Protein–Ligand Binding Mode and Binding Affinity Prediction: Lessons Learned from the D3R Challenges

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Outline

- Methodology
- D3R results and the lessons we've learned
- Conclusion

Challenges on protein-ligand binding mode and affinity predictions

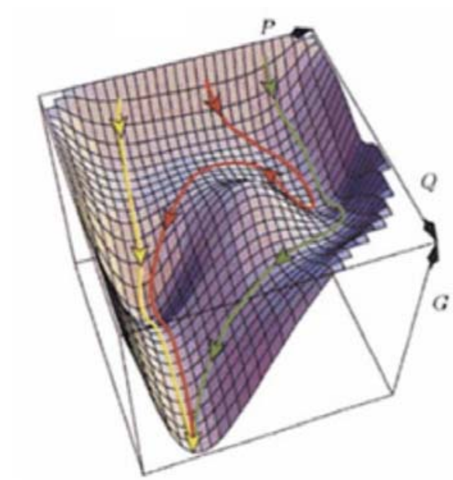
Binding mode prediction:

- Protein flexibility
- Scoring function

The affinity prediction is dependent on the mode prediction.

Binding affinity prediction:

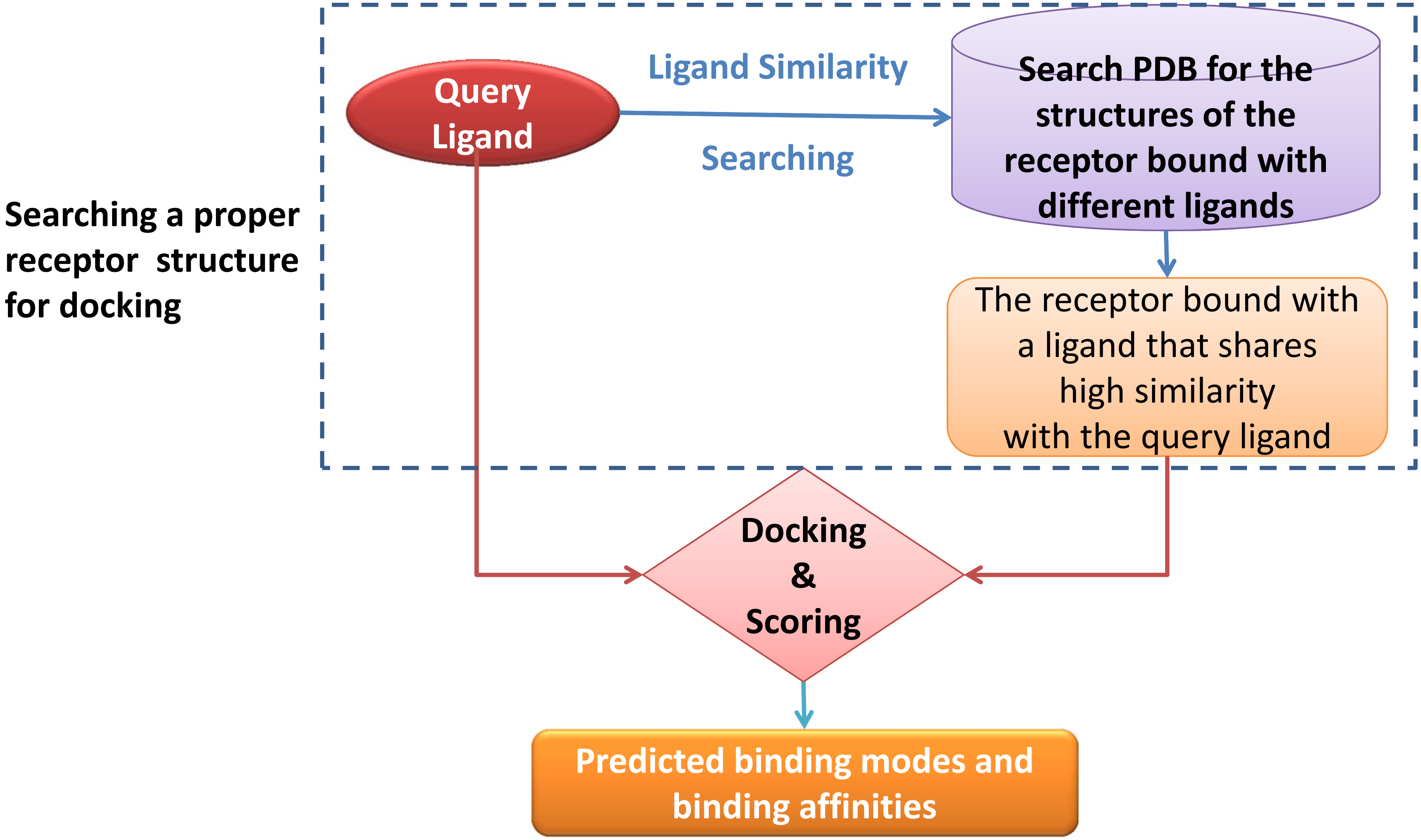
- Scoring function (Ranking)



David Wales. (2003) *Energy Landscapes: Applications to Clusters, Biomolecules, and Glasses*

Methodology

Searching a receptor structure with a bound ligand that shares high similarity with the query ligand for docking.

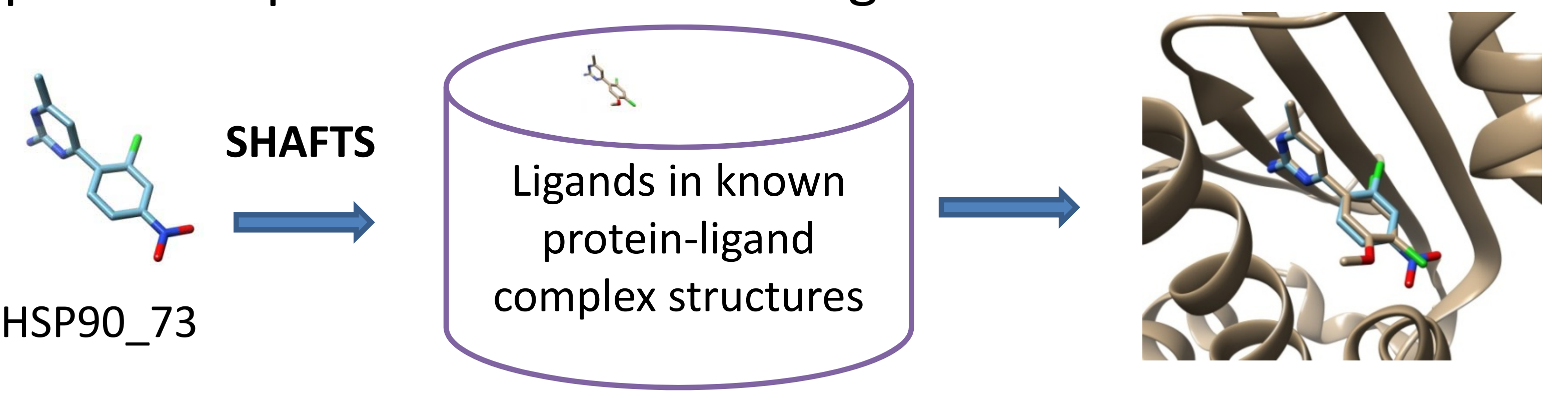


Step 1: Search a proper receptor structure for docking

- **Constructing a receptor structure database**, containing all the released **protein-ligand complex structures** based on Protein Data Bank.
- **3D ligand similarity calculation: SHAFTS**

  The similarity is based on the shape overlay and pharmacophore feature matching.

PDB code: 3RLP



HSP90_73

The receptor structure (3RLP) with a bound ligand that sharing the highest similarity with the query ligand (HSP90_73) will be used for docking.

Liu *et al.*, *J. Chem. Inf. Model.* 2011, 51, 2372–2385

Step 2: Molecular docking

Binding mode sampling:

Program: Modified AutoDock Vina 1.0

Receptor: rigid

Ligand: flexible

Exhaustiveness = 30

Output models = Up to 500

We have learned from the previous CSAR exercises that on-the-fly, flexible ligand docking is important for binding mode prediction.

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

Step 3: Scoring and ranking: ITScore

- A statistical potential-based scoring function, ITScore, was used to evaluate the generated models. The scores are also used for binding affinity prediction.
- The scoring function was developed using the iterative method based on the refined set of PDBbind 2012.
- If the database of known protein-ligand complex structures was large enough (e.g., 178 HSP90 complexes from the PDB), ITScore was re-calibrated using the known complex structures and setting the original pairwise potentials as the initial condition for the iterations.

Wang *et al.*, *J. Med. Chem.* 2005, 48, 4111−4119.
Cheng *et al.*, *J. Chem. Inf. Model.* 2009, 49, 1079−1093.
Huang and Zou, *J. Comput. Chem.* 2006, 27, 1866-1875.
Yan *et al.*, *J. Chem. Inf. Model.* 2015, DOI: 10.1021/acs.jcim.5b00504

Traditional formalism to derive the statistical pair potentials

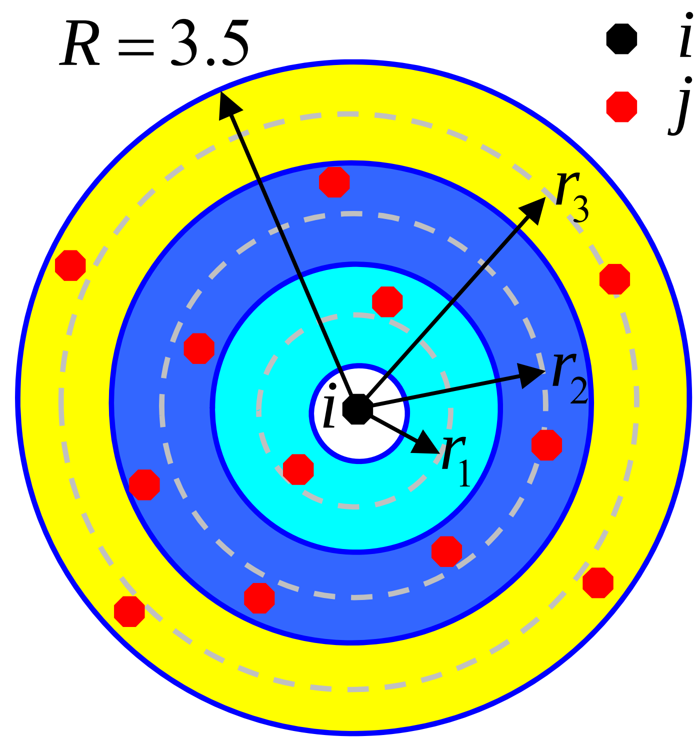
$$\rho_{ij}(r) = \rho_{ij}^{*}(r) \cdot \exp\left(-\frac{u_{ij}(r)}{k_B T}\right)$$

measurable

$$u_{ij}(r) = -k_{\mathrm{B}} T \ln \frac{\rho_{ij}(r)}{\rho_{ij}^{*}(r)}$$

reference state (u_{ij}=0)

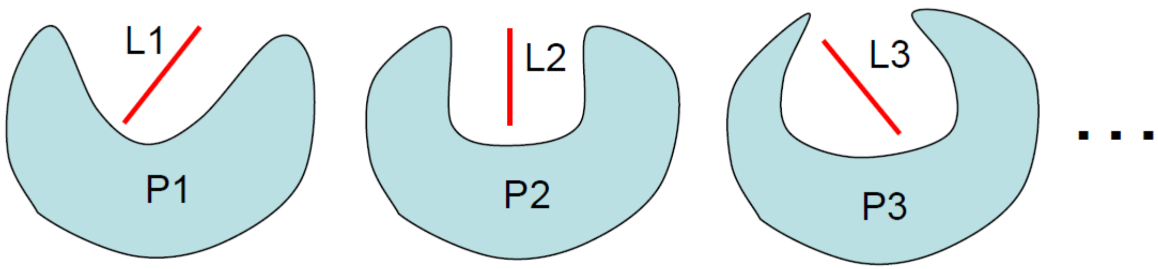
An example: "ideal gas"



$$\Delta G = \sum_{ij} u_{ij}(r)$$

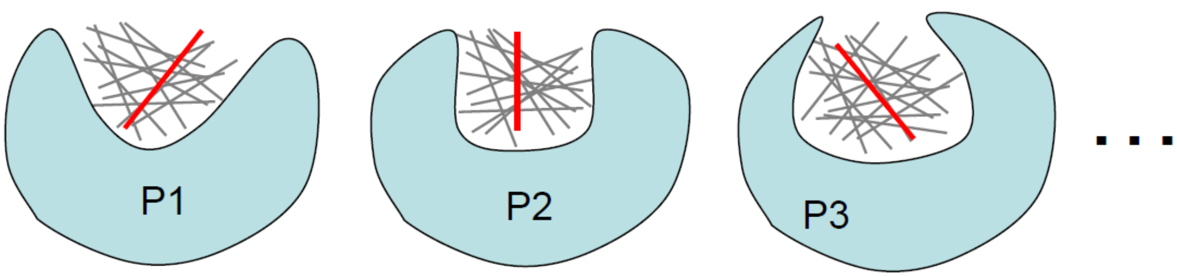
The reference state problem is a big hurdle for this inverse algorithm!

Derivation of the effective pair potentials using statistical mechanical principles



$$g_{ij}^{*}(r) = \frac{1}{K}\sum_{k=1}^{K} g_{ij}^{k*}(r)$$

$$g_{ij}^{k*}(r) = \rho_{ij}^{k*}(r)/\rho_{ij,\text{bulk}}^{k*}$$



$$g_{ij}^{(n)}(r) = \frac{1}{K}\sum_{k=1}^{K}\sum_{l=0}^{L} P_k^l g_{ij}^{kl}(r)$$

$$P_k^l = \frac{e^{-\beta E_k^l}}{Z_k} \quad Z_k = \sum_{l=0}^{L} e^{-\beta E_k^l}$$

Our physics-based iterative method circumvents the reference state problem

Step 0: $g_{ij}^{obs}(r)$

$$u_{ij}^{1}(r) = u_{ij}^{0}(r) + \Delta g_{ij}^{0}(r)$$

⋮

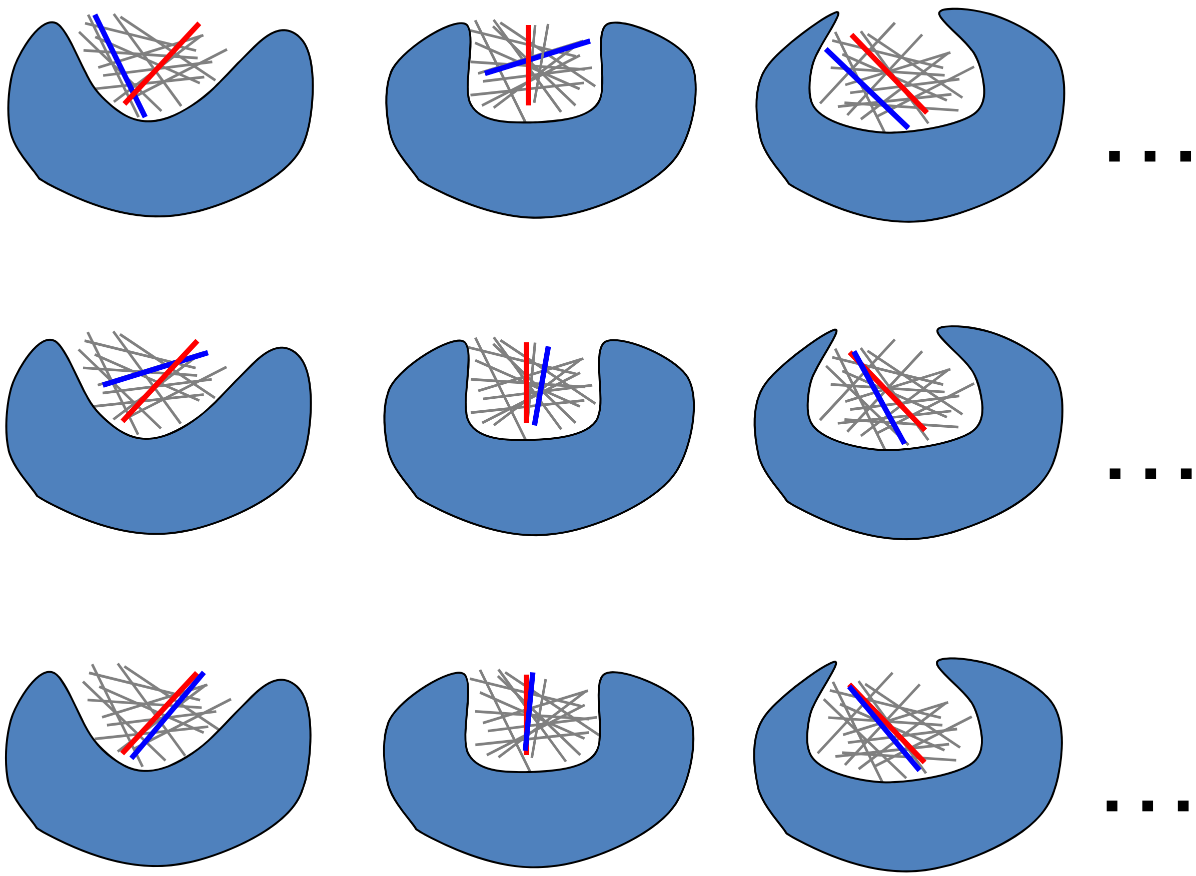
Step n: $g_{ij}^{n}(r)$

$$u_{ij}^{n+1}(r) = u_{ij}^{n}(r) + \Delta g_{ij}^{n}(r)$$

⋮

Step N : $g_{ij}^{N}(r)$

$$u_{ij}^{N+1}(r) = u_{ij}^{N}(r) + \Delta g_{ij}^{N}(r)$$



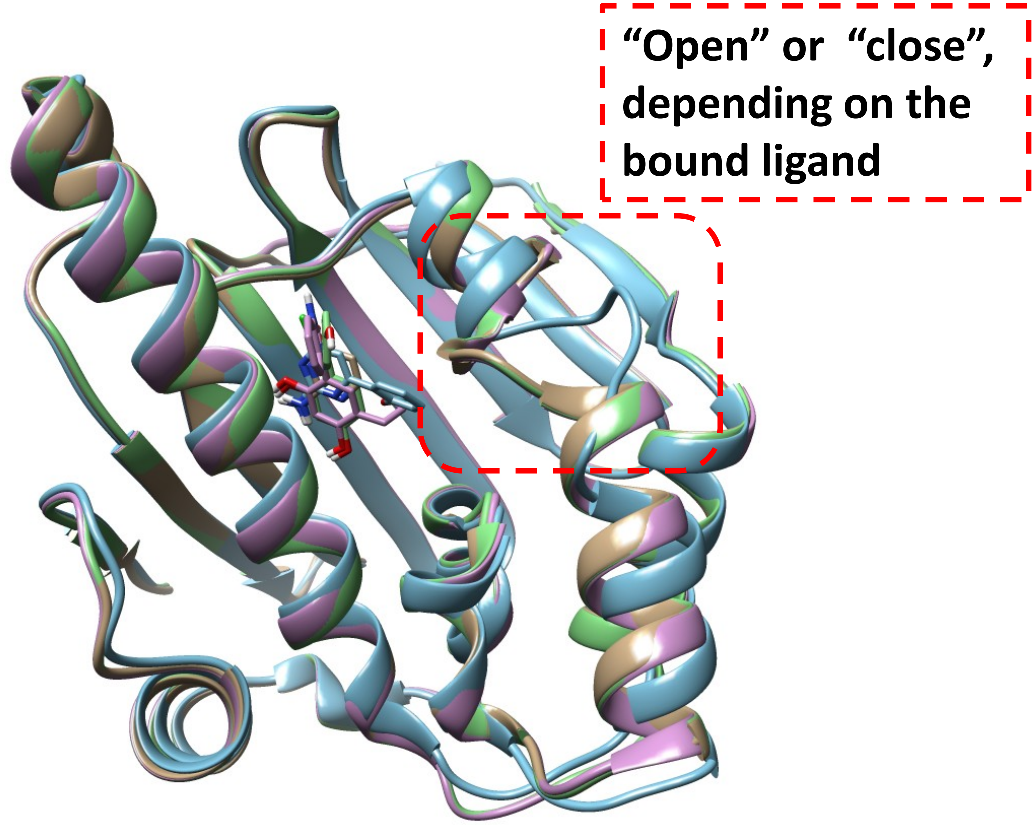
until $g_{ij}^{N}(r) \longrightarrow g_{ij}^{obs}(r)$

Huang and Zou, *J. Comput. Chem.* 2006, 27, 1866-1875.

D3R results and analysis: HSP90

180 compounds for binding affinity prediction;

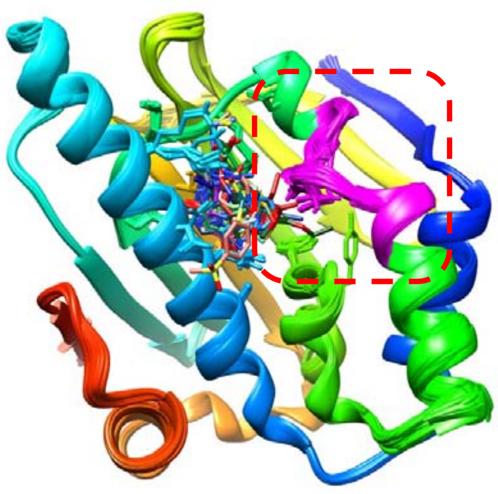
6 of them for binding mode prediction.



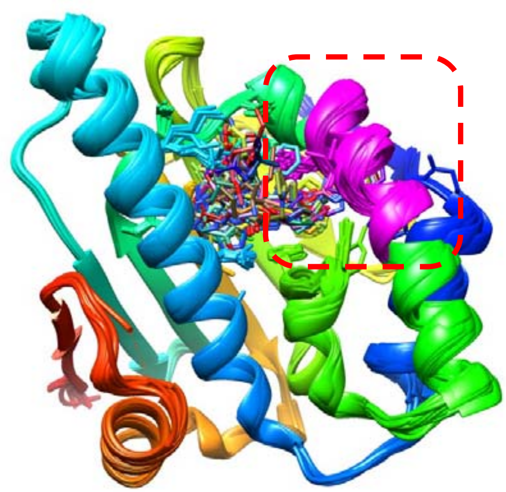
Four receptor structures (2JJC, 2XDX, 4YKR and 4YKY) provided by the D3R team

Known human HSP90-ligand complex structures

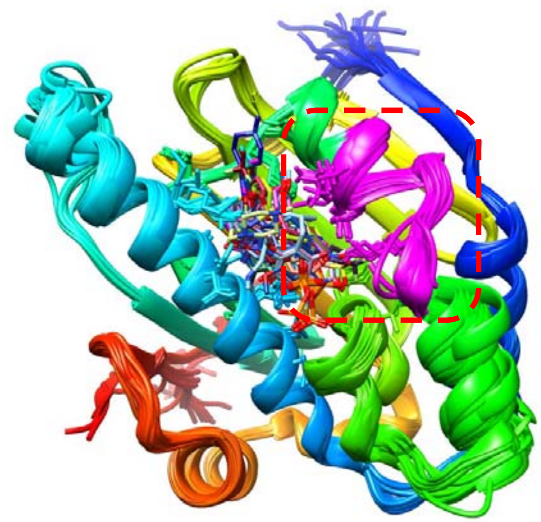
- A total of **178 human HSP90-ligand complex structures** collected from the PDB.
- The HSP90 conformations can be roughly grouped into three classes: “Close”, “Semi-close”, and “Open” states.
- The conformations in the same class are also slightly different with each other, due to the binding with different ligands.



“Close” states



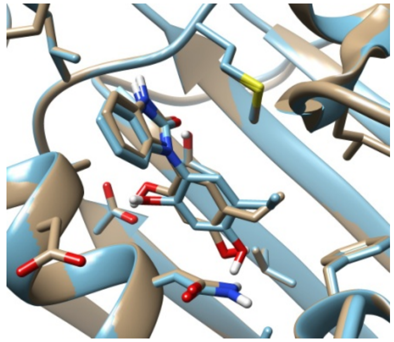
“Semi-close” states



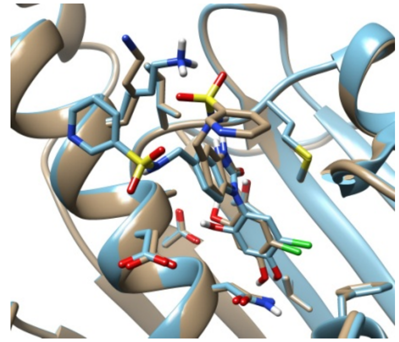
“Open” states

HSP90: Binding mode prediction

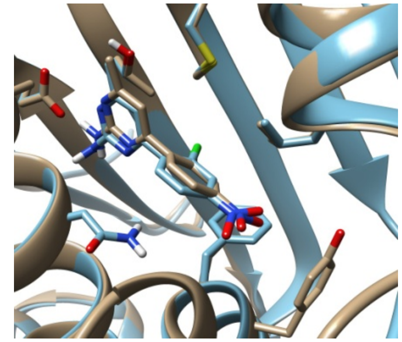
ligands	Receptors used for docking
HSP90_40	4YKR
HSP90_44	4YKR
HSP90_73	3RLP
HSP90_164	4YKY
HSP90_175	4YKY
HSP90_179	3B27



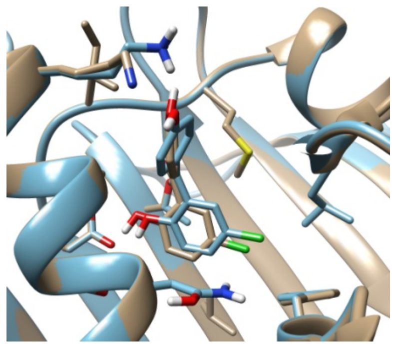
HSP90_40



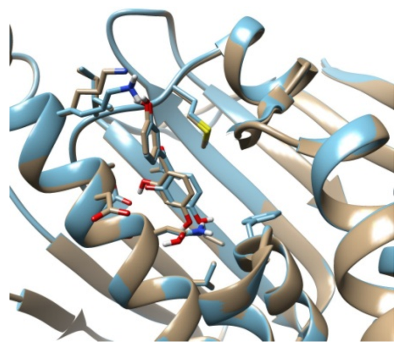
HSP90_44



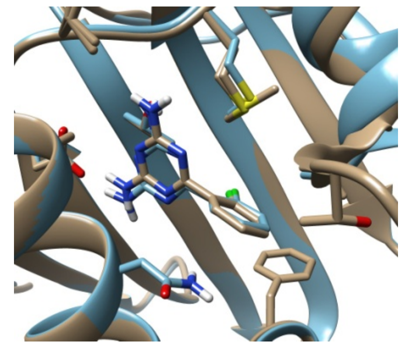
HSP90_73



HSP90_164



HSP90_75



HSP90_179

Number of ligands docked	Mean RMSD of Pose 1 (A)	Median RMSD of Pose 1 (A)	Mean RMSD of lowest-RMSD pose (A)	Median RMSD of lowest-RMSD pose (A)
6	1.41	0.80	1.08	0.59

For all the six mode prediction cases, our strategy successfully selected the correct conformation of the receptor for docking in each case. Low RMSDs were achieved.

HSP90: Binding affinity prediction

Submitted Results:

	Scoring functions	Number of Ligands	Number Matched	Pearson R	Kendall Tau	Matthews (active/inactive, 1 uM cutoff)	ROC	AUC
Stage 1	**ITScore-1**	**180**	**178**	**0.34**	**0.24**	**0.30**	**0.65**	**0.66**
	ITScore-2	180	178	0.27	0.19	0.21	0.60	0.62
	ITScore-3	180	178	0.28	0.20	0.23	0.62	0.63
Stage 2	**ITScore-1**	**180**	**178**	**0.35**	**0.25**	**0.32**	**0.66**	**0.67**
	ITScore-2	180	178	0.28	0.20	0.21	0.60	0.62
	ITScore-3	180	178	0.27	0.19	0.23	0.62	0.63

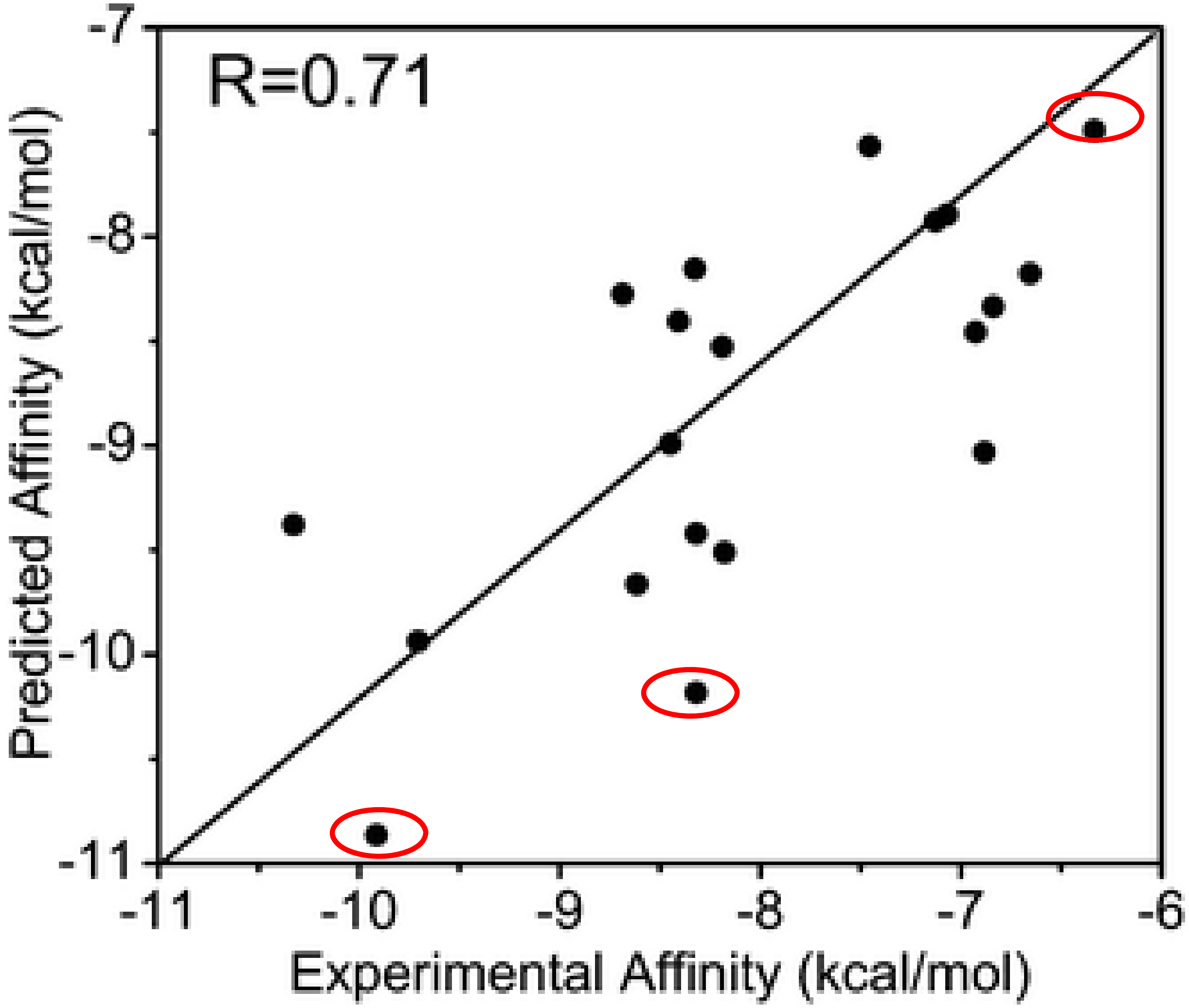
ITScore-2: the latest version of our in-house scoring function (2015).

ITScore-1: recalibrating ITScore-2 by using the known HSP90 complexes.

ITScore-3: recalibrating an old version of ITScore by adding known HSP90 complexes.

Stage 2: Six more HSP90-ligand complex structures were released after **Stage 1**.

Information from the known HSP90 complex structures dramatically improved the performance of our scoring function.


R=0.71
-7
-8
-9
-10
-11
Predicted Affinity (kcal/mol)
-11
-10
-9
-8
-7
-6
Experimental Affinity (kcal/mol)

Comparison with the prediction from docking the ligand to multiple protein structures (ensemble docking)

A: For each ligand, **a receptor structure selected** based on ligand similarity was used for docking.

B: For each ligand, the **4 high-quality receptor structures** (2JJC, 2XDX, 4YKR and 4YKY) provided by the D3R team were used for ensemble docking.

Binding mode prediction

Strategy	Number of ligands docked	Mean RMSD of Pose 1 (A)	Median RMSD of Pose 1 (A)	Mean RMSD of lowest-RMSD pose (A)	Median RMSD of lowest-RMSD pose (A)
A	6	1.41	0.80	1.08	0.59
B	6	2.61	1.76	1.16	0.60

Binding affinity prediction (R of IC_{50} using 150 active compounds):

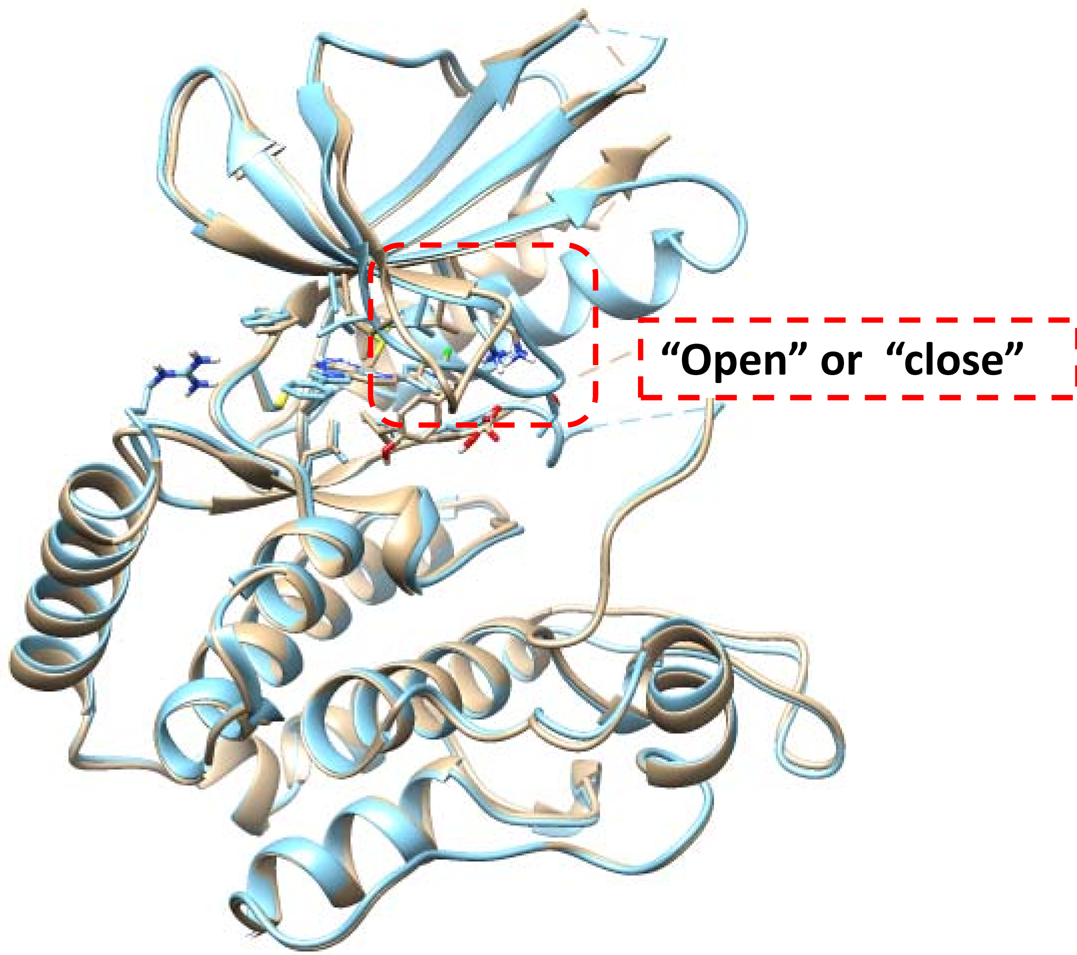
A: r = 0.37; B: r= 0.26

Our new strategy achieved better performance than ensemble docking on both mode prediction and affinity prediction.

D3R Results and analysis: MAP4K4

30 compounds for binding mode prediction;

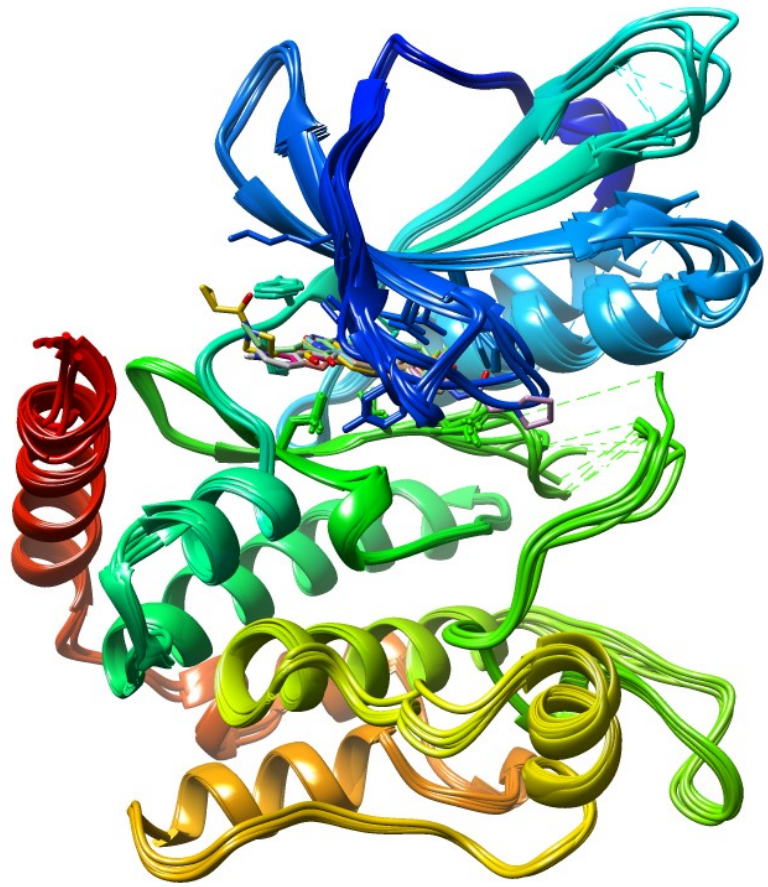
18 of them for binding affinity prediction.



Known human MAP4K4-ligand complex structures

Only 8 human MAP4K4-ligand complex structures were collected from the PDB.

PDB codes:
4OBO
4OBP
4OBQ
4RVT
4U43
4U44
4U45
4ZK5



MAP4K4: Binding mode prediction

Submitted Results:

Number of ligands docked	Mean RMSD of Pose 1 (A)	Median RMSD of Pose 1 (A)	Mean RMSD of the lowest-RMSD pose (A)	Median RMSD of the lowest-RMSD pose (A)
30	4.88	4.95	2.87	2.63

The prediction becomes challenge, because the number of known MAP4K4-ligand complex structures is limited (only 8 available complexes).

Encouragingly, our strategy of docking a query ligand onto a selected receptor still achieved good performance on mode prediction.

MAP4K4: Affinity prediction (Stage 1)

	Scoring functions	Number of Ligands	Number Matched	Pearson R	Kendall Tau	R of IC_{50}
Stage 1	ITScore-1	18	18	-0.04	0.02	0.03
	ITScore-2 (ensemble)	18	18	0.11	0.10	0.24
	ITScore-3	18	18	0.38	0.31	0.33
	ITScore-4 (ensemble)	18	18	0.36	0.25	0.41

ITScore-1: The latest version of our in-house scoring function. Using the selected receptor for docking.

ITScore-2: The latest version of our in-house scoring function. Ensemble docking.

ITScore-3: An old version of our in-house scoring function. Using the selected receptor for docking.

ITScore-4: An old version of our in-house scoring function. Ensemble docking.

If the receptor structure is not accurate, ensemble docking achieved better performance than single-receptor docking.

MAP4K4: Affinity prediction (Stage 2)

	Scoring functions	Number of Ligands	Number Matched	Pearson R	Kendall Tau	R of IC_{50}
Stage 2	ITScore-1	18	18	0.39	0.31	0.30
	ITScore-2	18	18	0.41	0.32	0.40
	ITScore-3 (redock)	18	18	0.38	0.28	0.24
	ITScore-4 (redock)	18	18	0.21	0.18	0.40

ITScore-1: the latest version of our in-house scoring function. The scores were calculated based on the bound crystal structures provided by D3R.

ITScore-2: an old version of our in-house scoring function. The scores were calculated based on the bound crystal structures provided by D3R.

ITScore-3: the latest version of our in-house scoring function. The scores were calculated based on re-docking the ligand onto the bound receptor structure.

ITScore-4: an old version of our in-house scoring function. The scores were calculated based on re-docking the ligand onto the bound receptor structure.

Correct binding mode is important to the binding affinity prediction. Redocking is not helpful.

The lessons we've learned from D3R

1) The embedded information extracted from known protein-ligand complex structures is important for both mode prediction and affinity prediction.

2) Docking with a reliable predicted receptor structure achieves better performance than docking with multiple receptor structures (ensemble docking).

3) If the predicted receptor structure is not reliable, ensemble docking achieves better performance than single-receptor docking.

4) Experimentalists can also learn from theorists.

Conclusion

- We developed a systematic strategy by using the information embedded in the known protein-ligand complex structures to improve both binding mode and affinity prediction.
- A 3D ligand similarity calculation method was employed to search a receptor structure with a bound ligand sharing high similarity with the query ligand for docking.
- Our in-house scoring function, ITScore, was recalibrated using the known HSP90-ligand complex structures with the iterative method to generated a system-specific (HSP90) scoring function.
- If there is no accurate receptor structures for docking, ensemble docking achieves better performance than single-receptor docking.

THANKS FOR YOU ATTENTION!

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