DrugDesignData Resource (D3R) Grand Challenge 2

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D3i4AD

Diagnostic and Drug Discovery Initiative for Alzheimer's Disease

Lilly

Dr. Matthew Baumgartner

- Marie Curie Post Doctoral Fellow at Eli Lilly and Company
- Ph.D. in Computational Biology at the University of Pittsburgh under Dr. Carlos Camacho

D3R 2016 Grand Challenge Data

- Industry affinity and structural data donated to D3R organizers by Roche
  - One target: farnesoid x receptor (FXR)
  - IC50 data for 102 compounds in 4 chemical series (potency range of 0.000335 – 62.37 μM for 92 compounds, and 10 having potency > 100 μM)
  - 36 co-crystal structures and 1 *apo* (resolution 1.8 - 2.6 Å)

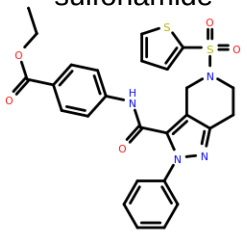
The Challenge

- Phase 1
  - Predict poses of 36 compounds with blinded co-crystal structures (can submit up to 5 poses/method)
  - Predict or rank the potencies of all 102 ligands
  - **After submission** deadline (Nov 21, 2016) all of the crystal structures were released
- Phase 2
  - Re-predict the potencies of all 102 ligands
  - **After competition** (Feb 1, 2017) all of the affinity data was released

Test set data

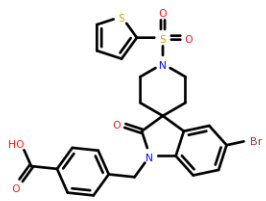
- Test set compounds:
  - 23 sulfonamides
  - 22 spiros
  - 47 benzimidazoles (PDB crystals)
  - 4 isoxazoles (PDB crystals)
  - 6 others (3 PDB crystals)
- 26 structures in the PDB in 3 sets:
  - 7 benzimidazoles (references: 3OMM, 3OKH)
  - 9 isoxazoles (reference: 3DCU)
  - 10 others (3 with similarity to the test set “others”)

sulfonamide



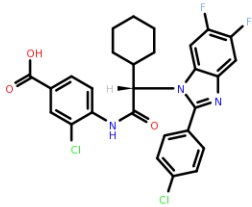
FXR_17

spiro



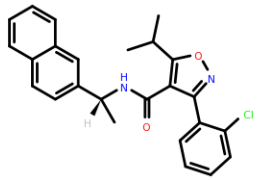
FXR_10

benzimidazole



FXR_27

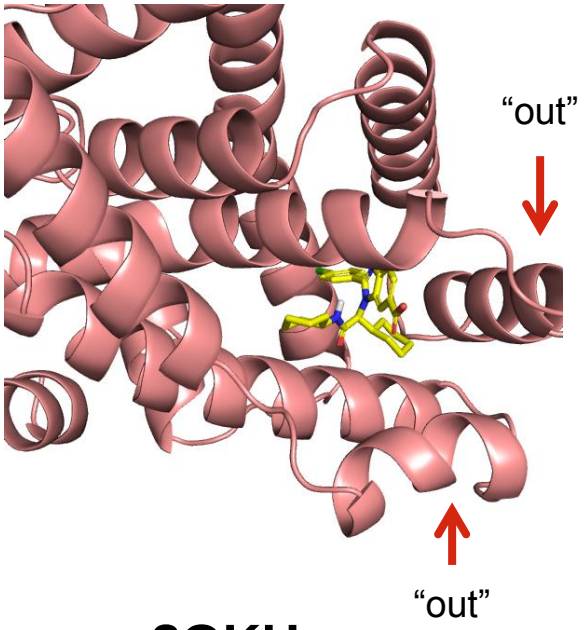
isoxazole



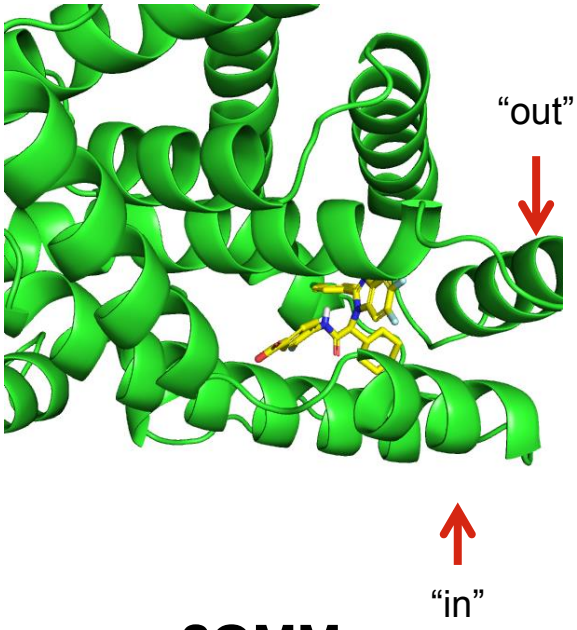
FXR_23

PDB reference structures

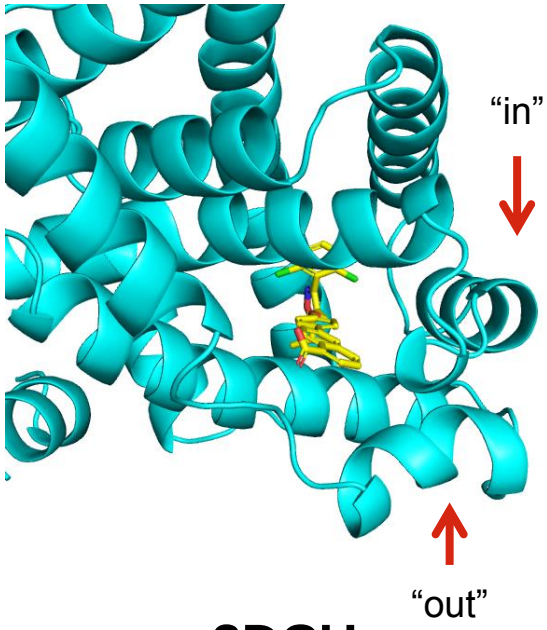
- Examined the PDB structures and identified three major conformations of the binding site



3OKH



3OMM



3DCU

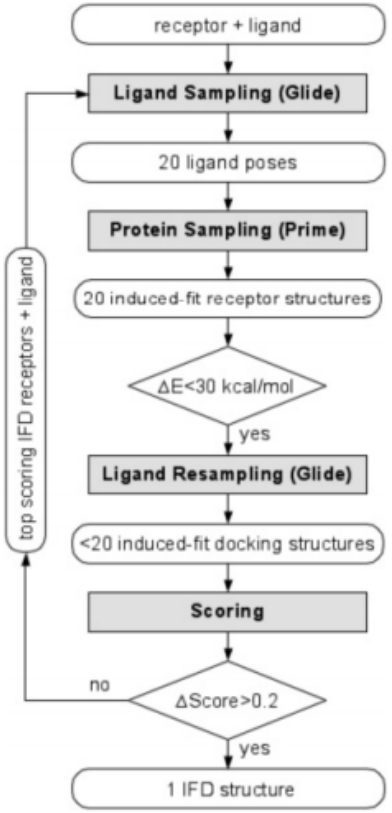
Prediction Approaches

- Pose prediction
  - **Align-Close** – Generate conformers and align (Cresset Forge) to most similar (by fingerprint) co-crystal ligand and minimize with Vina scoring function
  - **Smina docking** – rigid receptor, flexible ligand (Vina)
  - **Induced fit docking (IFD)** – flexible receptor side chains and ligand
  - **Metadynamics** - pose re-ranking of IFD poses
  - **Manual** – Manually look at all of the data and choose my top poses

Align-close	wax1j
Smina docking	x7jp3
IFD	piwlh
MetaD	qfu33
Manual	psiuj

Schrodinger's Induced Fit Docking

- Docking which allows protein side chains to move
- Iterative sampling of the ligand (with Glide) and the protein (with Prime)



Sherman, W.; Day, T.; Jacobson, M. P.; Friesner, R. A.; Farid, R., "Novel Procedure for Modeling Ligand/Receptor Induced Fit Effects," J. Med. Chem., 2006, 49, 534-553

Binding Pose Metadynamics

- Uses a metadynamics simulation to determine the force needed to displace a ligand from a starting position (IFD pose)
- The more force required to displace it, the better the pose was
- Schrodinger uses a complicated measure of the ligand RMSD and a measure of the number of contacts broken as the collective variable (CV)
- At the end, you get a score of the input pose

Structure Prediction Methods

- Docking of the test set compounds to the three reference receptors with smina
  - Took the top 5 scoring poses across the three dockings
- IFD + Metadynamics of test set compounds to 3 reference receptors
  - Top 5 scoring IFD poses were rescored using MetaD
- Submitted poses from top 5 IFD scored poses and top 5 MetaD scored poses (not necessarily the same poses)

My Results

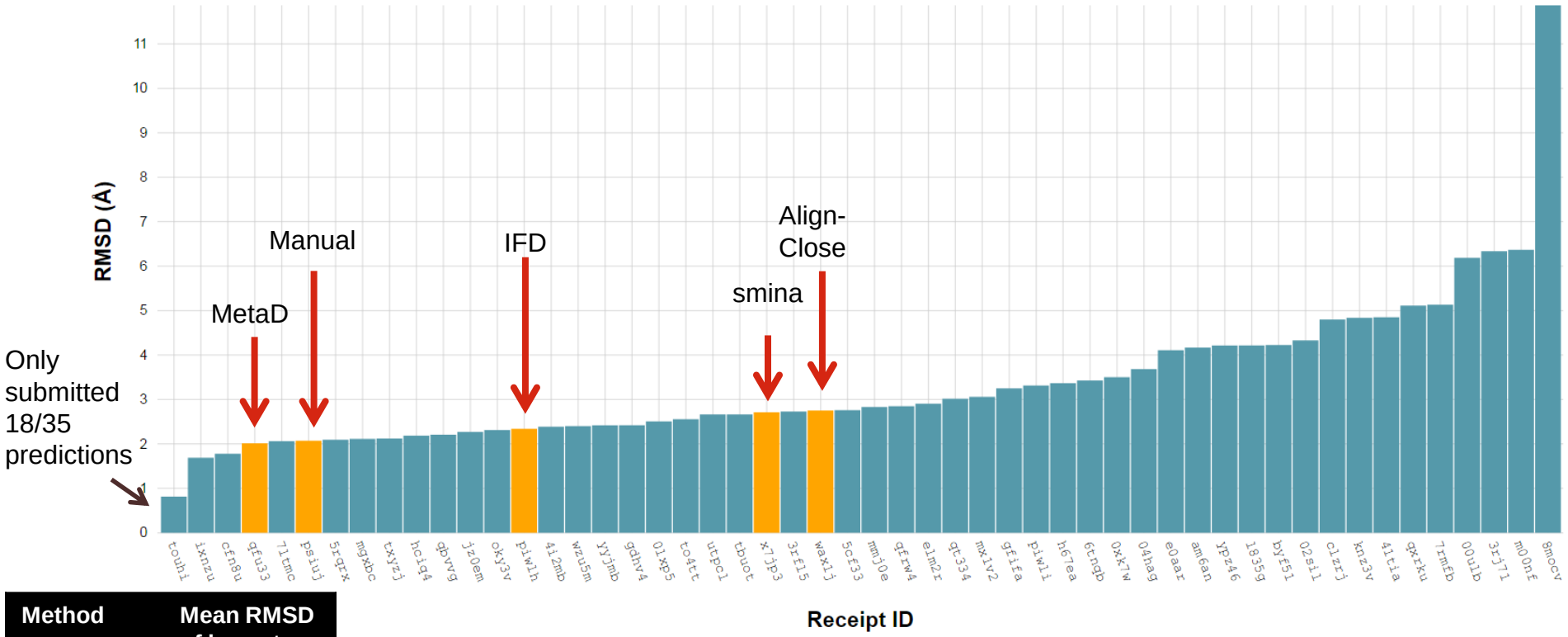
- Number of structures (out of 35) with a pose under 2A in the top N poses

	Top 5	Top 3	Top 1
Align-close	21	21	**20**
Smina	19	19	11
IFD	19	15	14
Metadynamics	**23**	19	16
Manual	**23**	**23**	18

- Metadynamics helped over IFD alone
- Smina samples just as well as IFD but is much faster
- Align-Close utilized the most structural info and did the best
- My manual picking also did pretty well which was nice

- The ligand one of the structures (FXR_33) does not match the test set smiles possibly due to oxidation during the crystallization process so it is excluded from all analysis
- Also note that some of the crystal structures have been identified as having errors (non-planar aromatic rings) so these may change slightly

Overall Results – Best Pose



Method	Mean RMSD of lowest RMSD pose
MetaD	2.01
Manual	2.07
IFD	2.34
Smina	2.71
Align-Close	2.75

Broken Down by Scaffold

- All of my methods were successful only on the most common scaffold (benzimidazole)
- They all did poorly on the other compound scaffolds

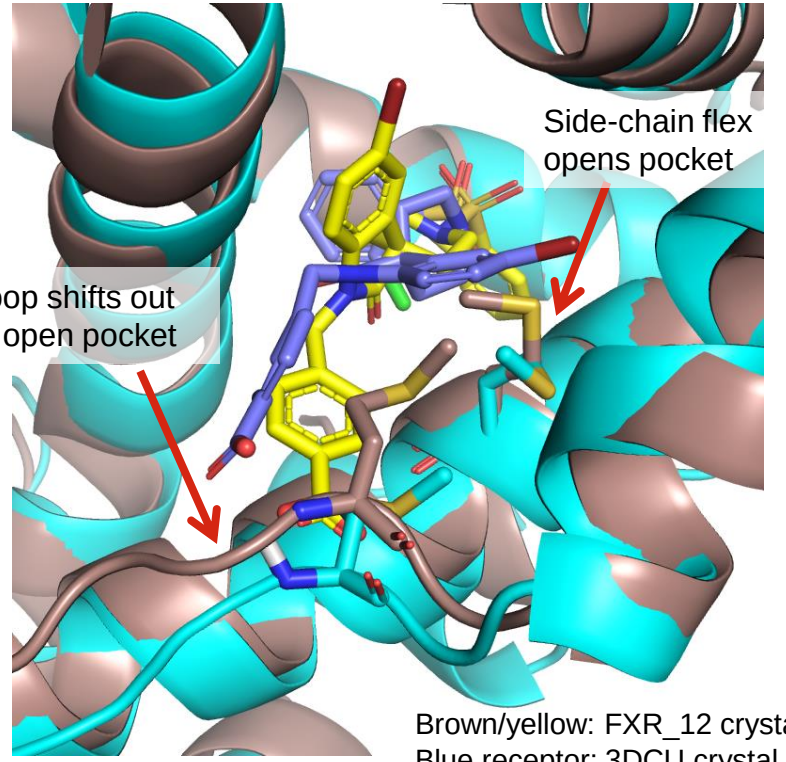
Number of compounds with pose under 2 Å RMSD in the top 5 poses

	Align Close	Smina	IFD	MetaD	Manual	Total
benzimidazole	20	18	17	20	21	22
isoxazole	0	1	0	1	1	2
spiro	**0**	**0**	**0**	**0**	**0**	3
sulfonamides	1	0	0	1	0	4
others	1	0	1	1	1	4

Best RMSD for each compound for all methods

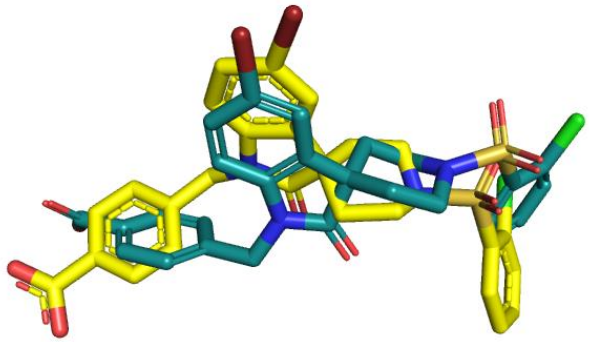
Compound		FXR_13	14	19	20	21	22	24	25	26	27	28	29	30	31	32	35	36	6	7	8	9	23	4	18	1	2	34	3	5	10	11	12	15	16	17
Scaffold	Avg.	benzimidazoles																					isoxazoles		misc						spiros			sulfonamides		
Average RMSD	3.39	4.88	1.71	1.50	2.23	1.89	2.81	1.85	2.22	2.63	1.33	1.61	1.61	2.78	2.16	2.70	1.86	2.22	1.74	3.15	2.61	2.24	6.16	4.91	8.16	5.35	5.81	4.97	4.79	2.43	4.52	5.34	4.45	5.74	4.59	3.57
touhi	0.81				0.60	0.87	2.35	1.22	0.70	0.71	0.68	0.62	0.41				0.67	0.65	0.56	1.12	0.58	0.80			0.60						0.96		0.54			
ixnzu	1.69	0.36	0.50	0.36	0.64	0.75	1.92	1.21	0.34	0.24	0.19	0.81	0.74	1.32	1.55	1.91	0.44	0.62	0.45	0.67	0.30	0.22	5.60	3.86	7.46	5.23	4.92	1.41	3.68	0.39	2.21	2.51	2.35	1.34	1.17	1.39
cfn8u	1.78	0.61	0.45	0.56	0.75	0.74	1.00	0.31	0.27	0.65	0.33	0.49	0.55	0.70	1.60	0.97	0.65	0.55	0.64	0.85	0.74	0.83	5.04	3.88	8.53	3.85	5.07	3.10	2.15	0.82	2.24	2.65	2.20	4.38	2.40	1.70
Metadynamics	**2.01**	**0.83**	**0.87**	**0.45**	**0.76**	**0.54**	**0.80**	**0.83**	**0.49**	**0.97**	**0.39**	**0.64**	**0.46**	**0.98**	**1.64**	**0.81**	**0.86**	**0.74**	**0.70**	**0.76**	**5.73**	**1.36**	**1.36**	**6.24**	**8.23**	**3.31**	**2.03**	**2.19**	**1.45**	**4.42**	**2.68**	**2.54**	**2.23**	**5.81**	**1.73**	**4.59**
7ltmc	2.06	0.27	0.48	0.57	0.44	0.65	1.94	1.14	0.38	0.28	0.44	0.55	0.61	0.64	1.59	1.95	0.71	0.95	0.61	0.87	0.38	0.34	7.71	4.05	9.53	3.64	5.00	3.01	1.08	0.45	1.37	4.11	1.92	9.45	1.61	3.39
Manual	**2.07**	**0.83**	**0.53**	**0.33**	**0.78**	**0.37**	**0.88**	**0.75**	**0.37**	**1.03**	**0.44**	**0.70**	**0.78**	**1.06**	**0.84**	**0.90**	**0.70**	**1.09**	**0.87**	**0.87**	**0.40**	**0.48**	**1.36**	**3.68**	**8.23**	**4.25**	**2.03**	**2.62**	**6.97**	**0.55**	**5.19**	**2.68**	**2.98**	**5.96**	**5.24**	**5.70**
5rqrx	2.09	0.48	0.32	0.44	0.43	0.59	2.04	0.80	1.69	0.91	0.65	0.74	0.47	1.80	1.70	1.00	0.92	0.65	0.67	0.66	0.63	0.80	7.15	5.39	8.49	3.66	5.82	3.09	2.06	0.57	1.84	4.01	2.42	5.64	1.31	3.40
mgxbc	2.11	0.64	0.53	0.69	0.59	0.58	2.12	1.23	0.47	0.63	0.96	0.59	0.55	0.39	0.66	2.02	0.45	0.88	0.46	0.61	0.64	0.61	6.97	5.66	7.93	4.52	5.72	2.11	4.25	0.85	2.12	2.67	2.27	5.77	2.62	4.16
txyzj	2.12	0.98	0.70	0.89	0.64	0.90	1.84	1.13	1.68	1.23	1.27	1.04	0.58	1.76	1.75	0.52	1.14	0.54	0.88	0.73	0.49	0.96	7.76	6.01	7.14	5.30	5.15	2.73	4.12	2.60	2.20	1.23	2.60	1.89	2.26	1.58
hciq4	2.19	1.11	0.53	0.47	0.69	0.39	1.96	1.17	0.31	0.34	0.42	0.52	0.55	0.72	1.61	2.04	0.79	0.50	0.51	1.13	0.50	0.38	7.91	3.84	8.98	6.12	7.56	3.51	2.22	0.79	3.12	3.75	3.17	5.71	1.70	1.51
qbvvg	2.21	1.62	0.49	1.04	3.91	0.34	0.77	1.19	0.42	1.17	0.89	0.73	0.76	1.74	0.78	2.15	1.45	0.99	0.85	1.38	0.73	0.80	4.84	6.66	6.22	3.82	5.41	4.04	5.13	0.84	1.94	2.38	2.23	4.30	3.74	1.47
jz0em	2.27	1.77	0.91	0.39	0.69	0.70	2.18	0.67	0.72	0.45	0.88	0.83	0.39	1.71	1.73	2.24	0.80	0.41	0.35	0.75	0.49	0.42	7.82	6.35	9.66	5.90	7.38	3.04	5.90	0.60	2.73	3.06	3.05	1.66	1.46	1.39
oky3v	2.31	0.57	0.68	0.53	0.82	0.80	2.20	1.19	0.33	0.99	0.31	0.86	0.39	0.89	0.96	2.26	1.23	0.92	0.53	0.52	0.44	0.32	7.76	6.77	8.42	5.99	7.47	3.54	6.91	0.38	2.14	2.49	2.48	5.66	1.57	1.63
IFD	**2.34**	**0.83**	**0.87**	**0.46**	**0.83**	**0.54**	**0.61**	**0.75**	**0.49**	**0.86**	**0.39**	**0.64**	**0.46**	**1.58**	**1.62**	**0.81**	**0.70**	**0.74**	**0.61**	**0.82**	**6.27**	**7.22**	**2.01**	**6.24**	**7.93**	**3.31**	**2.03**	**3.04**	**1.60**	**4.90**	**2.57**	**2.43**	**2.10**	**5.81**	**5.38**	**4.41**
4i2mb	2.39	4.46	0.49	1.04	0.89	0.34	0.77	1.19	0.42	1.17	0.89	0.73	0.76	1.74	0.78	0.69	1.64	0.99	0.85	1.38	0.73	0.80	4.82	6.66	7.58	7.07	5.13	4.09	2.04	0.84	2.25	8.21	2.58	4.30	3.74	1.47
wzu5m	2.40	7.74	0.31	0.36	0.58	0.54	0.94	0.44	0.51	0.34	0.40	0.52	0.77	1.02	0.69	0.68	0.77	0.87	0.56	1.10	0.49	0.41	3.96	6.38	8.75	4.35	6.48	2.22	1.89	0.79	8.62	4.45	2.54	5.23	5.54	2.75
yyjmb	2.42	4.60	0.61	0.78	0.73	0.76	0.69	0.74	1.73	1.32	0.50	0.57	0.80	1.84	1.15	0.98	1.10	1.10	0.70	1.10	1.21	1.04	6.49	5.49	8.31	3.60	4.85	3.69	7.03	0.48	2.33	2.68	2.54	5.08	5.31	2.68
gdhv4	2.42	4.74	0.49	1.04	0.89	0.34	0.77	1.19	0.42	1.17	0.89	0.73	0.76	1.74	0.78	0.69	1.45	0.99	0.85	1.38	0.73	0.80	4.84	6.66	7.58	4.82	1.62	4.09	6.42	0.84	5.06	5.14	2.60	8.83	1.88	1.47
0lxp5	2.51	7.29	0.87	1.30	0.60	0.95	0.92	1.18	0.98	1.23	1.25	0.77	0.79	1.82	1.60	2.08	0.40	1.37	0.42	1.20	0.92	0.54	3.39	3.82	8.46	2.97	5.39	5.64	4.70	5.84	4.96	4.32	2.78	4.25	1.25	1.47
to4tt	2.55	6.13	0.40	1.03	0.76	0.79	0.79	1.21	1.91	0.56	0.58	0.66	0.97	1.37	0.89	1.11	1.25	1.92	0.69	1.24	0.81	0.62	5.09	6.91	6.09	3.13	6.37	4.09	1.81	5.36	4.29	4.62	4.48	4.53	5.26	1.71
tbuot	2.66	4.60	0.61	0.79	0.73	0.76	0.69	0.74	1.73	1.32	0.50	0.57	0.80	1.83	1.15	2.06	1.10	1.10	0.70	1.10	3.87	0.89	6.49	3.89	7.56	3.90	7.31	3.91	4.75	0.48	4.44	2.69	8.44	4.66	4.32	2.69
utpcl	2.66	4.60	0.61	0.79	0.73	0.76	0.69	0.74	1.73	1.32	0.50	0.57	0.80	1.83	1.15	2.06	1.10	1.10	0.70	1.10	3.87	0.89	6.49	3.89	7.56	3.90	7.31	3.91	4.75	0.48	4.44	2.69	8.44	4.66	4.32	2.69
Smina	**2.71**	**5.79**	**0.69**	**0.58**	**0.84**	**0.58**	**2.12**	**0.49**	**0.69**	**1.06**	**0.92**	**1.04**	**0.89**	**1.58**	**1.58**	**0.90**	**0.51**	**1.26**	**0.72**	**0.93**	**0.70**	**0.70**	**3.99**	**1.75**	**8.87**	**3.02**	**7.66**	**2.08**	**5.70**	**4.47**	**4.60**	**2.68**	**5.81**	**6.65**	**5.24**	**7.78**
3rfl5	2.73	7.38	0.49	1.04	1.14	0.34	2.06	1.19	0.42	1.17	0.89	0.73	0.76	1.74	0.78	0.69	1.45	0.99	0.85	1.38	0.73	0.80	4.84	6.03	7.58	7.14	6.08	4.09	8.05	0.84	2.01	8.91	2.58	4.93	3.74	1.65
align-close	**2.75**	**1.40**	**0.50**	**0.33**	**0.71**	**0.37**	**0.83**	**0.26**	**0.37**	**0.51**	**0.31**	**0.85**	**0.77**	**1.06**	**0.84**	**1.01**	**1.27**	**1.21**	**0.96**	**1.13**	**0.40**	**0.48**	**7.50**	**6.41**	**8.50**	**5.17**	**7.55**	**3.69**	**6.79**	**0.55**	**7.60**	**3.33**	**9.14**	**6.27**	**6.29**	**1.91**
5cf33	2.76	0.36	0.69	0.38	6.95	0.50	0.53	1.20	0.46	1.13	0.43	0.92	0.78	1.53	1.71	0.85	1.14	1.09	1.01	7.48	0.63	0.61	7.35	1.45	8.68	5.26	5.11	2.44	2.42	0.78	4.25	11.75	2.52	9.35	2.43	2.38
mmj0e	2.83	7.38	0.49	1.04	0.89	0.34	2.06	1.19	0.42	1.17	0.89	0.73	0.76	1.74	0.78	2.15	1.45	0.99	0.85	1.38	0.73	0.80	4.39	5.14	7.58	4.31	5.41	4.04	5.09	0.84	8.64	9.28	8.74	4.30	1.59	1.47
qfrw4	2.85	7.84	0.43	0.52	0.53	0.44	1.96	1.23	1.59	0.33	0.57	0.86	0.86	1.34	1.68	2.00	0.87	1.23	0.33	1.04	0.57	0.32	4.23	6.64	15.41	4.82	3.61	4.37	6.85	0.35	2.75	3.29	2.98	7.32	5.57	4.90
elm2r	2.90	6.04	0.54	0.38	4.00	0.50	1.87	0.74	0.53	0.45	0.92	0.54	0.80	1.23	1.70	2.02	0.73	1.07	0.44	1.23	0.60	0.46	7.26	3.52	6.00	5.24	5.14	4.65	5.26	0.69	4.56	6.28	4.85	4.06	7.77	9.57
qt334	3.02	7.18	0.40	1.03	0.76	**4.69**	**2.08**	1.21	1.91	0.56	0.58	**1.07**	**5.22**	1.37	0.89	1.11	1.25	1.92	0.69	**5.81**	**4.58**	0.62	7.33	4.78	6.09	3.91	1.30	8.30	5.61	2.03	1.91	4.62	4.48	4.53	4.03	1.71
mx1v2	3.06	7.18	0.40	1.03	0.76	**0.79**	**0.79**	1.21	1.91	0.56	0.58	**0.66**	**5.20**	1.37	0.89	1.11	1.25	1.92	0.69	**4.88**	**5.08**	0.62	7.01	3.81	5.90	5.35	6.36	4.06	7.08	6.13	1.91	5.79	4.48	4.53	4.03	1.71
gfifa	3.25	0.51	0.40	1.02	4.56	0.49	0.81	0.59	1.74	0.79	0.43	0.83	1.11	1.73	1.61	2.09	0.72	1.13	0.95	0.79	1.09	0.95	17.98	7.00	6.36	4.77	7.72	4.13	6.12	1.08	8.77	2.63	2.59	8.72	8.16	3.42
piwli	3.31	7.88	0.72	0.77	0.85	1.01	1.45	1.24	0.36	7.49	1.06	0.98	0.54	1.63	1.64	2.01		0.70	1.19	0.82	6.46	7.40	7.87	6.69	8.78	4.29	5.16	3.20	1.88	0.69	4.64	3.19	5.60	6.81	6.11	1.49
h67ea	3.37	7.44	0.52	0.92	1.06	0.80	6.40	0.88	0.59	5.27	0.90	0.76	0.56	0.94	1.07	2.29	0.87	3.02	0.58	6.41	0.45	0.45	7.88	5.17	8.51	6.71	7.79	13.25	3.85	1.28	4.21	4.32	4.06	4.26	2.25	2.09
6tnqb	3.43	7.46	0.52	0.92	1.06	0.80	6.40	1.23	0.59	5.28	0.91	0.76	0.56	1.76	1.82	2.29	0.87	3.02	0.58	6.41	0.45	0.45	7.95	5.17	8.54	6.75	7.81	13.25	3.85	1.28	4.21	4.33	4.06	4.26	2.25	2.09
0xk7w	3.50	6.13	0.40	1.03	0.76	0.79	0.79	1.21	4.48	0.56	0.58	5.05	4.96	1.37	0.89	1.11	1.25	1.92	0.69	6.59	6.09	0.62	4.83	5.29	6.09	5.19	5.72	4.06	5.61	2.03	9.98	7.76	6.68	5.59	4.71	1.71
04hag	3.68	8.00	0.58	0.50	0.63	0.58	6.68	0.46	1.65	0.72	0.50	0.86	0.81	1.65	1.62	0.78	1.06	1.15	0.72	0.74	6.42	7.40	5.02	3.73	6.47	5.20	5.48	5.11	6.03		10.07	4.49	9.43	7.42	7.55	5.71
e0aar	4.11	4.96	4.02	4.74	4.02	2.99	4.16	3.09	3.03	4.52	6.17	4.38	4.43	4.36	4.43	4.19	4.19	3.88	3.08	6.40	2.94	4.28	6.89	4.58	5.38	6.94	5.92	4.12	6.81	1.64	1.50	2.26	1.09	6.44	1.04	0.90
am6an	4.17	1.25	6.47	1.32	1.19	1.24	1.68	1.62	1.23	1.42	1.33	1.10	1.44	2.01	1.82	1.39	2.47	1.78	6.66	1.16	6.51	6.87	4.50	7.04	9.31	7.72	7.42	9.59	6.43	7.34	3.28	9.42	3.37	6.28	5.95	6.24
ypz46	4.21	7.33	0.69	1.02	1.30	6.28	1.86	0.56	4.88	7.32	0.98	0.70	0.74	1.70	1.03	4.23	0.94	6.95	1.40	6.56	1.22	1.19	5.10	1.70	16.93	6.26	6.39	5.70	3.44	2.72	4.00	7.79	7.37	3.22	6.64	11.34
l835g	4.22	7.71	0.68	0.90	6.31	6.25	**0.91**	6.39	1.73	7.66	1.33	0.57	0.92	6.45	1.71	4.29	0.77	7.82	0.57	0.72	5.19	0.37	7.53	3.77	8.59	4.99	7.79	5.52	4.57	6.42	3.81	3.73	4.73	7.04	7.84	1.92
byf51	4.22	7.71	0.68	0.90	6.31	6.25	**1.22**	6.39	1.73	7.66	1.33	0.57	0.92	6.45	1.71	4.29	0.77	7.82	0.57	0.72	5.19	0.37	7.53	3.77	8.59	4.99	7.79	5.52	4.57	6.42	3.81	3.73	4.73	7.04	7.84	1.92
02sil	4.33	10.58	0.68	0.91	1.11	0.57	7.02	1.10	1.84	4.62	0.85	1.12	1.08	2.02	1.80	2.16	1.56	1.68	1.35	4.91	1.04	4.64	6.47	6.81	6.76	4.33	7.58	6.47	6.19	0.57	8.77	9.87	9.63	6.77	7.59	11.06
clzrj	4.80	7.33	0.78	1.02	5.13	0.78	6.20	6.00	5.15	7.60	0.98	4.11	1.67	5.81	1.03	4.44	0.94	6.82	0.94	4.80	5.62	6.88	4.44	3.40	7.79	7.41	7.39	7.62	3.09	2.72	4.65	8.86	8.86	2.69	4.23	10.76
knz3v	4.84	8.09	3.79	3.07	5.43	3.65	6.84	3.55	7.73	7.71	2.73	2.96	3.74	3.18	3.77	3.76	3.21	5.55	4.63	6.75	3.38	4.55	6.90	3.73	6.21	6.76	3.34	4.49	6.61	1.55	1.34	10.10	1.64	9.30	7.45	1.80
41tia	4.85	4.90	2.87	4.73	3.93	4.71	5.20	5.52	3.03	7.87	6.15	4.18	4.43	5.93	3.84	5.68			4.52	7.26	3.18	4.39	6.70	4.58	7.27	6.65	5.87	4.02	7.16	1.57	1.42	10.21	1.31	9.22	0.97	0.73
qxrku	5.11	8.37	6.61	6.28	6.34	5.78	7.06	1.54	5.86	6.01	1.27	4.87	1.33	3.84	7.22	6.84	4.88	1.04	6.87	6.68	6.31	7.85	4.71	3.37	5.72	6.28	5.52	1.94	7.57	5.04	5.17	2.72	2.31	6.15	4.61	4.95
7rmfb	5.13	7.64	5.35	4.77	4.15	6.16	0.86	6.56	1.88	7.70	1.24	5.89	5.78	1.81	1.81	4.27	1.18	7.06	6.25	0.73	6.28	7.33	6.41	3.84	9.19	5.28	6.85	4.09	4.55	0.86	8.61	10.39	8.96	6.82	7.05	2.02
00ulb	6.19	7.60	5.18	5.65	7.31	7.30	6.21	7.35	7.19	7.55	5.63	6.22	6.09	6.53	5.58	6.20	6.34	7.83	7.05	5.96	5.90		8.00	1.55	3.06	4.79	5.70	11.64	5.58	7.87	7.70		5.15	9.89	1.26	1.29
3rj71	6.33	5.68	5.35	4.91	4.60	7.53	5.50	5.90	5.94	5.65	8.39	8.30	6.63	8.05	5.81	7.58	7.48	9.40	6.56	5.09	4.80	5.60	5.21	6.74	8.66	4.18	7.00	4.61	3.46	7.94	8.97	9.45	4.62	4.57	4.26	7.31
m00nf	6.37	9.32	4.28	5.63	7.71	6.23	5.74	3.90	7.26	6.02	5.05	5.25	5.21	13.18	3.23	5.70	2.83		3.52	16.39	7.45	8.33	7.51	4.80	8.89	4.87	6.14	4.92	5.50	5.83	2.53	3.38	2.83	5.73	7.56	13.75
8mocv	11.87	7.24	19.61	4.82	7.10	5.25	20.08	1.29	21.05	1.34	1.39	1.88	0.79	19.95	19.44	20.23	20.46	1.22	11.36	21.34	4.74	7.38	5.84	6.04	23.37	21.62	7.44	23.61	7.53	6.60	19.54	21.06	19.79	7.56	24.20	3.22
# methods <2		17	41	42	36	39	30	42	41	36	**46**	42	42	38	43	22	42	39	42	35	30	37	**2**	4	**1**	**0**	**2**	**2**	6	31	9	**1**	5	3	13	24

No good poses for any of the spiros



Brown/yellow: FXR_12 crystal
Blue receptor: 3DCU crystal
Blue ligand: 3DCU MetaD pose 1

- Significant differences in the crystals used to predict the pose and the actual pose limited predictions
- The FXR_12 structure is fairly dissimilar to the other structures (avg pocket RMSD 3.6 Å ± 1.5)



Yellow: FXR_12 crystal
Green: Lowest RMSD pose
from all methods (IFD, pose 4)

Is using an ensemble score better?

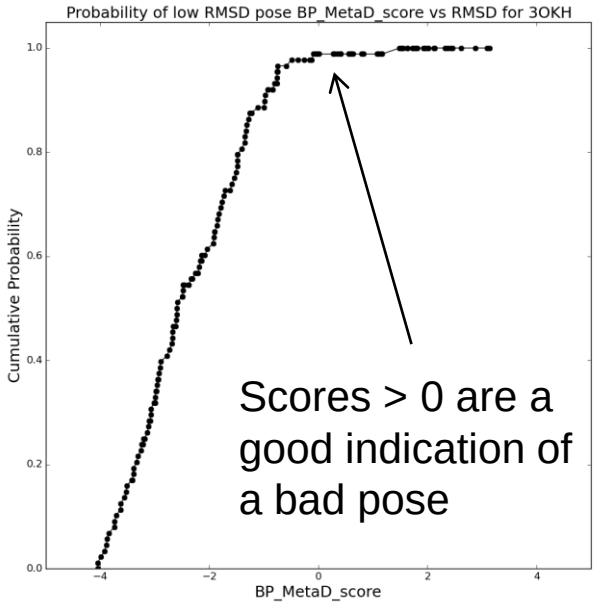
- For the metadynamics, I took the top 5 scoring poses from the IFD runs to the three structures
- Was this a good idea?
- Not really, 3DCU performed terribly
- Just using 3OKH would have done better than the ensemble method (23/35)

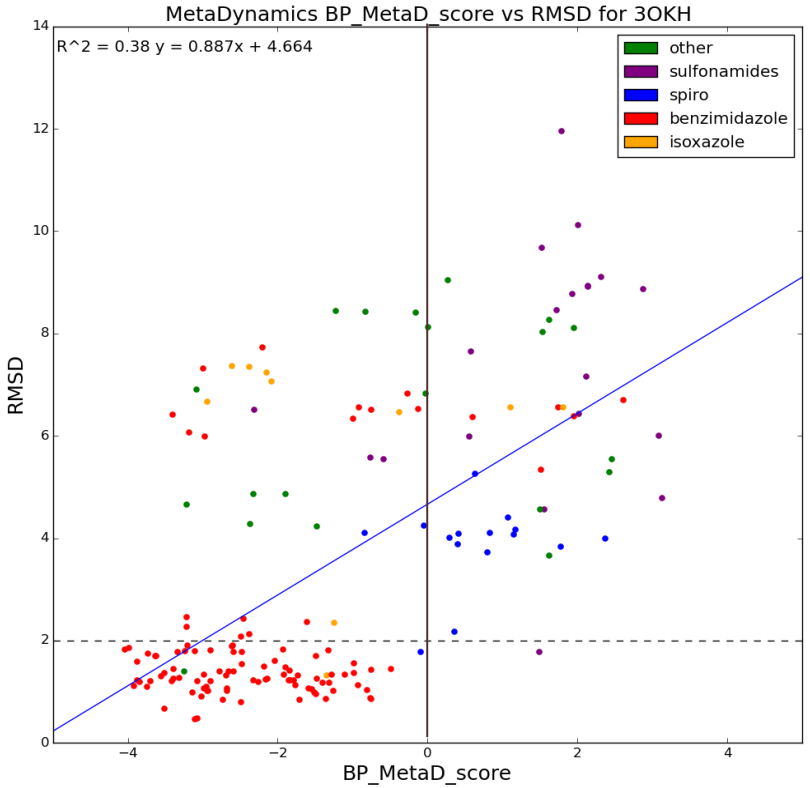
Minimum RMSD of the top 5 poses from Metadynamics

Compound ID	testset_scaffold	3OKH	3OMM	3DCU
FXR_13	benzimidazole	1.21	1.39	6.16
FXR_14	benzimidazole	1.79	1.74	5.86
FXR_19	benzimidazole	0.46	1.23	6.93
FXR_2	benzimidazole	6.55	6.09	2.16
FXR_20	benzimidazole	0.91	1.54	5.12
FXR_21	benzimidazole	1.2	1.64	6.44
FXR_22	benzimidazole	1.78	1.51	7.45
FXR_24	benzimidazole	1.11	1.64	6.37
FXR_25	benzimidazole	1.1	1.46	7.76
FXR_26	benzimidazole	1.19	1.64	3.96
FXR_27	benzimidazole	1.04	1.62	6.74
FXR_28	benzimidazole	0.86	1.55	6.86
FXR_29	benzimidazole	0.86	1.65	2.73
FXR_30	benzimidazole	1.23	2.35	3.94
FXR_31	benzimidazole	1.05	2.18	4.45
FXR_32	benzimidazole	1.07	1.7	7.37
FXR_35	benzimidazole	0.96	1.68	1.75
FXR_36	benzimidazole	0.84	1.32	5.21
FXR_6	benzimidazole	1.19	1.76	4.18
FXR_7	benzimidazole	0.84	1.48	5.31
FXR_8	benzimidazole	6.33	6.59	6.1
FXR_9	benzimidazole	1.07	7.3	5.79
FXR_23	isoxazole	1.32	2.18	4.65
FXR_4	isoxazole	6.46	5.61	5.1
FXR_18	other	8.13	8.58	4.9
FXR_3	other	1.39	1.98	4.76
FXR_34	other	3.66	5.62	2.25
FXR_5	other	4.23	5.06	7.75
FXR_10	spiro	1.77	2.27	1.75
FXR_11	spiro	3.84	3.87	2.41
FXR_12	spiro	3.72	2.01	2.11
FXR_1	sulfonamides	5.98	3.53	5.41
FXR_15	sulfonamides	8.77	5.87	5.11
FXR_16	sulfonamides	1.78	5.23	1.92
FXR_17	sulfonamides	4.56	4.46	
Total under 2 Å		**24**	**18**	**3**

Examining the BPMetaD Score

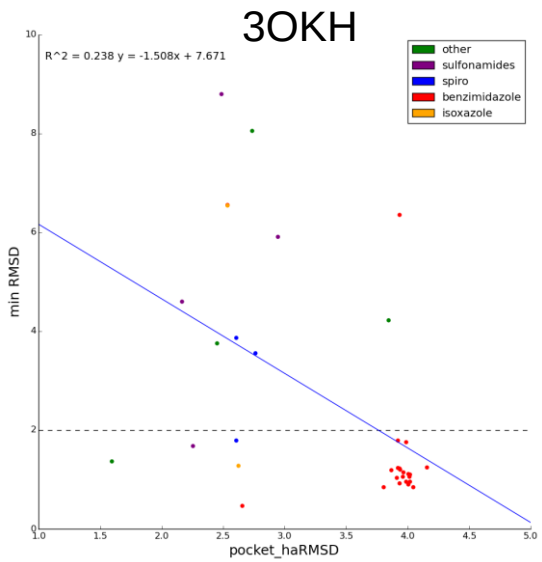
- Seems to do pretty well at determining if a pose is bad
  - 96%+ True negative rate
  - 69.6% True positive rate

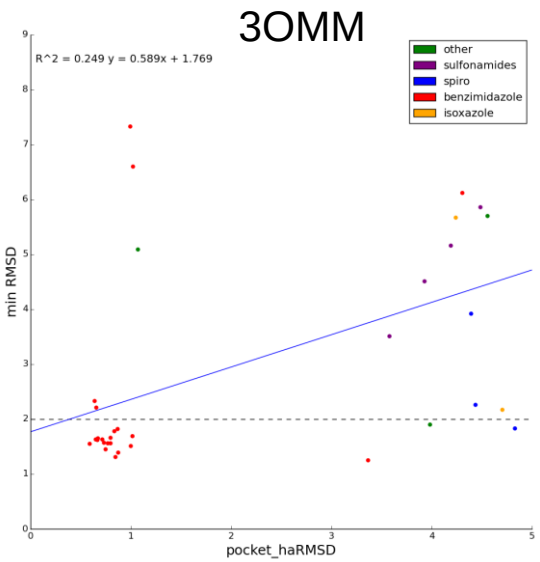


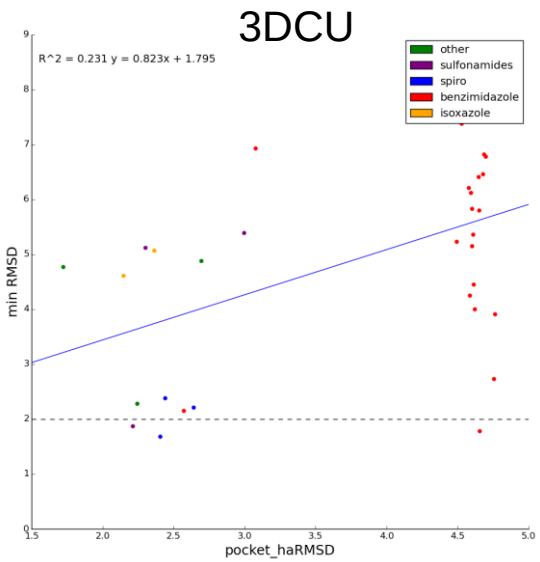


Worse structures generally give worse predictions

- Calculated the heavy atom RMSD of pocket residues between the three reference structure and the actual crystals
- Generally more changes lead to worse predictions
- Except for 3OKH where the benzimidazoles are tolerant of very different structures

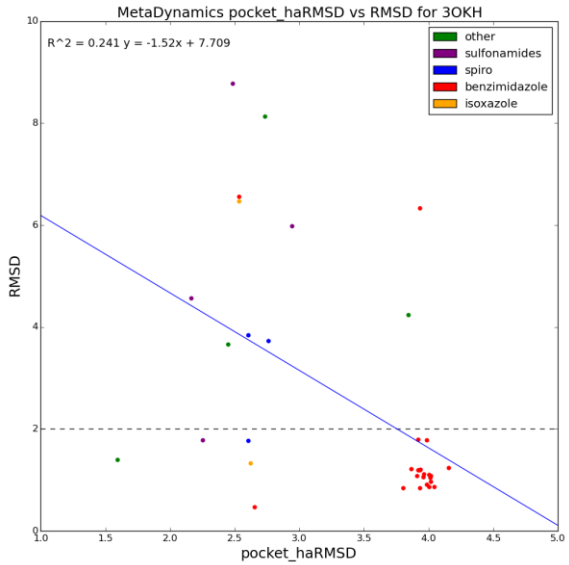


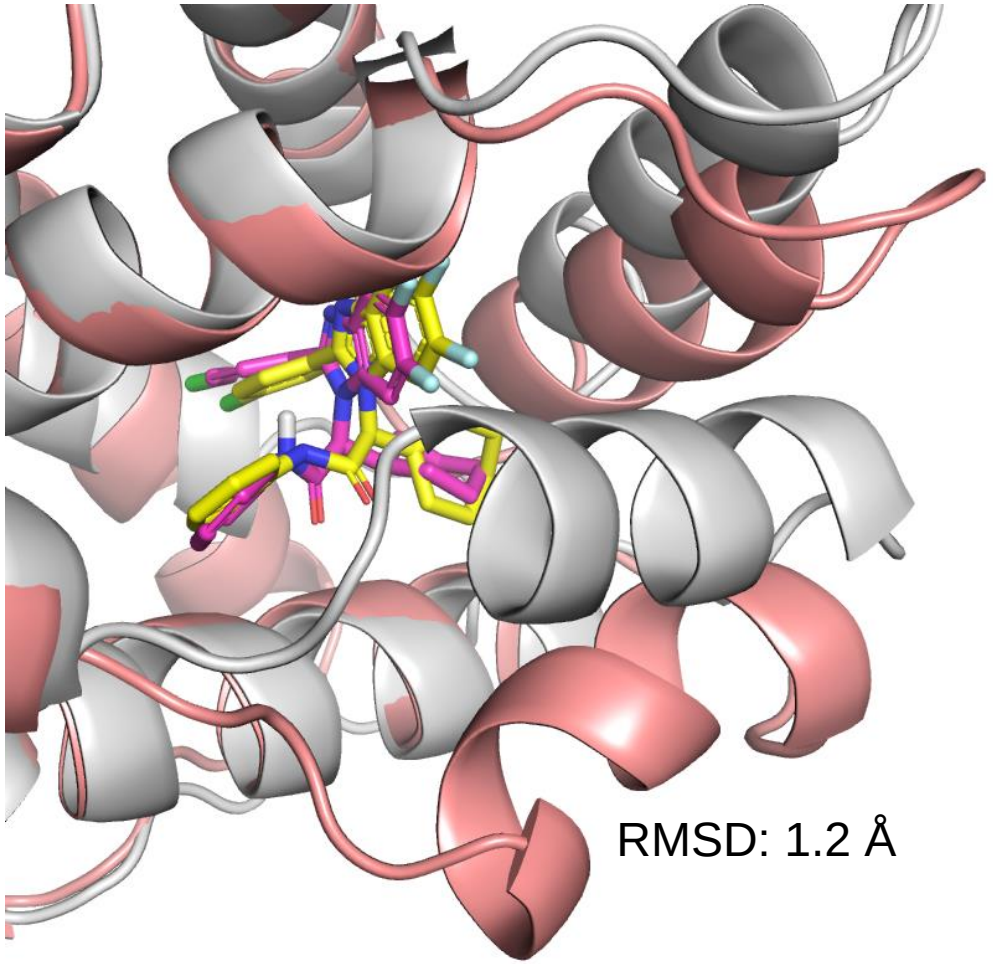




Large differences in the pocket tolerated for the benzimidazoles

- Most of the benzimidazoles docked well to 3OKH using IFD + MetaD despite large differences in pocket residues
- The ligands site far enough back in the pocket further from the major difference

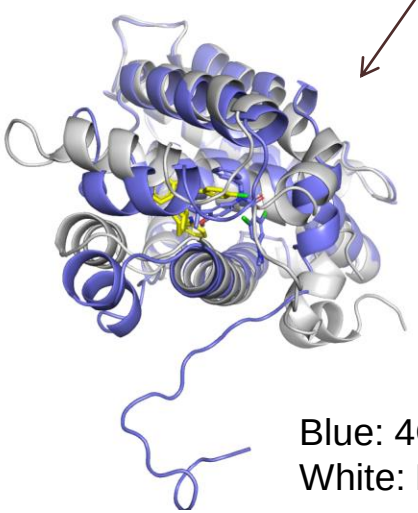




White/yellow: FXR_21 crystal
Peach: 3OKH crystal
Purple: Best predicted pose from MetaD

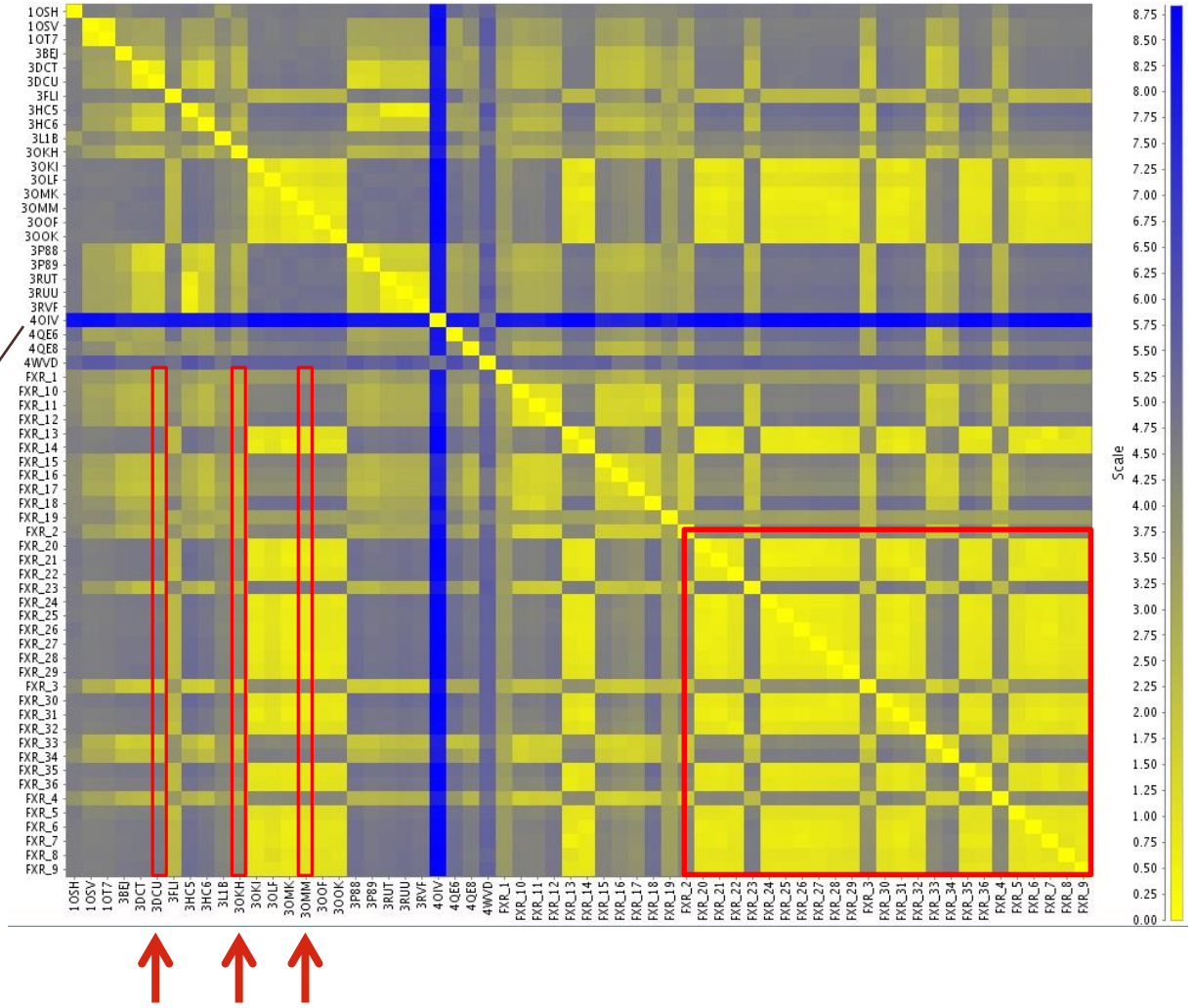
Diversity of Binding Sites

- A large number of the FXR compounds are self similar
- Despite inferior performance, 3OMM is more similar to the FXR structures than 3OKH



Blue: 4OIV
White: FXR_21

Pocket Residues Heavy atom RMSD



Reference structures

Visual inspection of the models provides accurate prediction of model quality

- For my final Manual method, I visually inspected the poses generated by all of the other models and manually chose poses
- I noted my assessment of the quality of the pose during the selection process
- My evaluation of the 3OKH Metadynamics poses compares favorably to the actual RMSDs

Compound ID	Manual Evaluation	Min RMSD
FXR_19	very good	0.47
FXR_29	good	0.84
FXR_36	good	0.84
FXR_28	very good	0.9
FXR_7	very good	0.92
FXR_20	very good	0.96
FXR_35	very good	0.96
FXR_32	good	1.03
FXR_27	very good	1.05
FXR_31	very good	1.05
FXR_9	very good	1.1
FXR_25	very good	1.11
FXR_24	very good	1.14
FXR_13	good	1.19
FXR_21	very good	1.2
FXR_26	very good	1.22
FXR_6	very good	1.23
FXR_30	very good	1.24
FXR_23	bad	1.28
FXR_3	ok	1.37
FXR_16	bad	1.68
FXR_22	good	1.76
FXR_10	bad	1.79
FXR_14	very good	1.79
FXR_12	bad	3.55
FXR_34	ok	3.76
FXR_11	bad	3.87
FXR_5	bad	4.22
FXR_17	bad	4.6
FXR_1	bad	5.91
FXR_8	bad	6.35
FXR_4	ok	6.54
FXR_2	bad	6.55
FXR_18	ok	8.05
FXR_15	bad	8.8

Pose Prediction

- This was actually a quite tough challenge which is a departure from previous years
  - In the PL-2016-1 mini challenge, my average RMSD was 0.7 Å (N=5)
  - In the 2015 challenge our average RMSD was 0.32 Å (HSP90, N=6) and 1.32 Å (MAP4K4, N=30)
  - In the 2014 challenge my average RMSD was 1.2 Å (N=14)

Affinity Prediction

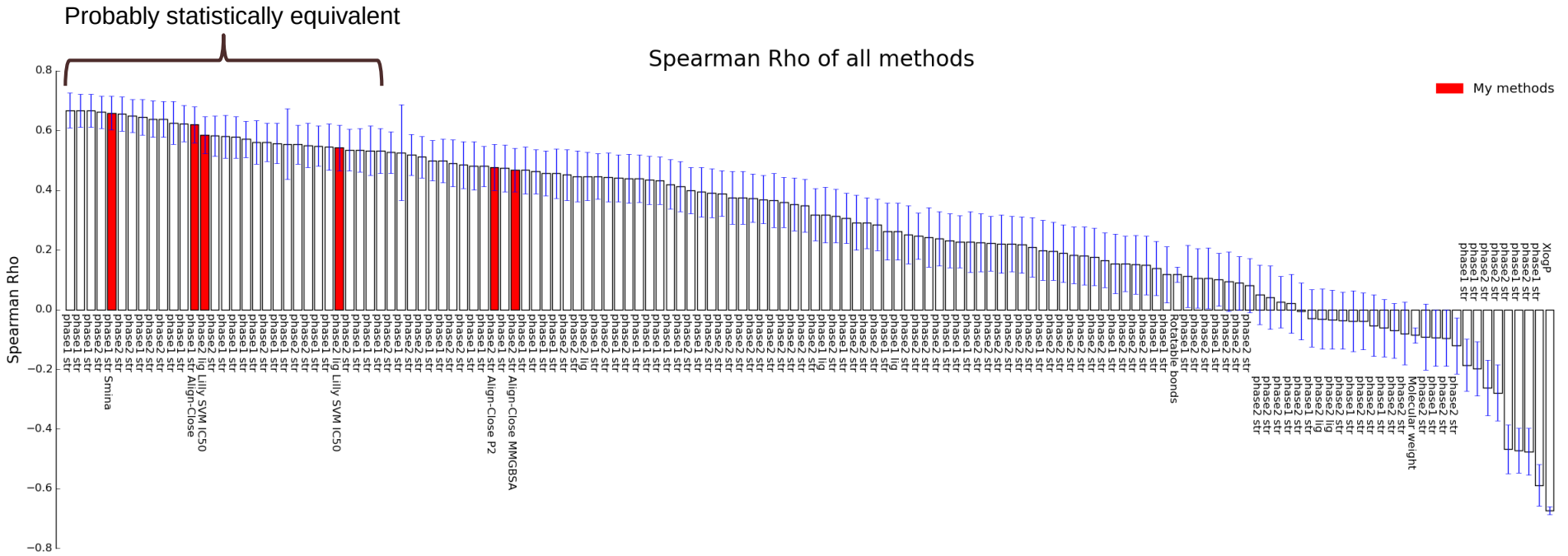
- Challenged to rank 102 compounds (including the 35 crystallized compounds) in 4 chemical series
- Able to submit predictions as part of Phase 1 and re-submit predictions for Phase 2 after receiving the crystal structures from Phase 1

My Affinity Prediction Methods

- Phase 1:
  - **Smina ensemble docking –** Dock to the three reference structures and take the top scoring pose
  - **Align-Close** – rank the compounds by the top scoring minimized pose (Vina)
- Phase 2:
  - **Align-Close 2 –** Same as for Phase 1 but includes 35 structures from Phase 1
  - **Align-Close MMGBSA** – Minimize poses with MMGBSA
  - **Lilly SVM QSAR –** 2D QSAR methods on trained using **IC50** or **EC50** data of FXR binders from ChEMBL

Smina ensemble	gzd7a
Align-Close P1	aaveo
Align-Close P2	6mjkt
Align-Close MMGBSA	vovuk
Lilly SVM IC50	hj31e
Lilly SVM EC50	naex2

All Affinity Prediction Results



- The Autodock Vina scoring function in Smina performed quite well
- Strangely, the Align-Close method did worse in Phase 2 when it had access to the additional structures from Phase 1
- The QSAR models were the best of the 7 ligand based methods and compared favorable to the structure based methods

Acknowledgements

- We thank the European Union's Seventh Framework Programme for Research, Technological Development, and Demonstration for funding the Diagnostic and Drug Discovery Initiative for Alzheimer's Disease (612347, 2014-2018)
- Schrödinger for providing temporary Desmond and Prime licenses for this competition and Davide Branduardi for critical advice on best usage of the Metadynamics simulations
- Ian Watson for assistance with the QSAR scripts