Strategies to choose the optimal receptors for virtual screening: results from the D3R Grand Challenge

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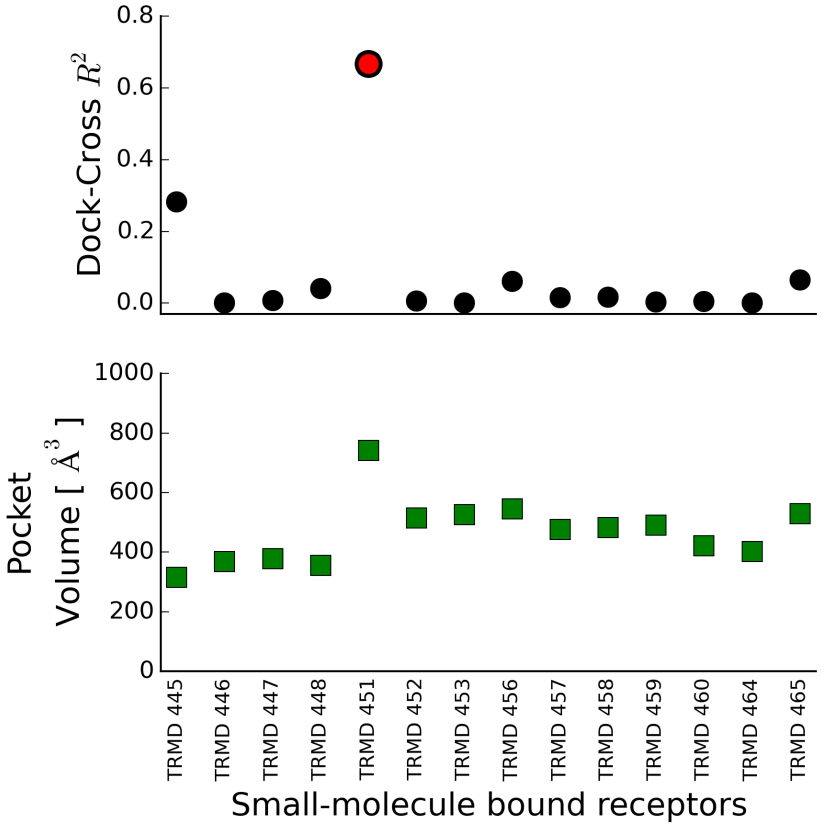
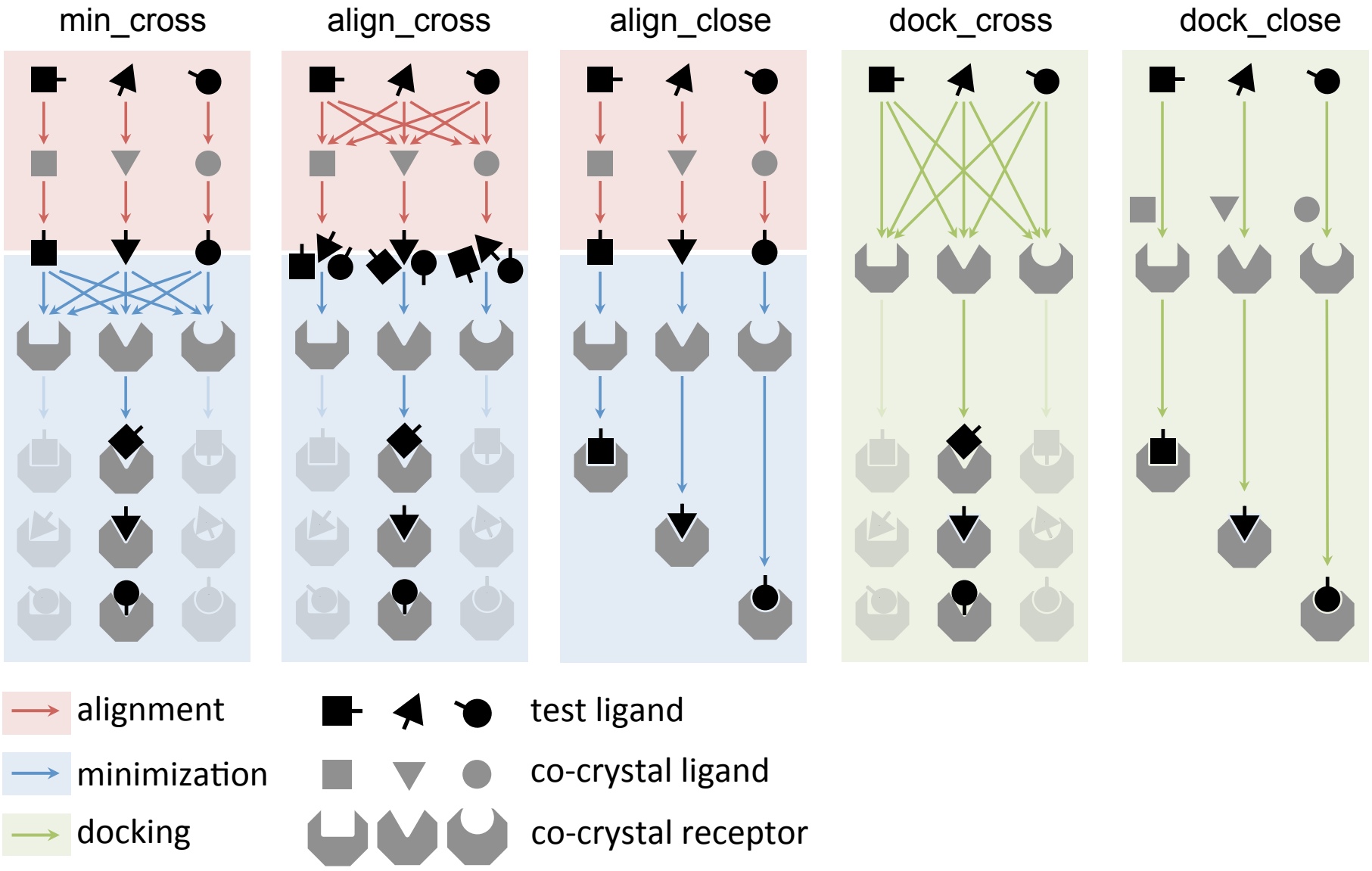
Background

- When multiple structures are available, choosing an optimal receptor for virtual screening is important.
- Previously, we showed that pocket size is an important feature for selecting the optimal receptor in TRMD[1].
- We have developed several strategies for selecting the optimal receptor(s).



[1] Baumgartner, M. P., and Camacho C. J. "Choosing the Optimal Rigid Receptor for Docking and Scoring in the CSAR 2013/2014 Experiment." *J. chem. info. model.* (2015).

Methods

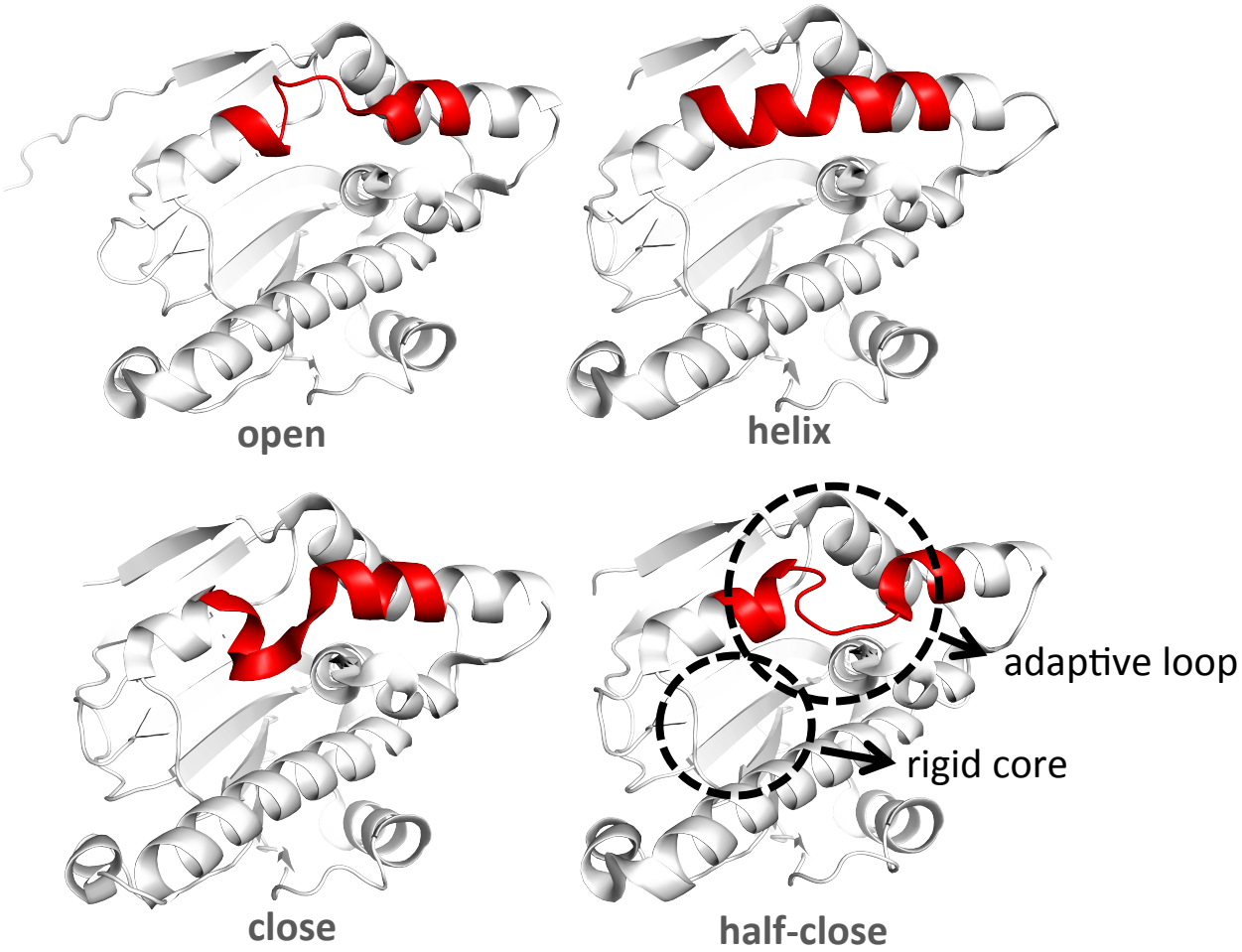

min_cross
align_cross
align_close
dock_cross
dock_close
alignment
minimization
docking
test ligand
co-crystal ligand
co-crystal receptor

HSP90 challenge

input: (1) 179 cocrystal from PDB (58 IC50) and 2 from challenge

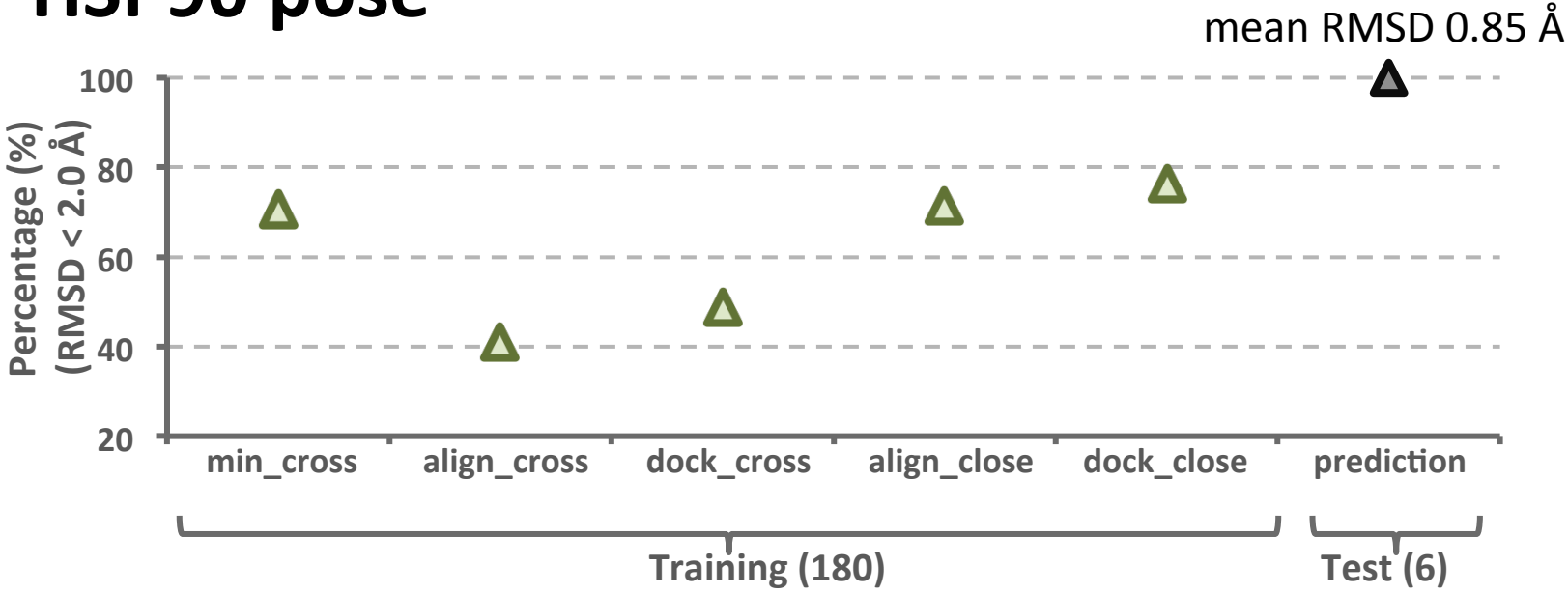
output: (1) Predict crystal poses of 6 compounds
(2) Predict IC50 / IC50 ranking for 180 compounds

HSP90 pocket

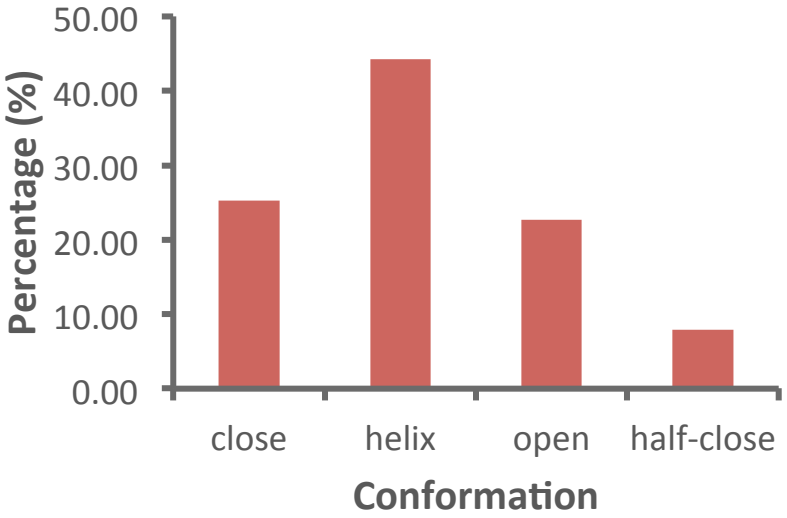


- HSP90 ligand-binding pocket consists of a **rigid core** and an **adaptive loop**.

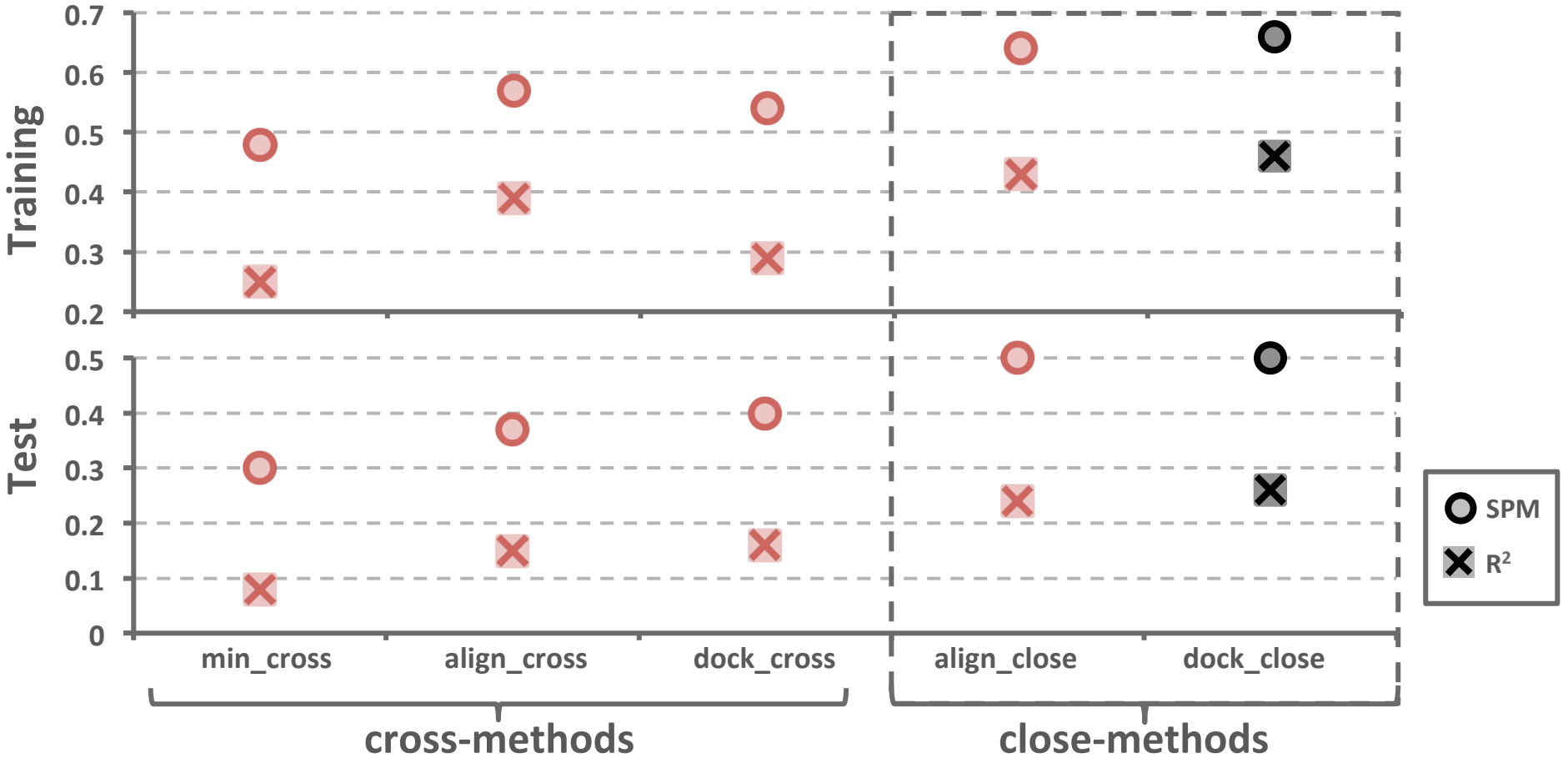
HSP90 pose



- The 6 test cmps all have high-similarity cmps in training group.
- Select poses from dock-close and align-close.
- Hsp90-44 have a flexible functional group sticking out that is stabilized by lysine from second monomer in dimer structure. We docked to monomer.

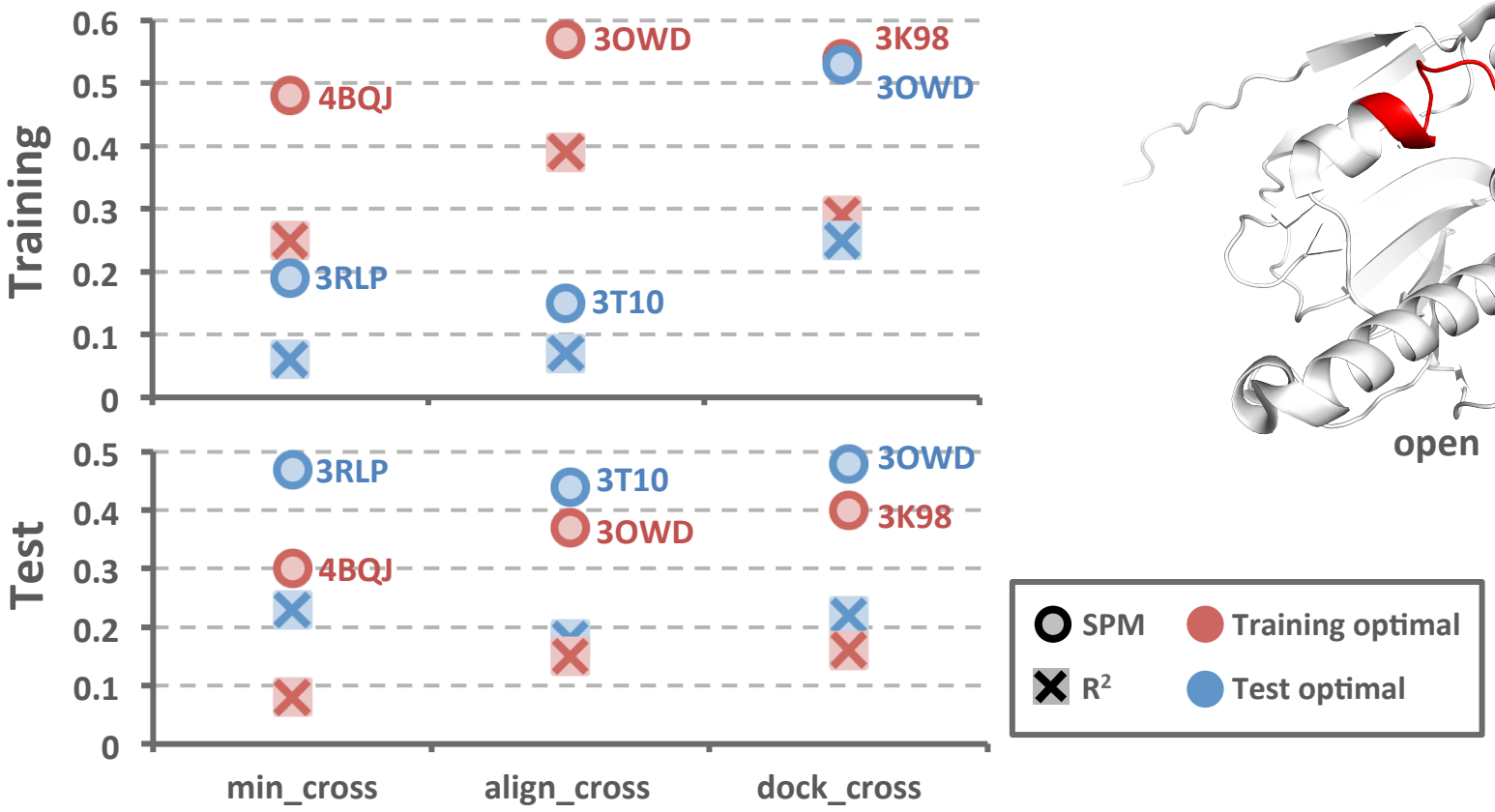


HSP90 ranking: methods comparison



- **Close-methods** perform better than **cross-methods**.
  One single receptor can't adapt to ligand-induced conformation changes.
- **Multiple receptors methods, dock-close** and **align-close,** perform the best.

HSP90 ranking: optimal receptor for cross-methods



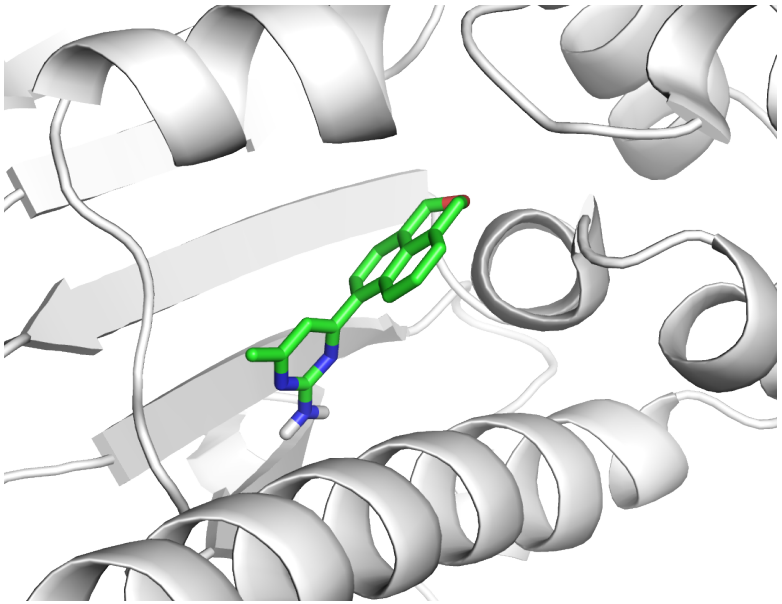
- Differences could be explained by different distribution of binding modes.
- Optimal receptors have **open-conformation** for cross-methods for HSP90

HSP90 ranking: human filtering active vs. inactive

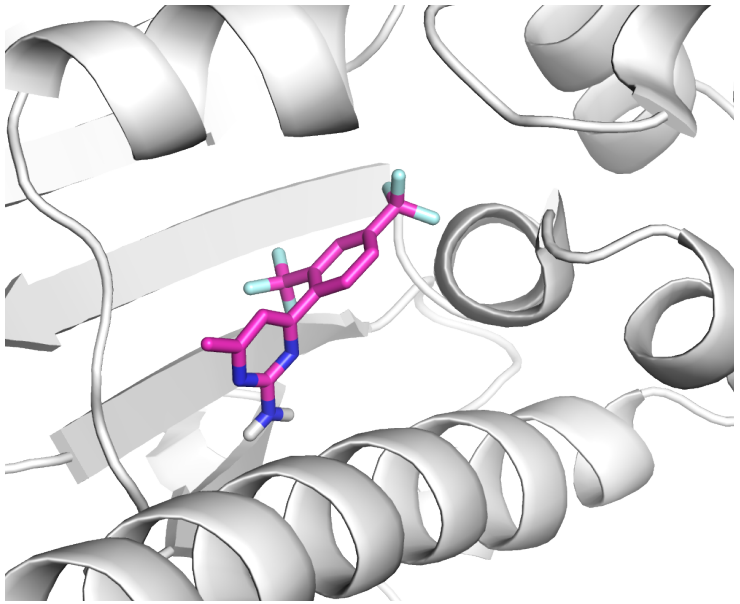
- How we filtered the inactives.

Take the best pose from close-methods → Manually distinguish by the poses → Shuffle the ranking

- Blind methods did better than human filtered methods
- Binding and potency have correlations, but not necessarily ensure “good binding good potency”.



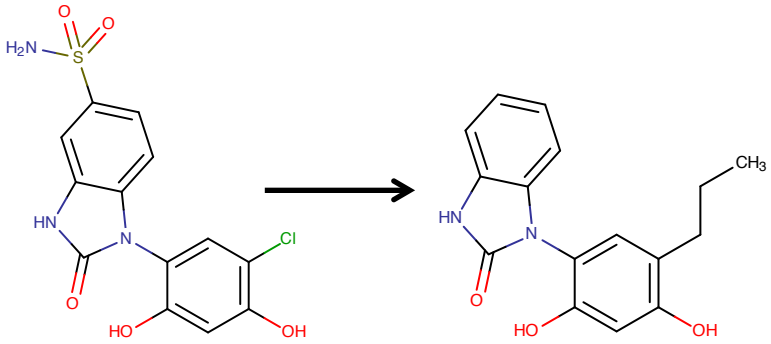
3B26



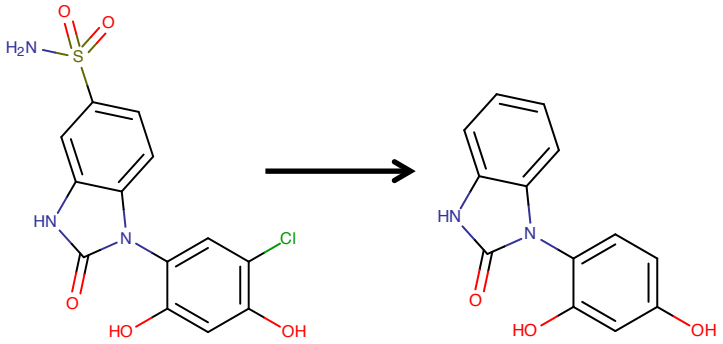
hsp110 (>50 µM) on 3B26 receptor

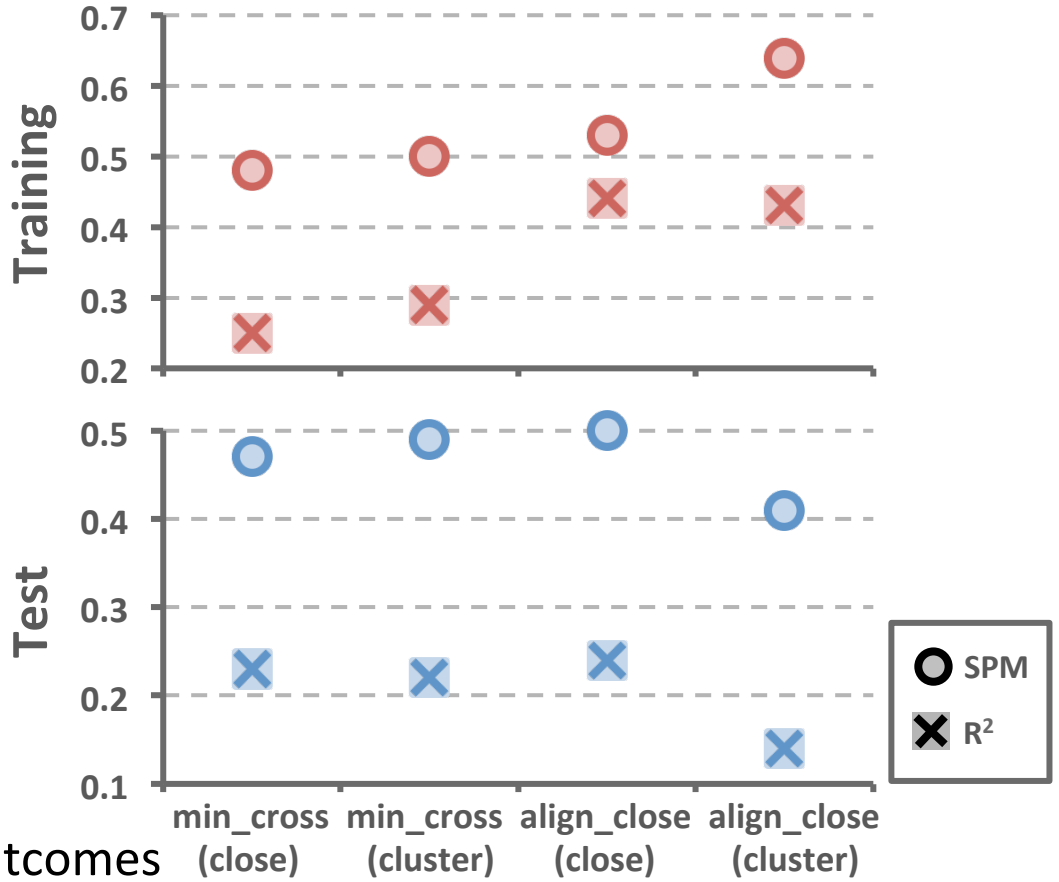
HSP90 ranking: align to molecule or to scaffold?

- In min-cross & align-close methods, the first step is aligning test cmps to a model.
  (1) chemically closest ligand



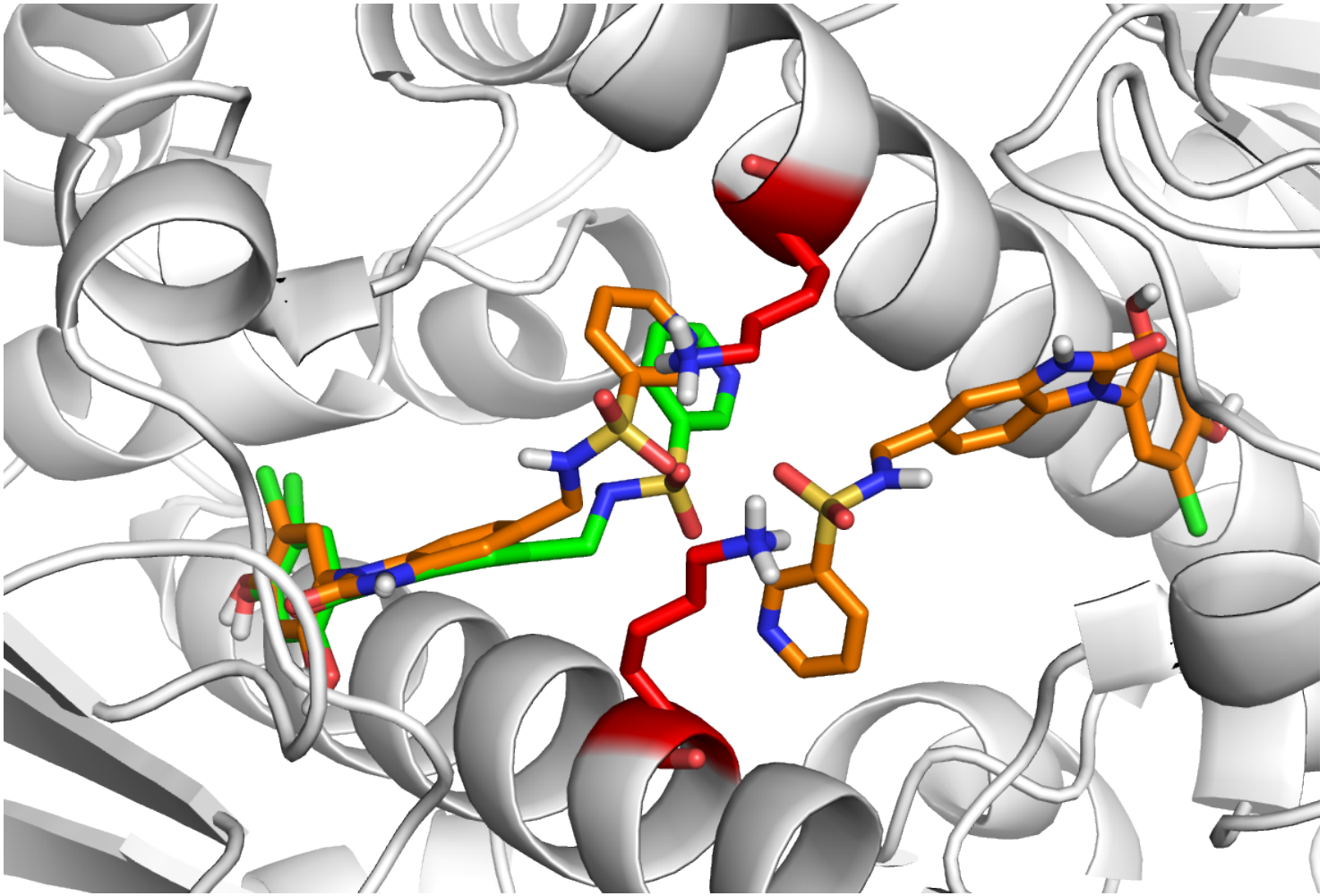
(2) The scaffold (one of three)





- Align to scaffold had improved outcomes in training group but not in testing.
  (1) minimization can resolve the differences in the alignments
  (2) benzophenone-like compound series do not follow scaffold of known binders
  (3) functional groups can be better placed when align to a good closest ligand

- Hsp90-44 have a flexible functional group sticking out that is stabilized by lysine from another molecule of Hsp90.

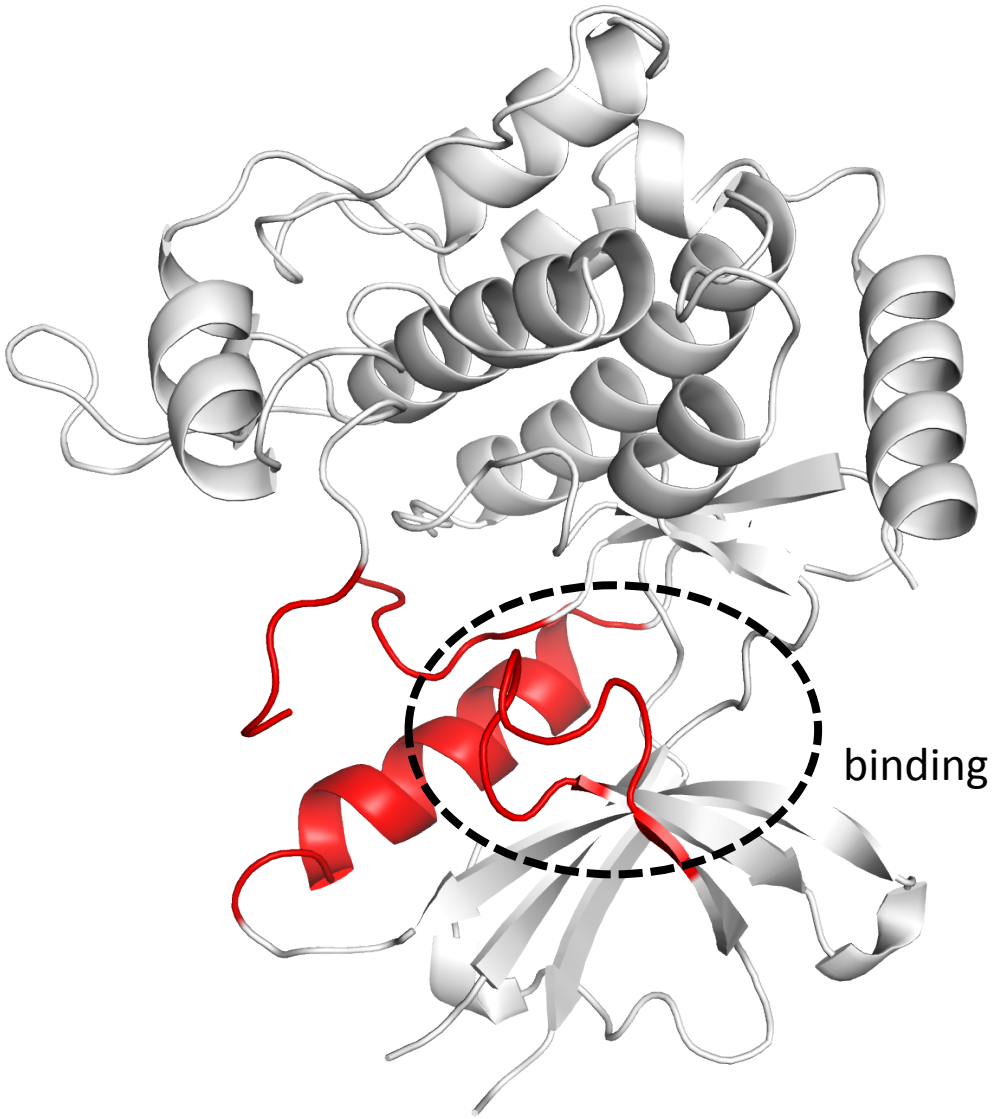


MAP4K4 challenge

input: (1) 8 cocrystal from PDB (8 IC50)

output: (1) Predict crystal poses of 30 compounds
(2) Predict IC50 / IC50 ranking for 18 compounds

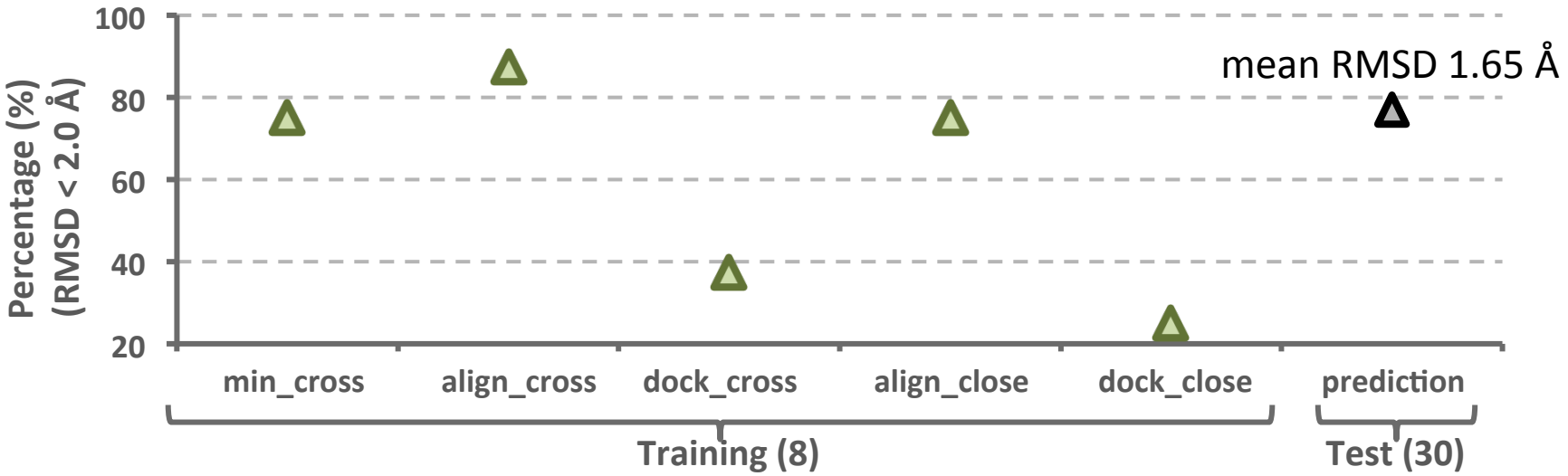
MAP4K4 pocket



Many of red regions are missing in co-crystals, making comparisons more difficult

- MAP4K4 ligand-binding pocket is a **large pockets with flexible loops around.**

MAP4K4 pose

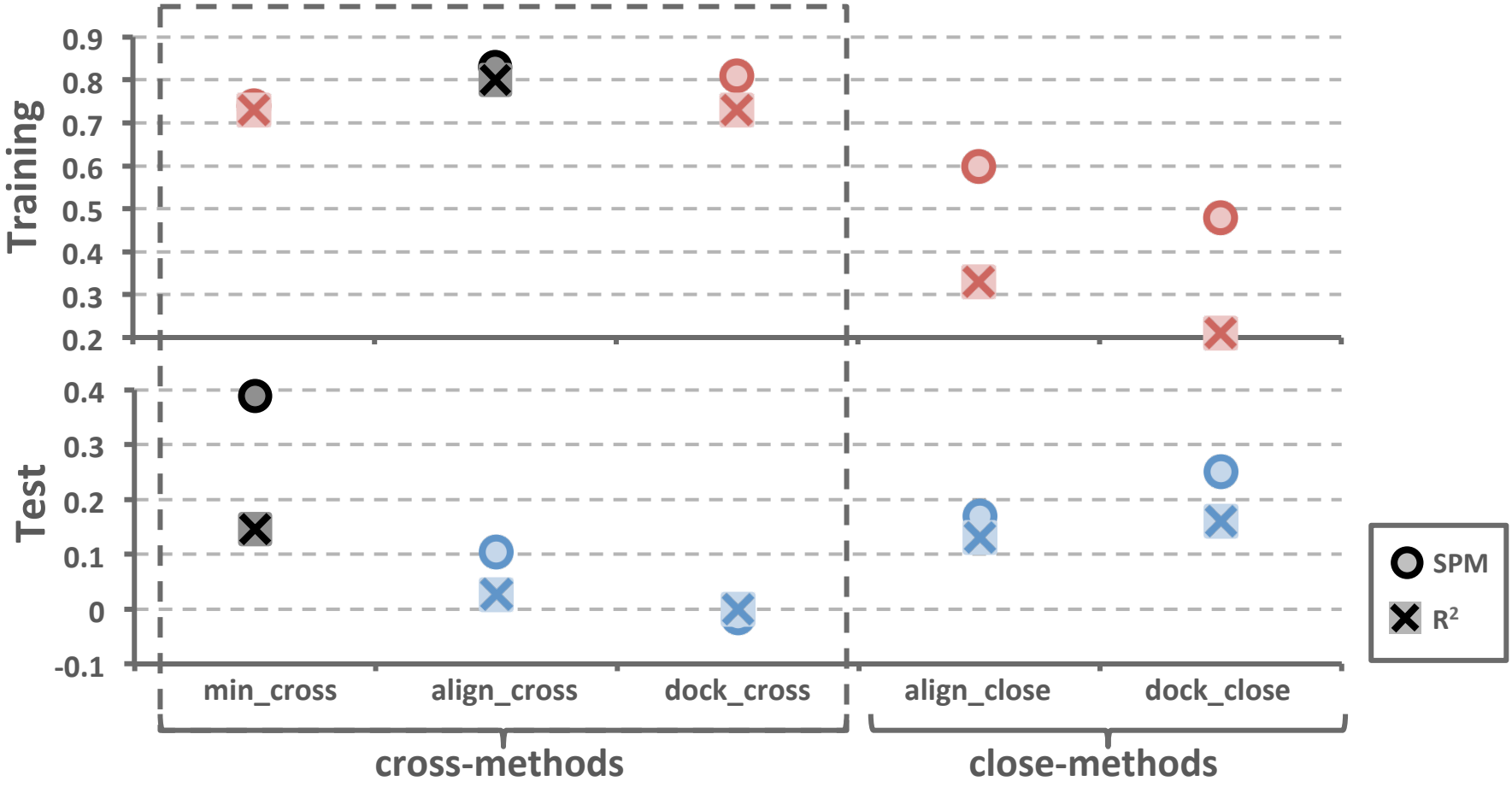


- Chemical similarities in test set:
  (1) 12 of the test cmps have similar cmps in training set
  (2) 15 have similar cmps binding to different kinases
  (3) 3 have no similar cmps

- We chose poses from a various align-close method:
  (1) align to the closest cmps from any kinases
  (2) minimize to the MAP4K4 structures

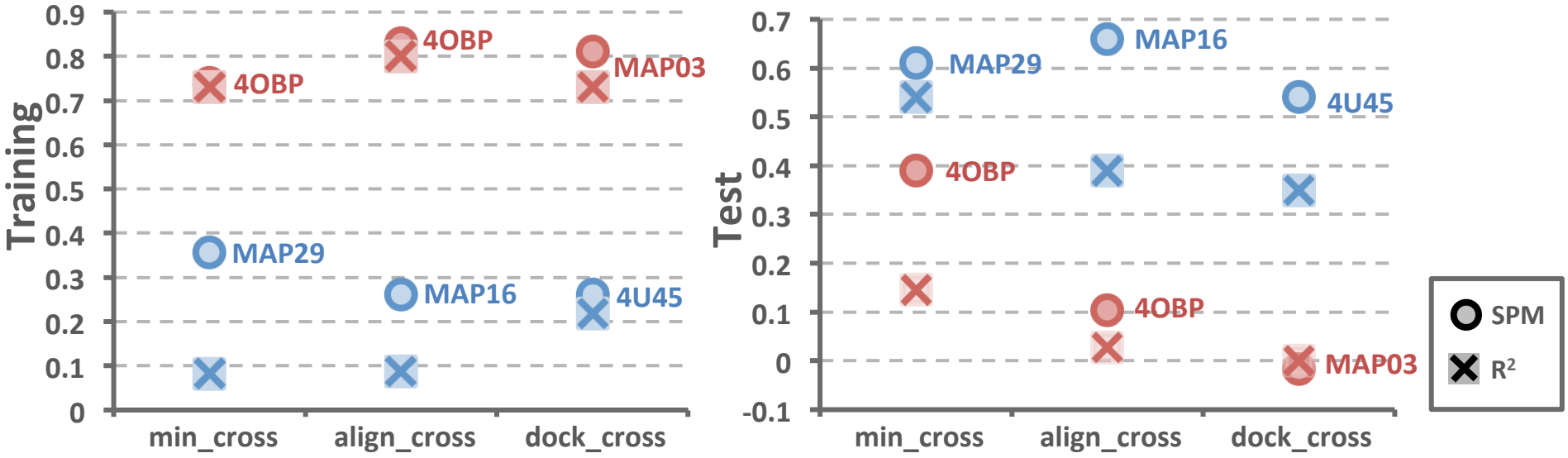
- For the 3 without similar cmps, we chose poses from align-cross.

MAP4K4 ranking: methods comparison



- **Opposite to HSP90, cross-methods preformed better than close-methods**
- The training data is limited to 8 IC50.

MAP4K4 ranking: optimal receptor for cross-methods?



- We failed to select the optimal receptor

  (1) The eight IC50s are from only two scaffolds, and get over-fitted in the training set.

  (2) The large pocket makes either docking or align-minimizing difficult to get a good pose for scoring.

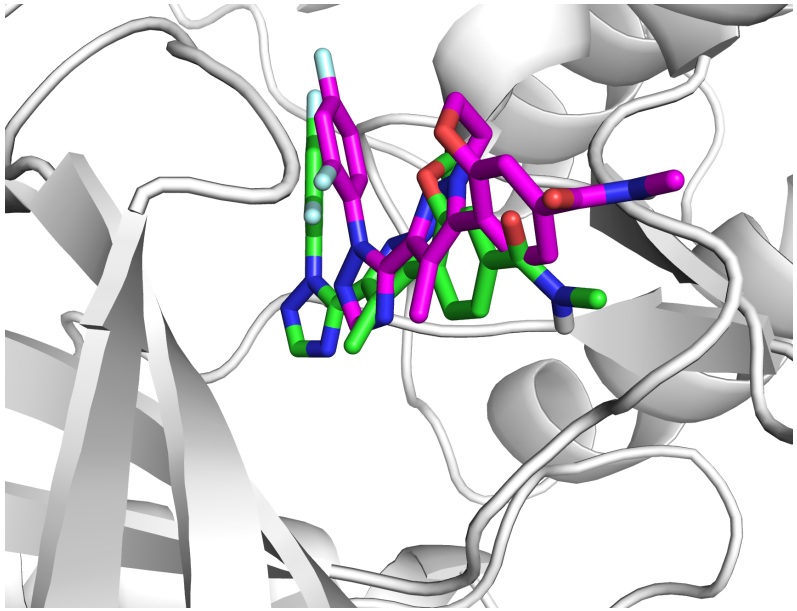
- The optimal receptor can be chose from **min-cross**.

MAP4K4 pose

The poses that me miss

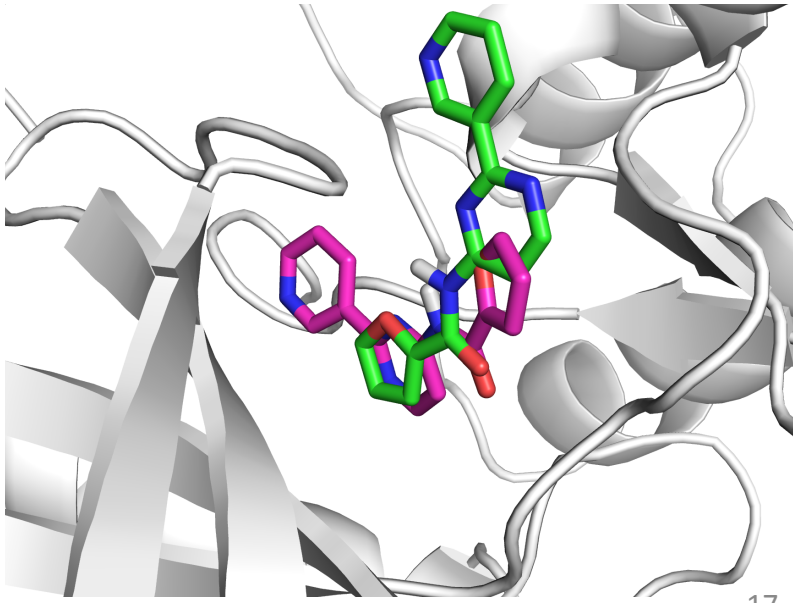
- MAP17: we expect the the cmp to get more buried in the pocket. But it is off the binding groove.

magenta: crystal
green: prediction



- MAP20 & MAP26: we predicted the binding poses in a reverse way (there are other crystals binding in that way).

magenta: crystal
green: prediction



Brief Summary

- Differences in pockets result in different performance of cross-methods and close-methods.
- Close-methods are very useful in pose prediction.
- The optimal receptor(s) for HSP90 should either have an open-conformation or use the closest co-receptors.
- The optimal receptor for MAP4K4 should be the one from min-cross (MAP29).

Acknowledgement

- Thanks Carlos for all the guidance
- Thanks Matt for all the advice and help
- Thanks all other group members and department staffs for all support
- Thanks D3R groups for all the hard work
- Thanks NIH and CSC for funding and research opportunities