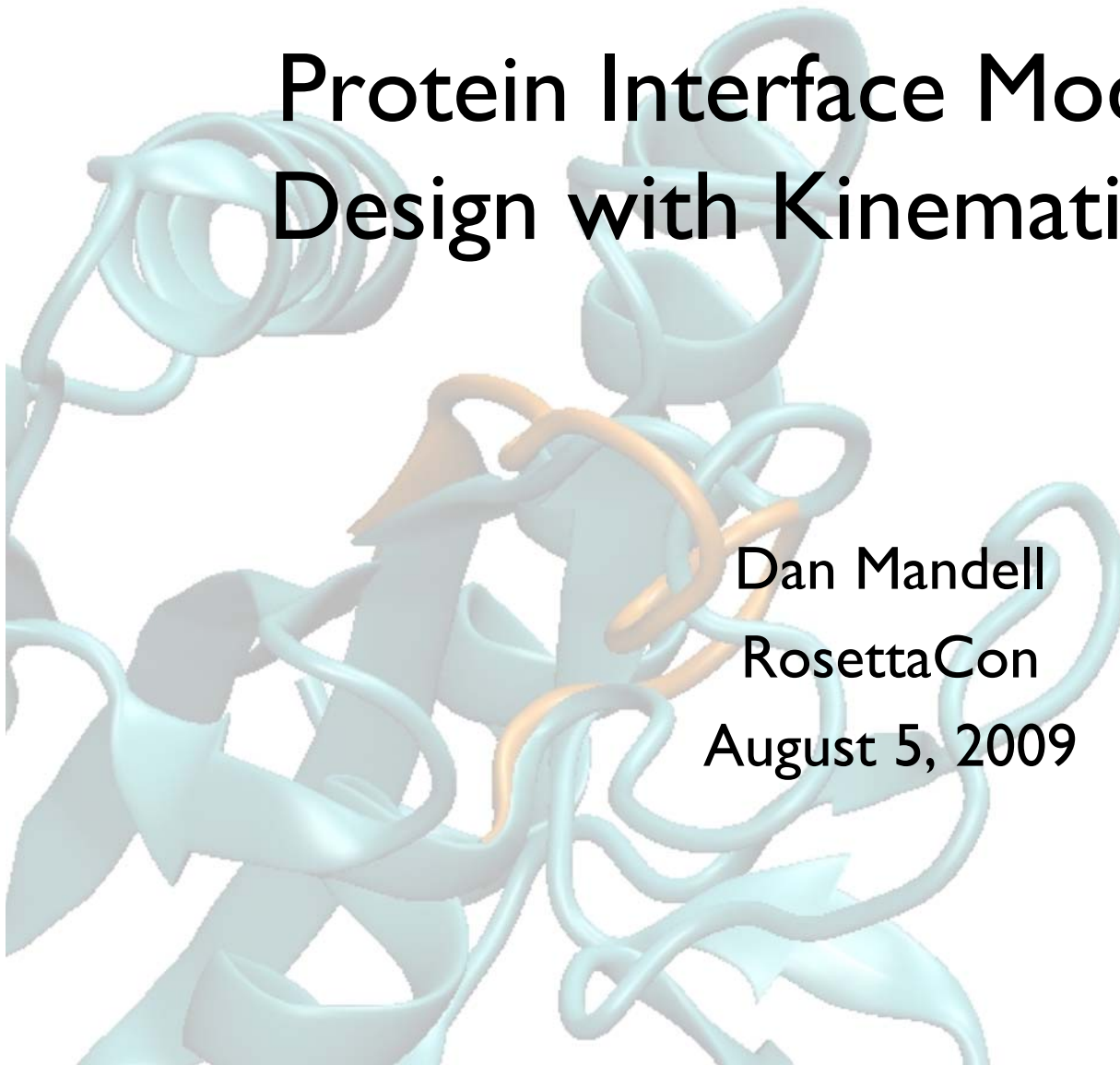


Protein Interface Modeling and Design with Kinematic Closure

Dan Mandell

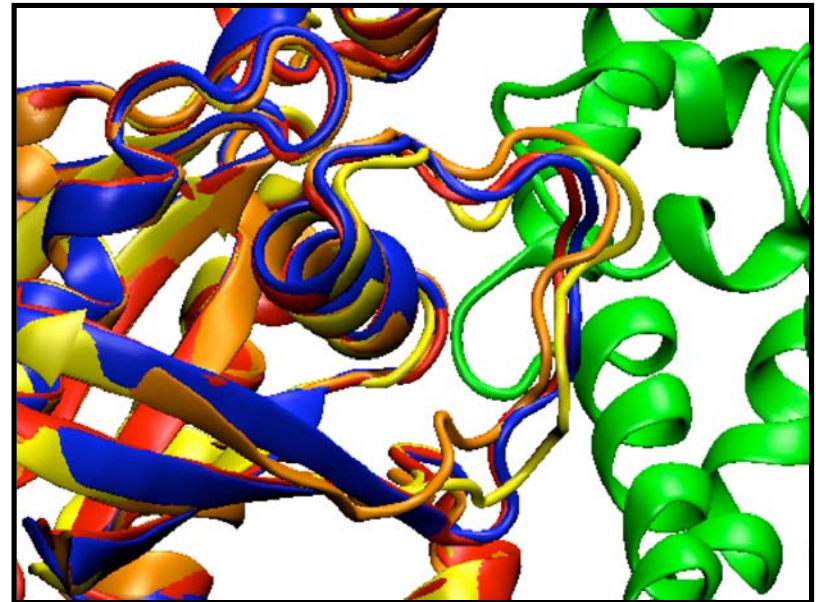
RosettaCon

August 5, 2009



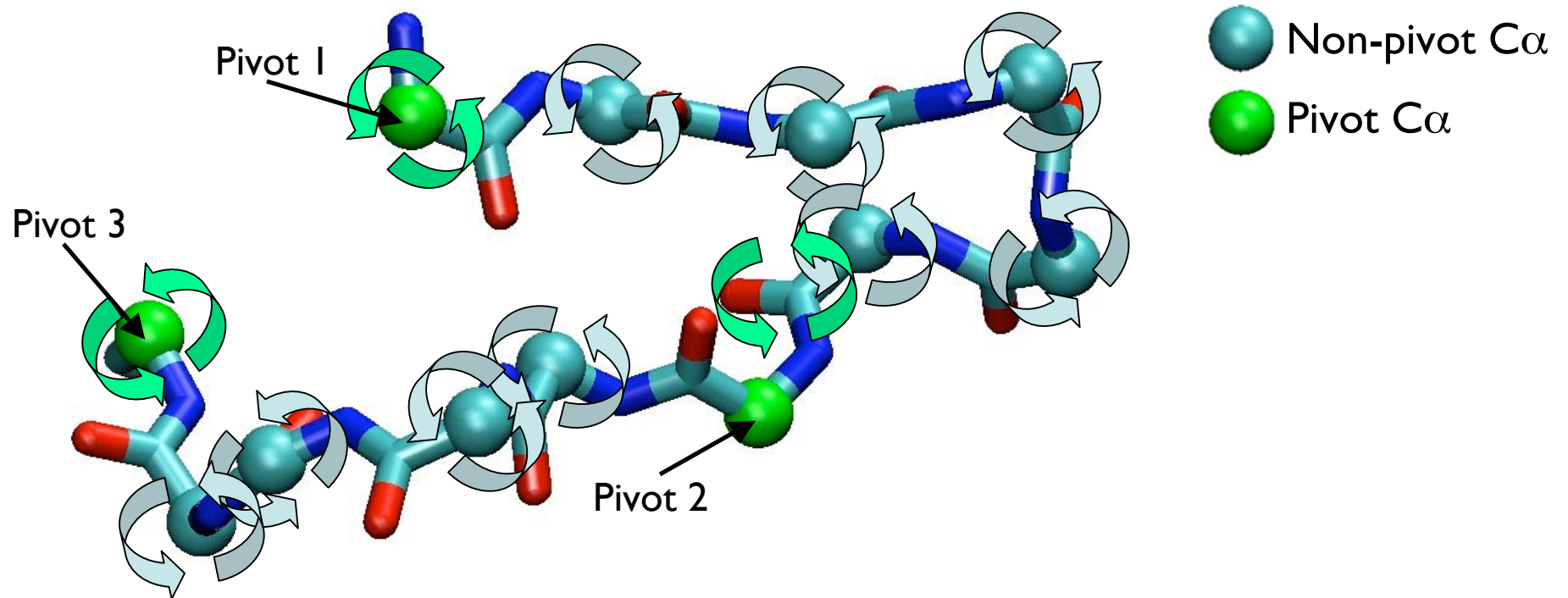
Conformational plasticity in protein recognition

Flexible interface loops facilitate binding of multiple partners, as in the Rac GTPase



If we can accurately remodel protein interfaces, we can better engineer new functional protein interactions

The kinematic closure (KC) move for peptide chains

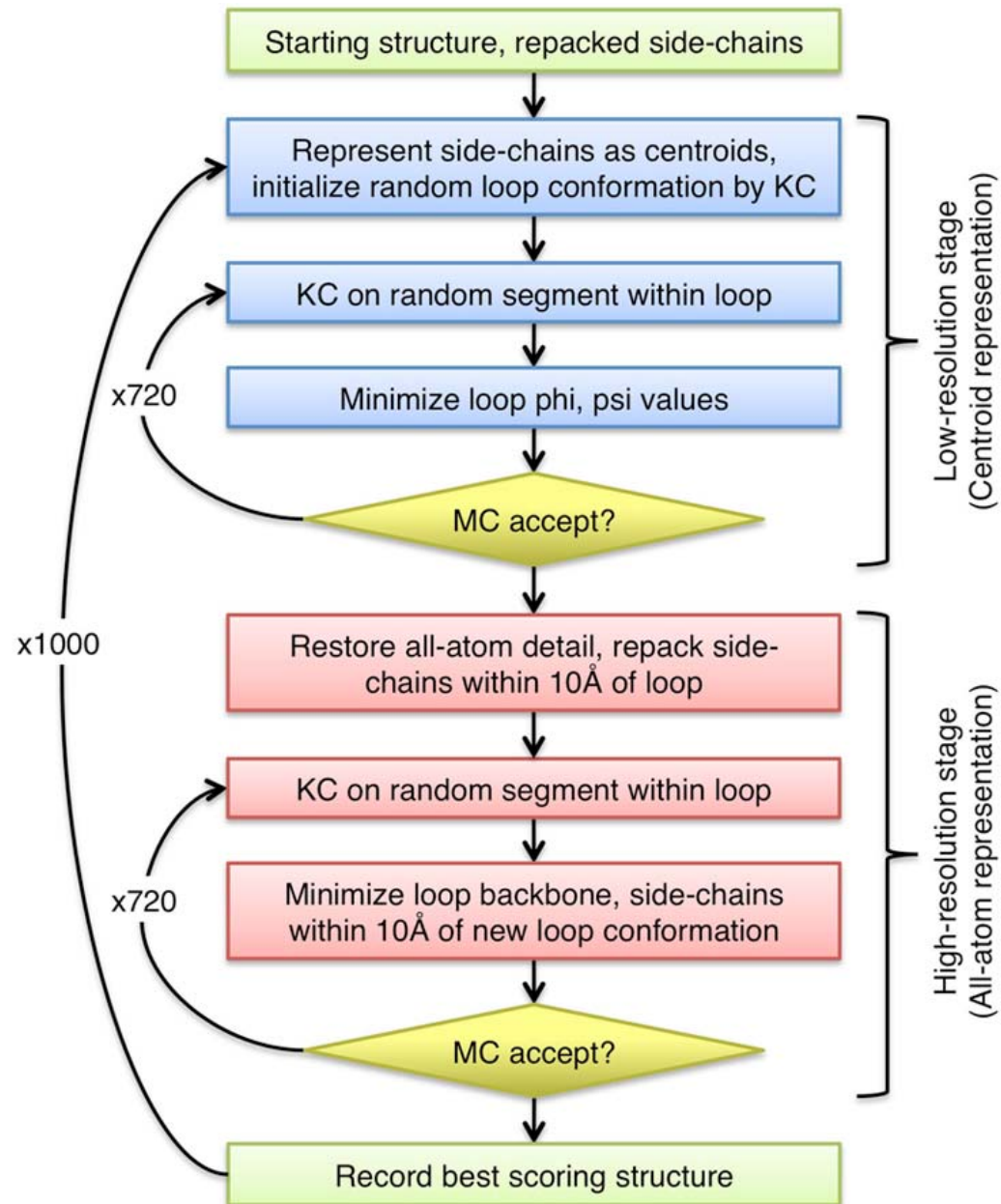


Non-pivot torsions, sampled from Ramachandran space

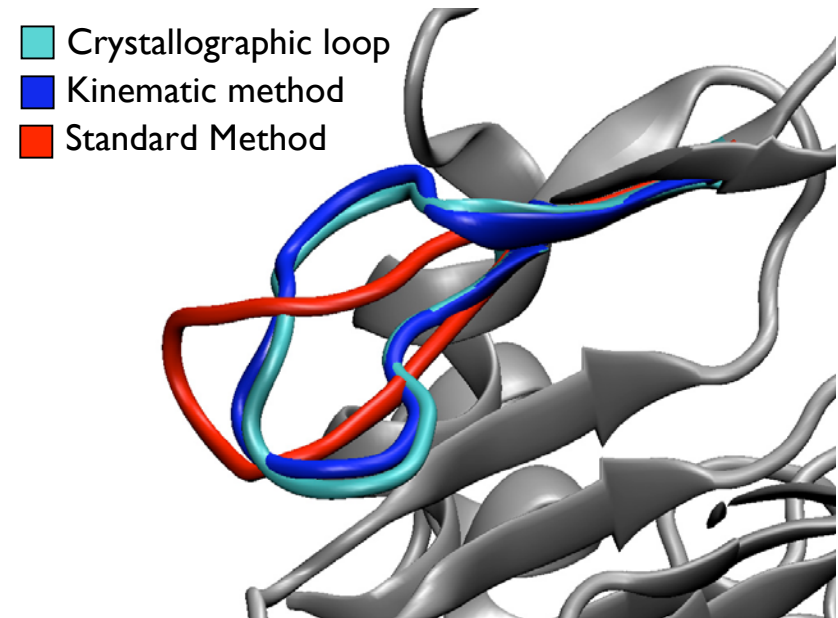
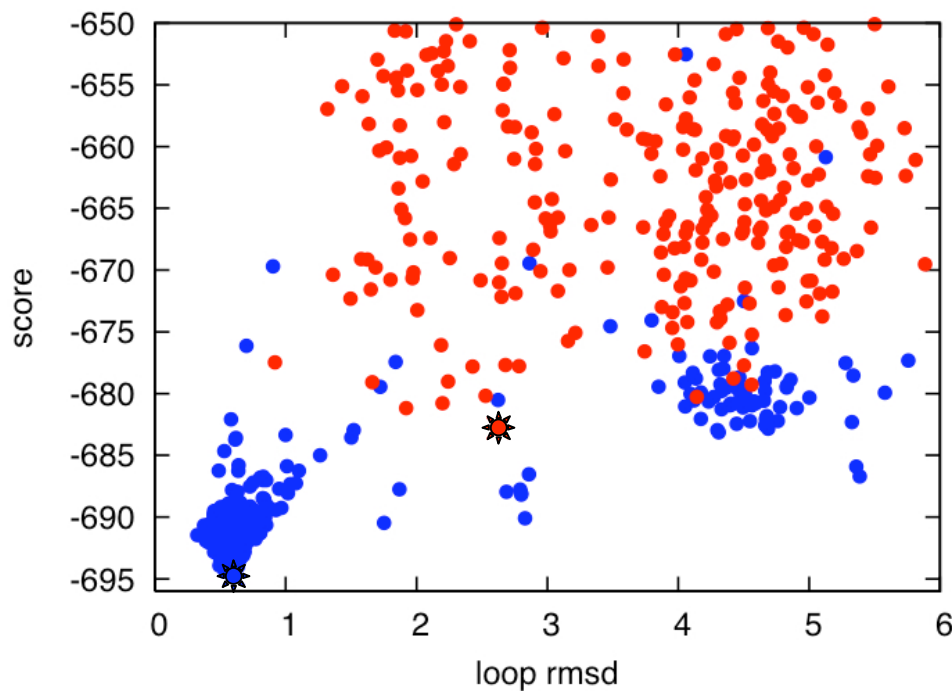


Pivot torsions, solved by closure

Kinematic closure loop modeling protocol

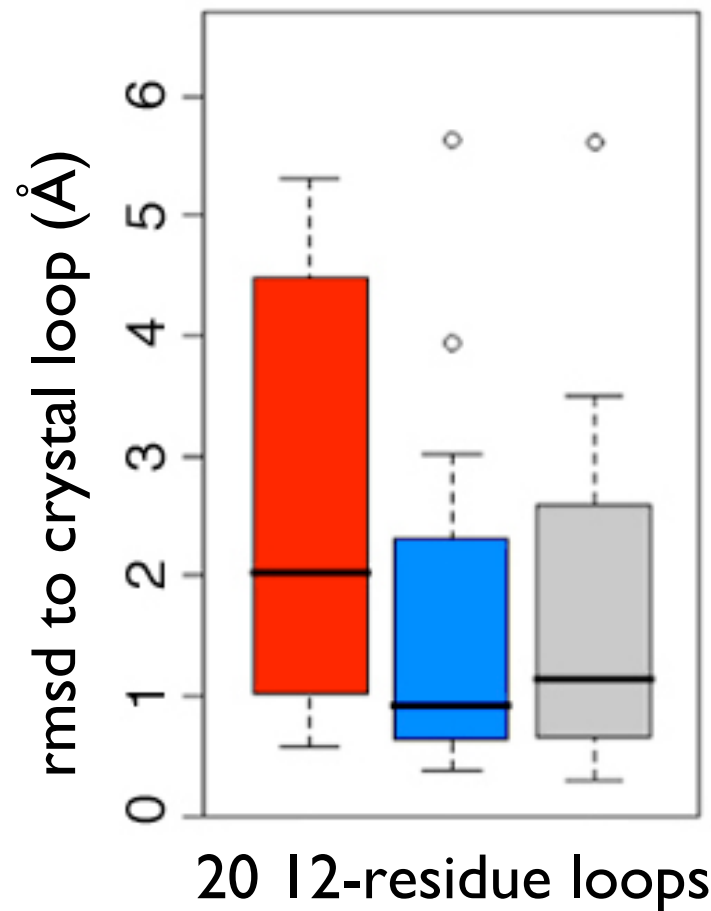


Near-native sampling by KC can yield high accuracy predictions



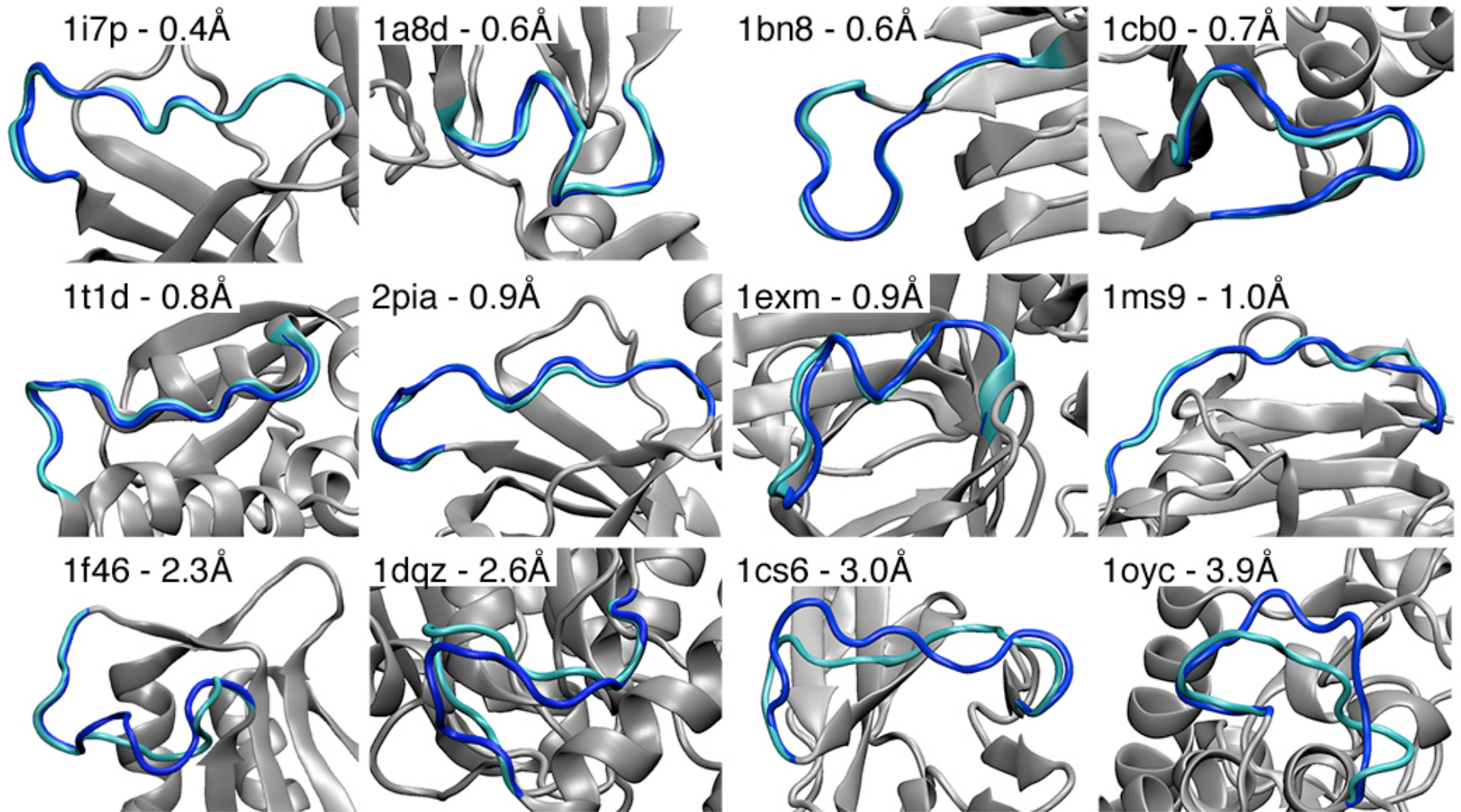
Performance across methods

Standard KC Molecular Mechanics



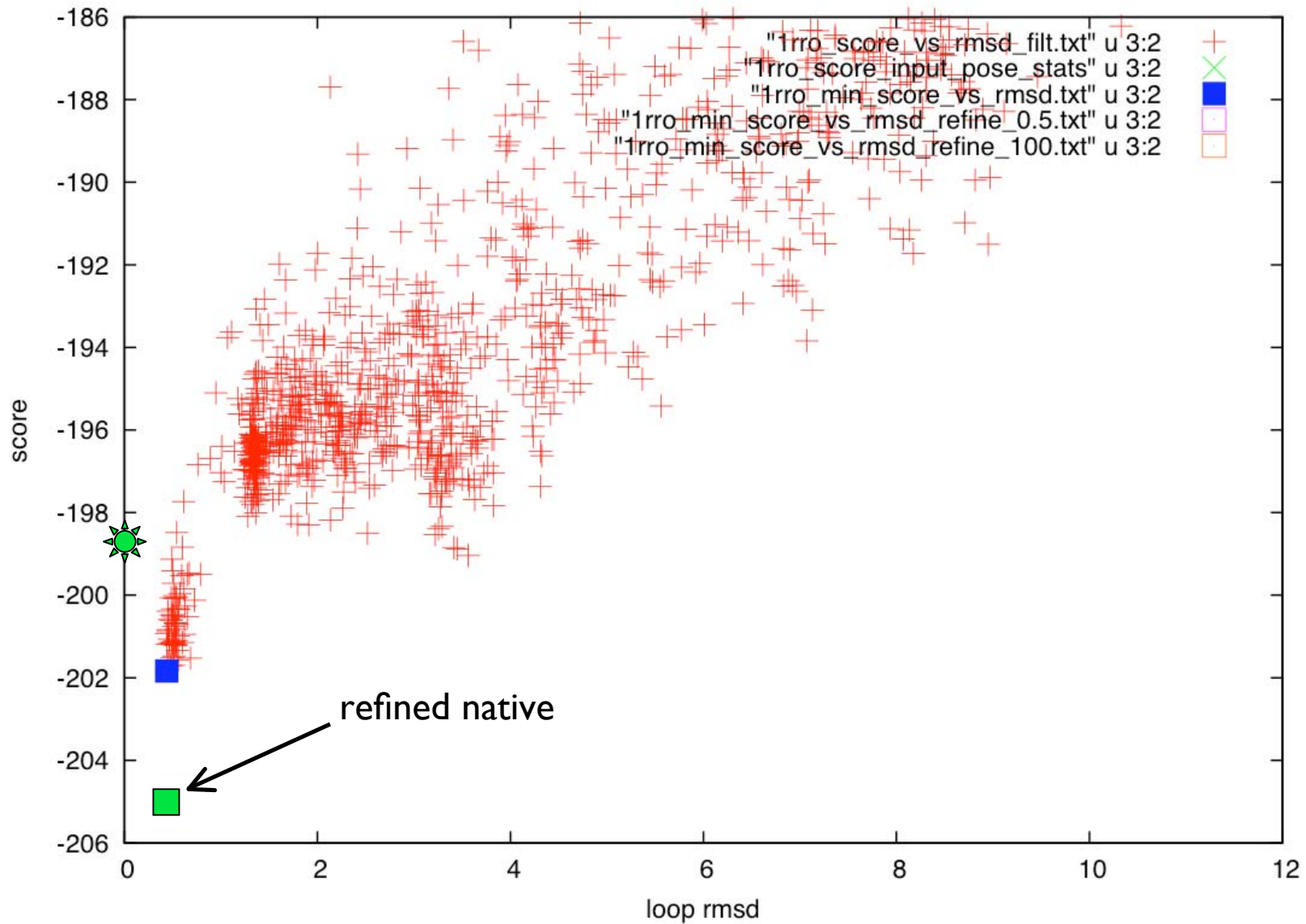
Mandell, Coutsiias & Kortemme. (2009). *Nat Methods* 6(8):551-2

Representative set of reconstructions

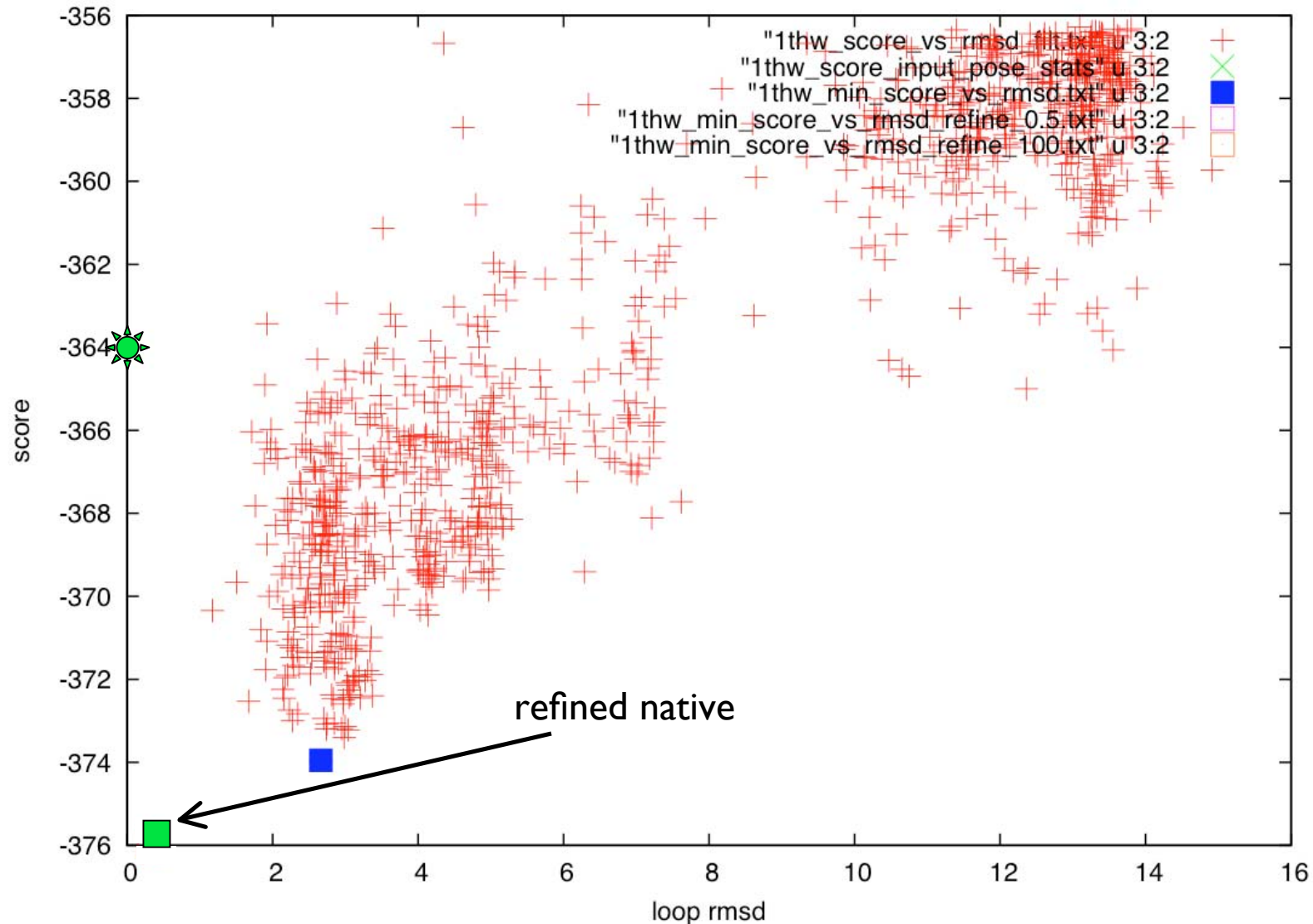


Mandell, Coutsiias & Kortemme. (2009). *Nat Methods* 6(8):551-2

Effect of refining natives



KC can reveal that some purported scoring errors are actually sampling errors



KC improves model accuracy by improved conformational sampling

KC Protocol		Standard Protocol	
Pdb	best scoring model score – crystallographic loop score	Pdb	best scoring model score – crystallographic loop score
1a8d	9.36	1a8d	21.98
1f46	7.91	1cnv	18.88
1cnv	5.25	1qlw	16.86
1i7p	4.69	1dqz	16.66
1qlw	4.18	1bhe	14.89
1cs6	2.41	1f46	9.63
1my7	-0.56	1arb	6.32
2pia	-1.63	1bn8	6.12
1m3s	-3.89	1cs6	5.36
1oyc	-5.58	1cb0	5.33
		1m3s	2.82
		1ms9	1.39
		1oyc	1.13
		1my7	0.61
		2pia	0.61

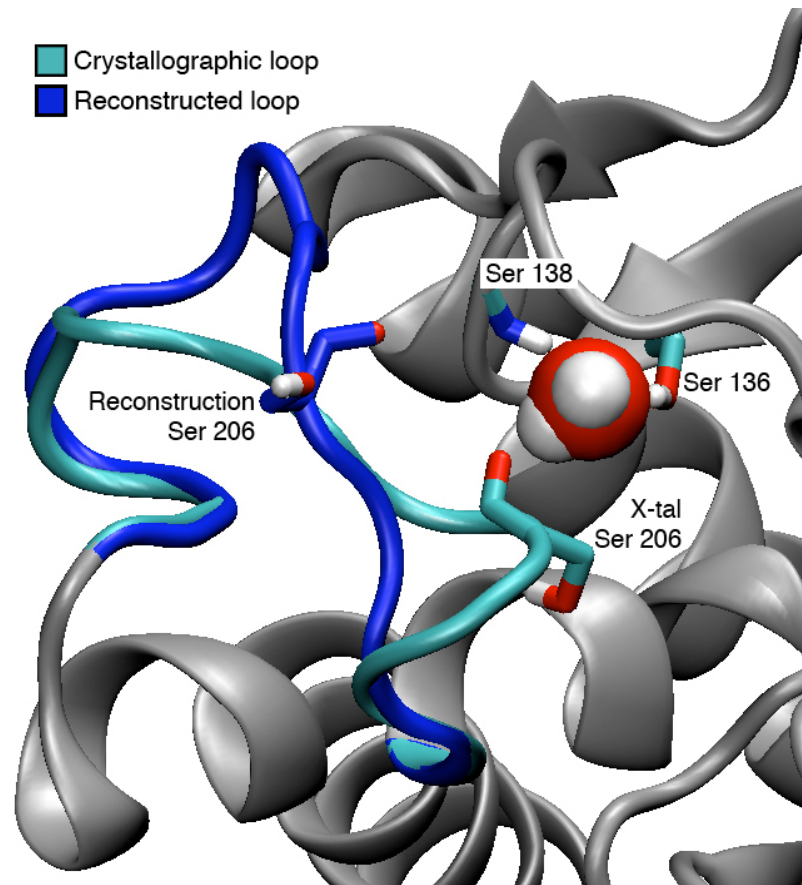
KC

10 Failures
6 Sampling
4 Scoring

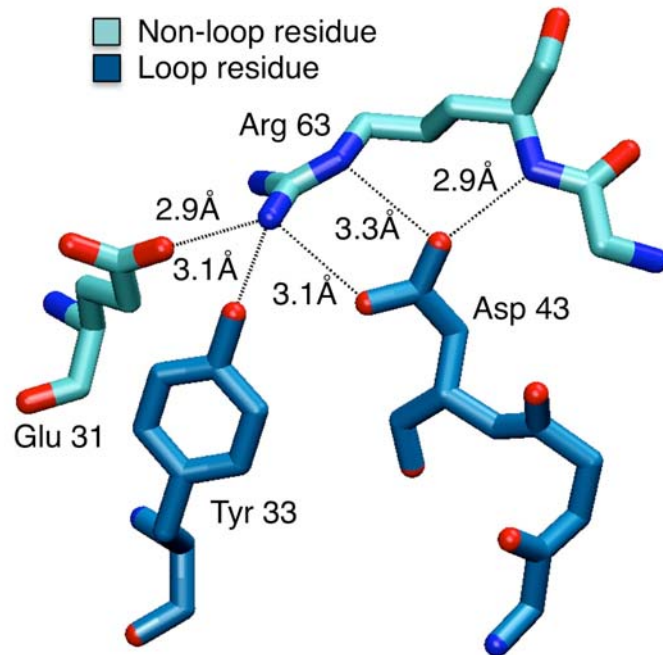
Standard

15 Failures
15 Sampling
0 Scoring

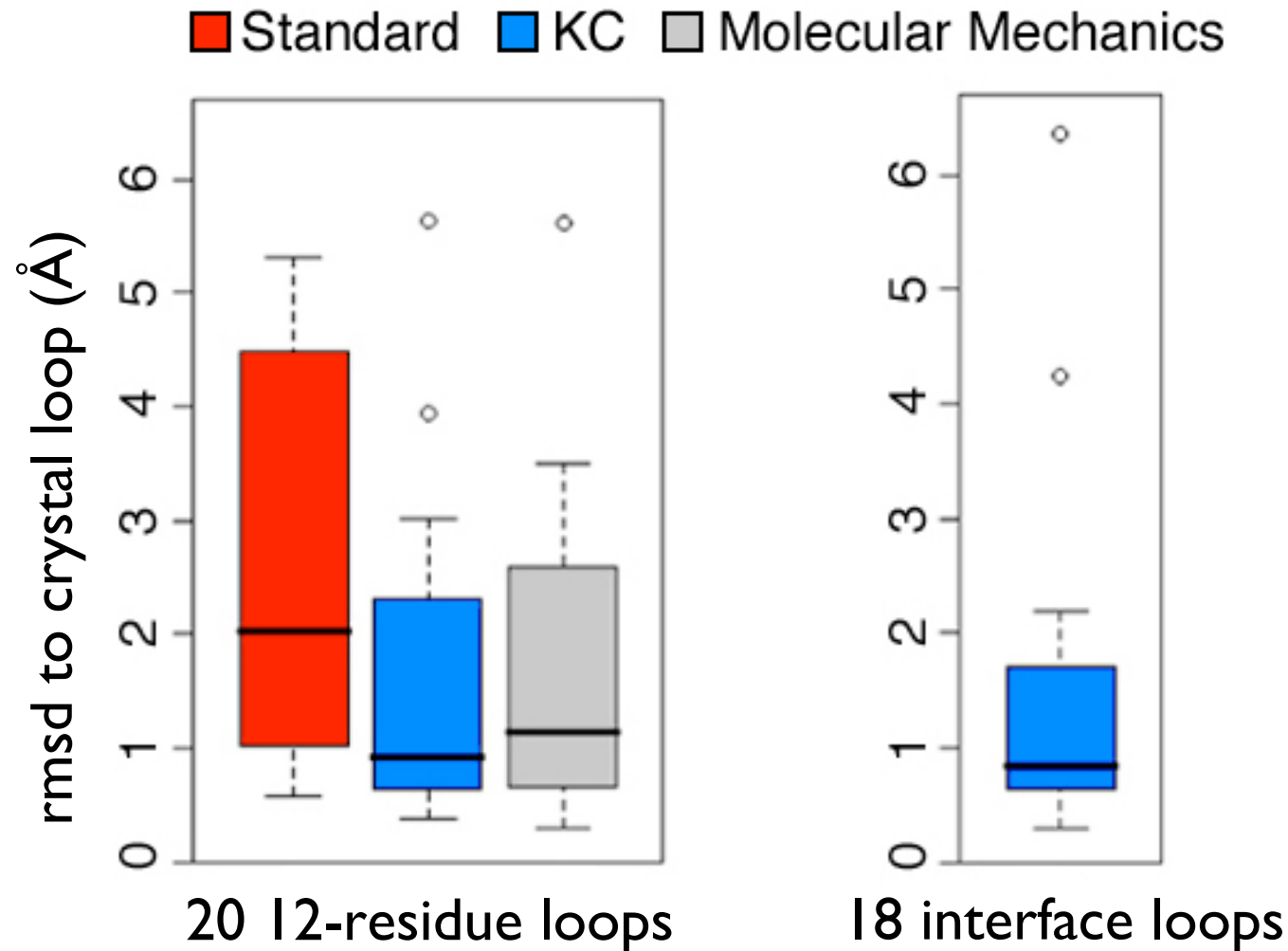
Explicit water molecules not modeled



Complex hydrogen bonding networks can be difficult

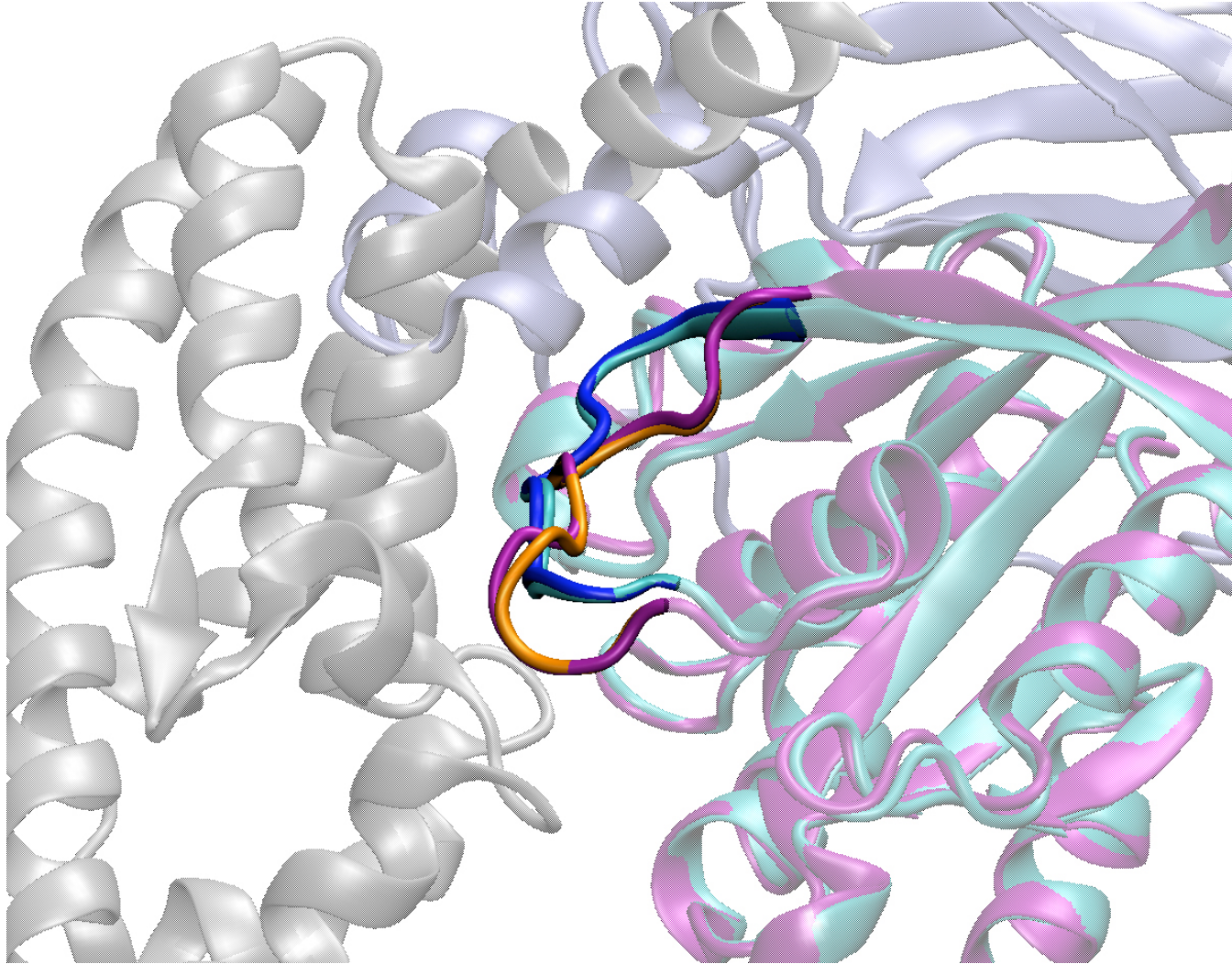


Conformational plasticity in interfaces

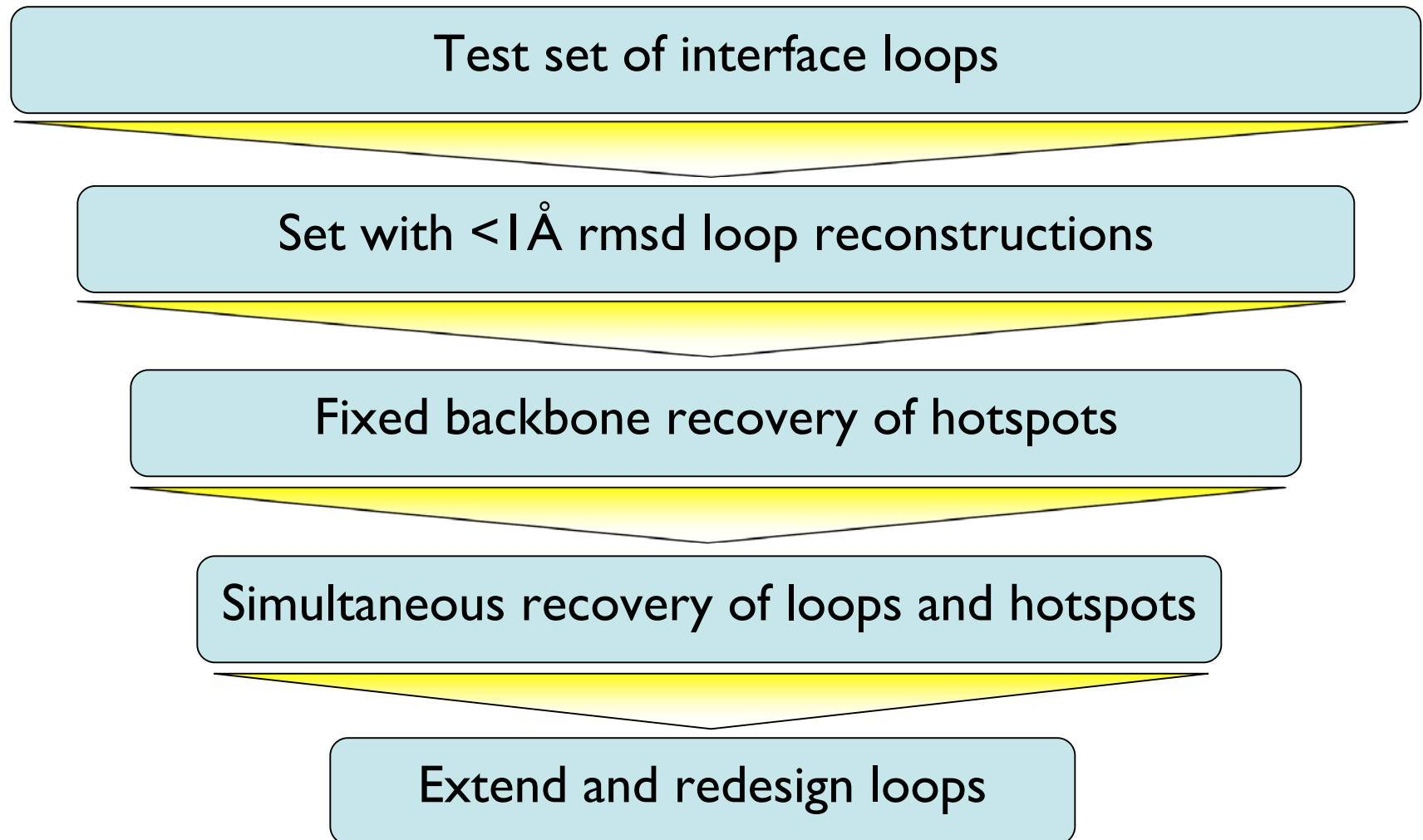


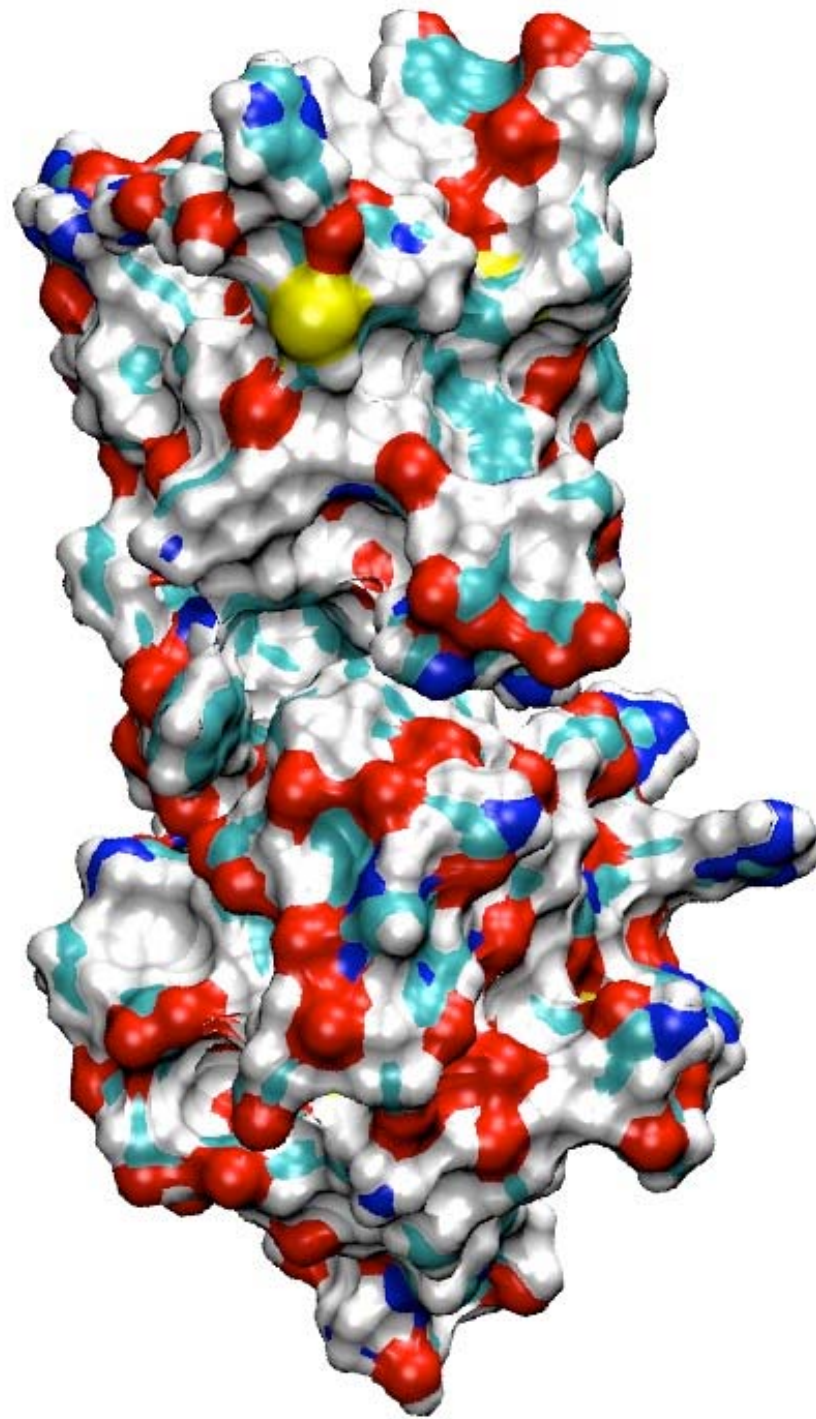
Mandell, Coutsiias & Kortemme. (2009). *Nat Methods* 6(8):551-2

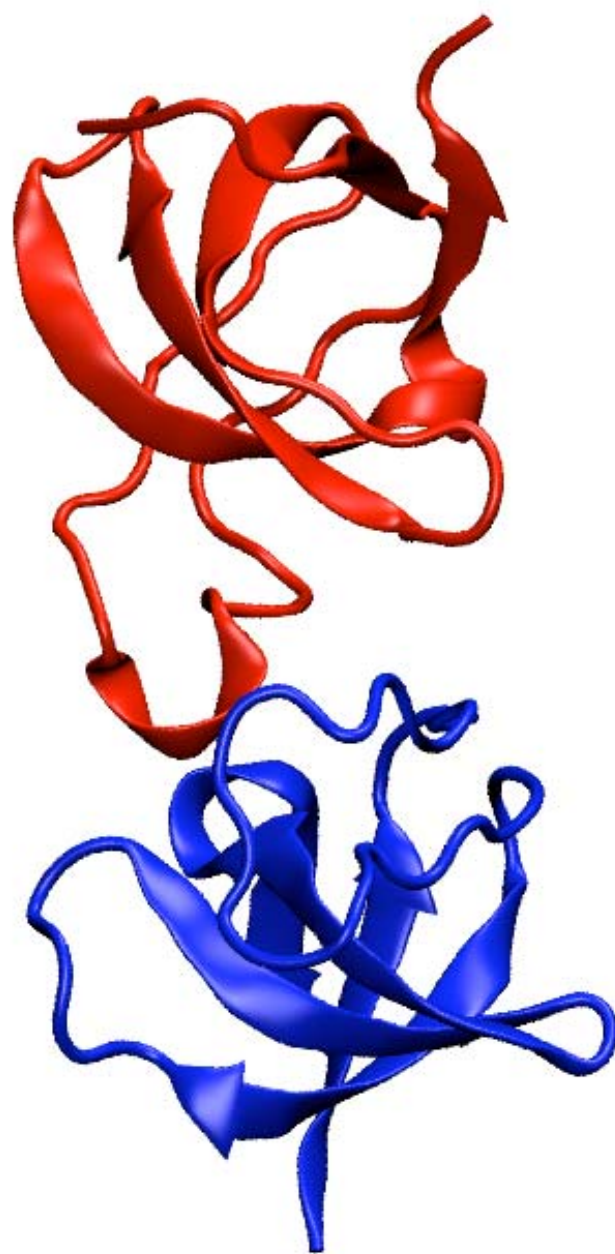
Conformational plasticity in interfaces

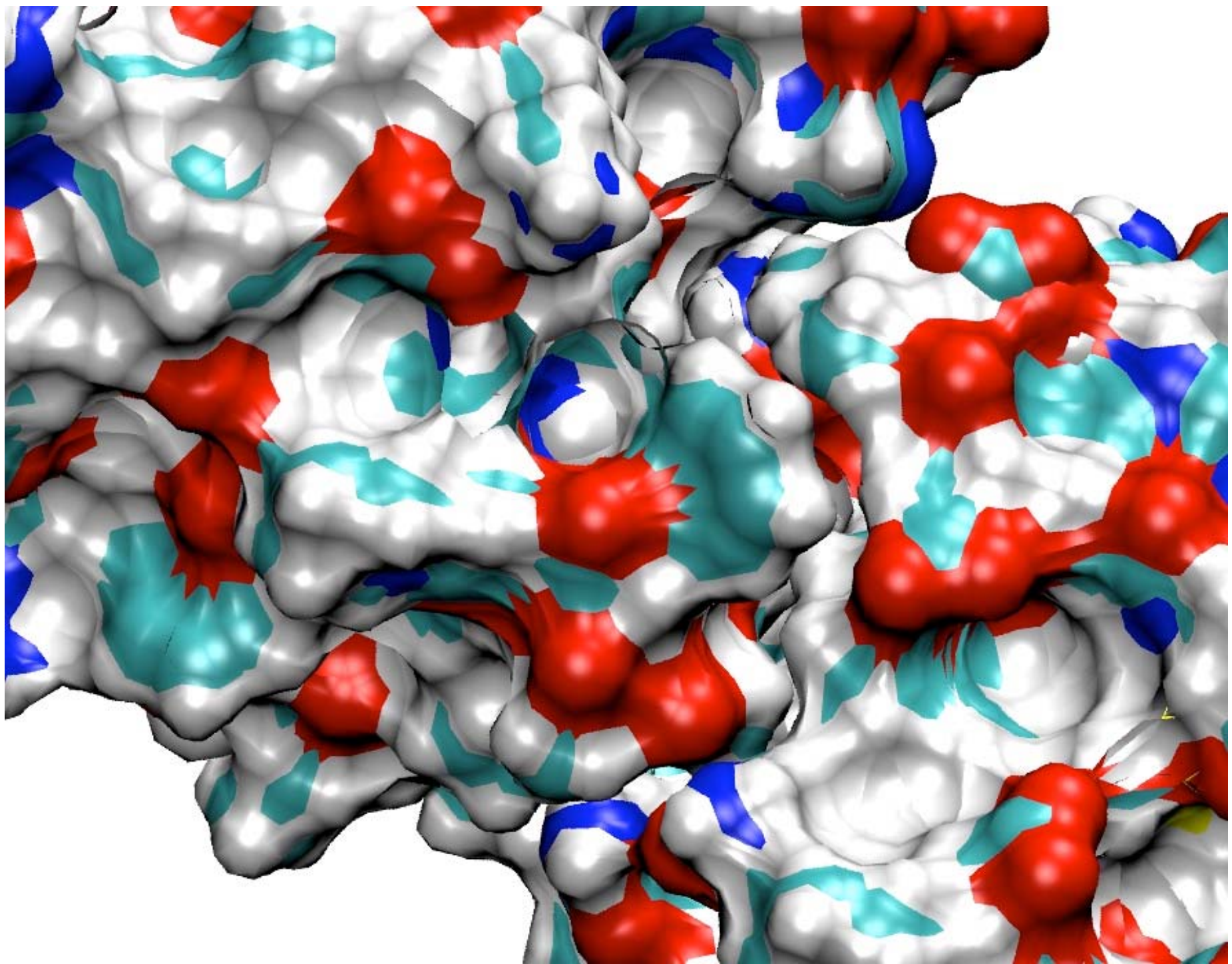


Kinematic modeling and design protocol









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