Computational modeling of protein-protein interactions

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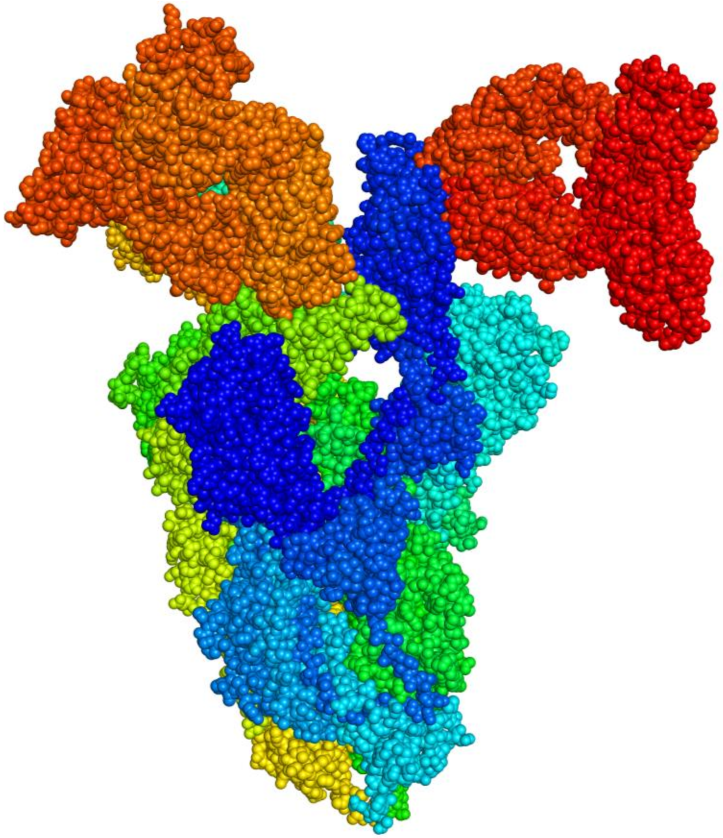
Z. Liu, A. T. Grigas, J. Sumner, E. Knab, C. M. Davis, and C. S. O’Hern, “Identifying the minimal sets of distance restraints for FRET-assisted protein structural modeling,” *Protein Science* (2024).

J. Sumner, G. Meng, N. Brandt, A. T. Grigas, A. Cordoba, M. D. Shattuck, and C. S. O”Hern, “Assessment of scoring functions for computational models of protein-protein interactions,” submitted to Journal of Computational Chemistry (2025).

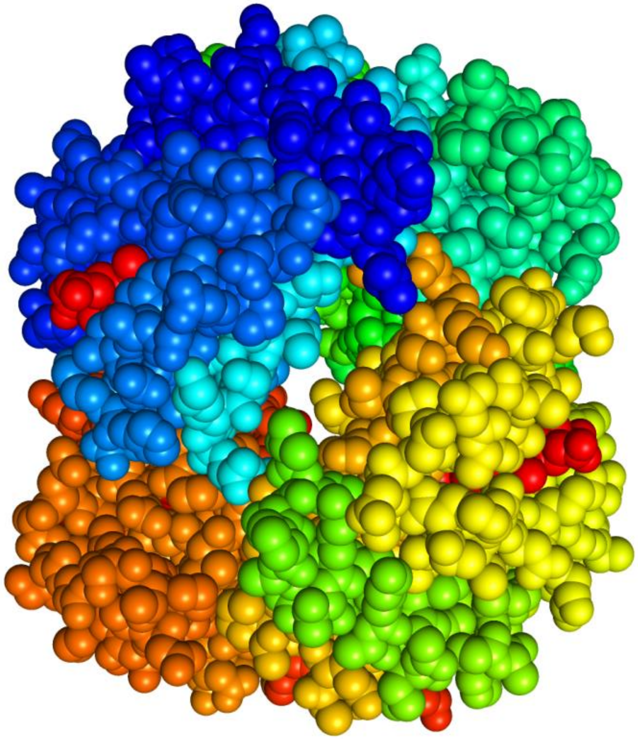
A. T. Grigas, Z. Liu, L. Regan, and C. S. O’Hern, “Corey packing of well-defined xray and NMR protein structures is the same,” Protein Science 31 (2022) e4373.

NIH T32 GM 008384
NIH T32 GM 008283

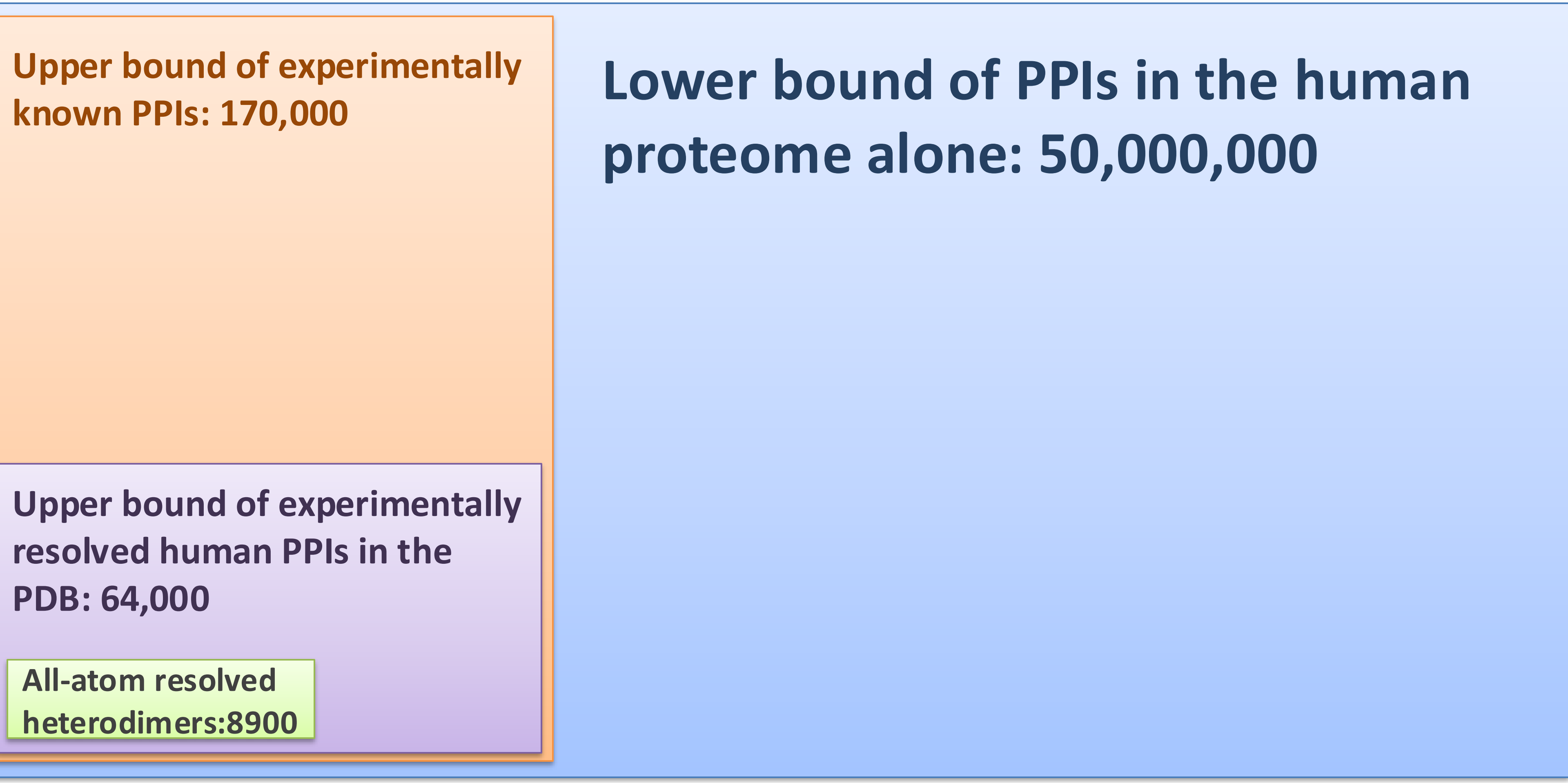
Protein-protein binding/interactions



SARS-CoV-2 spike protein with complexed antibodies



Hemoglobin – complex of 8 proteins – oxygen transporter



Lower bound of PPIs in the human proteome alone: 50,000,000

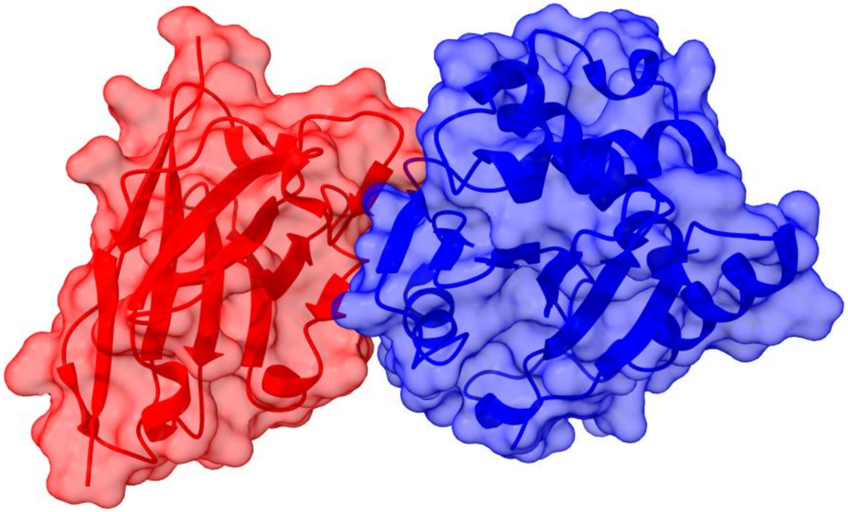
Upper bound of experimentally known PPIs: 170,000

Upper bound of experimentally resolved human PPIs in the PDB: 64,000

All-atom resolved heterodimers:8900

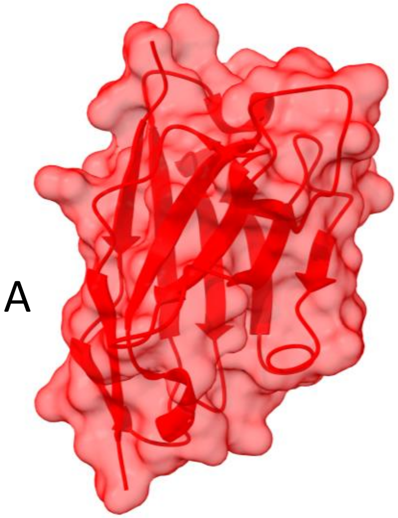
PDBID: 5sv3

heterodimer



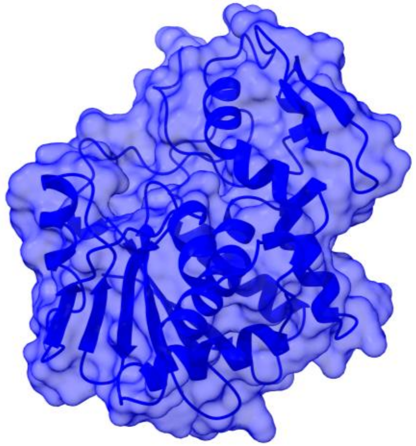
PDBID: 5sv4

Monomer A



PDBID: 1ift

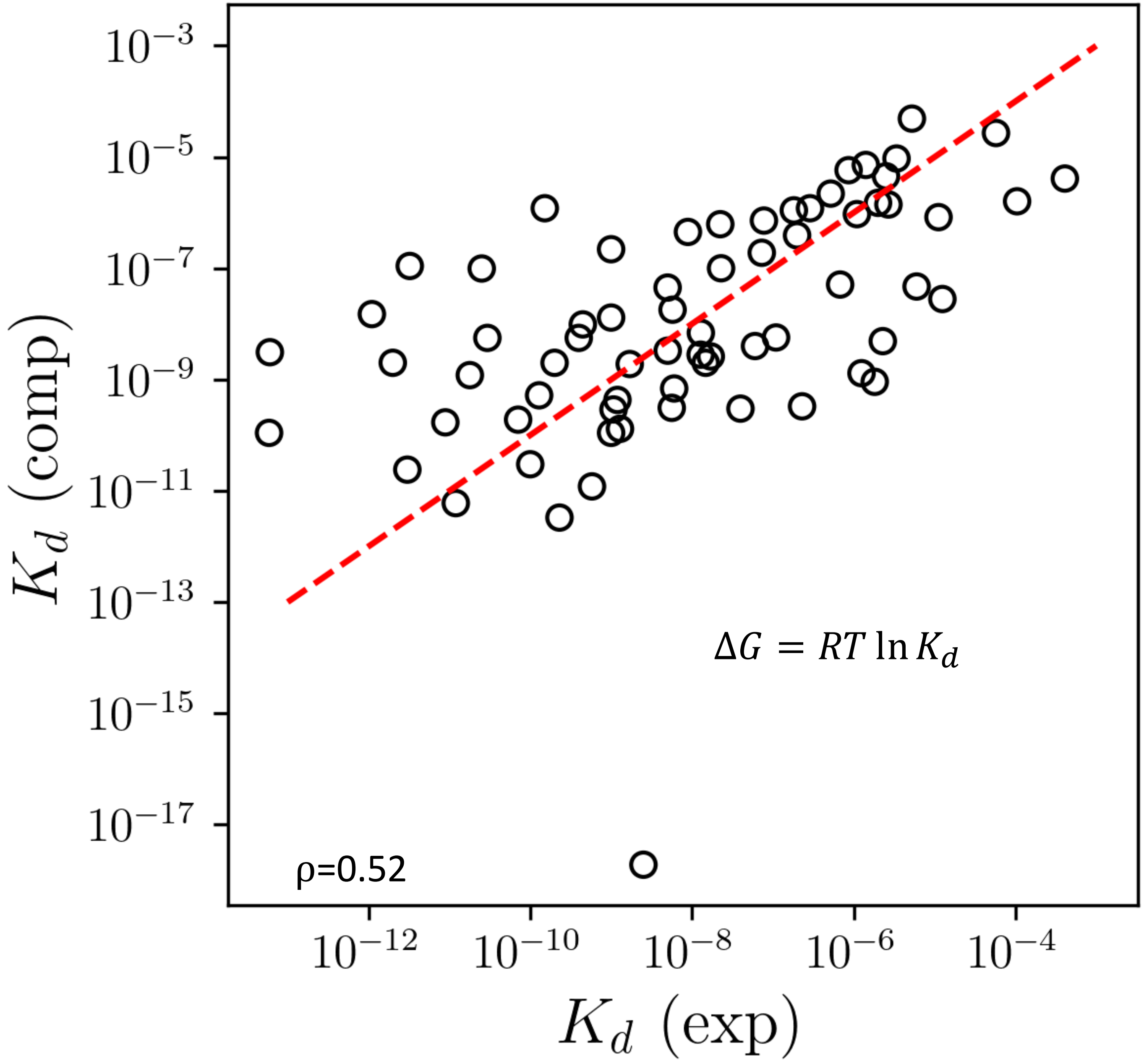
Monomer B



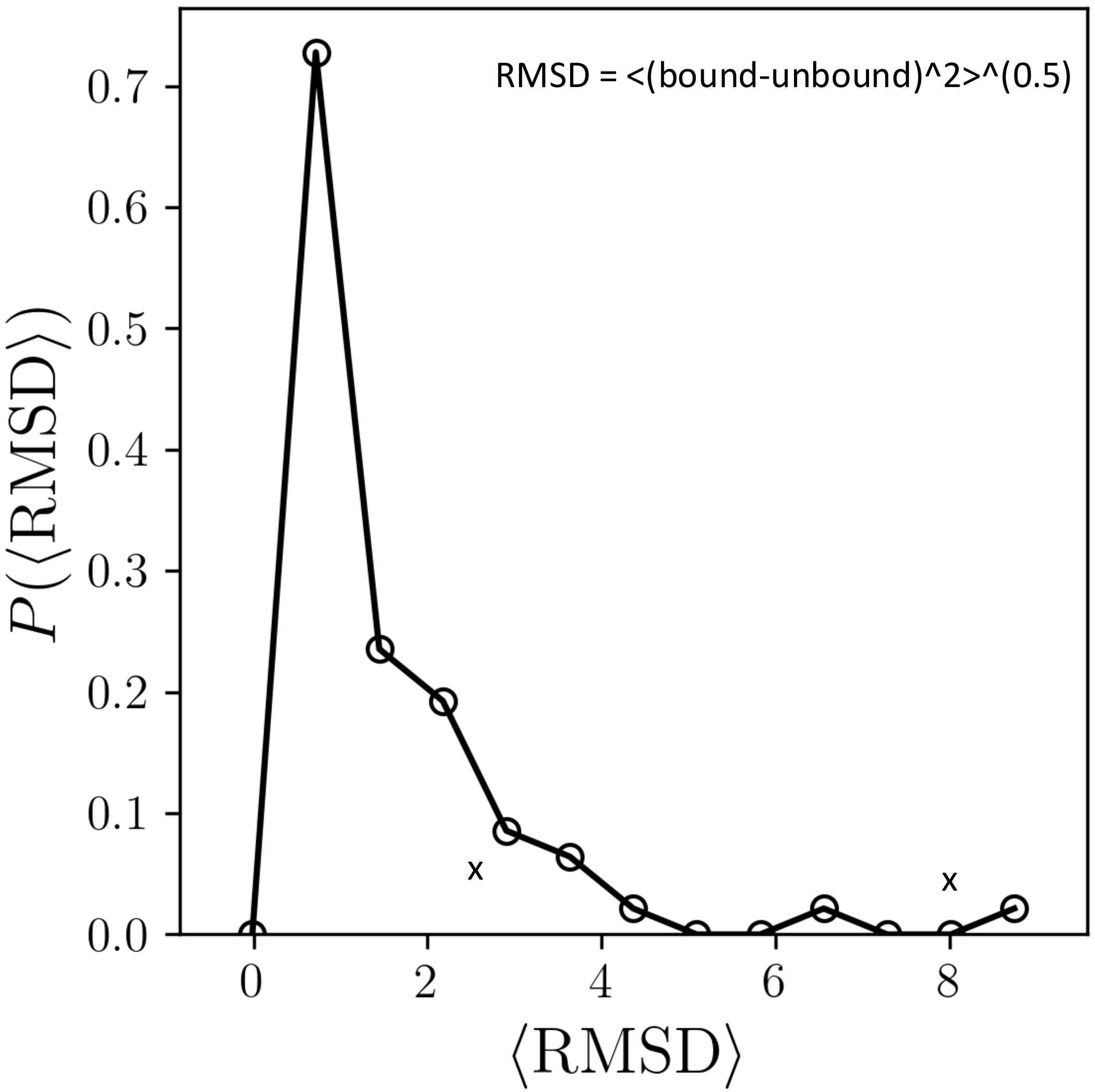
Possible Questions about Heterodimers

- Do proteins A and B bind? How strongly do proteins A and B bind?

- Where do proteins A and B bind and in what conformations?



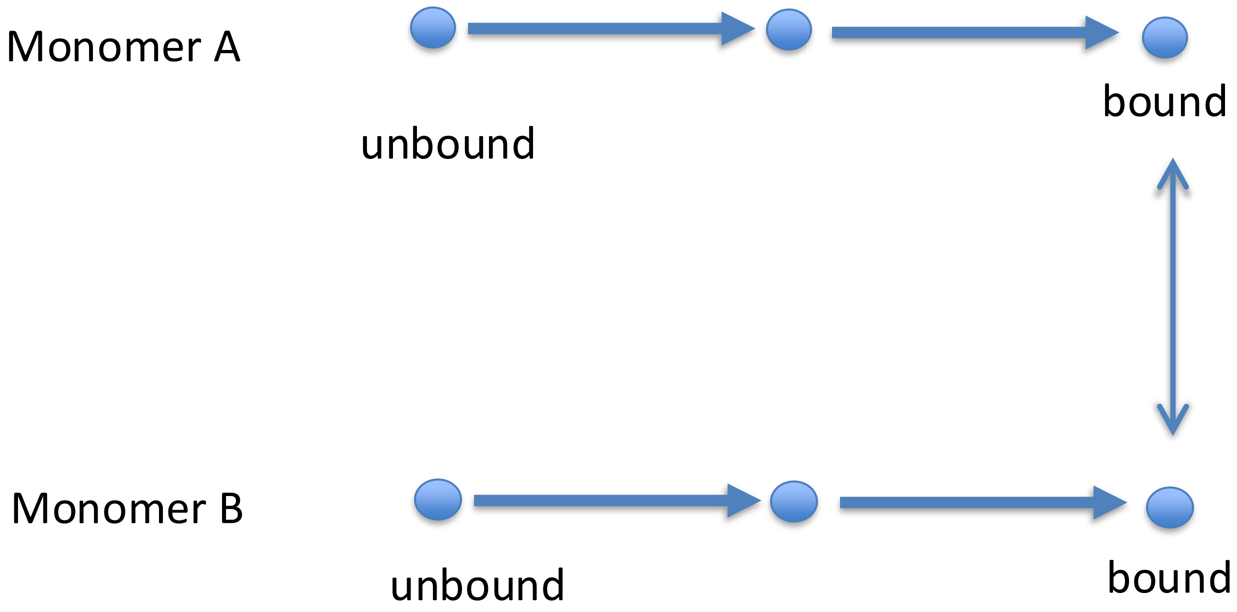
Vangone A, Bonvin AM. Contacts-based prediction of binding affinity in protein-protein complexes. Elife. 2015 Jul 20;4:e07454. doi: 10.7554/eLife.07454.


RMSD = <(bound-unbound)^2>^(0.5)
$P(\langle\mathrm{RMSD}\rangle)$
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
2
4
6
8
$\langle\mathrm{RMSD}\rangle$
x
x

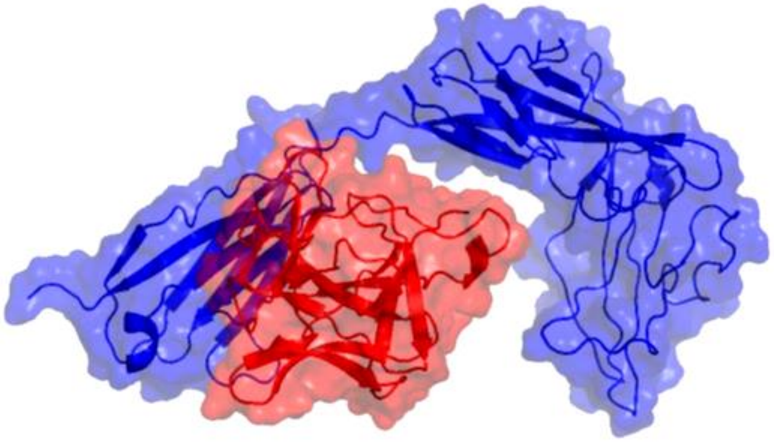
1acb

1ira

Sampling and Scoring

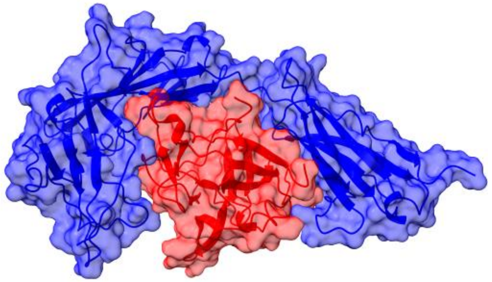


Sampling of Bound Forms

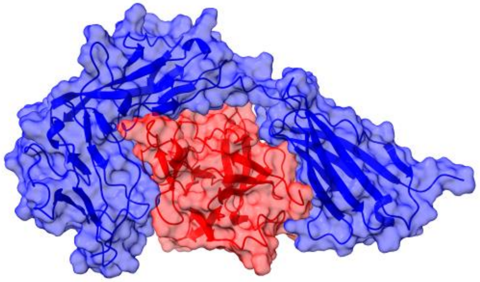


PDB: 1ITB

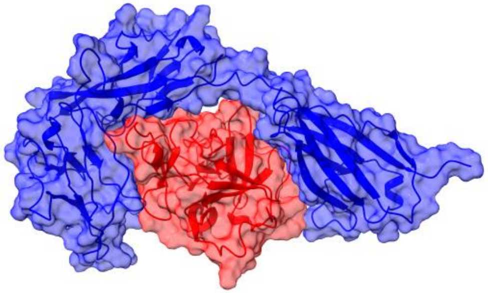
PPI decoy scoring using ground truth



Crystal structure
DockQ: 1.0

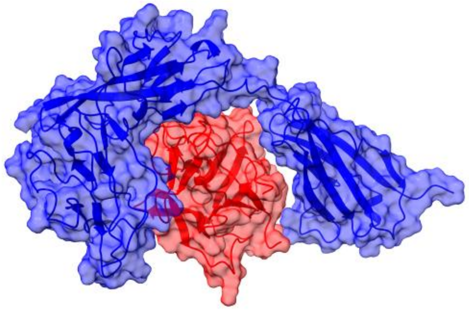


DockQ: 0.847
CAPRI: High

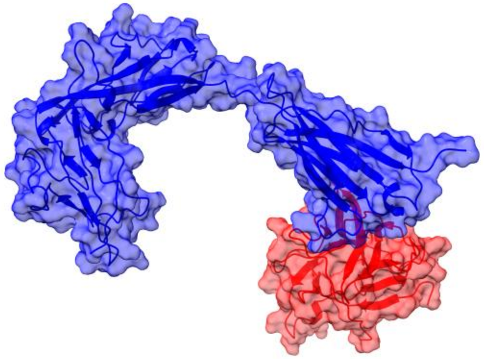


DockQ: 0.506
CAPRI: Medium

shown



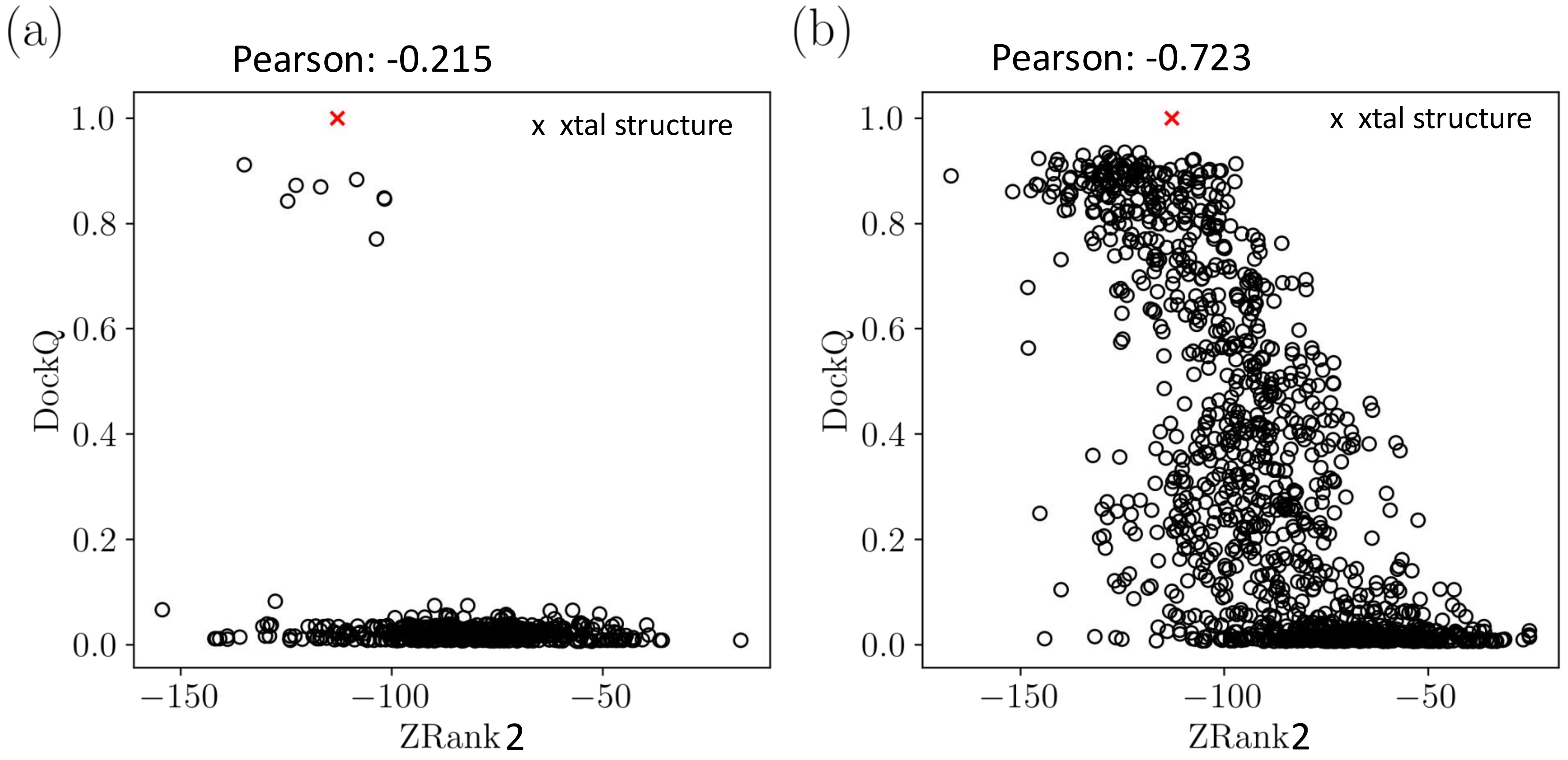
DockQ: 0.286
CAPRI: Acceptable



DockQ: 0.012
CAPRI: Incorrect

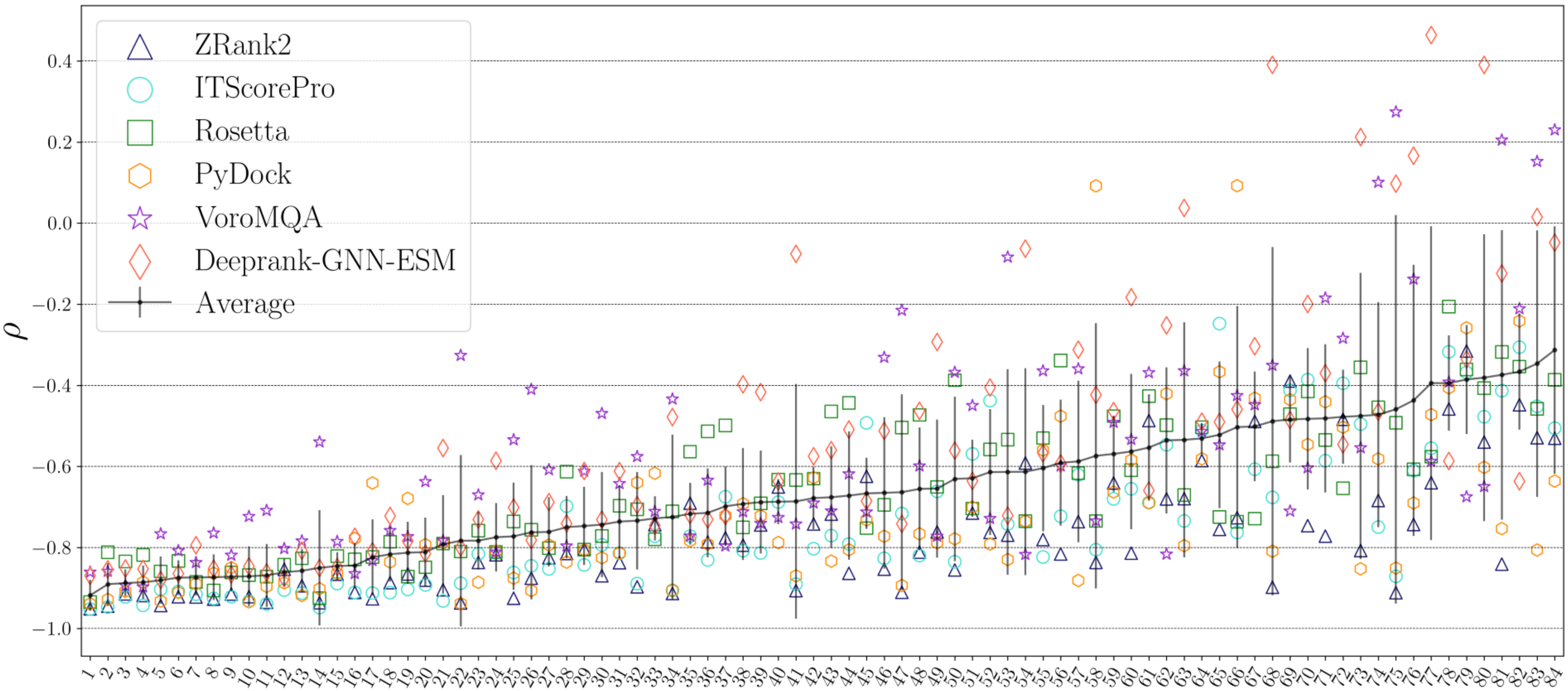
What is the performance of PPI scoring functions on models obtained from bound forms?

Correlation between ground truth and PPI scoring functions



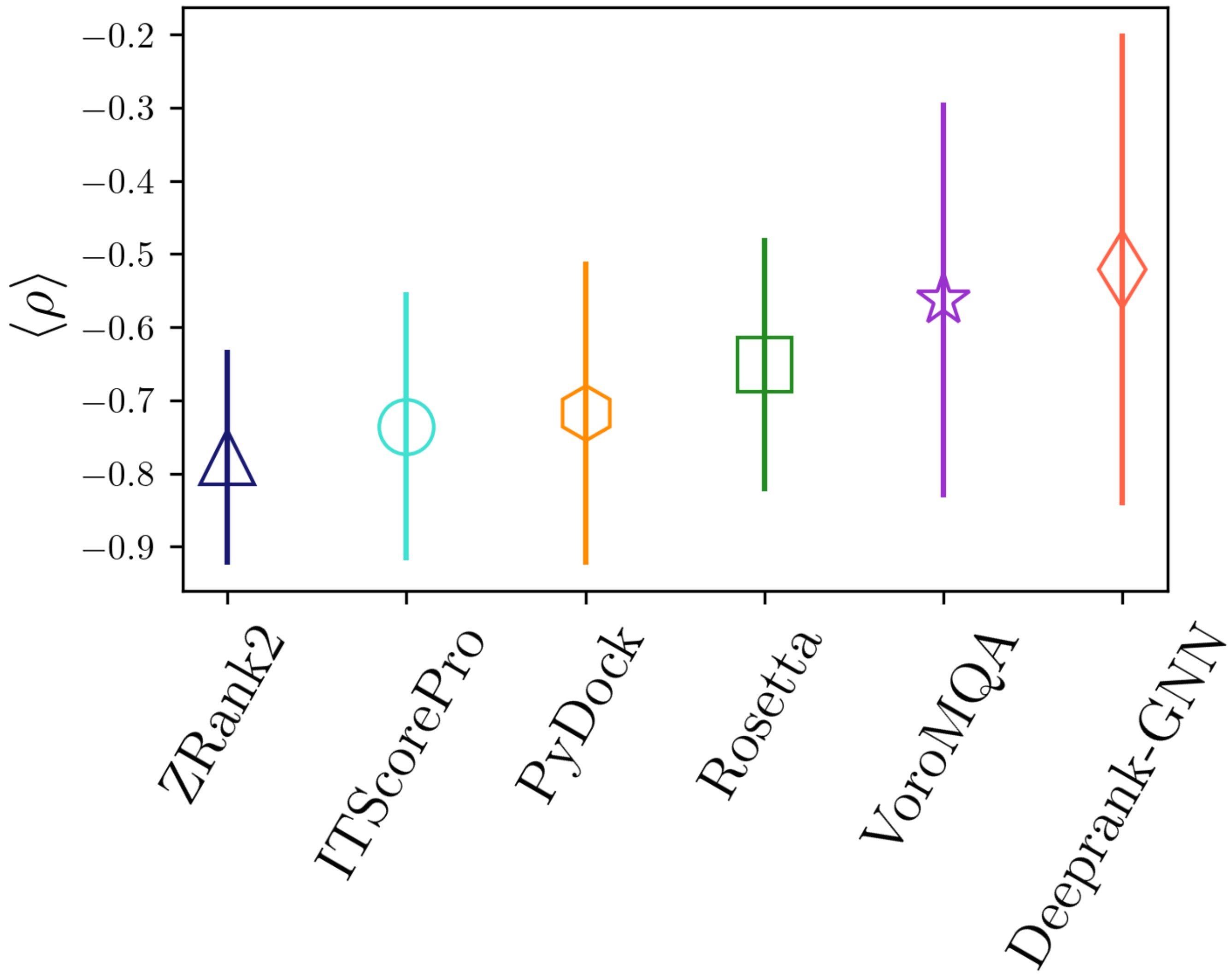
PDBID: 1XG2

Pearson correlation between DockQ and scoring function

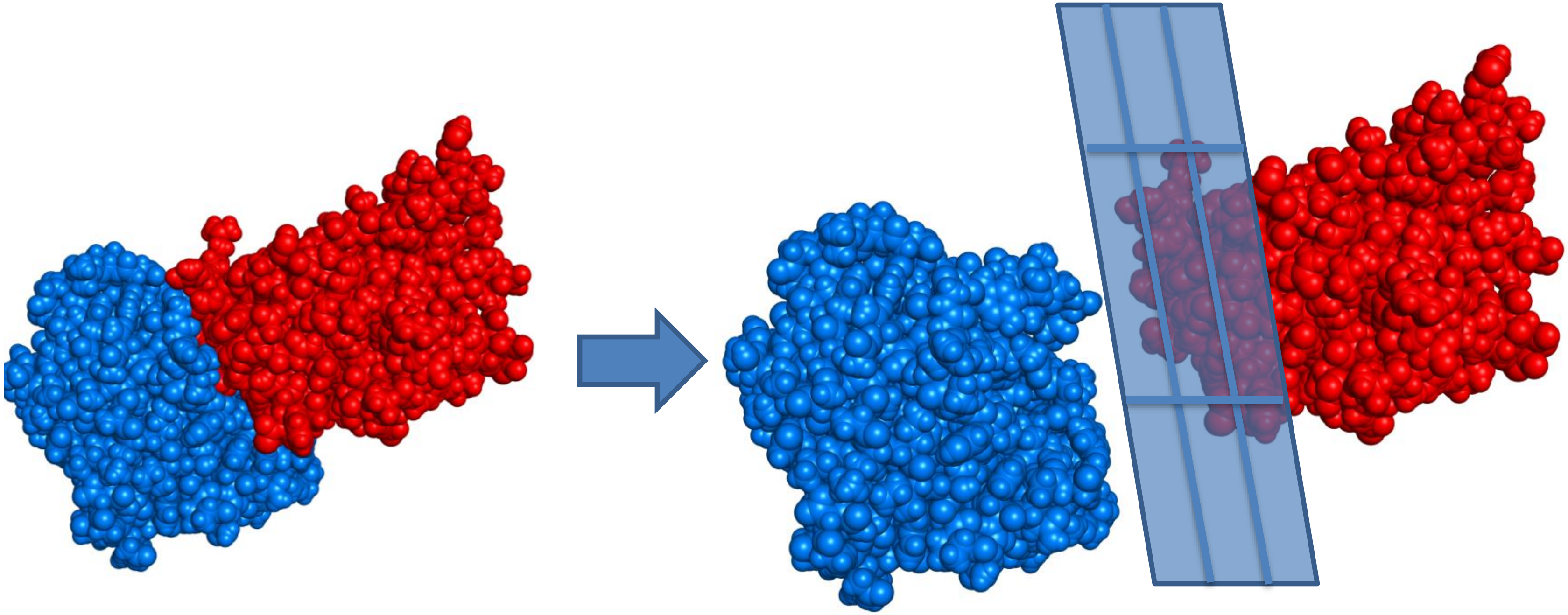


PPI target

Average correlations for state-of-the-art scoring functions



Physical Features

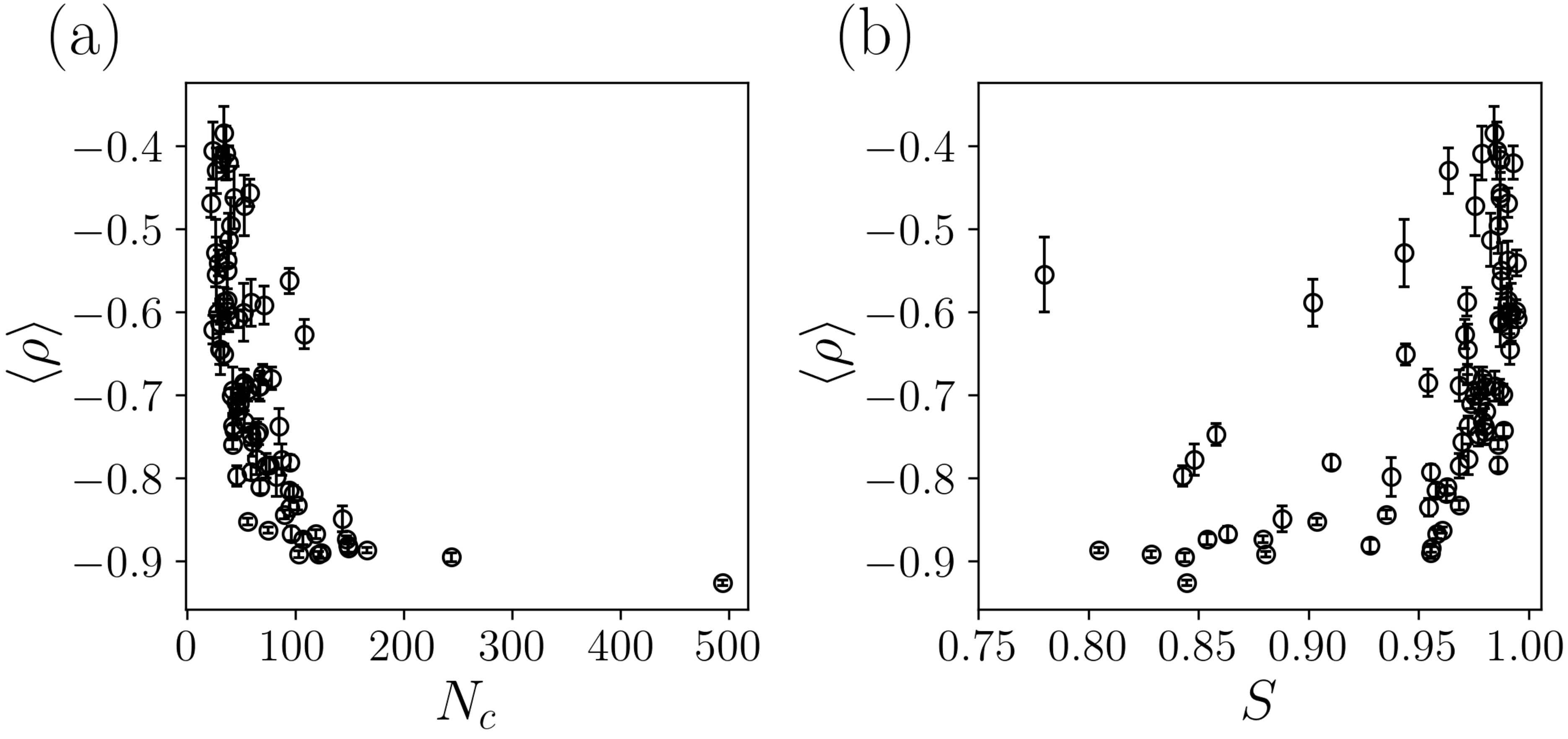


Intertwined score

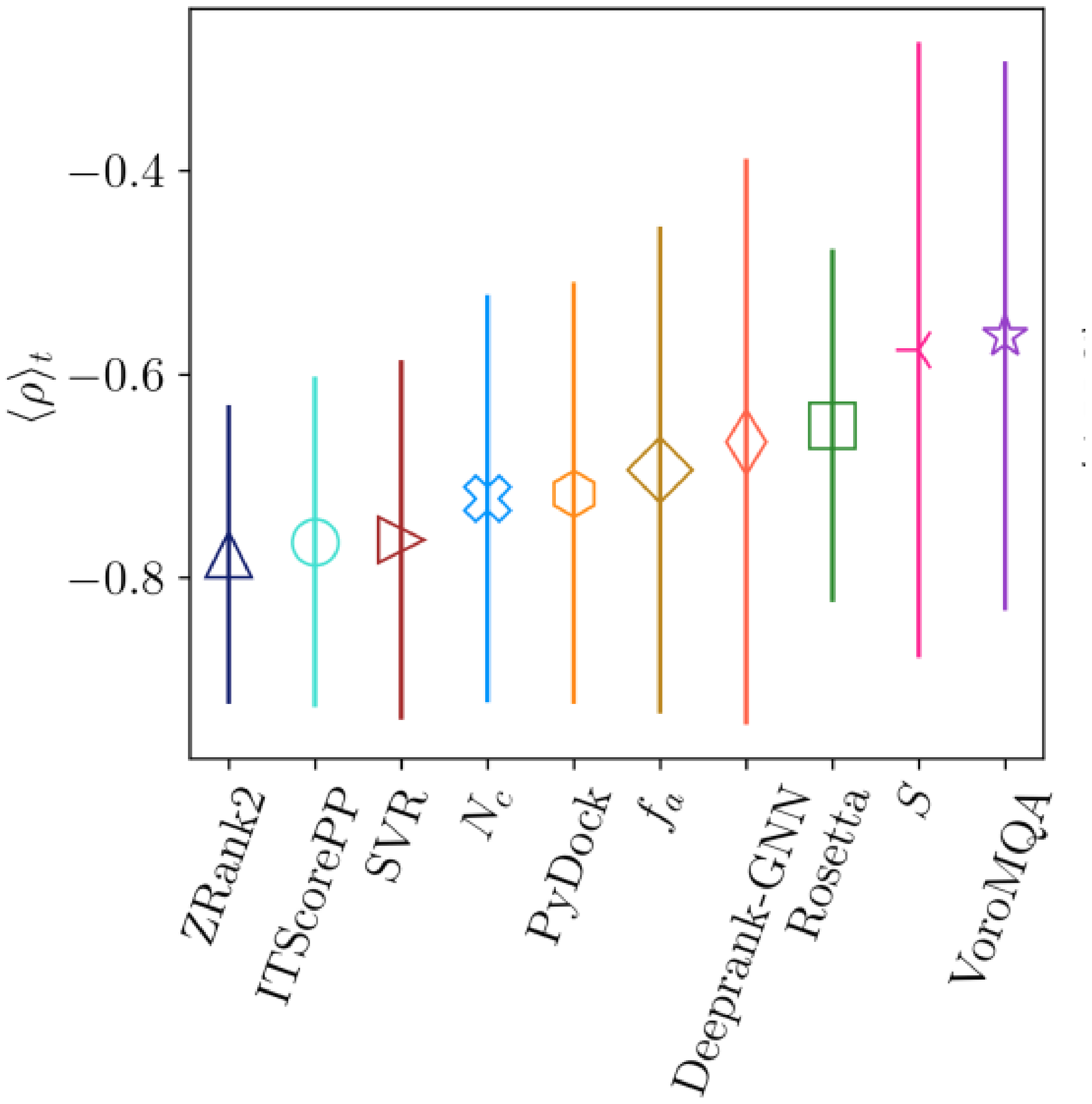
0.5 = intertwined interface

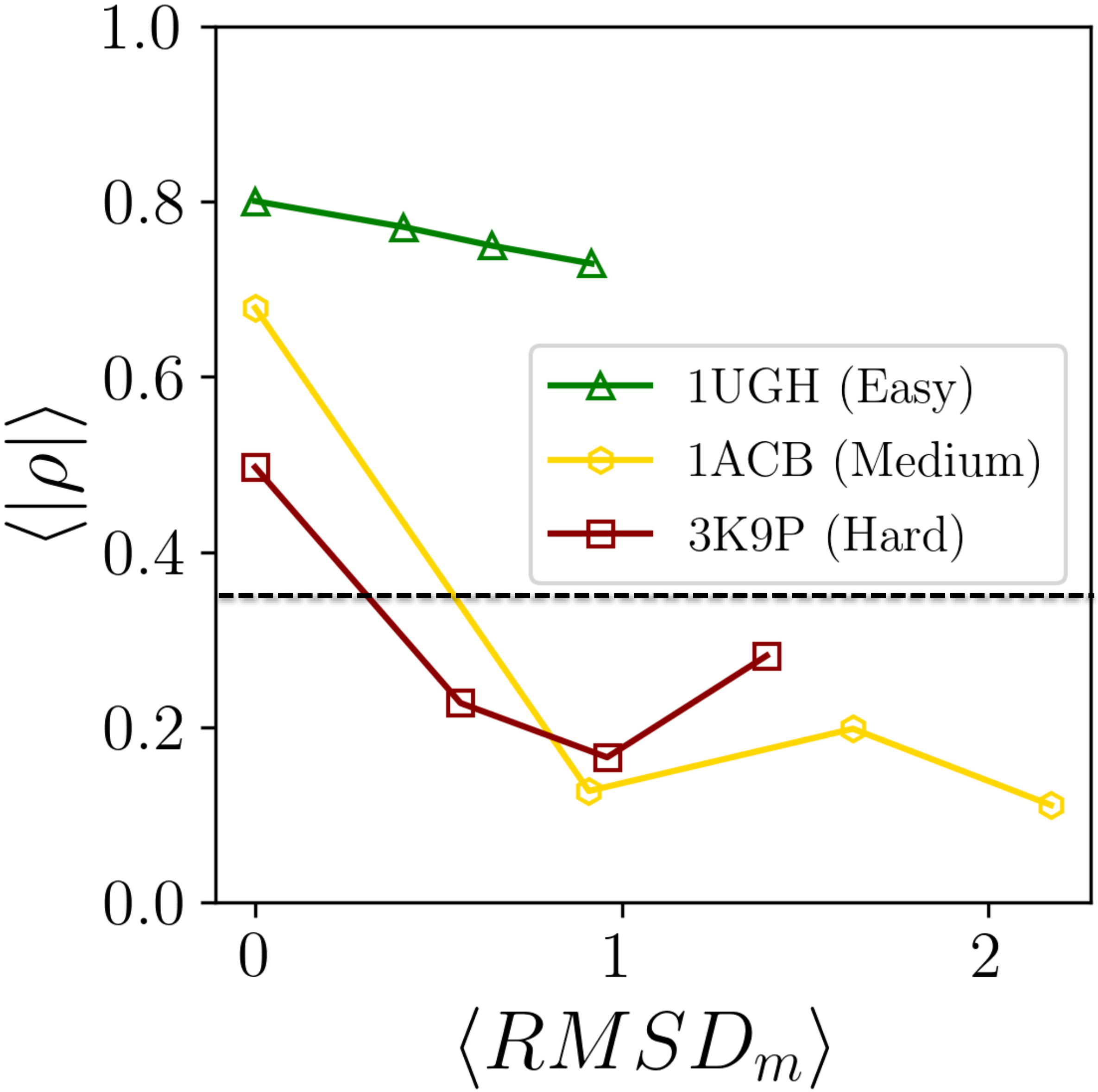
1.0 = completely flat interface

How do we improve PPI scoring functions: Identify important physical features of interface



What progress have we made in 20 years?



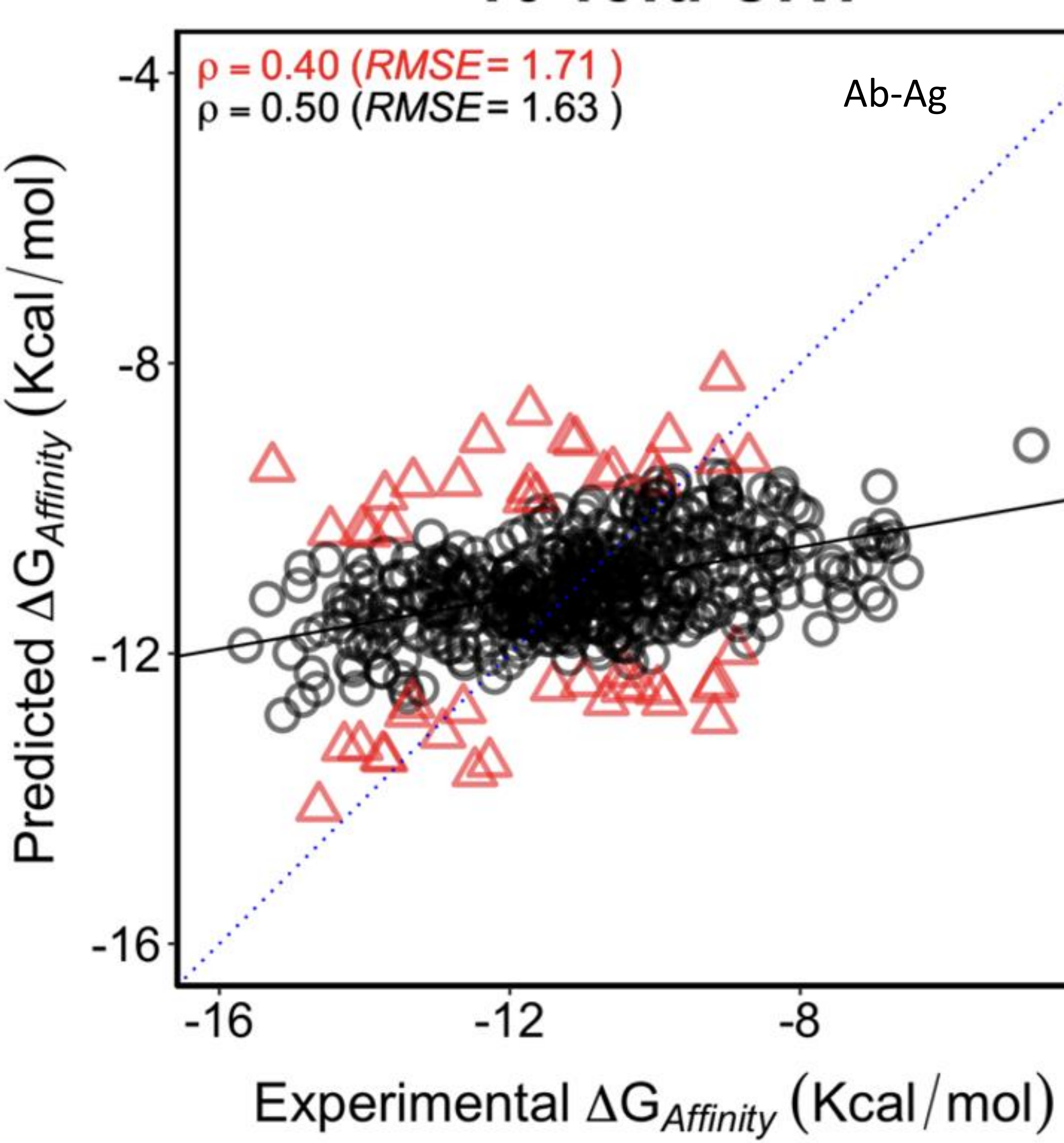

1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
$\langle|\rho|\rangle$
$\langle RMSD_m \rangle$
1UGH (Easy)
1ACB (Medium)
3K9P (Hard)

Conclusions and Future Directions

- PPI decoy scoring for even rigid-body docking of bound forms needs improvement. Previous studies of PPI scoring have mostly focused on identifying a single high-quality model, not correlation between PPI score and ground truth score.

- Promising physical features for scoring functions include flatness of interface and fraction of interface contacts. Develop new scoring function with physical features that achieves $|\rho| \sim 1$ for bound forms of all targets.

- What is the characteristic RMSD beyond which we cannot obtain large $|\rho|$? Develop methods to bring monomer conformations from unbound to bound forms, e..g low-frequency vibrational modes.



Yoochan Myung, Douglas E V Pires, David B Ascher, CSM-AB: graph-based antibody–antigen binding affinity prediction and docking scoring function, *Bioinformatics*, 38 (2022) 1141.