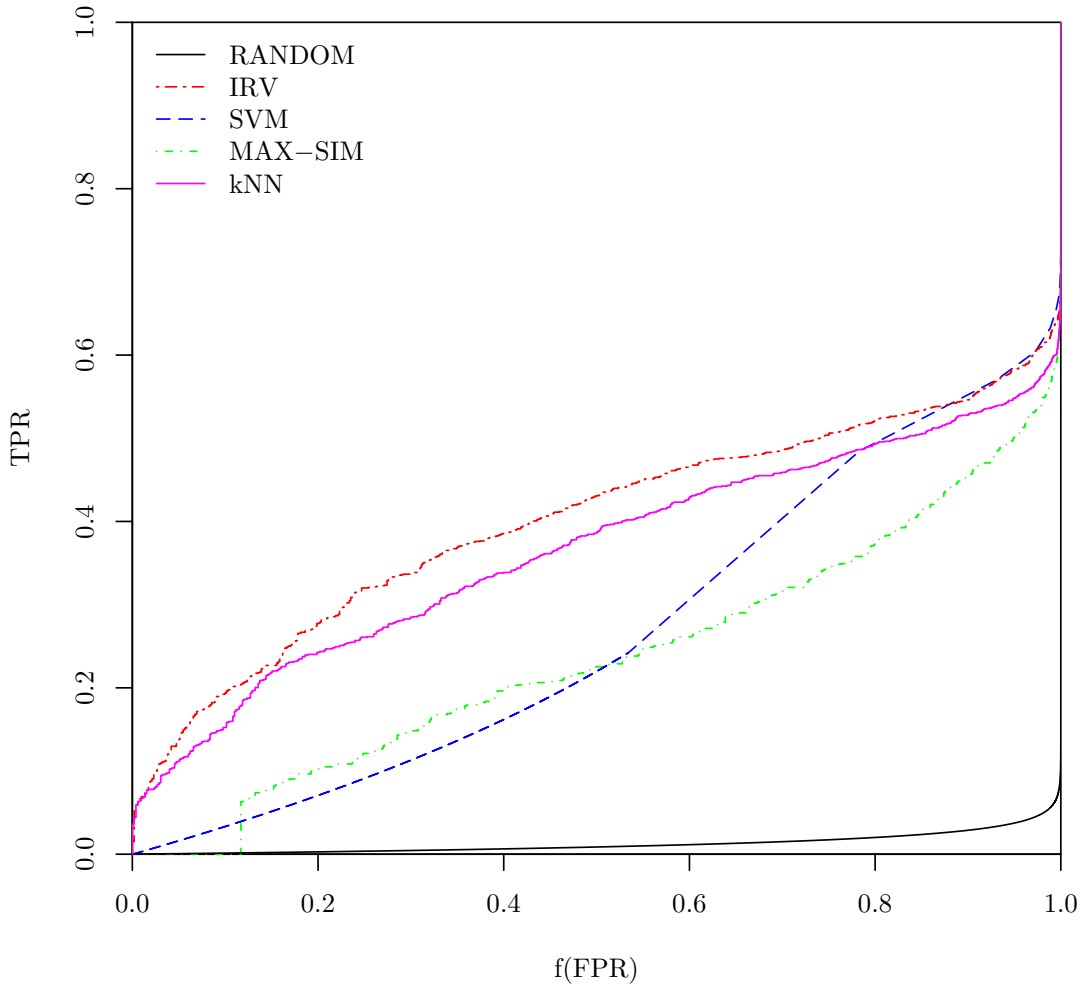
# Early Recognition (HIV)

## CROC Curves ($\alpha = 7$)



# Early Recognition (HIV)

## CROC Curves ($\alpha = 80$)



# Early Recognition (HIV)

| | ROC | CROC ($\alpha = 7$) | CROC ($\alpha = 80$) |
|---|---|---|---|
| SVM | 0.852 (± 0.004) | 0.644 (± 0.003) | 0.310 (± 0.006) |
| kNN | 0.832 (± 0.003) | 0.638 (± 0.004) | 0.365 (± 0.005) |
| IRV | 0.845 (± 0.002) | 0.656 (± 0.003) | 0.400 (± 0.004) |

# Statistical Significance

- Significance of the observed difference in CROC performance?
- Permutation test:
  - pool the ranks of the actives from both methods
  - repeatedly partition them at random into equally sized sets of ranks
  - p-value = fraction of sampled differences in performance greater than the observed difference

| | SVM vs. IRV | kNN vs. IRV |
|---|---|---|
| ROC | 0.094 | 0.094 |
| pROC | 0.016 | 0.025 |
| CROC ($\alpha = 7$) | 0.001 | 0.055 |
| CROC ($\alpha = 80$) | 0.002 | 0.010 |

# Maximizing Early Retrieval

- After each epoch, reweight the training examples
- Give higher weights to higher ranked examples
- Initialize at 1/N
- Weight Update Schemes:

$$w_{t+1}(r) = Ce^{-\gamma r(t)} \qquad w_{t+1}(r) = \frac{C}{r(t)^{\gamma+1}}$$

- Multiply by density of the scores in the neighborhood

$$w_{t+1}(r) = Ce^{-\gamma r(t)} g(r) \qquad w_{t+1}(r) = \frac{C}{r(t)^{\gamma+1}} g(r)$$

- Increase $\gamma$ at each epoch $\rightarrow$ avoid getting stuck in local minima by starting with low values of $\gamma$

# Maximizing Early Retrieval

- Exponential weighting scheme: performance about the same, but convergence sped up (from 100 to 4-8)
- Power weighting scheme

| | AUC[CROC] ($\alpha = 7$) | | |
|---|---|---|---|
| | $w_r = 1$ | $w_r = 1/r$ | $w_r = g(r)/r$ |
| 1 iter | 0.569 | 0.598 | 0.611 |
| 3 iters | 0.641 | 0.646 | 0.652 |
| convergence | 0.660 | 0.660 | 0.661 |

# Conclusion

- New vHTS algorithm, the IRV
  - Suitable for early recognition
  - Achieves state-of-the-art performance
  - Interpretable underlying inferences
  - Probabilistic semantic of the output predictions
  - Short training time
- New early recognition evaluation method, the CROC
  - CROC curve (visualization)
  - Area under the CROC curve (performance measure)
  - CROC optimization

# Future Directions

- Apply the IRV to non-biological data (e.g. information retrieval)
- Incorporate more information in the IRV
- Learning algorithms that optimize the area under the CROC curve


S. J. Swamidass, C.-A. Azencott, T. -W. Lin, H. Gramajo, S. Tsai, and P. Baldi.
The Influence Relevance Voter: An Accurate And Interpretable Virtual High-Throughput Screening Method,
*J. Chem. Inf. Model*, March 2009


S. J. Swamidass, C.-A. Azencott, K. Daily, and P. Baldi.
A CROC Stronger than ROC: Measuring, Visualizing, and Optimizing Early Retrieval,
*Bioinformatics*, accepted with minor revisions

Acknowledgements

- Dr. S. Joshua Swamidass and Prof. Pierre Baldi
- OpenBabel and OpenEye Scientific Software Academic Licences; SVMTorch implementation; ROCR package for R.
- NIH/NLM Biomedical Informatics Training Grant; NSF Grants 0321290 and 0513376; Microsoft Research Award to PB; IBM PhD Fellowship to CA.

Thank you!