D3R 2015 Grand Challenge: Evaluation of Predictions for the Pose and Affinity Challenges

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Drug Design Data Resource

Background

Improvement of computational methods is a major goal for enhancing rational drug design in the drug discovery process. The Drug Design Data Resource (D3R) aims to advance the technology of computer-aided drug discovery (CADD) by engaging the community through blinded prediction challenges as a way of testing and improving ligand-protein docking algorithms and scoring protocols. The 2015 Grand Challenge was based on co-crystal structures and binding affinity datasets of two human protein targets donated by AbbVie, CSAR and Genentech and curated by D3R. The SMILES strings and SDFiles of all (active and inactive) ligands, example co-crystal structures and a brief background of the targets, including the pH of the assays used to determine the binding data, were provided through the D3R website (www.drugdesigndata.org). The 2015 Grand Challenge encompassed two stages – the prediction of crystallographic poses and affinity rankings in Stage 1 and a repeat of affinity rankings in Stage 2 considering the unblinded co-crystal structures, that is, the co-crystal structures were provided to the participants. Multiple metrics were used for evaluation of the results submitted by the participants and included symmetry-corrected RMSD to crystallographic conformations and rank correlation coefficients.

2015 Grand Challenge Datasets

The HSP90 Dataset (AbbVie, CSAR)

- Chaperone protein. ATPase domain inhibitor binding site.

Challenging facts about this target

- Water-mediated interactions, conformations - 'open' and 'closed'.[1]

The MAP4K4 Dataset (Genentech)

- Serine/threonine kinase. ATP-competitive inhibitor binding site.

Challenging facts about this target

- Conformational flexibility; P-loop has folded, closed or extended conformation.[2]

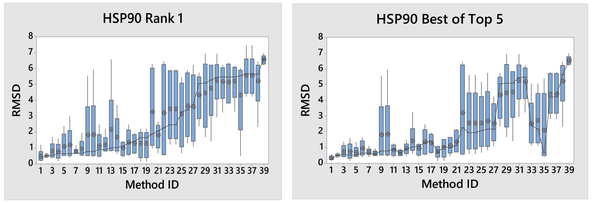
Chemical series	No. of cpds	Activity range for active compounds IC_{50} (μM)	No. of inactives IC_{50} > 50μM	No. of blinded experimental structures	Resolution(Å) range of blinded crystal structures
3	180	0.00522 - 50	33	6	1.6 - 1.95

Chemical series	No. of cpds	Activity range for active compounds IC_{50} (μM)	No. of blinded experimental structures	Resolution(Å) range
Diverse	18	0.00311 - 16.7	30	1.59 – 3.04

(1) Chemical Biology & Drug Design **2007**, 70, 1. (2) BMCL **2014**, 24, 4546.

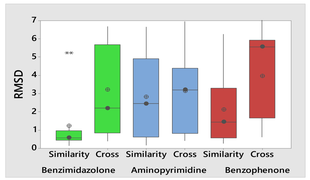
Evaluation of Predictions

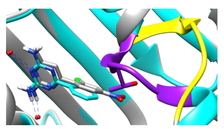
HSP90 & MAP4K4 Correlation of Pose Prediction Performance with Docking Method



- Half of the submissions provided rank 1 poses with median RMSD < 2Å.
- Not obvious success of submissions can be attributed to docking software.
- Range of successful tools used (rDOCK, AutoDock Vina or variations, Gold, and Surflex, Gold-PlantsPLP-rDock, RosettaLigand-Omega-PoPPs-ROCS, Grim-Surflex and Glide-Prime-Desmond-Qsite).
- Submissions using similar or the same software packages yielded differing levels of accuracy, e.g., AutoDock Vina and Glide methods are scattered through the ranking.
- ¼ of successful protocols used visual inspection; none of the less successful used human intervention.

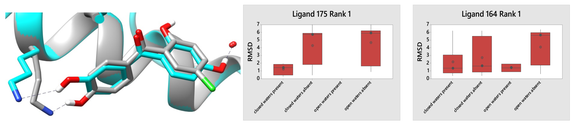
HSP90 Correlation of Performance with other factors





Conformations of ligands 73 (grey) and 179 (cyan) in the experimental co-crystal structures

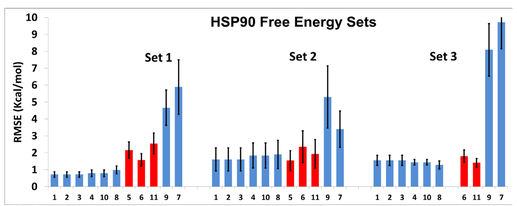
- "Similarity" - chemical series chemotypes, not overall Tanimoto similarity.
- Aminopyrimidine ligand co-crystal structures - 73 binds to an open conformation (yellow), 179 binds to a closed conformation (purple).



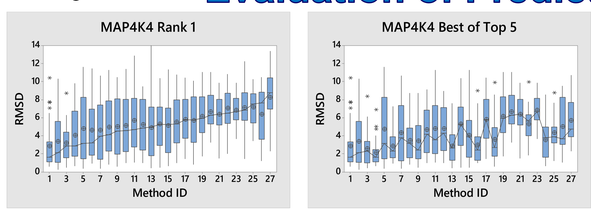
Left: 164 (grey) and 175 (cyan) in the experimental co-crystal structures.

Right: RMSD distributions for rank 1 poses of ligands HSP90_175 and HSP90_164, separated according to the conformation of the structure used and presence of water during docking.

- Both co-crystal structures have the same closed conformation.
- Difference is a water-mediated interaction for ligand HSP90_175 (absent for HSP90_164), although the water position is identical in both cases.

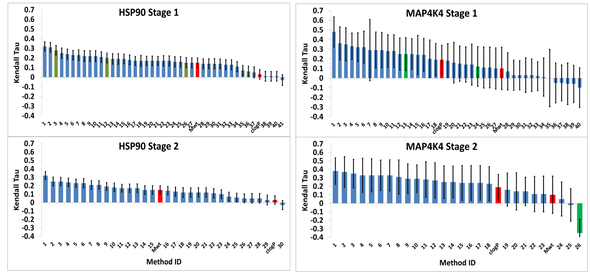


5 & 11 – Sire
6 - Amber



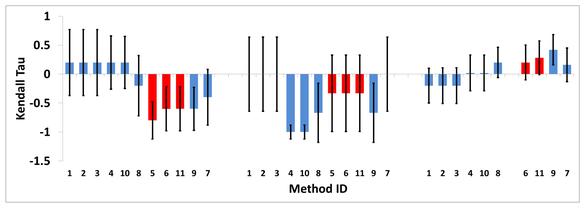
- MAP4K4 predictions are considerably less accurate than those for HSP90.
- Only one out of 27 submissions has a median RMSD below 2.0 Å for rank 1 poses, compared to 20 out of 39 for HSP90.
- The MAP4K4 pose prediction challenge was anticipated to be more challenging than HSP90 for a number of reasons.
  - ❖ 8 versus > 200 PDB structures for human HSP90.
  - ❖ A large binding site size - conformation of the glycine-rich P-loop.
- **Method 1**, Glide SP-Qsite, and **Method 4**, RosettaLigand-Omega-PoPPs-ROCS, were the only submission with a median RMSD less than 2.0 Å for the rank 1 and best of top 5 poses respectively.
- Both approaches were among the more accurate ones used for HSP90.

Predictions of Binding Potency



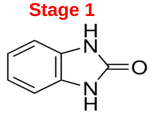
Green bars are for ligand-based scoring methods, and red bars are for null models. The error bars are 1σ confidence intervals based on 10,000 bootstrap samples.

- Almost all correlate positively with the experimental ranking
  - ❖ Mean and median tau values of 0.15 and 0.17, - HSP90, and
  - ❖ Mean and median tau values of 0.18 and 0.24 - MAP4K4.
- However, the correlations are not particularly high, with maximum values of about 0.32 for HSP90 and 0.48 for MAP4K4.
- Information about ligand poses did not lead to more accurate affinity rankings.
- Null models tau values fall near or below the median of the predictions.

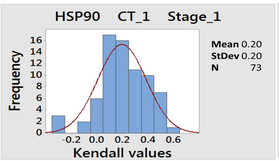


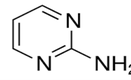
HSP90 Kendall Tau Correlation Coefficients by Chemotype

Stage 1 **Stage2**

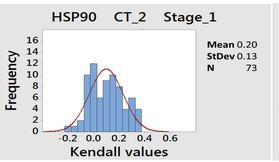


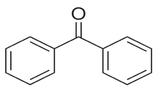
Benzimidazolone



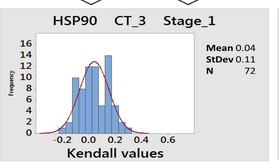


Aminopyrimidine





Benzophenone-like



- The rankings of CT1 are better than the full set.
- CT1 easier to rank, CT3, harder.
- CT3 harder probably due to:
  - ❖ Lower molecular weights / weak affinities, relative to other series.
  - ❖ More chemotype diversity than the others.

Upcoming Challenge

❑ **Farnesoid X receptor Dataset (Roche)**

- **36 co-crystal structures**
- **102 affinity data**
- **September 15th, 2016**

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