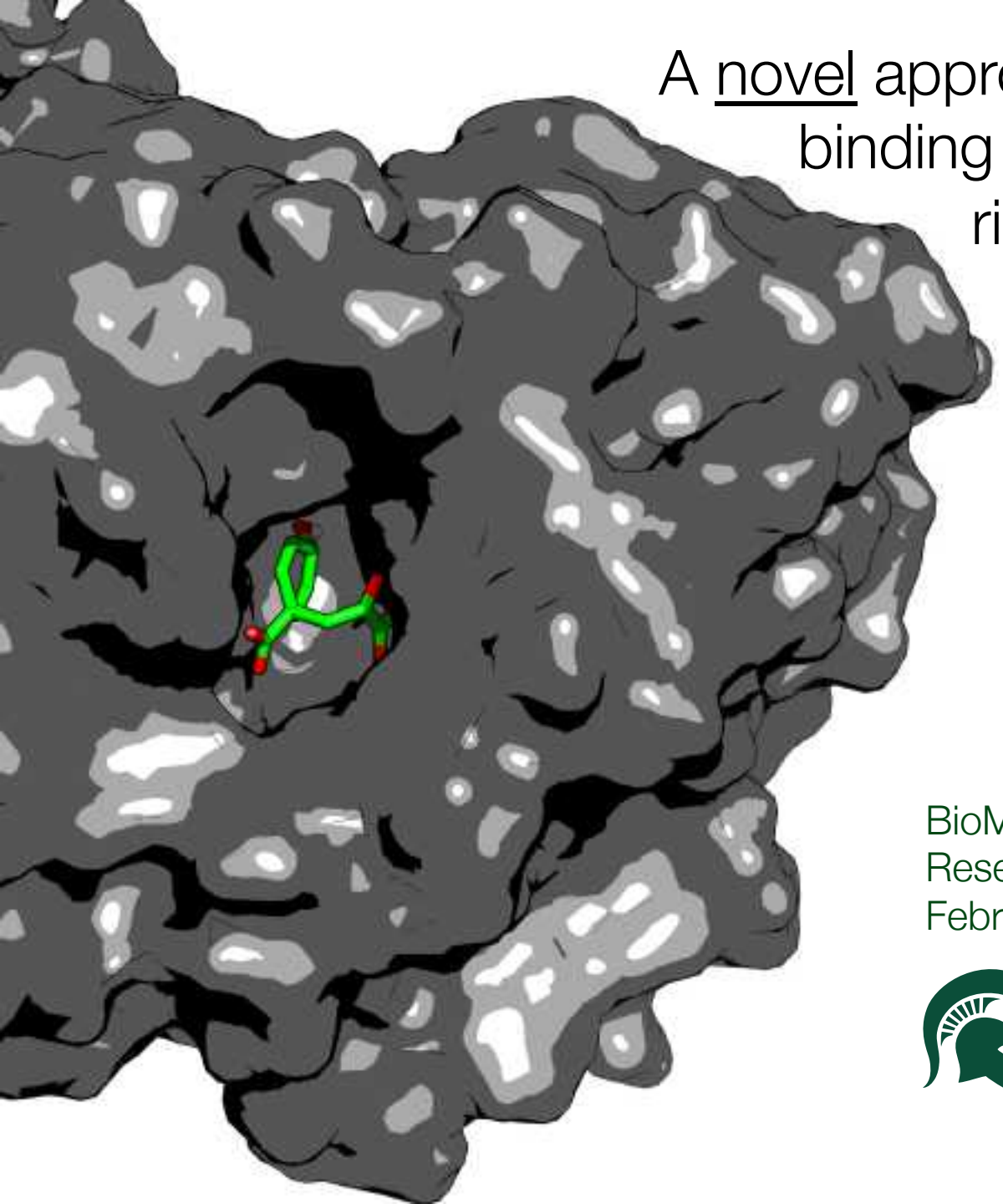


A novel approach to protein-ligand binding mode prediction by rigidity analysis using graph theory

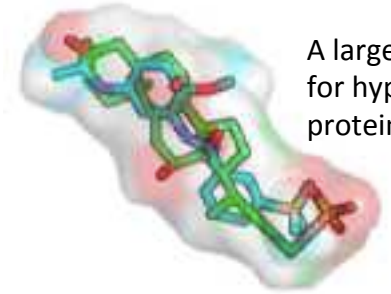
Sebastian Raschka

BioMolecular Science Gateway
Research Forum
February 8, 2016

MICHIGAN STATE
UNIVERSITY

A little bit about myself …

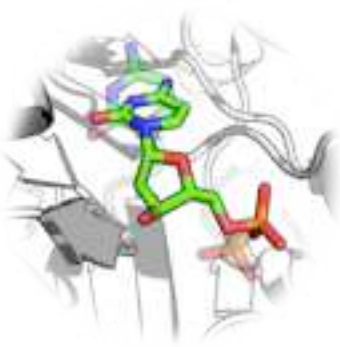
SeaScreen



A large-scale virtual screening framework for hypothesis-driven ligand-based protein-inhibitor discovery

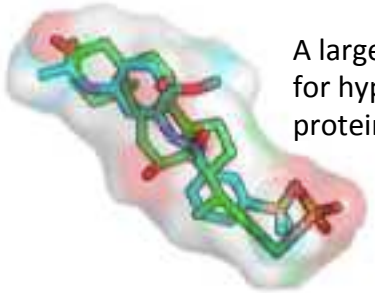
A truly novel algorithm for protein-ligand docking based on graph theory

SiteInterlock



A little bit about myself …

SeaScreen



A large-scale virtual screening framework for hypothesis-driven ligand-based protein-inhibitor discovery

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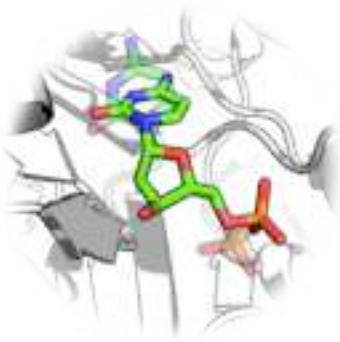
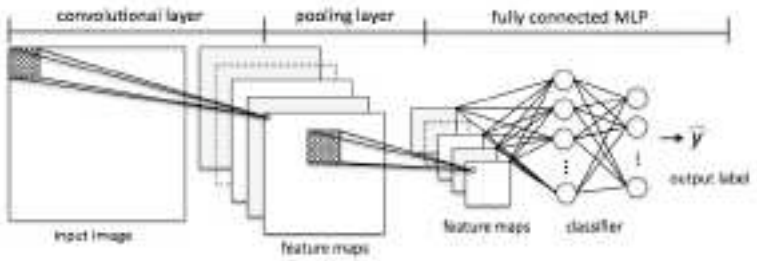
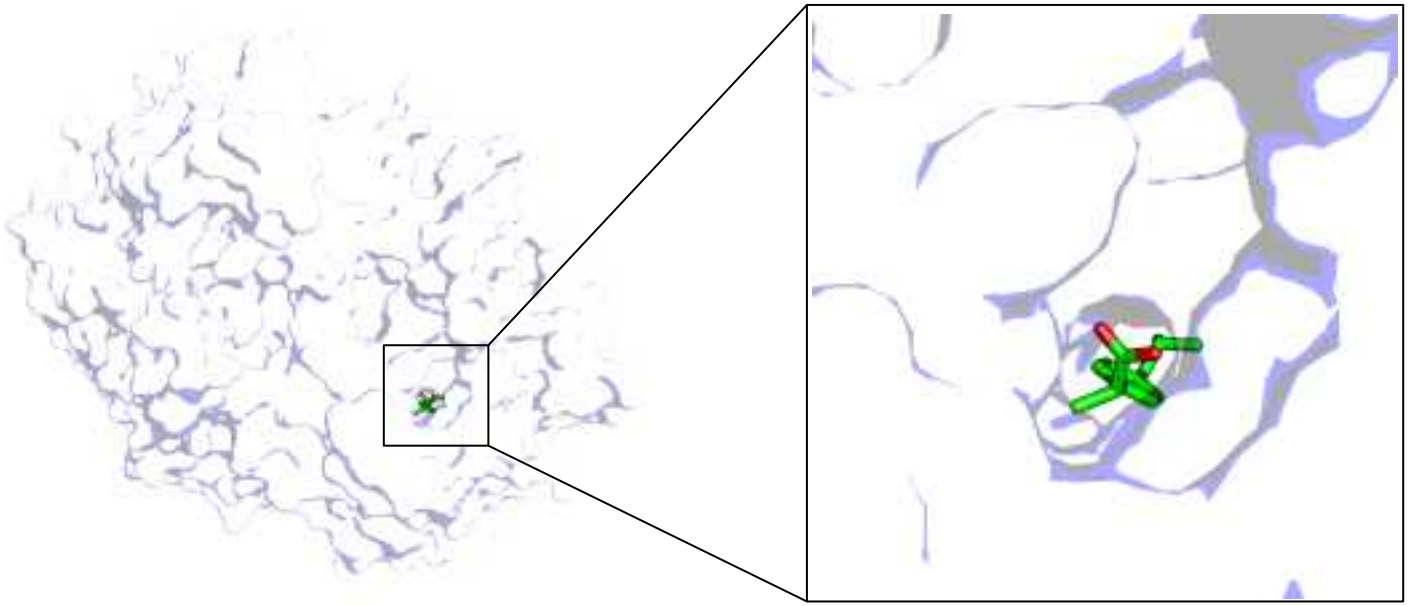




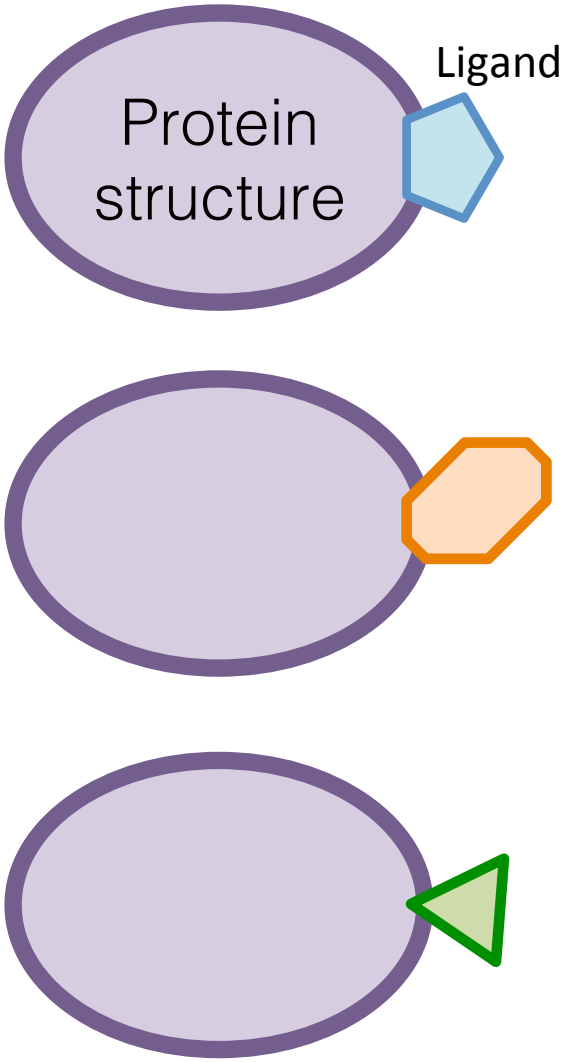
Protein Ligand Docking

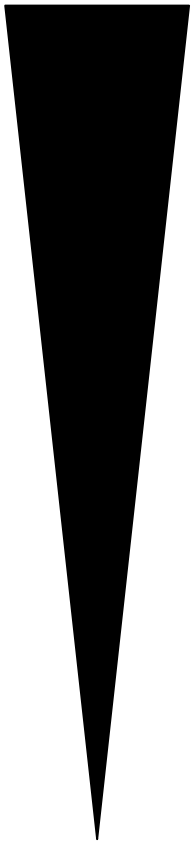
When & Why?



Structure of Ibuprofen bound to cyclooxygenase-2
Orlando, B. J., Lucido, M. J., & Malkowski, M. G. (2015)
(PDB code: 4ph9)

Ranking and Discovery

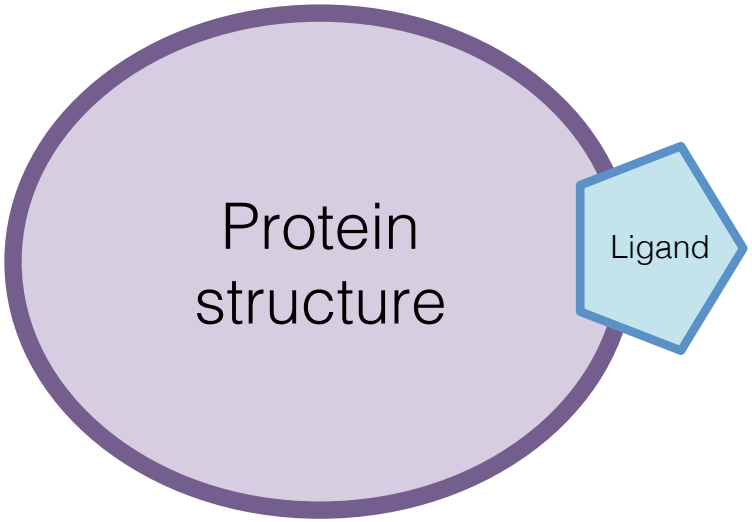


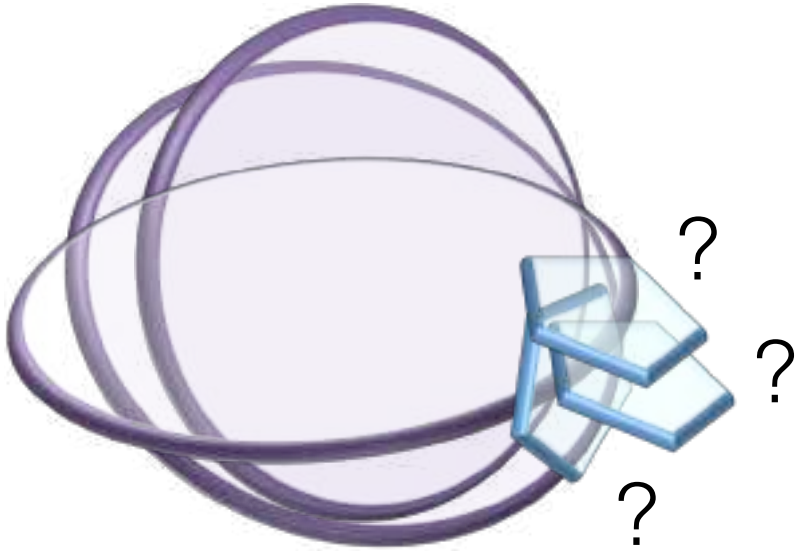


Absolute or relative binding affinity

[scoring function]

Binding Mode Prediction



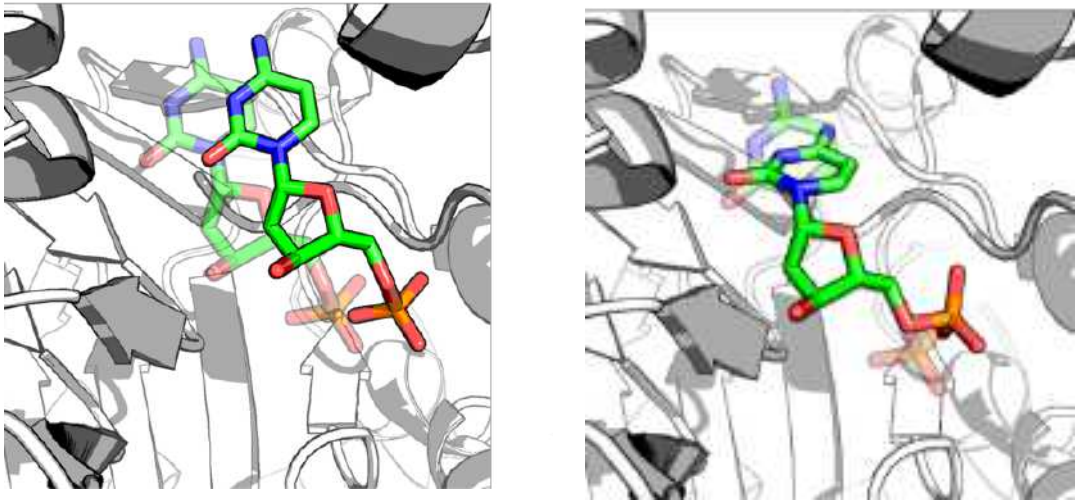


[scoring function]

Binding Mode Prediction

Ligand “Pose”

Orientation + Conformation

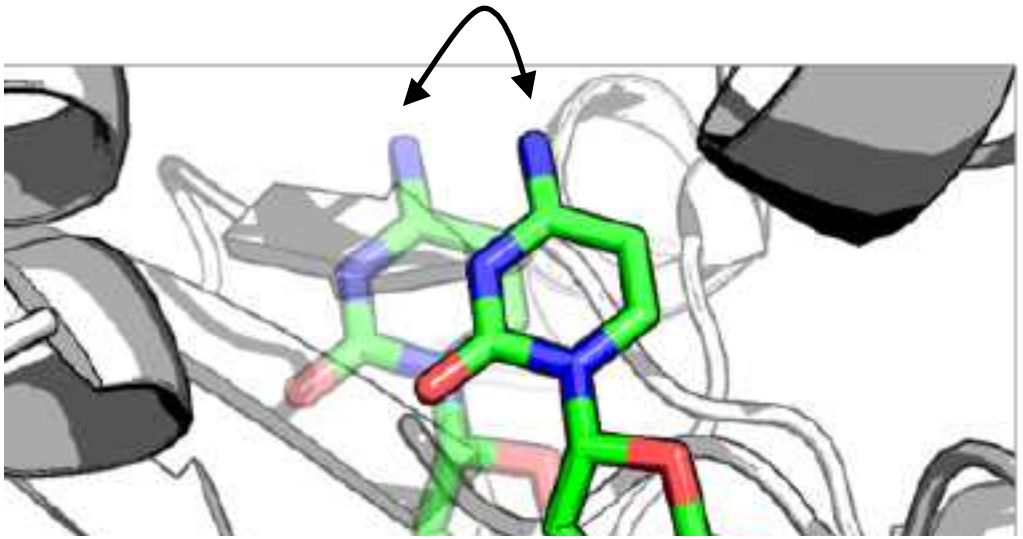


deoxycytidylate hydroxymethylase cognate ligand 2'-deoxycytidine-5'-monophosphate
(PDB code: 1b5e)

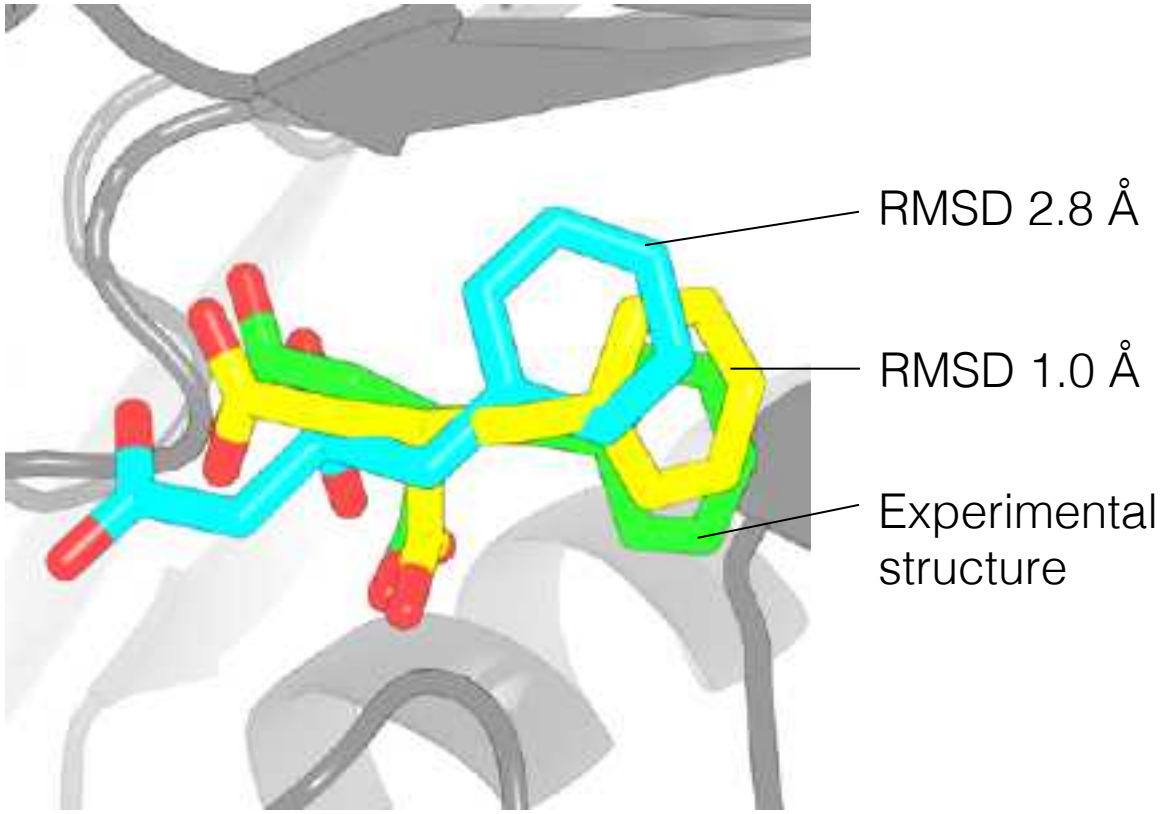
[+ flexible protein side chains]

Evaluation Metric

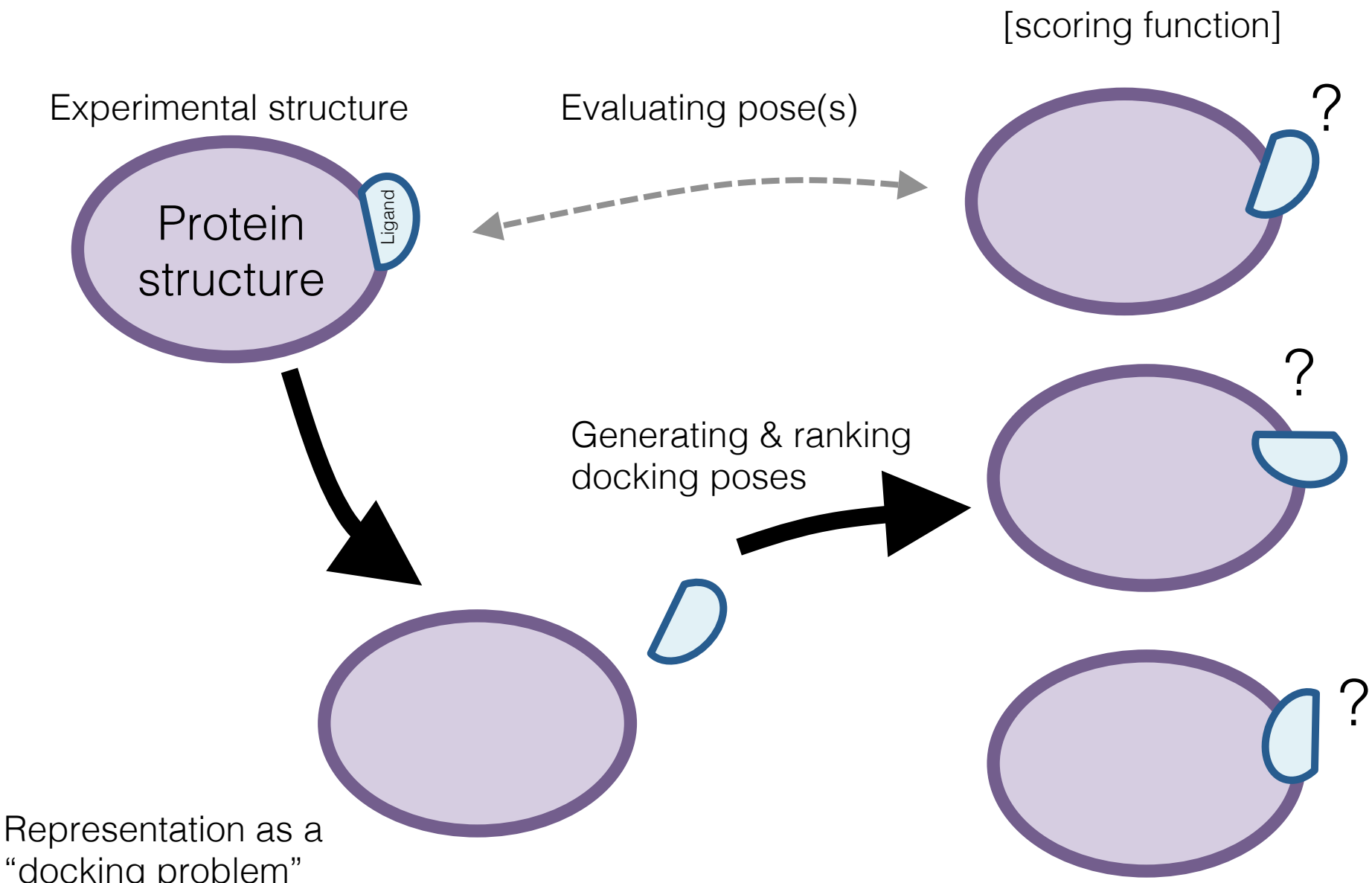
$$\mathrm{RMSD}(a,b) = \sqrt{\frac{1}{n}\sum_{i=1}^{n} ||a_i - b_i||^2}$$



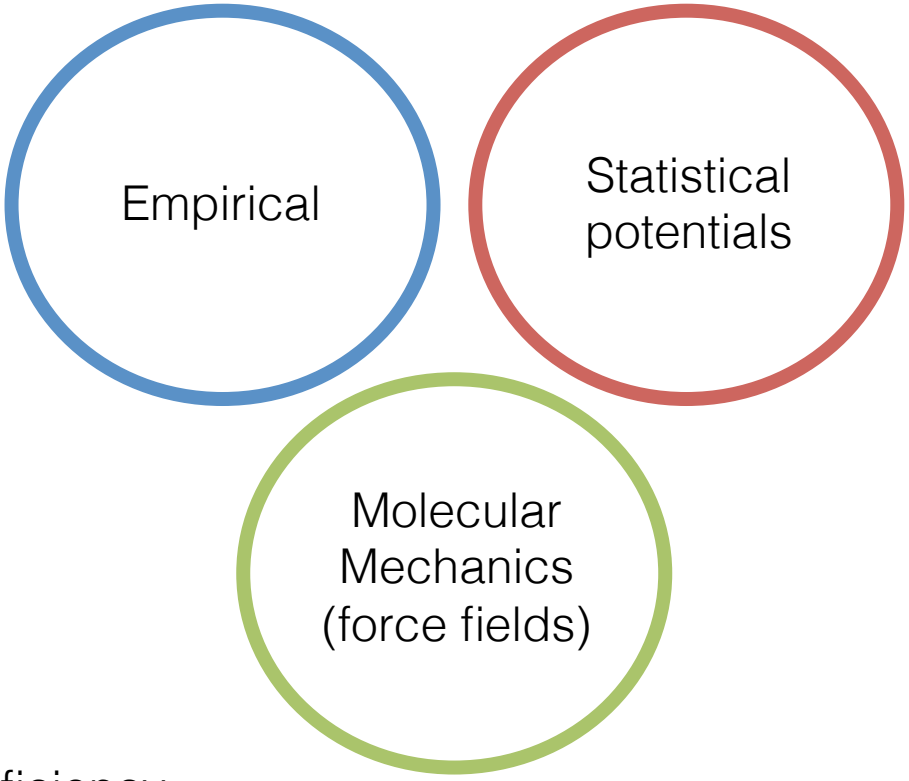
Evaluate against hold-out data



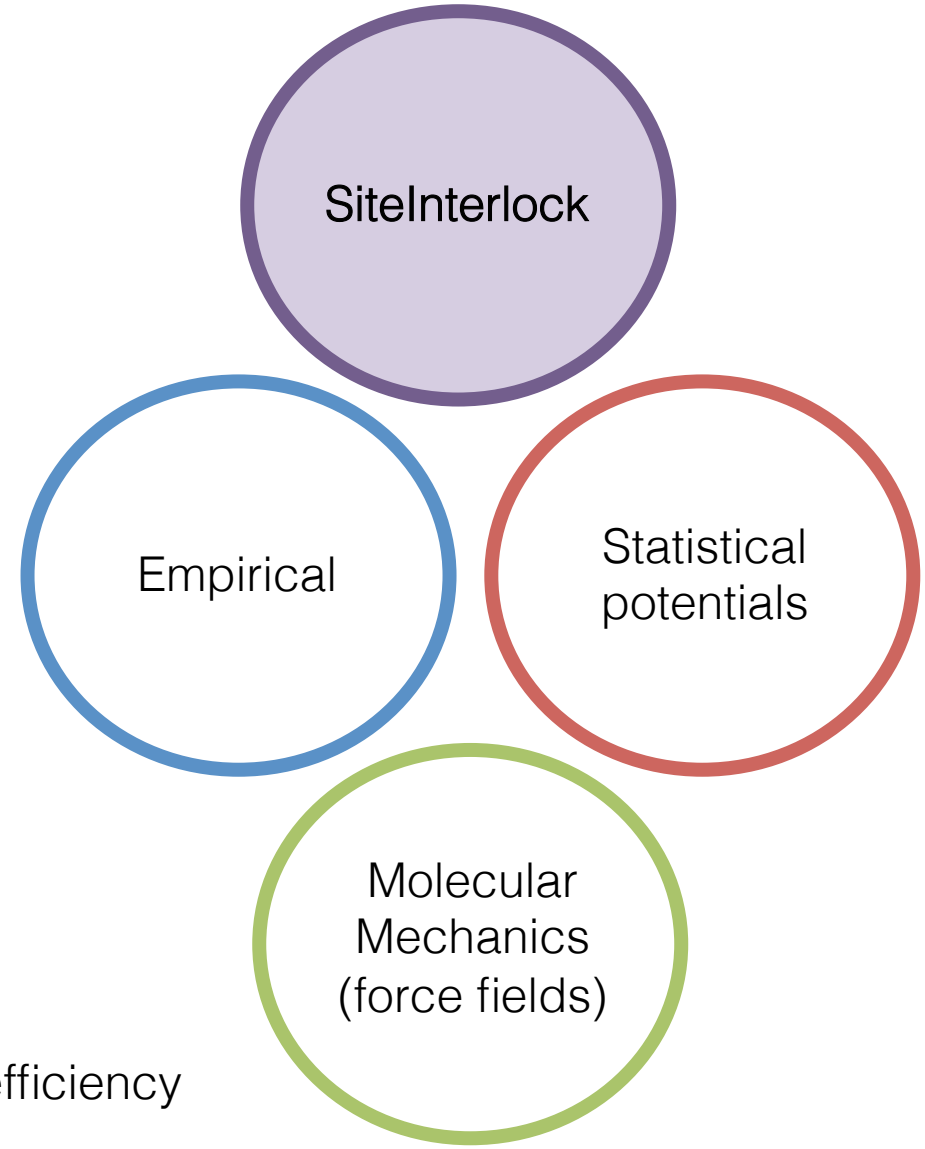
Carboxypeptidase A + inhibitor L-benzylsuccinate (PDB code: 1cbx)


[scoring function]
Experimental structure
Evaluating pose(s)
Protein structure
Ligand
?
?
Generating & ranking docking poses
?
Representation as a "docking problem"

Internal Scoring Metrics



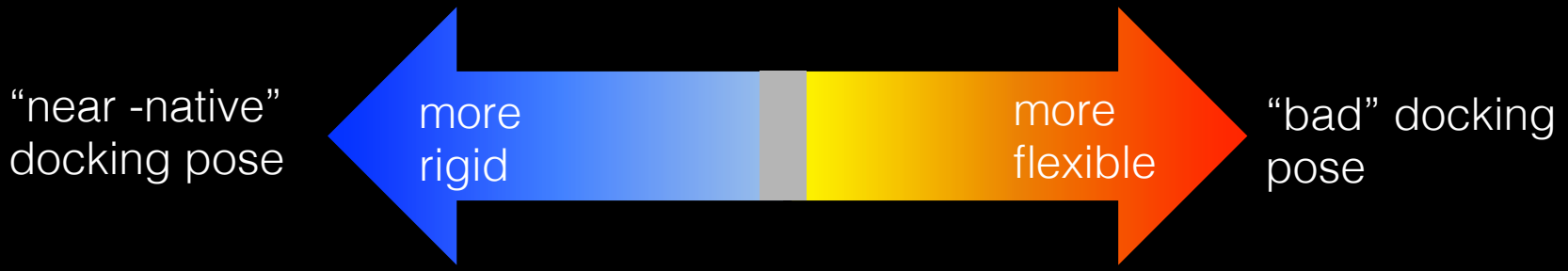
- Accuracy
- Computational efficiency
- Apo-structures



- Accuracy
- Computational efficiency
- Apo-structures

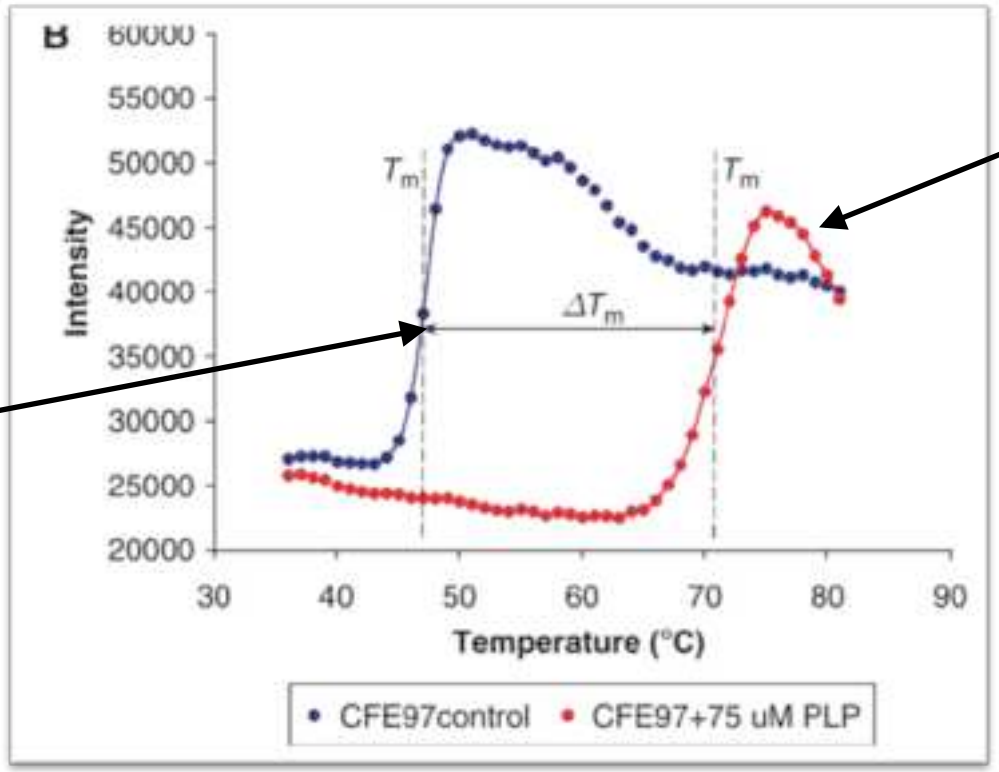
Hypothesis

We can detect a local rigidity increase upon protein-ligand complex formation



Thermal Shift Assay

Thermal Shift Assay



Protein

Protein
+ Ligand

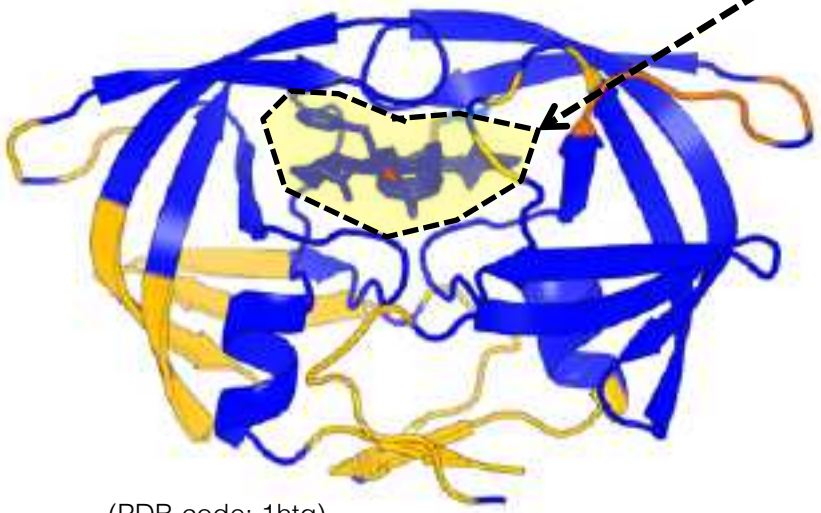
M. D. Cummings, M. A. Farnum, and M. I. Nelen. Universal screening methods and applications of thermofluor. Journal of biomolecular screening, 11(7):854–863, 2006.

Predicting Flexibility via ProFlex

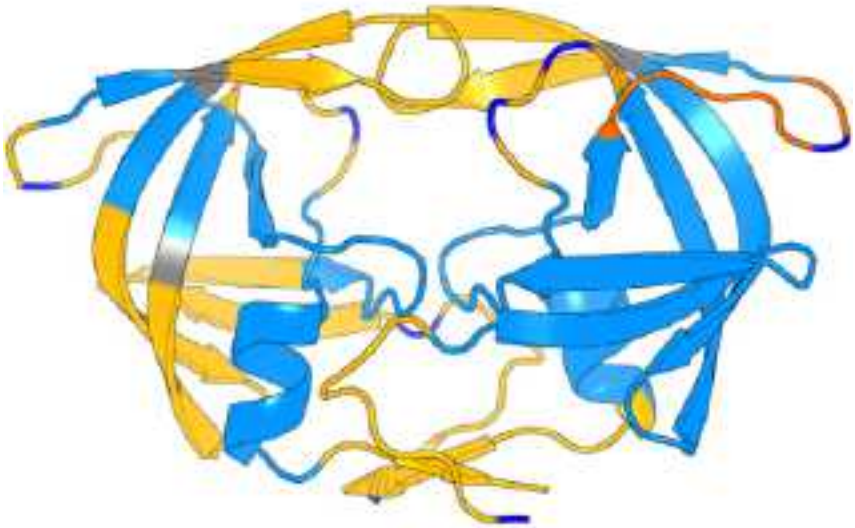
D. J. Jacobs, A. J. Rader, L. A. Kuhn, and M. F. Thorpe. Protein flexibility predictions using graph theory. Proteins: Structure, Function, and Bioinformatics, 44(2):150–165, 2001.

Crystal structure
of HIV protease

Penicillin-derived
asymmetric inhibitor

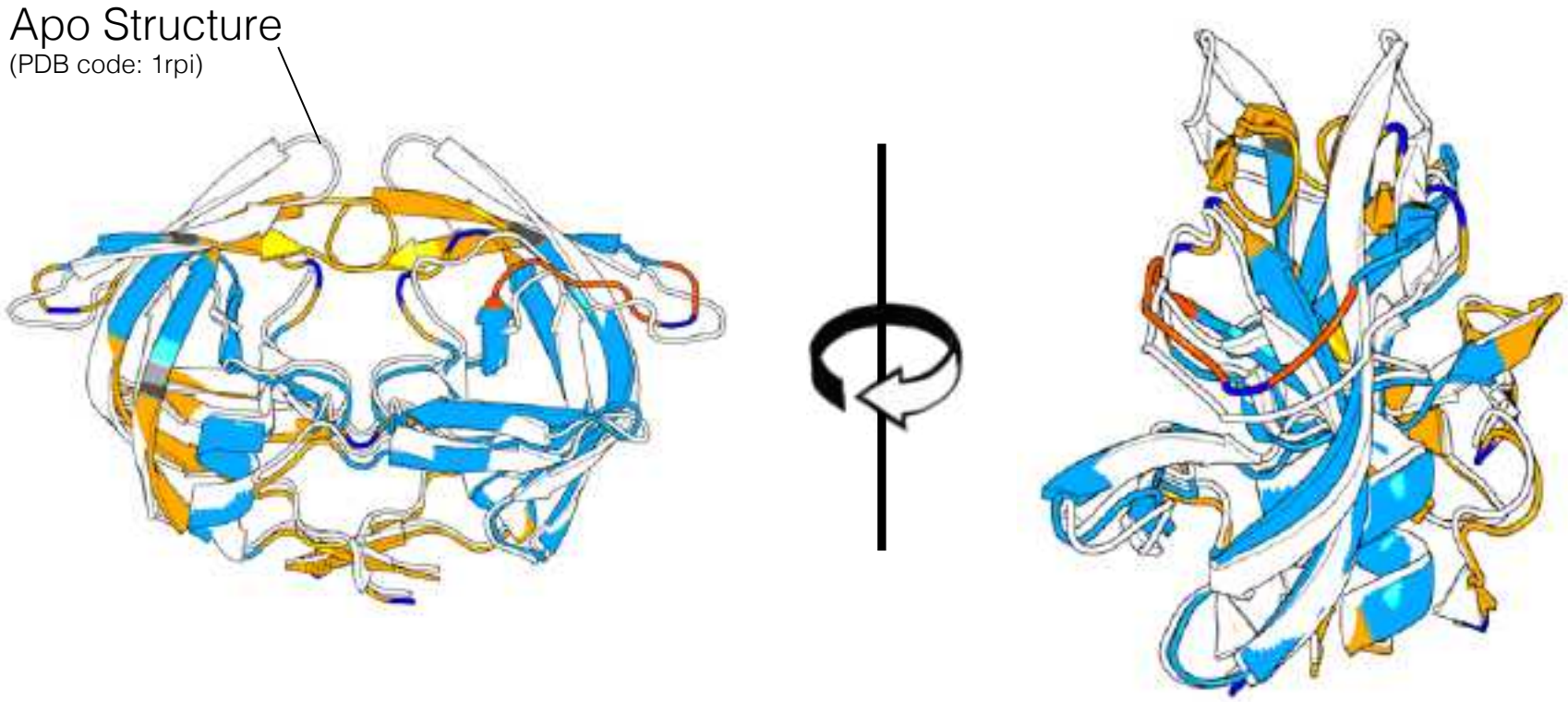


(PDB code: 1htg)

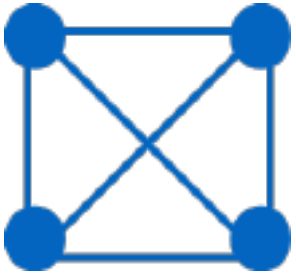


Crystal structure
(after **deleting** the ligand)

Apo Structure

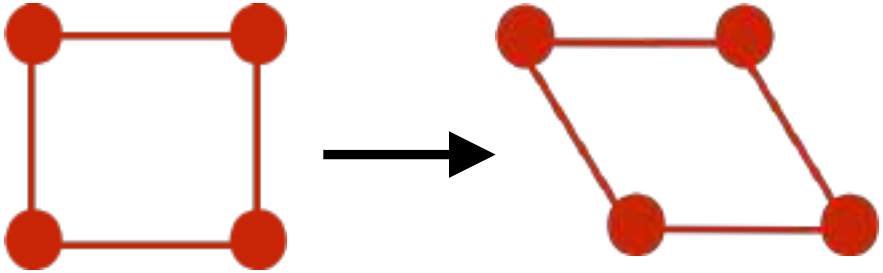


How ProFlex works

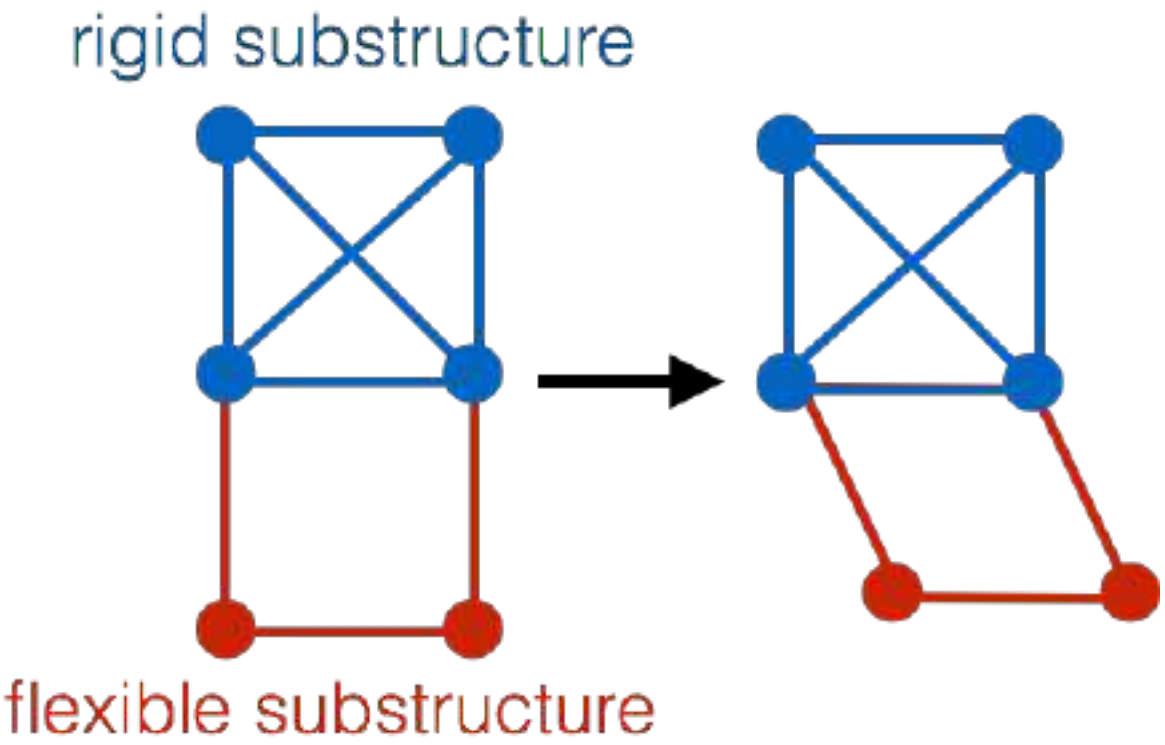


over-constrained
(rigid)

isostatic
(just rigid)



under-constrained
(flexible)

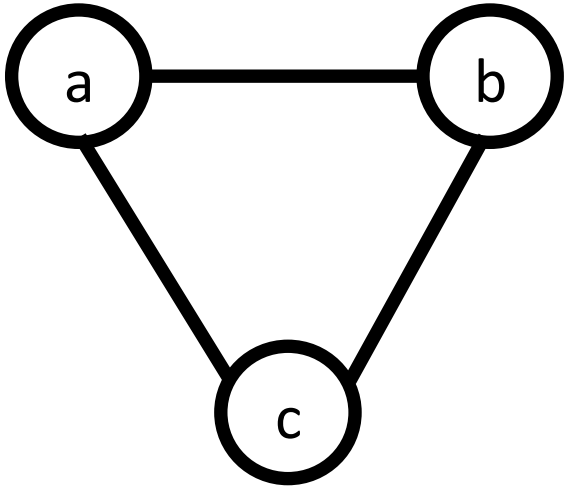

rigid substructure
flexible substructure

2D Pebble Game

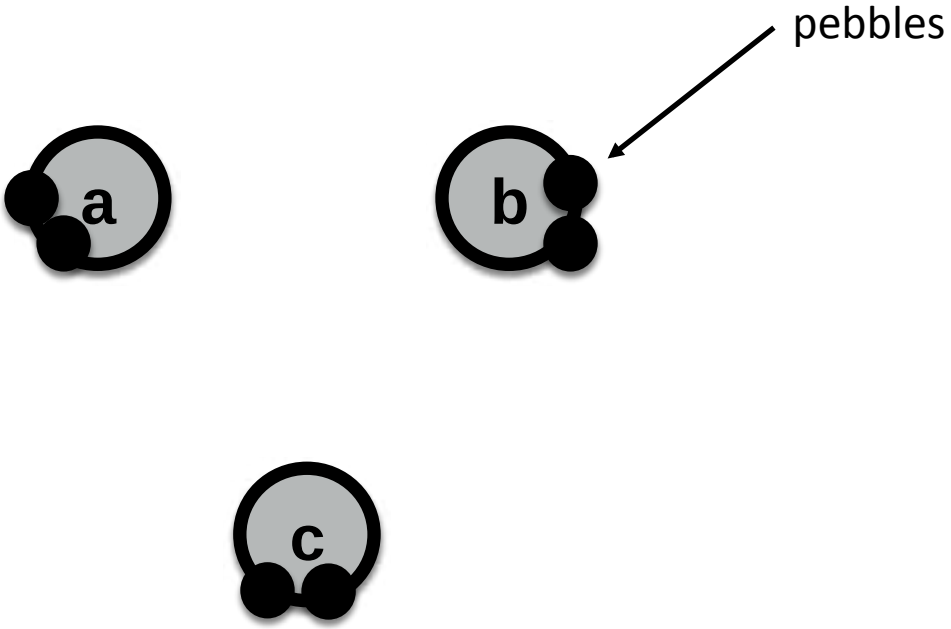
Jacobs and Thorpe. Generic rigidity percolation: The pebble game. Phys Rev Lett, 75(22):4051–4054, Nov 1995.

minimally rigid graph with *n* nodes and *m* edges

$m = 2n - 3$ (2,3 counting)

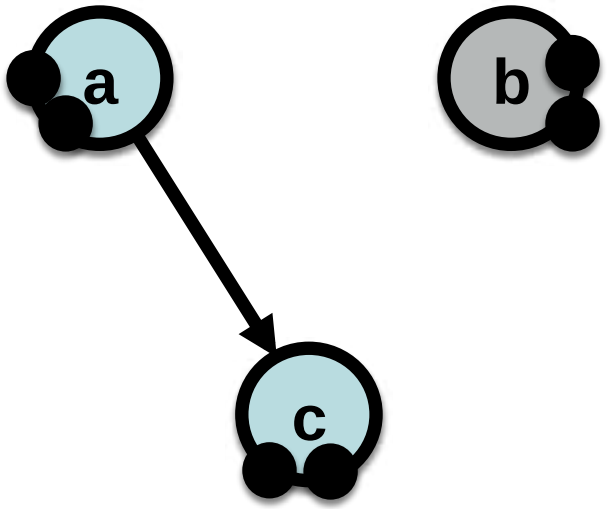


2D Pebble Game



2D Pebble Game

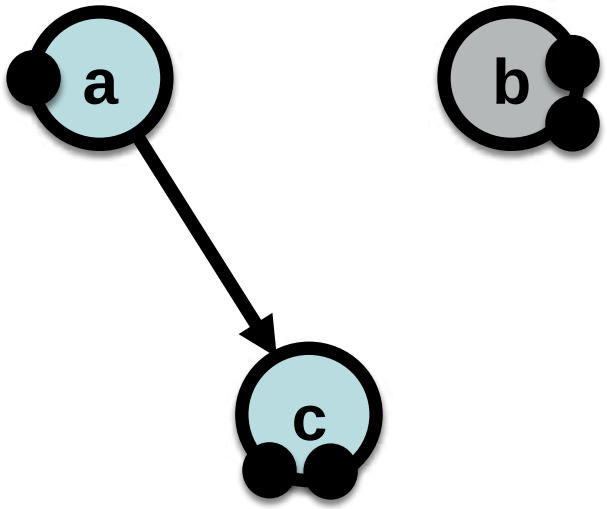
1) Draw an edge if 2 pebbles are present at both nodes.



2D Pebble Game

1) Draw an edge if 2 pebbles are present at both nodes.

   Next, consume 1 pebble from the starting node.

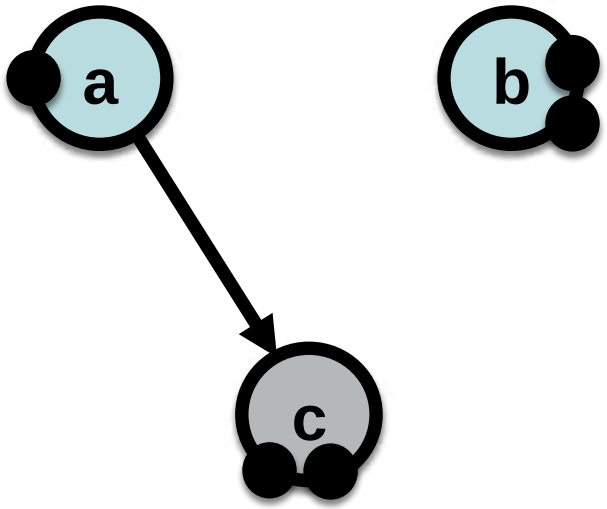


2D Pebble Game

1) Draw an edge if 2 pebbles are present at both nodes.

   Next, consume 1 pebble from the starting node.

2) Do a depth-first search to recover pebbles



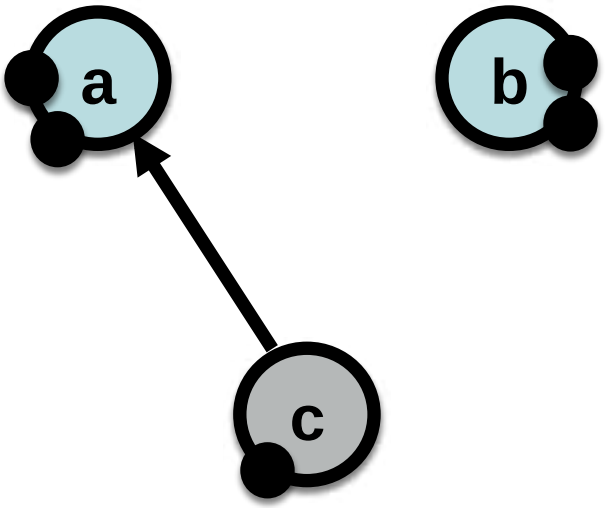
2D Pebble Game

1) Draw an edge if 2 pebbles are present at both nodes.

   Next, consume 1 pebble from the starting node.

2) Do a depth-first search to recover pebbles

3) Revert the edge and bring the pebble back to the node



2D Pebble Game

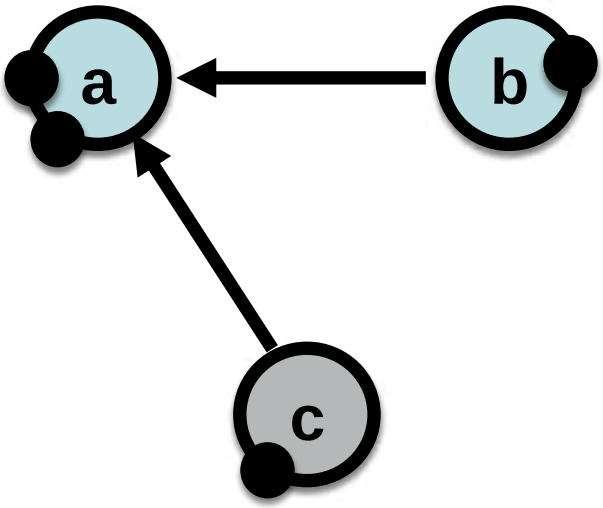
1) Draw an edge if 2 pebbles are present at both nodes.

   Next, consume 1 pebble from the starting node.

2) Do a depth-first search to recover pebbles

3) Revert the edge and bring the pebble back to the node

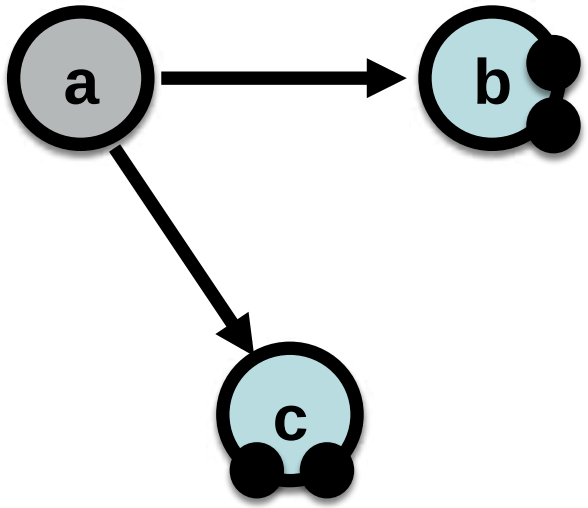
4) Go back to 1) and Insert a new edge



2D Pebble Game

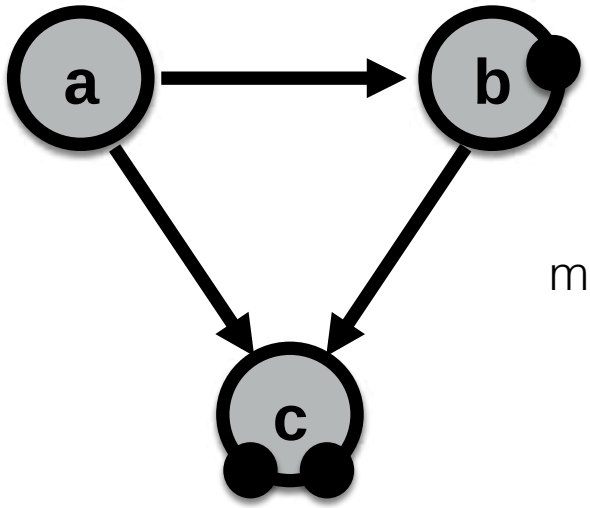
2) Do a depth-first search to recover pebbles

3) Revert the edge and bring the pebble back to the node



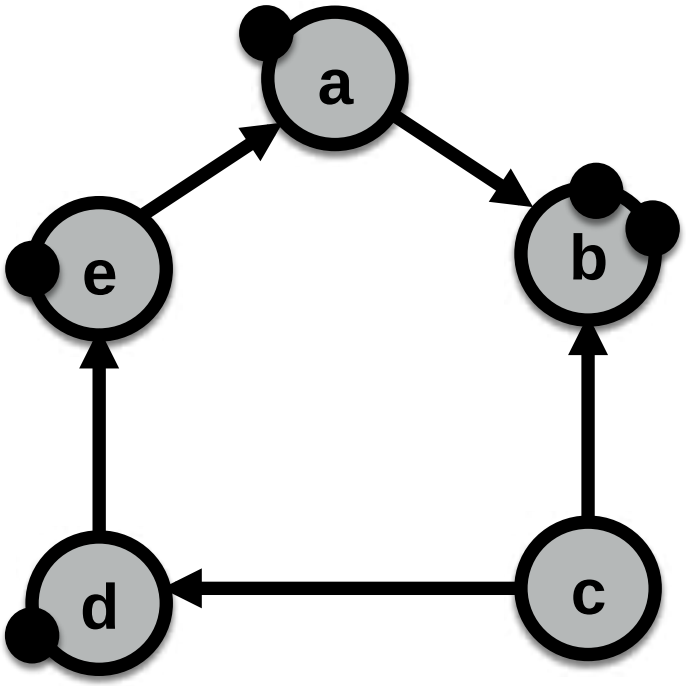
2D Pebble Game

4) Go back to 1) and Insert a new edge



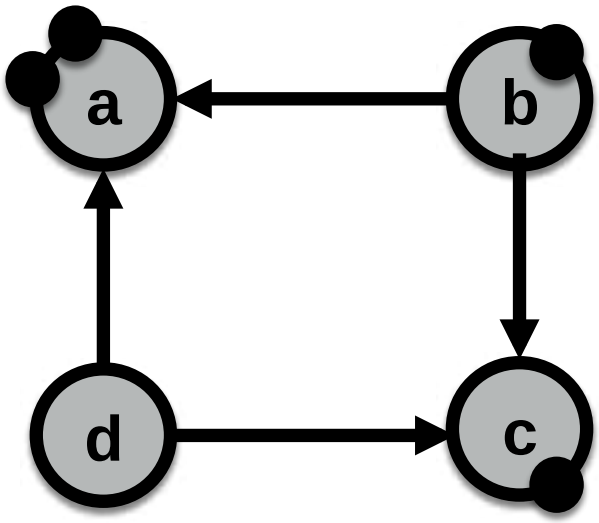
minimally rigid

2D Pebble Game

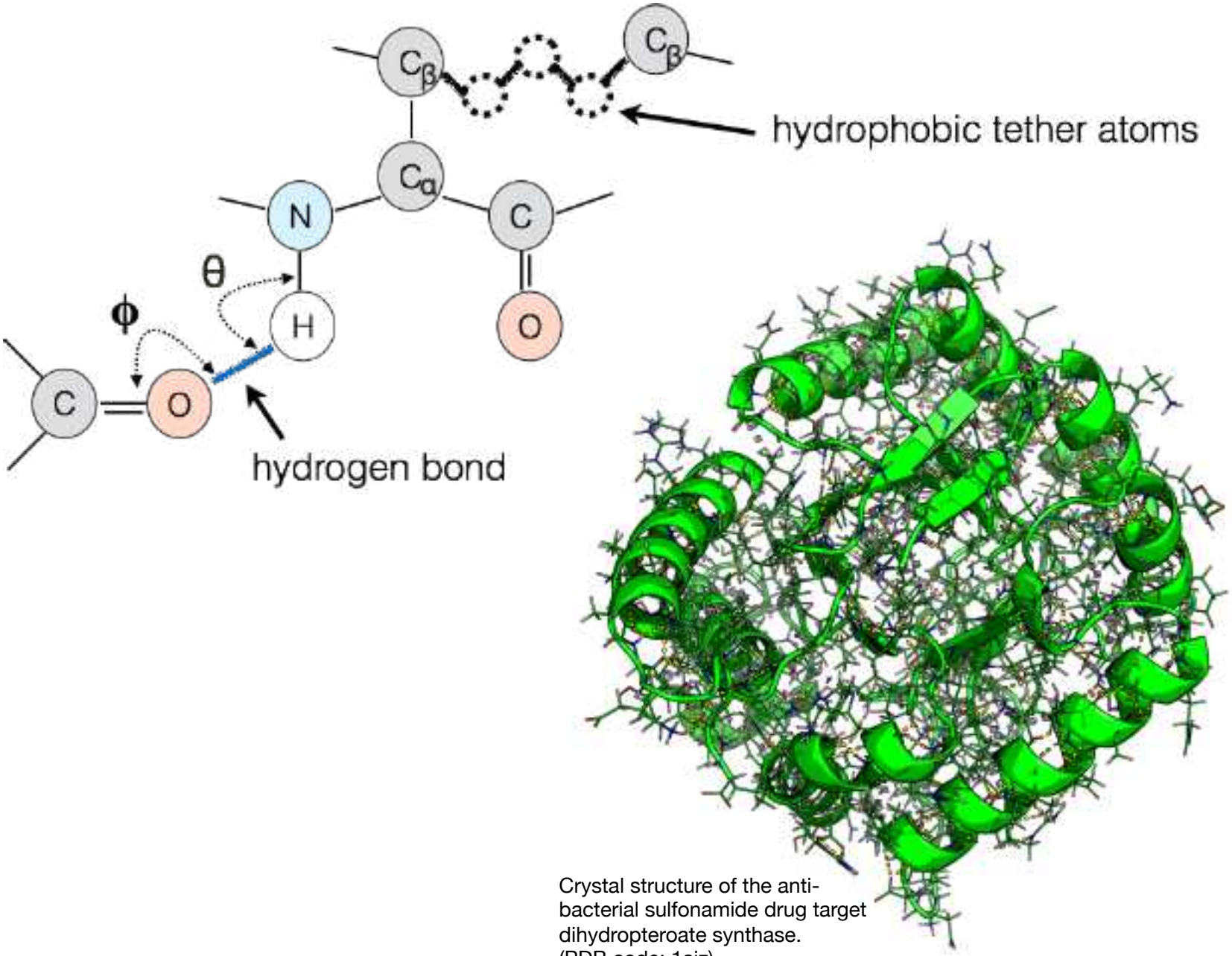


flexible (2 d.o.f.)

2D Pebble Game



flexible (1 d.o.f.)



Crystal structure of the anti-bacterial sulfonamide drug target dihydropteroate synthase.
(PDB code: 1ajz)

Selecting the best ligand binding pose with ProFlex

Take crystal pose

Generate low-energy conformations

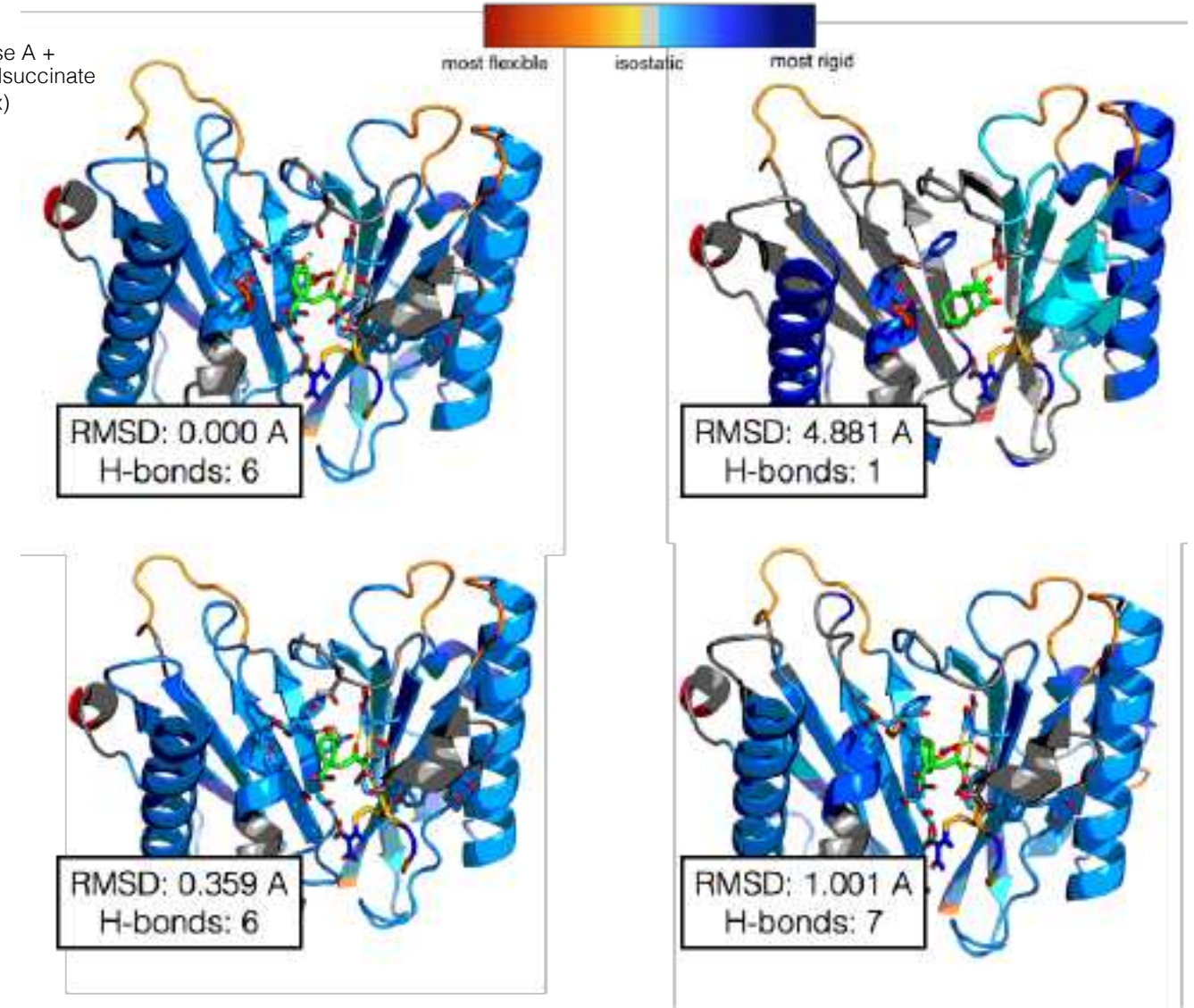
Dock low-energy conformations

Score docked complexes

Compare best-scoring pose to crystal

Protein Flexibility Changes in Docking Poses

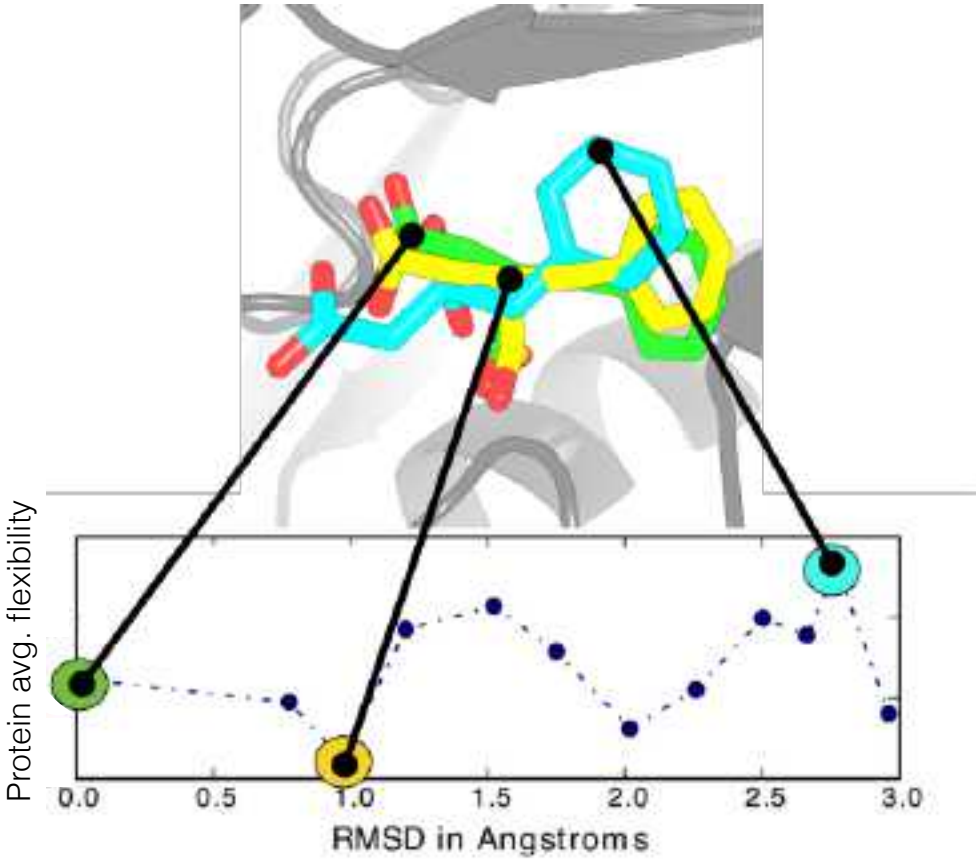
Carboxypeptidase A +
inhibitor L-benzylsuccinate
(PDB code: 1cbx)

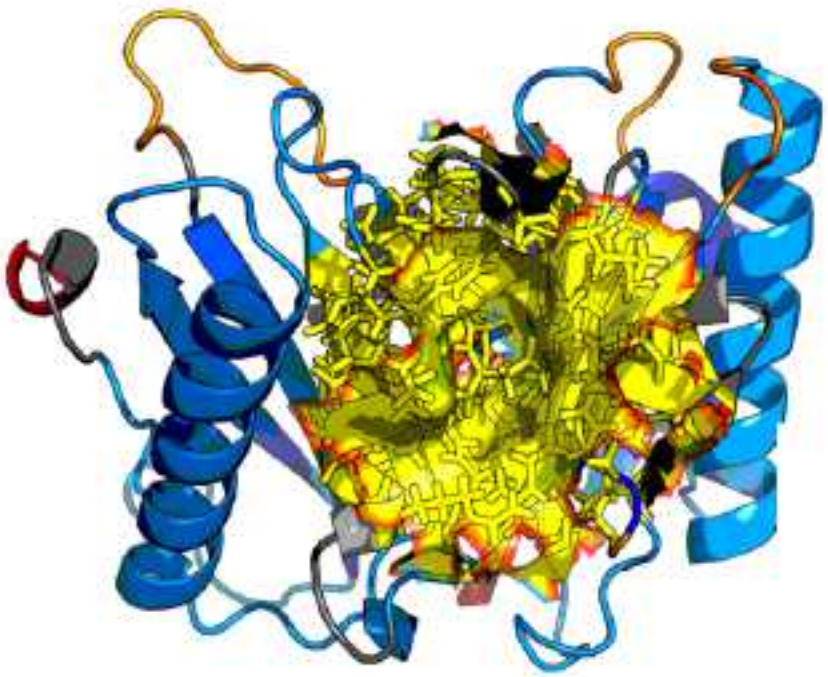


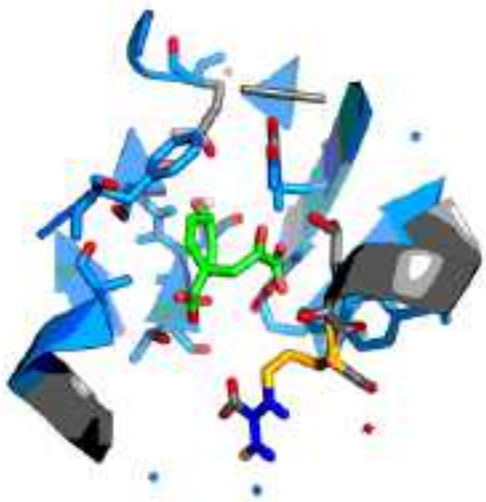
"least rigid"
protein

"most rigid"
protein

Protein Flexibility Changes in Docking Poses



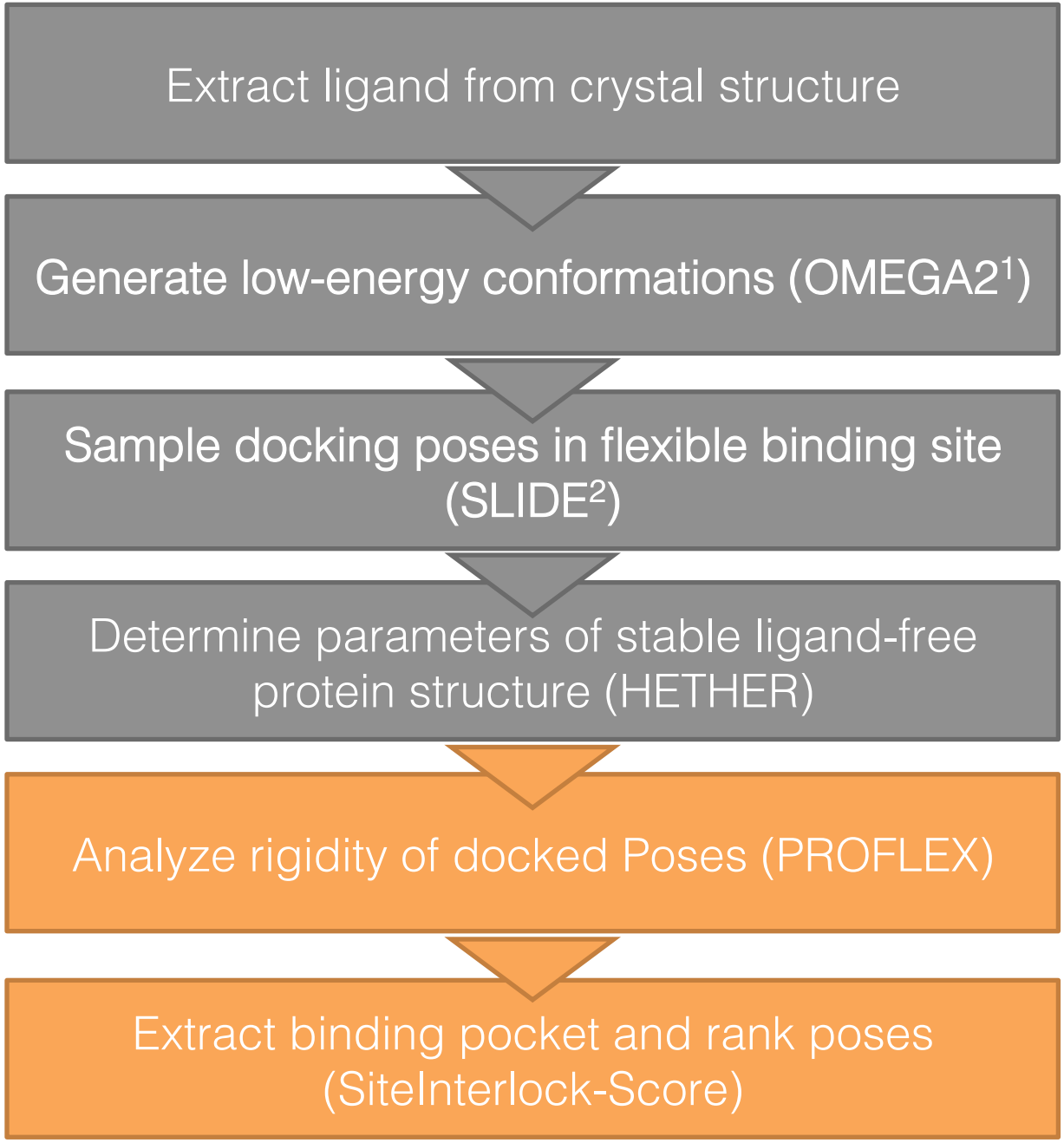




SiteInterlock-Score

$$\frac{1}{2}\left(\frac{x_p-\mu_p}{\sqrt{\frac{1}{n_p}\sum_{i=1}^{n_p}(x_i-\mu_p)^2}}+\frac{x_l-\mu_l}{\sqrt{\frac{1}{n_l}\sum_{i=1}^{n_l}(x_i-\mu_l)^2}}\right)$$

n_p : Protein atoms within 9 A of a ligand's heavy atom.
n_l : Ligand's heavy atoms.
x : Average flexibility of a docking pose.
μ : Average flexibility of all docking poses for one case.



[1] P. C. D. Hawkins, A. G. Skillman, G. L. Warren, B. A. Ellingson, and M. T. Stahl. Conformer generation with omega: algorithm and validation using high quality structures from the protein databank and cambridge structural database. J Chem Inf Model, 50(4):572–84, Apr 2010.

[2] M. I. Zavodszky, P. C. Sanschagrin, L. A. Kuhn, and R. S. Korde. Distilling the essential features of a protein surface for improving protein-ligand docking, scoring, and virtual screening. Journal of computer-aided molecular design, 16(12):883–902, 2002.


1a9x


1amu


1b5e


1bgv


1bx4


1c96


1cbs

19 x Holo


1cbx


1ccw


1chm


1com


1coy


1cps


1did


1hwr


1rx1


7tim


3ks9


3odu

11 x Apo

(holo ligand \
apo protein)


10gs / 16gs


1ahb / 1ahc


1aj2 / 1ajz


1gmr / 1gmq


1kel / 1kem


1nsc / 1nsb

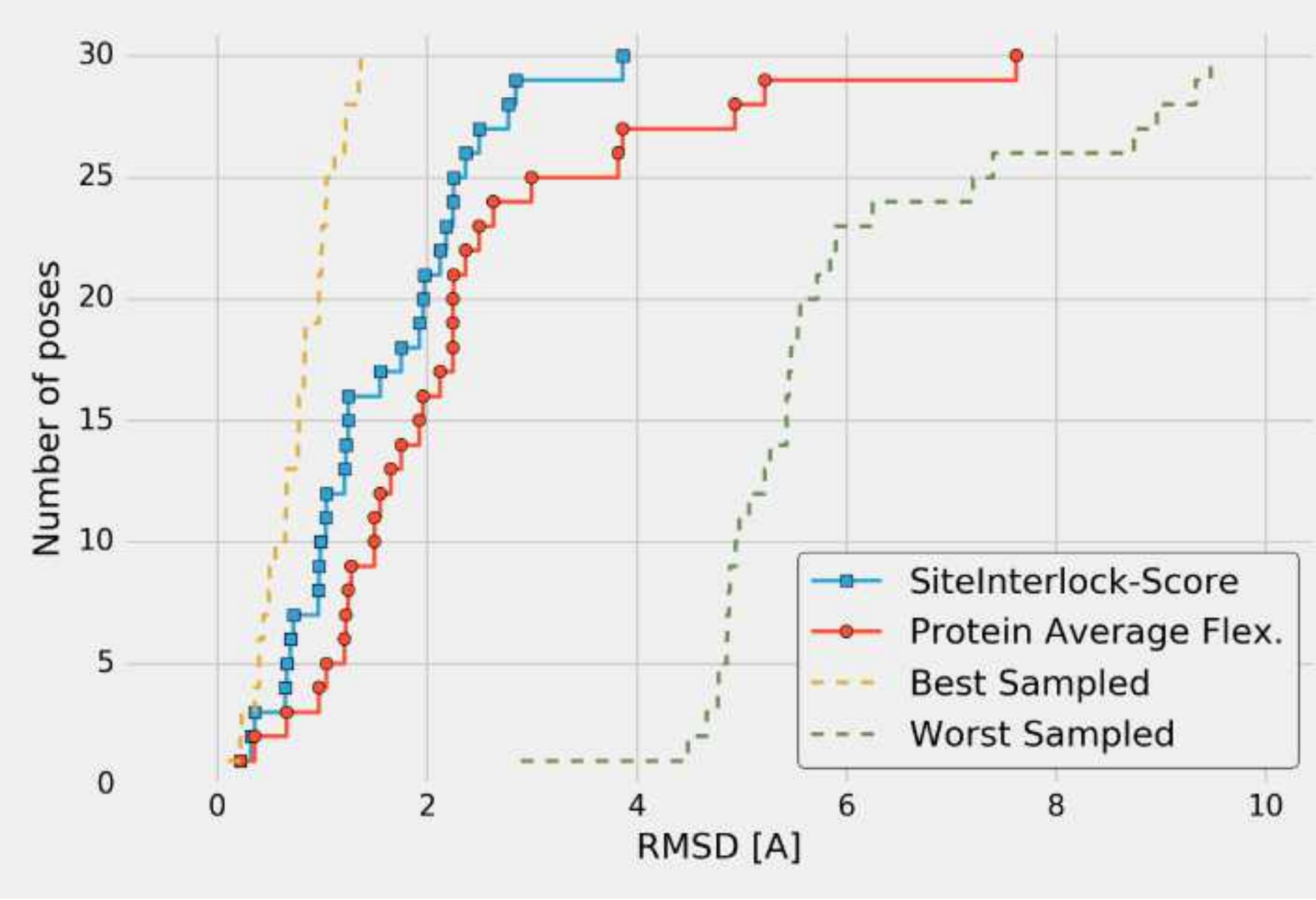

1swd / 1swa

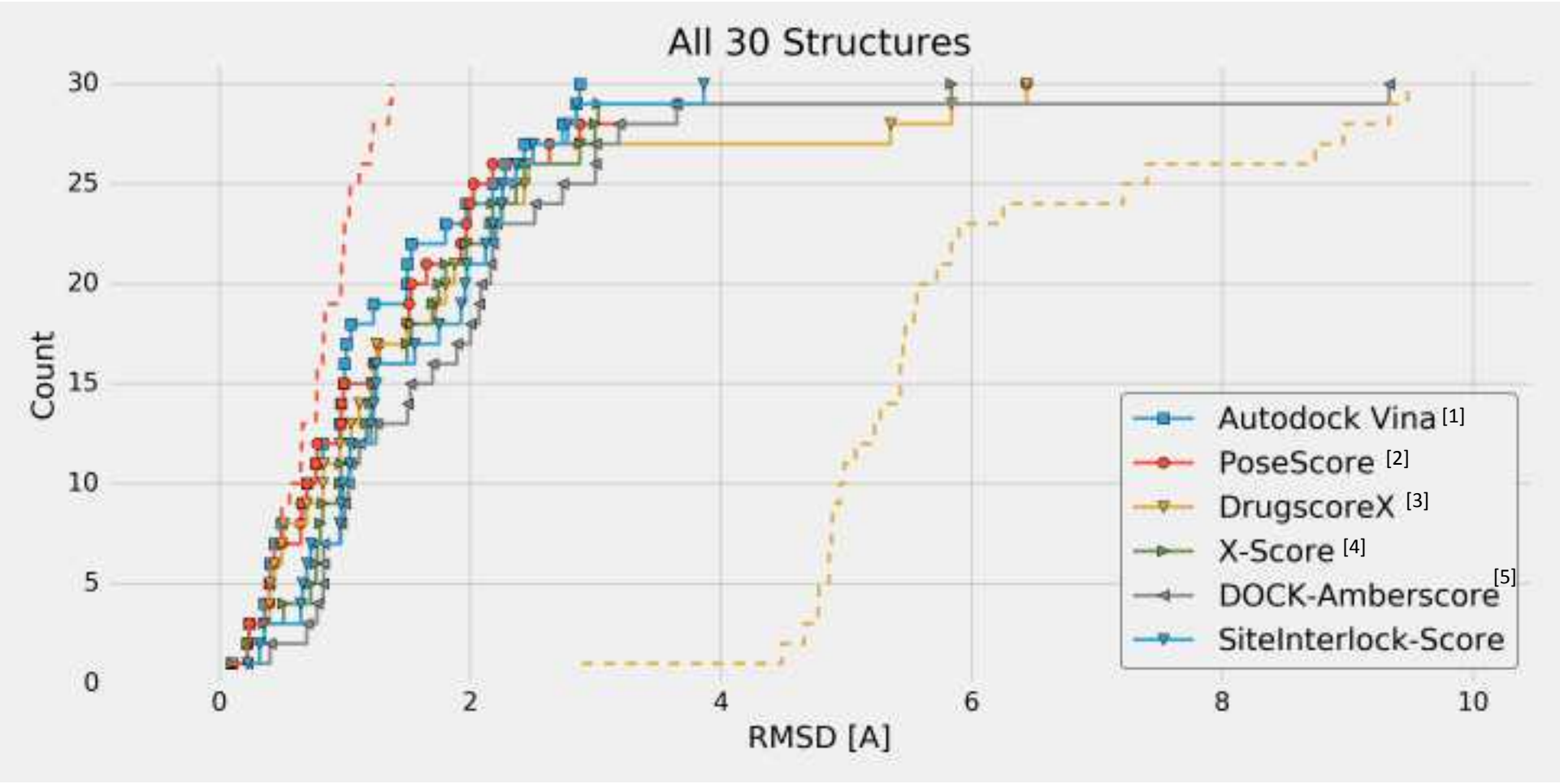

3tmn / 1tli


1tmt / 1vr1


1ydb / 1ydc


5sga / 2sga


30
25
20
15
10
5
0
Number of poses
0
2
4
6
8
10
RMSD [A]
SiteInterlock-Score
Protein Average Flex.
Best Sampled
Worst Sampled



[1] Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, *31*(2), 455-461.

[2] Fan, H., Schneidman-Duhovny, D., Irwin, J. J., Dong, G., Shoichet, B. K., & Sali, A. (2011). Statistical potential for modeling and ranking of protein–ligand interactions. *Journal of chemical information and modeling*, *51*(12), 3078-3092.

[3] Neudert, G., & Klebe, G. (2011). DSX: a knowledge-based scoring function for the assessment of protein–ligand complexes. *Journal of chemical information and modeling*, *51*(10), 2731-2745.

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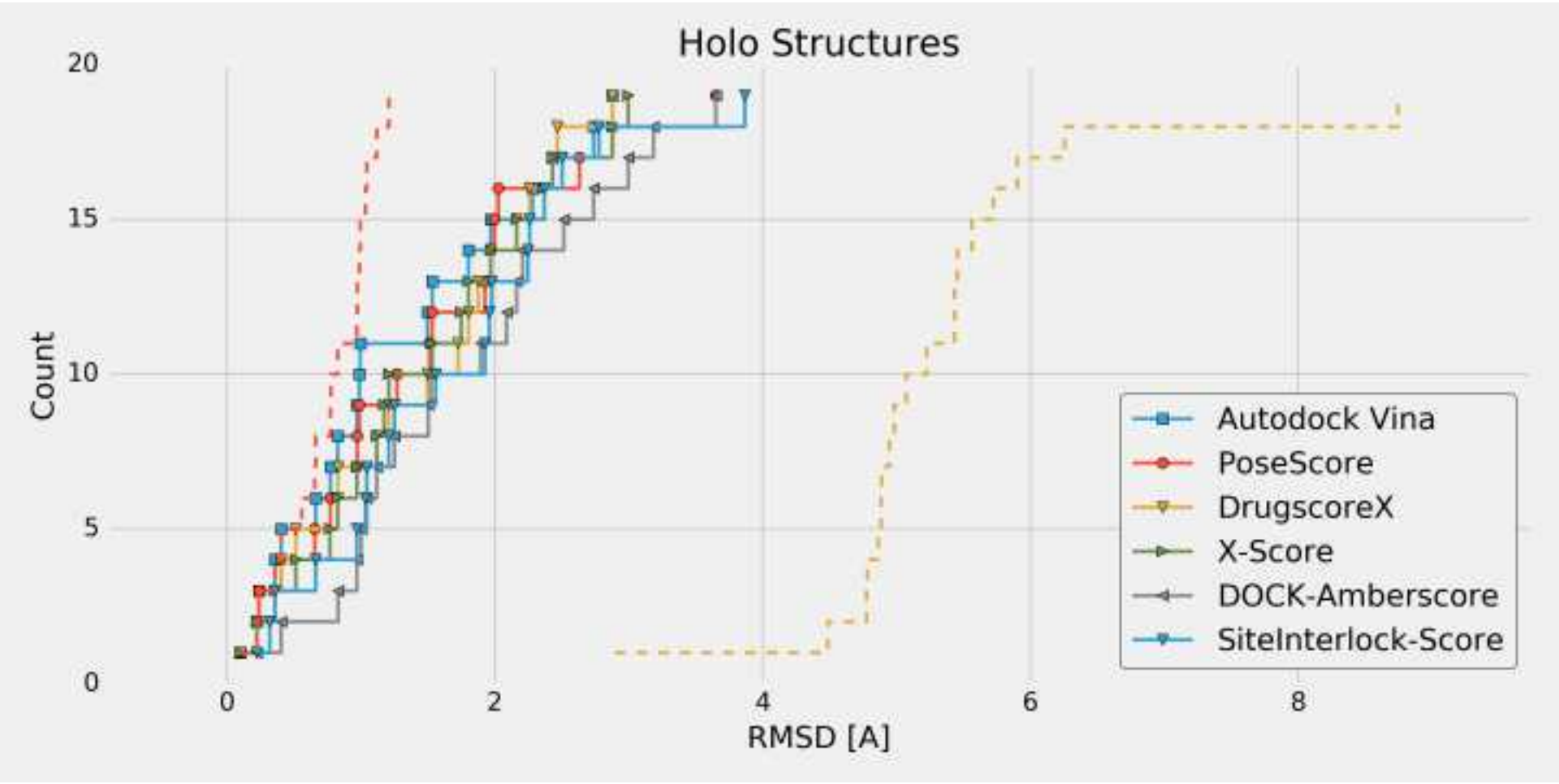
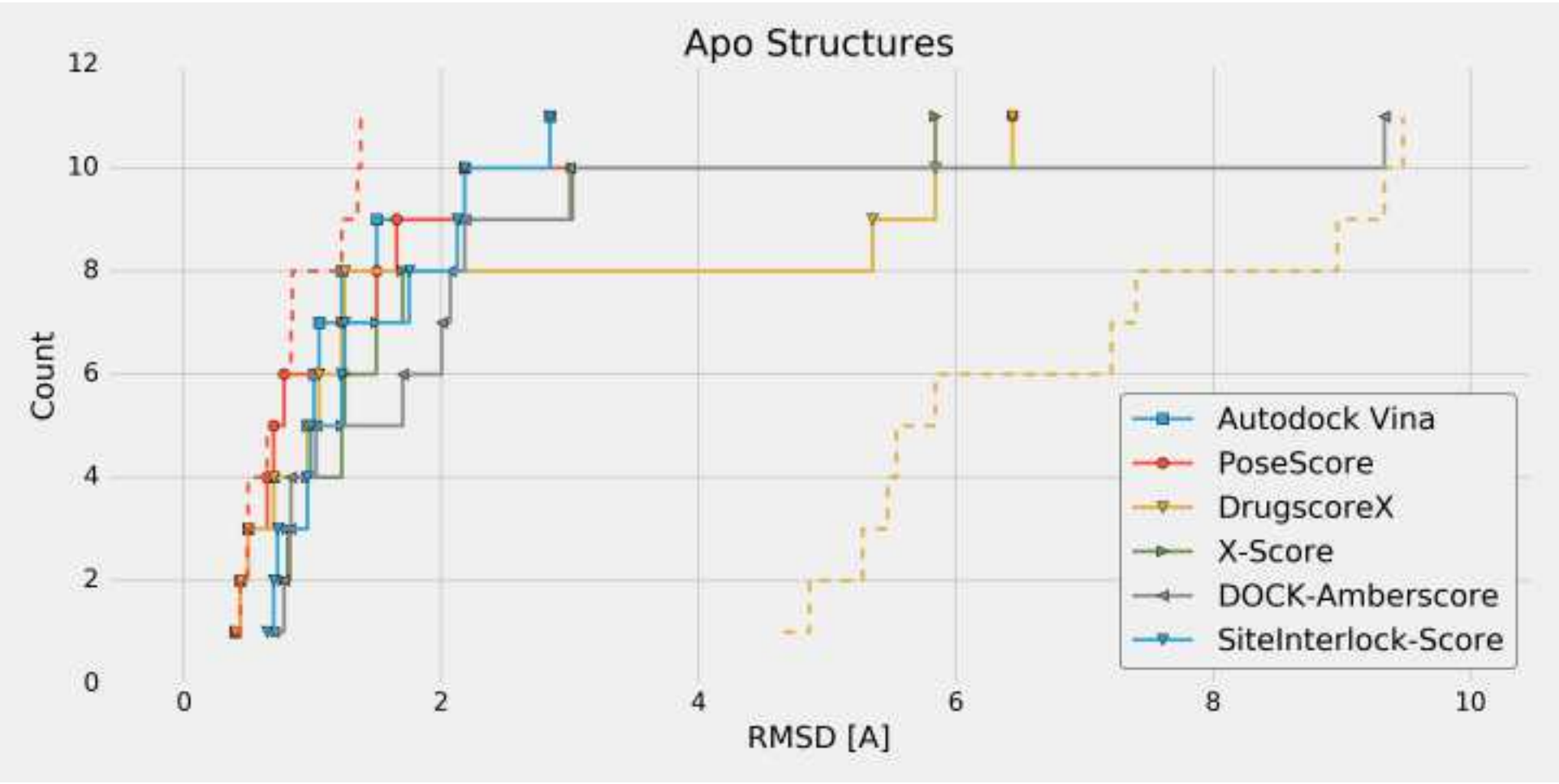

Holo Structures
Count
RMSD [A]
0
5
10
15
20
0
2
4
6
8
Autodock Vina
PoseScore
DrugscoreX
X-Score
DOCK-Amberscore
SiteInterlock-Score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Count
RMSD [A]
0
2
4
6
8
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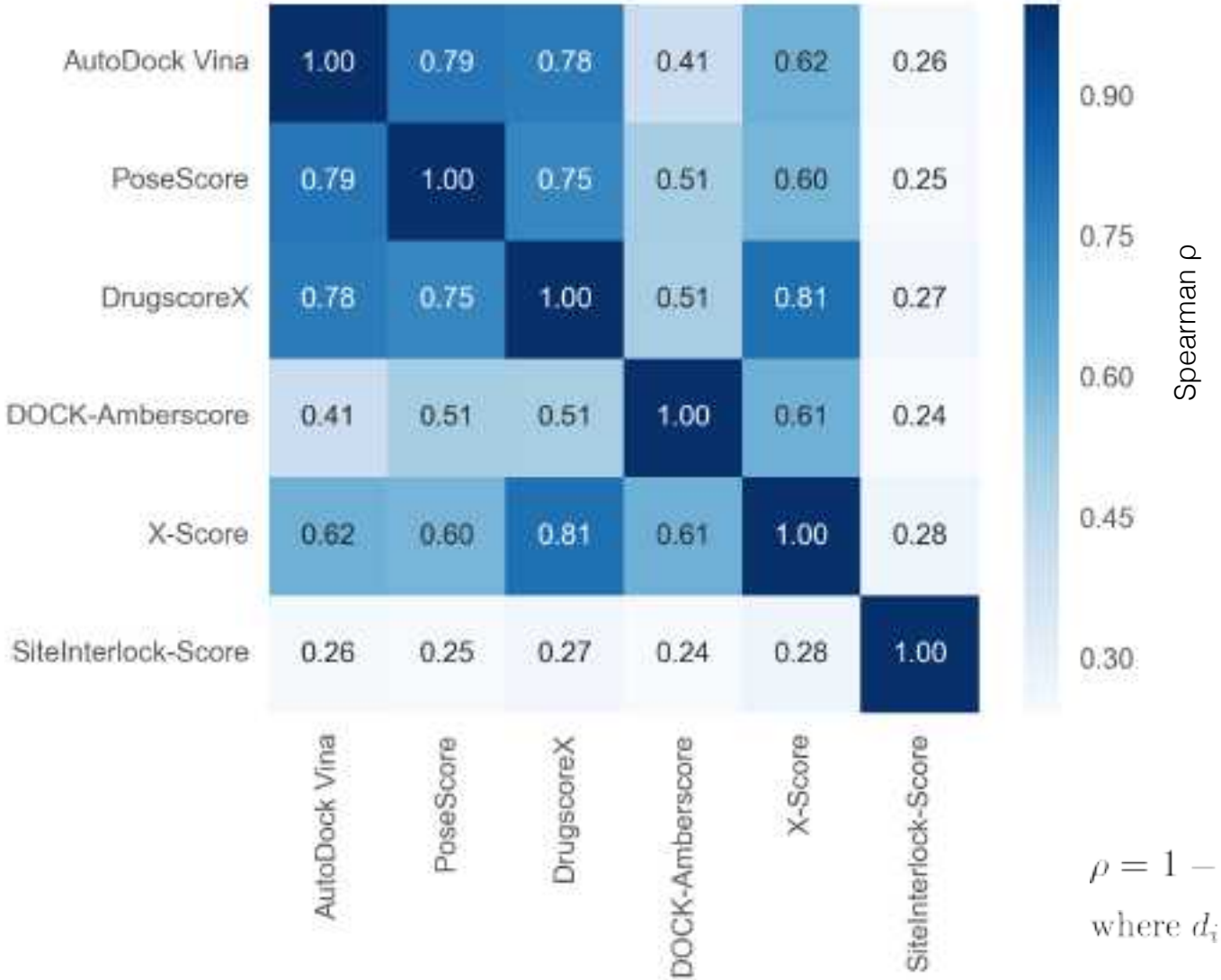
12
Autodock Vina
PoseScore
DrugscoreX
X-Score
DOCK-Amberscore
SiteInterlock-Score

A “unique” signal



$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2-1)}.$$

where $d_i = x_i - y_i$

Future Directions

Acknowledgements

The Kuhn Lab

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