MD Simulation in Pose Refinement and Scoring Using AMBER Workflows

Yuan Hu *(On behalf of Merck D3R Team)*

D3R Grand Challenge 2 Webinar

Department of Chemistry, Modeling & Informatics

Merck Research Laboratories, Merck & Co., Inc.

March 27, 2017

MERCK
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Outline

- **Overview of the D3R Predictions from Merck**
  - ***Today just the Stage 1 results***
  - *Merck Team & Result Ranking*
- **Overall Pose Prediction and Scoring Approach**
  - *Structure Preparation & Docking*
  - *AMBER Workflows for Pose Refinement & Ranking*
- **Case Study & Lessons Learned**
  - *Ranking with Ensemble-based MD-MMGBSA*
  - *Pose Exploration with MD*

Acknowledgement
Merck D3R Team

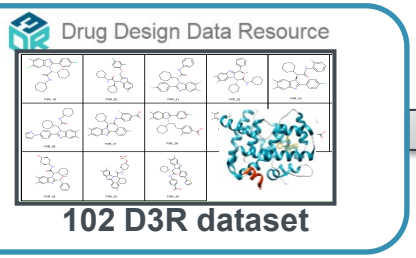
- **Modeling**
  - Ying-Duo Gao
  - Xavier Fradera
  - Yuan Hu
  - Andreas Verras
  - Deping Wang
  - Hongwu Wang
  - James Fells
  - Kira Armacost
  - Alejandro Crespo
  - Brad Sherborne
- **Informatics**
  - Huijun Wang
  - Zhengwei Peng
  - Robert Sheridan

Motivation

- To refine and share our best practices
- To be engaged in the scientific community
- To better understand the capability of sciences in industry & academia

Overall Approach for Stage 1

Step 1: preparation as a team



Literature search
Data mining from PDB and CHEMBL

Structure Preparation
Schrodinger's ligprep/prepwizard
(Protomer/Tautomer, fill missing loop)

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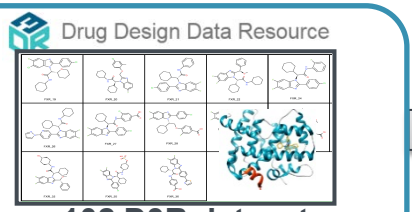

102 D3R dataset

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Step 2: docking experiments

Glide Ensemble Docking	Colony Entropy Docking	Glide+Gold Docking	Visual Inspection (A+C)
Submission A	Submission B	Submission C	Submission E

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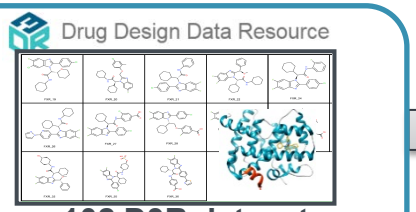

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Step 3: MD-MMGBSA

MD simulations using multiple replicates

MD pose refinement
Submission D

Ensemble-based MMGBSA ranking

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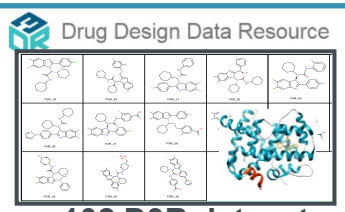

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- ***Can MD be used to refine docking pose?***
- ***How does MD-MMGBSA perform in ranking?***

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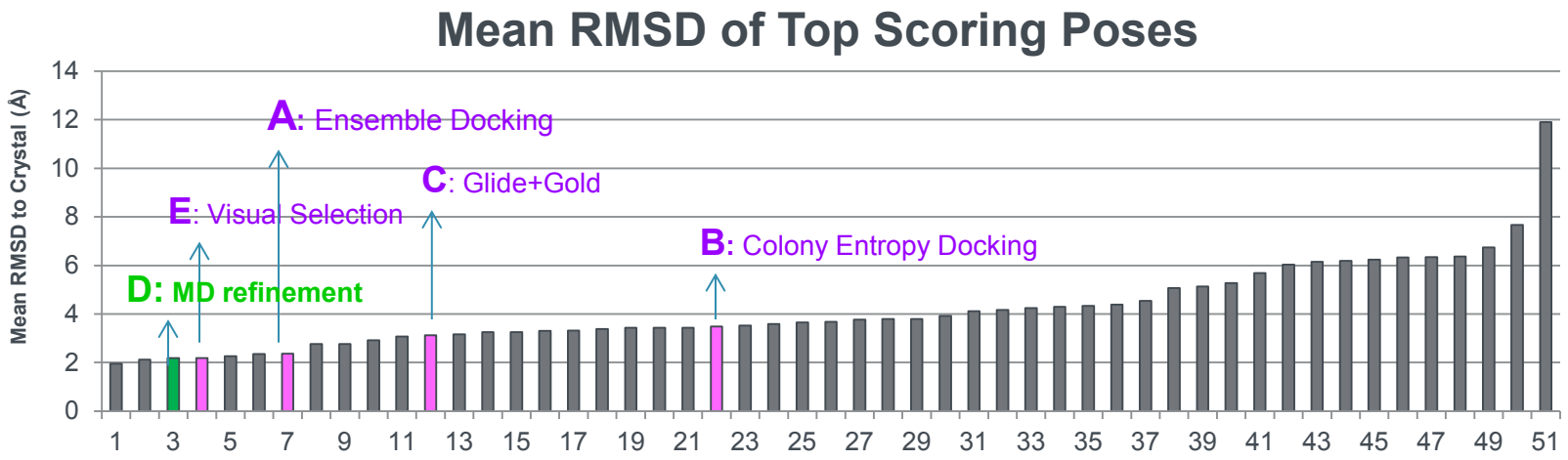
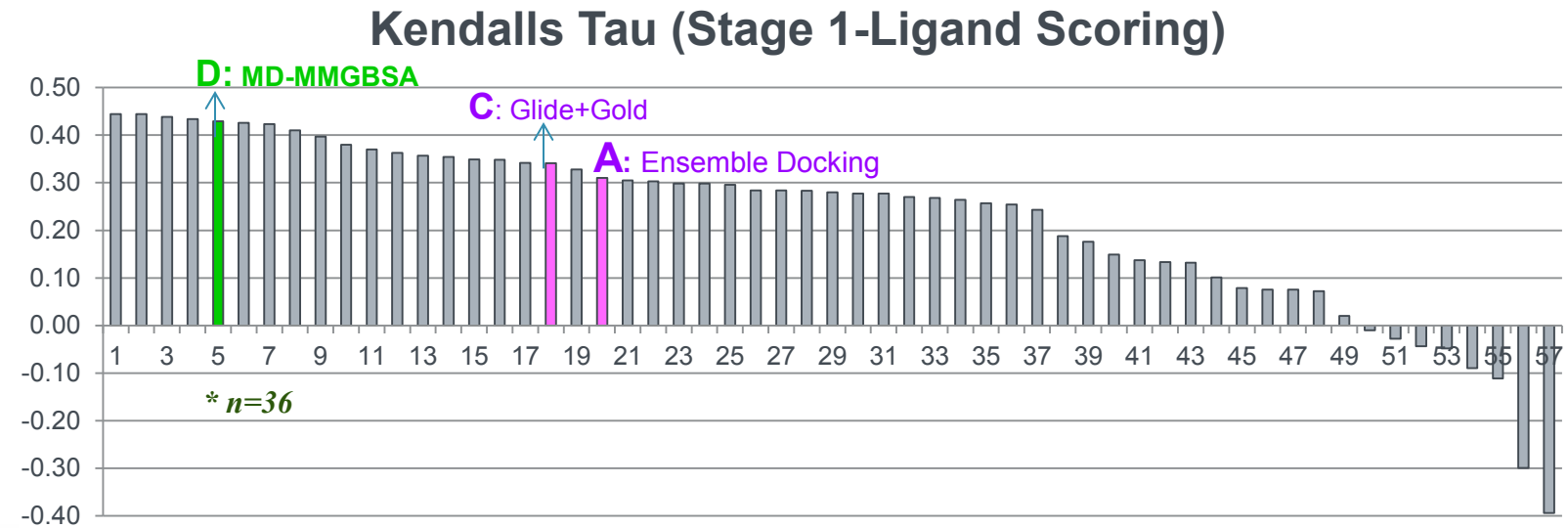
Overall conclusion:
MD improves pose prediction and ranking





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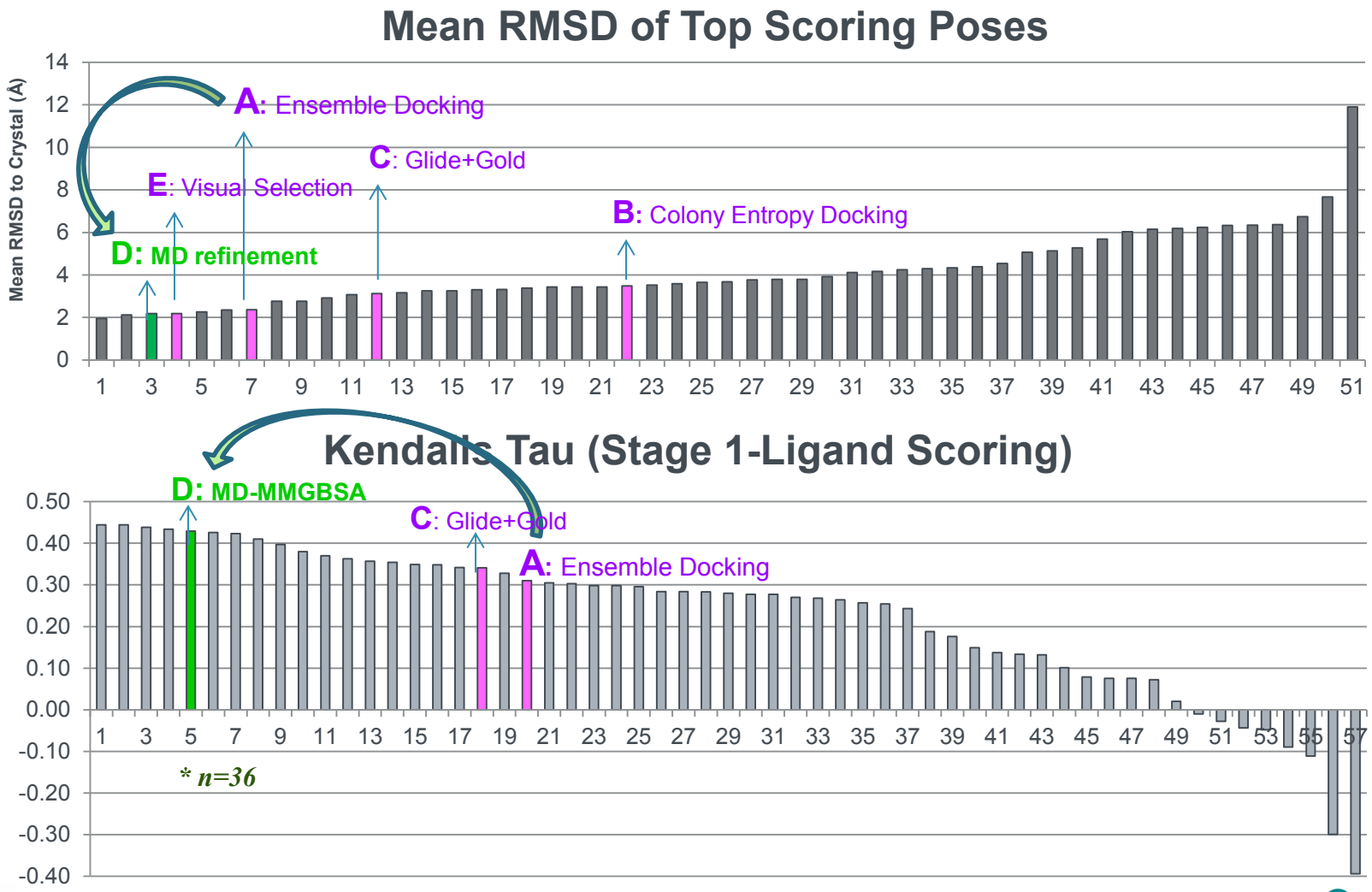


Glide Ensemble Docking & AMBER workflows Completely automated

Ensemble Docking

Ligand/Protein Structure Preparation

↓

Glide XP Ensemble Docking
36 ligands x40 templates =1,440

↓

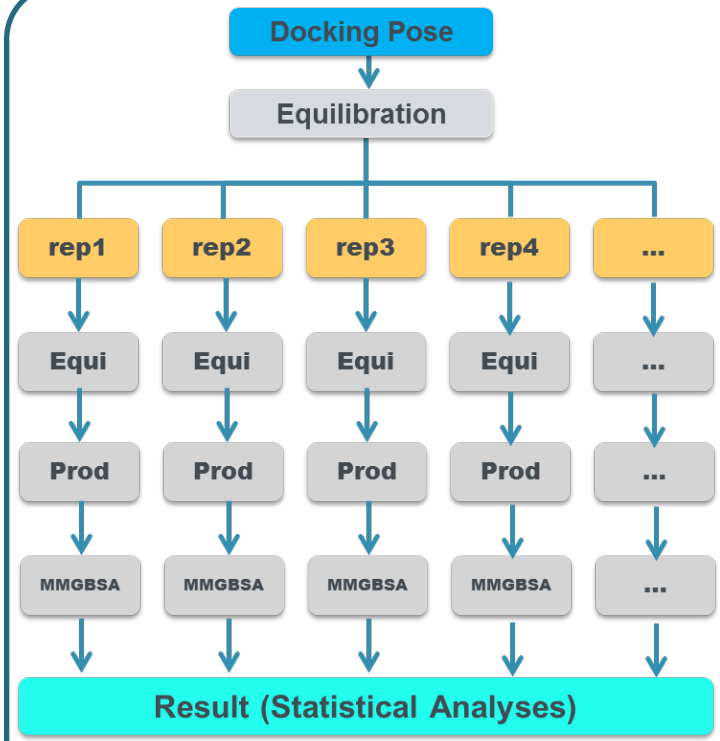
Pose selection
- Rank by score
- rmsd >= 1.0 A to previously selected pose to ensure diversity

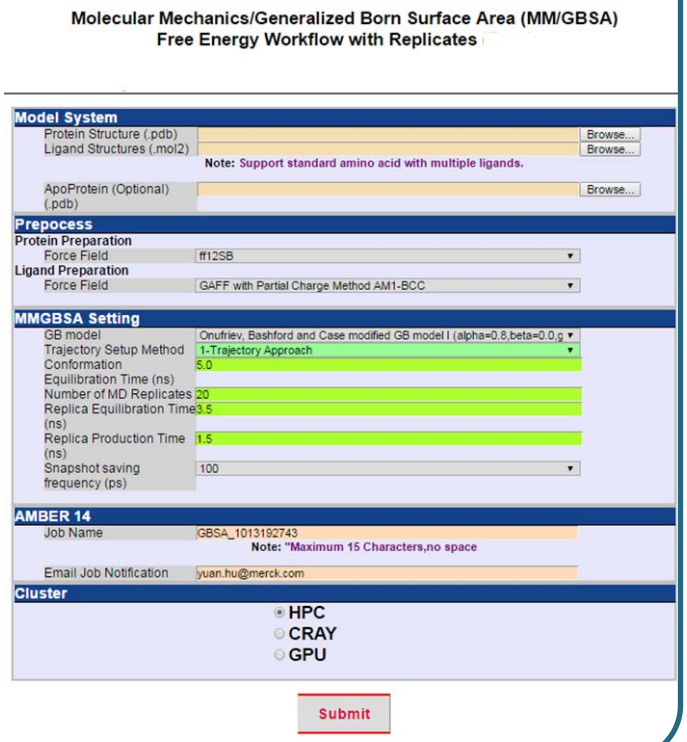
↓

Top Scoring Pose

**Workflow was validated before on 40 native ligands*

AMBER MD-MMGBSA workflows





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Y. Hu, B. Sherborne, Z. Guo, et al.. "How to Obtain Reliable and Reproducible MMGBSA Results?" manuscript in preparation.

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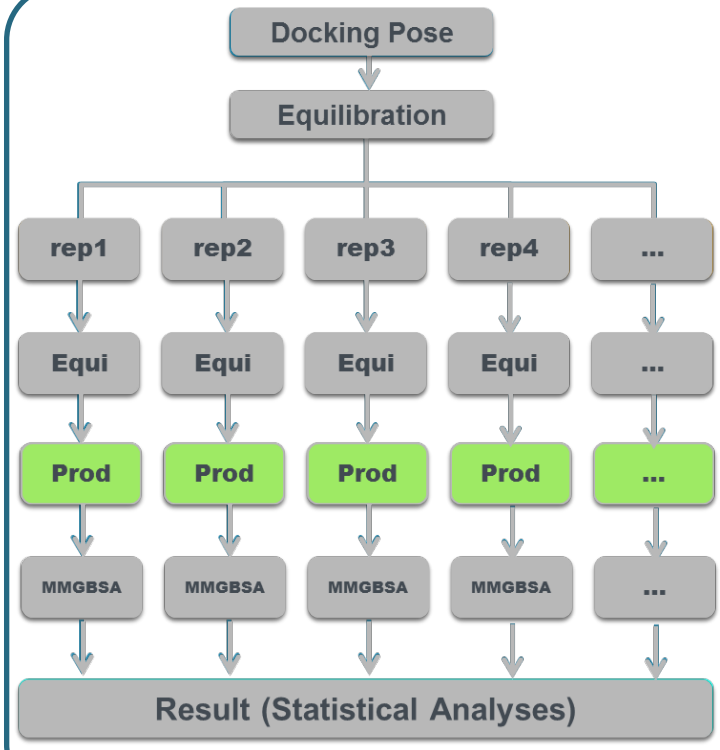

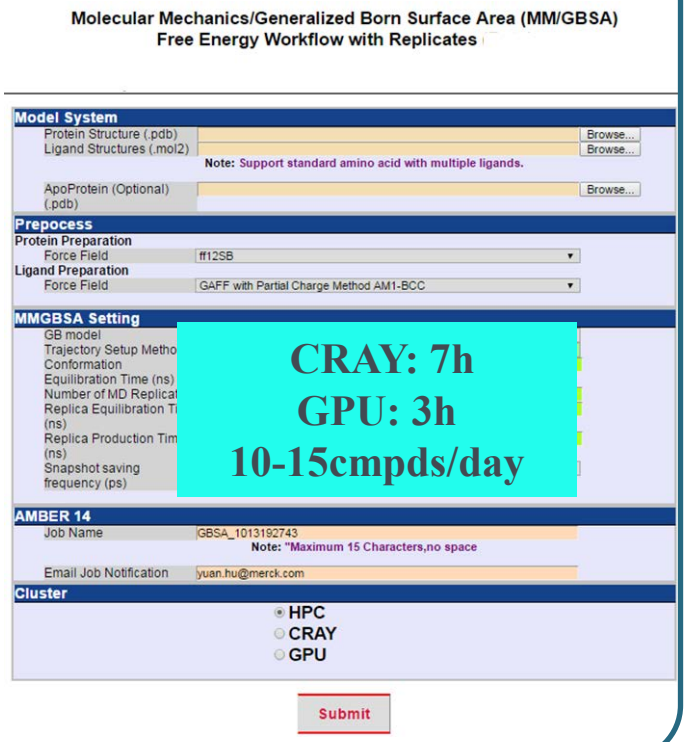

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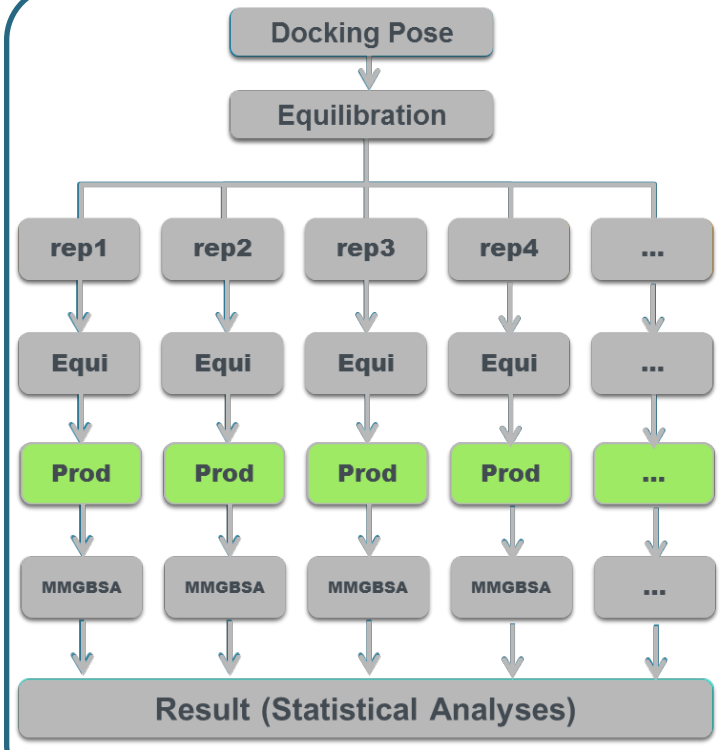

Pose Selection

- Structure of the lowest free energy snapshot
- Average structure of the lowest 10 % free energy snapshots scored by MMGBSA
- Average structure of the lowest 10 % VDW snapshots scored by MMGBSA
- Average structure of the highest 10 % ELEC snapshots scored by MMGBSA
- Highest population cluster generated by using structural similarity

**Workflow was validated in large data sets.*
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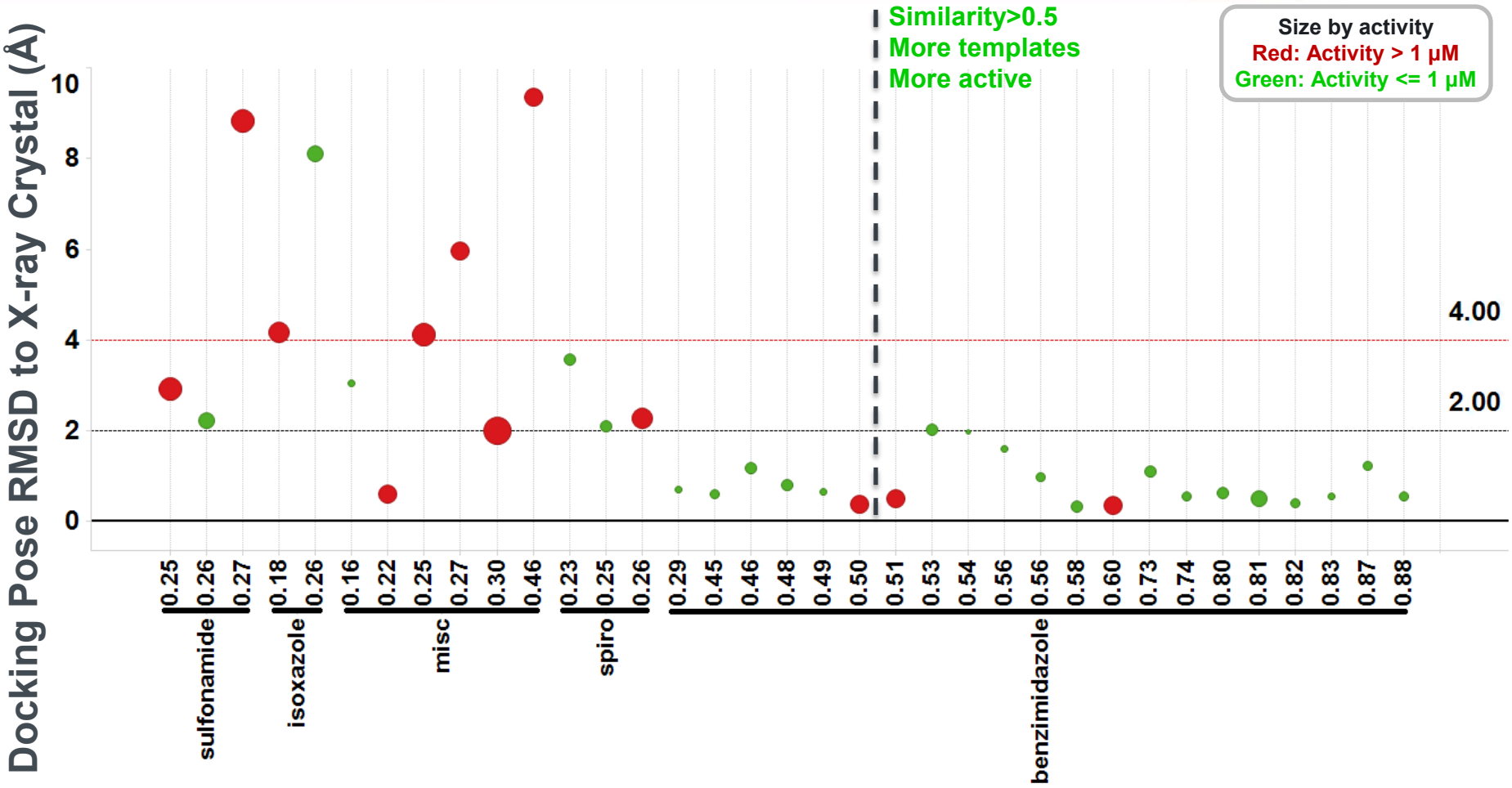
Good template is important for docking… Similarity matters



2D Similarity of closest template ligand in ensemble of complexes (descriptor: ECFP6)

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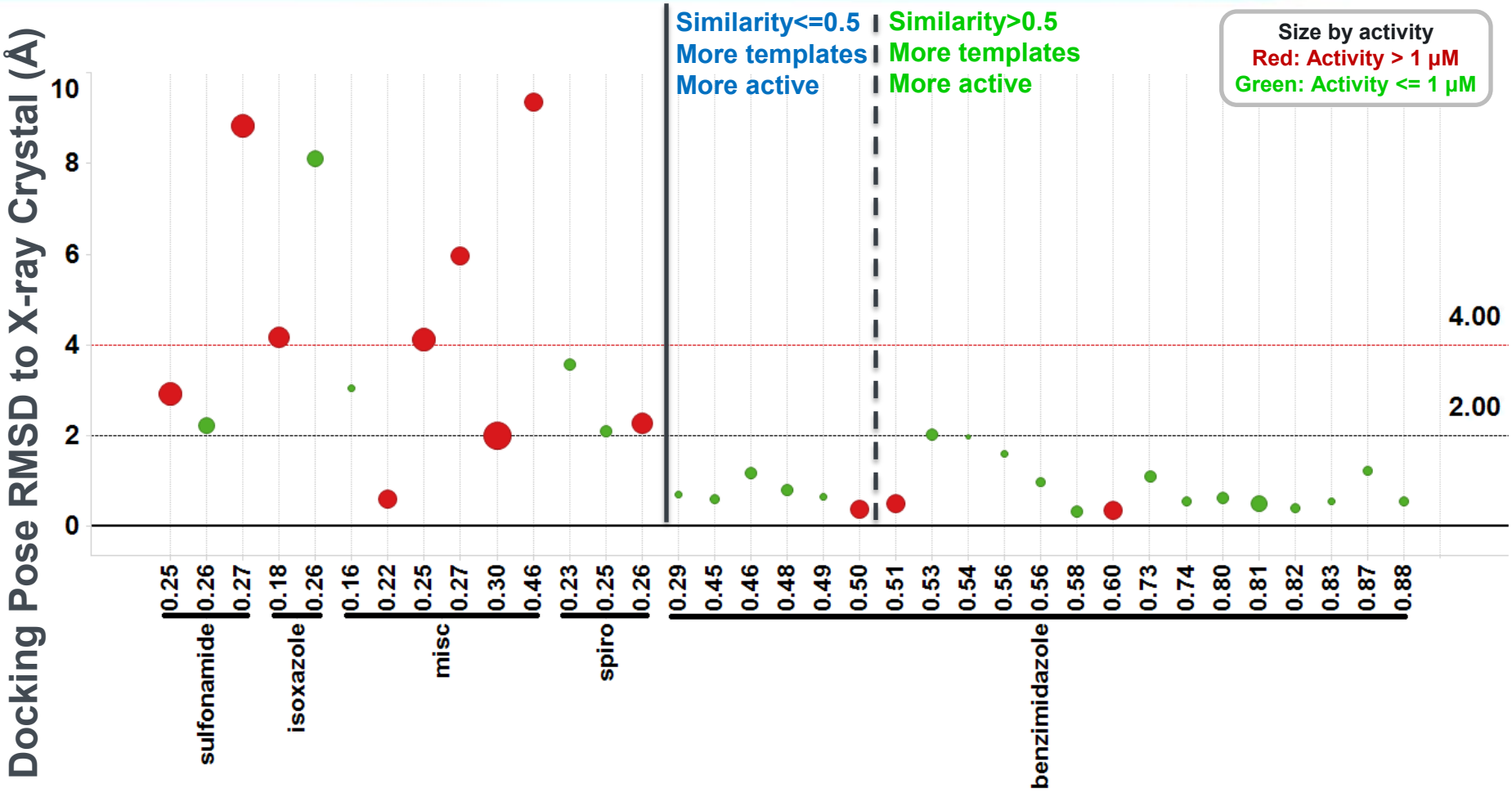

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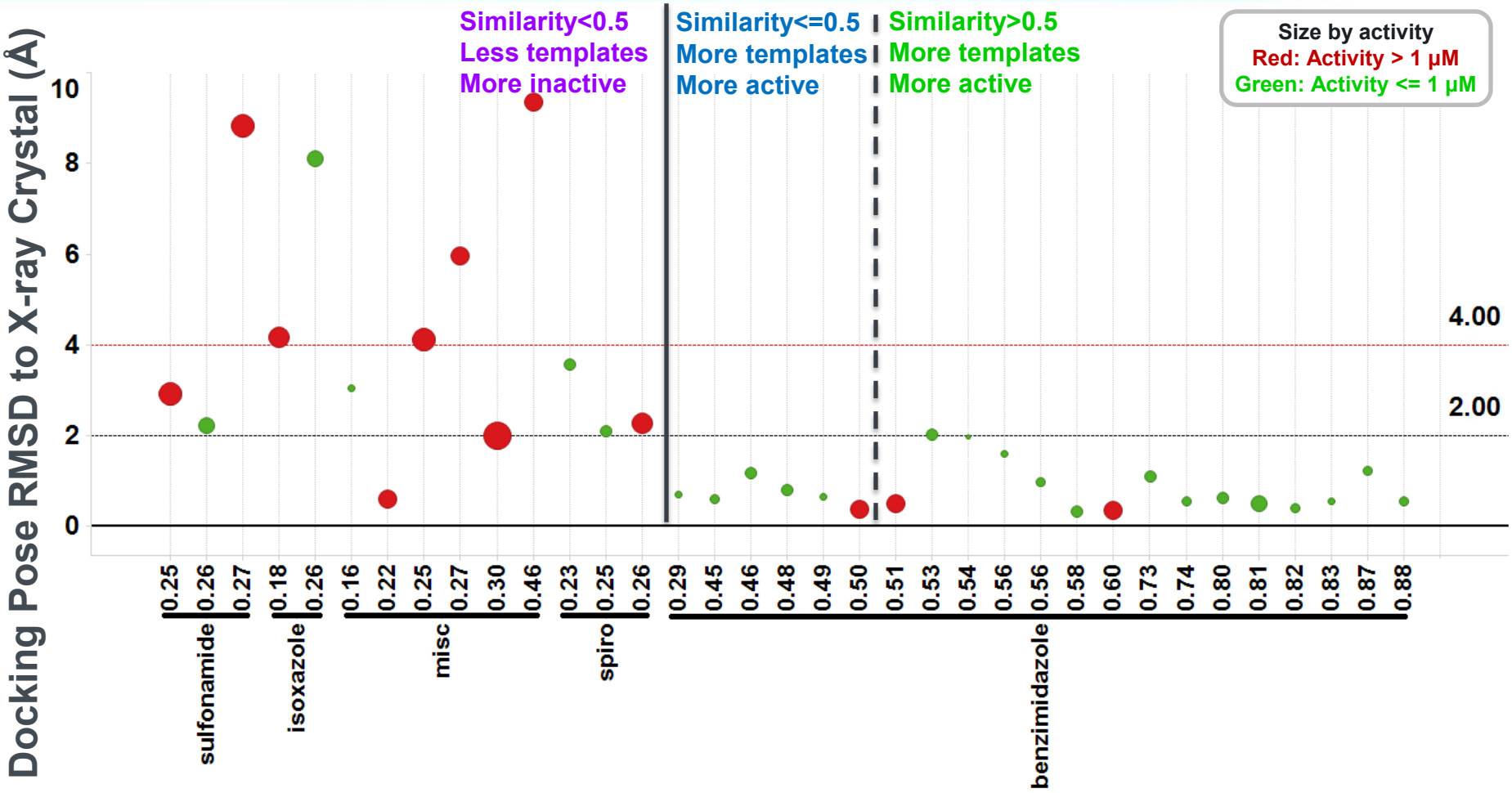

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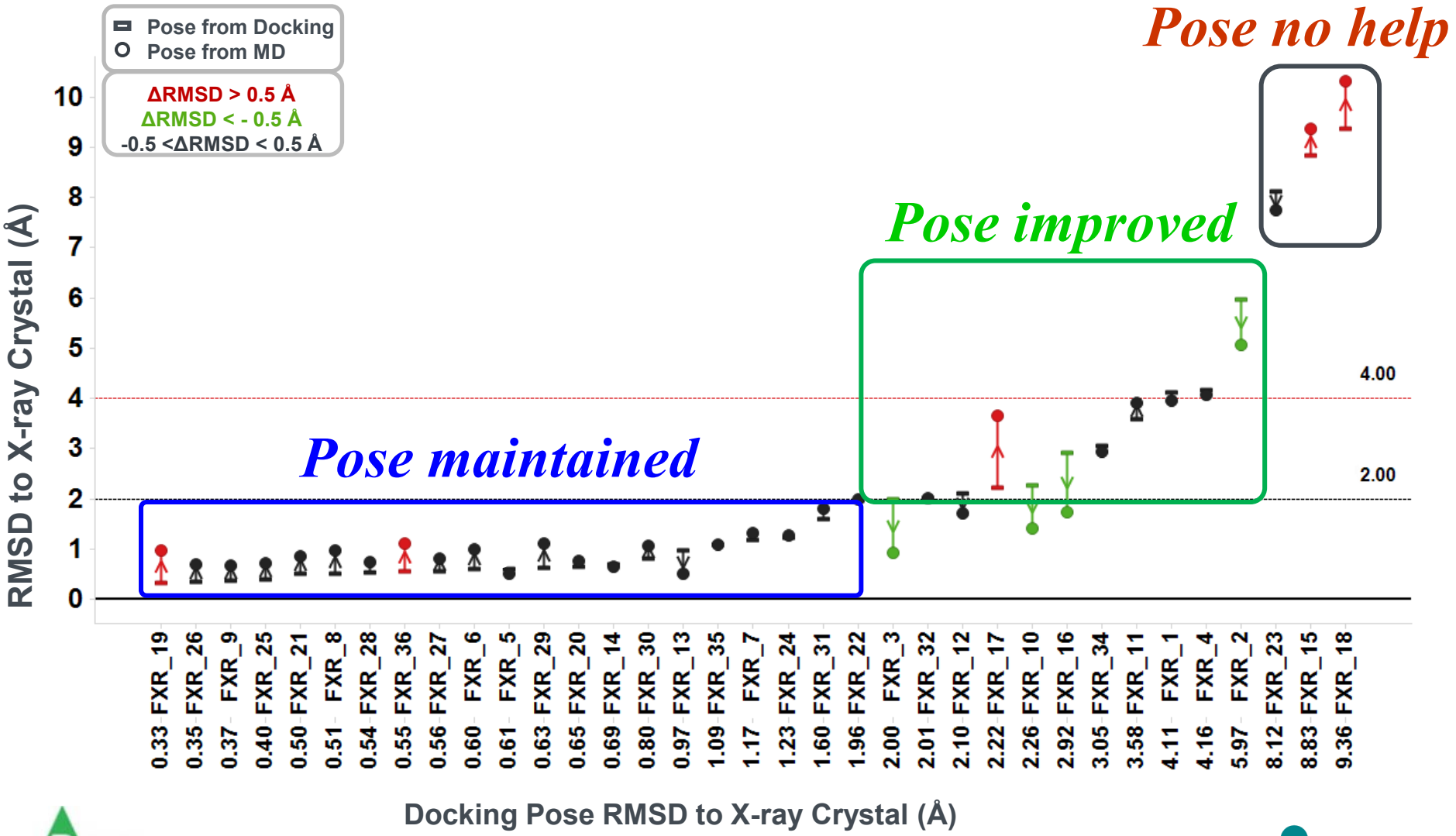
Question 1

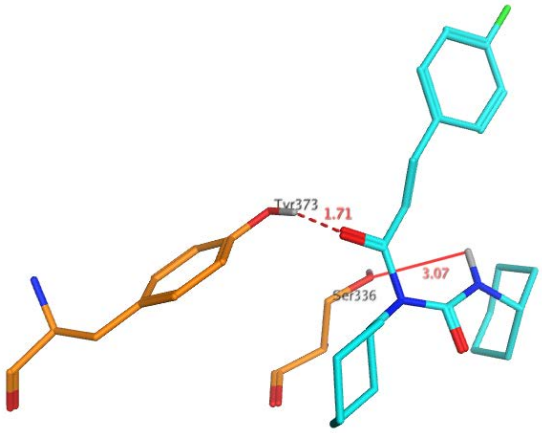
Can MD be used to refine docking pose?

Pose refinement with MD

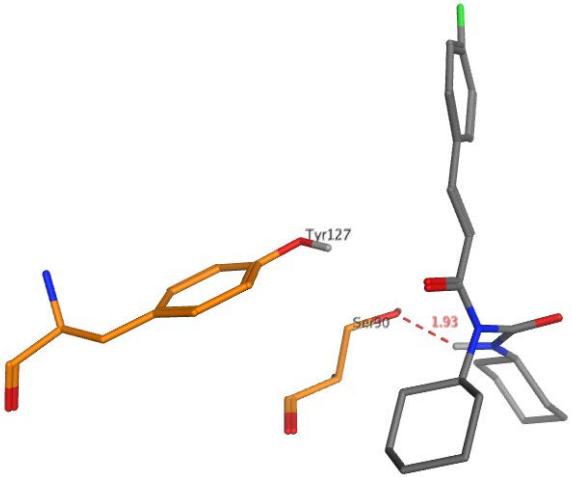


Case Study-success: FXR_3
Ligand interactions optimized through MD

- Ligand moves to create stable H-bond

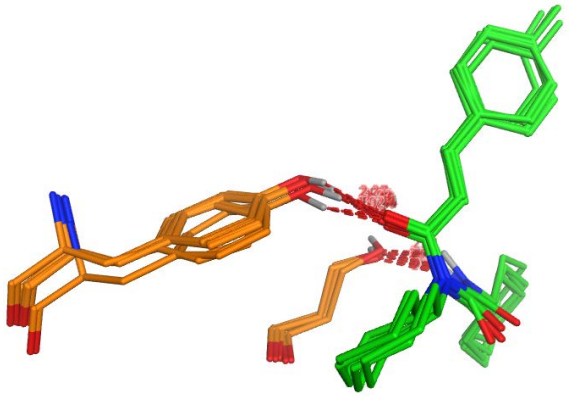


Crystal Structure



Docking Pose

RMSD 2.00 Å



MD refinement

RMSD 0.92 Å

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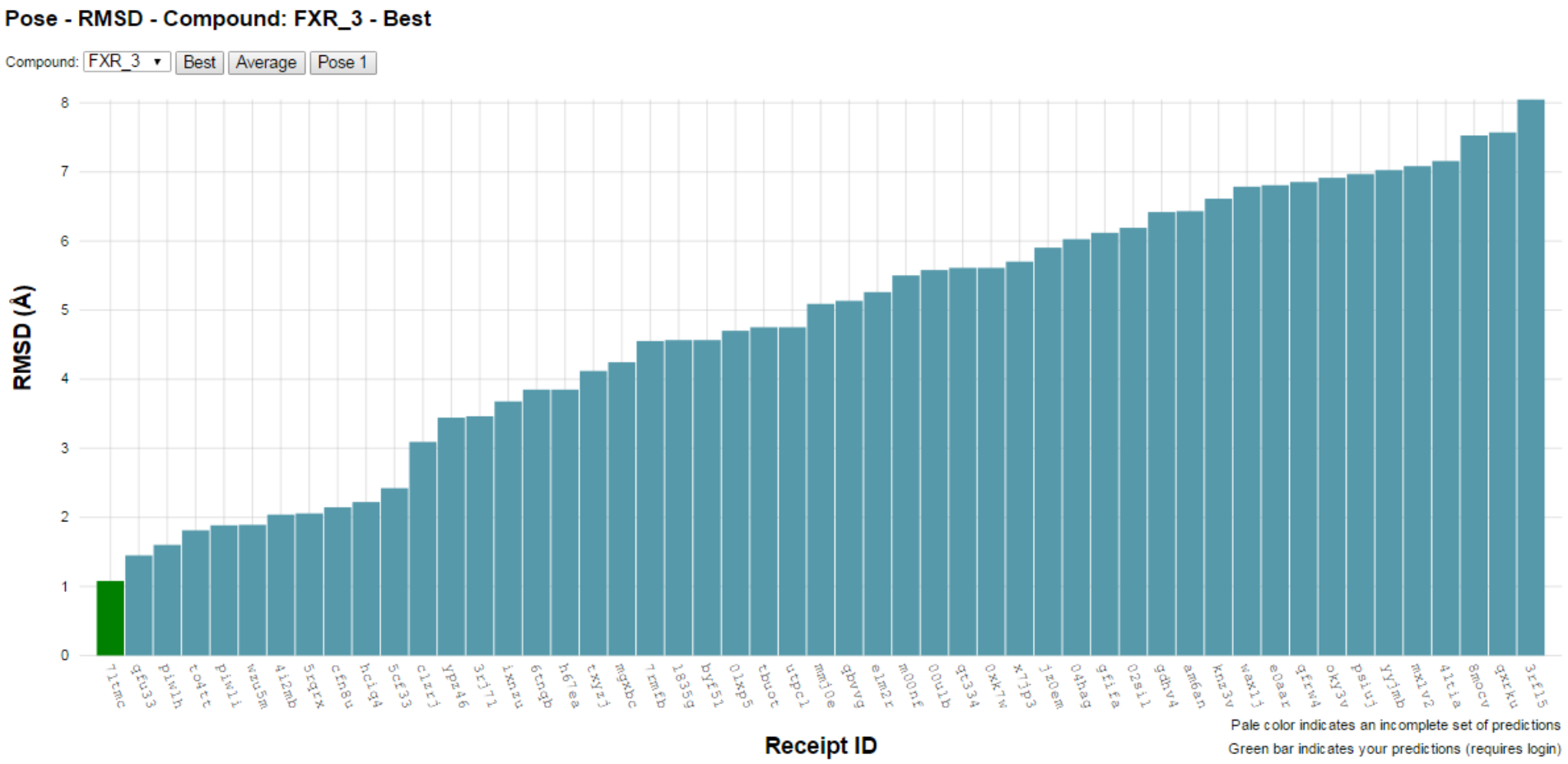
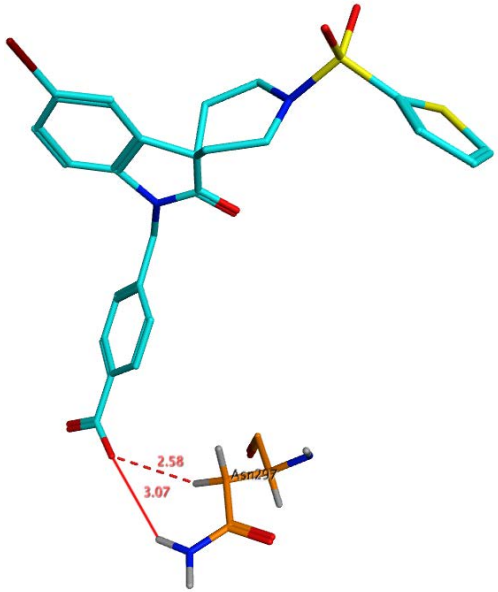


Case Study-success: FXR_10 Protein optimized through MD

- MD reorients the Asn to make H-bond contact



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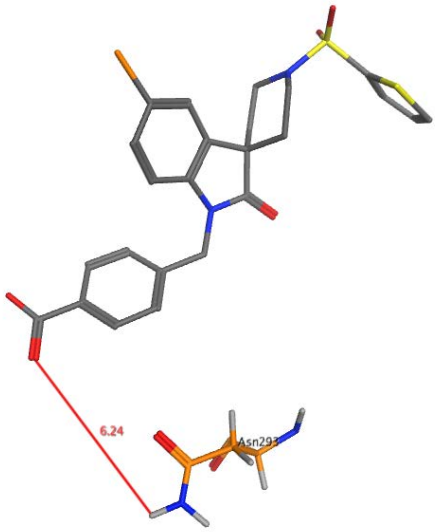
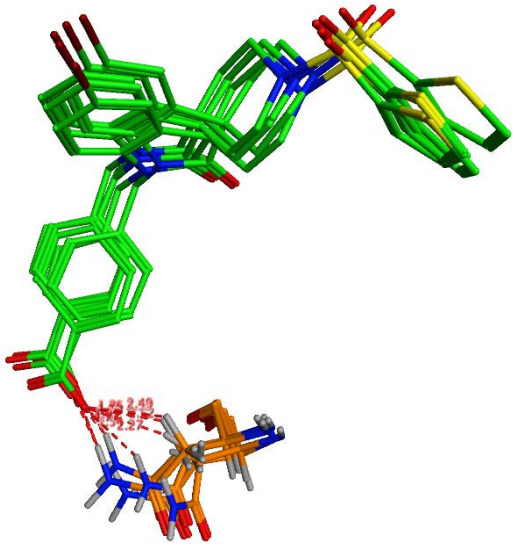


Docking Pose

RMSD 2.26 Å



MD refinement

RMSD 1.41 Å

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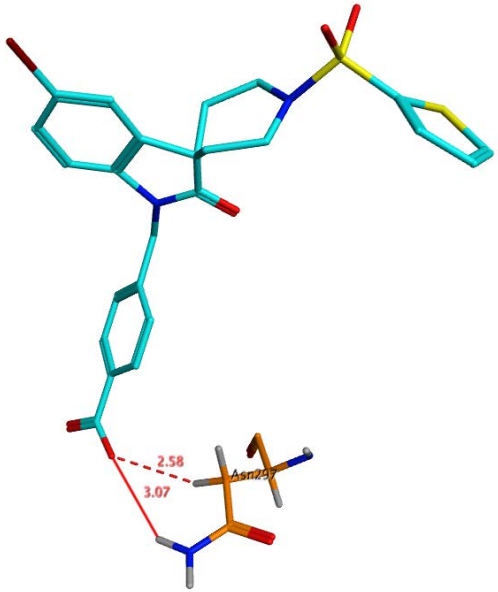

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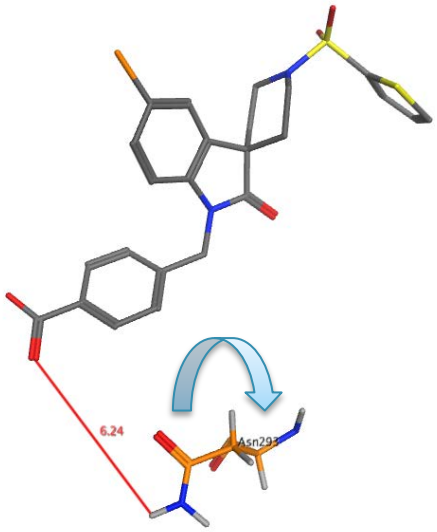

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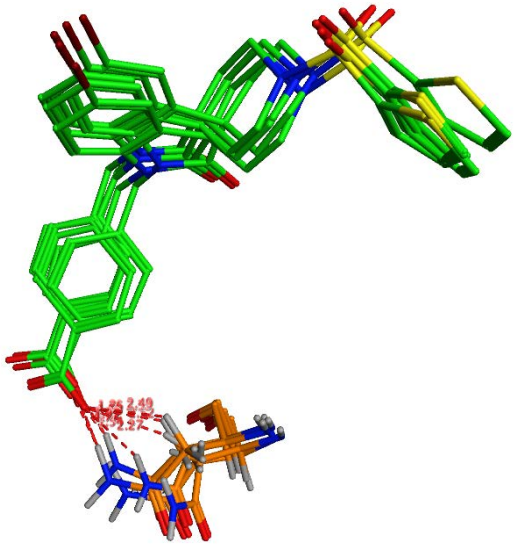

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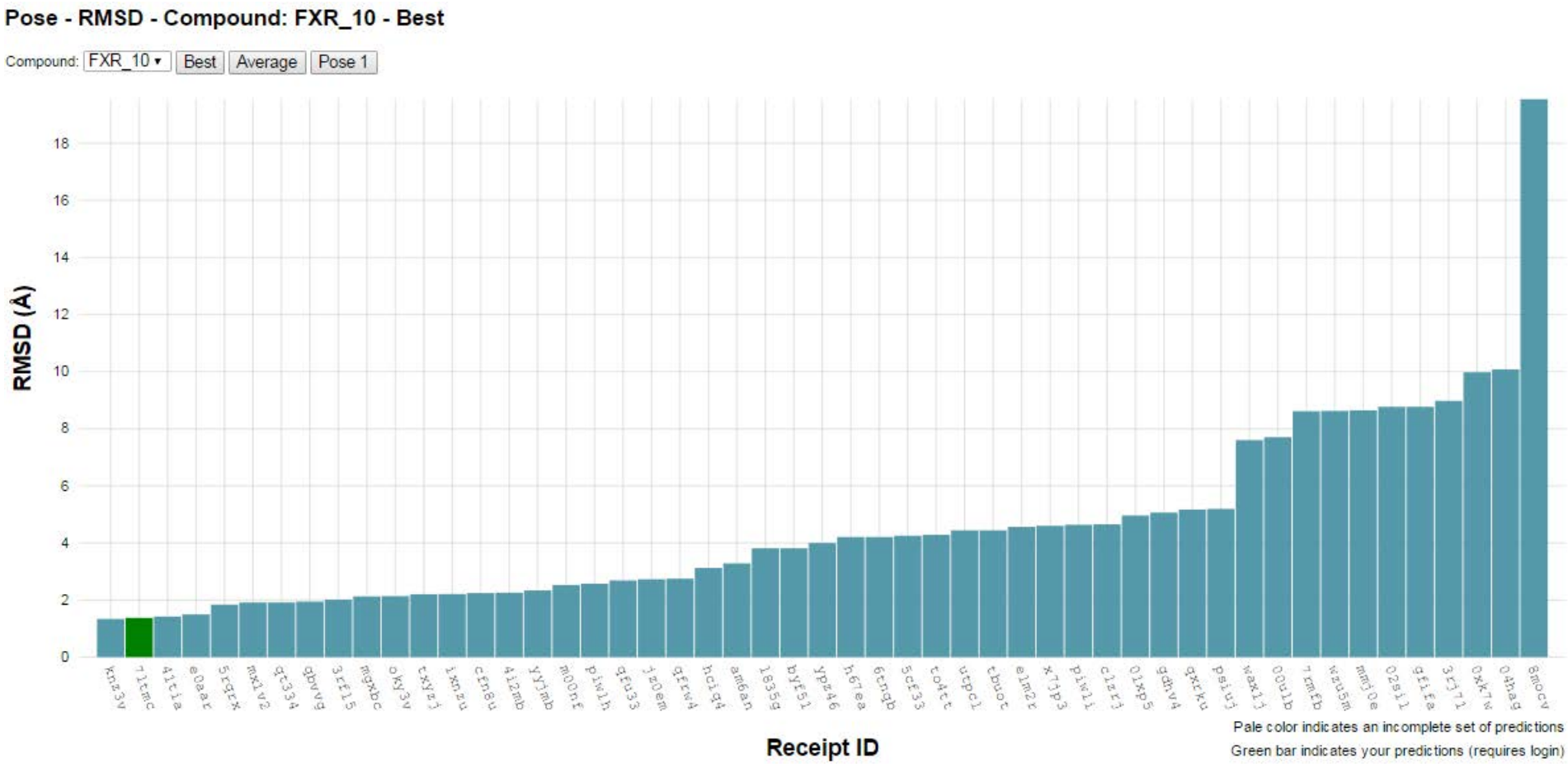
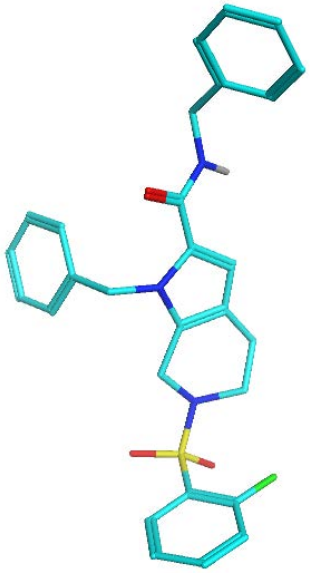


Case Study-failure: FXR_15
MD workflow can't rescue reversed pose

- The docked pose has a reverse direction comparing to x-ray
- Hard to refine the structure with MD…



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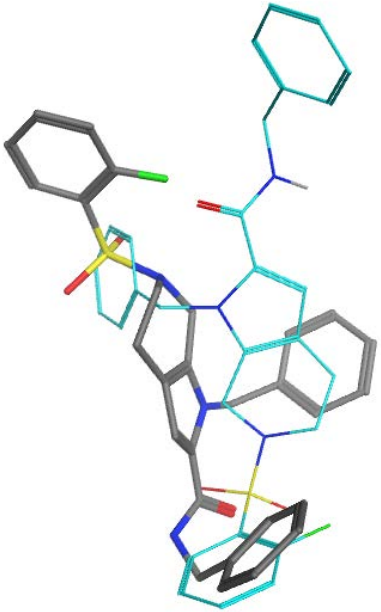
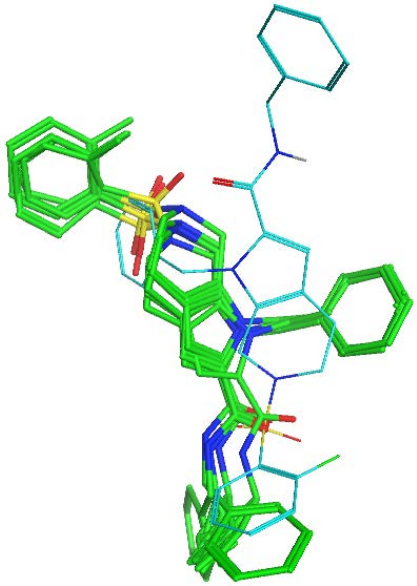


Docking Pose

RMSD 8.83 Å



MD refinement

RMSD 9.37 Å

Case Study-failure: FXR_15
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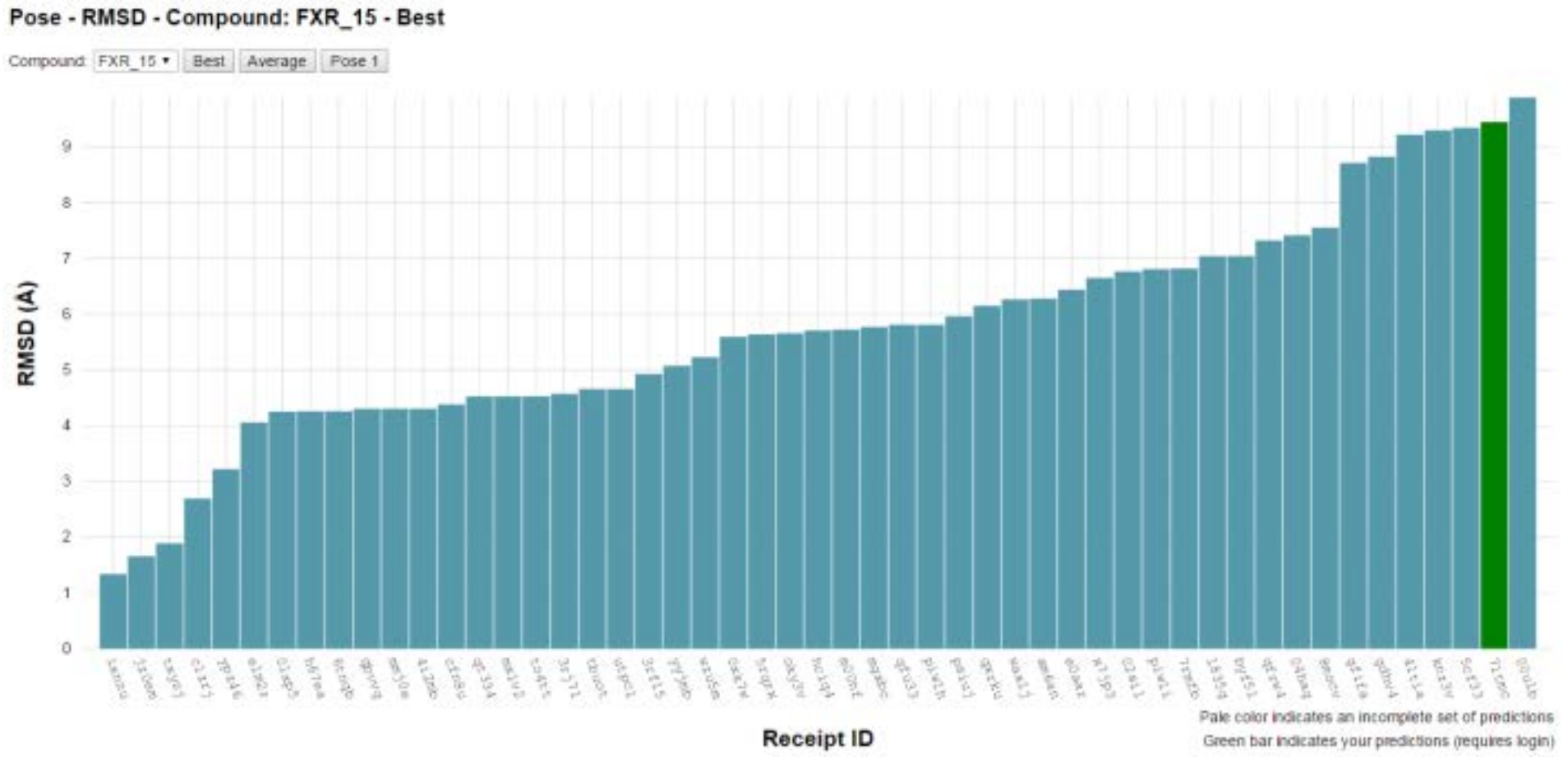
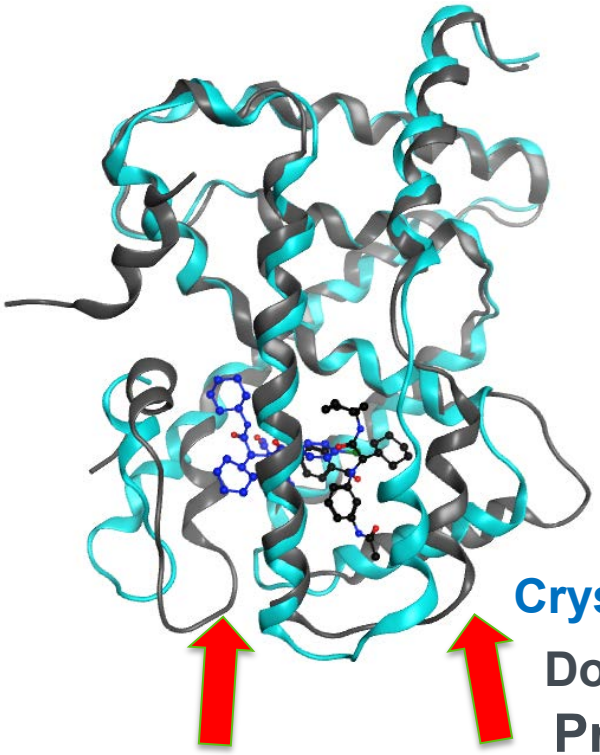


Case Study-failure: FXR_18
MD workflow can't address very large protein movements

- Protein conformation change



Crystal Structure

Docking Template

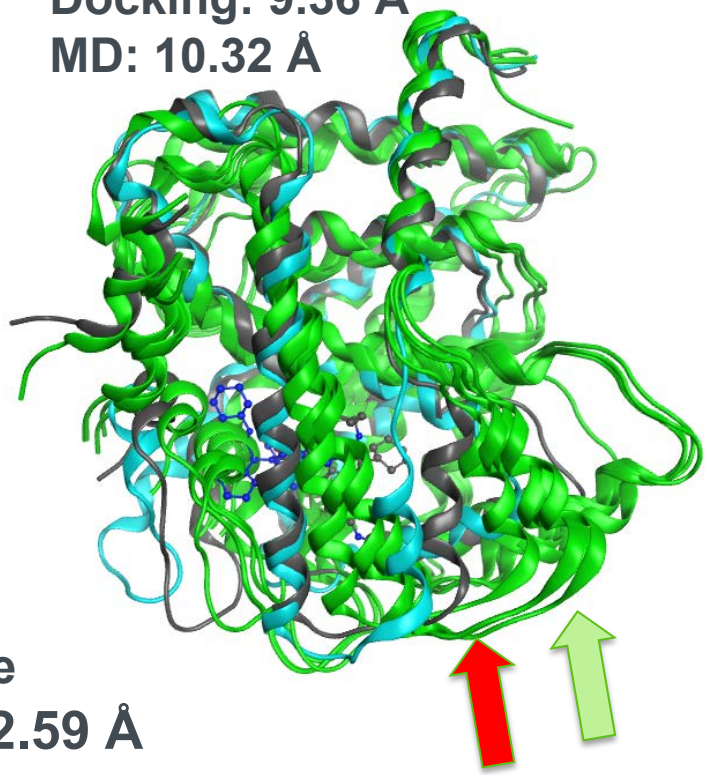
Protein RMSD 2.59 Å

Chain opened up in template

Ligand RMSD to X-ray

Docking: 9.36 Å

MD: 10.32 Å



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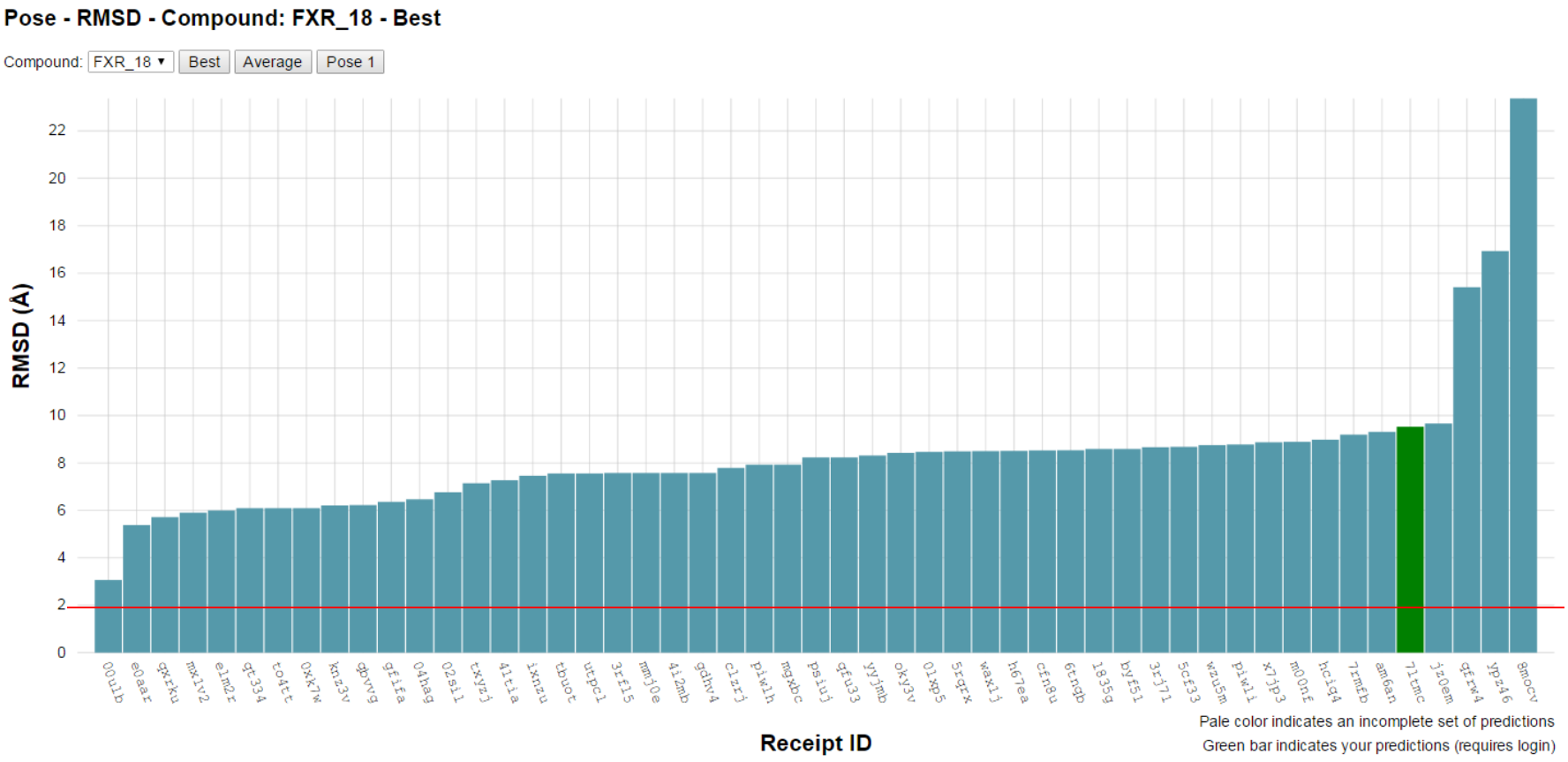


Lesson learned from previous D3R challenge:

"Explicit solvent free energy methods have not yet outperformed faster scoring methods in blinded protein-ligand affinity predictions."

-D3R website (Posted October 11, 2016)

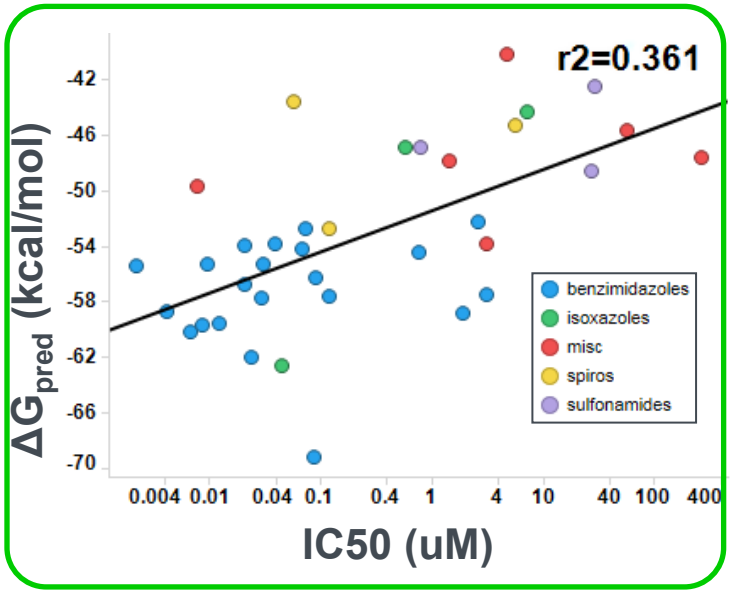
https://drugdesigndata.org/about/what-we-have-learned

Question 2

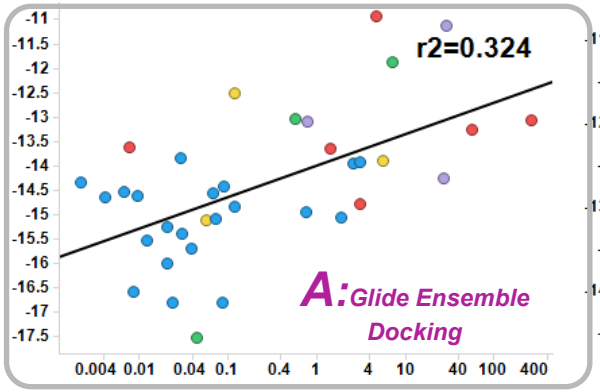
How does MD-MMGBSA perform in ligand scoring?

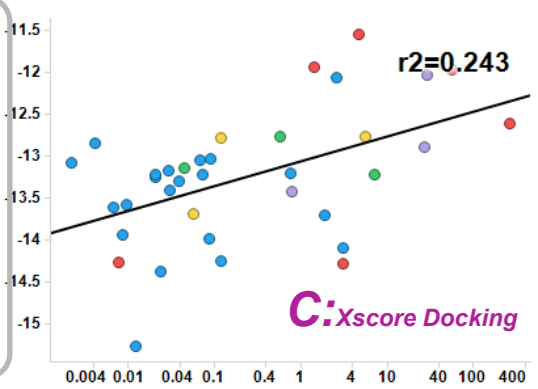
MD-MMGBSA improves on docking scores

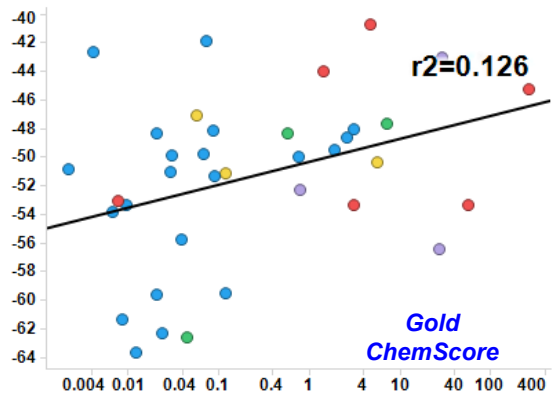
D: MD-MMGBSA

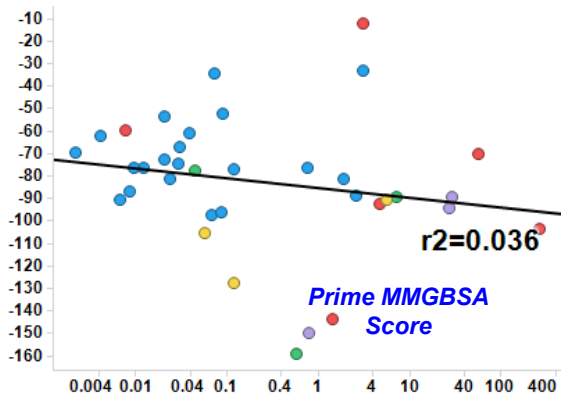


Docking Methods

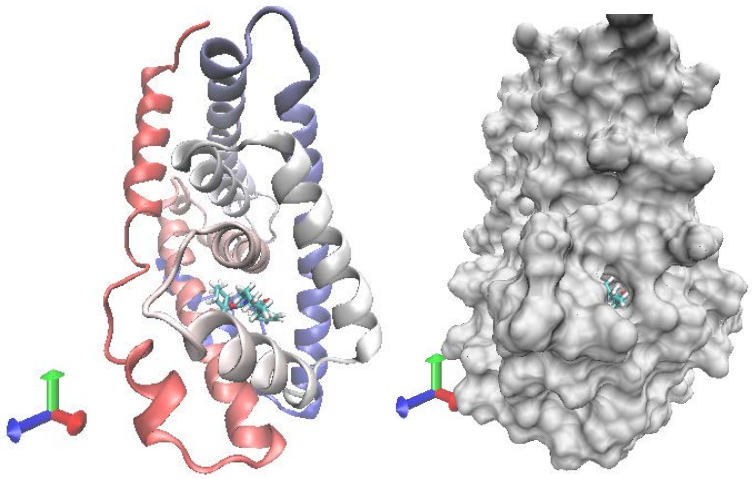








Stage1: 36cmpds

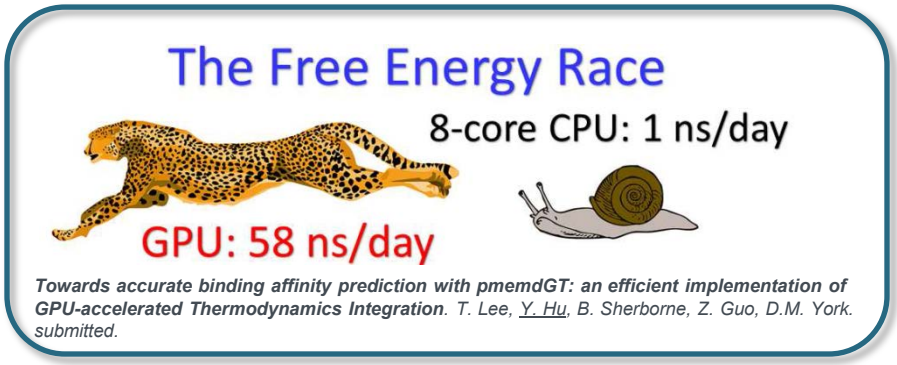


binding pocket is deep inside challenge data set for implicit model (MMGBSA)

MERCK

Summary

- Lessons
  - Ensemble docking performs well in pose prediction & ranking, if there are suitably close protein complexes available
  - MD maintains or refines docking poses (protein and ligand) and extends the limit of prediction
    - MD can't refine challenging poses
  - Ensemble-based MD-MMGBSA ranking improves on docking scores
  - Teamwork broke the challenge down to manageable portions
- Next
  - AMBER MD-MMGBSA to AMBER TI
  - CPU to GPU

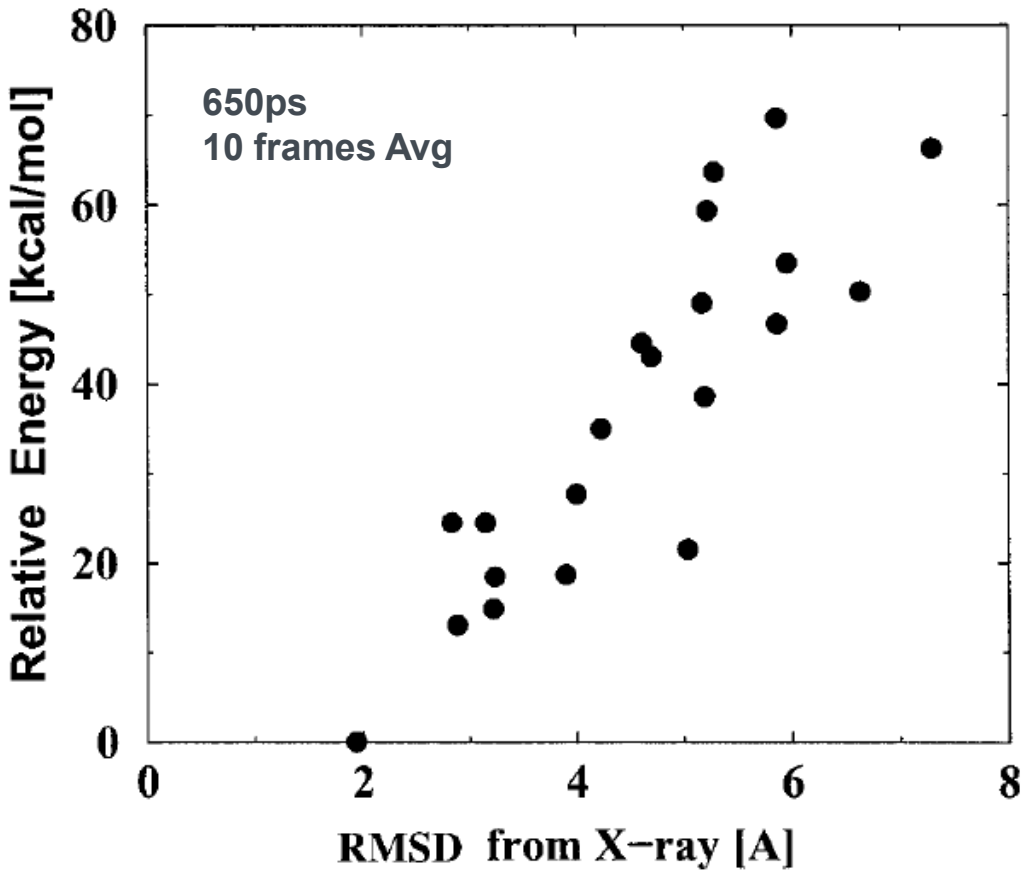


Towards accurate binding affinity prediction with pmemdGT: an efficient implementation of GPU-accelerated Thermodynamics Integration. *T. Lee, Y. Hu, B. Sherborne, Z. Guo, D.M. York. submitted.*

Thank You!

Pose exploration with MD

Multiple studies show that the low energy snapshots correlate with best pose prediction



**average energy of the 10 lowest energy snapshots for each trajectory of 22 MD simulations differed by the initial position.*

Onufriev, A.; Bashford, D.; Case, D. Proteins, 2004, 55, 383–394.

Hou, et al. J Comput Chem. 2011 Apr 15;32(5):866-77