Improvement of computational methods is a major goal for enhancing rational drug design in the drug discovery process. The Drug Design Data Resource (DDR) 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 DDR. The SMILES strings and SDFiles of all (active and inactive) ligands, example co-crystal structures and a brief background of the targets, were provided through the DDR website (www.ddrdesigndata.com). 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.”
- 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

HSP90 & MAP4K4 Correlation of Pose Prediction Performance with Docking Method

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- Evaluation of Predictions
  - HSP90 Kendall Tau Correlation Coefficients by Chemotype
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Background

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

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Upcoming Challenge

* Farnesoid X receptor Dataset (Roche)
  - 36 co-crystal structures
  - 1:2 affinity data
  - September 15th, 2016

Acknowledgements

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OpenEye Scientific Software, Santa Fe, NM
MKG is a founder of and has an equity interest in VeraChem LLC

Conclusion

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