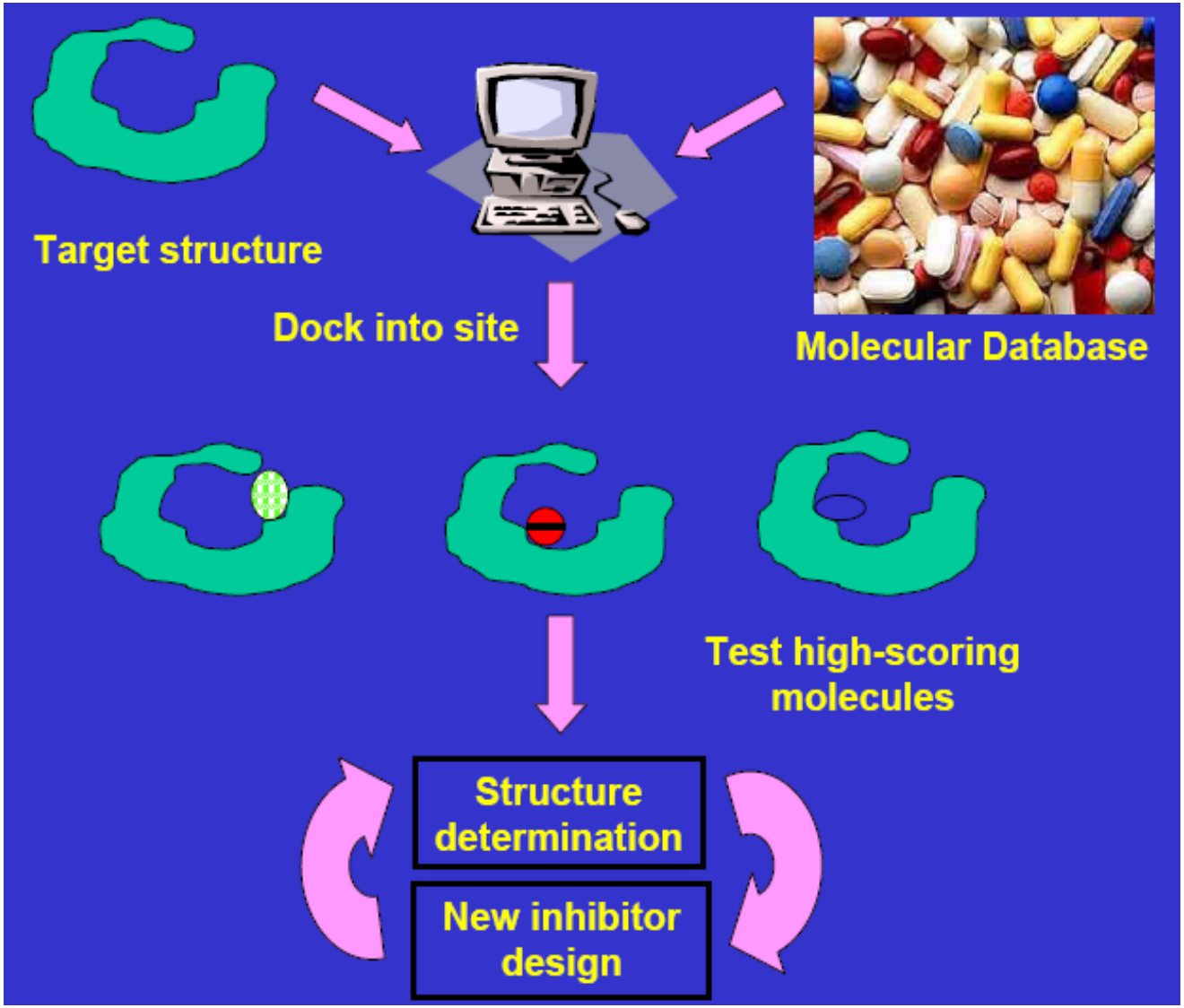
Development of Protein-ligand Scoring Functions

Yingkai Zhang
Department of Chemistry, New York University
NYU-ECNU Center for Computational Chemistry
at NYUSH

Docking methods are widely employed in drug design



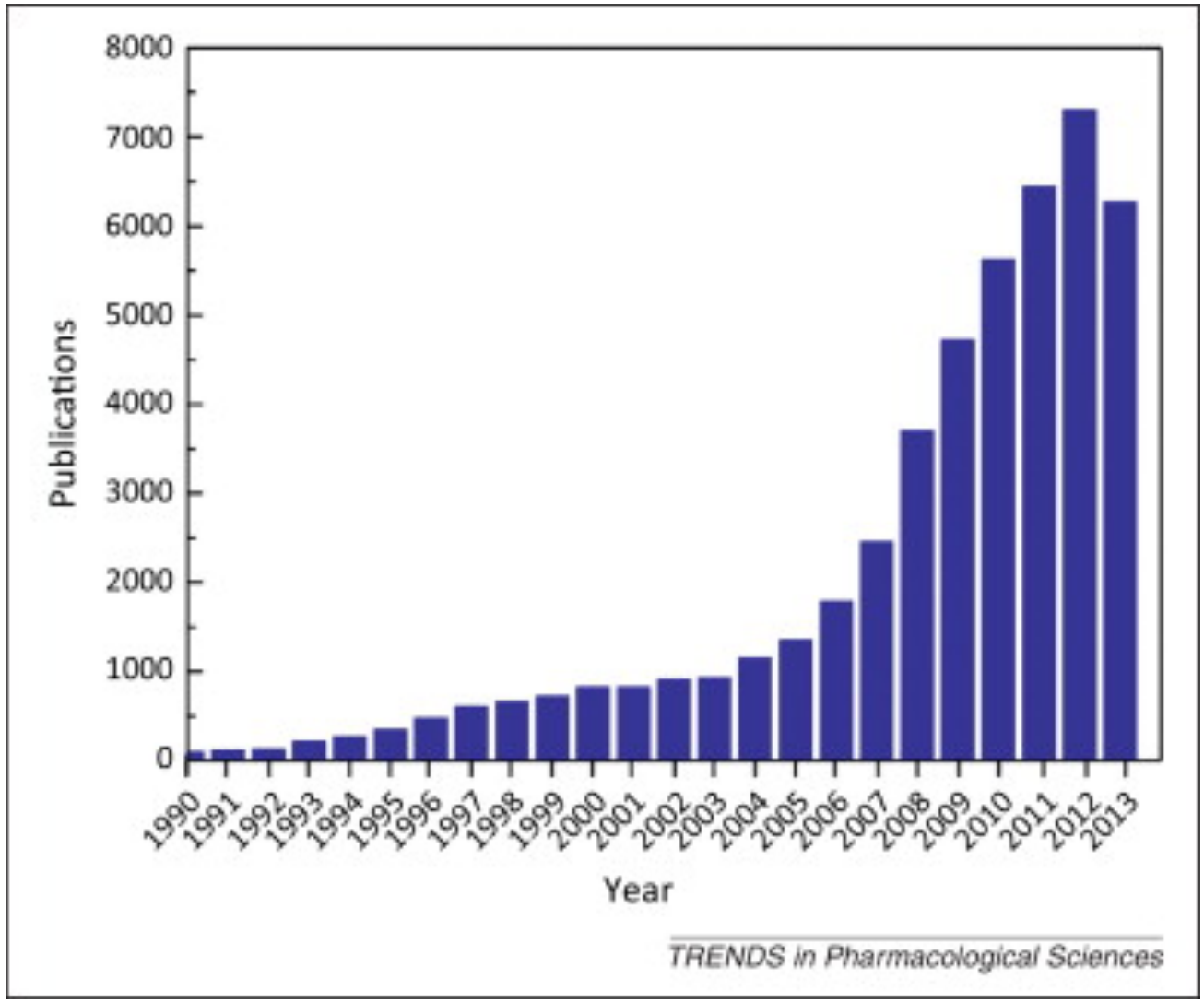


Figure 1. The increase in the number of papers, from 1990 to 2013, retrieved from the PubMed Central (PMC)-NCBI database (http://www.ncbi.nlm.nih.gov/pmc/). Keywords were ‘docking’ or ‘dock’ shown in the abstract or title.

http://dx.doi.org/10.1016/j.tips.2014.12.001

Docking: to find best ways to put two molecules together

➢Three Steps

- Obtain 3D structures of two molecules.
- Locate the best binding site
- Determine the best binding mode

- Ligand docking: inhibitor discovery or design (autodock4, vina, dock, FlexX, Gold, Glider …)
- Protein-protein docking: to predict how two proteins bind and how strong they bind
- Protein-DNA docking ….

Aspects of Docking Problem

- Sampling docked complexes: location, orientation, conformation
- Scoring docked complexes: the lower the binding free energy, the stronger the binding
- Ideal approach: Fast sampling, accurate scoring.

To discriminate different binding modes/conformations, compounds

To search for possible geometries for binding,
A global optimization problem

Scoring methods

A fast and simplified estimation of binding energy

$$P + L \underset{k_d}{\overset{k_a}{\rightleftharpoons}} PL$$

$$K_a = K_d^{-1} = \frac{[PL]}{[P][L]}$$

Binding free energy

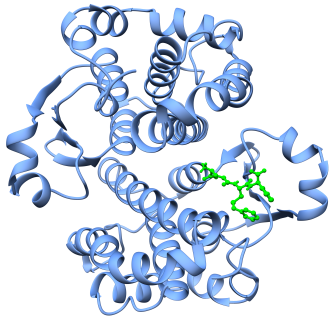
$$\Delta G_{bind} = -RT \ln K_a = RT \ln K_d$$

1 nm inhibitor: the free energy of binding = $0.5961 * \log(10^{-9}) = -12.4$ kcal/mol. $pK_d = 9$

1 um inhibitor: the free energy of binding = $0.5961 * \log(10^{-6}) = -8.2$ kcal/mol. $pK_d = 6$

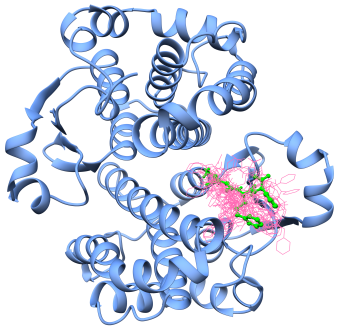
Scoring Function is Important in Protein-Ligand Docking Applications

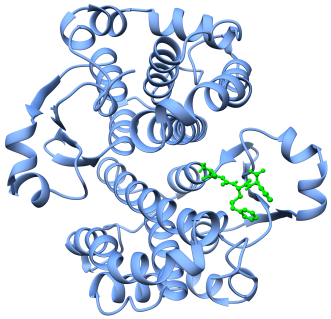
- Binding affinity prediction



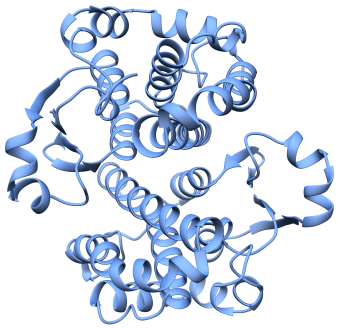
pK_d

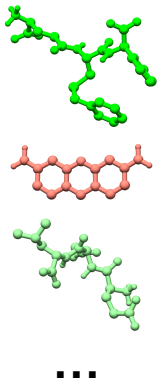
- Binding mode identification





- Virtual screening





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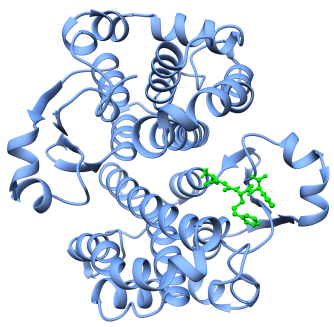
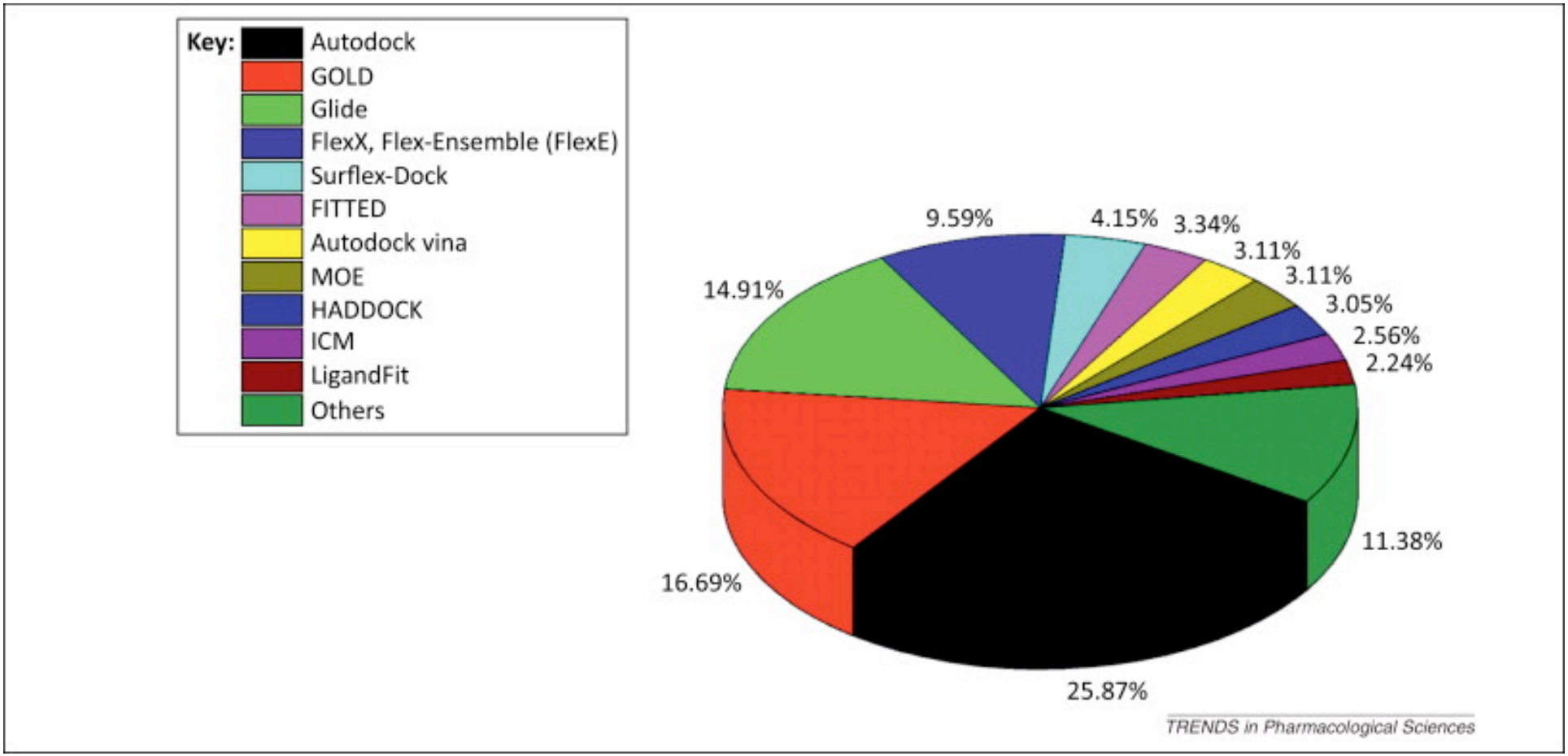


Classification of scoring functions

- Force Field-Based Scoring Function
  - Using non-bonded interaction terms from classical force field
  - Sometimes including solvation terms by GB/SA or PB/SA
- Empirical Scoring Function
  - Sum of several physical meaningful terms
  - Coefficients are derived from the regression analysis on experimental data
- Knowledge-Based Scoring Function
  - Statistical potential by using probability of finding atom pairs at a given distance between P and L
  - Require large number of terms
- Descriptor-Based Scoring Function
  - A pool of descriptors related to protein-ligand interaction
  - Machine learning algorithm to build the model

Liu, J.; Wang, R. *J. Chem. Inf. Model.* **2015,** 55, 475-482


Key:
Autodock
GOLD
Glide
FlexX, Flex-Ensemble (FlexE)
Surflex-Dock
FITTED
Autodock vina
MOE
HADDOCK
ICM
LigandFit
Others
9.59%
4.15%
3.34%
3.11%
3.11%
3.05%
2.56%
2.24%
14.91%
11.38%
16.69%
25.87%
TRENDS in Pharmacological Sciences

AutoDock History

1990 - AutoDock 1

First docking method with flexible ligands

1998 - AutoDock 3

Free energy force field and advanced search methods

AutoDockTools Graphical User Interface

2009 - AutoDock 4

Current version of AutoDock

Many parameters available to user

2009 - AutoDock Vina

Rewritten by Oleg Trott, new approach to scoring and search

One step solution to docking

AutoDock3, 4

(autodock.scripps.edu)

The docking free-energy scoring function used by Autodock is given by:

$$\Delta G = \Delta G_{\text{vdw}} + \Delta G_{\text{hbond}} + \Delta G_{\text{elec}} + \Delta G_{\text{tor}} + \Delta G_{\text{sol}} \qquad (1)$$

Each of the terms is defined as follows:

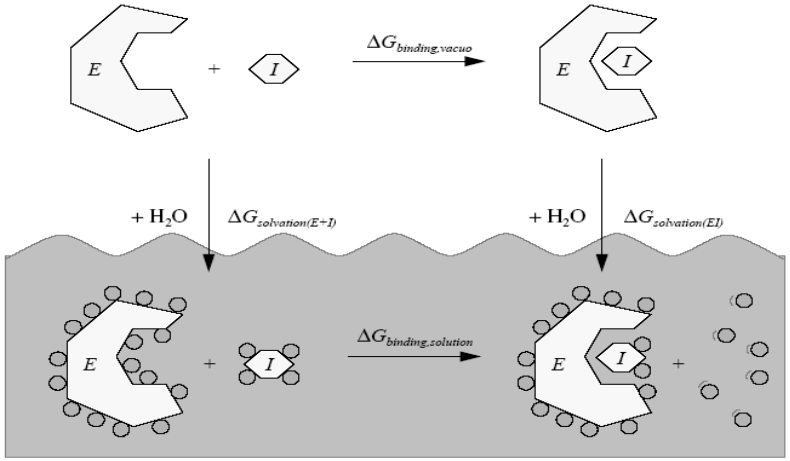
$$\Delta G_{\text{vdw}} = W_{\text{vdw}} \times \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) \qquad (2)$$

$$\Delta G_{\text{hbond}} = W_{\text{hbond}} \times \sum_{i,j} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} + E_{\text{hbond}} \right)$$

$$\Delta G_{\text{elec}} = W_{\text{elec}} \times \sum_{i,j} \frac{q_i q_j}{\epsilon(r_{ij}) r_{ij}}$$

$$\Delta G_{\text{tor}} = W_{\text{tor}} \times N_{\text{tor}}$$

$$\Delta G_{\text{sol}} = W_{\text{sol}} \sum_{i,j} (S_i V_j + S_j V_i) \exp(-r_{ij}^2 / 2\sigma^2)$$

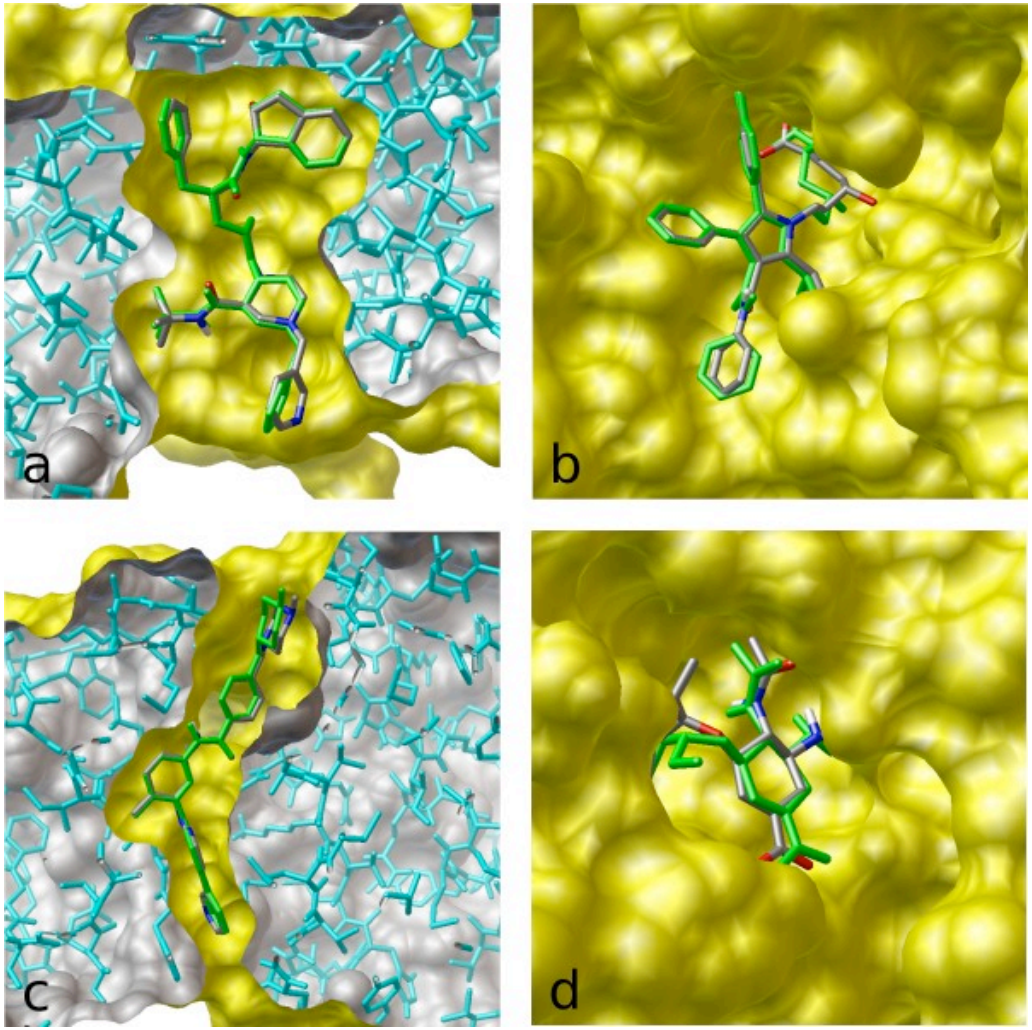


The hydrogen bond term has an angle-dependent directional weight, $E(t)$, based on the angle, t, between the probe and the target atom. E_{hbond} is the empirically estimated average energy of the hydrogen bonding of water with a polar atom. The electrostatic term uses a distance-dependent dielectric function to model solvent screening based on the work by Mehler and Solmajer.[24] The torsional term is proportional to N_{tor}, the number of sp^3 bonds in the ligand. In the desolvation term, S_i and V_i are the solvation parameter and the fragmental volume of atom i,[25] respectively. All five terms have weighting factors, W, obtained by fitting a large set of energetic analyses of ligand−receptor complexes.[2]

Automated Docking of Flexible Ligands to Receptors

Sampling: Simulated annealing, Genetic algorithm .

AUTODOCK VINA



O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461

AutoDock Vina

- Gauss$_1$, Gauss$_2$, Repulsion, Hydrophobic, HBond, N$_{rot}$
- First five based on surface distance

$$d_{ij} = r_{ij} - R_{t_i} - R_{t_j}$$

$$c_{\text{inter}} = \sum_{i}^{\text{ligand}} \sum_{j}^{\text{protein}} (\omega_1 \text{gauss}_1(d_{ij}) + \omega_2 \text{gauss}_2(d_{ij}) + \omega_3 \text{Repulsion}(d_{ij})) + \sum_{i,i\in\text{HP}}^{\text{ligand}} \sum_{j,j\in\text{HP}}^{\text{protein}} \omega_4 \text{Hydrophogic}(d_{ij}) + \sum_{i,i\in\text{HB}}^{\text{ligand}} \sum_{j,j\in\text{HB}}^{\text{protein}} \omega_5 \text{HBond}(d_{ij})$$

$$g(c_{\text{inter}}) = \frac{c_{\text{inter}}}{1 + \omega N_{rot}}$$

$$\text{pK}_d\text{(Vina)} = -0.73349 * g(c_{\text{inter}})$$

Weight	Term
-0.0356	gauss$_1$ (ω_1)
-0.00516	gauss$_2$ (ω_2)
0.840	Repulsion (ω_3)
-0.0351	Hydrophobic (ω_4)
-0.587	Hydrogen bonding (ω_5)
0.0585	N$_{rot}$ (ω)

$$\text{gauss}_1(d) = e^{-(d/0.5)^2}$$

$$\text{gauss}_2(d) = e^{-((d-3)/2))^2}$$

$$\text{repulsion}(d) = \begin{cases} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}$$

$$\text{Hydrophobic}(d) = \begin{cases} 1.0 & d < 0.5 \\ 1.5 - d & 0.5 \leq d \leq 1.5 \\ 0.0 & d > 1.5 \end{cases}$$

$$\text{HBond}(d) = \begin{cases} 1.0 & d < -0.7 \\ d/(-0.7) & -0.7 \leq d \leq 0 \\ 0.0 & d > 0 \end{cases}$$

Trott, O.; Olson, A.J.; *J. Comput. Chem.* **2010,** 31, 455-461

PROTOCOL

Computational protein–ligand docking and virtual drug screening with the AutoDock suite

Stefano Forli, Ruth Huey, Michael E Pique, Michel F Sanner, David S Goodsell & Arthur J Olson

Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, California, USA. Correspondence should be addressed to A.J.O. (olson@scripps.edu).

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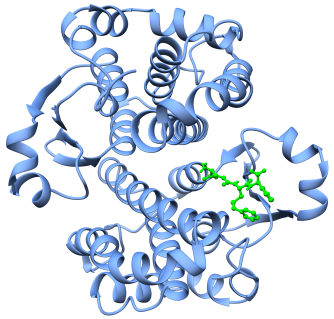
Option (Step 5)	Method	Description
A	Single-docking experiment with AutoDock Vina	Basic docking method for study of a single ligand with a single receptor
B	Single-docking experiment with AutoDock	Basic docking method for study of a single ligand with a single receptor, with explicit calculation of affinity maps
C	Virtual screening with Raccoon2 and AutoDock Vina	Virtual screen of a library of ligands with a single receptor, often used for drug discovery
D	AutoDock Vina with flexible side chains	Docking method for a single ligand with a single receptor, incorporating limited receptor flexibility
E	Active site prediction with AutoLigand	Method for analysis of receptor binding sites, for prediction of druggable sites
F	Docking with explicit waters	Advanced docking method for a single ligand with a single receptor incorporating explicit bridging water molecules

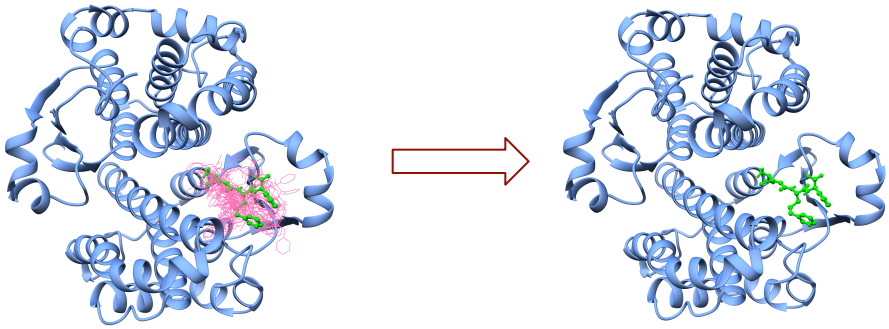
Scoring Function is the key in Protein-Ligand docking applications

- Binding affinity prediction

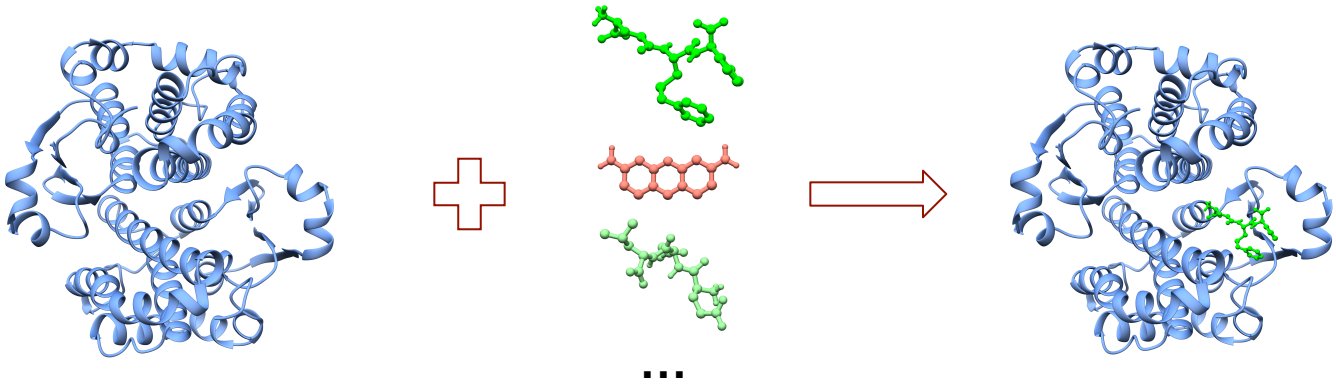


pK_d

- Binding mode identification



- Virtual screening



Evaluation Metrics of Scoring Functions

Comparative Assessment of Scoring Function (CASF) benchmark

Scoring power (binding affinity prediction)

- Linear correlation between predicted binding affinity and experimental binding affinity

Docking power (binding mode identification)

- Success rate of identifying the native binding mode among computer generated decoys

Screening power (Virtual screening)

- Success rate of Identifying the true binders to a given target protein among a pool of random molecules

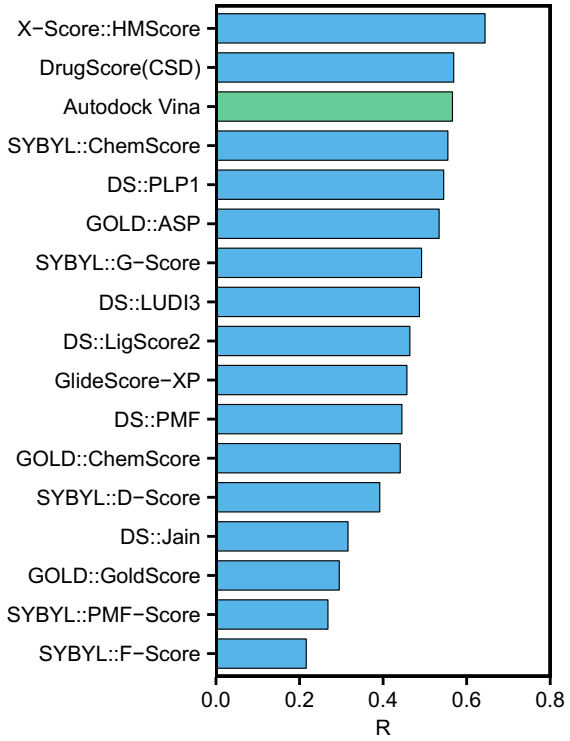
- CASF-2007: Scoring and docking powers
- CASF-2013: Scoring, docking and screening powers

Cheng, T.; Li, X.; Li, Y.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2009,** 49, 1079-1093
Li, Y.; Han, L.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2014,** 54, 1717-1736

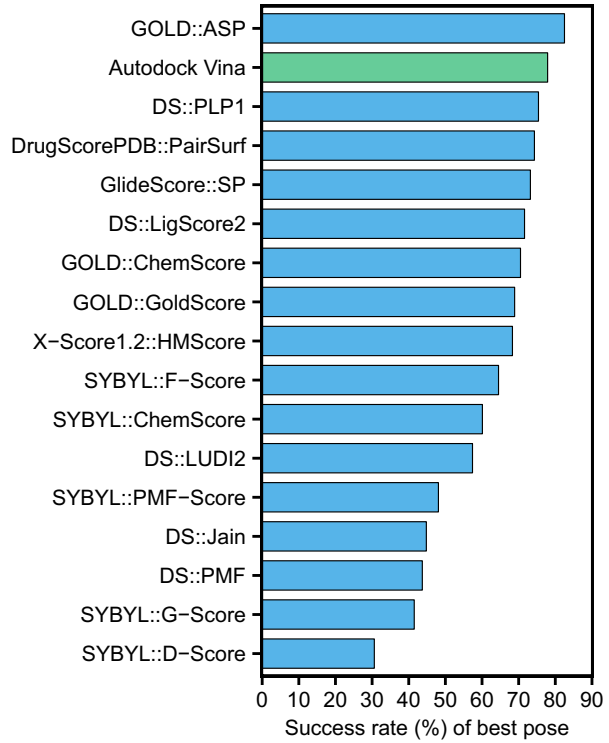
Scoring power is less satisfactory than docking/screening power

16 Scoring functions and Autodock Vina are evaluated in CASF-2007

? Scoring power
0.216 to 0.644
Autodock Vina: 0.566



✔ Docking power
30.6% to 82.5%
Autodock Vina: 77.9%



Cheng, T.; Li, X.; Li, Y.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2009,** 49, 1079-1093

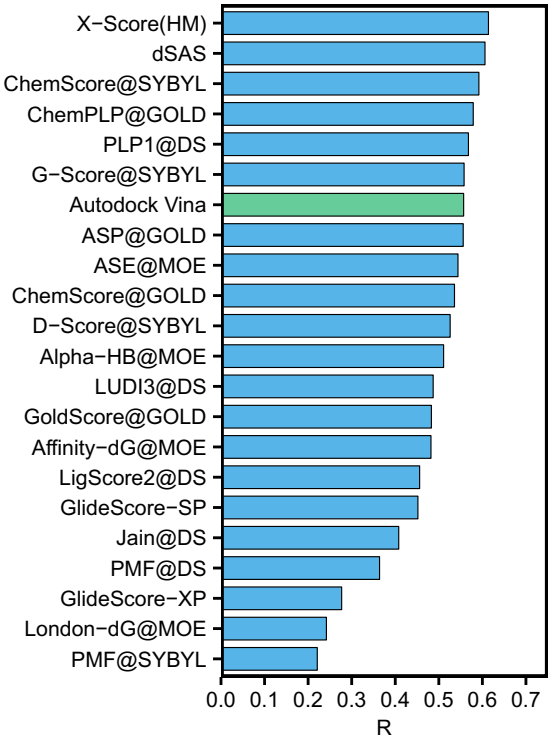
Scoring power is less satisfactory than docking/screening power

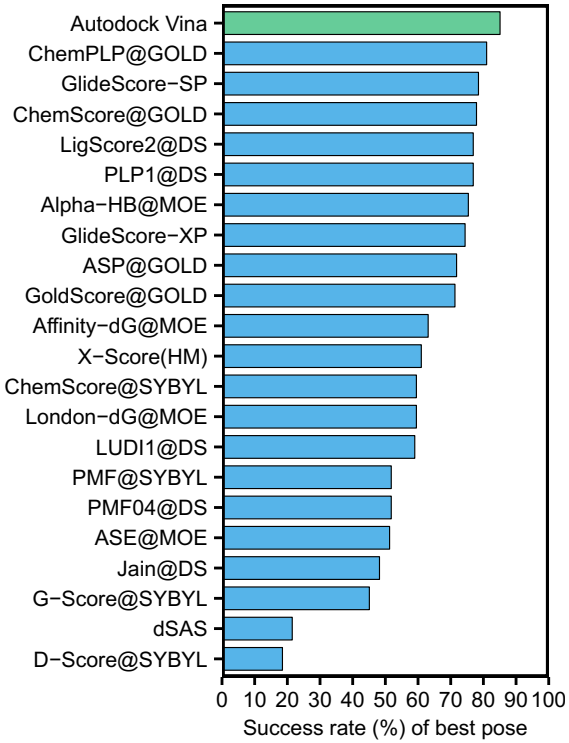
20 Scoring functions and Autodock Vina are evaluated in CASF-2013

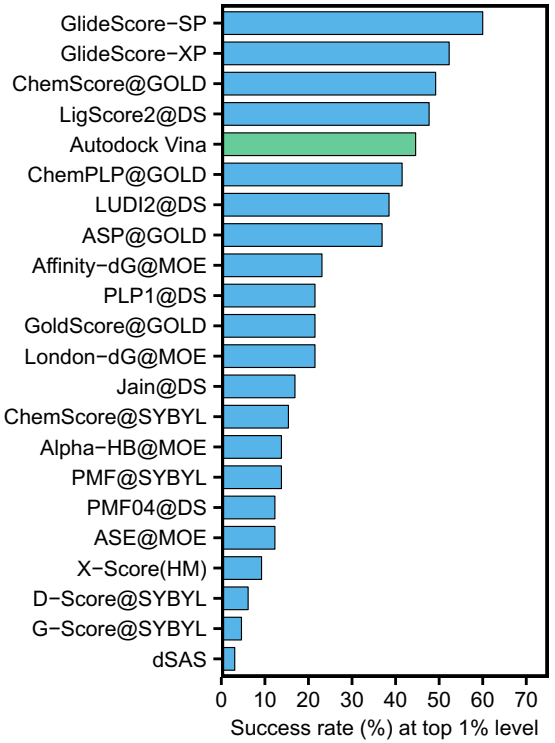
? Scoring power (R)
0.221 to 0.614
Autodock Vina: 0.557

✔ Docking power
18.5% to 85.1%
Autodock Vina: 85.1%

✔ Screening power
3.08% to 60.0%
Autodock Vina: 44.6%







Li, Y.; Han, L.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2014,** 54, 1717-1736

RFbScores Achieve Excellent Scoring Power

Random Forest-based Scoring Function (RFbScore)

- Superior performance in predicting experimental protein-ligand binding affinity

CASF-2007

function	scoring power (R)
RF-Score::Elem-v2	0.803
RF-IChem	0.791
SCFscore^{RF}	0.779
X-Score^{HM}	0.644

CASF-2013

function	scoring power (R)
RF-Score::VinaElem	0.752
X-Score^{HM}	0.614

Ballester, P. J.; Mitchell, J. B. O. *Bioinformatics* **2010**, 26, 1169-1175
Ballester, P. J.; Schreyer, A.; Blundell, T. L. *J. Chem. Inf. Model.* **2014**, 54, 944-955
Li, H.J.; Leung, K.S.; Wong, M.H.; Ballester, P.J. *Molecules* **2015**, 20, 10947-10962
Zilian, D.; Sotriffer, C.A. *J. Chem. Inf. Model.* **2013**, 53, 1923-1933
Gabel, J.; Desaphy, J.; Rognan, D. *J. Chem. Inf. Model.* **2014,** 54, 2807-2815
Cheng, T.; Li, X.; Li, Y.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2009,** 49, 1079-1093
Gabel, J.; Desaphy, J.; Rognan, D. *J. Chem. Inf. Model.* **2014,** 54, 2807-2815

RFbScores Fail in Docking and Screening

Random Forest-based Scoring Function (RFbScore)

- Superior performance in predicting experimental protein-ligand binding affinity
- Fail in docking/screening tests

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

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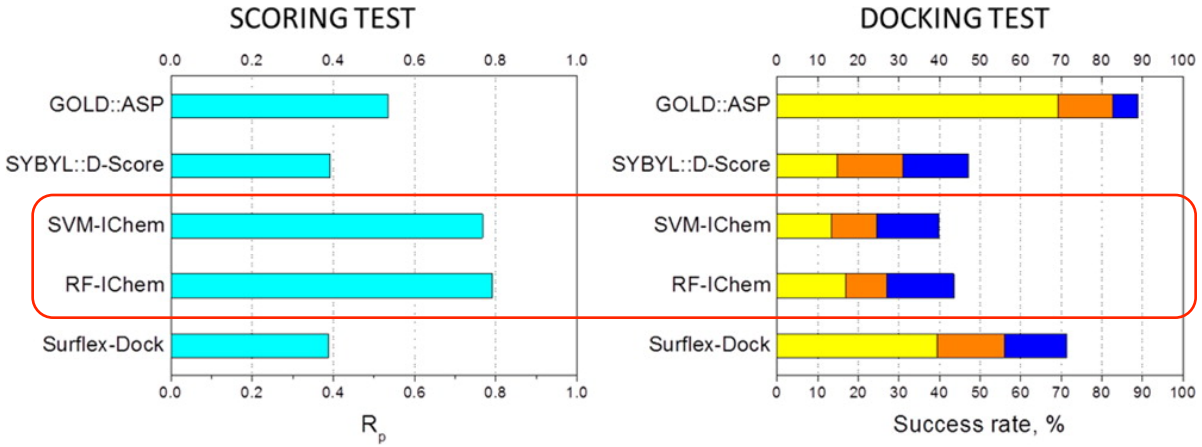
Beware of Machine Learning-Based Scoring Functions—On the Danger of Developing Black Boxes

Joffrey Gabel, Jérémy Desaphy, and Didier Rognan*

Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS-Université de Strasbourg, 74 route du Rhin, F-67400 Illkirch, France



Gabel, J.; Desaphy, J.; Rognan, D. *J. Chem. Inf. Model.* **2014**, 54, 2807-2815

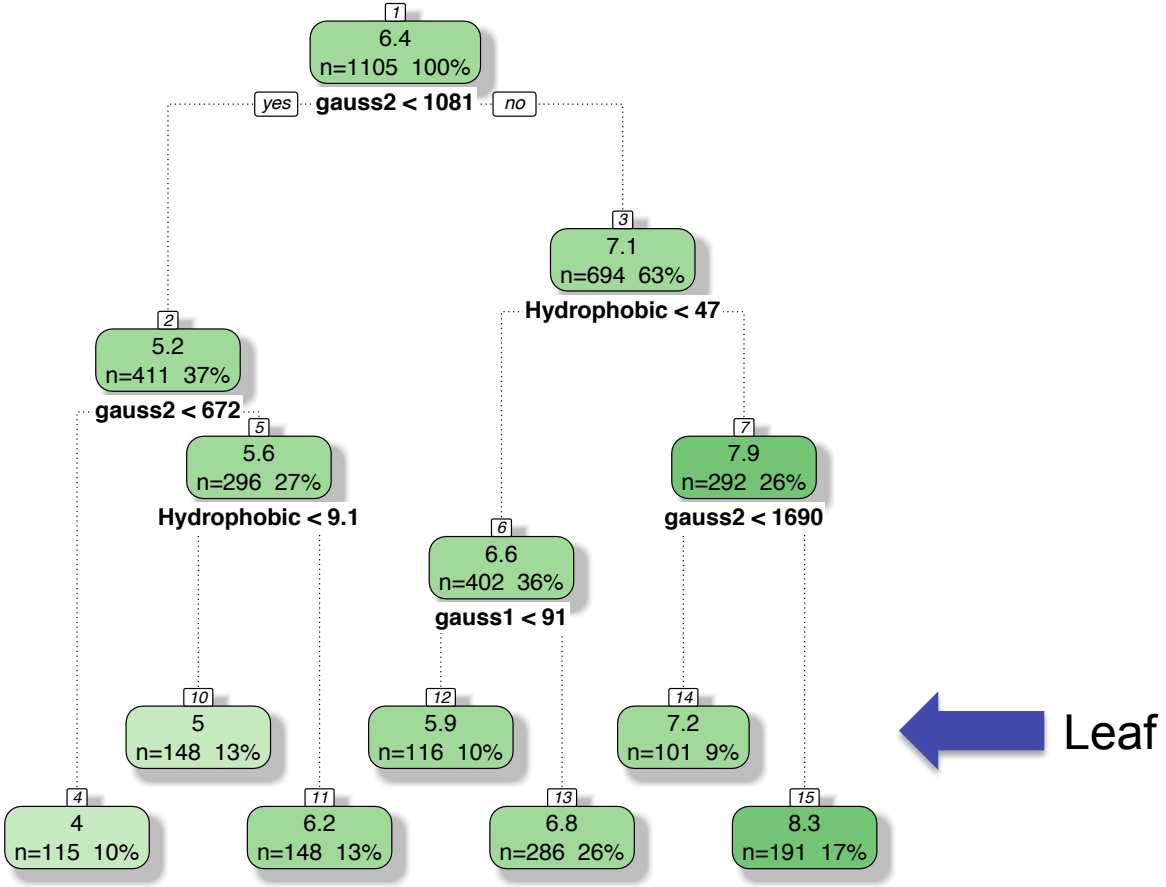
Random Forest

- An ensemble learning method based on the aggregation of numerous decision trees
- Performs remarkably well with very little tuning required
- Can handle a large feature set and correlated features
- Can also be used for assessing feature importance and feature selection.

Breiman, L. *Machine Learning* **2001**, 45, 5-32
Hastie, T.; Tibshirani, R.; Friedman, J. *The Elements of Statistical Learning*, 2nd ed.; Springer New York Inc.: New York, 2009
Wyner, A.J.; Olson, M.; Bleich, J.; Mease, D. **2015**, arXiv:1504.07676
Wager, S.; Walther, G. **2015**, arXiv:1503.06388

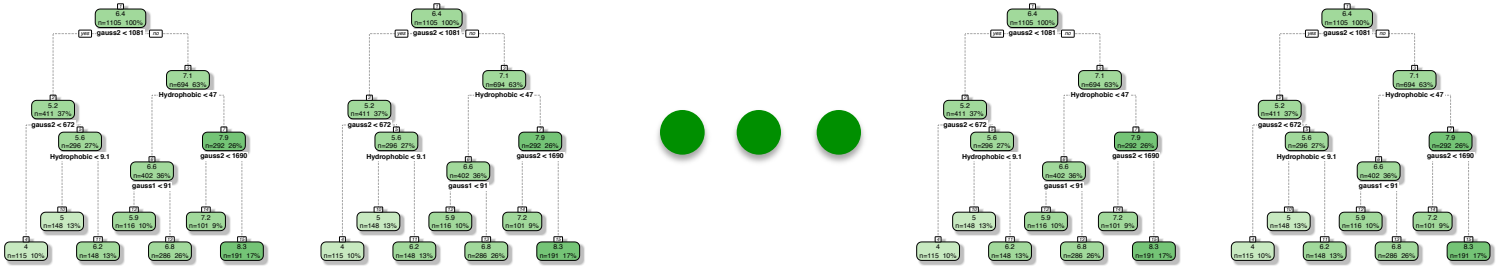
Random Forest – Interpolating

- Given input features (variable, predictor) $X^T = (X_1, X_2, \ldots, X_p)$
- Real-valued output Y_{train}
- The predicted Y_{pred} for each tree is in range [min(Y_{train}), max(Y_{train})]
- Each leaf in the tree is an average value of a Y_{train} subset.



Random Forest – Self-averaging

B Trees



Predict point x

$f^{*1}(x)$ $f^{*2}(x)$ $f^{*B-1}(x)$ $f^{*B}(x)$

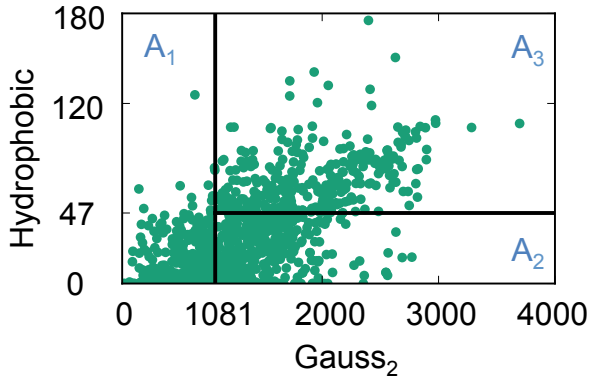
$$f_{bag}(x) = \frac{1}{B}\sum_{b=1}^{B} f^{*b}(x)$$

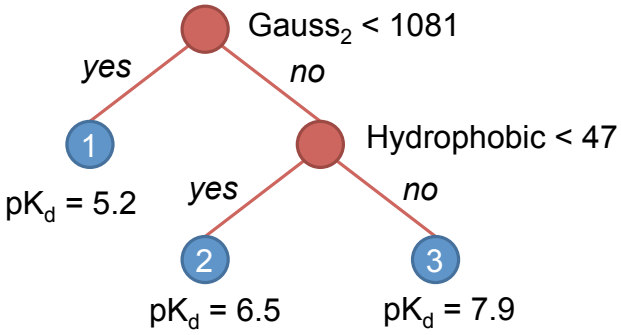
- The predicted Y_{pred} for each tree is in range [min(Y_{train}), max(Y_{train})]
- The predicted Y_{pred} for random forest is in range [min(Y_{train}), max(Y_{train})]

Predicted Value from Random Forest is Bounded by Training Set

Regression Tree Demo

- Each green point presents one training set complex from PDBBind v2007
- $Gauss_2$ and Hydrophobic are two features from Autodock Vina
- Each leaf node contains a subset of training set
- Averaged pK_d of subset complexes is used as predicted value





$$T(X; D_{train}^{*}) = \frac{1}{N_A} \sum_{i \in A} pK_d^{(i)}$$

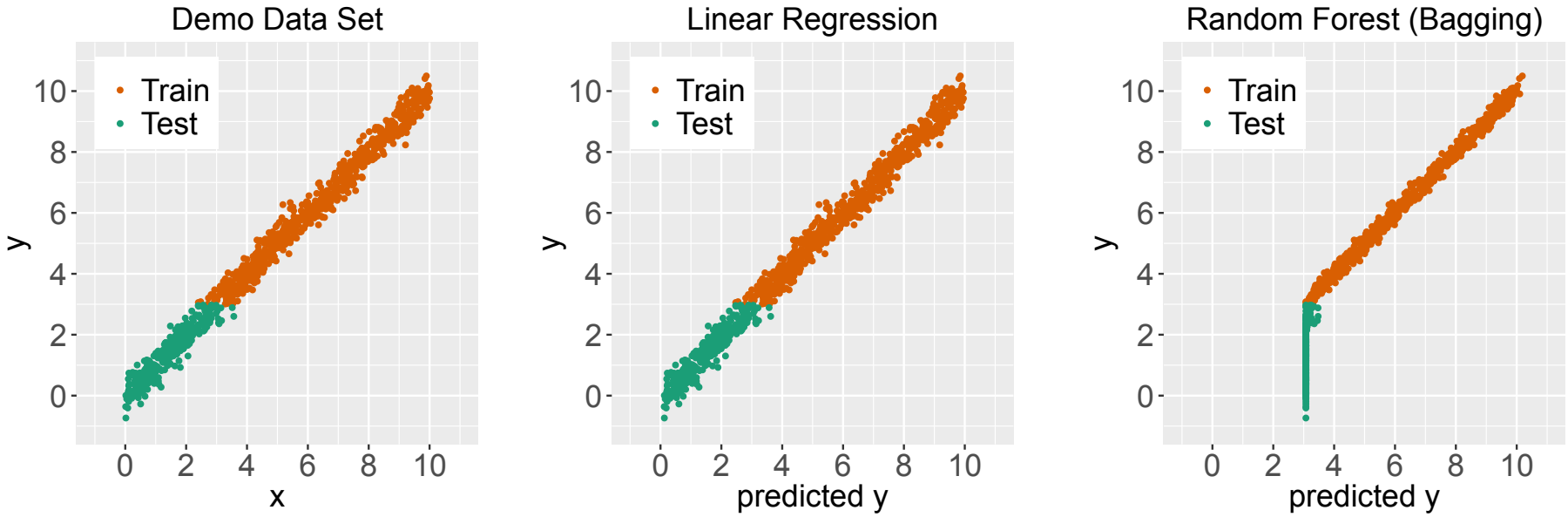
- The predicted $pK_{d\,pred}$ from each tree is in range [min($pK_{d\,train}$), max($pK_{d\,train}$)]
- The predicted $pK_{d\,pred}$ from random forest is in range [min($pK_{d\,train}$), max($pK_{d\,train}$)]

Wyner, A.J.; Olson, M.; Bleich, J.; Mease, D. *arXiv:1504.07676*
Wager, S.; Walther, G. *arXiv:1503.06388*

Random forest can only do **interpolation** and CANNOT do extrapolation

Example: y = x + *N*(0, 0.3), 1000 points

- Linear regression can do extrapolation
- Random forest can only predict data point in training space

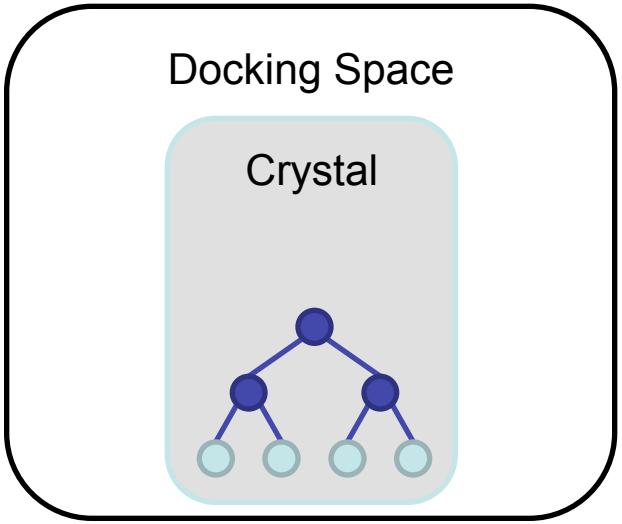


Wyner, A.J.; Olson, M.; Bleich, J.; Mease, D. *arXiv:1504.07676*
Wager, S.; Walther, G. *arXiv:1503.06388*

Extrapolation is Needed for Docking/ Screening

- Random forest is designed to do interpolation and CANNOT do extrapolation
  - The predicted value from random forest is bounded by the training set

- Inferior performance of docking/screening for RFbScores comes from
  1. Only using crystal structure as training set
  2. Interpolation nature of Random Forest



Cheng, T.; Li, X.; Li, Y.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2009,** 49, 1079-1093
Li, Y.; Liu, Z.; Li, J.; Han, L.; Liu, J.; Zhao, Z.; Wang, R.; *J. Chem. Inf. Model.* **2014,** 54, 1700-1716
Dunbar, J.B.; et al; *J. Chem. Inf. Model.* **2011,** 51, 2036-2046

Two-pronged Strategy

1. Expanding the training set
   - Experimental subset
   - Decoy subset

2. Δ_{vina}RF approach use RF to parameterize correction to Vina score to take advantage of
   - the excellent docking power of Vina
   - the strength of RF in improving scoring accuracy

$\Delta_{vina}RF_{20}$ is a scoring function based on Δ_{vina}RF approach with 20 features.

Ramakrishnan, Dral, Rupp, von Lilienfeld, J. Chem. Theory Comput. 2015, 11, 2087.
Wang, C.; Zhang, Y.K.; *J. Comput. Chem.* **2017,** 38, 169-177.

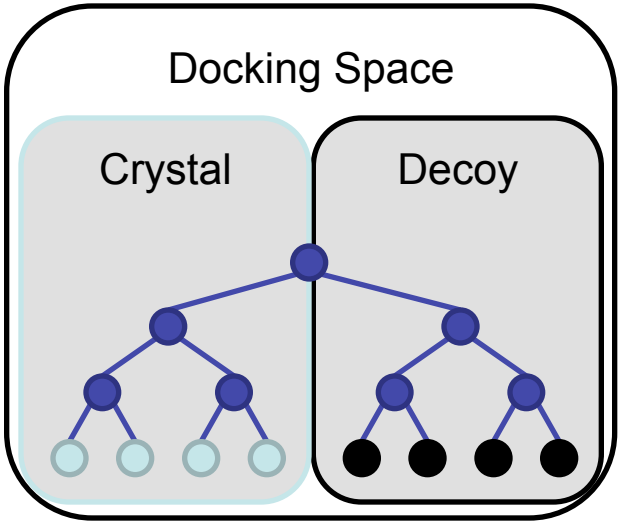
Expanding the Training Set

Two Subsets of Training Set

Experimental subset (3336)

Crystal structures with experimental binding affinity.

PDBbind-v2014



Decoy subset (3322)

Decoy structures generated by docking with binding affinity estimated by Vina.

CSAR-decoys

No overlap with CASF-2007 and CASF-2013

Dunbar, J.B.; et al; *J. Chem. Inf. Model.* **2011,** 51, 2036-2046
Huang, S.Y.; Zou, X.Q. *J. Chem. Inf. Model.* **2011,** 51, 2107-2114
http://www.csardock.org/downloads/DECOY_ALL.htm
Li, Y.; Liu, Z.; Li, J.; Han, L.; Liu, J.; Zhao, Z.; Wang, R.; *J. Chem. Inf. Model.* **2014,** 54, 1700-1716
Wang, C.; Zhang, Y.K.; *J. Comput. Chem.* **2017,** 38, 169-177.

Δ_{vina}RF approach

Vina score as base scoring function.

Taking care of extrapolation & Good docking power of Vina.

$pK_d(\Delta_{vina}RF) = pK_d(Vina) + \Delta pK_d(RF)$

Correction to Vina score by random forest model

Taking advantages of RF in improving scoring accuracy.

Autodock Vina

- Gauss_1, Gauss_2, Repulsion, Hydrophobic, HBond, N_{rot}
- First five based on surface distance

$$d_{ij} = r_{ij} - R_{t_i} - R_{t_j}$$

$$c_{\text{inter}} = \sum_{i}^{\text{ligand}} \sum_{j}^{\text{protein}} (\omega_1 \text{gauss}_1(d_{ij}) + \omega_2 \text{gauss}_2(d_{ij}) + \omega_3 \text{Repulsion}(d_{ij})) + \sum_{i,i\in\text{HP}}^{\text{ligand}} \sum_{j,j\in\text{HP}}^{\text{protein}} \omega_4 \text{Hydrophogic}(d_{ij}) + \sum_{i,i\in\text{HB}}^{\text{ligand}} \sum_{j,j\in\text{HB}}^{\text{protein}} \omega_5 \text{HBond}(d_{ij})$$

$$g(c_{\text{inter}}) = \frac{c_{\text{inter}}}{1 + \omega N_{rot}}$$

$\text{pK}_d\text{(Vina)} = -0.73349 * g(c_{\text{inter}})$

Weight	Term
-0.0356	gauss_1 (ω_1)
-0.00516	gauss_2 (ω_2)
0.840	Repulsion (ω_3)
-0.0351	Hydrophobic (ω_4)
-0.587	Hydrogen bonding (ω_5)
0.0585	N_{rot} (ω)

$$\text{gauss}_1(d) = e^{-(d/0.5)^2}$$

$$\text{gauss}_2(d) = e^{-((d-3)/2))^2}$$

$$\text{repulsion}(d) = \begin{cases} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}$$

$$\text{Hydrophobic}(d) = \begin{cases} 1.0 & d < 0.5 \\ 1.5 - d & 0.5 \leq d \leq 1.5 \\ 0.0 & d > 1.5 \end{cases}$$

$$\text{HBond}(d) = \begin{cases} 1.0 & d < -0.7 \\ d/(-0.7) & -0.7 \leq d \leq 0 \\ 0.0 & d > 0 \end{cases}$$

Trott, O.; Olson, A.J.; *J. Comput. Chem.* **2010,** 31, 455-461

20 Features in $\Delta_{vina}RF_{20}$

10 Autodock Vina Features (source code)

5 Interaction Terms

- Non-hydrophobic
- Hydrogen bond
- Solvation from Autodock4
- Electrostatic term with x = 1 and x = 2

$$\frac{q_{a_1} \cdot q_{a_2}}{d^x}$$

5 ligand dependent Terms

- Number of heavy atoms
- Number of hydrophobic atoms
- Number of torsions
- Number of rotors
- Ligand length

10 Pharmacophore-based buried SASA Features

9 pharmacophore types

- Positive
- Negative
- Donor-Acceptor
- Donor
- Acceptor
- Aromatic
- Hydrophobic
- Polar
- Halogen

1 Total SASA

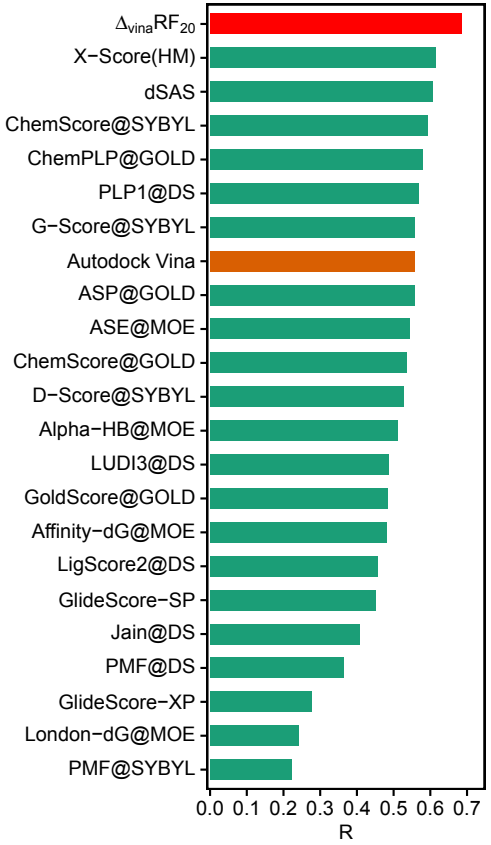
$\Delta_{vina}RF_{20}$ Performs Superior in CASF2013

Scoring power (R)

$\Delta_{vina}RF_{20}$: 0.686

Autodock Vina: 0.557

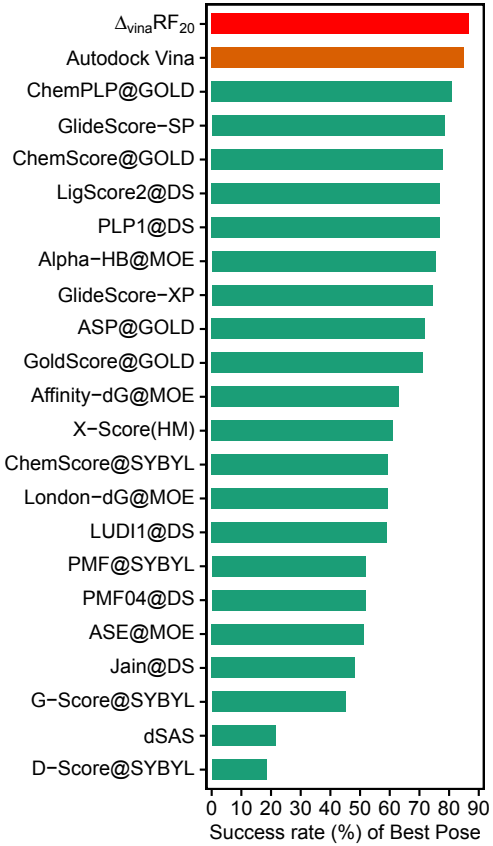
X-ScoreHM: 0.614



Docking power

$\Delta_{vina}RF_{20}$: 86.7%

Autodock Vina: 85.1%

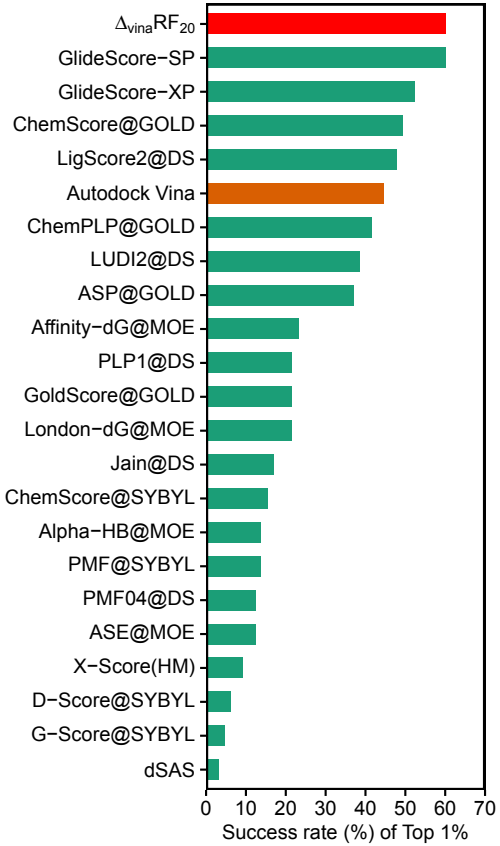


Screening power

$\Delta_{vina}RF_{20}$: 60.0%

Autodock Vina: 44.6%

GlideScore-SP: 60.0%



Li, Y.; Han, L.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2014,** 54, 1717-1736

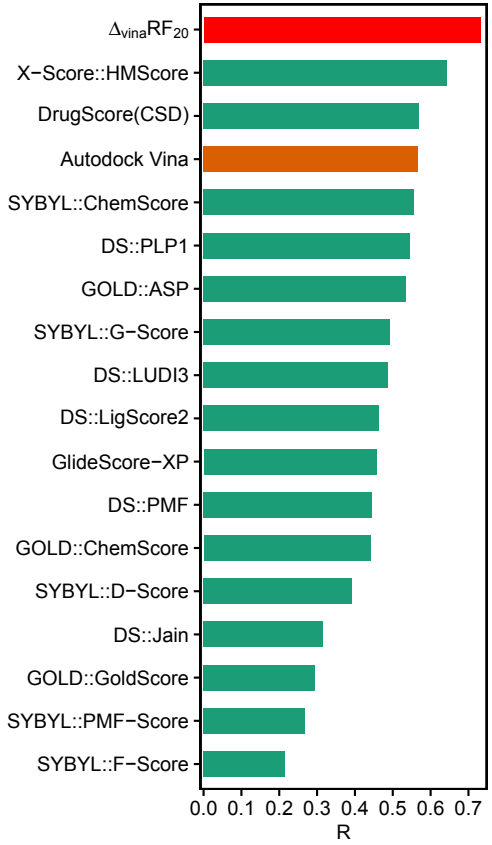
$\Delta_{vina}RF_{20}$ Performs Well in CASF-2007

Scoring power

$\Delta_{vina}RF_{20}$: 0.732

Autodock Vina: 0.566

X-ScoreHM: 0.644

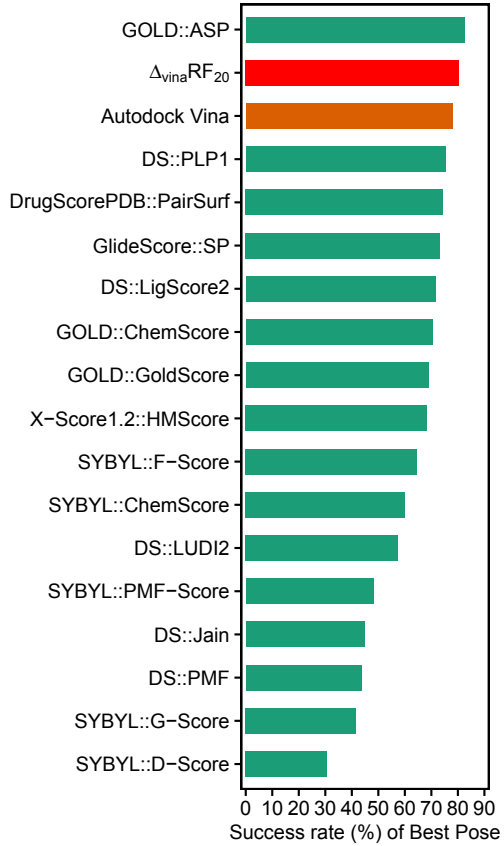


Docking power

$\Delta_{vina}RF_{20}$: 80.5%

Autodock Vina: 77.9%

Gold::ASP: 82.5%



Cheng, T.; Li, X.; Li, Y.; Liu, Z.; Wang, R.; *J. Chem. Inf. Model.* **2009,** 49, 1079-1093

Summary

$\Delta_{vina}RF_{20}$ is a scoring function based on $\Delta_{vina}RF$ approach with 20 features achieves supeior performance in scoring, docking and screening power for CASF-2007 and CASF-2013 benchmarks in comparison with classical scoring functions.

- Expanding the training set
  - Experimental subset
  - Decoy subset
- $\Delta_{vina}RF$ approach
  - the excellent docking power of Vina
  - the strength of RF in improving scoring accuracy
- 20 Features
  - 10 Features from Autodock Vina Source Code
  - 10 Pharmacophore-based SASA

C. Wang and Y. Zhang, J. Comput. Chem. , 38 , 169-177 (2017).

Acknowledgement

Dr. Cheng Wang

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