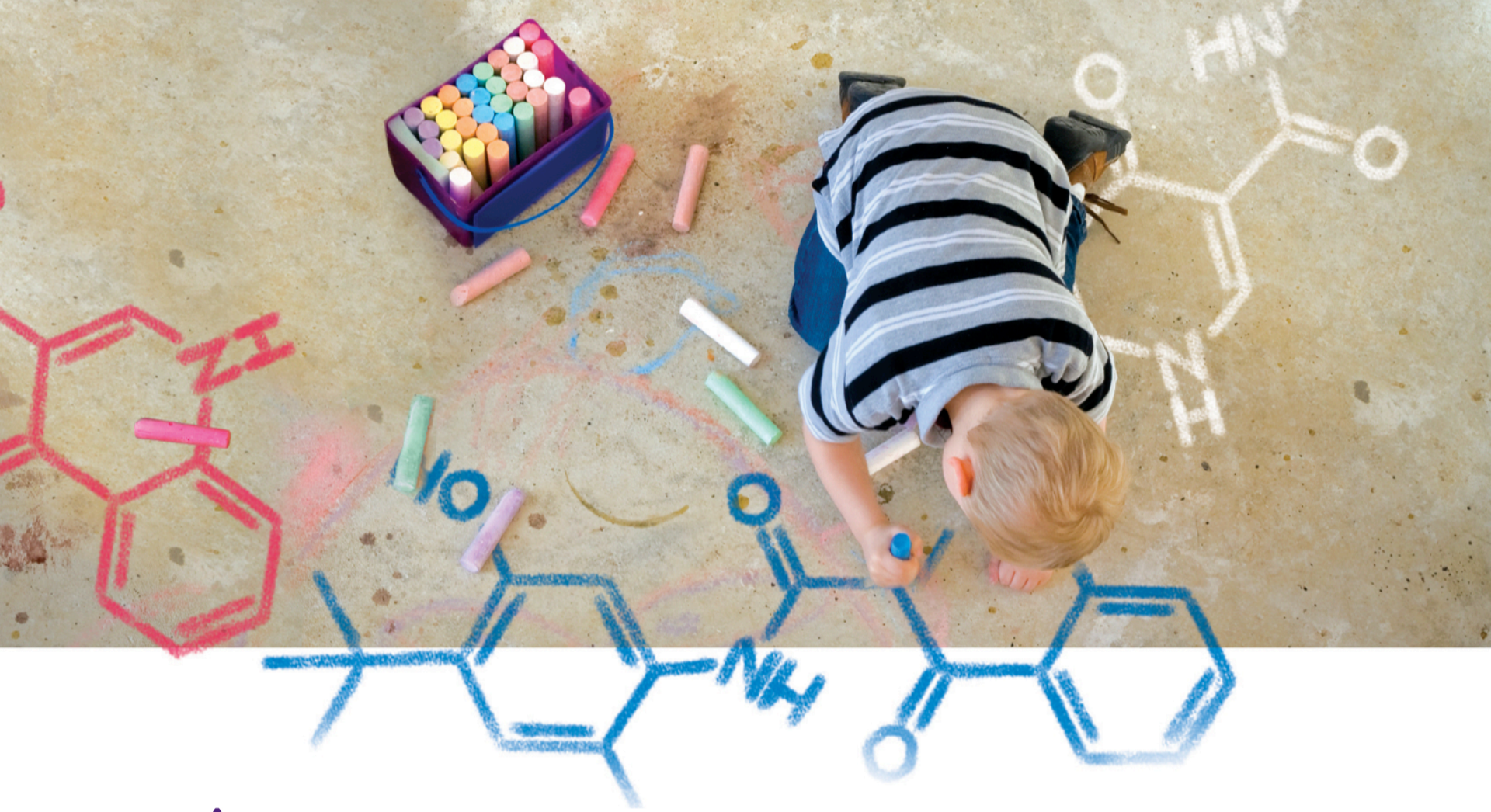


VERTEX™

THE SCIENCE *of* POSSIBILITY

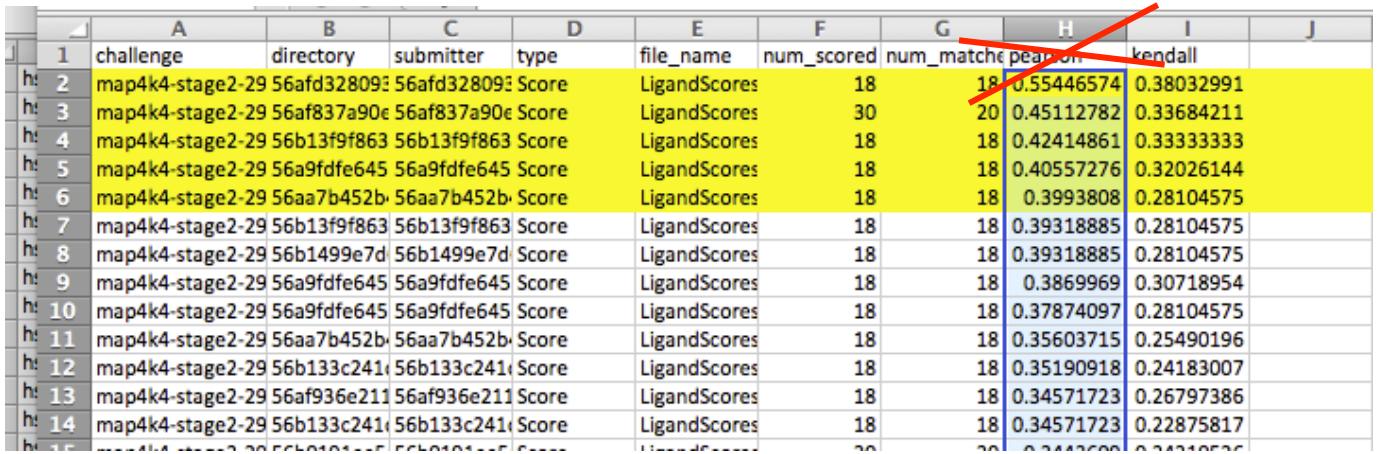
Evaluation Overview of Grand Challenges

Pat Walters

Safe Harbor Statement

- I've spent a lot of time working with the D3R submissions
- I'll let you know I've learned so far
- I still have a lot to do with/learn from this data

Spearman



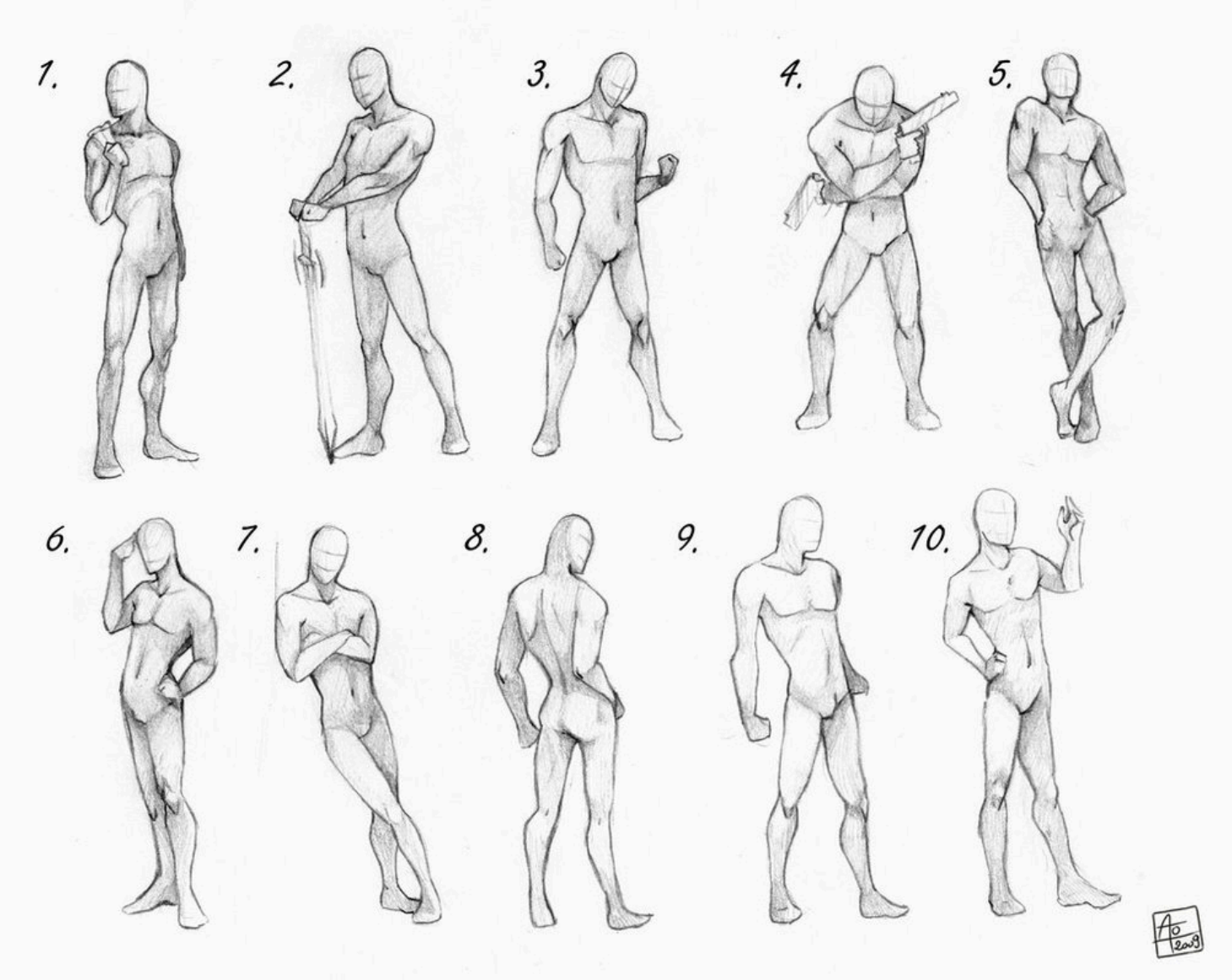
	A	B	C	D	E	F	G	H	I	J
1	challenge	directory	submitter	type	file_name	num_scored	num_matche	pearson	kendall	
2	map4k4-stage2-29	56afd328093	56afd328093	Score	LigandScores	18	18	0.55446574	0.38032991	
3	map4k4-stage2-29	56af837a90e	56af837a90e	Score	LigandScores	30	20	0.45112782	0.33684211	
4	map4k4-stage2-29	56b13f9f863	56b13f9f863	Score	LigandScores	18	18	0.42414861	0.33333333	
5	map4k4-stage2-29	56a9fdfe645	56a9fdfe645	Score	LigandScores	18	18	0.40557276	0.32026144	
6	map4k4-stage2-29	56aa7b452b	56aa7b452b	Score	LigandScores	18	18	0.3993808	0.28104575	
7	map4k4-stage2-29	56b13f9f863	56b13f9f863	Score	LigandScores	18	18	0.39318885	0.28104575	
8	map4k4-stage2-29	56b1499e7d	56b1499e7d	Score	LigandScores	18	18	0.39318885	0.28104575	
9	map4k4-stage2-29	56a9fdfe645	56a9fdfe645	Score	LigandScores	18	18	0.3869969	0.30718954	
10	map4k4-stage2-29	56a9fdfe645	56a9fdfe645	Score	LigandScores	18	18	0.37874097	0.28104575	
11	map4k4-stage2-29	56aa7b452b	56aa7b452b	Score	LigandScores	18	18	0.35603715	0.25490196	
12	map4k4-stage2-29	56b133c241	56b133c241	Score	LigandScores	18	18	0.35190918	0.24183007	
13	map4k4-stage2-29	56af936e211	56af936e211	Score	LigandScores	18	18	0.34571723	0.26797386	
14	map4k4-stage2-29	56b133c241	56b133c241	Score	LigandScores	18	18	0.34571723	0.22875817	

VERTEX

Outline

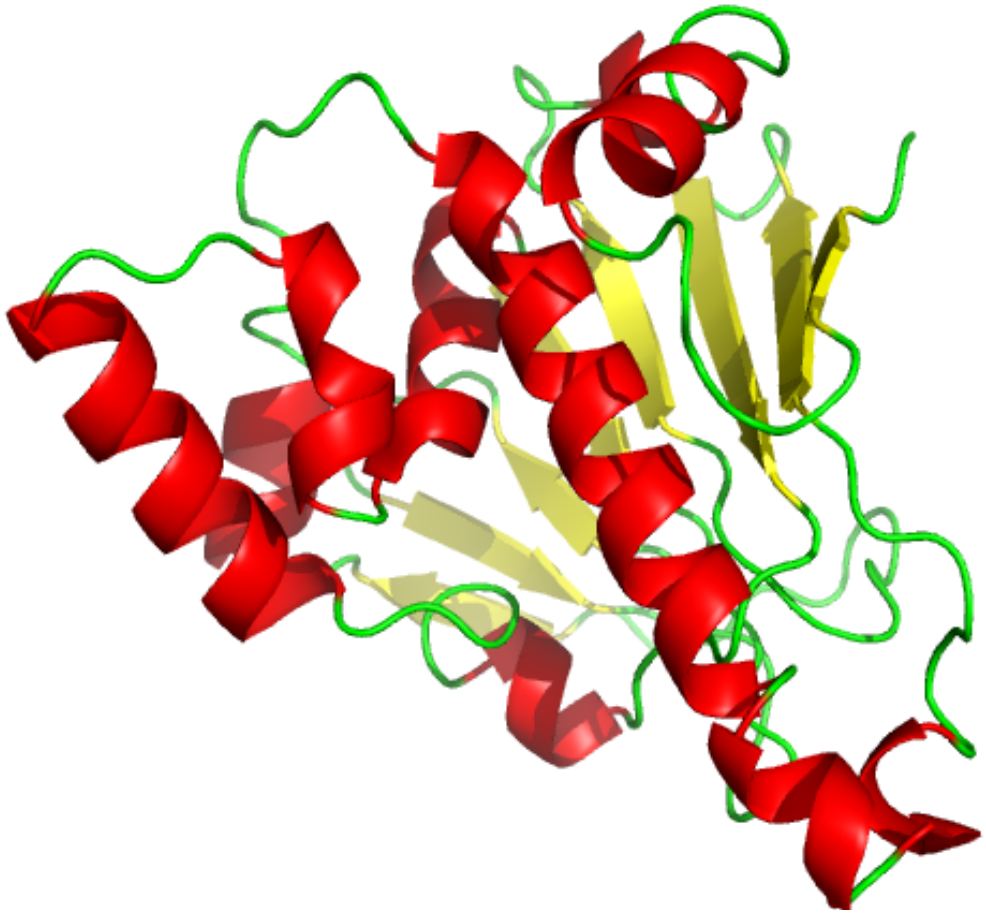
- Pose Prediction
  - HSP90
  - MAP4K4
- Ranking
  - HSP90
  - MAP4K4
- Free Energy
  - HSP90
  - MAP4K
- Closing thoughts

Pose Prediction

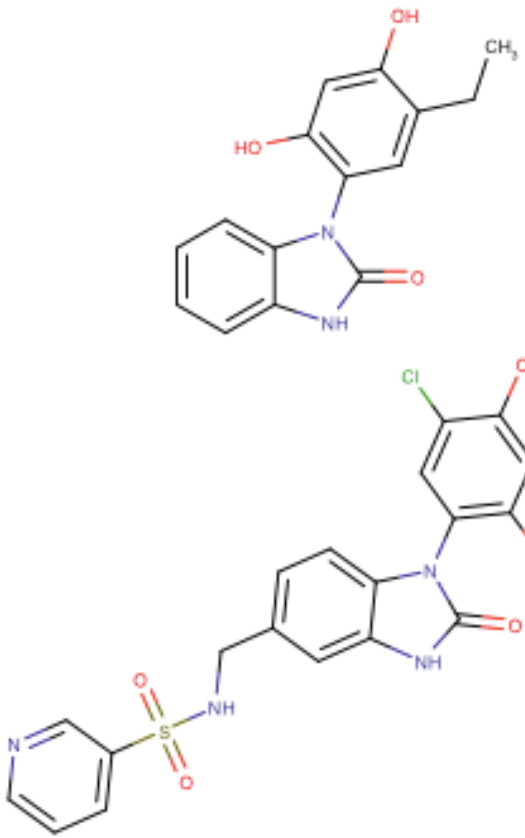


HSP90

- 6 Ligands to dock

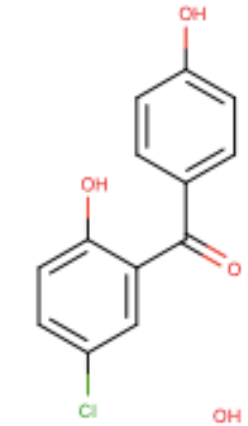


3 Pairs of HSP90 Ligands

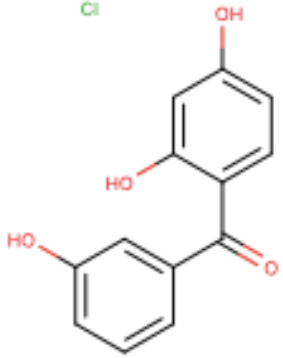


40

44



164



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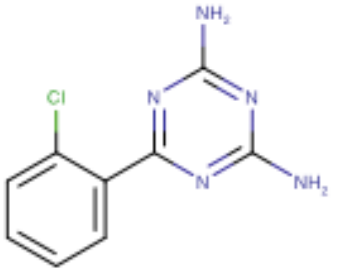
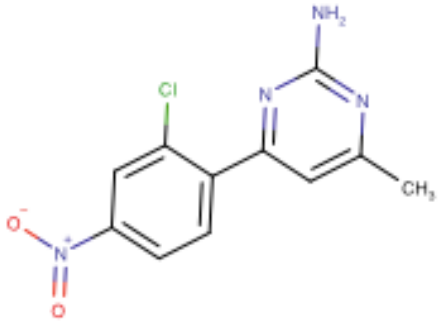
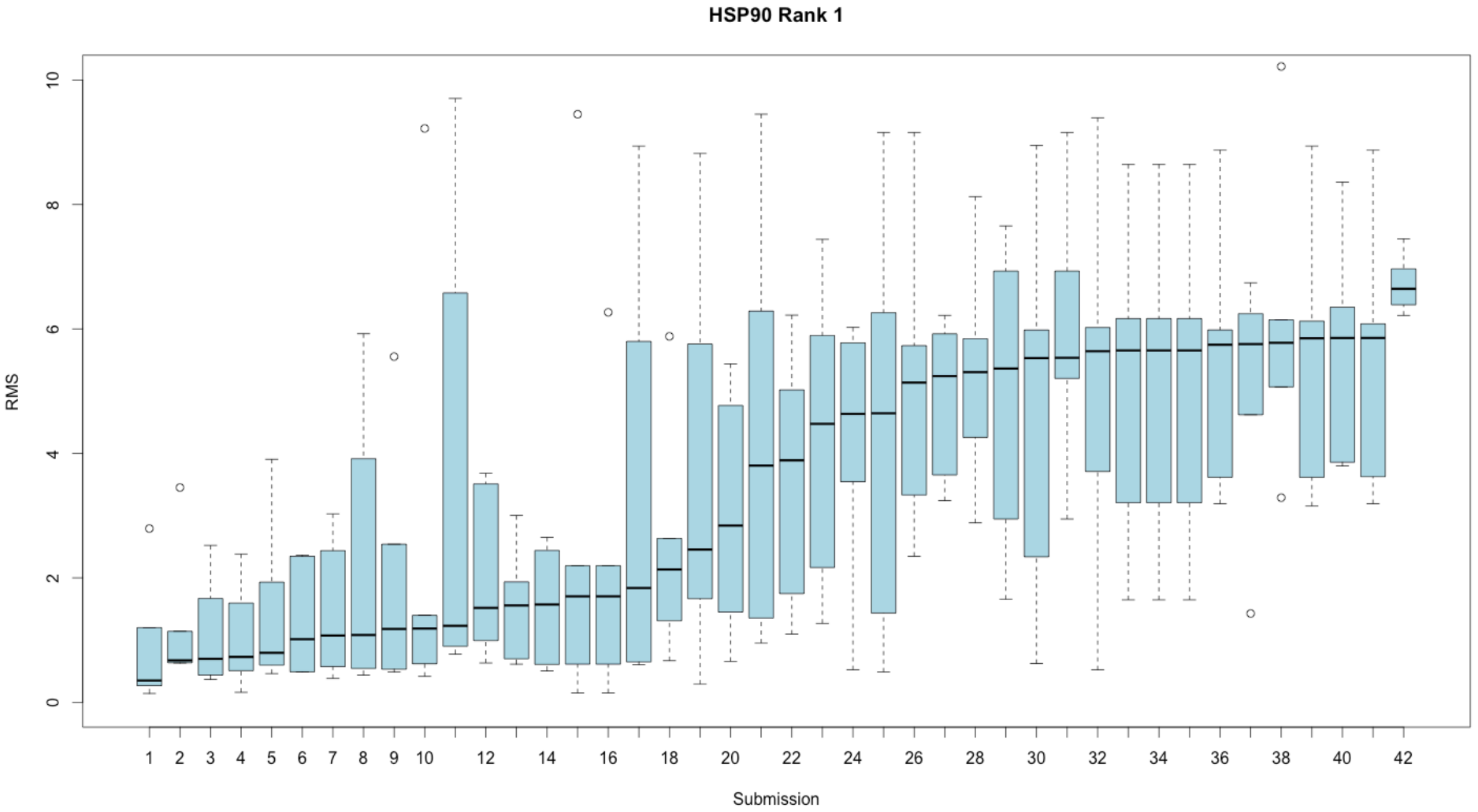


179

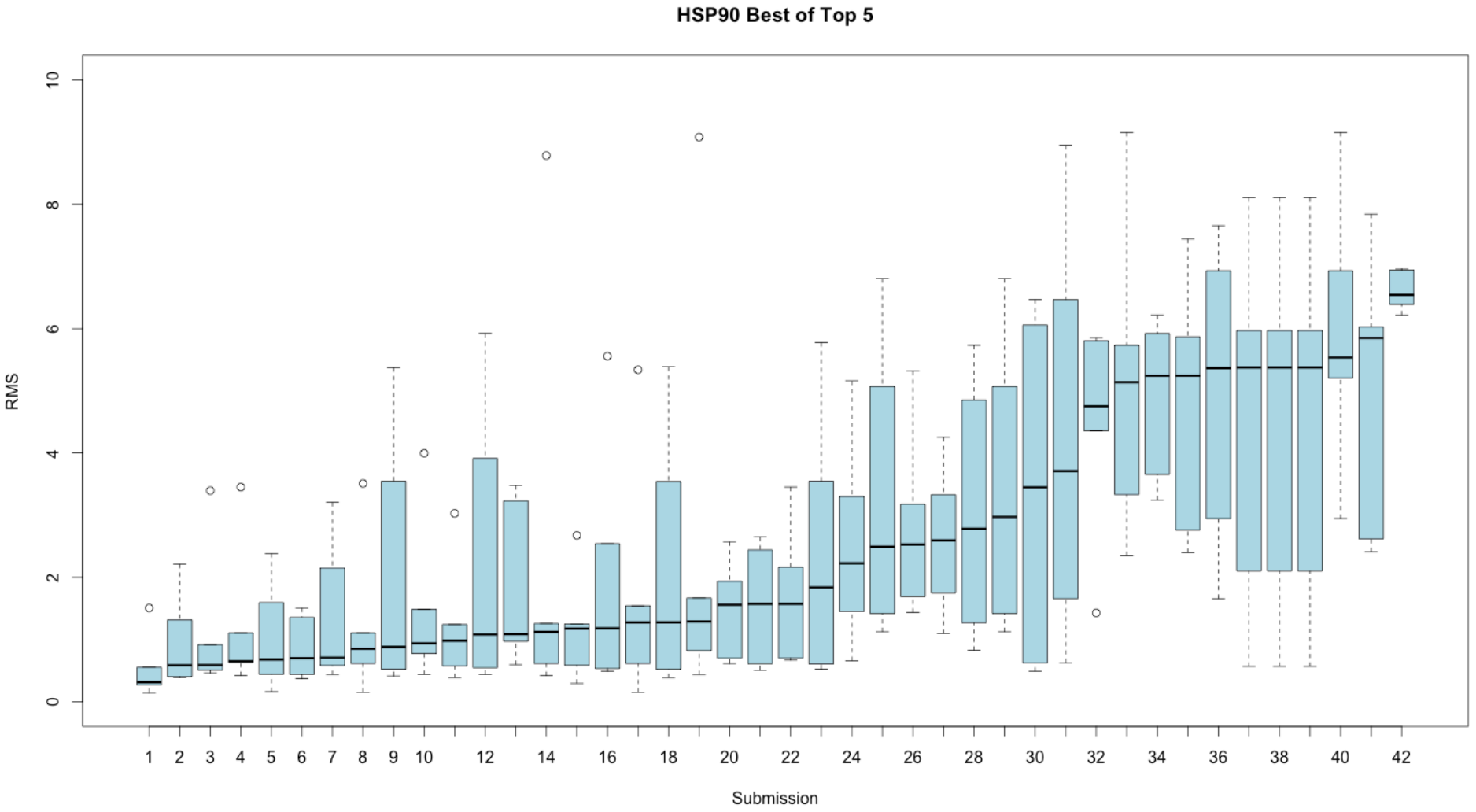


73

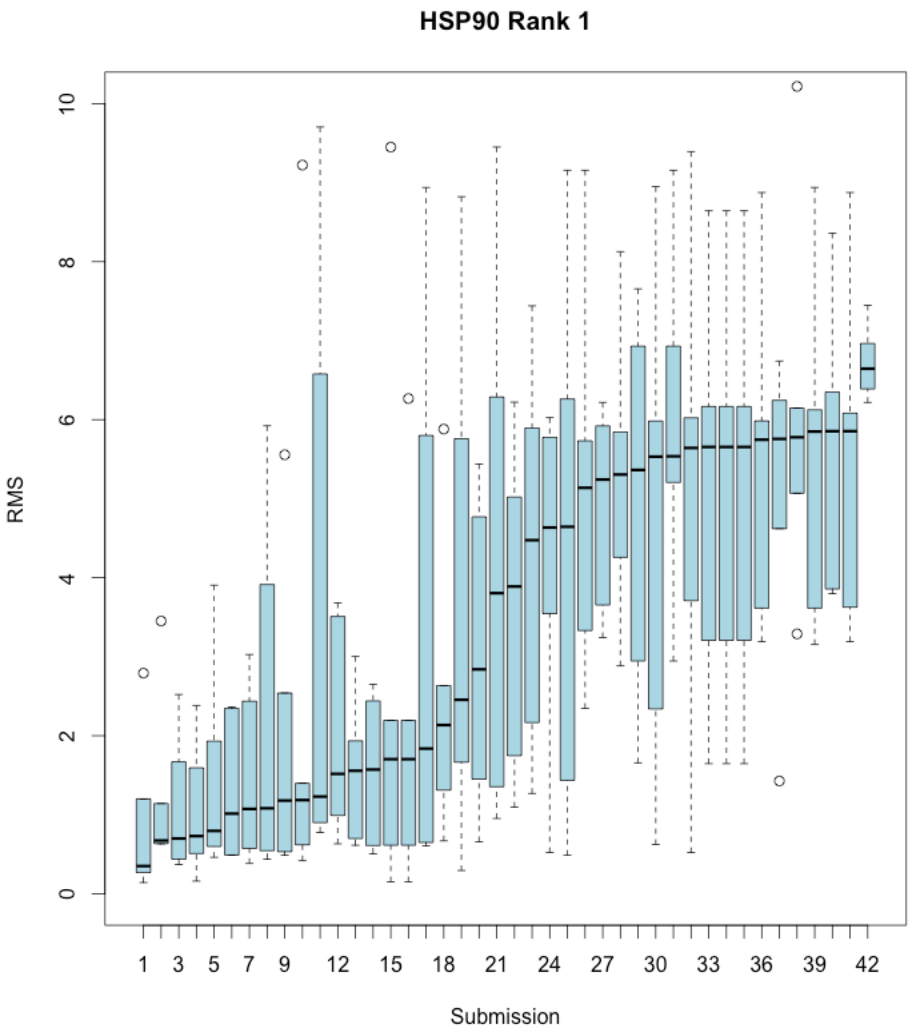
RMS for Top Ranking HSP90 Dockings

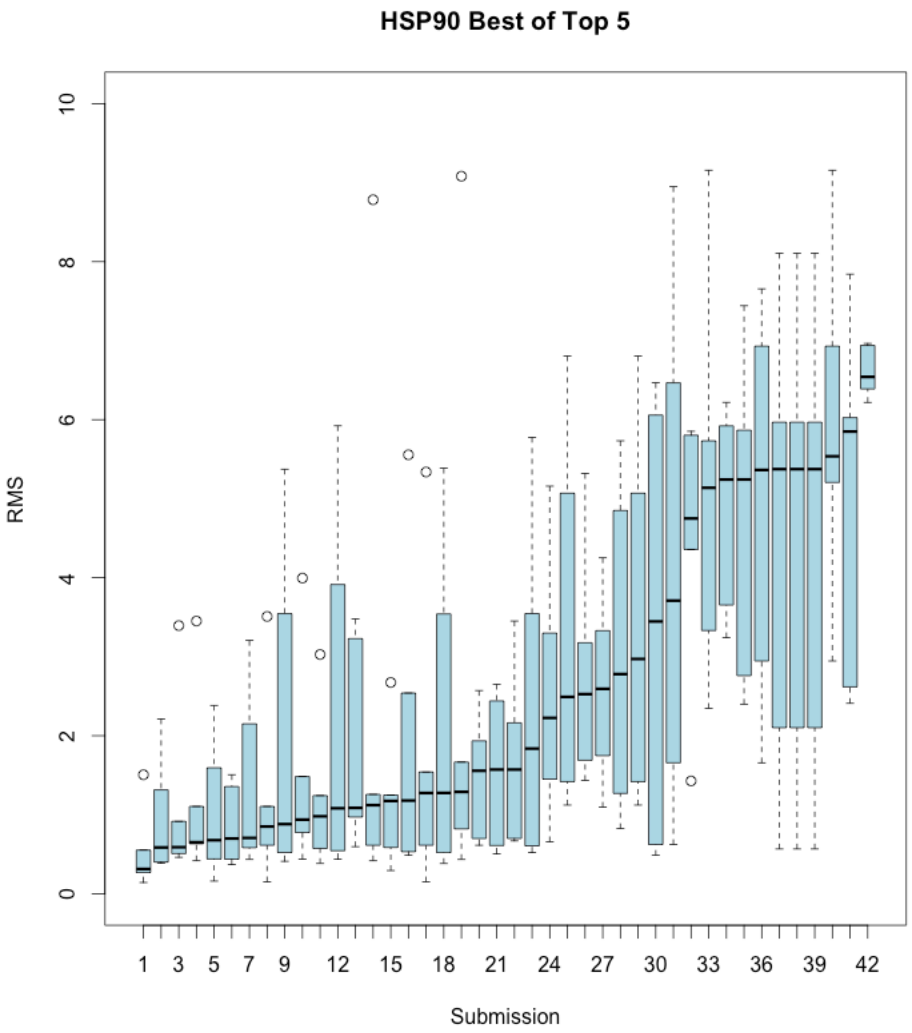


RMS for Best Fit of Top 5 HSP90 Dockings

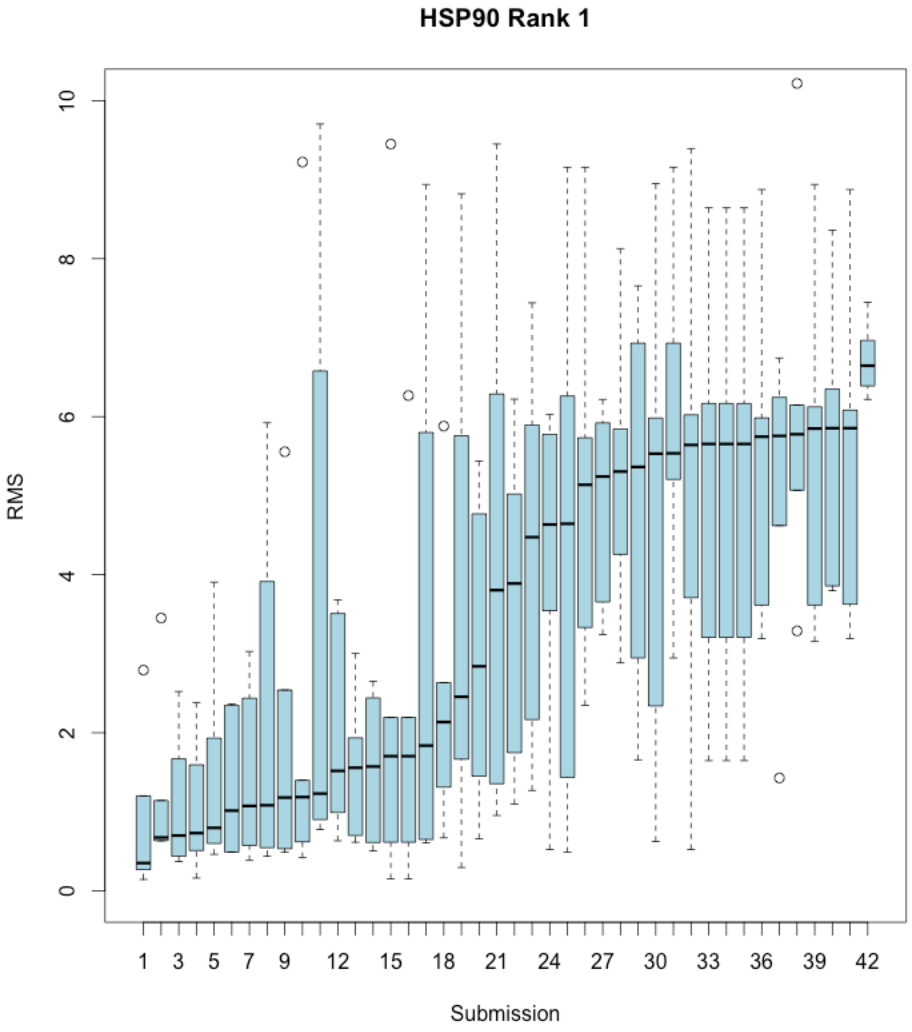


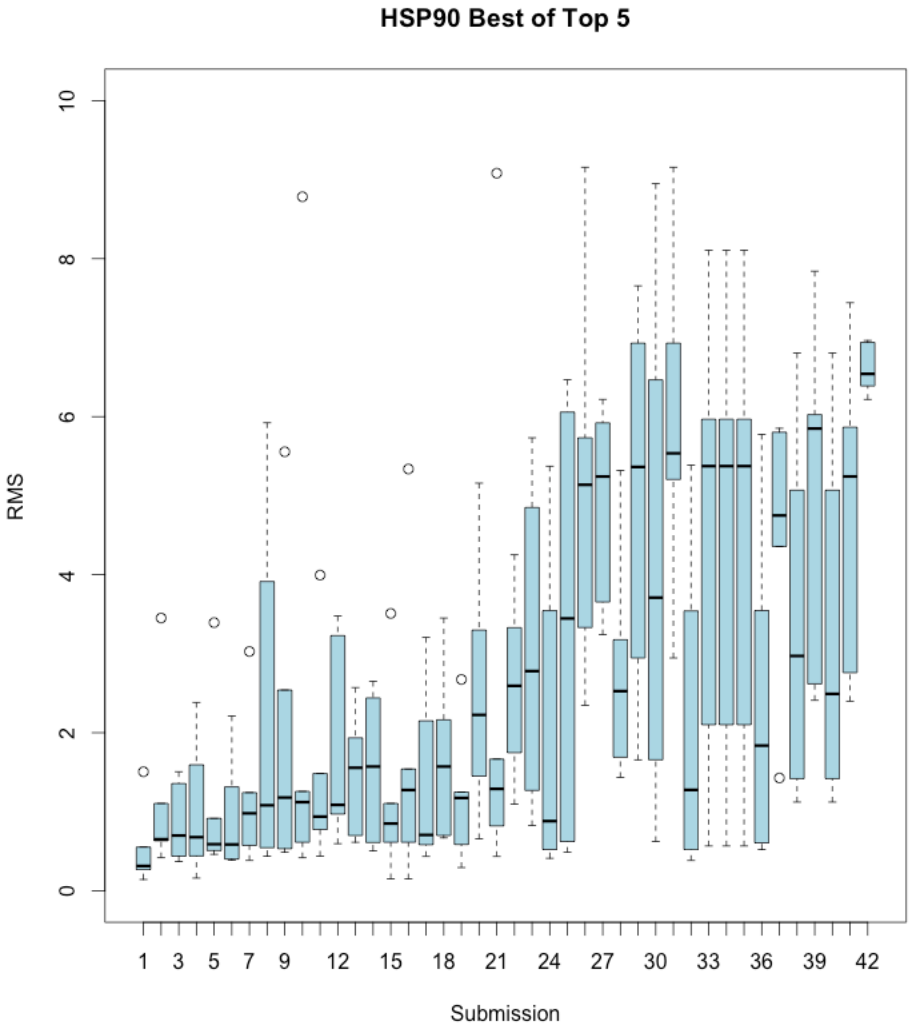
Comparing Top and Best Ranks for HSP90



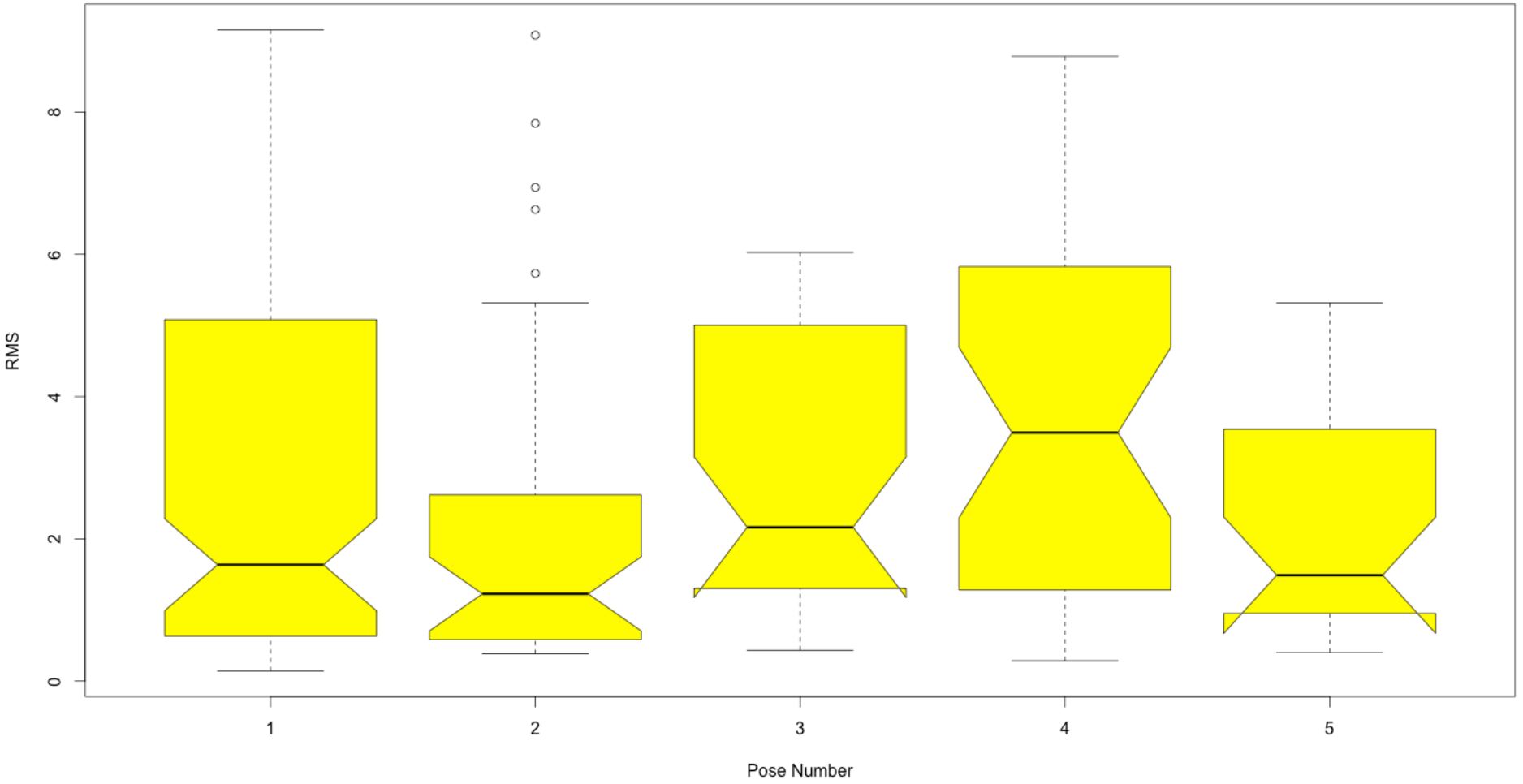


Comparing Top and Best Ranks for HSP90 (Same Ordering)

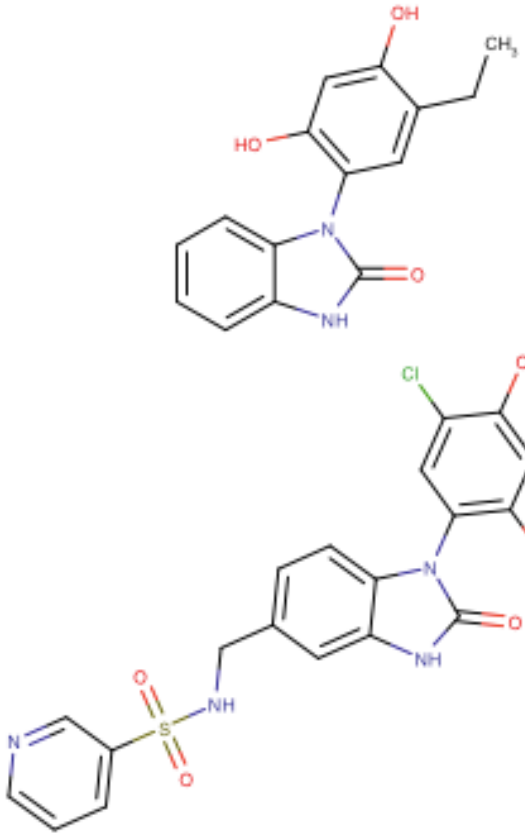




Minimal Differences in RMS for Top 5 Poses



3 Pairs of HSP90 Ligands



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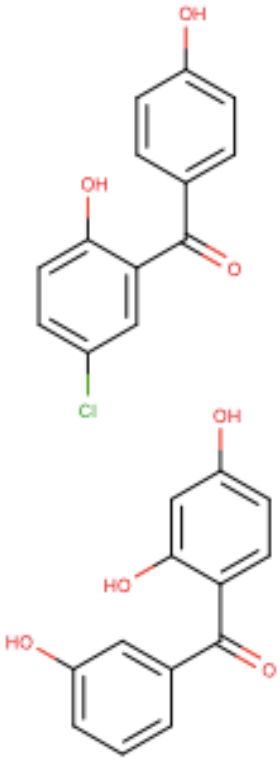
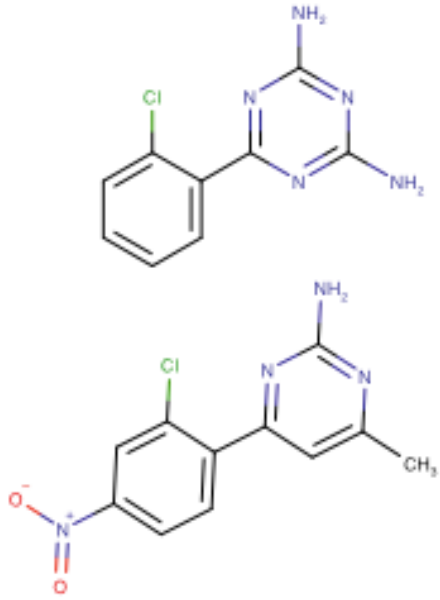
44



164

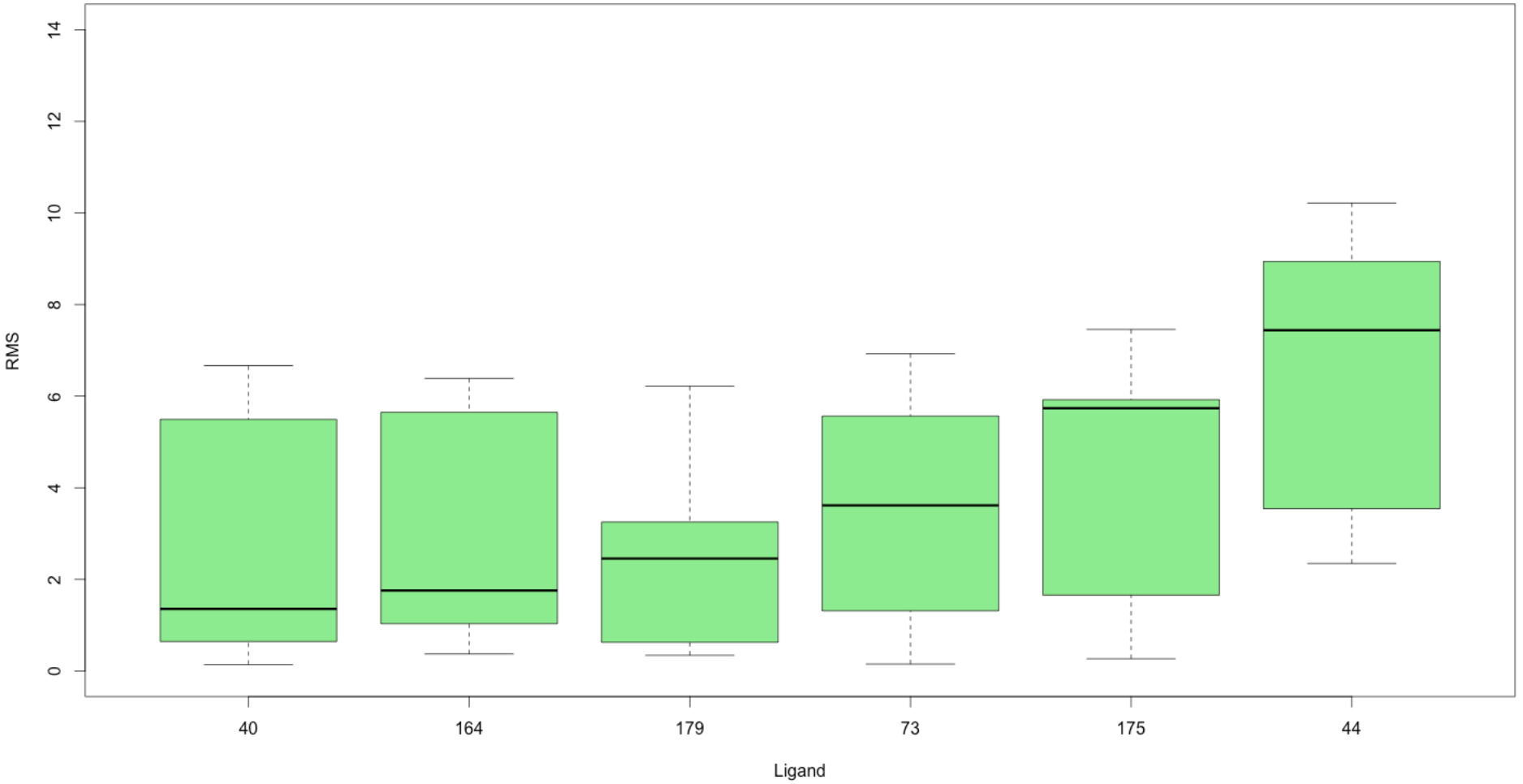
175



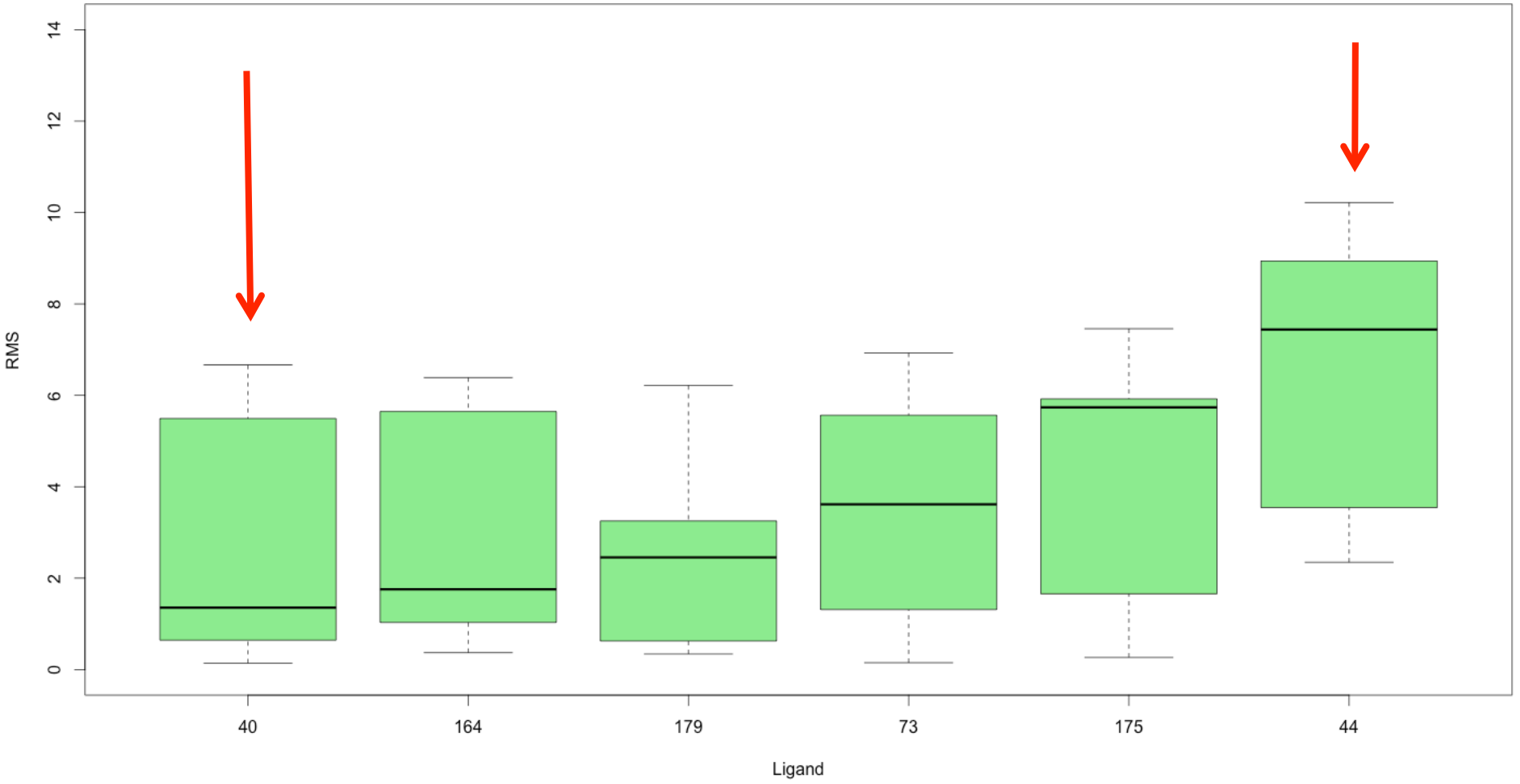
179

73

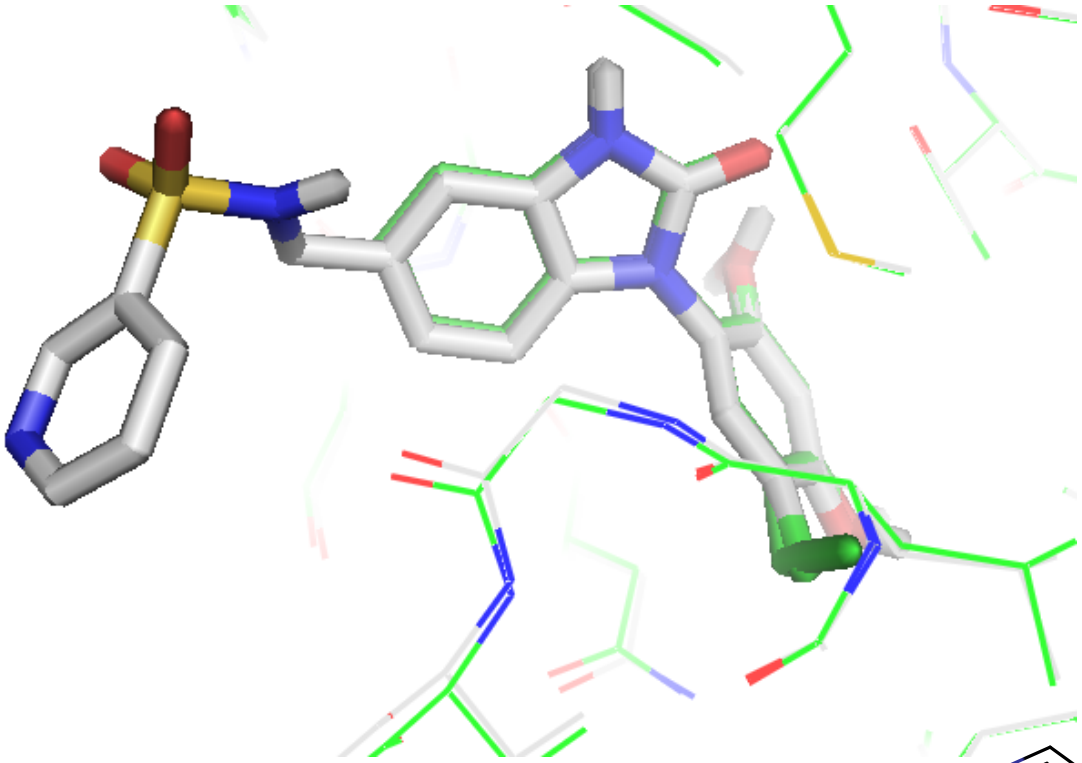
Some Ligands Appear More Difficult to Dock

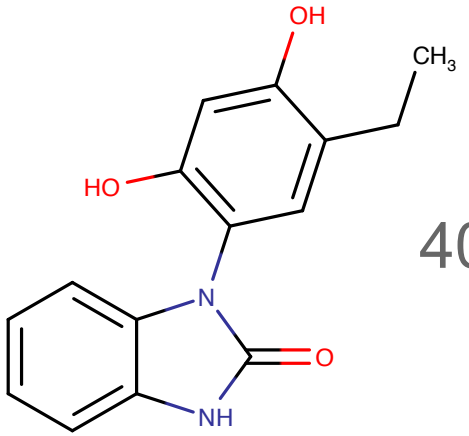


Comparing Ligands 40 and 44



Ligands 40 and 44 have similar poses





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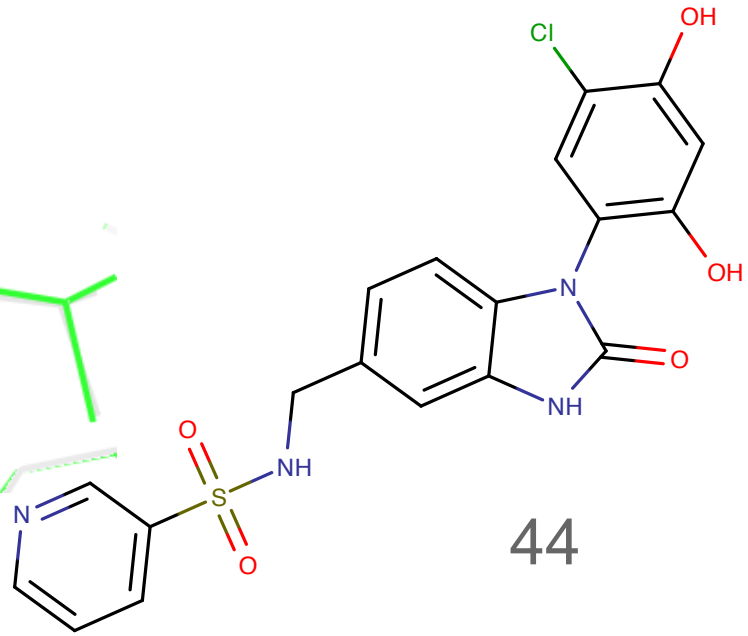

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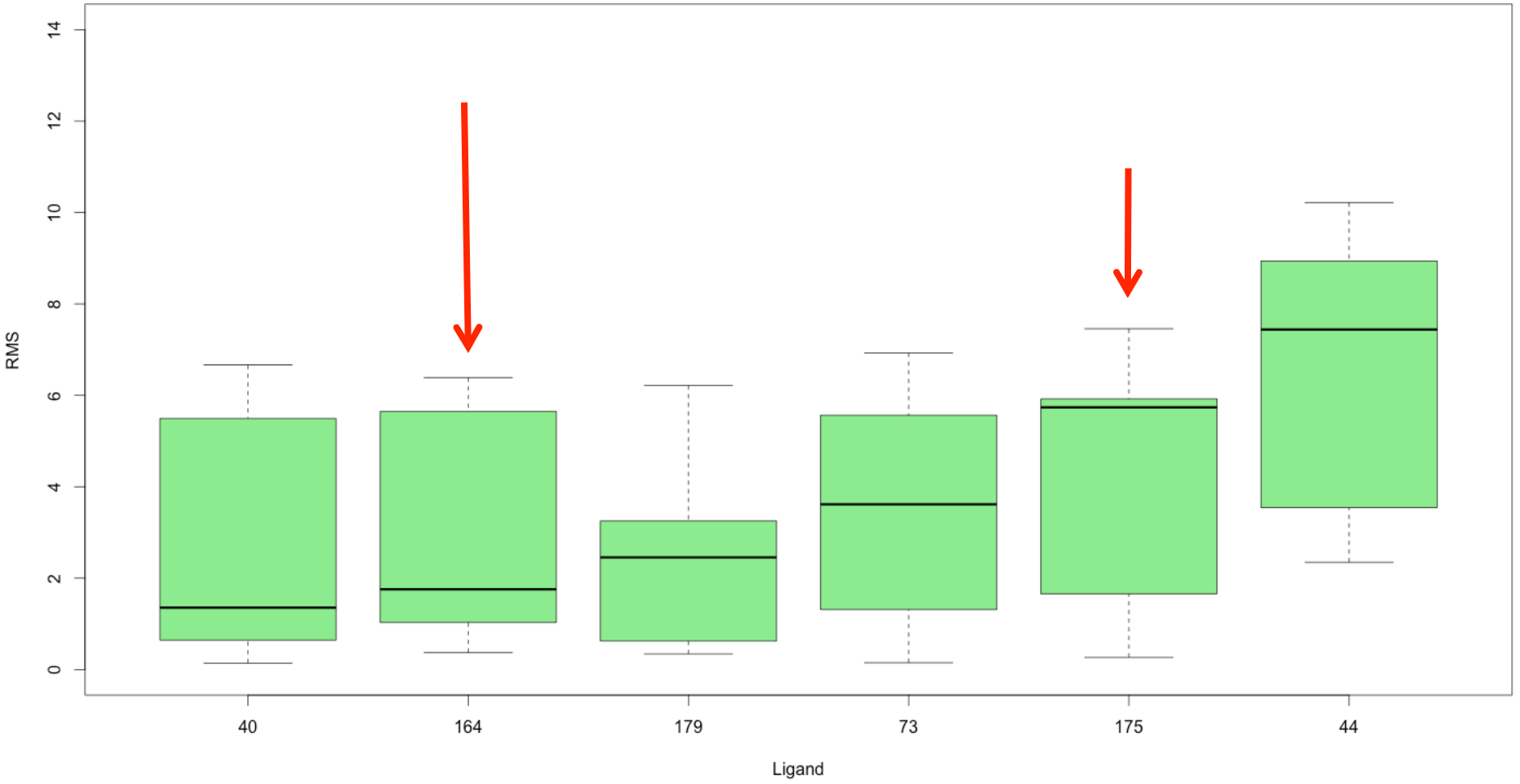
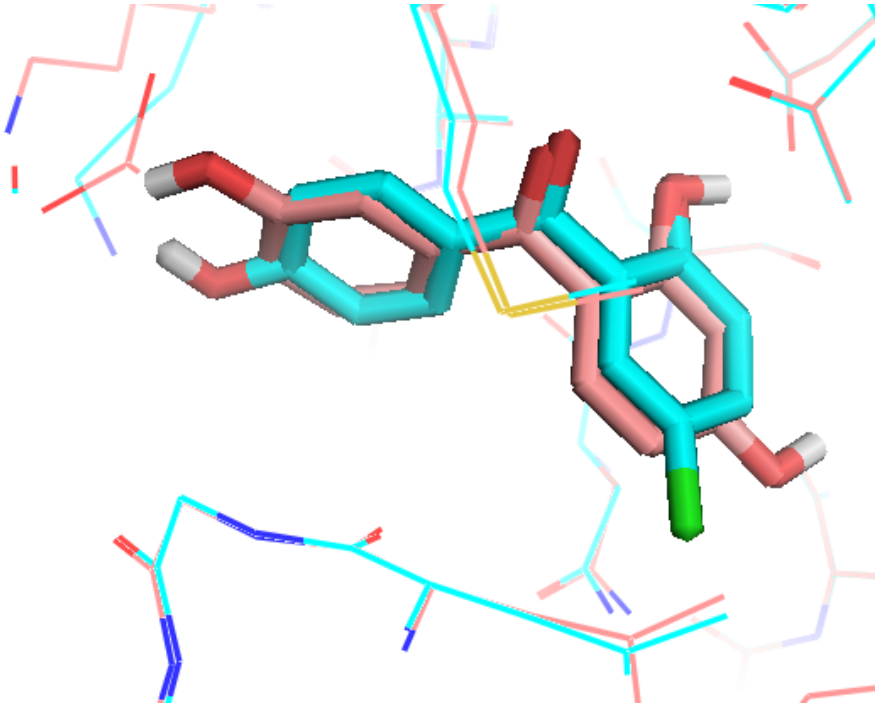
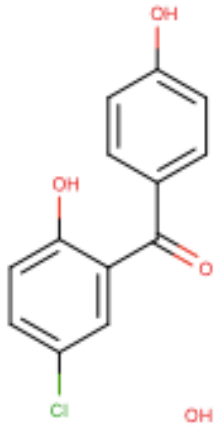
Comparing Ligands 164 and 175



Comparing 164 and 175





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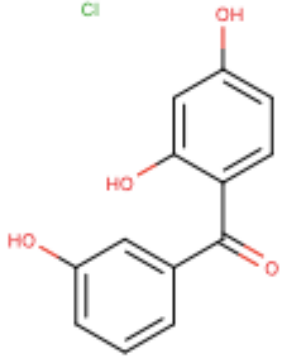
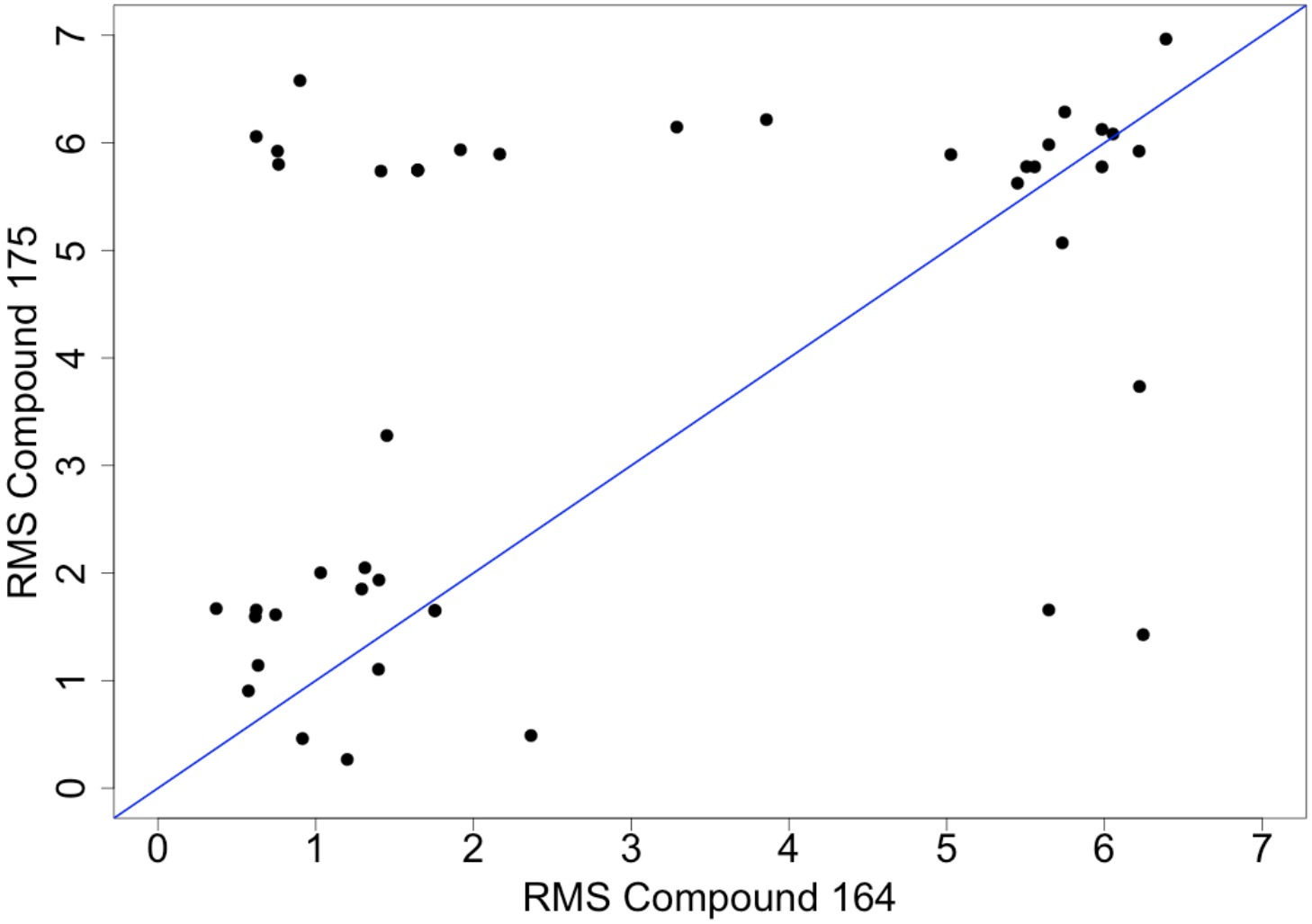
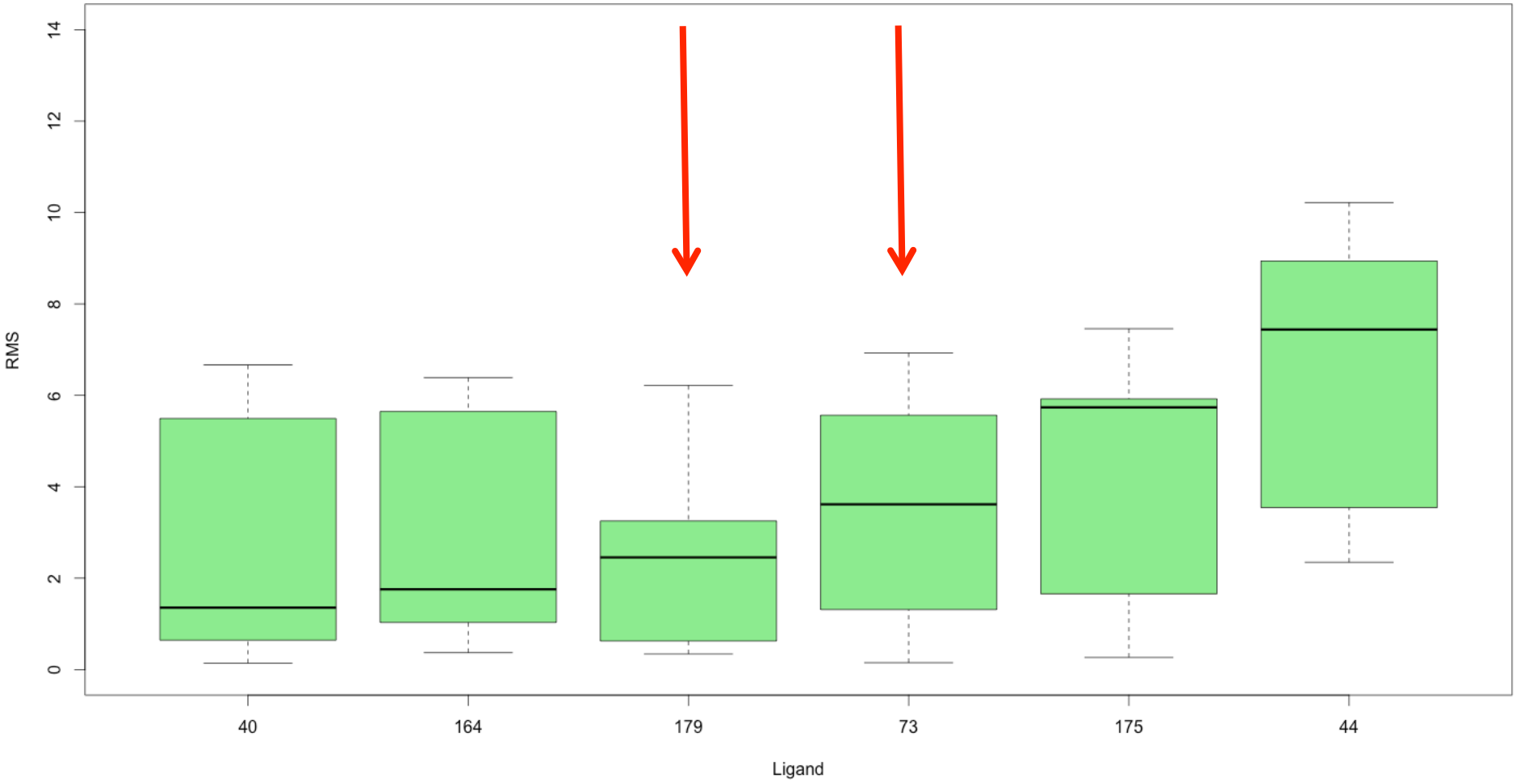


175

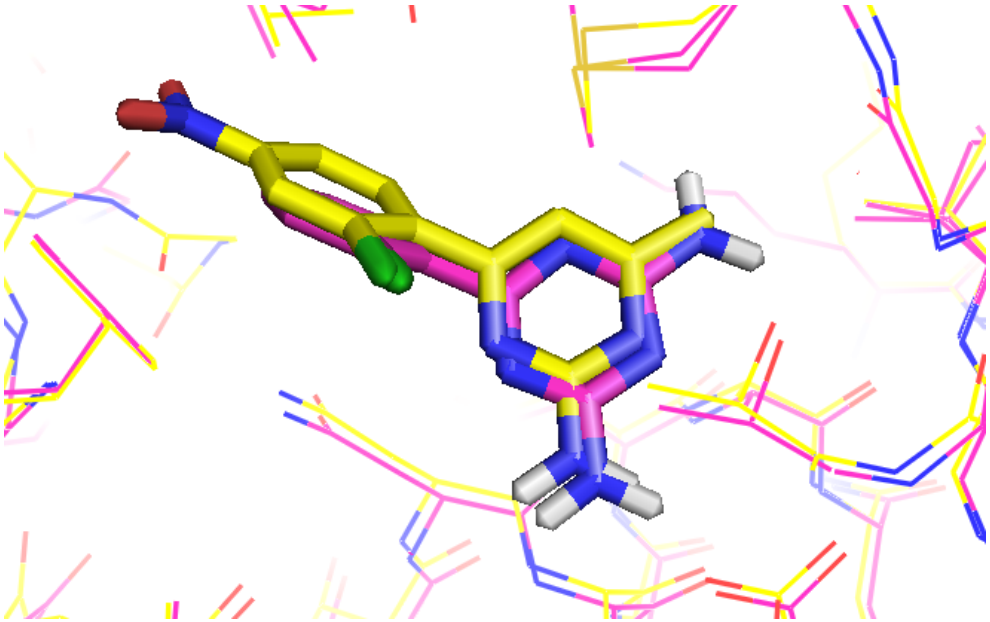
Different Docking Accuracy for 164 and 175

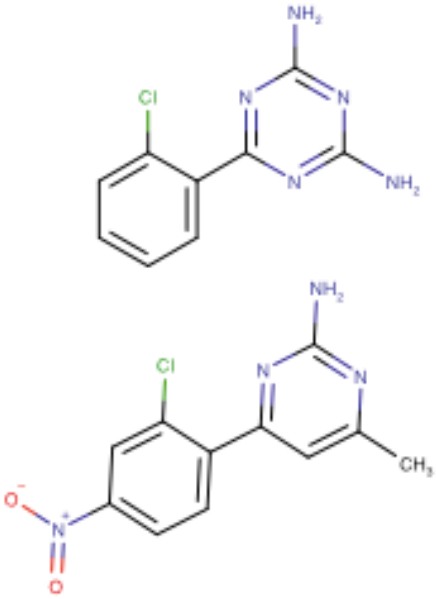


Comparing Ligands 179 and 73

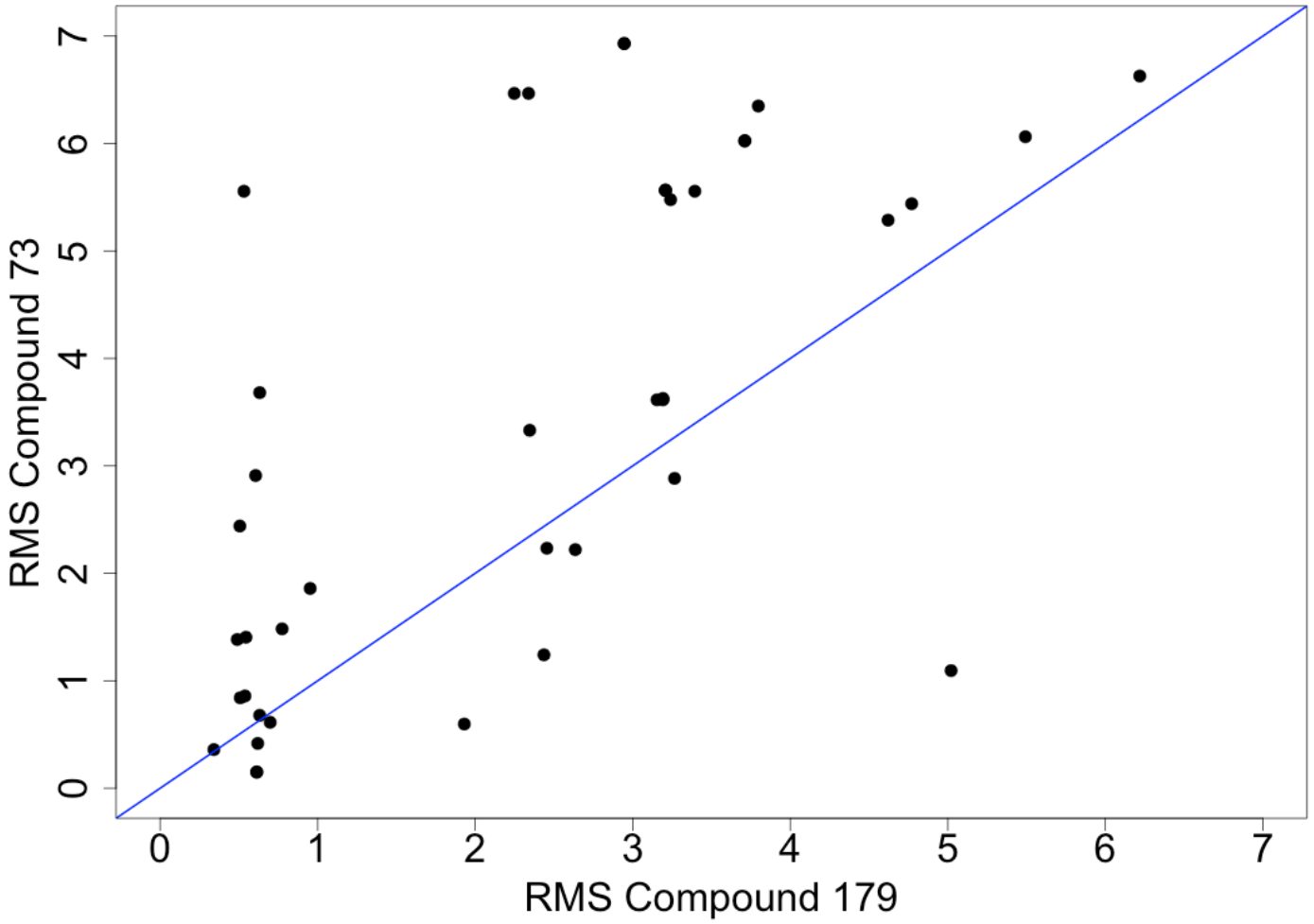


Comparing Ligands 179 and 73



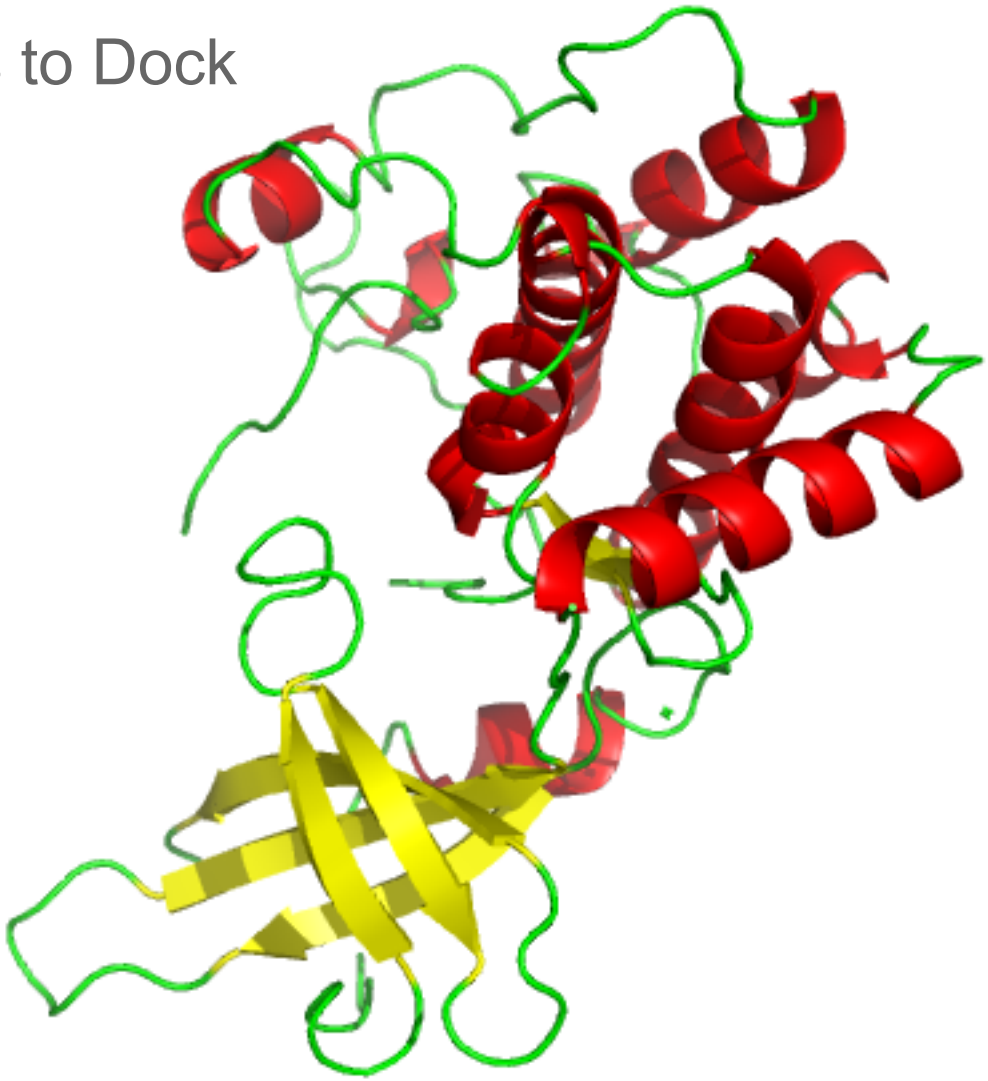


Different Docking Accuracy for 179 and 73



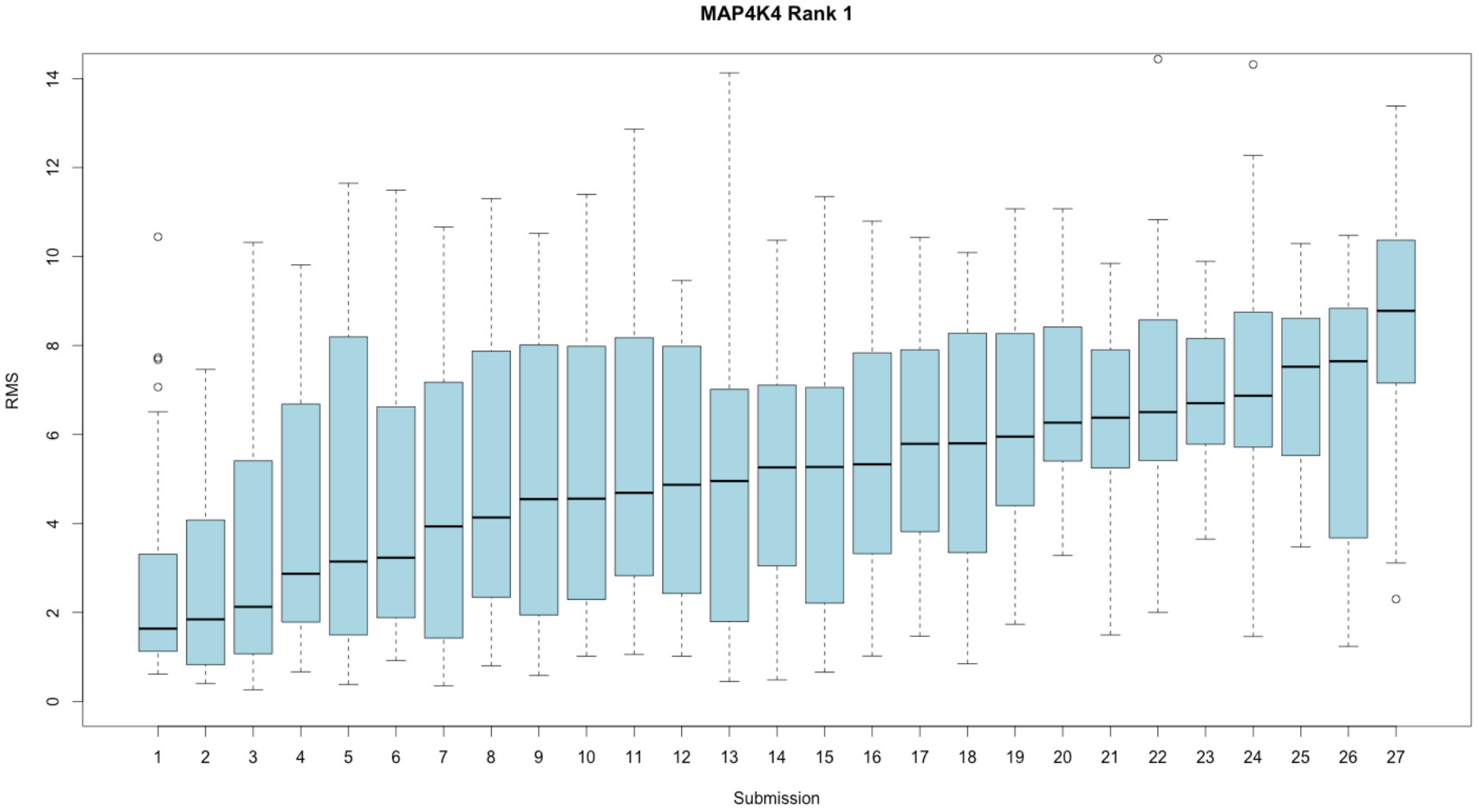
MAP4K4

30 Ligands to Dock

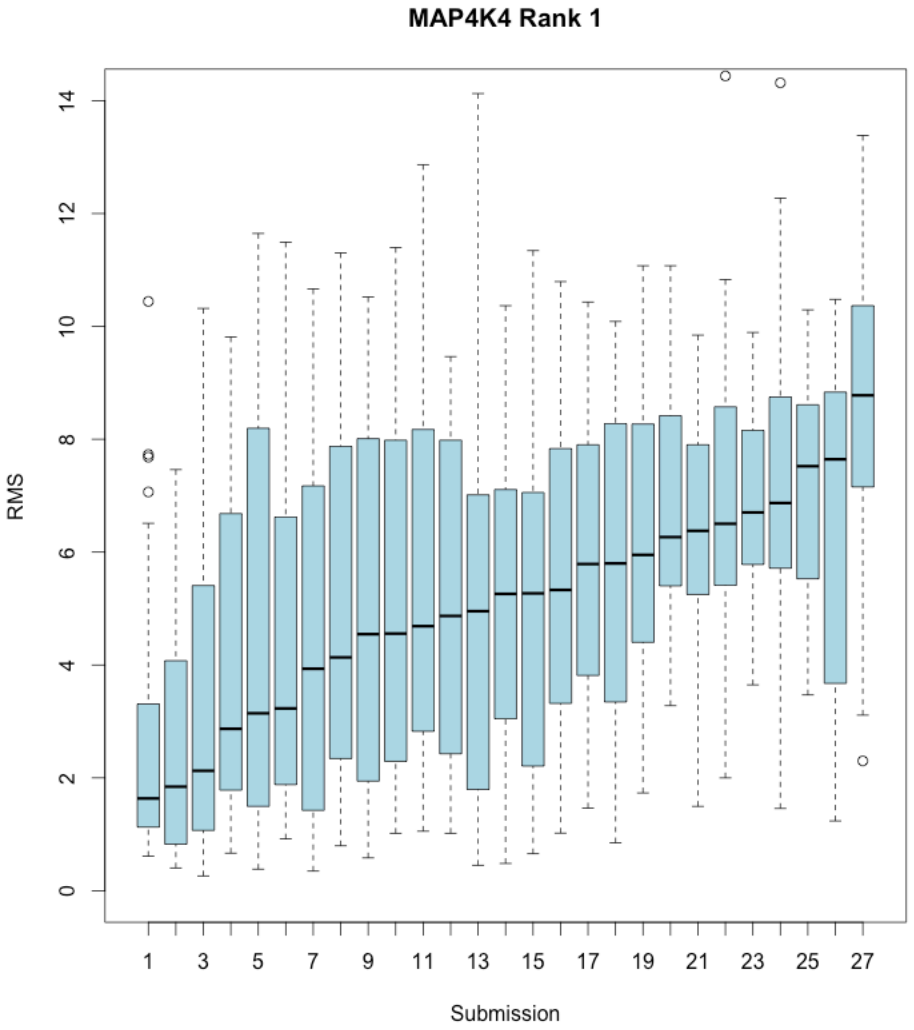


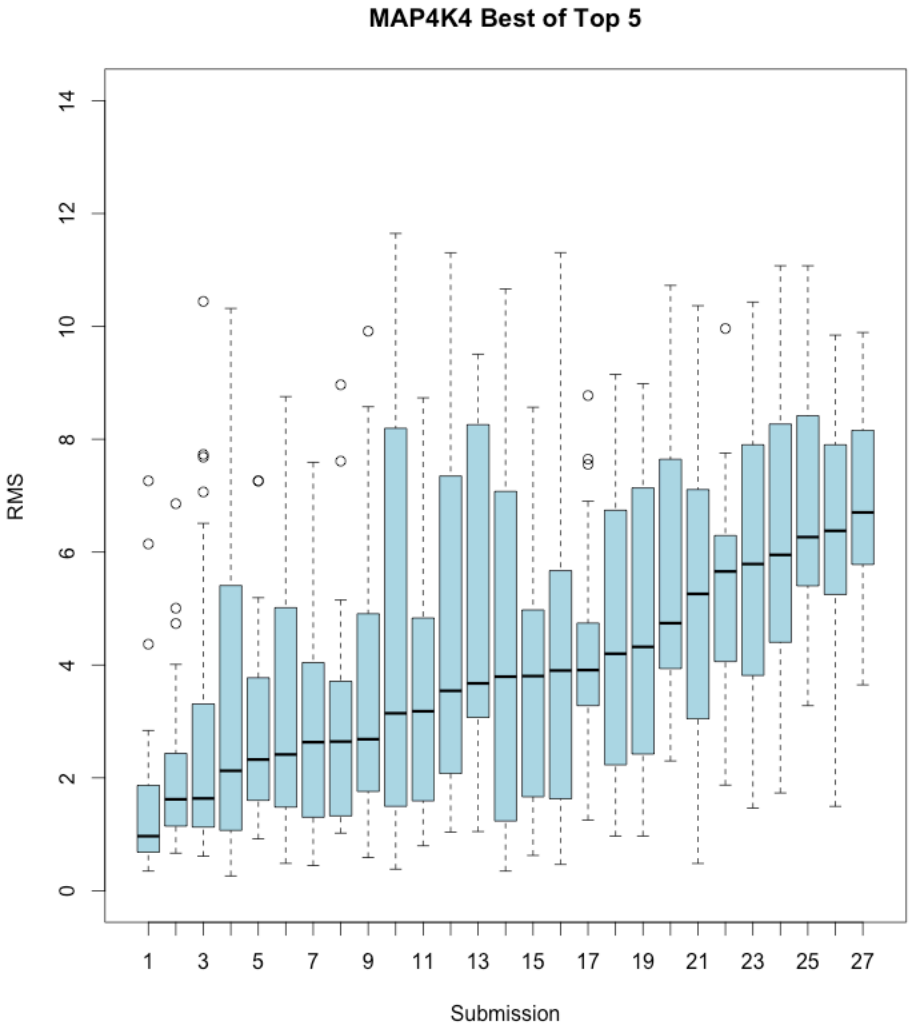
VERTEX

RMS for Top Ranking MAP4K4 Dockings

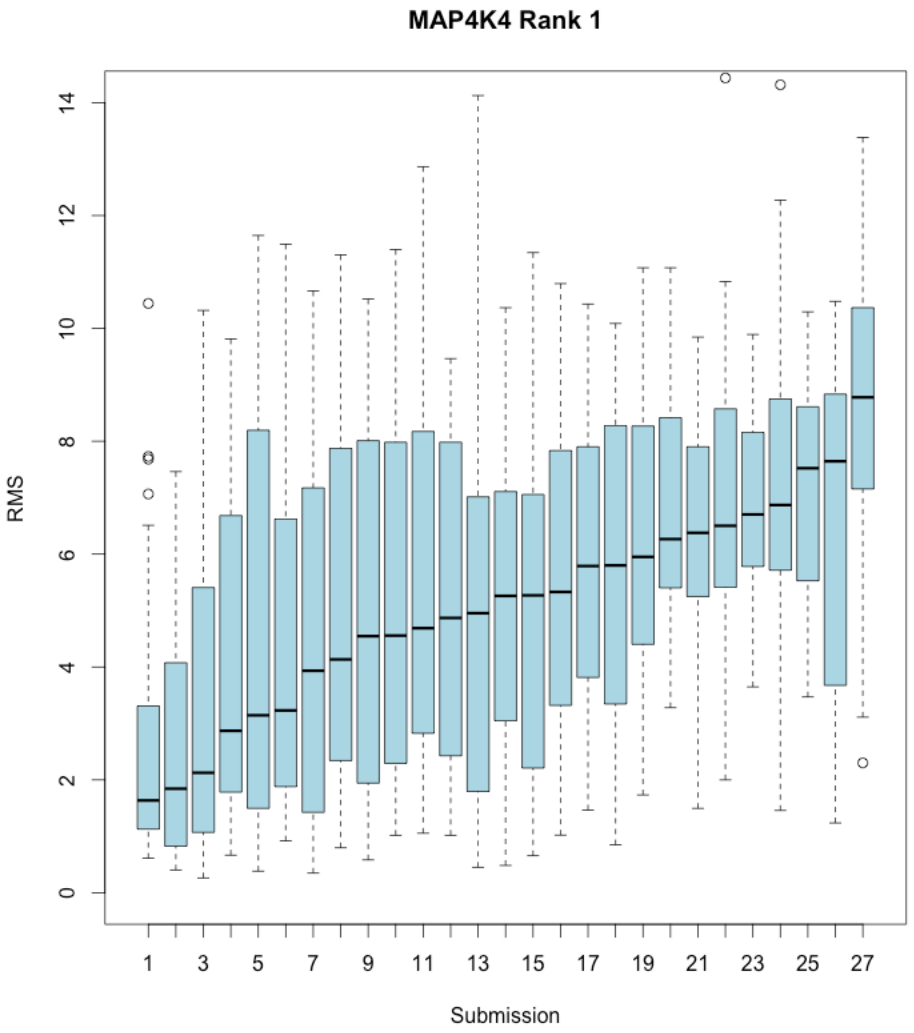


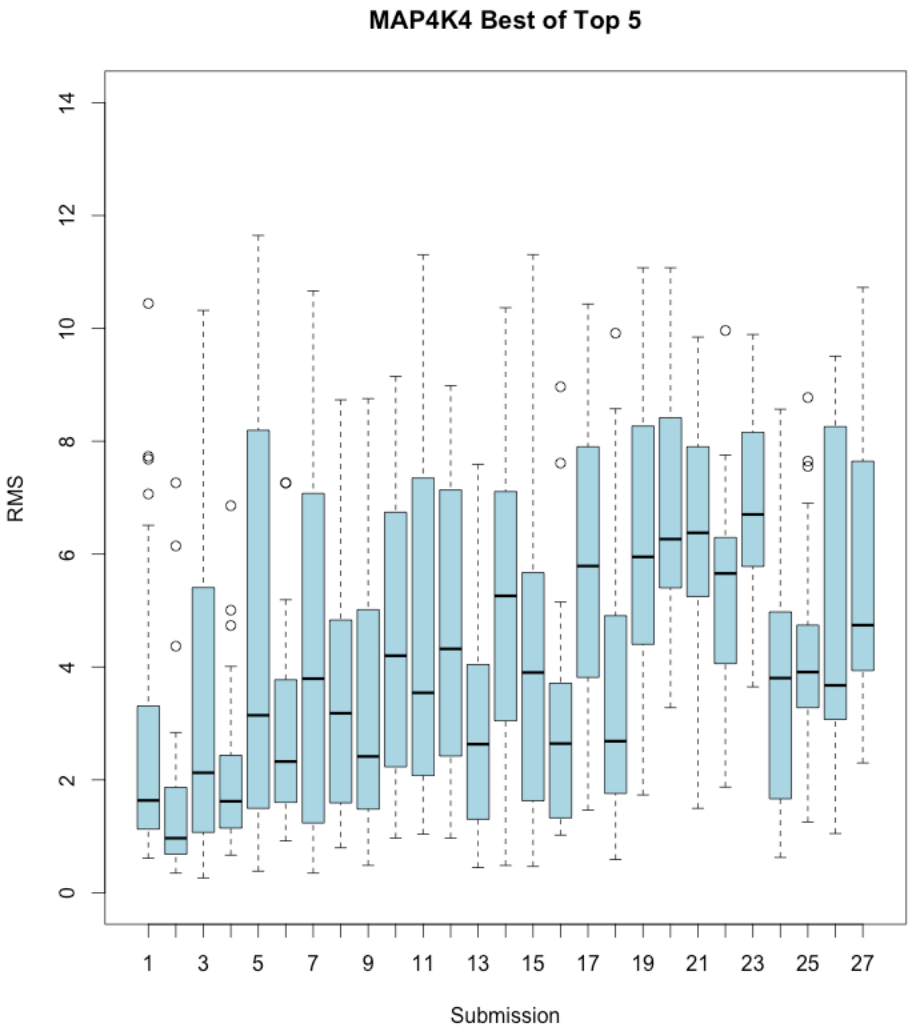
Comparing Top and Best Ranks for MAP4K4



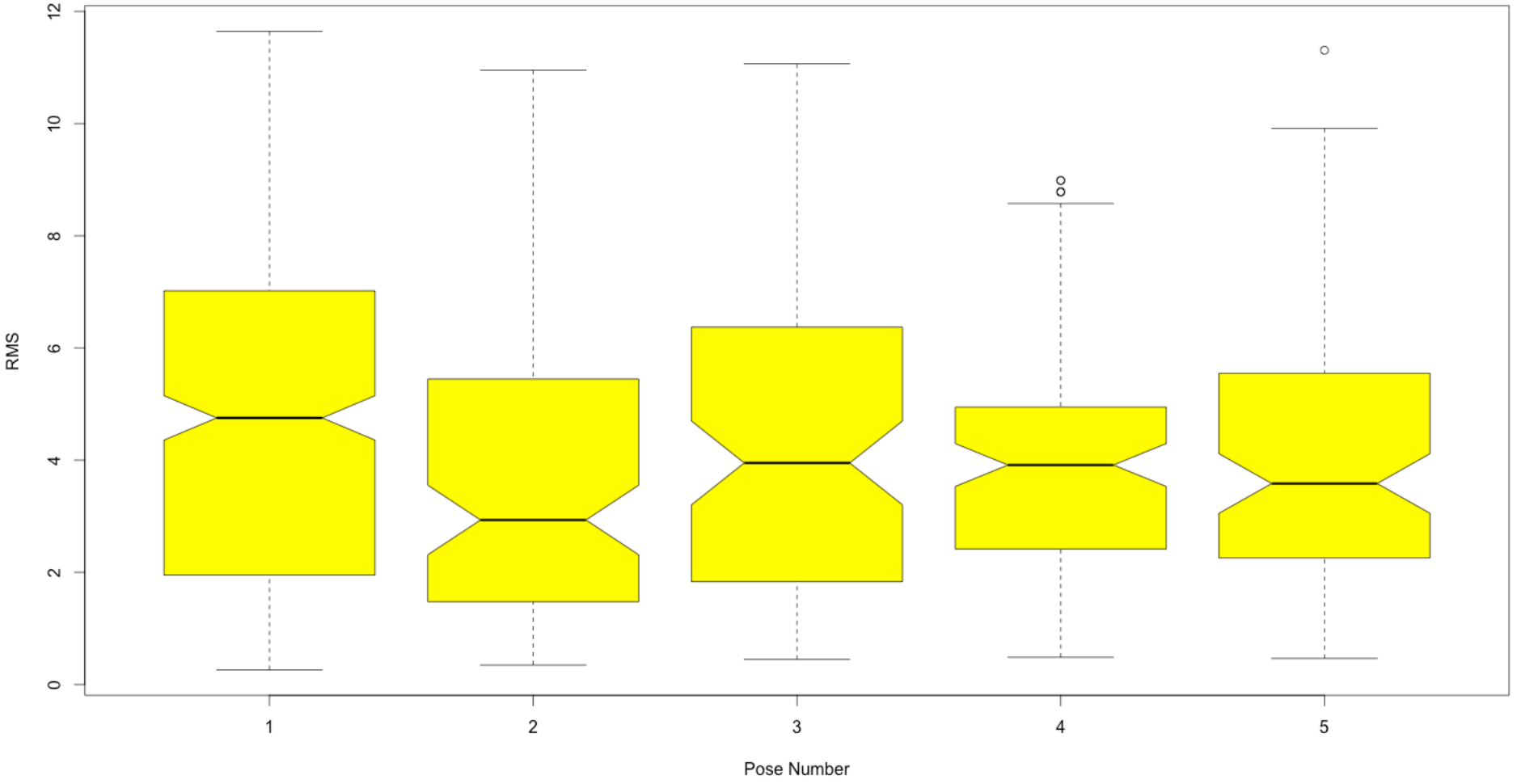


Comparing Top and Best Ranks for MAP4K4 (Same Ordering)

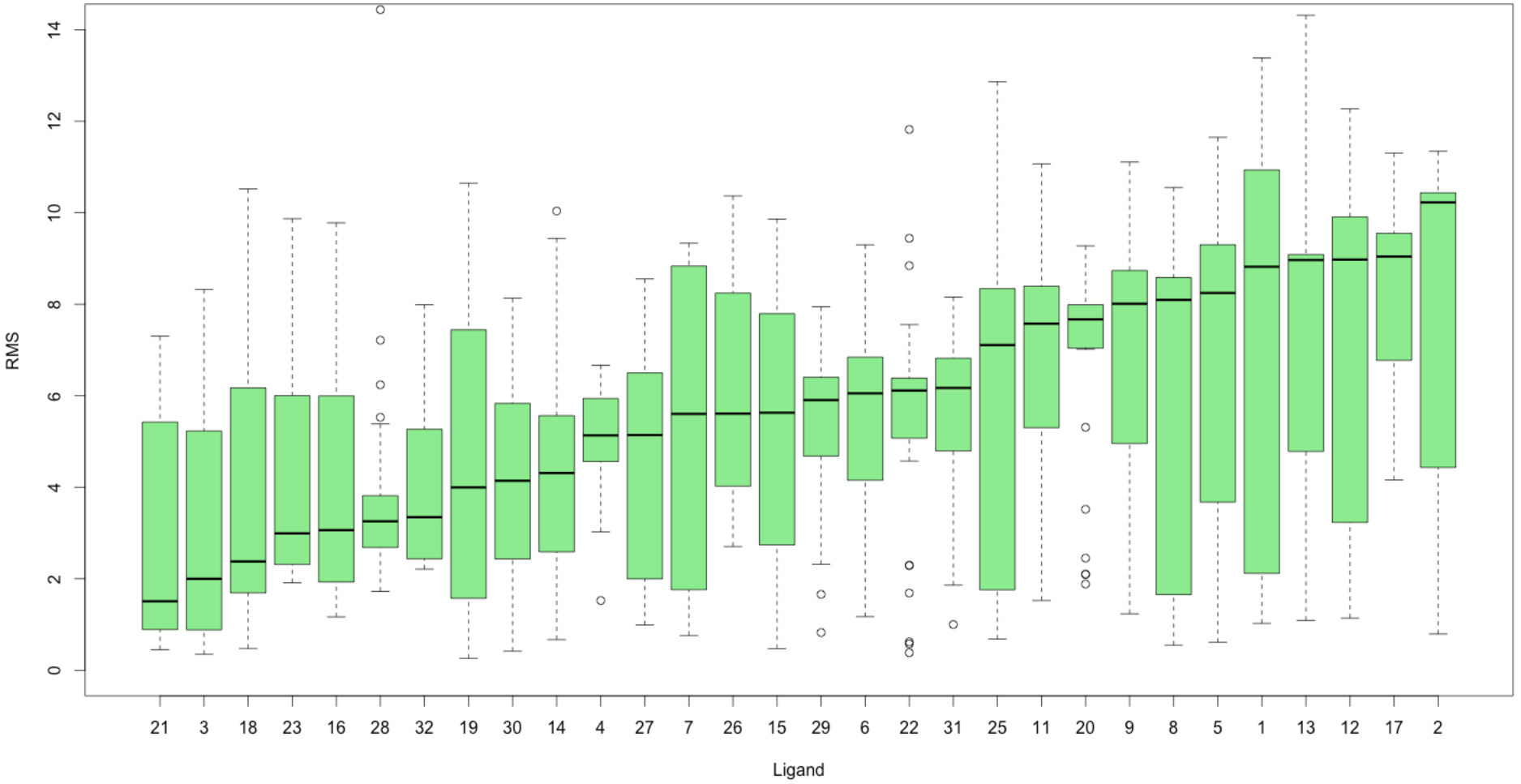




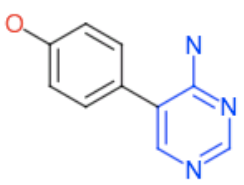
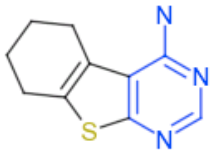
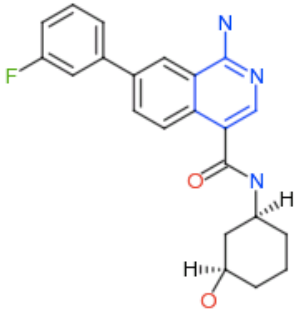
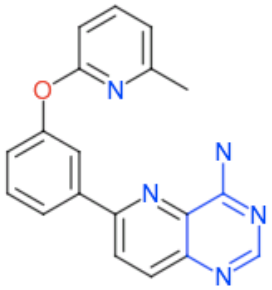
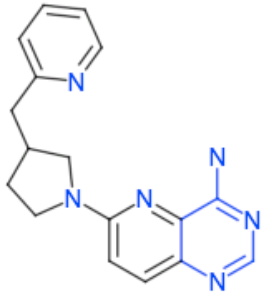
Top Ranked Poses Did Not Have the Best RMS



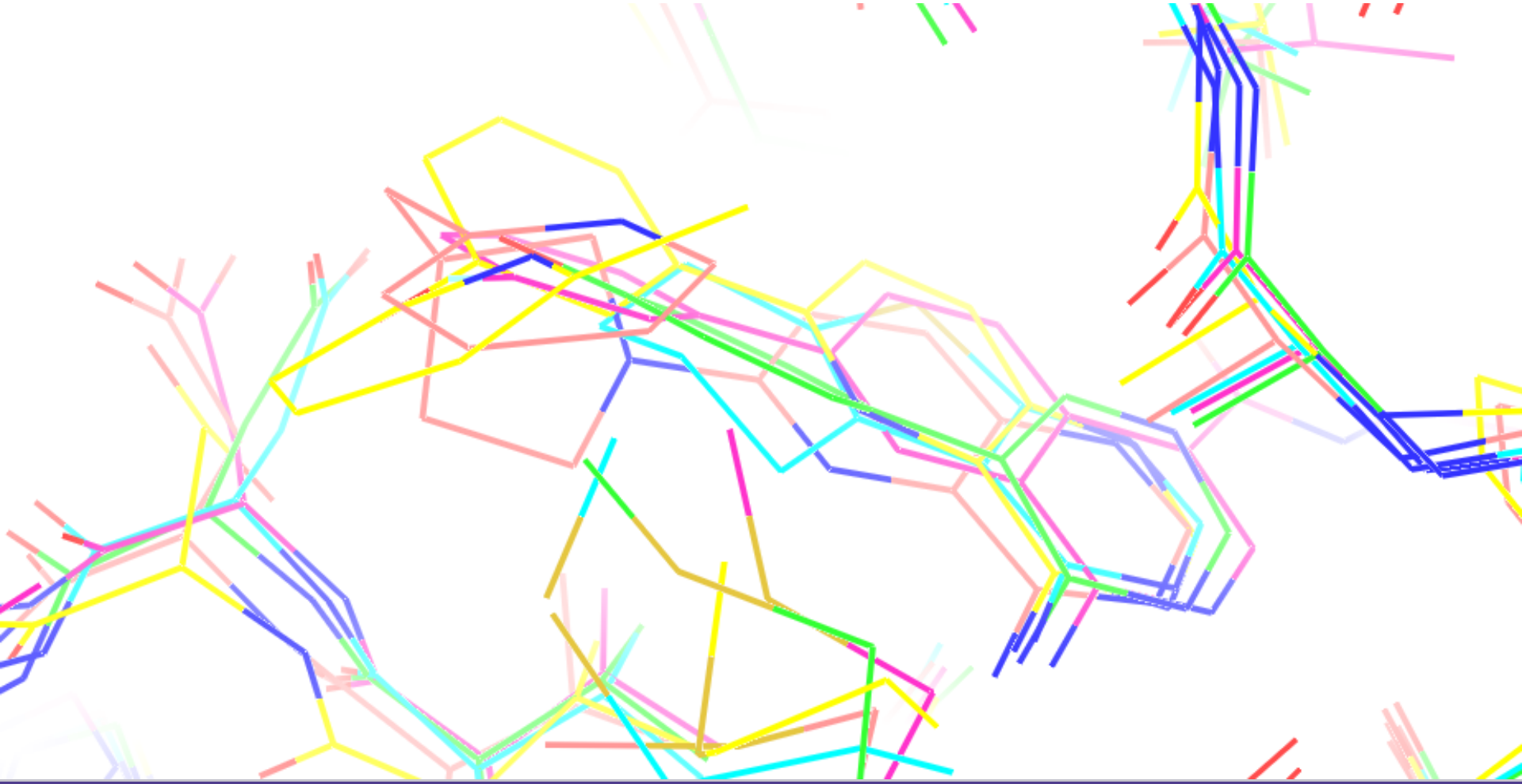
Which Ligands Were Easiest to Dock into MAP4K4?



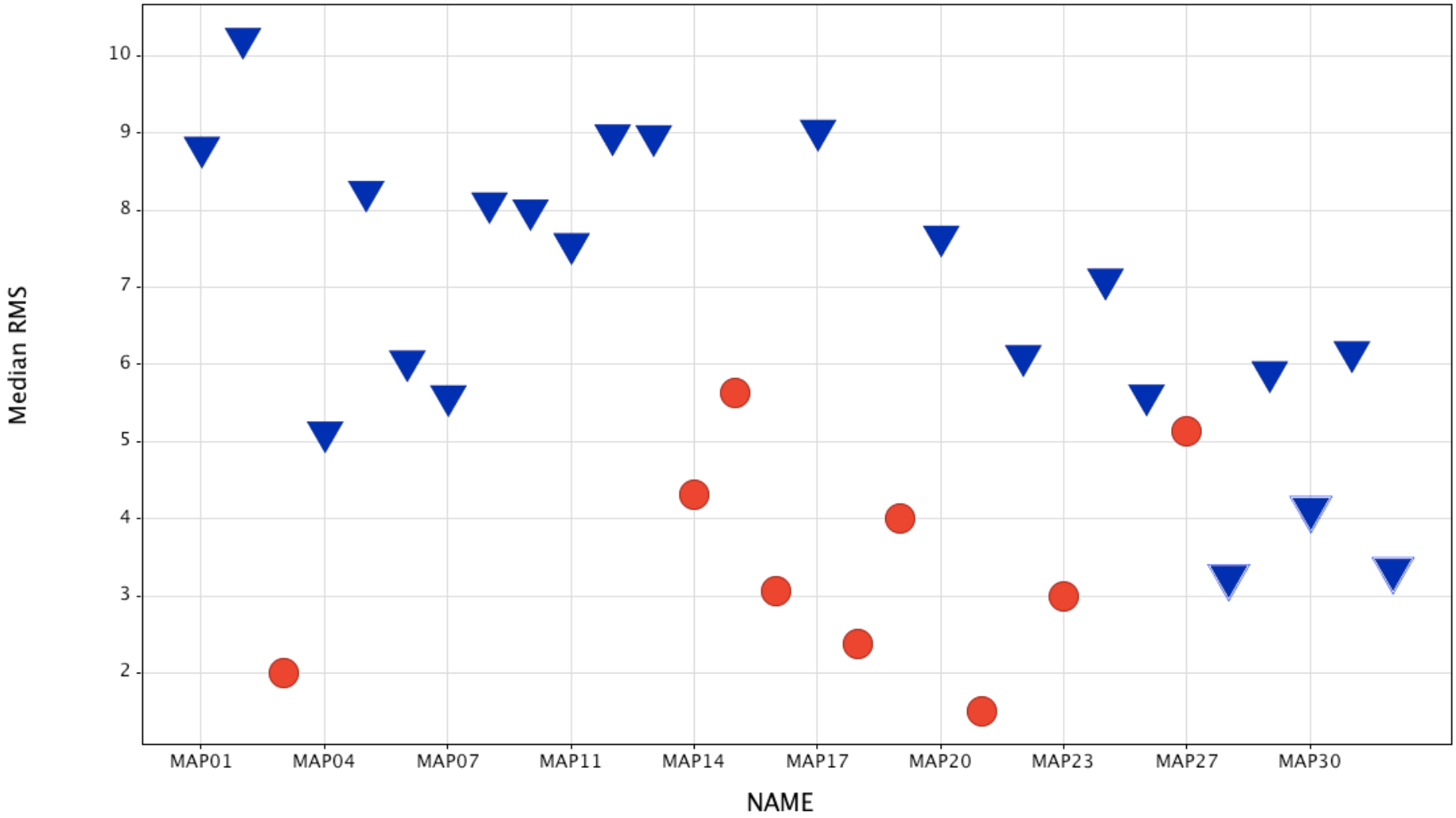
Common Motif in Correctly Docked Structures

NAME	MAP21	MAP03	MAP18	MAP23	MAP16
SMILES					
Median RMS	1.51	2	2.38	2.99	3.06

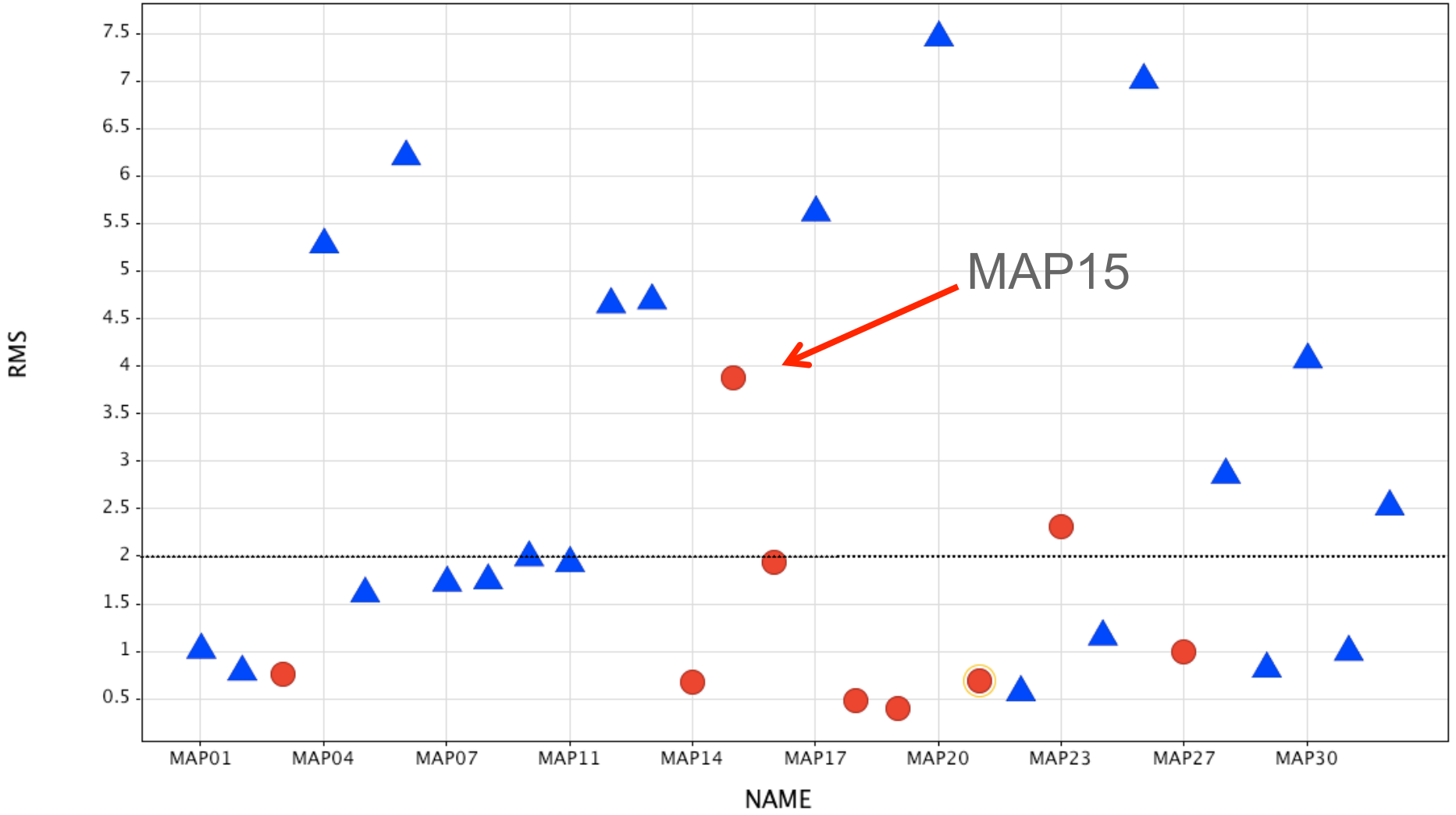
Structures Have a Common Binding Mode



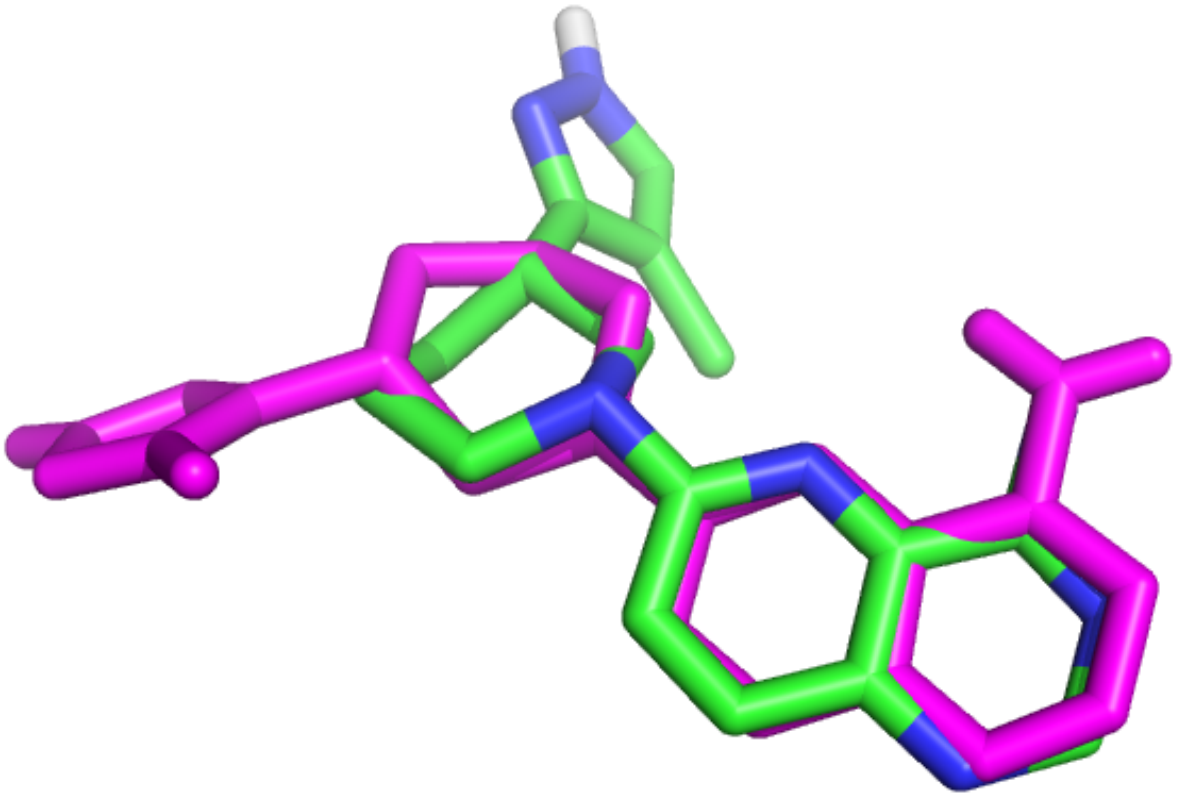
Pyridyl Anilines Have Lower Median RMS



Similar Trends in High Scoring Entries

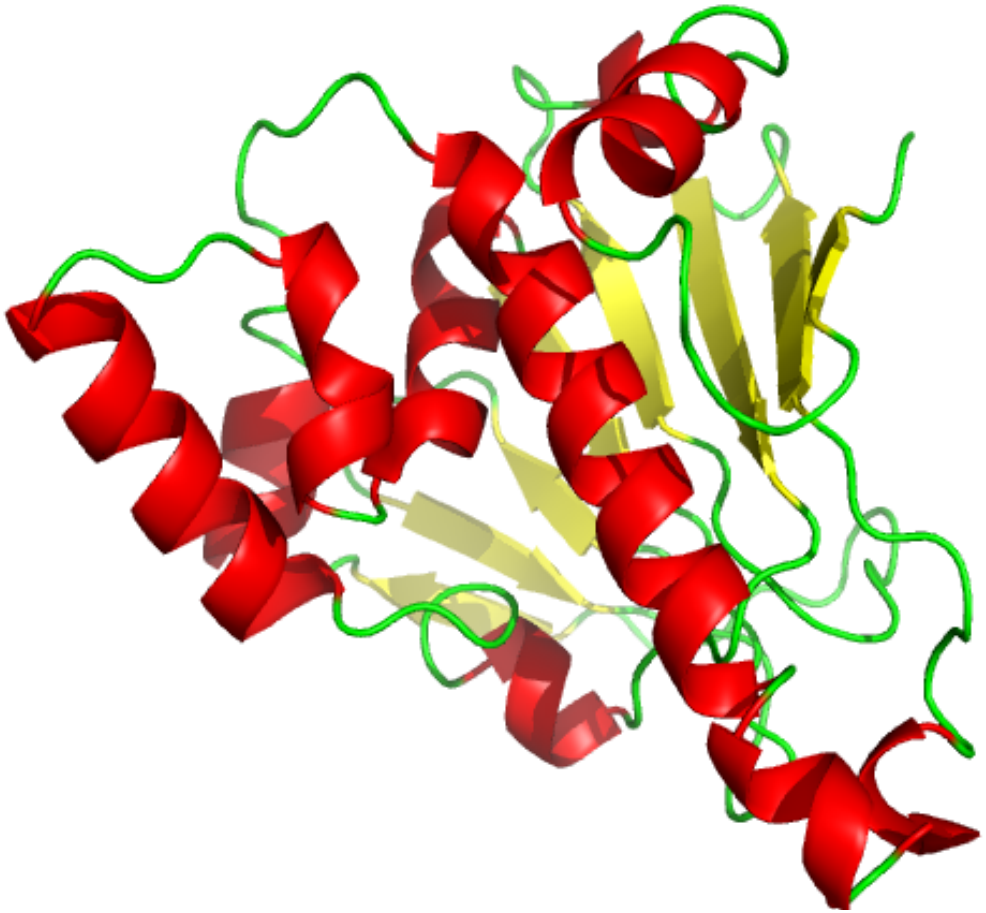


Detail on MAP15

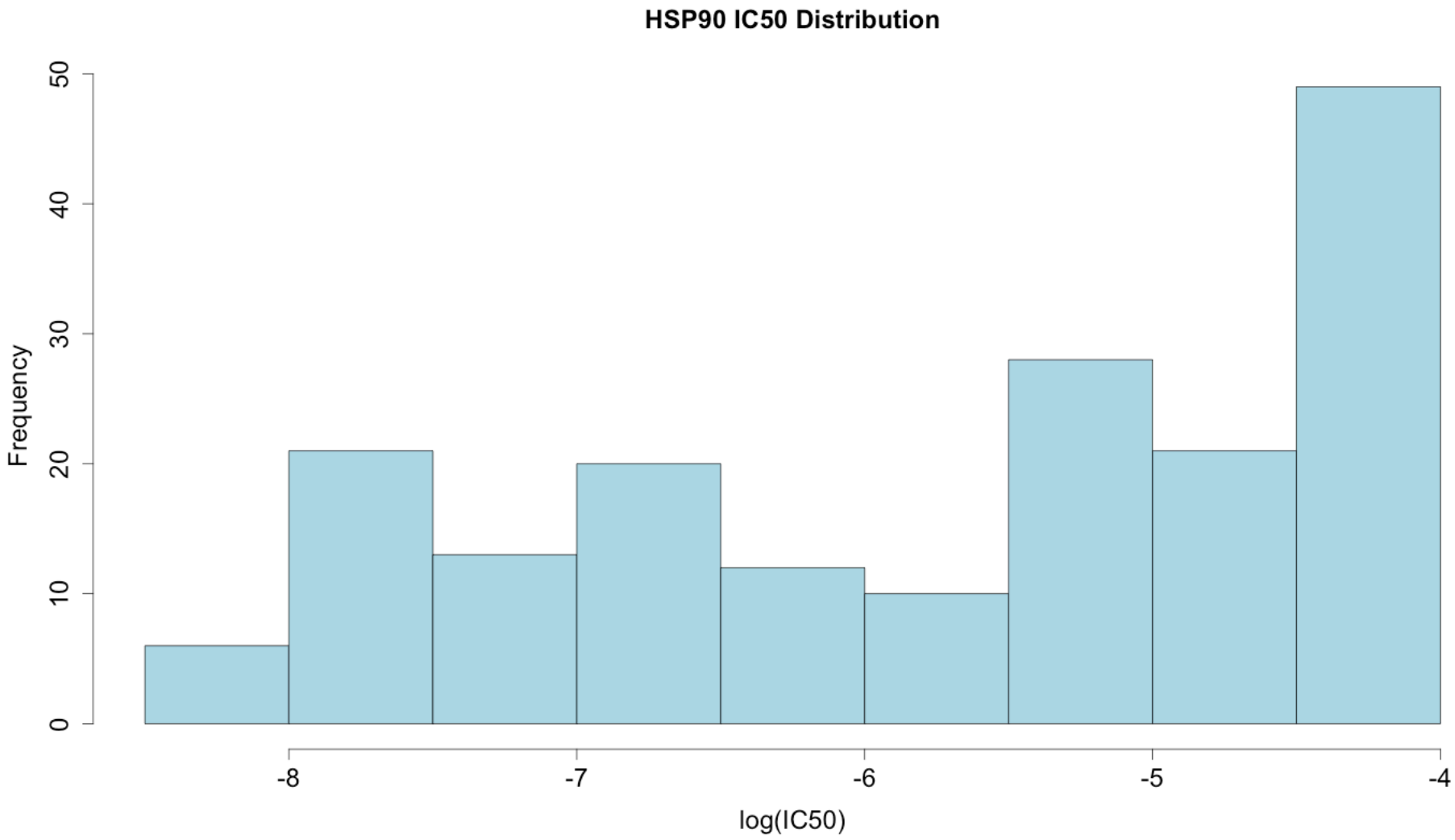


Rank Ordering

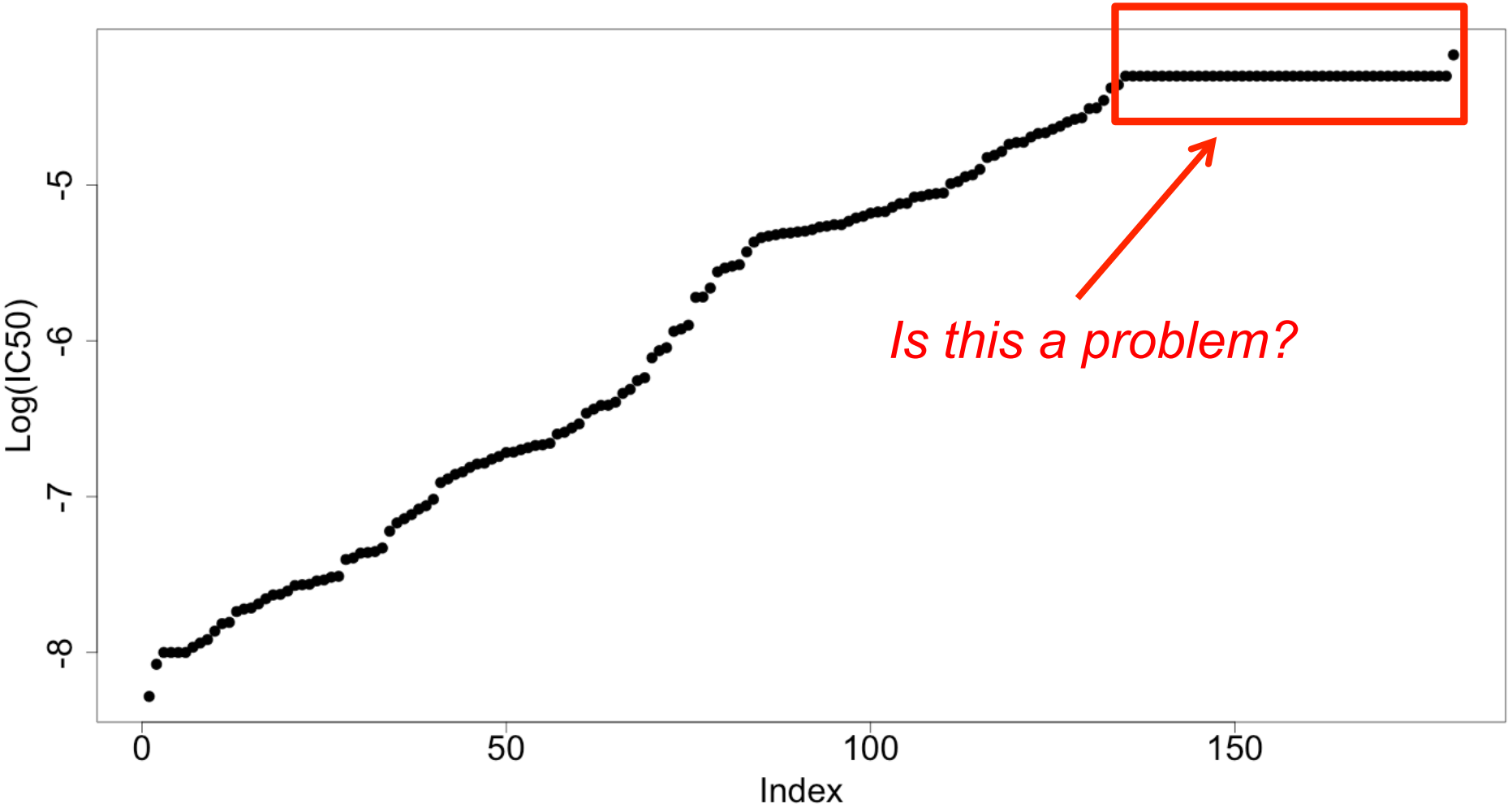
HSP90



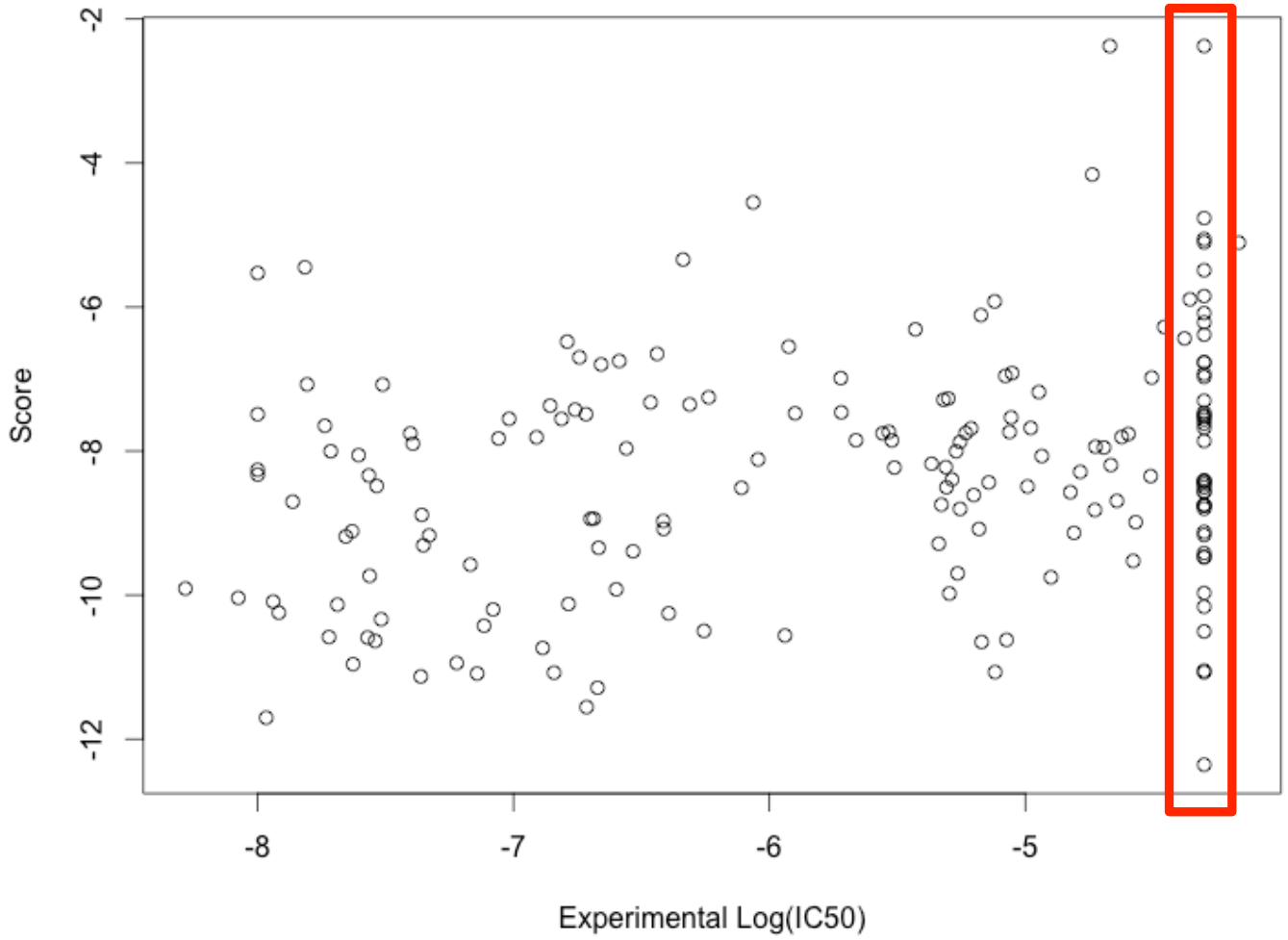
HSP90 Activity Distribution



HSP90 Activity Distribution



Drop the Inactive Compounds?



Can we regress the HSP90 dataset?

- Many compounds with the same activity
  - 48 inactive compounds
  - Activities not evenly distributed
- How will different ranks for the same activity affect correlation?

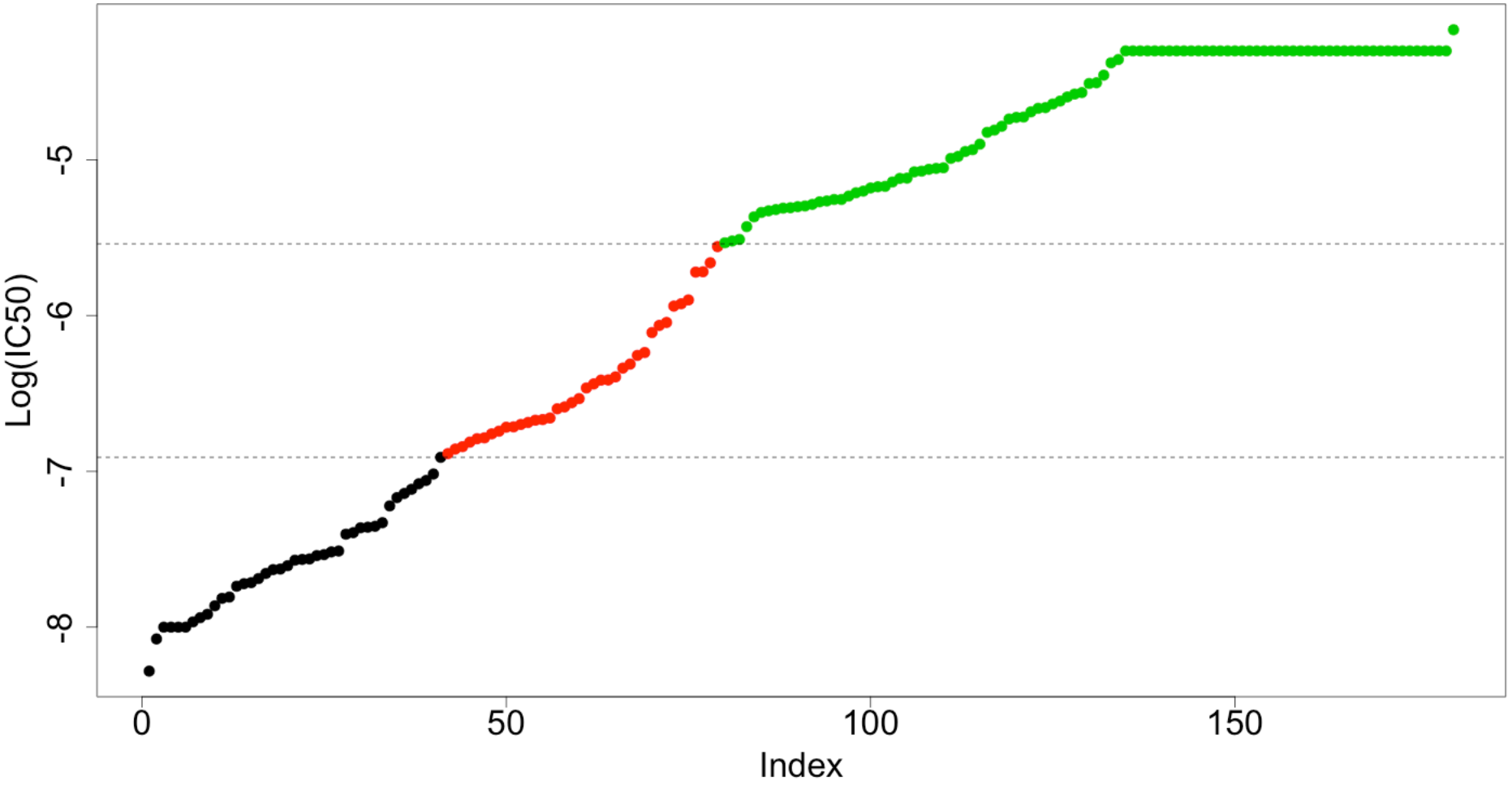
VERTEX

Simulate Activity Prediction

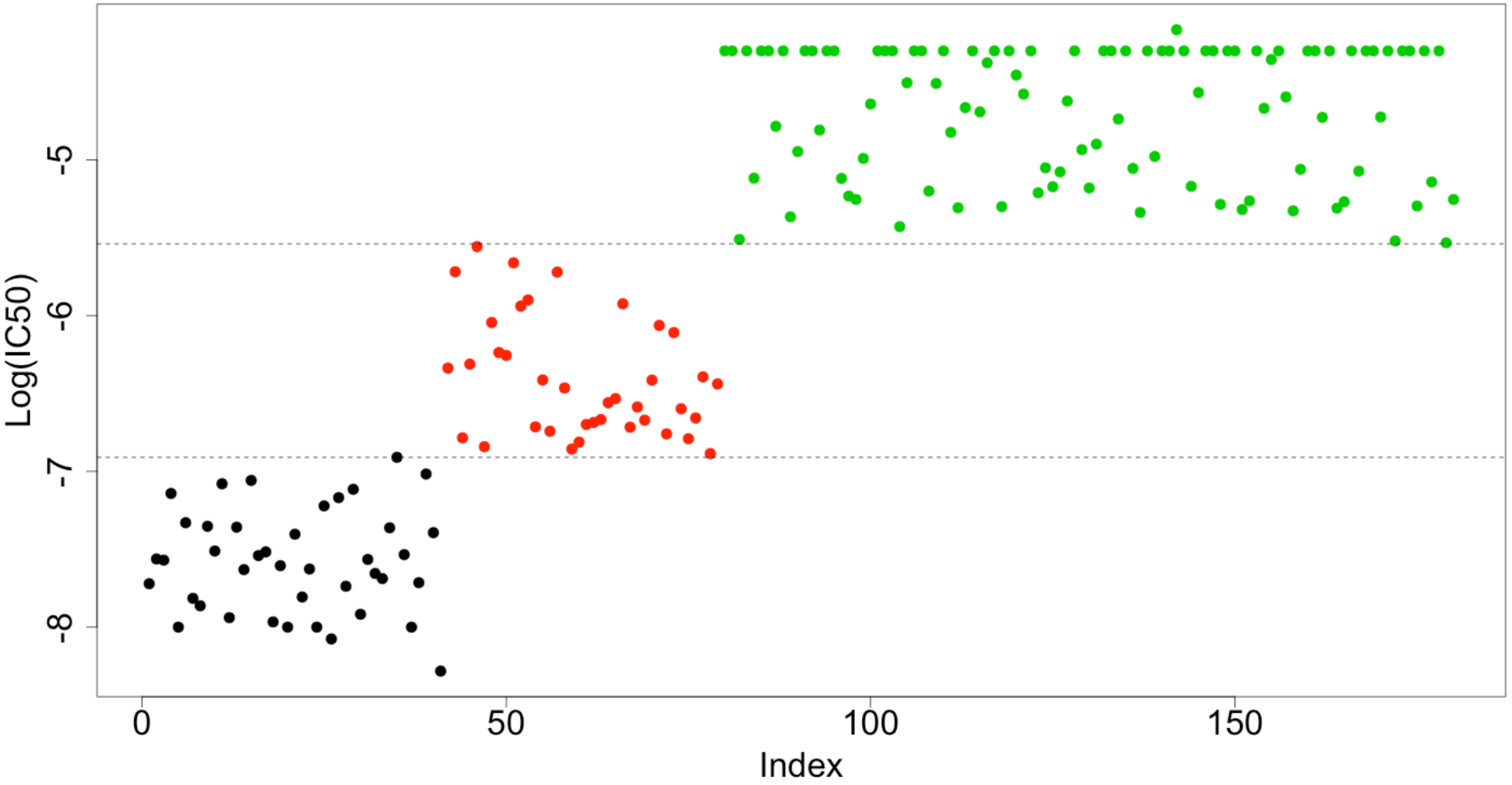
- Divide ranks into bins based on activity
  - 3 to 10 bins
- Permute ranks within bins
- Calculate correlations between initial and permuted bins

VERTEX

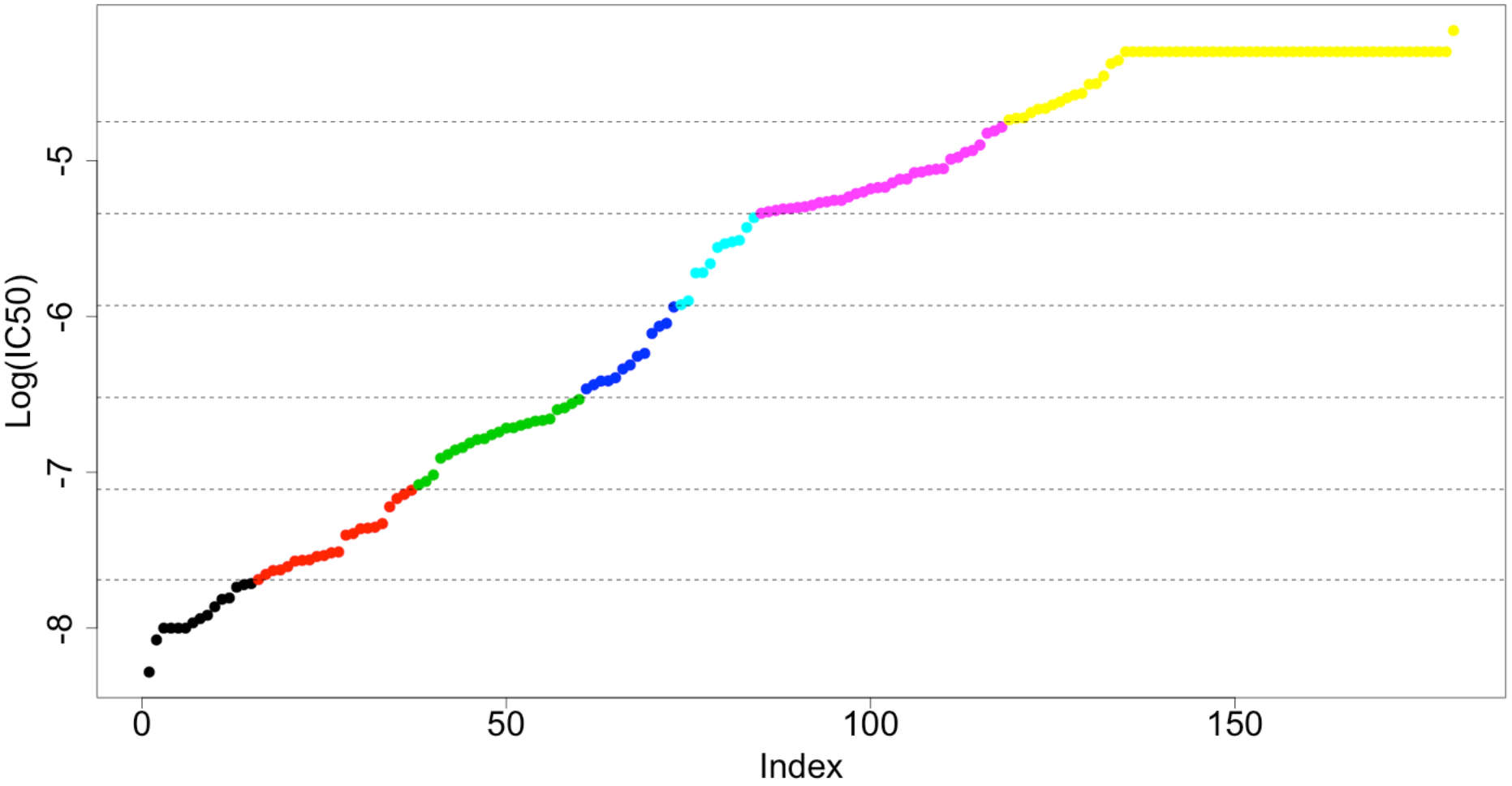
Divide Data Into 3 Bins



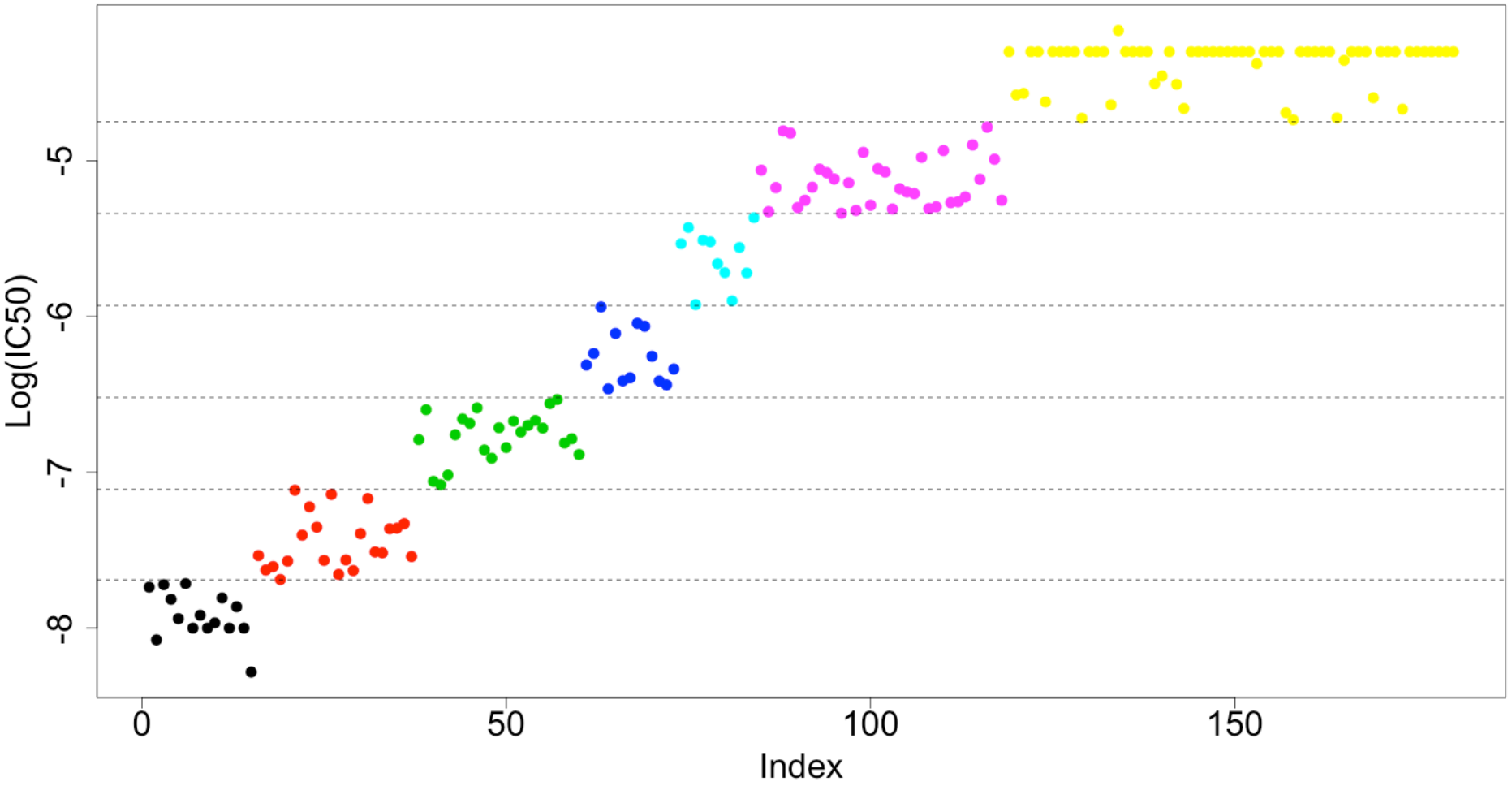
Permute Within the Bins



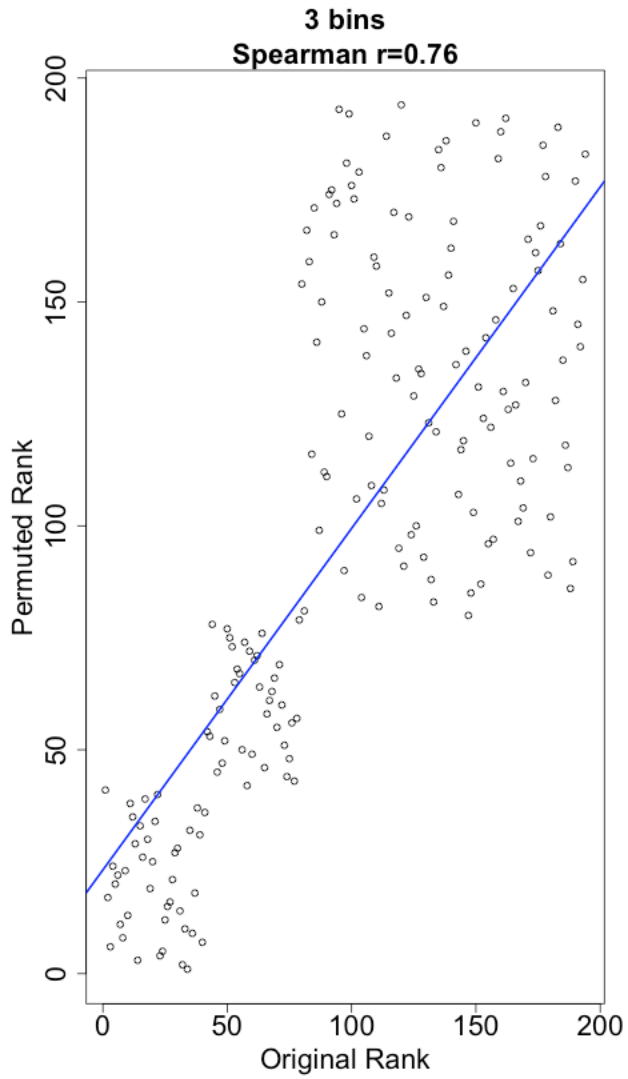
Divide Data Into 7 Bins

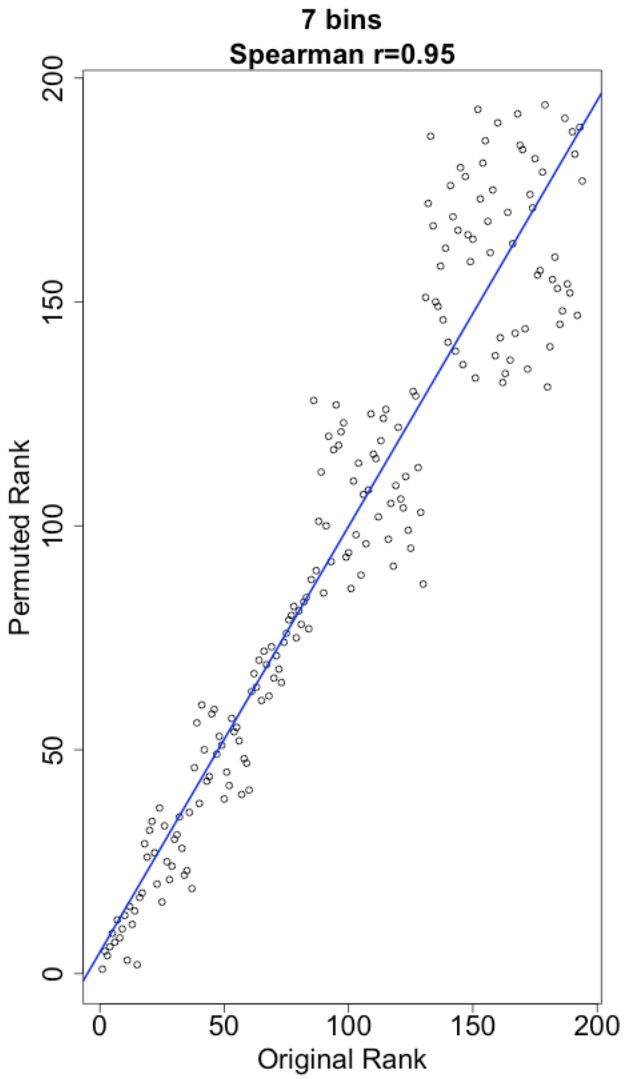


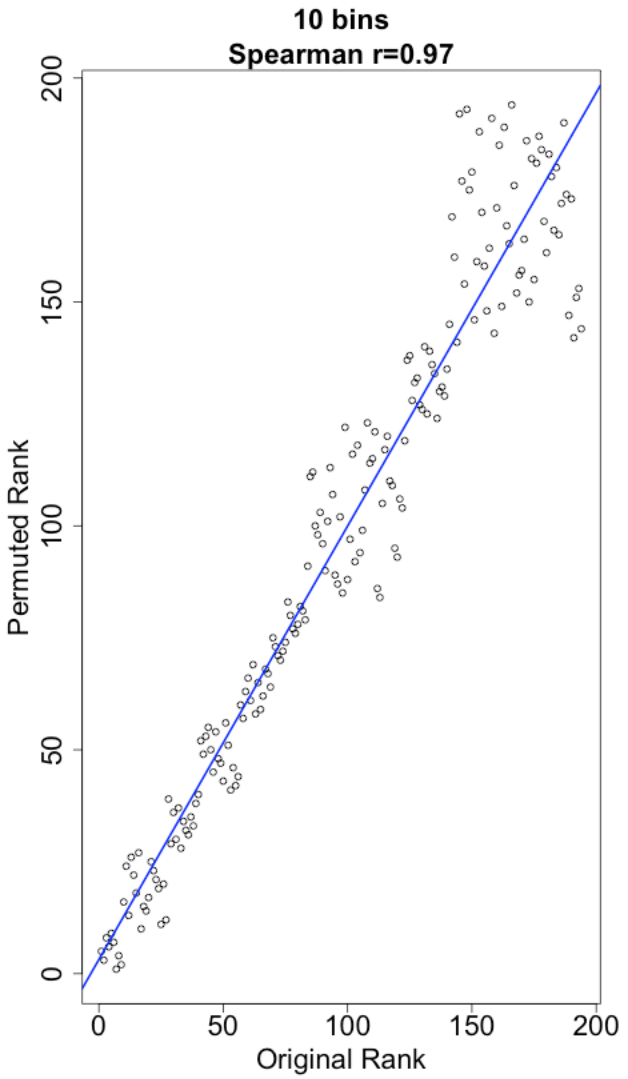
Permute Within 7 Bins



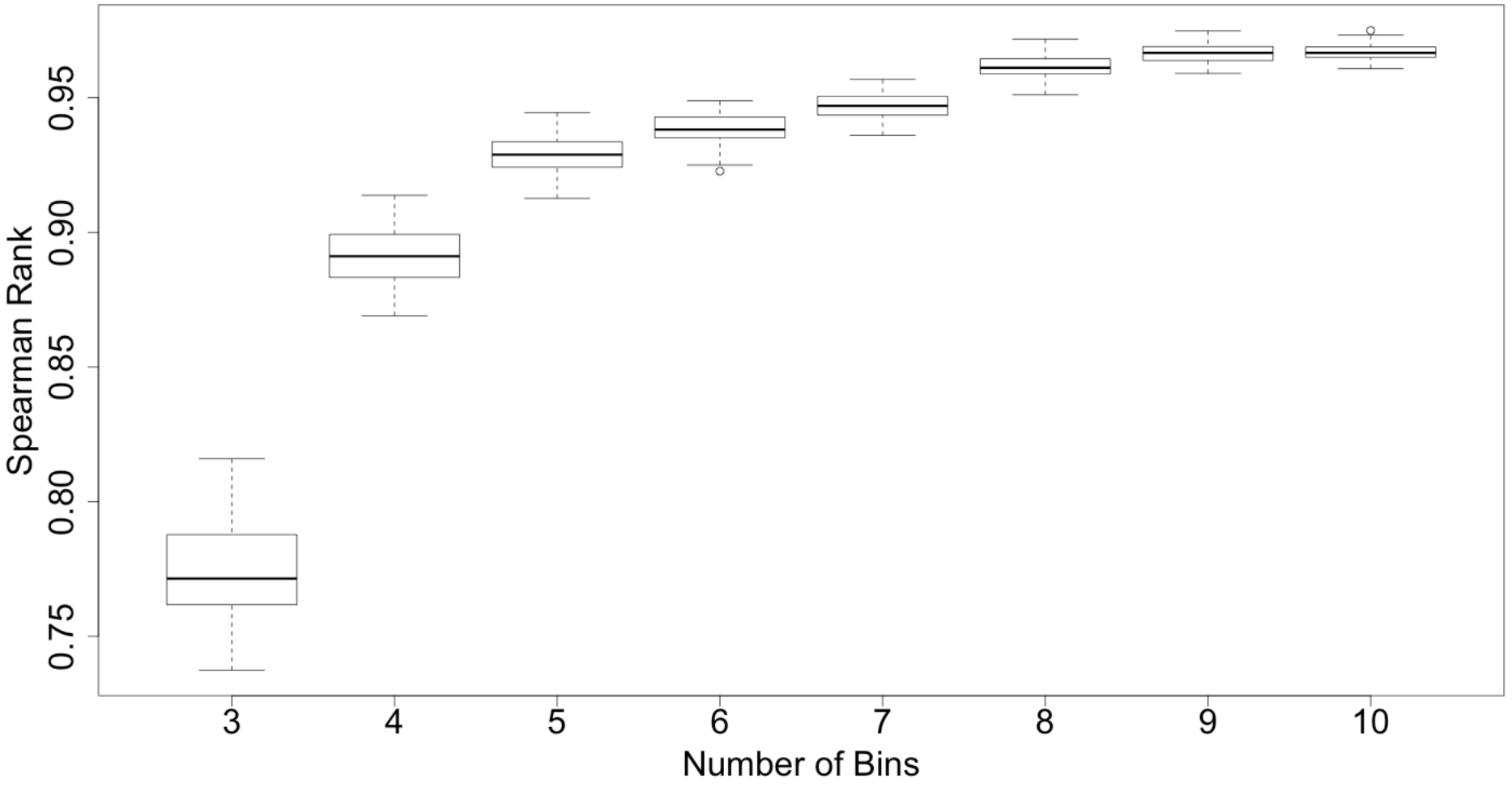
Impact of Binning on Correlation







Reasonable Correlations Are Achievable



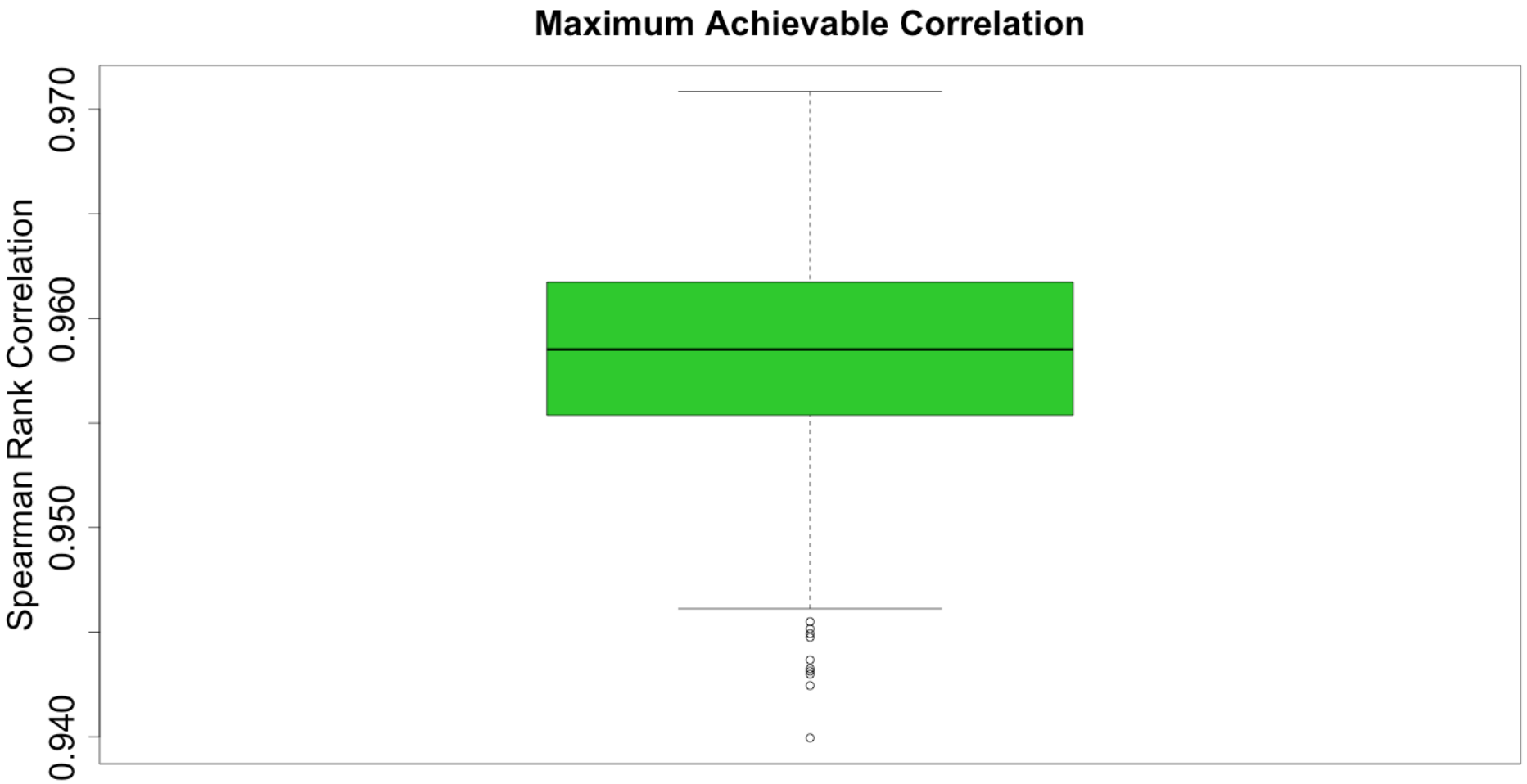
Maximum Achievable Correlation

- Start with experimental data
- Add Gaussian error
  - Mean = 0.0
  - Standard deviation = 0.3 log
- Calculation correlation
- Repeat 1000 times

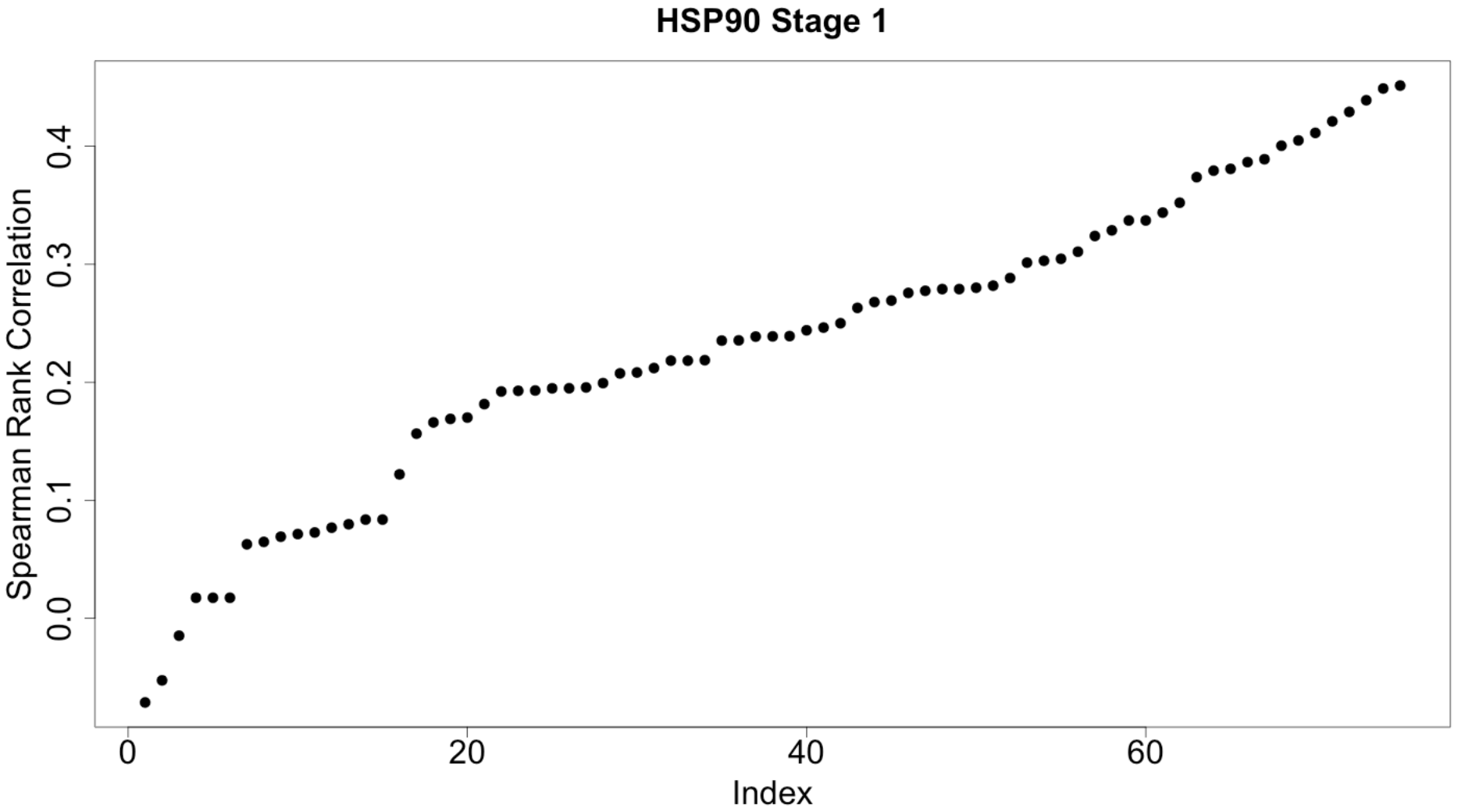
Brown, Scott P., Steven W. Muchmore, and Philip J. Hajduk. "Healthy skepticism: assessing realistic model performance." *Drug Discovery Today* 14.7 (2009): 420-427.

VERTEX

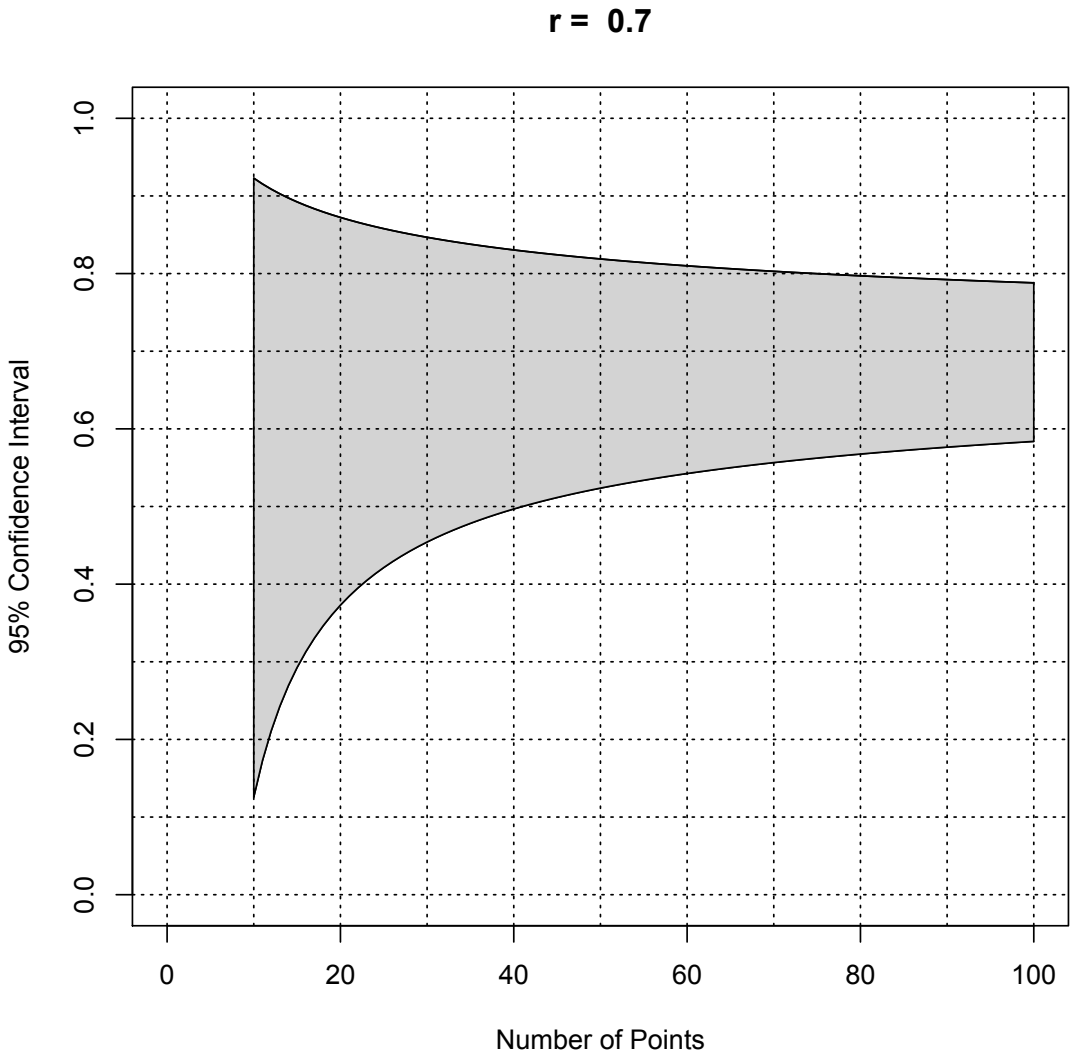
Maximum Achievable Correlation for HSP90



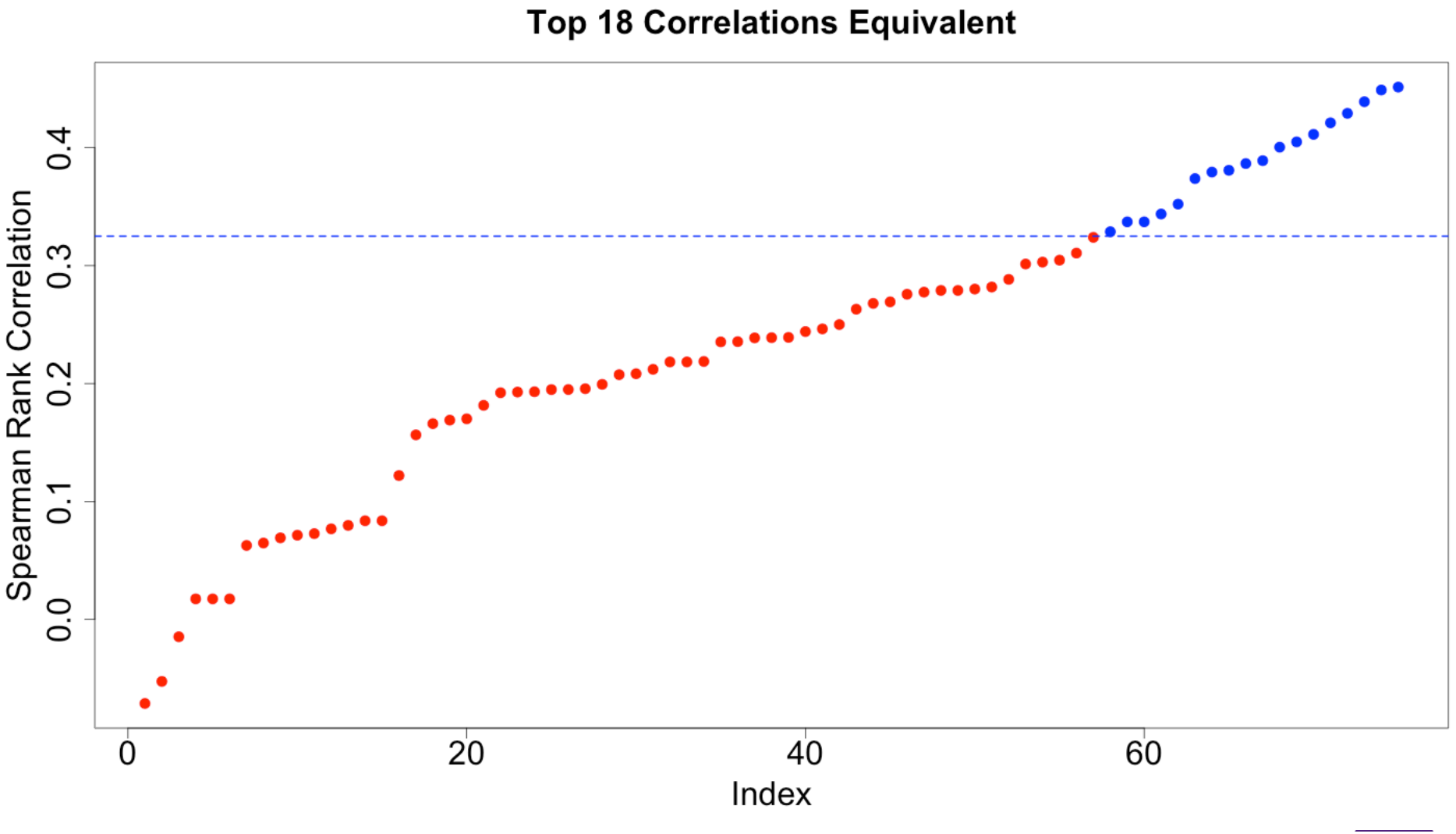
HSP90 Stage 1 Rank Correlations



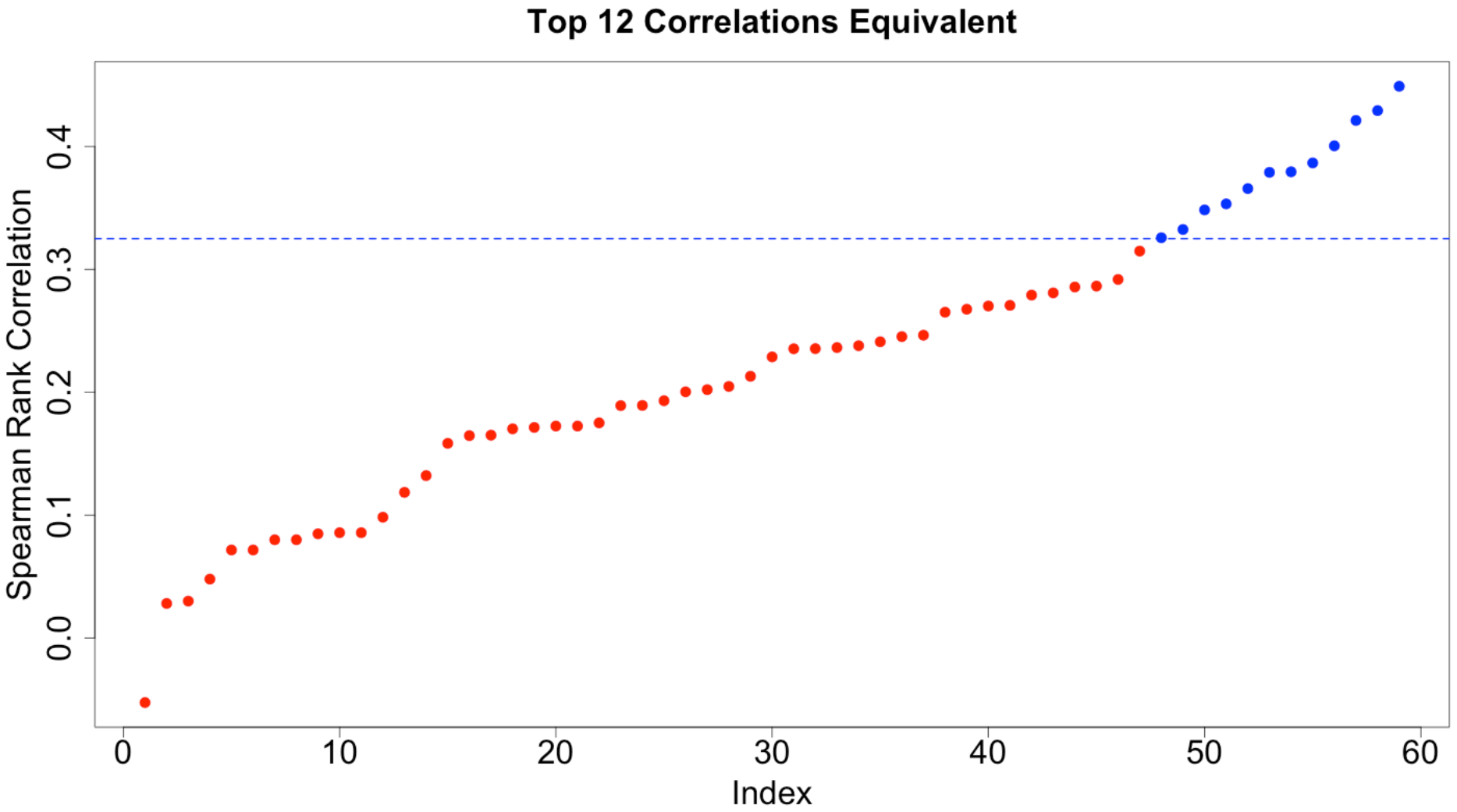
Remember That Correlations Have Confidence Intervals



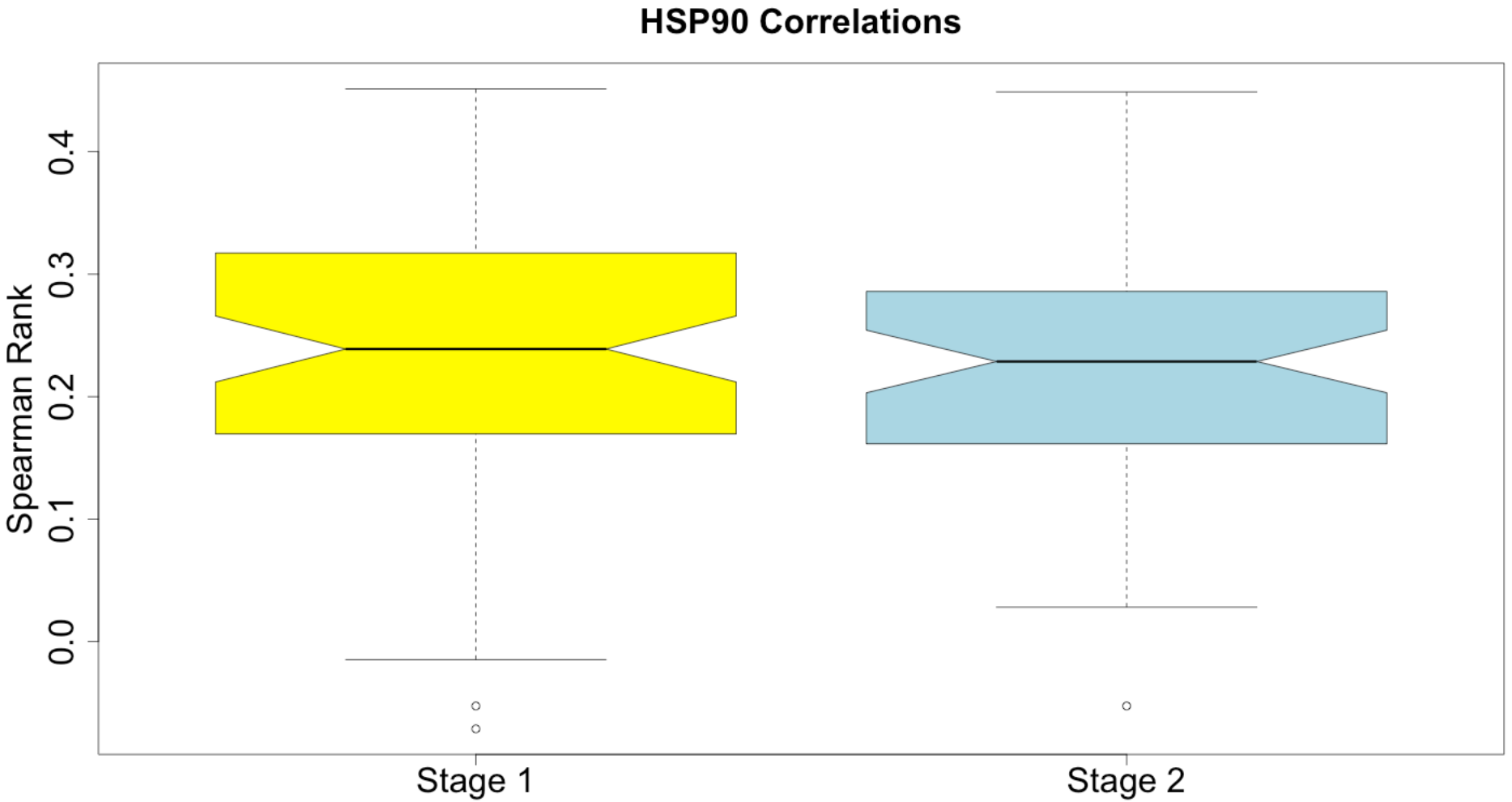
Comparing HSP90 Stage1 Correlations



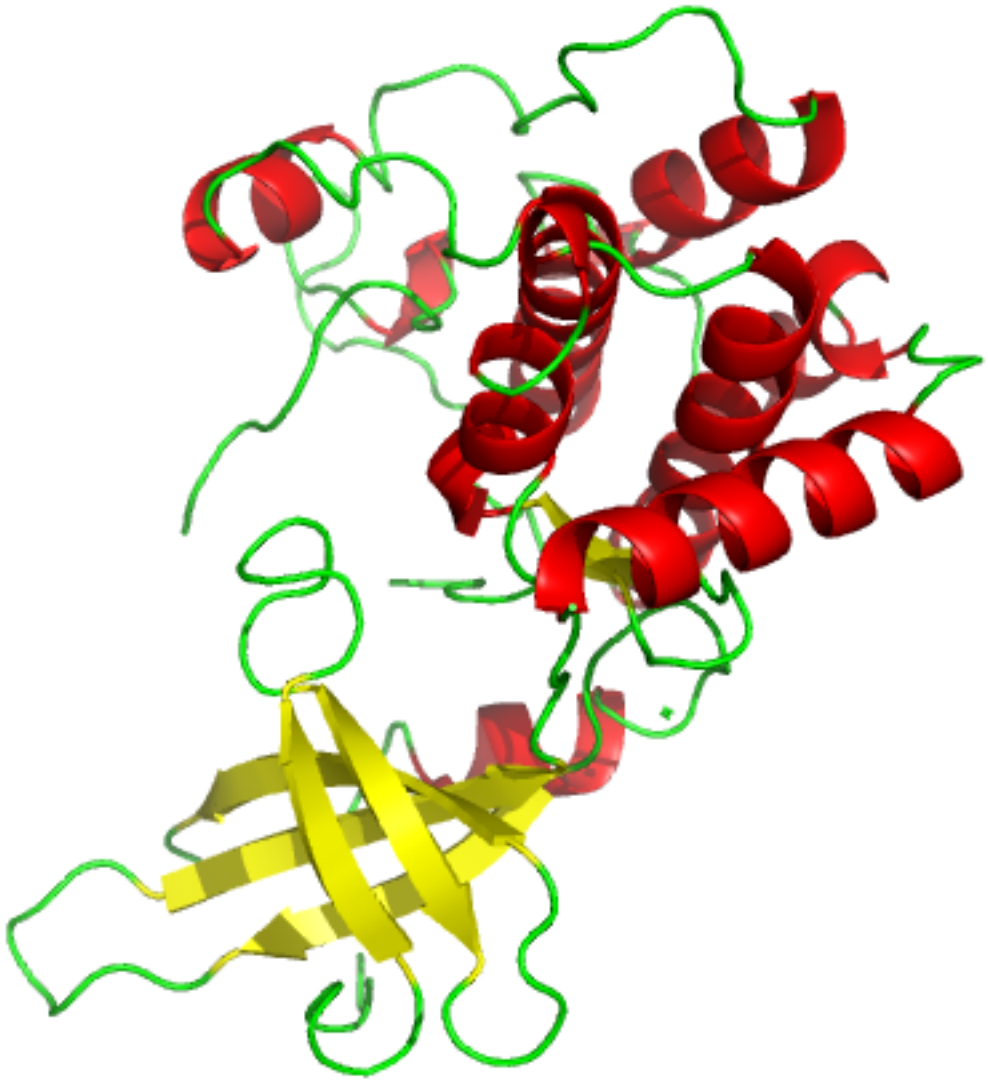
Comparing HSP90 Stage 2 Correlations



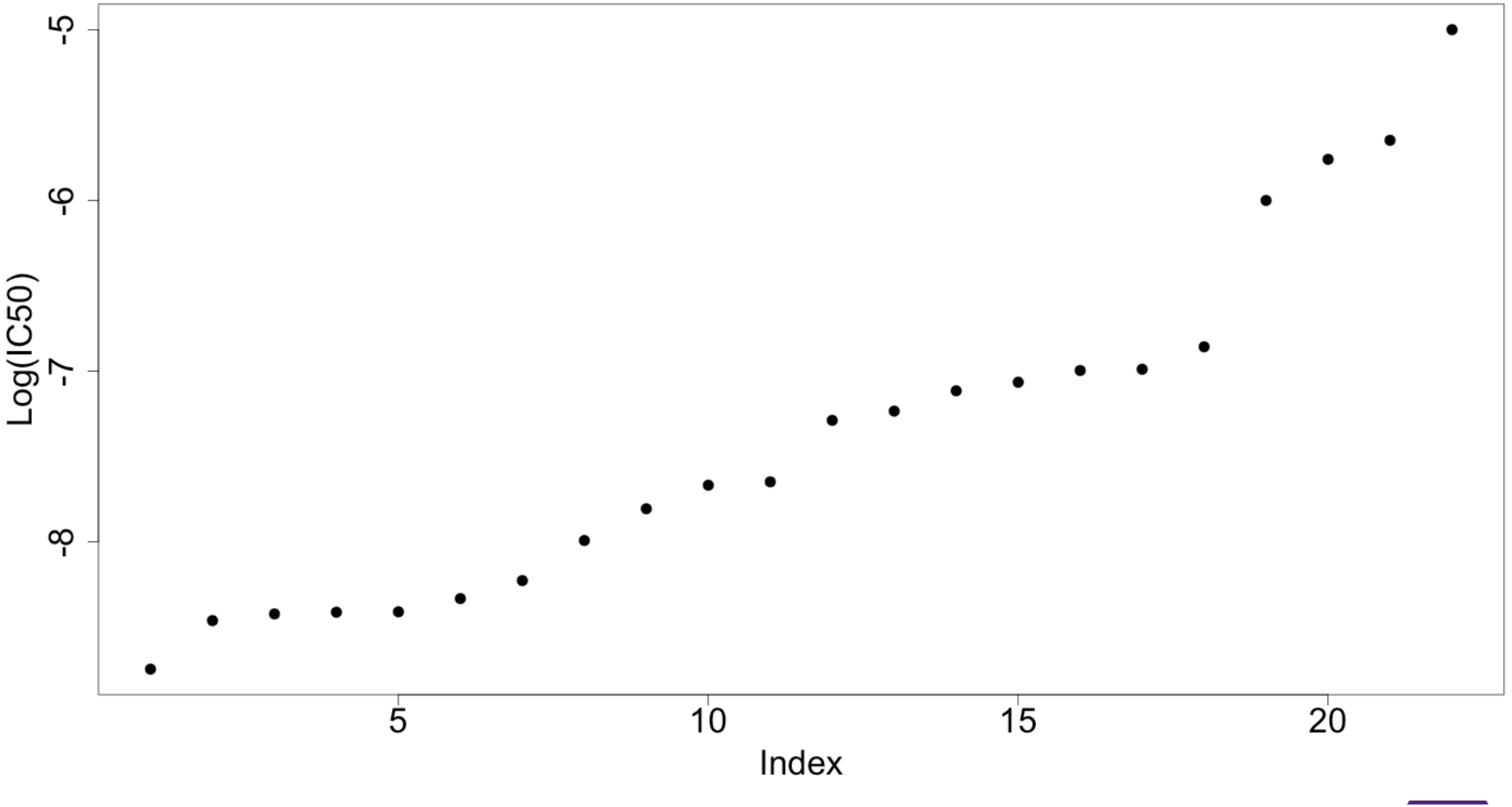
Similar Performance Between Stage 1 and Stage 2



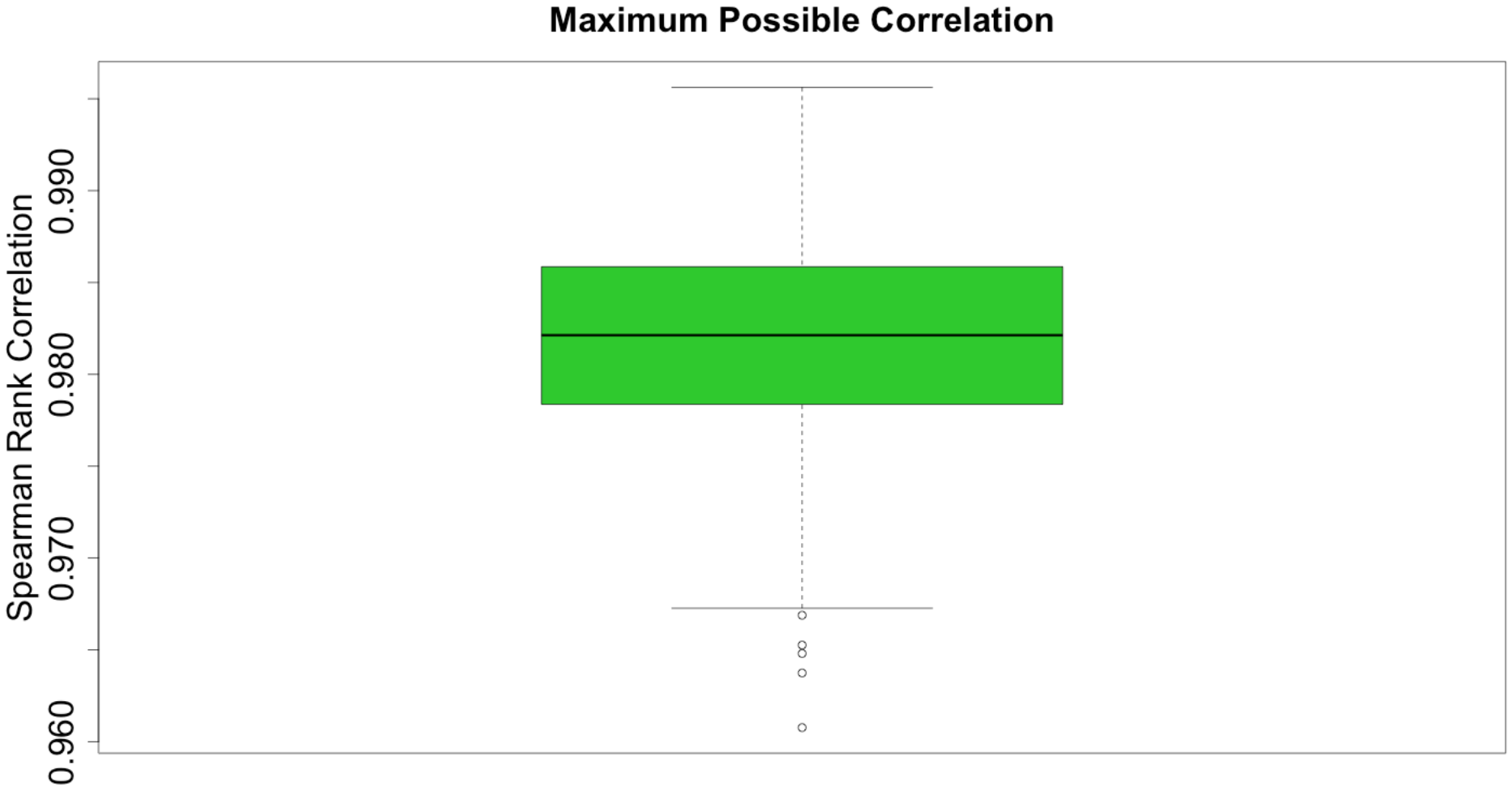
MAP4K4



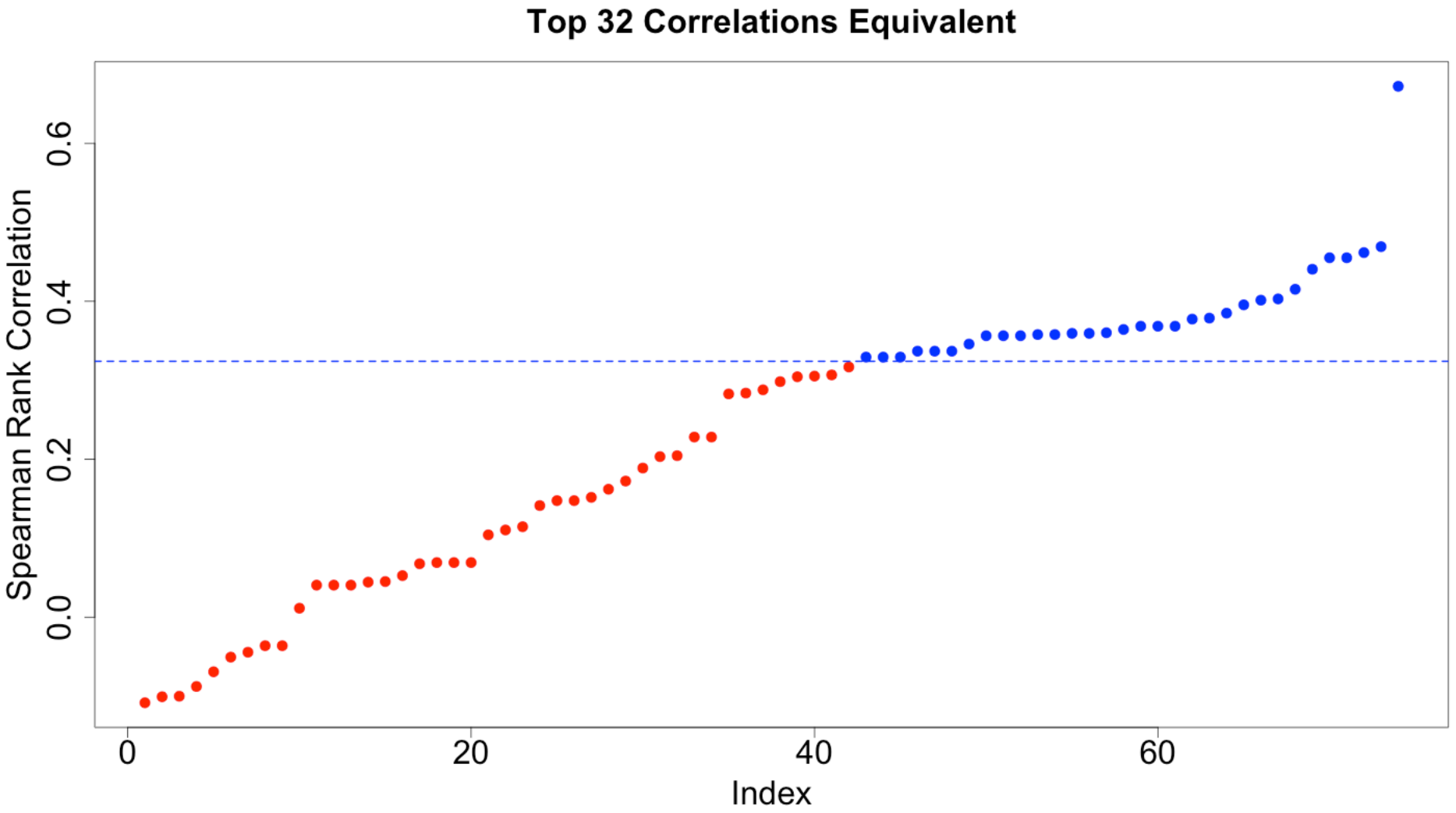
MAP4K4 Activity Distribution



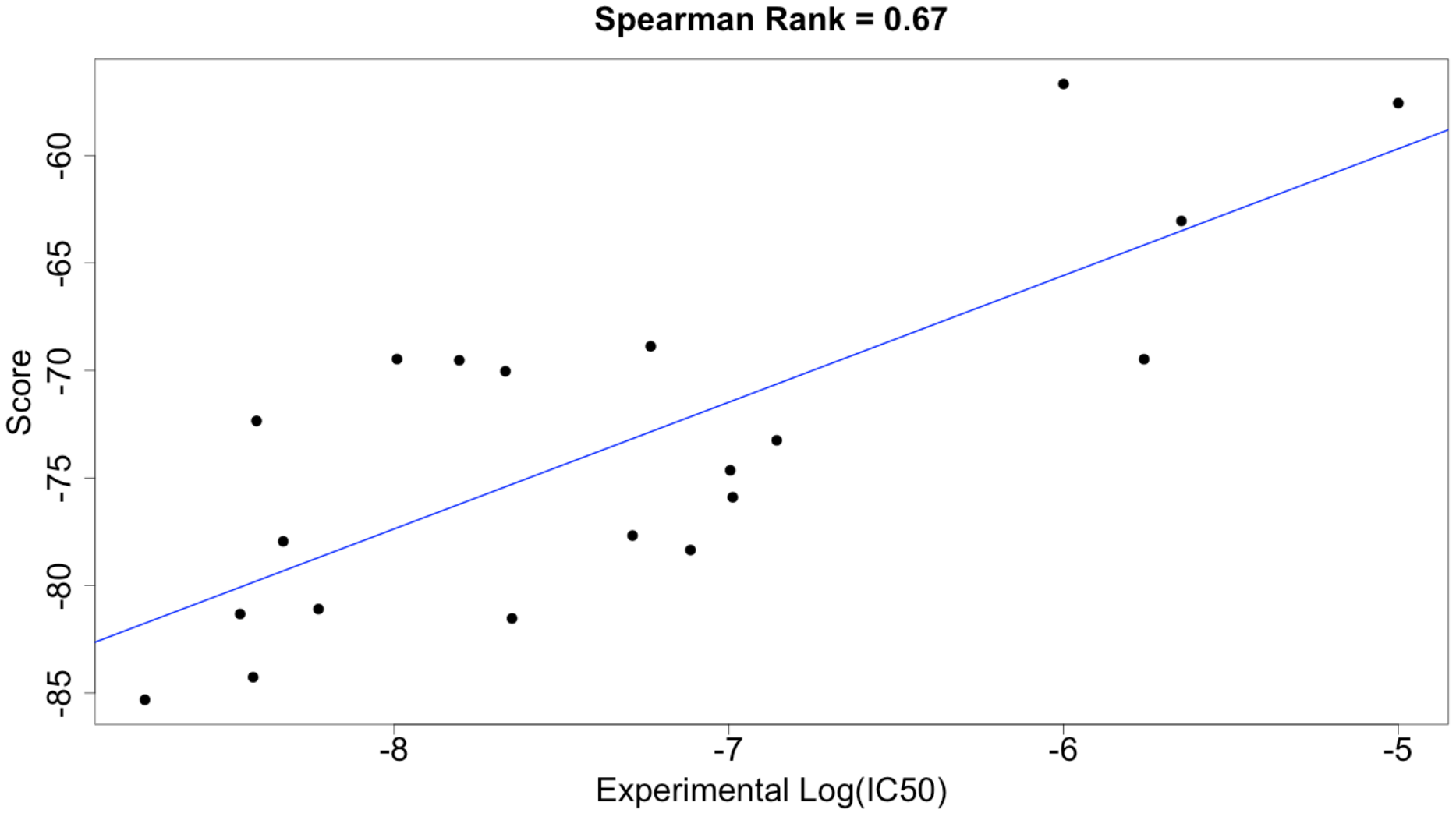
Maximum Achievable Correlation for MAP4K4



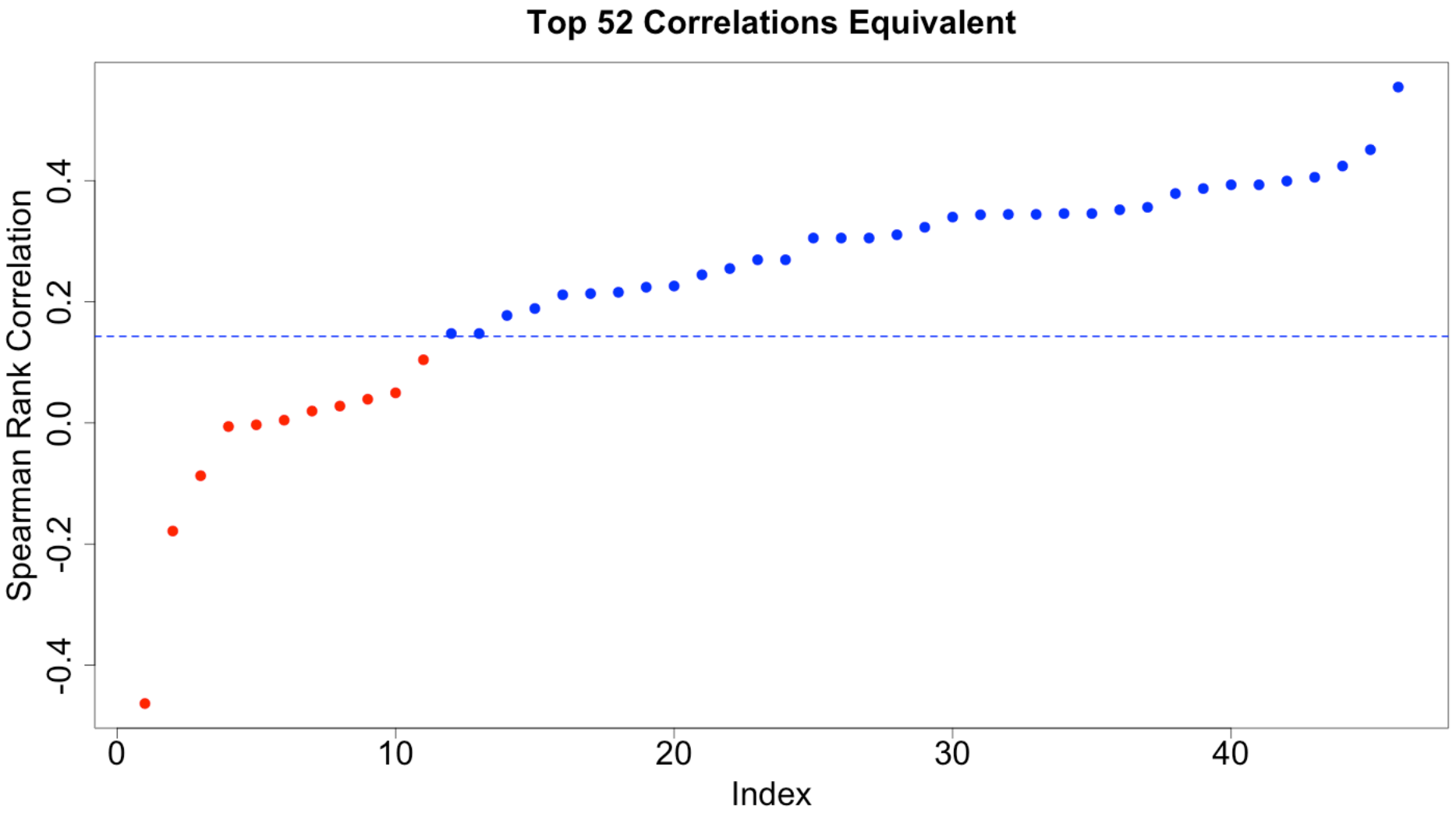
Comparing MAP4K4 Stage1 Correlations



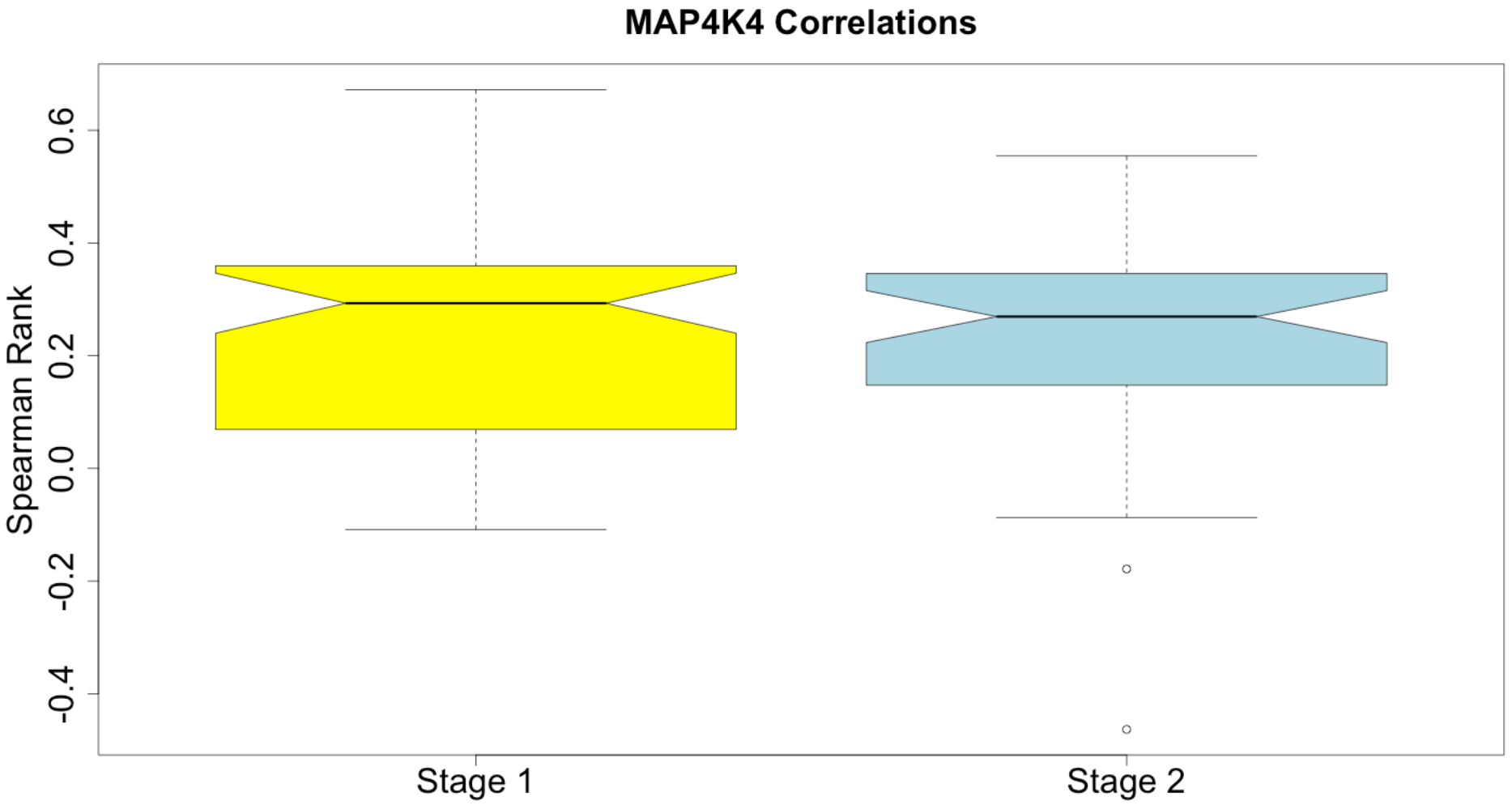
Best MAP4K4 Stage 1 Correlation



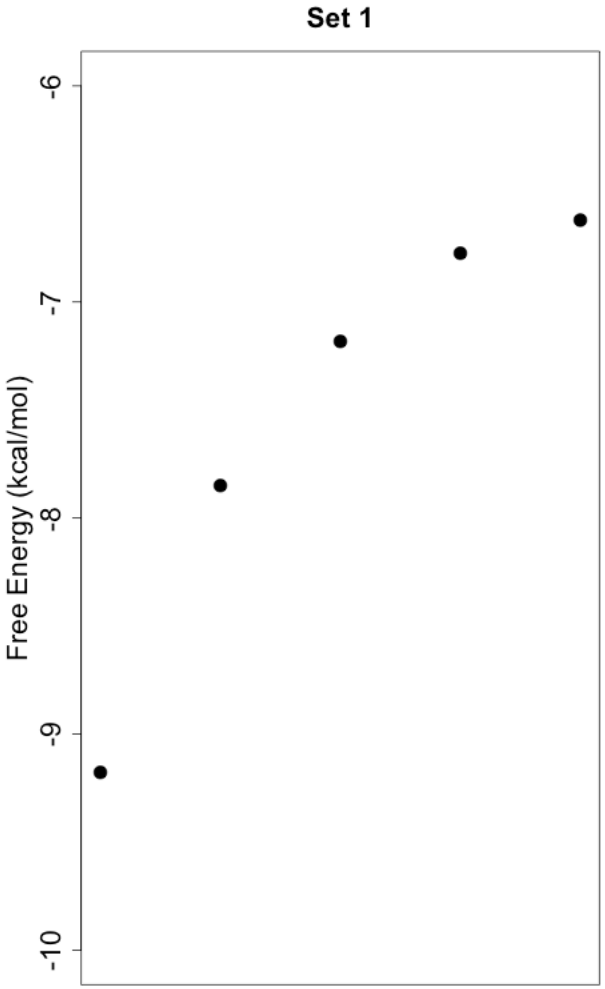
Comparing MAP4K4 Stage2 Correlations

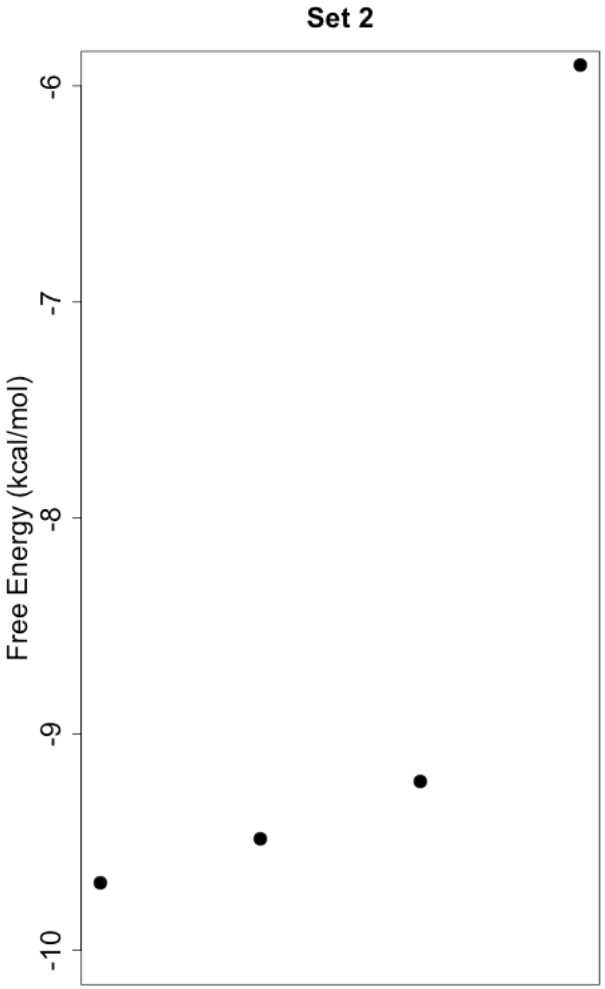


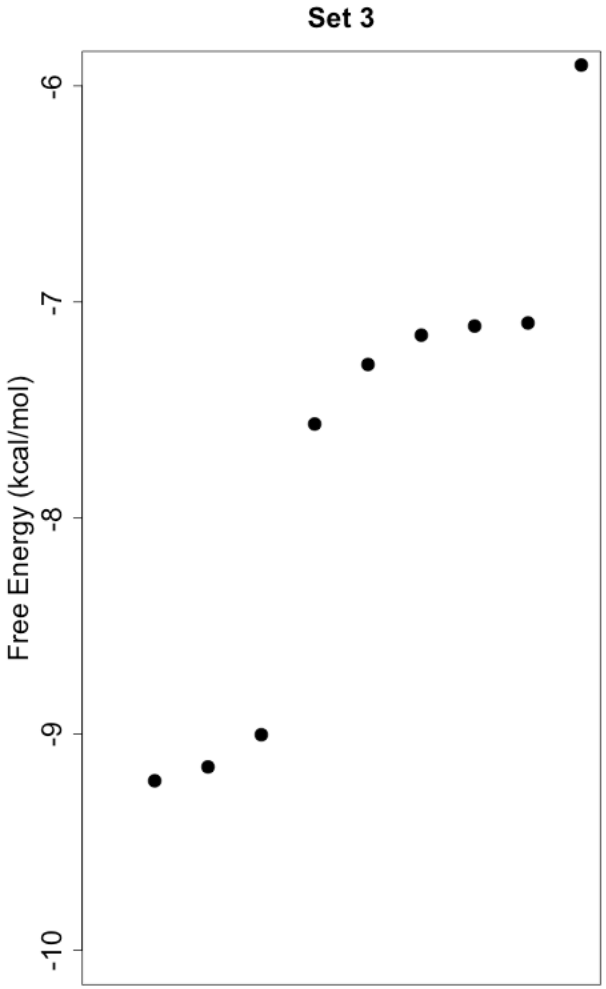
Similar Performance Between Stage 1 and Stage 2



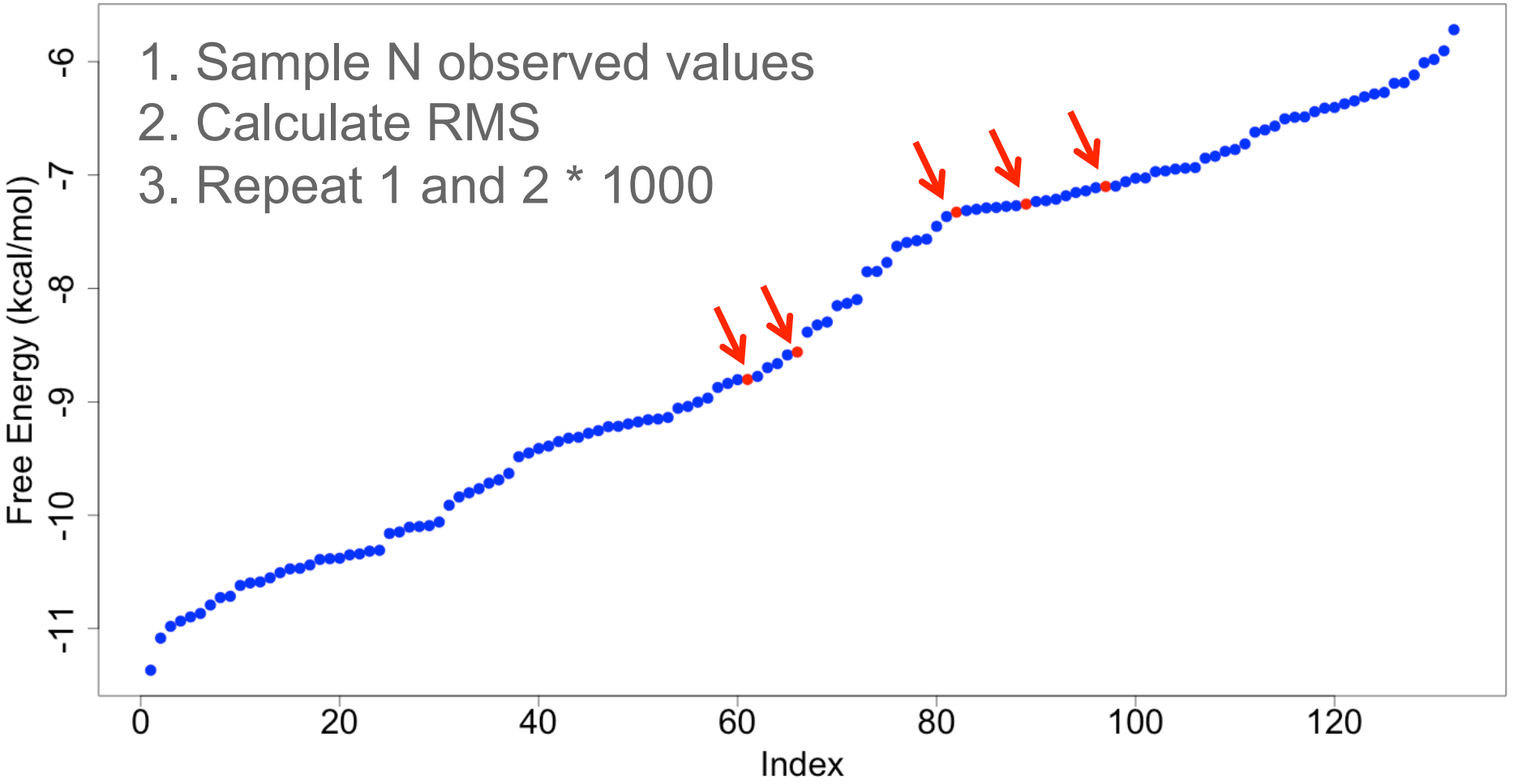
Free Energy Distributions



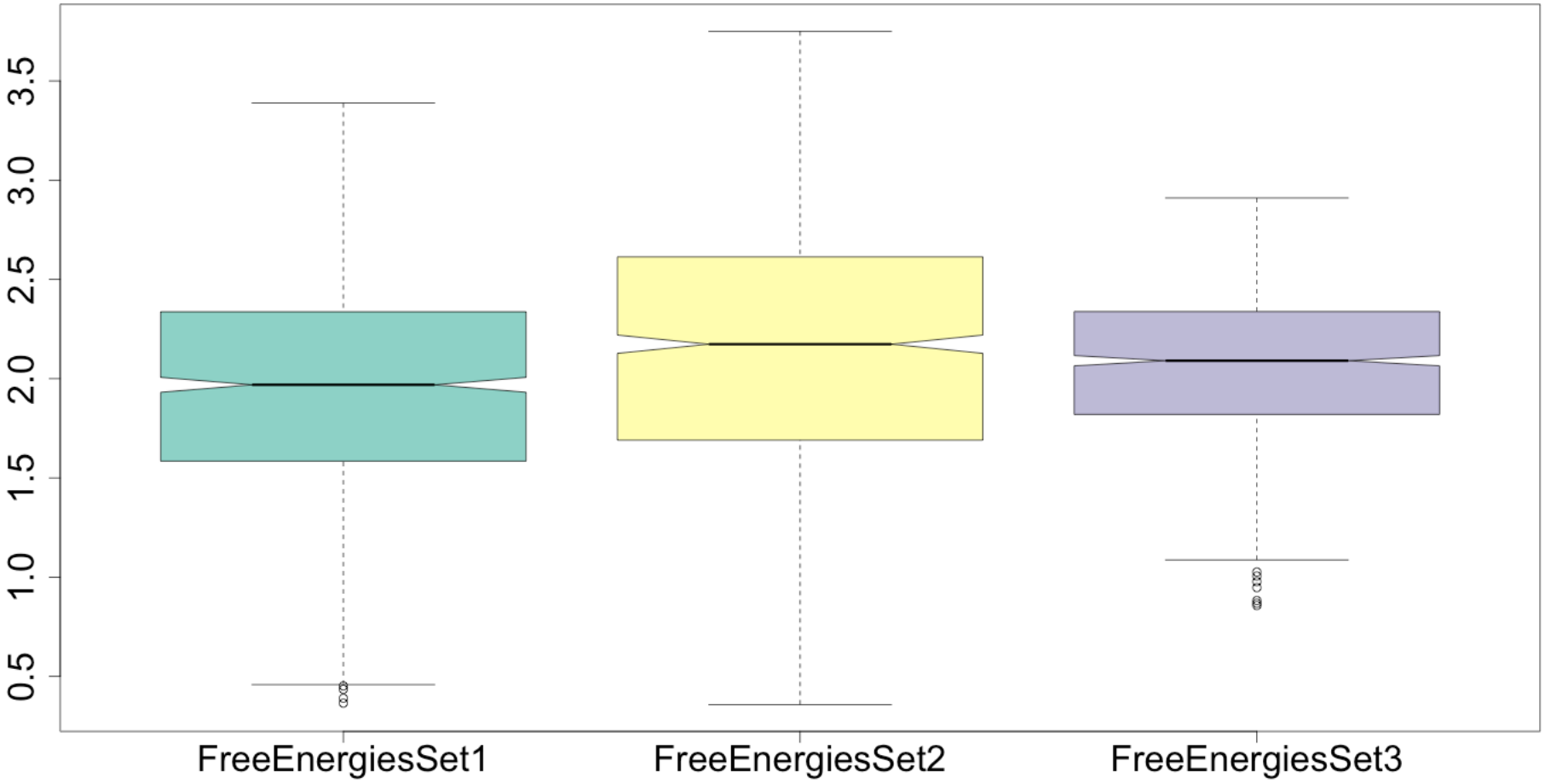




A Null Model for Free Energies?

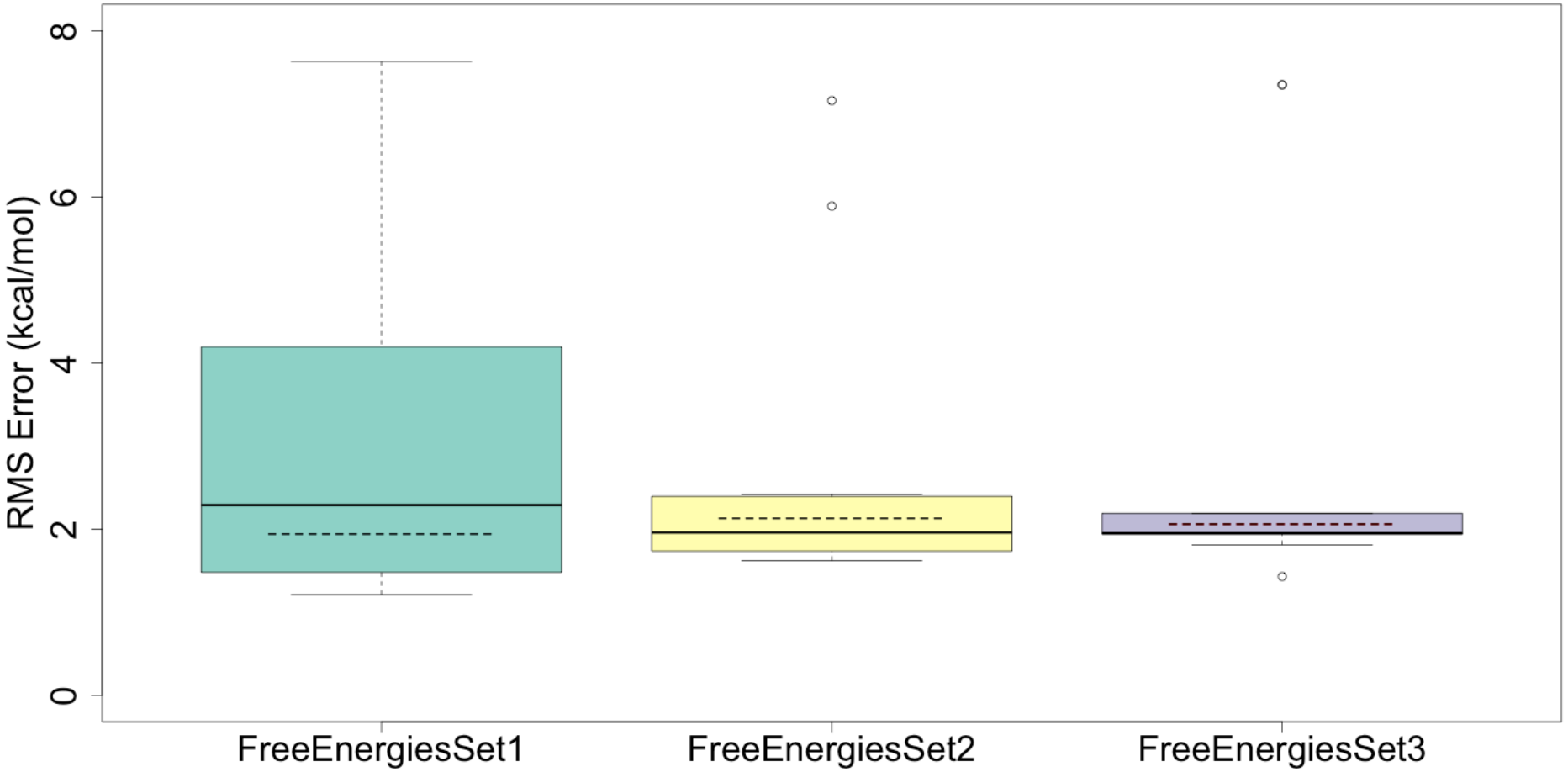


A Null Model for Free Energy

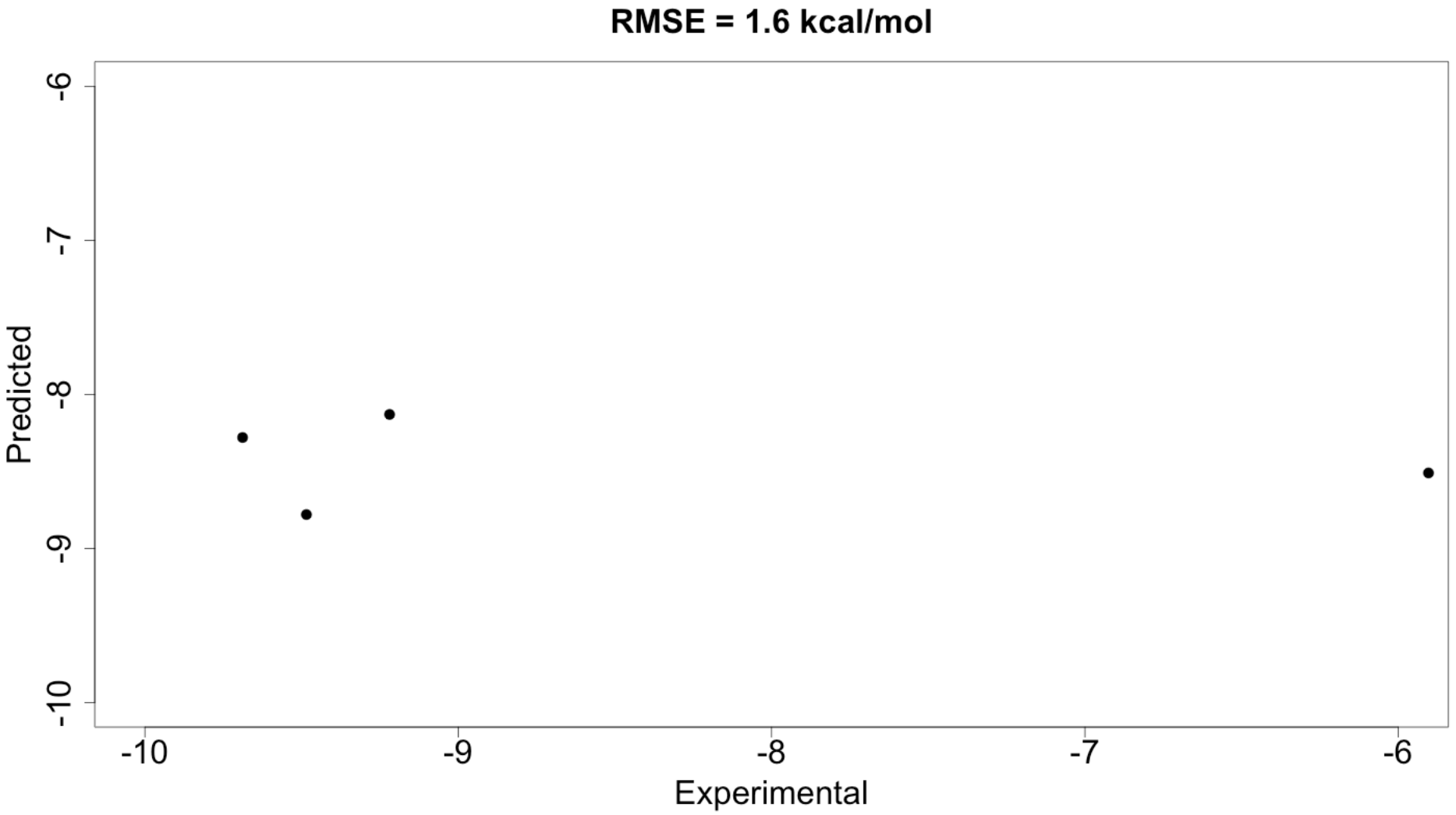


Free Energy RMS Error

Dashed line indicates the null model



Free Energy Set 2 - Lowest RMSE – Useful?



A Few Technical Issues

- PDB format makes RMS calculations difficult
- Score files were not formatted consistently
- Score files were not named consistently
- Free energy files were not named and formatted consistenly

VERTEX

Improperly Formatted PDB files

Incorrect

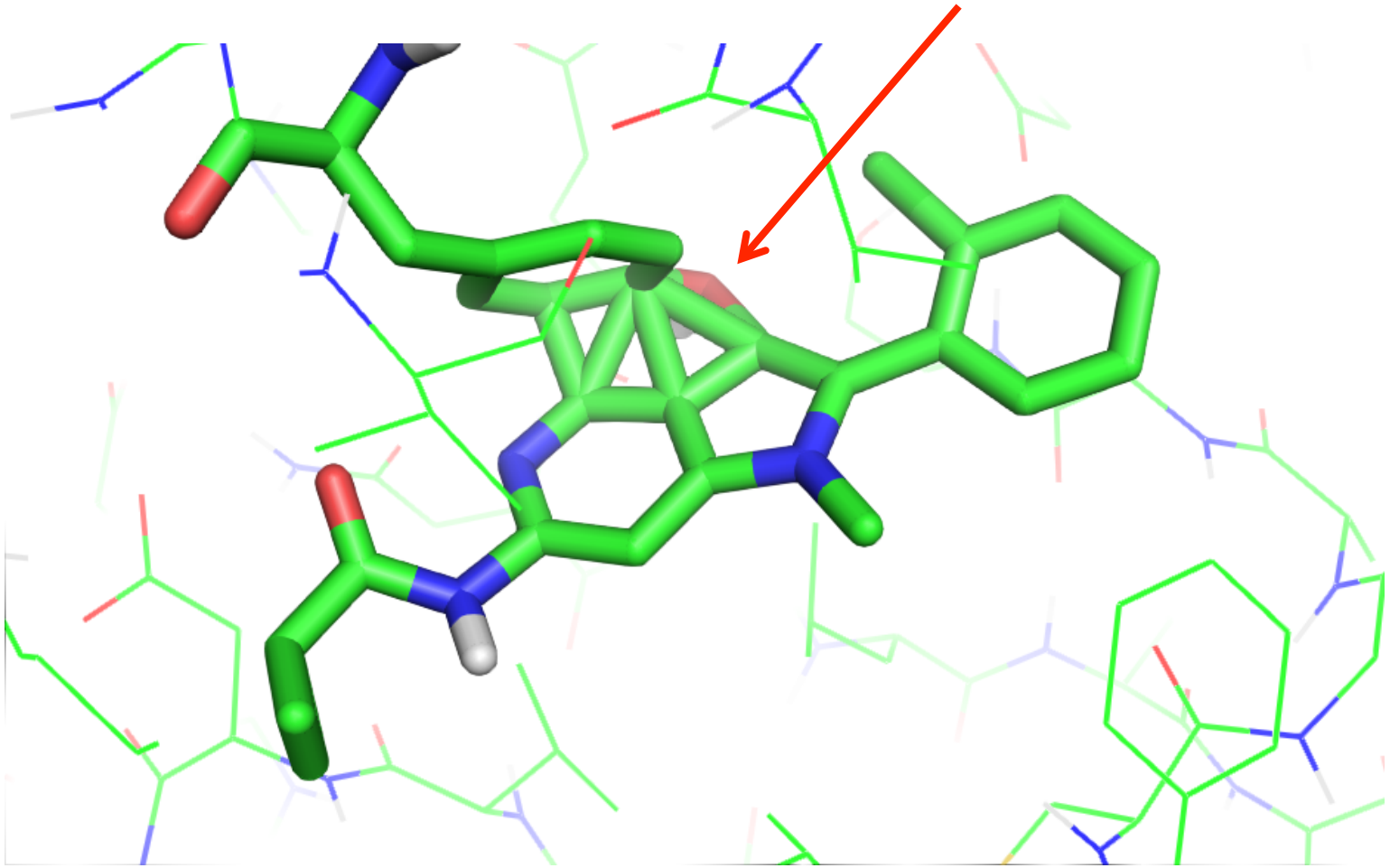
```
ATOM   3273  C11 LIG   208      -1.480   8.493  28.087  1.00  0.00      SYST C
ATOM   3274  C12 LIG   208      -1.030   7.703  27.066  1.00  0.00      SYST C
ATOM   3275  C13 LIG   208       0.029   6.790  27.307  1.00  0.00      SYST C
ATOM   3276  C11 LIG   208       0.896  11.872  24.337  1.00  0.00      SYST C
ATOM   3277  H1  LIG   208      -5.162  10.808  25.309  1.00  0.00      SYST H
ATOM   3278  H2  LIG   208       2.002   5.790  29.700  1.00  0.00      SYST H
```

Correct

```
HETATM 1645 CL   LIG B   1       0.892  12.514  23.277  1.00 41.41          Cl
HETATM 1646  C10 LIG B   1      -0.672  11.835  23.662  1.00 36.86           C
HETATM 1647  C9  LIG B   1      -0.816  11.109  24.823  1.00 35.88           C
HETATM 1648  H6  LIG B   1       0.077  10.810  25.369  0.00 35.70           H
HETATM 1649  C11 LIG B   1      -1.752  12.136  22.857  1.00 33.25           C
HETATM 1650  H7  LIG B   1      -1.608  12.683  21.929  0.00 33.13           H
HETATM 1651  C12 LIG B   1      -3.015  11.729  23.256  1.00 32.92           C
```

VERTEX

Can’t Infer Connectivity From Incorrect Geometry



Conclusions

- As a community we are pretty good a pose prediction
- Unfortunately ranking and free energy have ways to go
- Hopefully we can all learn from these datasets
- Hopefully we will all share what we learn
- We need to make some improvements to the submission process
- The next round should be even better

VERTEX

Acknowledgments

- Rommie Amaro
- Mike Gilson
- Vicki Feher
- Shuai Liu