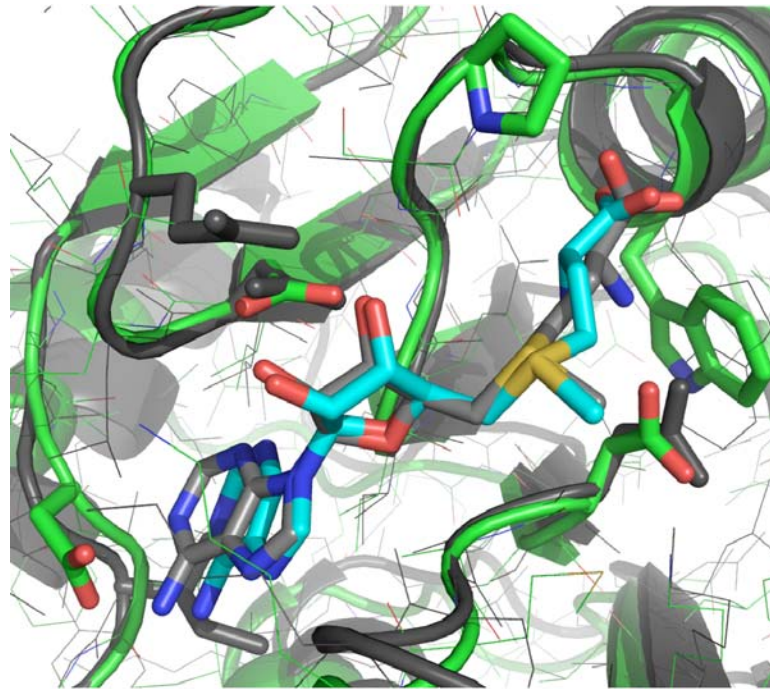


Docking to CASP 8 Models with RosettaLigand



Rosetta Conference 2009

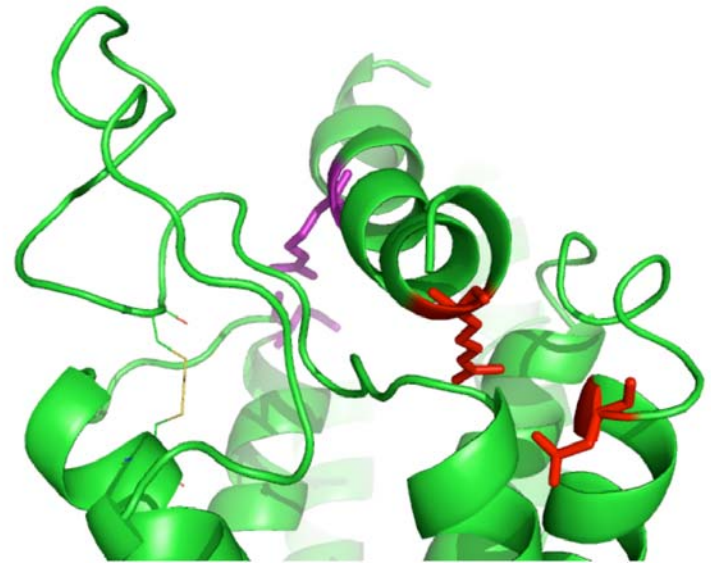
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Docking to Comparative Models is Becoming Common Place

- A PubMed search
 - 41 papers with “Homology modeling and Docking” in the title so far in 2009
 - 12 papers list drug design and docking

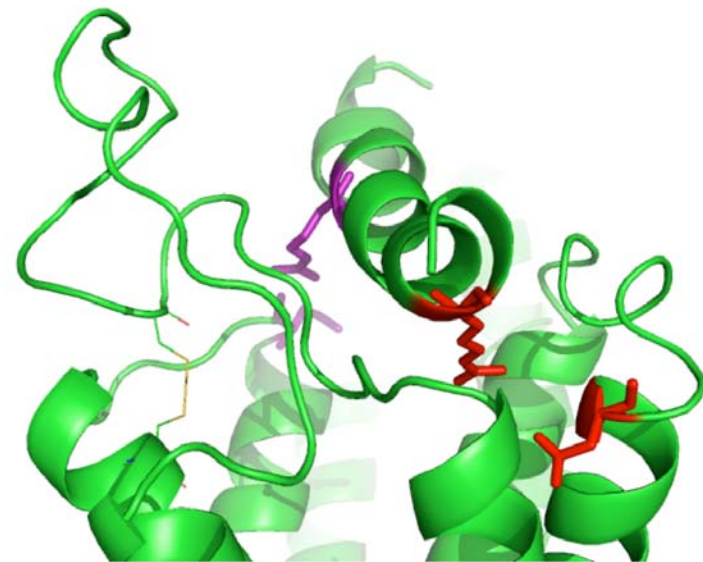
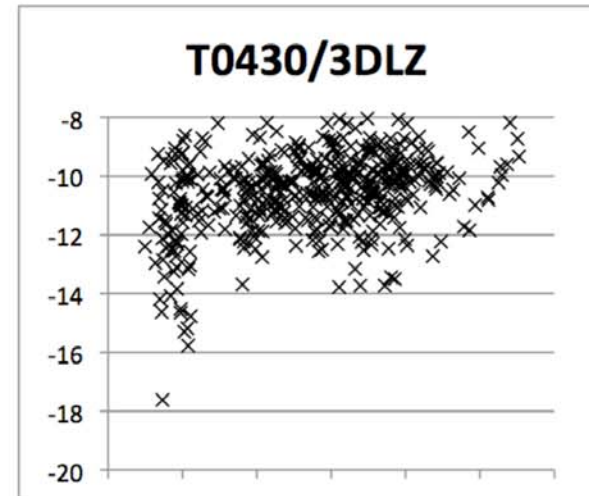


But, Docking to Comparative Remains Relatively Unexamined

- Most studies focus on one target
 - Ferrara published a study testing the utility of homology models for a docking study on the insulin-like growth factor 1 receptor. J. Mol. Model. 2007 v. 13 p. 897
- Two exceptions
 - DeWeese-Scott analyzed 10 targets taken from CASP 2-4. Instead of testing docking programs DeWeese-Scott assumed an optimal solution for her analysis. Proteins 2004 v.55 p. 942
 - Kairys performed a benchmark of docking for virtual screening purposes on a set of 5 proteins each with multiple templates. J. Chem. Inf. Model. 2006 v. 46 p. 365

Motivation

- Provide a quantitative measure of docking performance to comparative models
- Demonstrate the utility of RosettaLigand in comparative modeling
- Spur development of new assessment metrics of expected model quality



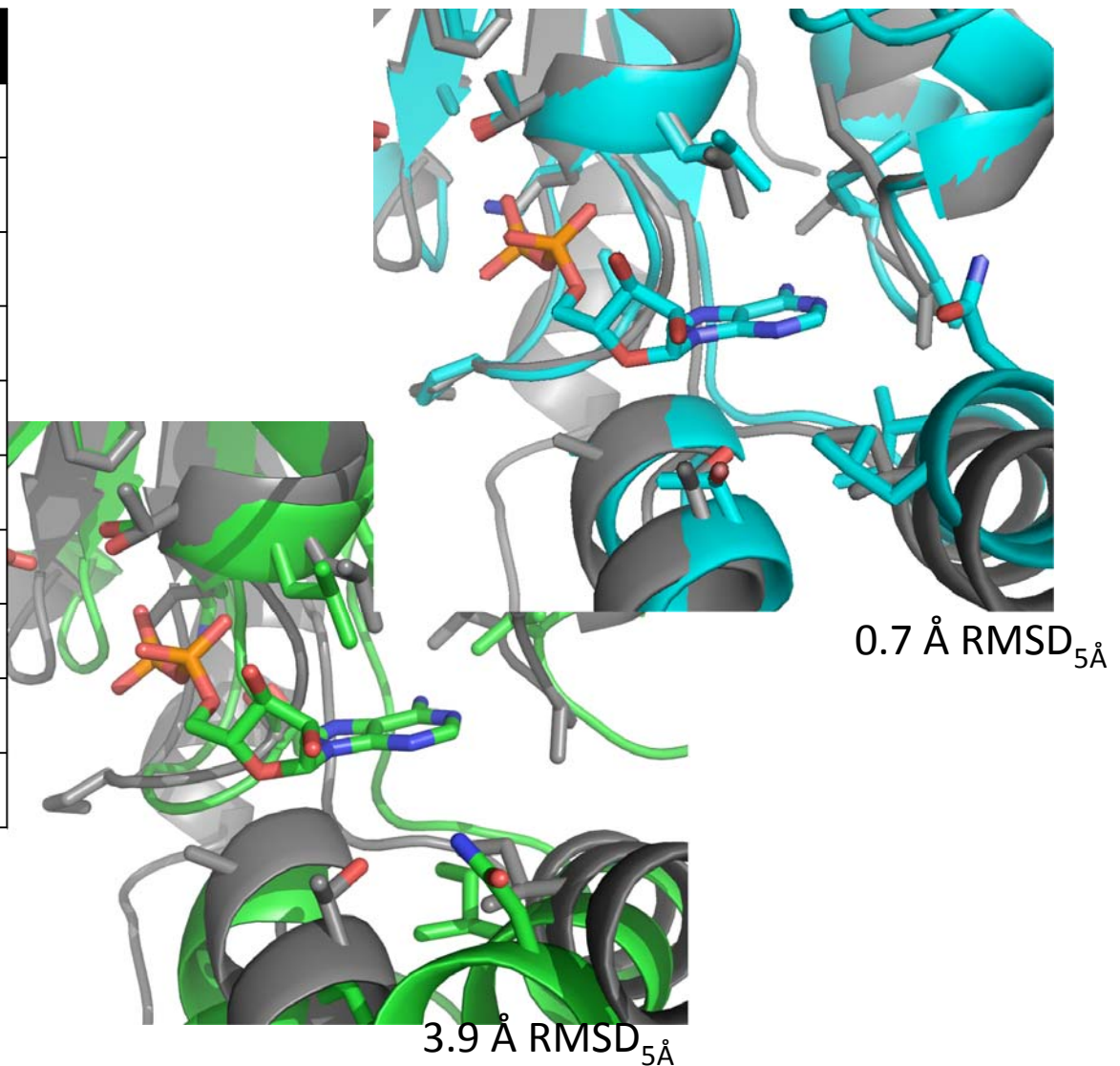
Using Models from CASP 8 Benchmarks the Best Available Modeling Practices

	PDB	Templ. Seq. ID.	Ligand
T0422	3D8B	50%	ADP
T0430	3DLZ	14%	AMP
T0445	3DAO	22%	Citrate
T0450	3DA1	44%	FAD
T0477	3DKP	32%	ADP
T0483	3DLS	32%	ADP
T0485	3DLC	16%	SAM
T0490	3DME	19%	FAD
T0508	3DOU	31%	SAM

- Nine targets with cofactors
 - 3 ADP
 - 1 AMP
 - 1 Citrate
 - 2 FAD
 - 2 S-adenosyl methionine (SAM)
- Sequence identity to template ranges from moderate to low

Optimally Positioned Ligands Demonstrates Possibility of High Quality Models

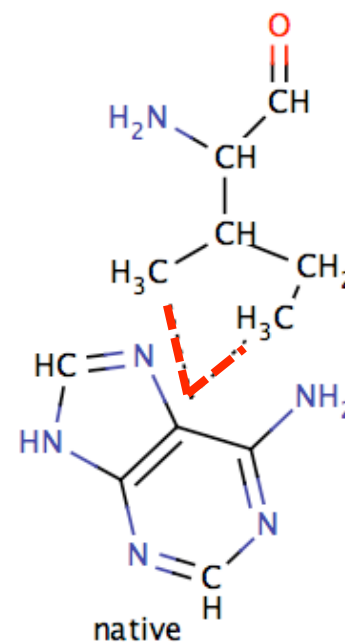
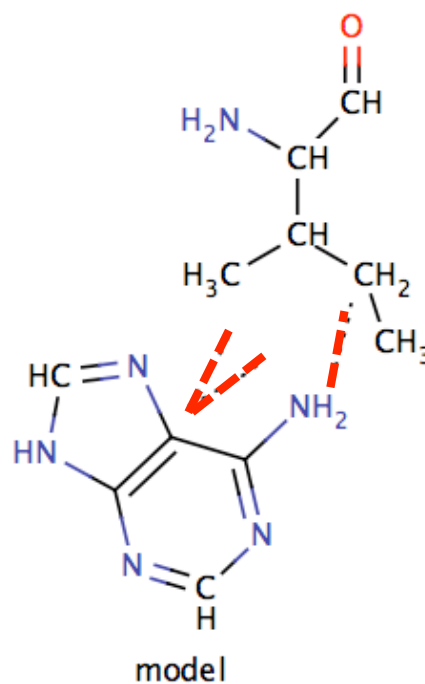
	$\text{RMSD}_{\text{CA}} \text{ \AA}$	$\text{RMSD}_{5\text{A}} \text{ \AA}$
T0422	2.4 – 23.9	0.7 – 3.9
T0430	9.8 – 21.2	3.0 – 13.6
T0445	2.5 – 5.9	0.3 – 2.4
T0450	1.6 – 9.5	0.7 – 6.0
T0477	3.2 – 18.2	0.8 – 6.4
T0483	4.5 – 11.7	1.3 – 4.3
T0485	5.2 – 18.2	0.9 – 10.1
T0490	2.5 – 9.0	2.4 – 6.0
T0508	1.4 – 4.2	0.4 – 7.0



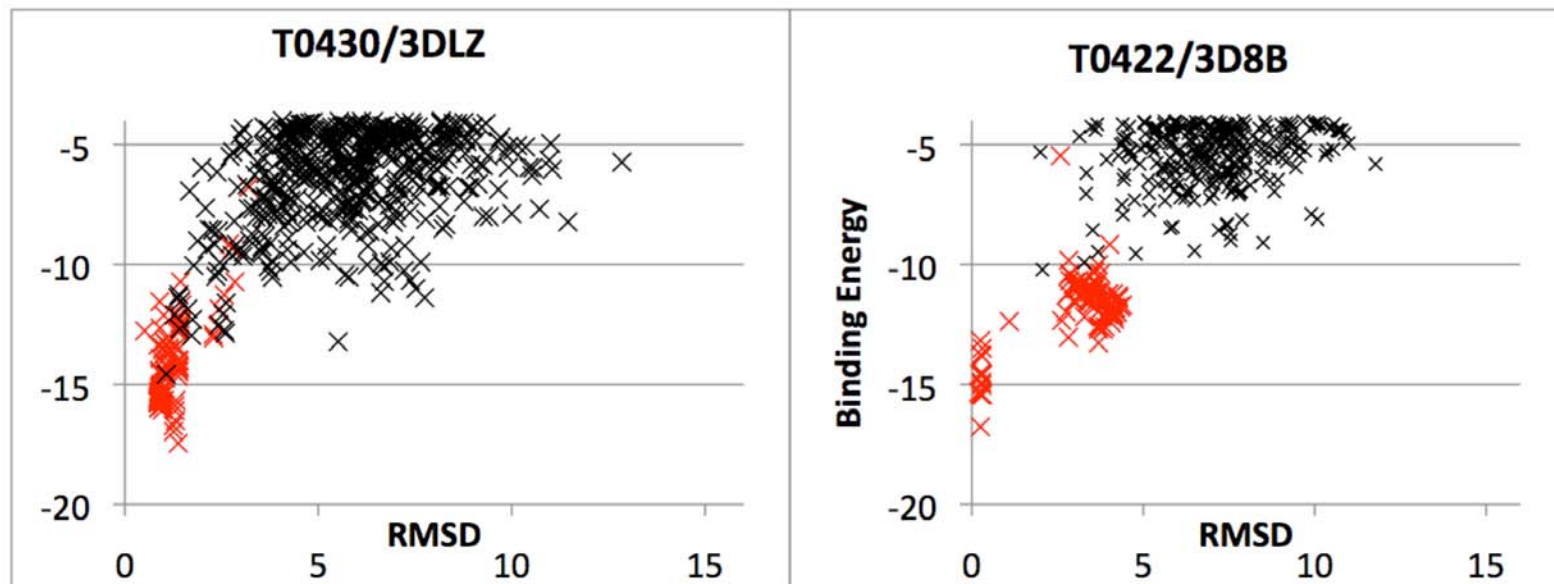
Optimally Positioned Ligands

Demonstrates Possibility of High Quality Models

	% Contact 5 Å +/- 0.5 Å	% True Positive
T0422	16-81 %	14-81 %
T0430	7-50 %	5-46 %
T0445	13-70 %	25-85 %
T0450	17-78 %	17-89 %
T0477	12-73 %	11-78 %
T0483	10-50 %	14-70 %
T0485	9-58 %	10-85 %
T0490	16-62 %	12-65 %
T0508	33-83 %	30-89 %



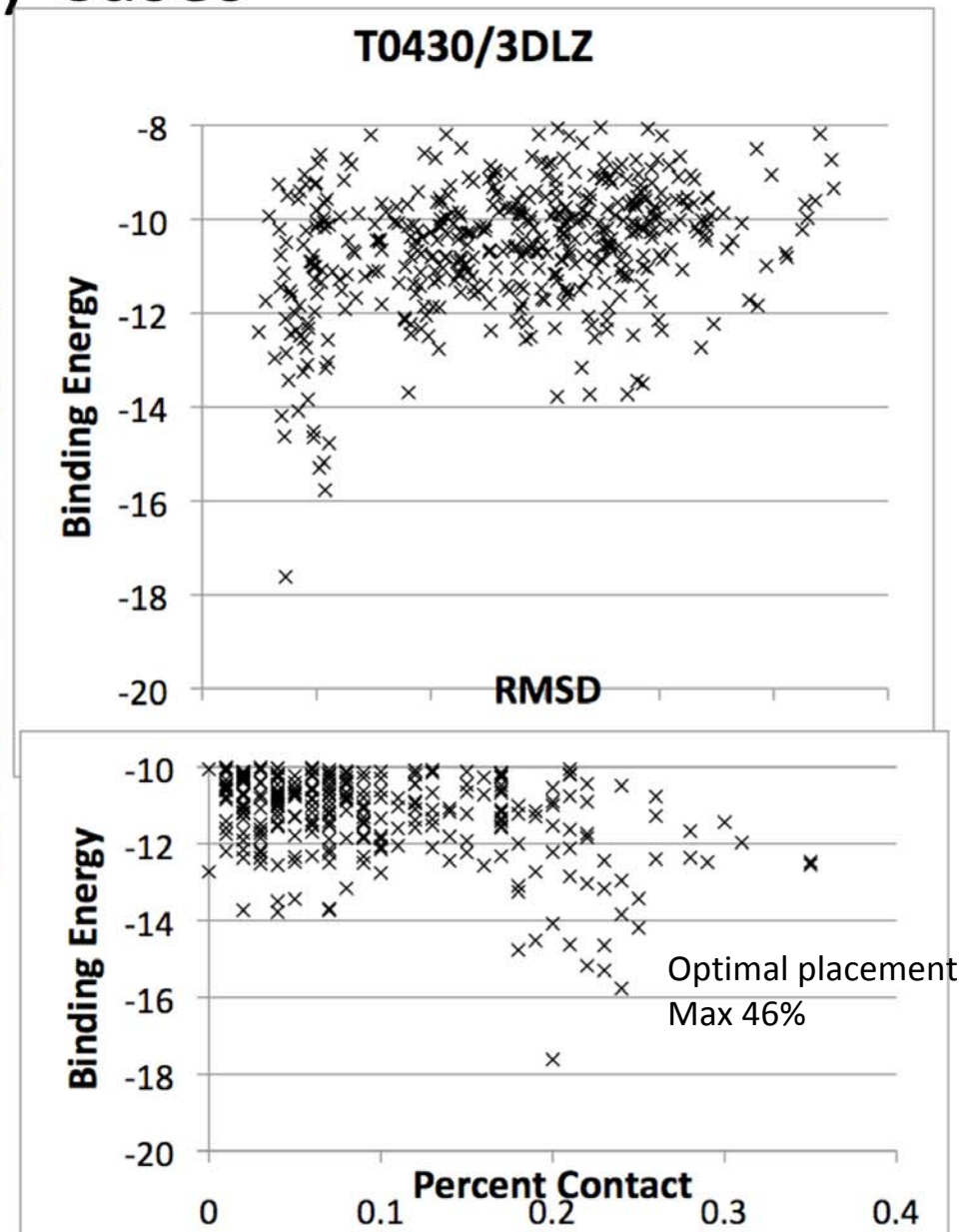
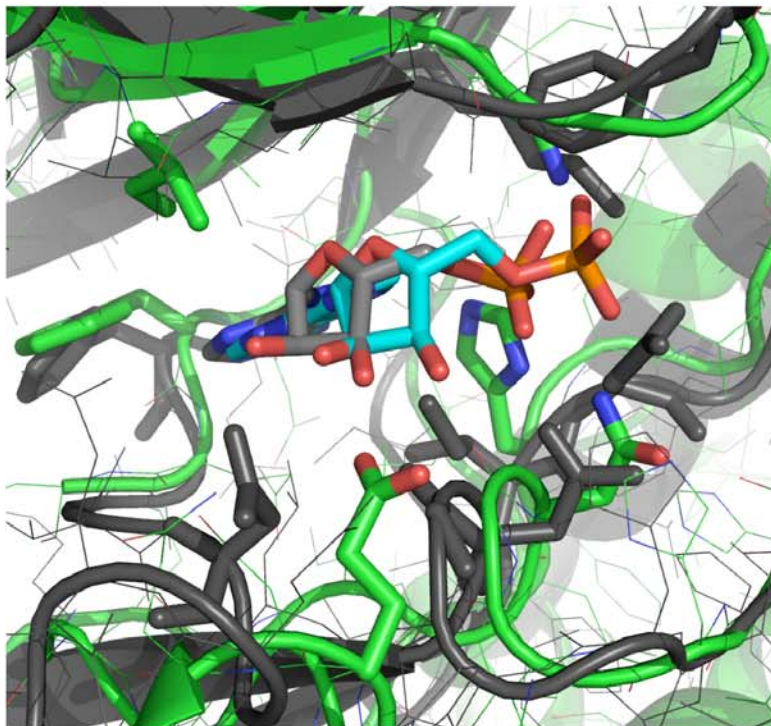
Docking to Native PDB shows Protocol Performs Correctly in Most Cases



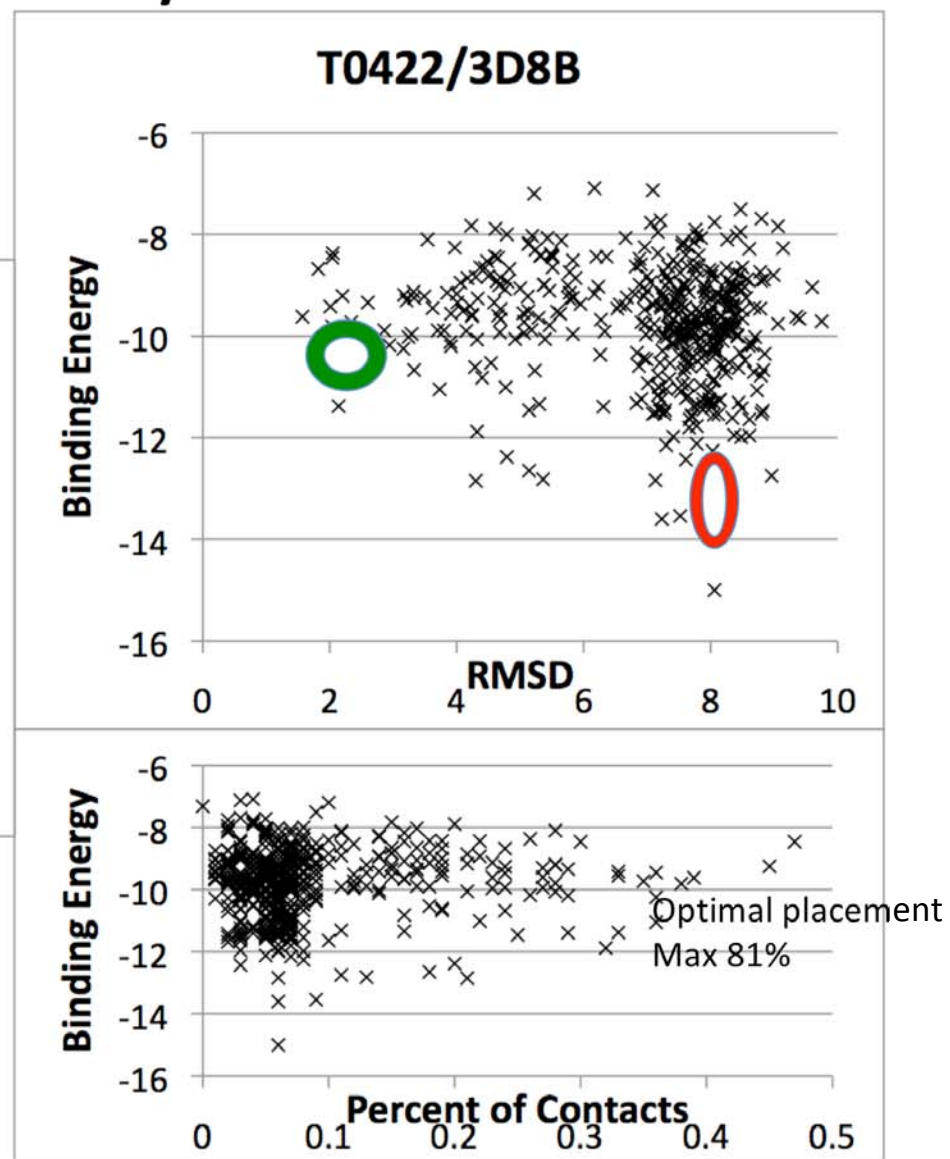
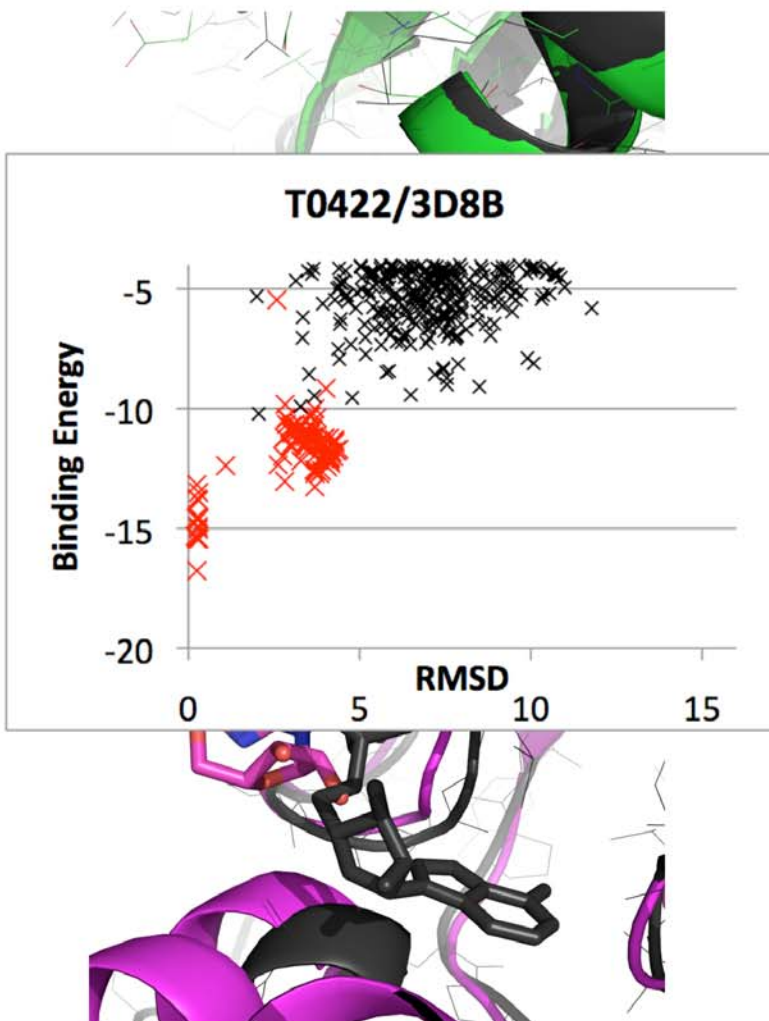
✕ Native Minimized Models

✕ Docking Models

Docking the CASP Models Performs Well in Many Cases



... And Marginally in Some



Overall Results Indicate Current Template Based Models are Suitable for Docking

Target	RMSD Rank 1	Best RMSD rank 10	Best rank <2.5Å	Best rank <2.0Å
T0422	8.06	4.30/4	2.14/43	1.57/222
T0430	1.46	1.39/9	1.46/1	1.46/1
T0445	2.84	2.84/1	2.40/29	1.84/60
T0450	0.52	0.38/10	0.52/1	0.52/1
T0477	8.59	2.20/3	2.20/3	1.30/98
T0483	1.95	1.95/1	1.95/1	1.95/1
T0485	3.27	0.77/5	1.40/3	1.40/3
T0490	2.61	1.04/5	1.04/5	1.04/5
T0508	0.79	0.79/1	0.79/1	0.79/1

Further Questions

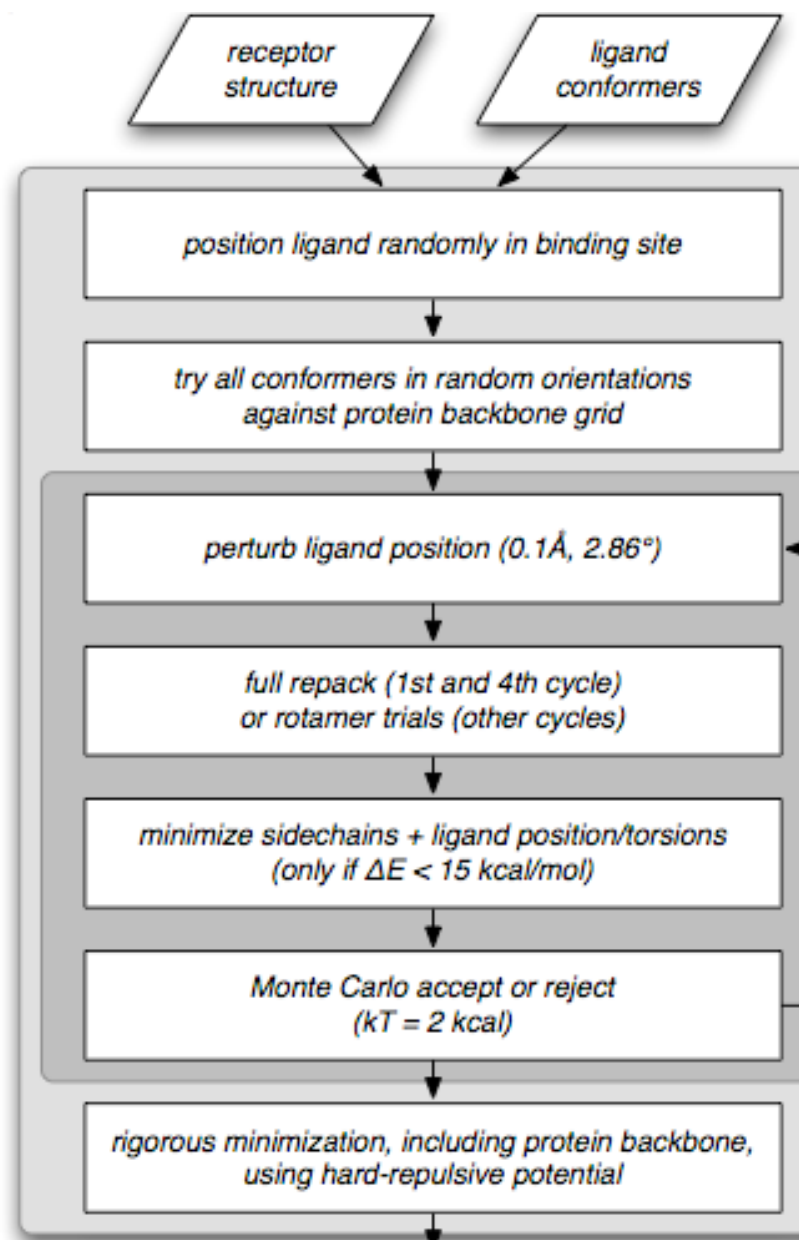
- Are there scoring methods suitable for prioritizing models for docking runs?
 - Template quality measures
 - Model quality assessment method

Acknowledgements

- Jens Meiler
- Gordon Lemmon
- Eric Dawson
- Steven Combs
- Artez Sims
- NIDA



Davis Docking Protocol



Davis and Baker
JMB 2009