RosettaLigand Docking:
Flexible Ligands, Flexible Receptors

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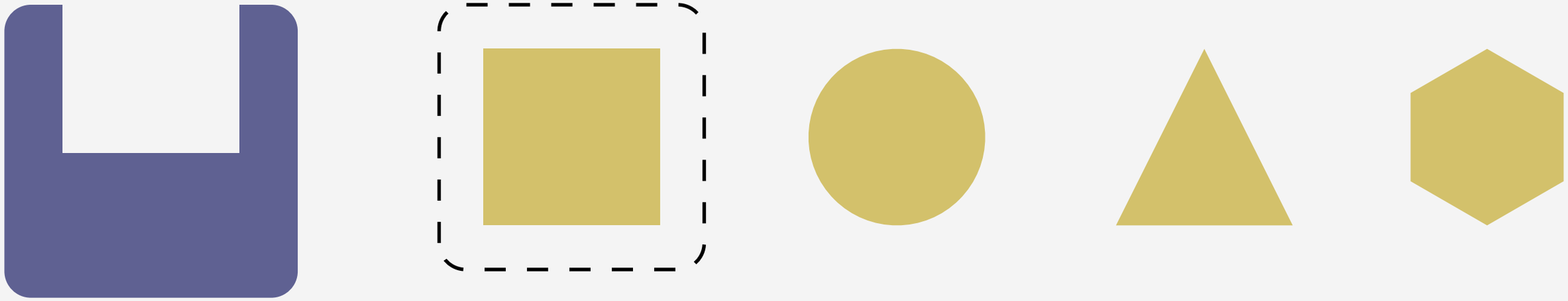
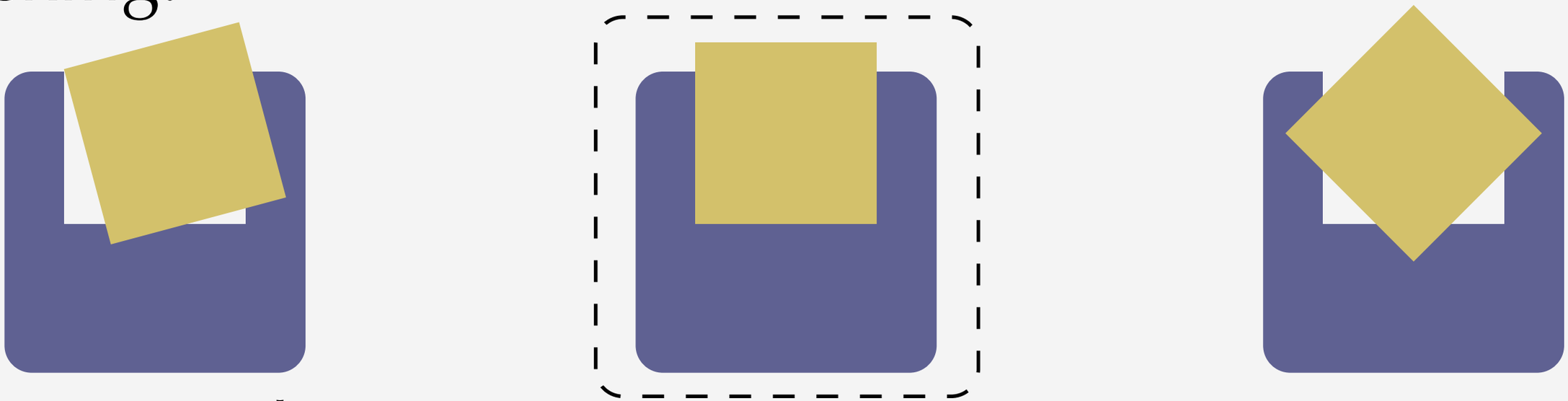
RosettaCon · 23 July 2008

Virtual Screening:



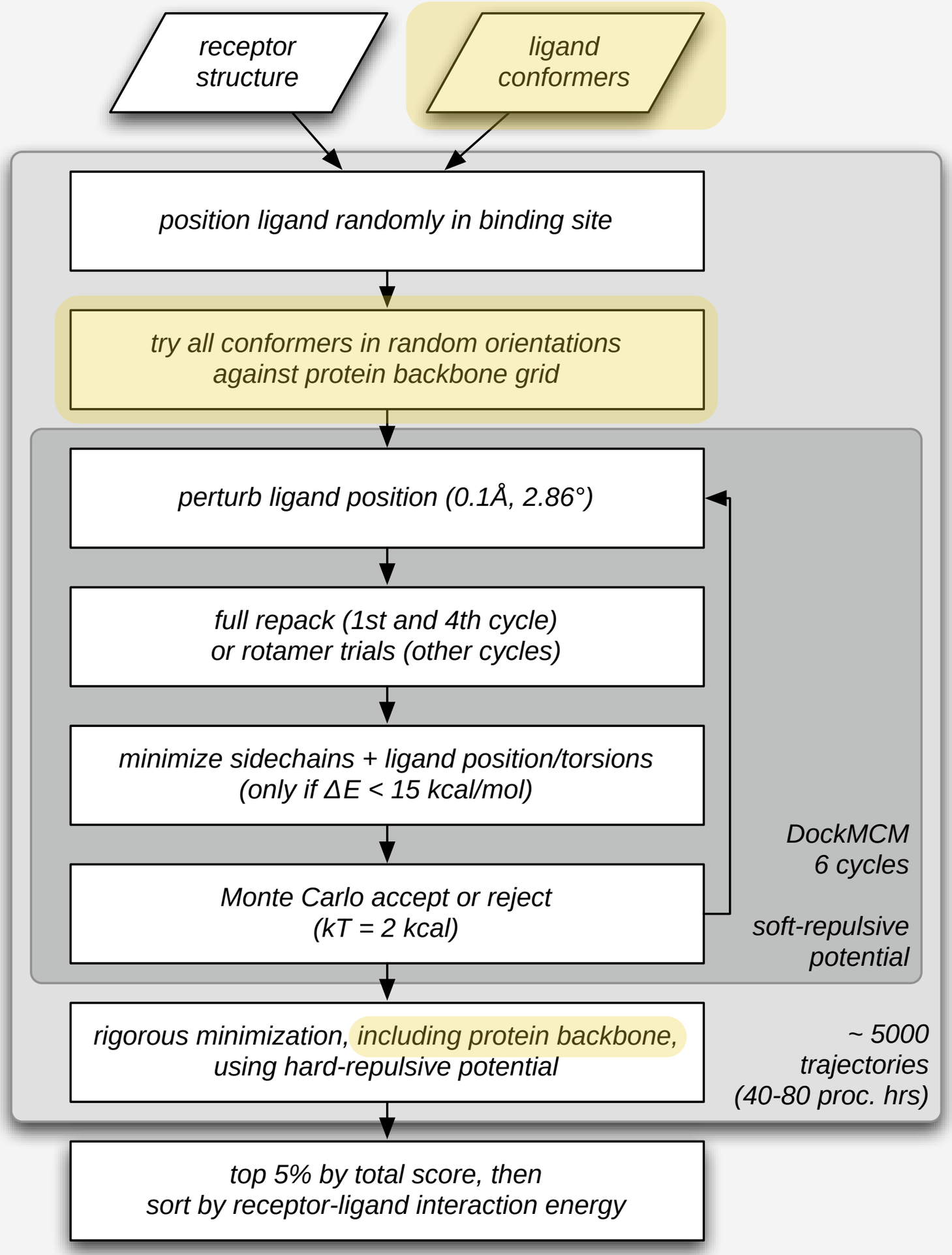
Docking:



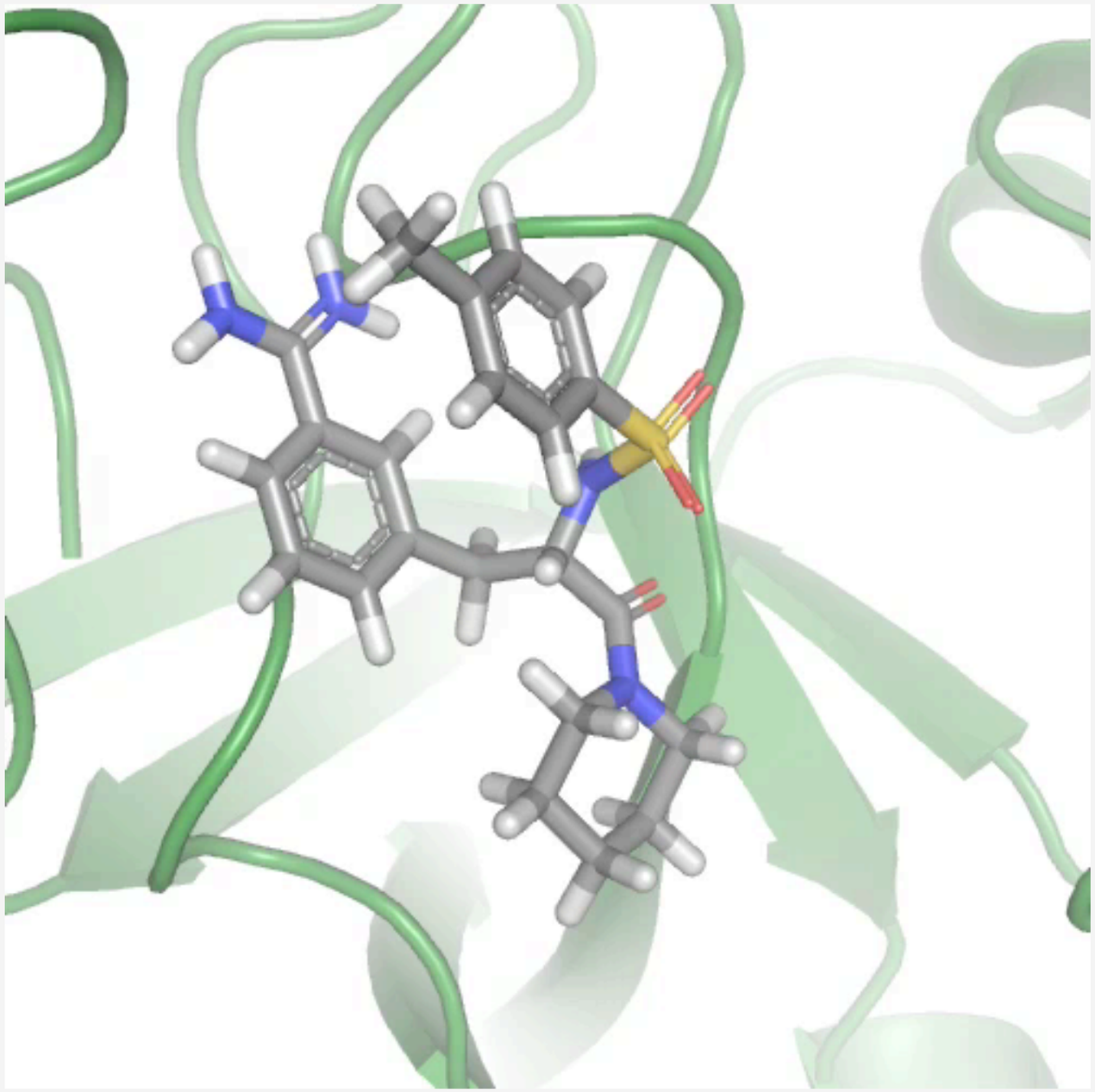
Affinity Prediction:

$$\Delta G = ?$$

Protocol


receptor structure
ligand conformers
position ligand randomly in binding site
try all conformers in random orientations against protein backbone grid
perturb ligand position (0.1Å, 2.86°)
full repack (1st and 4th cycle) or rotamer trials (other cycles)
minimize sidechains + ligand position/torsions (only if ΔE < 15 kcal/mol)
Monte Carlo accept or reject (kT = 2 kcal)
DockMCM 6 cycles
soft-repulsive potential
rigorous minimization, including protein backbone, using hard-repulsive potential
~ 5000 trajectories (40-80 proc. hrs)
top 5% by total score, then sort by receptor-ligand interaction energy

Ligand conformers in the packer



1pph

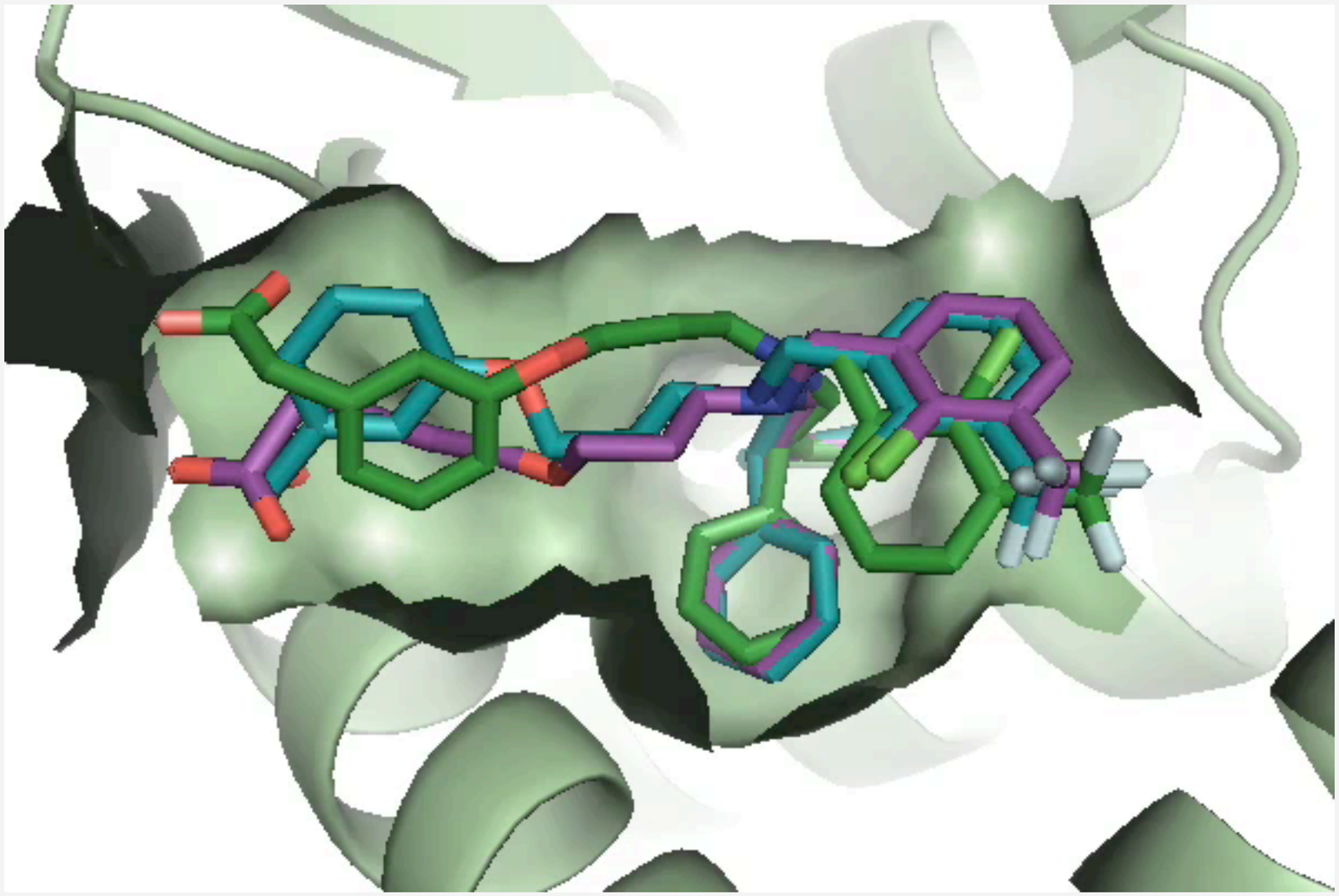
OMEGA

.mol2 / .sdf

(molfile_to_params.py)

```
HETATM     1  C1   PH1 X    1       -5.198    6.258   20
HETATM     2  C2   PH1 X    1       -5.189    7.540   20
HETATM     3  C3   PH1 X    1       -4.096    5.420   20
HETATM     4  C4   PH1 X    1       -5.836    5.673   25
HETATM     5  C5   PH1 X    1       -4.490    7.410   20
HETATM     6  C6   PH1 X    1       -4.702    4.871   25
HETATM     7  C7   PH1 X    1       -3.357    6.608   20
HETATM     8  C8   PH1 X    1       -2.974    7.147   21
...
TER
HETATM     1  C1   PH1 X    1       -2.899    8.634   22
HETATM     2  C2   PH1 X    1       -4.205    8.557   21
HETATM     3  C3   PH1 X    1       -2.070    7.513   22
HETATM     4  C4   PH1 X    1       -5.696    5.818   25
HETATM     5  C5   PH1 X    1       -4.351    7.554   20
HETATM     6  C6   PH1 X    1       -4.562    5.015   25
HETATM     7  C7   PH1 X    1       -3.217    6.752   20
HETATM     8  C8   PH1 X    1       -3.854    6.239   20
...
TER
```

Conformer search failures



Native

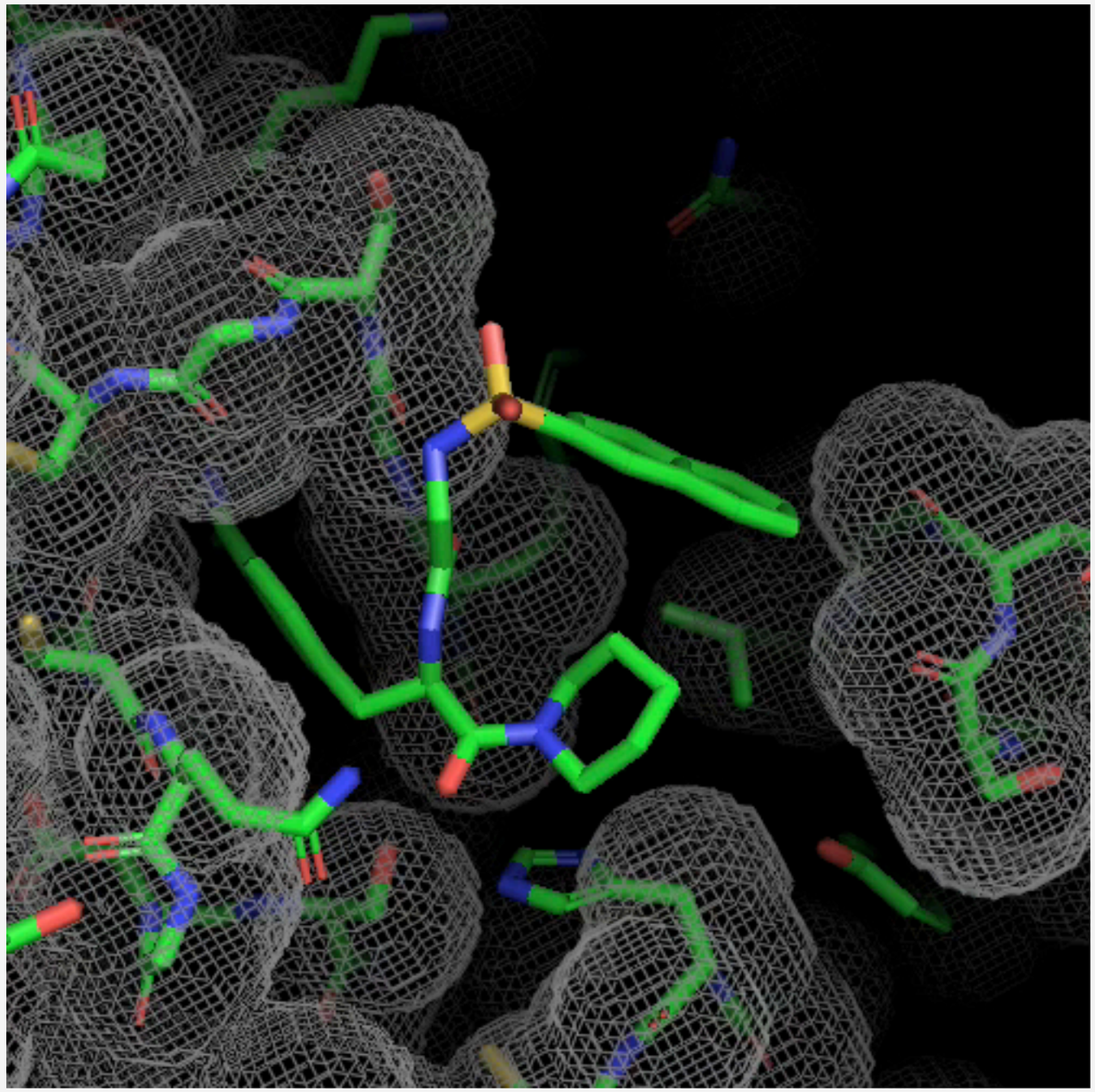
Docked

Docked

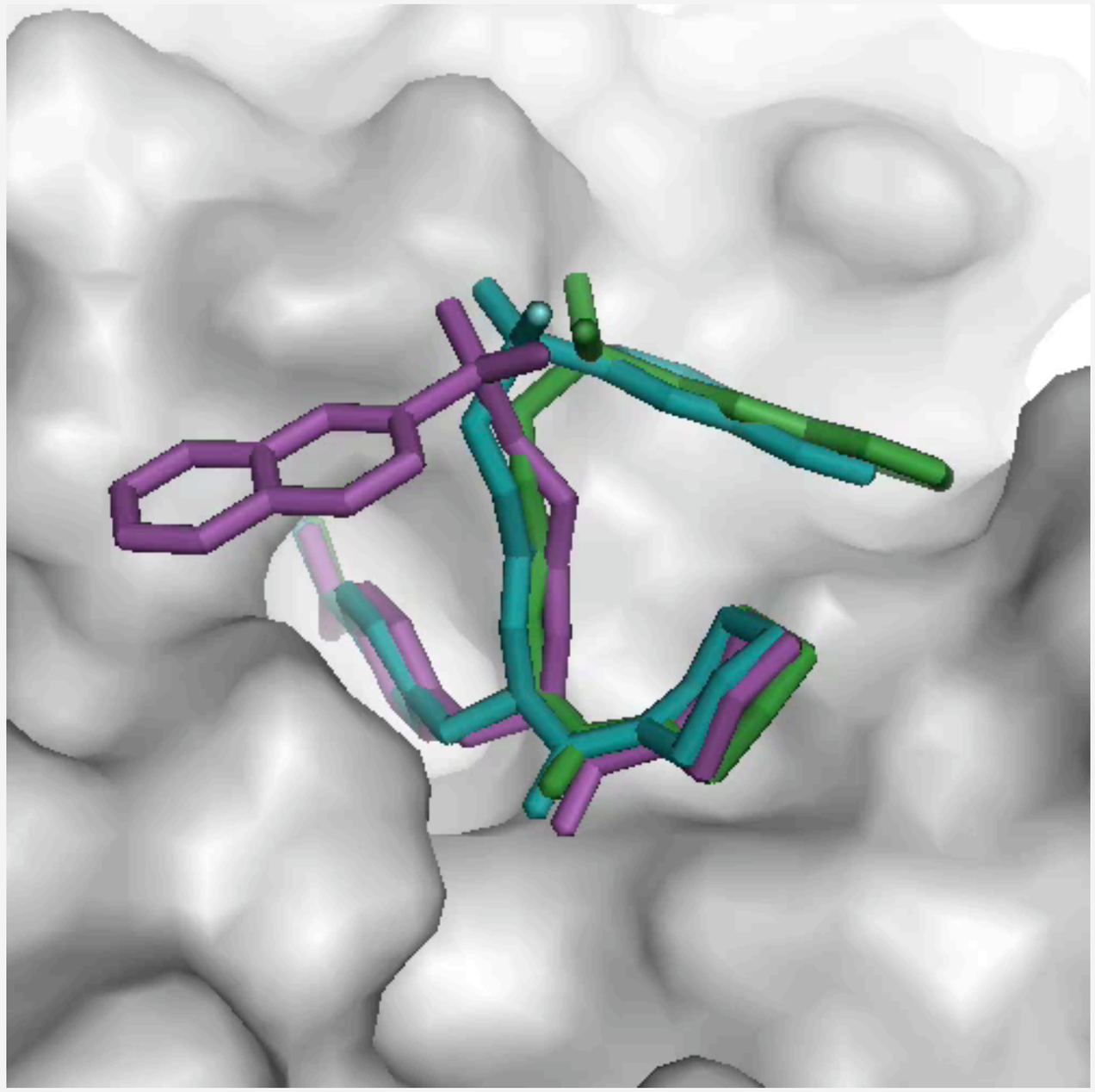
Protocol: rigid-body search

- ONE position
- ~1000 orientations * *N* conformers

- +1 within 2.25Å of backbone + Cβ
- -1 between 2.25 - 4.75Å of any non-H
  - scored on enz-des style grid for speed
- minimize repulsion, then maximize attraction
  - capped at 85% of max -- sticking through sidechains, etc.
- filter out low-RMS duplicates



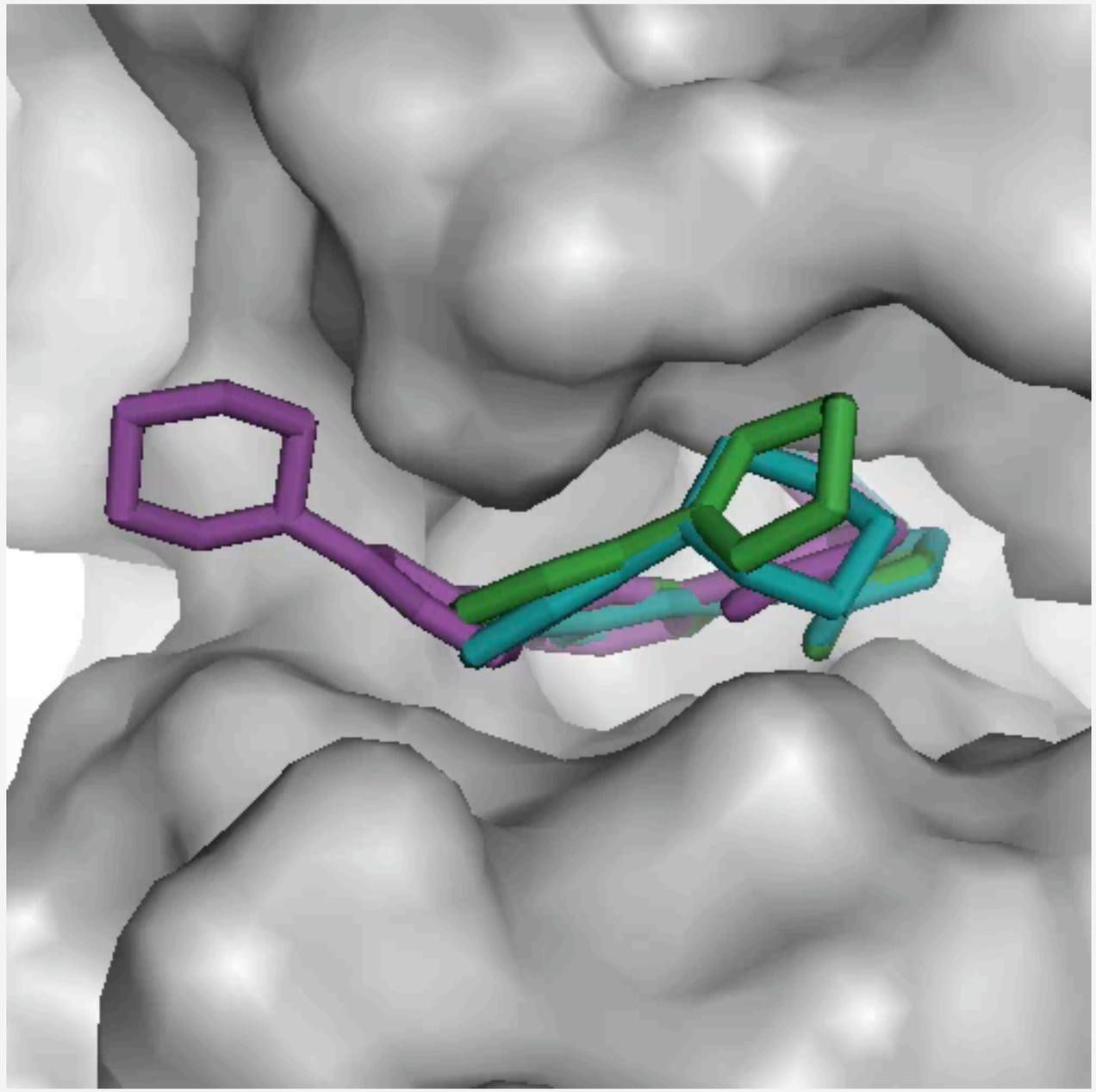
Rigid-body search



Native
Docked
Docked

trypsin (1pph)

Rigid-body search #2



Native

Docked

Docked

JNK3 kinase w/ ligand #8

rigid backbone

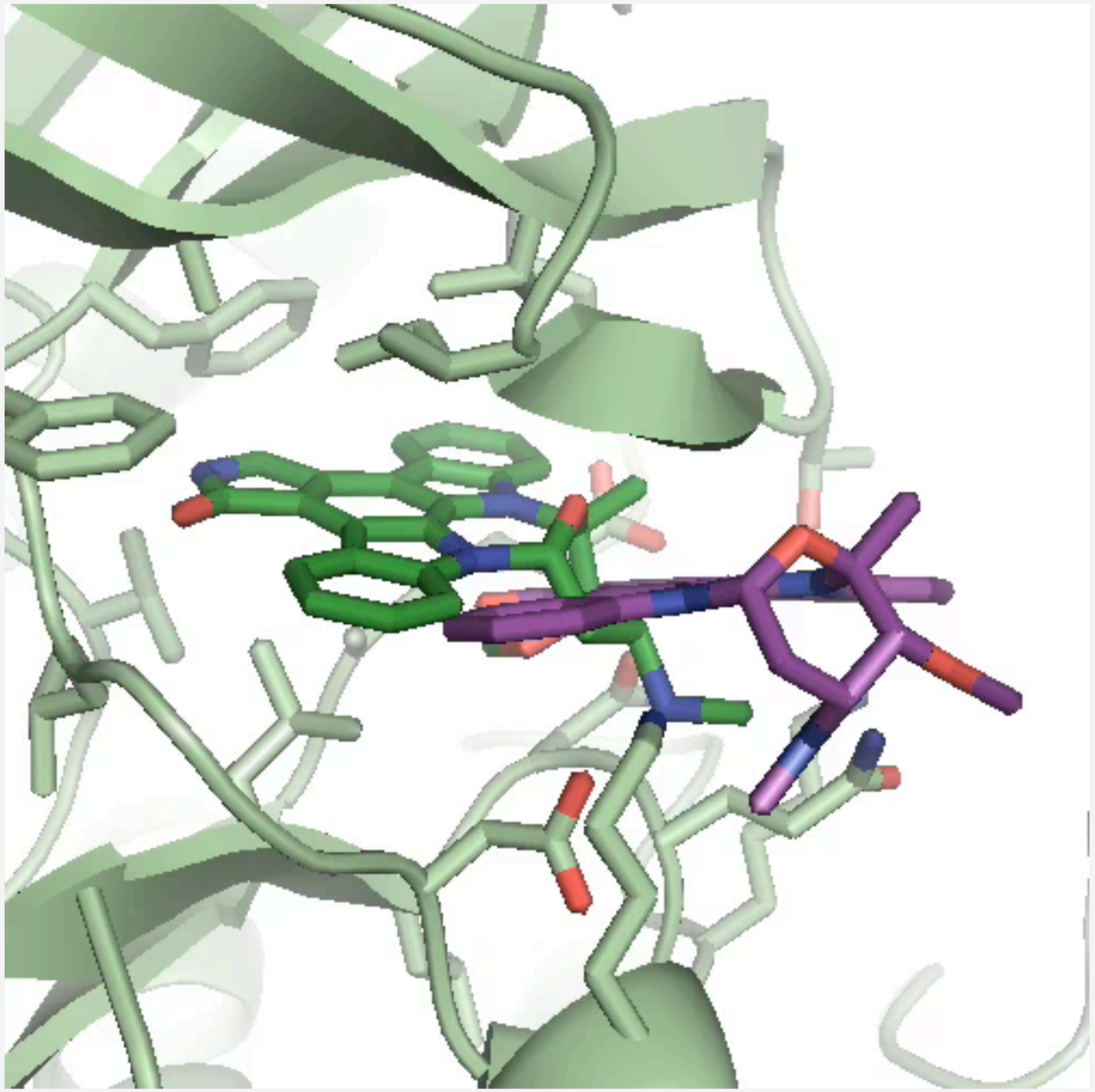
flexible backbone

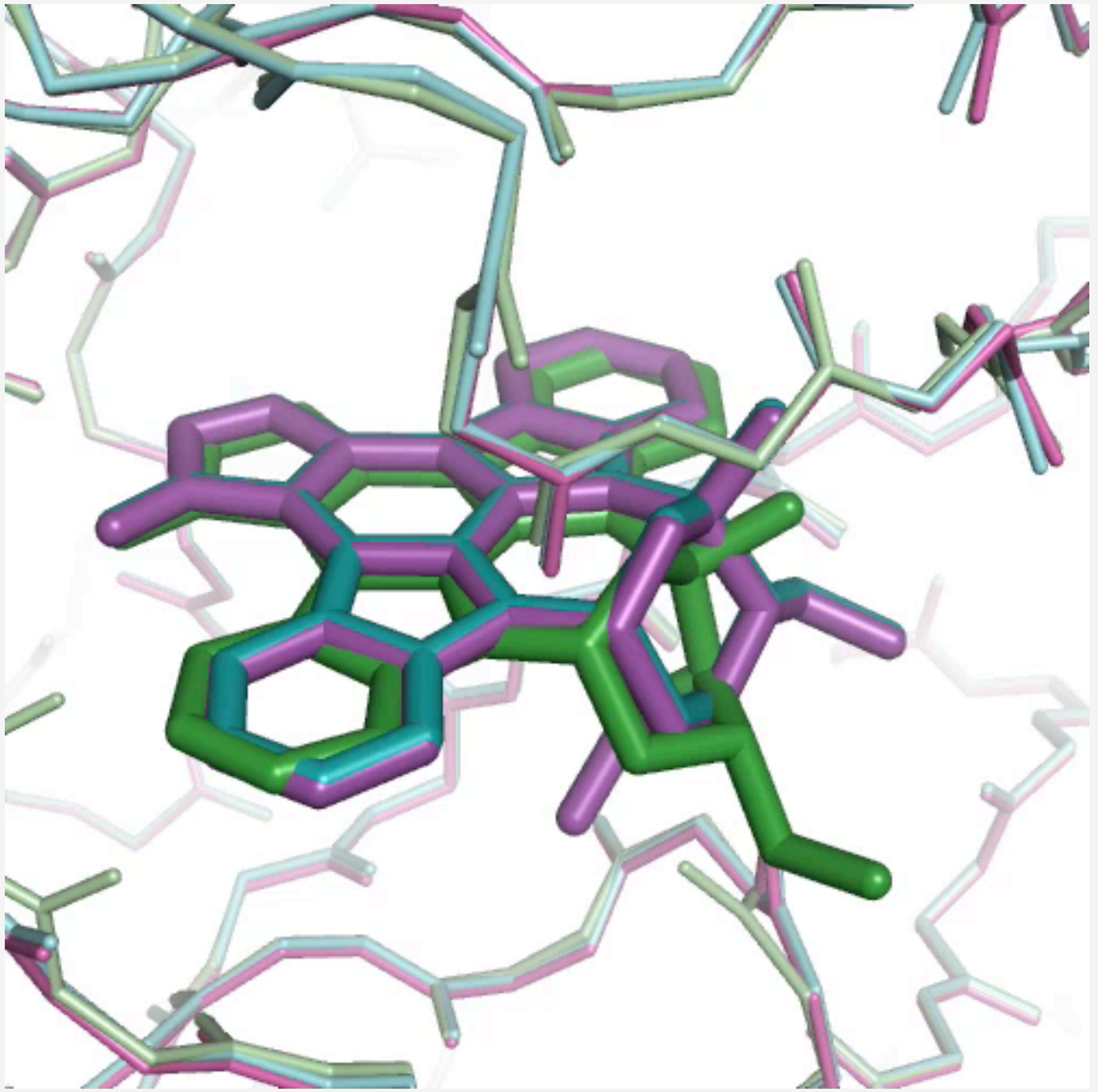
interaction energy

RMSD to native (Å)

all poses
best 5% poses
best pose
min. native

Backbone minimization





CDK2 (1dm2) w/ staurosporine

Benchmark sets

- Meiler & Baker 2006
  - 17 complexes -- 17 self-dock and 20 cross-dock (3 LXRβ)
  - Used for testing changes to the protocol

- SAMPL-1 (still no official results from OpenEye...)
  - 2 receptors and ~100 ligands -- all cross-docked
  - Truly blind in Feb. '08, not run again until "final" protocol finished

Training set (Meiler & Baker 2006)

	Simple protocol				Rigid-backbone protocol				Flexible-backbone protocol			
	RMS of #1 (Å)		Rank < 2Å		RMS of #1 (Å)		Rank < 2Å		RMS of #1 (Å)		Rank < 2Å	
receptor	**self**	**cross**	**self**	**cross**	**self**	**cross**	**self**	**cross**	**self**	**cross**	**self**	**cross**
1aq1	7.48	5.40	2	2	1.39	0.80	1	1	1.39	0.42	1	1
1dm2	0.97	6.28	1	---	0.82	6.22	1	---	1.14	1.36	1	1
1dbj	0.55	1.59	1	1	0.38	0.94	1	1	0.46	1.22	1	1
2dbl	1.25	5.77	1	3	1.24	0.58	1	1	1.35	0.85	1	1
1dwc	5.59	3.85	---	---	7.05	6.88	2	---	1.15	8.23	1	---
1dwd	7.78	7.54	---	---	1.40	1.48	1	1	4.47	1.34	15	1
1fm9	3.18	2.33	---	2	5.90	8.35	19	18	5.72	8.39	11	2
2prg	1.20	8.80	1	---	8.28	10.62	17	---	8.30	4.07	5	34
1p8d	1.21	3.76	1	78	1.49	2.06	1	158	1.39	2.24	1	6
1pq6	2.22	4.34	3	7	2.05	1.20	11	1	2.08	1.27	3	1
1p8d	1.21	1.47	1	1	1.49	1.78	1	1	1.39	2.29	1	19
1pqc	0.70	1.43	1	1	0.49	0.98	1	1	0.53	0.98	1	1
1pq6	2.22	3.49	3	12	2.05	3.46	11	7	2.08	3.61	3	25
1pqc	0.70	8.10	1	93	0.49	3.70	1	181	0.53	2.20	1	128
1ppc	7.61	6.37	---	---	3.16	4.39	4	2	1.62	1.16	1	1
1pph	4.37	8.94	---	---	0.90	3.04	1	8	1.00	5.63	1	2
2ctc	0.90	6.31	1	---	0.70	8.49	1	---	0.73	3.64	1	---
7cpa	4.63	0.52	---	1	4.30	4.51	---	3	4.62	4.60	---	4
4tim	5.27	1.25	2	1	1.07	1.35	1	1	0.95	1.34	1	1
6tim	1.22	2.12	1	5	1.16	2.13	1	7	1.25	0.70	1	1
average	**3.01**	**4.48**			**2.29**	**3.65**			**2.11**	**2.78**		

JNK3 Kinase (SAMPL-1)

		SAMPL-1 predictions		Flexible backbone	
Compound	**Torsions**	**RMS of best**	**rank < 2A**	**RMS of best**	**rank < 2A**
jnk.pp.1-1	6	0.84	1	1.17	1
jnk.pp.1-3	4	1.40	1	0.51	1
jnk.pp.1-7	5	1.07	1	1.00	1
jnk.pp.1-8	5	3.40	22	0.73	1
jnk.pp.1-9	4	2.23	9	1.92	1
jnk.pp.1-10	5	1.10	NA*	0.96	1
jnk.pp.1-11	5	0.91	1	1.07	2
jnk.pp.1-12	5	0.74	1	0.71	1
jnk.pp.1-14	3	1.28	1	1.22	1
jnk.pp.1-15	4	4.00	6	0.36	1
jnk.pp.1-18	7	0.94	2	1.19	2
jnk.pp.1-19	7	0.64	21*	0.67	1
jnk.pp.1-22	4	1.55	1	0.47	1
jnk.pp.1-24	3	5.56	NA	2.70	23
jnk.pp.1-25	5	0.69	4	0.67	1
jnk.pp.1-26	4	0.61	1	0.71	1
jnk.pp.1-27	5	0.90	1	0.50	1
jnk.pp.1-28	3	0.79	1	3.41	31
jnk.pp.1-32	4	1.39	1	0.45	1
jnk.pp.1-33	6	3.44	NA	2.78	NA
jnk.pp.1-34	3	0.89	1	0.71	1
jnk.pp.1-35	6	0.87	1	0.65	1
jnk.pp.1-37	7	2.25	4	1.27	1
jnk.pp.1-38	4	2.48	6	0.83	1
jnk.pp.1-39	4	0.47	NA*	0.68	1
jnk.pp.1-40	5	0.55	NA*	0.64	1
jnk.pp.1-41	5	1.52	NA*	1.13	1
jnk.pp.1-42	6	0.95	1	0.85	1
jnk.pp.1-46	8	4.89	NA	5.34	NA
jnk.pp.1-48	4	5.81	5	1.21	2
jnk.pp.1-49	3	1.15	1	0.96	1
jnk.pp.1-51	1	1.39	1	1.33	1
jnk.pp.1-52	5	0.64	1	6.89	NA
jnk.pp.1-55	6	1.92	1	1.01	1
jnk.pp.1-56	4	9.47	6	0.73	2
jnk.pp.1-59	5	4.18	3	0.66	1
jnk.pp.1-60	4	10.91	20	0.98	7
jnk.pp.1-62	5	10.61	NA	5.28	NA
#1 < 2A		**0.66**		**0.84**	
#1 < 3A		**0.74**		**0.89**	
avg. RMS		**2.49**		**1.43**	

Urokinase (SAMPL-1)

		SAMPL-1 predictions		Flexible backbone	
Compound	**Torsions**	**RMS of best**	**rank < 2A**	**RMS of best**	**rank < 2A**
uk.pp.1-1	0	3.27	3	2.19	16
uk.pp.1-2	5	1.01	1	1.19	1
uk.pp.1-3	6	0.76	1	1.04	1
uk.pp.1-5	4	3.78	NA	2.27	81
uk.pp.1-6	3	5.59	3	5.85	10
uk.pp.1-7	3	1.46	1	0.80	1
uk.pp.1-8	3	2.34	5	2.17	13
uk.pp.1-9	8	3.28	34	7.39	NA
uk.pp.1-10	3	1.16	1	1.95	3
uk.pp.1-11	1	0.72	1	0.54	1
uk.pp.1-13	5	1.48	1	2.03	NA
uk.pp.1-14	1	0.52	1	0.64	1
uk.pp.1-15	4	2.38	2	2.10	11
uk.pp.1-16	5	2.94	3	2.56	15
uk.pp.1-18	2	2.09	2	1.40	1
uk.pp.1-19	4	2.17	2	2.21	NA
uk.pp.1-20	6	3.83	5	3.50	50
uk.pp.1-21	3	8.27	37	7.93	49
uk.pp.1-22	8	3.75	NA	4.33	NA
uk.pp.1-23	1	0.58	1	0.43	1
uk.pp.1-24	3	2.41	14	3.09	10
uk.pp.1-25	2	1.31	1	0.67	1
uk.pp.1-29	6	1.45	1	1.70	3
uk.pp.1-30	3	0.62	1	0.59	1
uk.pp.1-31	4	1.17	1	3.04	5
uk.pp.1-32	3	4.11	NA	2.22	49
uk.pp.1-34	4	2.12	2	1.98	2
#1 < 2A		**0.44**		**0.44**	
#1 < 3A		**0.70**		**0.74**	
avg. RMS		**2.39**		**2.44**	

What next?

- Weight fitting: decoy discrim. + ΔG_{bind} + seq. recovery
- More backbone flexibility!
- Comparative models and docking?
- Waters and docking?

- Better torsional potential (Kristian, Gordon)
- Incremental ligand conformational search (Kristian)

Thanks!

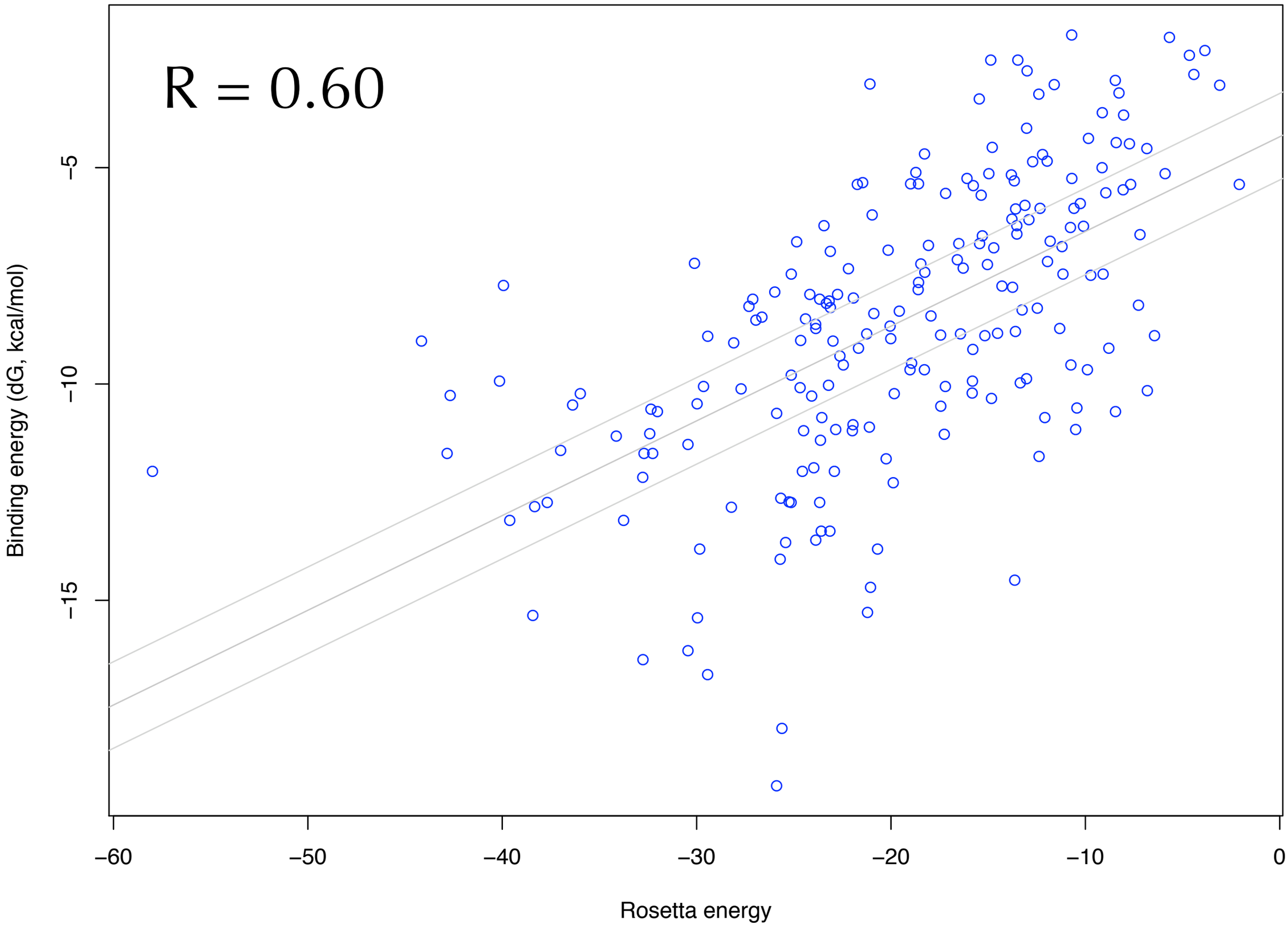
Andrew LF, Phil
Chu, Eric, Daniela, Florian, John

Kristian, Gordon
Jens

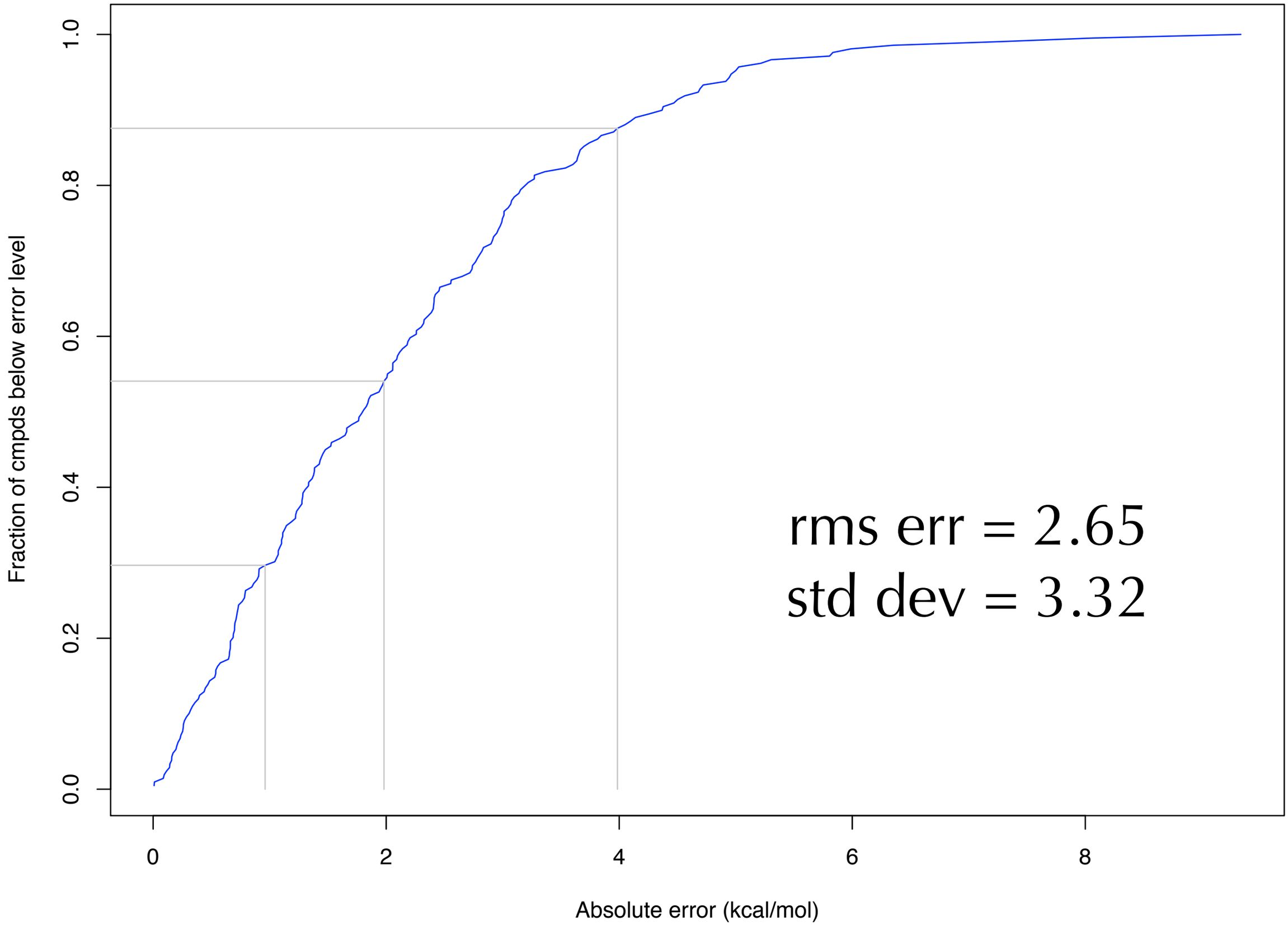
Baker / Schief labs
David B.

Genome Sciences training grant

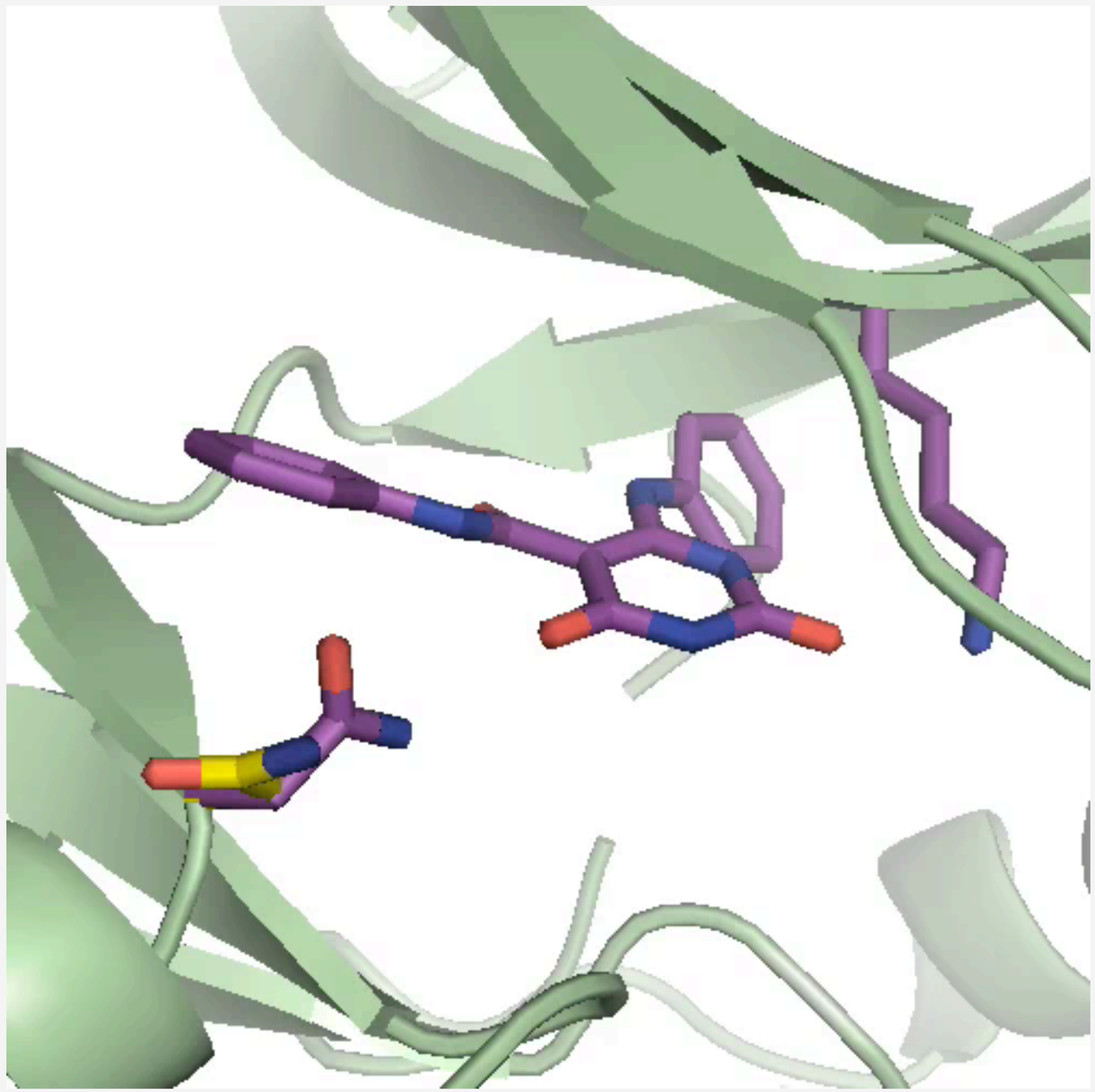
Predicting binding affinity



Predicting binding affinity



Rotamer search



Input

Input

Docked

Be careful what you calculate...

Ligand	Min. Omega rms with automorphisms	rms of Rosetta++ "rotamerized" ligand	Rotatable bonds* (H)
1aq1	1.24	0.01	2
1dwc	0.61	0.82	10
1dwd	1.10	1.04	9
1fm9	1.10	0.65	12
1p8d	0.56	0.25	4 (1)
1ppc	0.69	0.72	9
1pph	0.93	0.50	7
1pq6	1.67	1.06	14
1pqc	0.38	0.17	8 (1)
2ctc	0.22	0.38	3 (1)
2dbl	0.72	0.40	6 (1)
2prg	0.54	1.02	7
4tim	0.69	0.57	4 (1)
6tim	0.44	0.40	4 (2)
7cpa	1.65	0.98	15
average	**0.84**	**0.60**	**7.6**