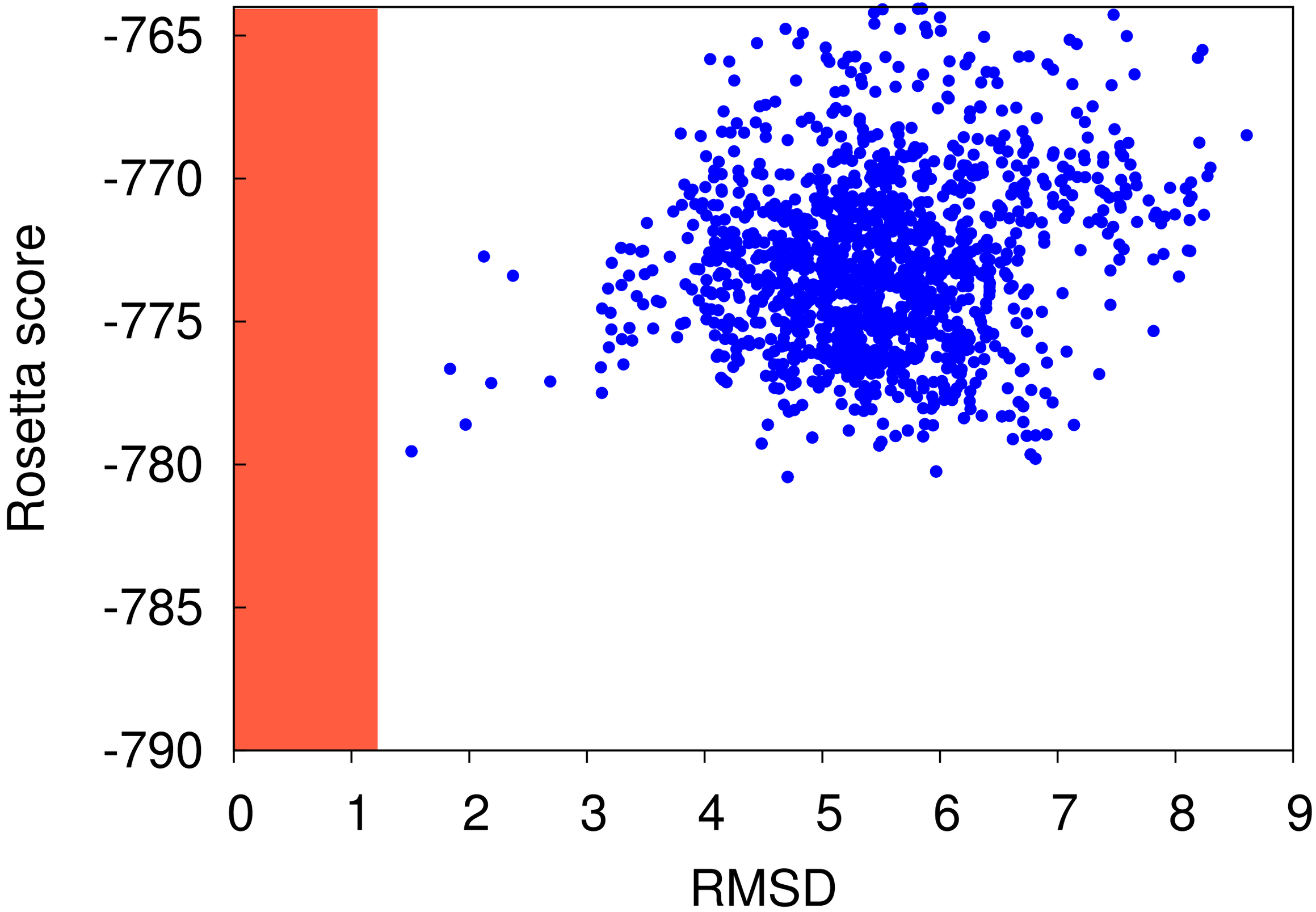
Increased sampling of near-native conformations

Amelie Stein
Kortemme Lab

RosettaCon 2012


-765
-770
-775
-780
-785
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Rosetta score
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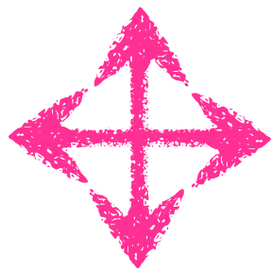
RMSD

Key problems and approaches

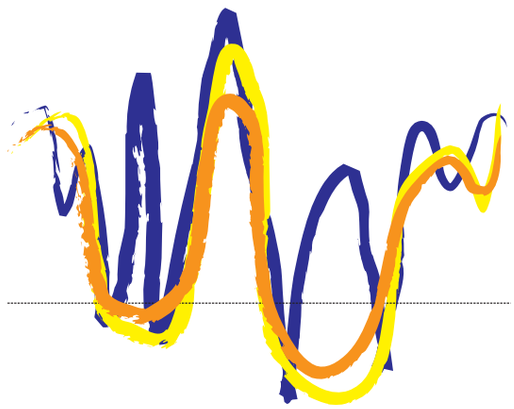
sampling

- vast conformational space



<u>diversification</u>

- large energy barriers and narrow minima



<u>annealing</u>

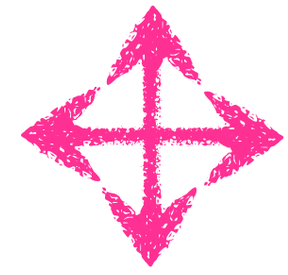
<u>intensification</u>

scoring

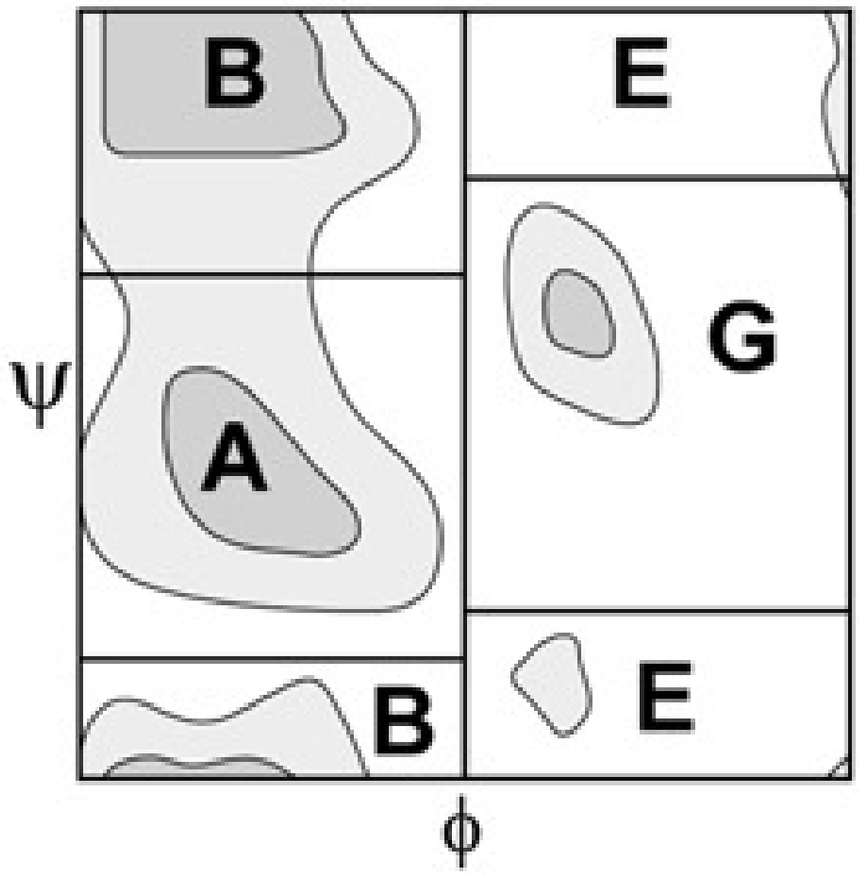
- inherently coupled to sampling

Overview of sampling improvement strategies

- **Taboo Sampling** promotes diversity in centroid stage models
  - keep track of the torsion bins that have been sampled so far
  - pick phi/psi combinations from underrepresented bins instead of randomly



Bin Qian
DE Kim *et al.*, JMB 2009



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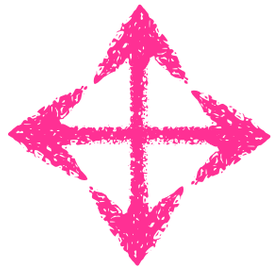

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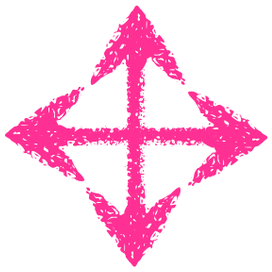

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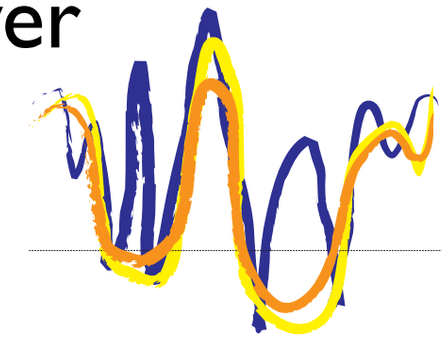
- **Ramp** the weight of `fa_rep` and `rama` to get over energy barriers and into narrow minima



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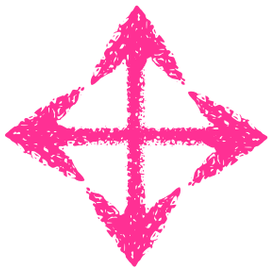

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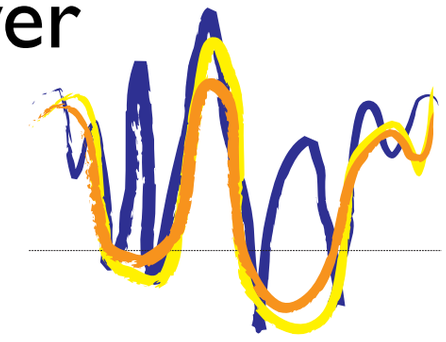


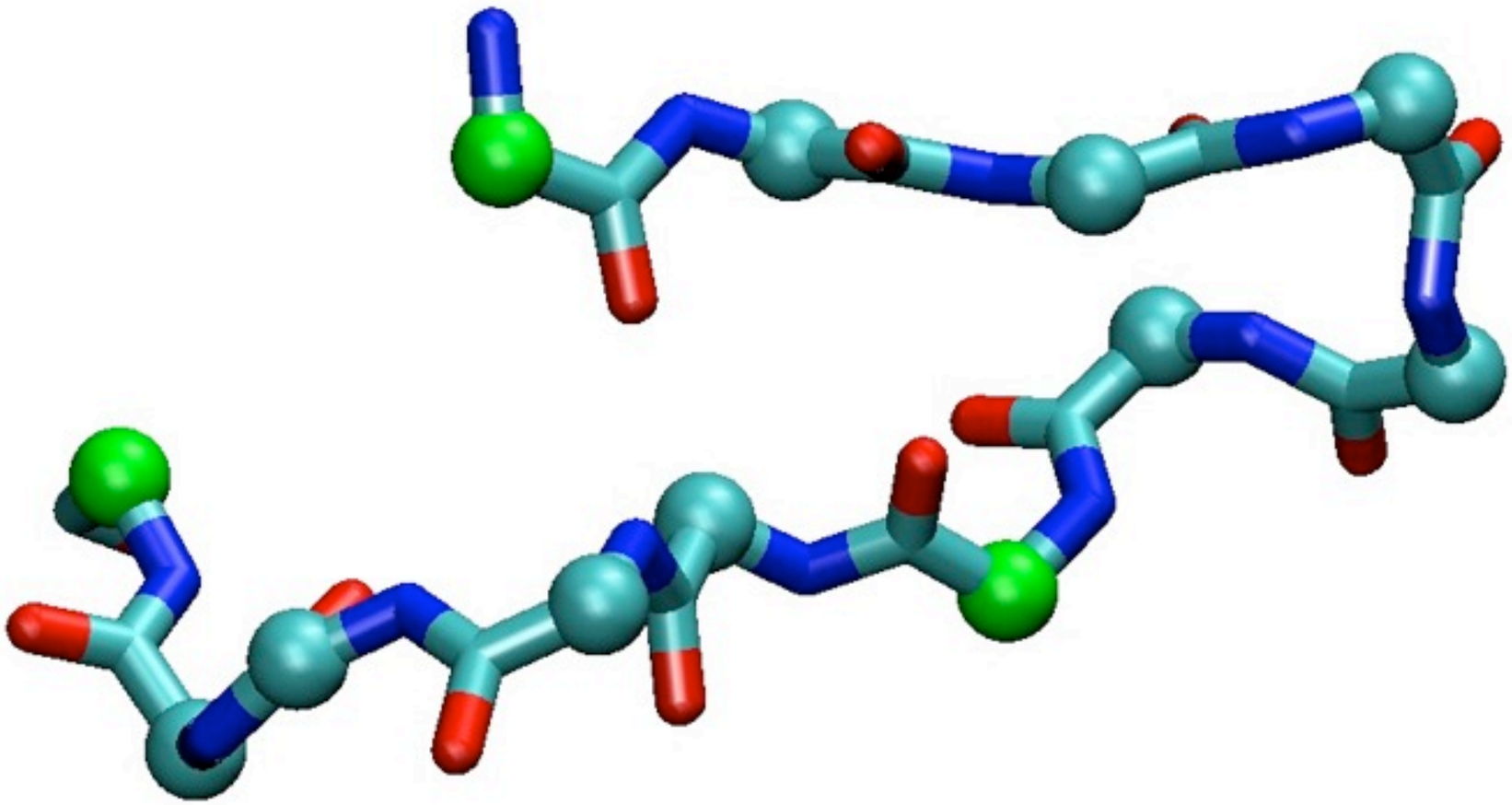
- **Neighbor-dependent Ramachandran distributions** (**rama2b**) enable sampling phi/psi combinations considering the adjacent residues

Ting *et al.*, PLoS Comp Biol 2010

Local conformational sampling as a "model system" to test new strategies

- "tractable"
  - small enough that a considerable fraction of the conformational space can in principle be sampled
- "diverse"
  - success and failure cases
- established benchmark set
  - we have a performance baseline
  - measurable improvements are not trivial

The robotics-inspired Kinematic Closure method (KIC) can be generalized to work for protein segments of any length



Coutsias *et al.* J Comp Chem 2004.
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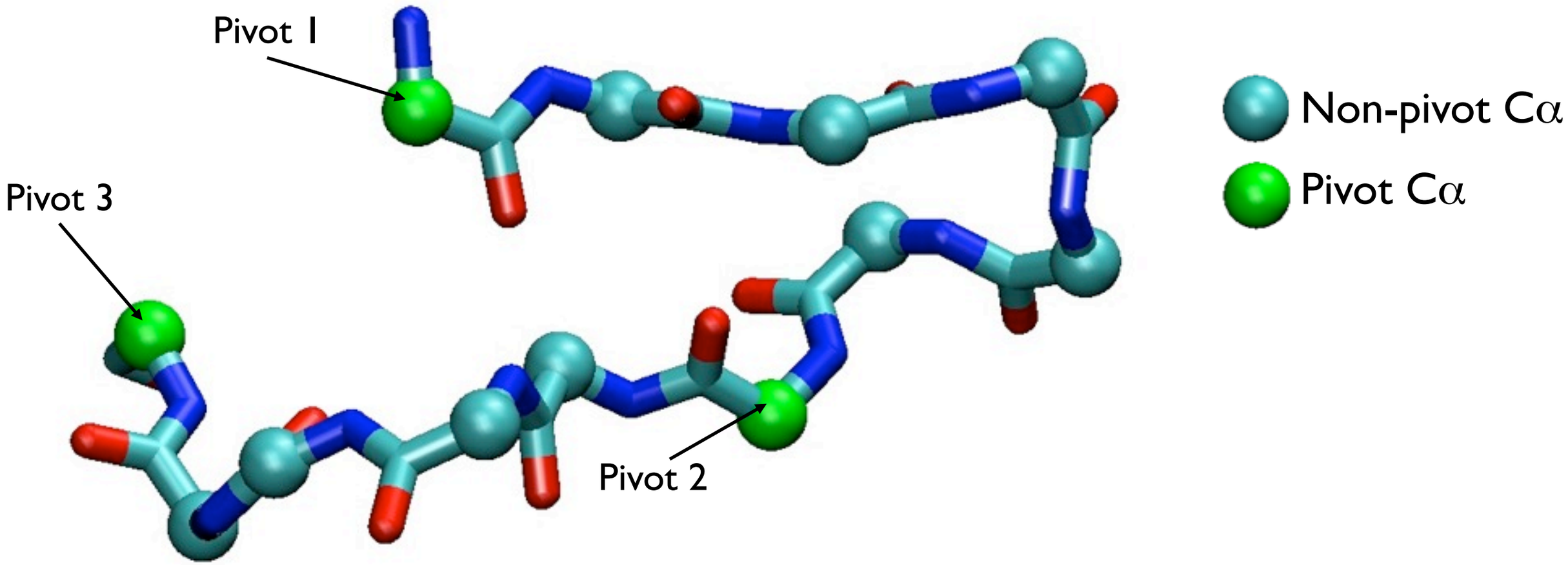

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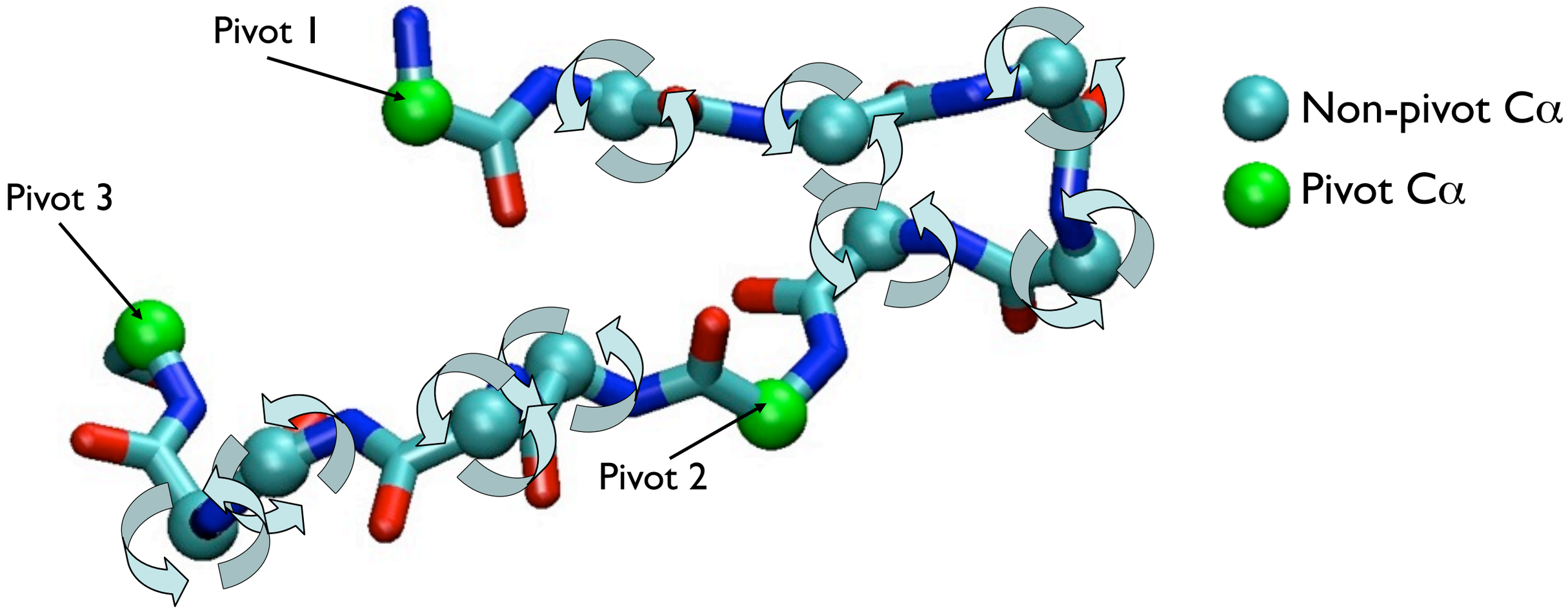

Non-pivot torsions, sampled from Ramachandran space

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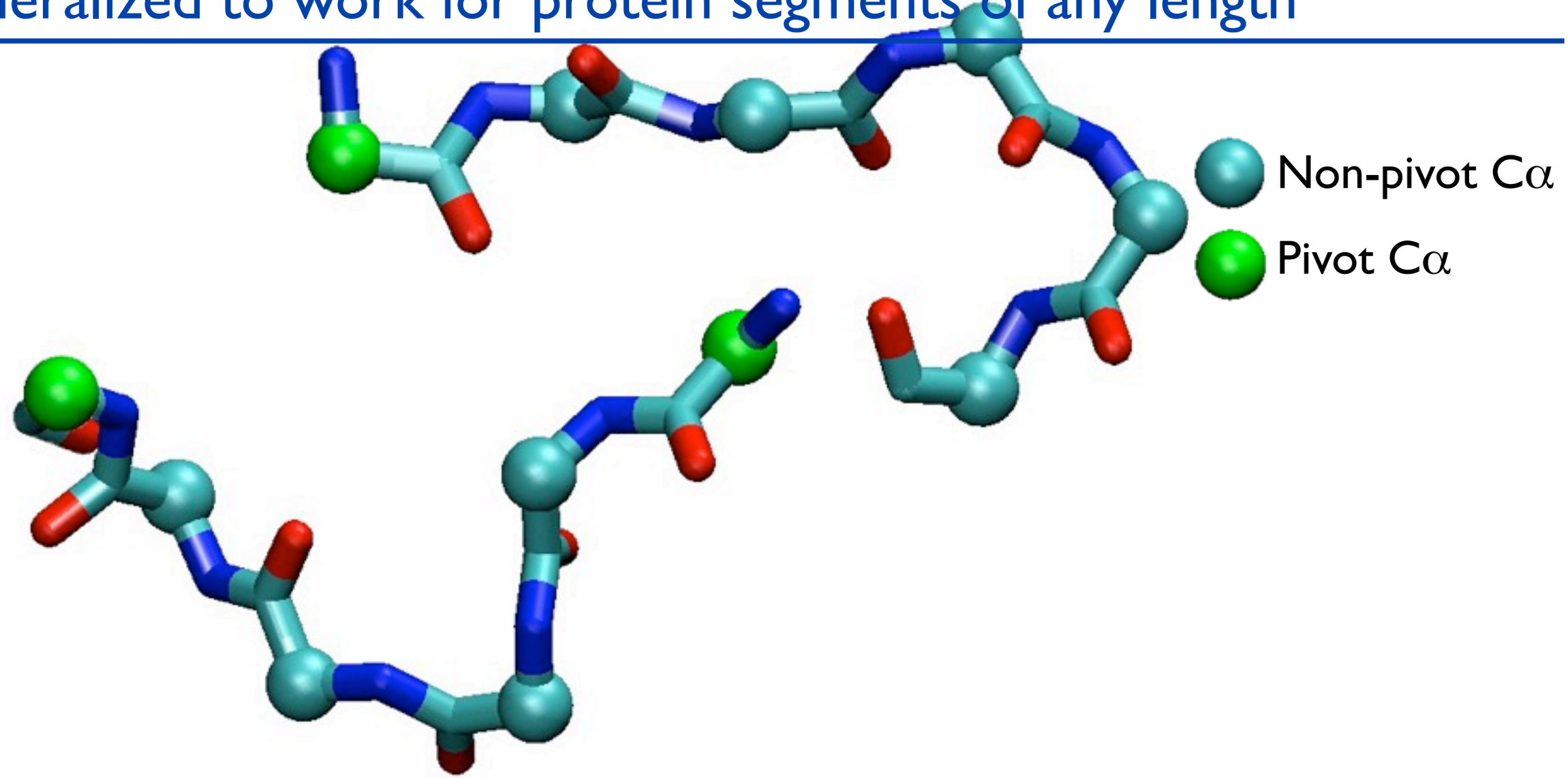

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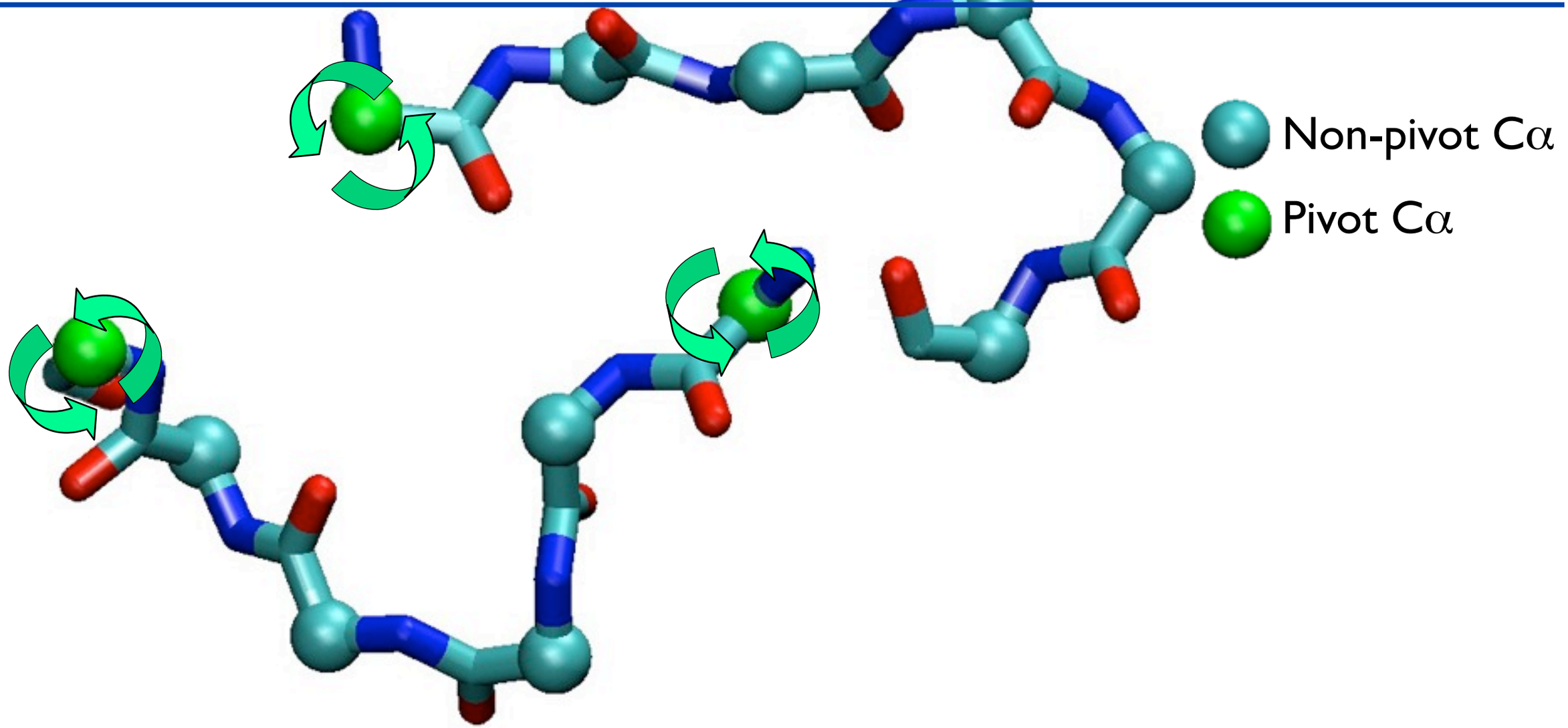

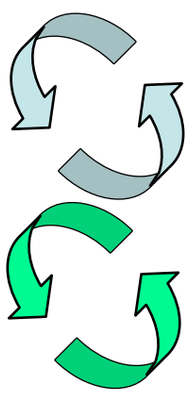

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Pivot torsions, solved analytically by closure

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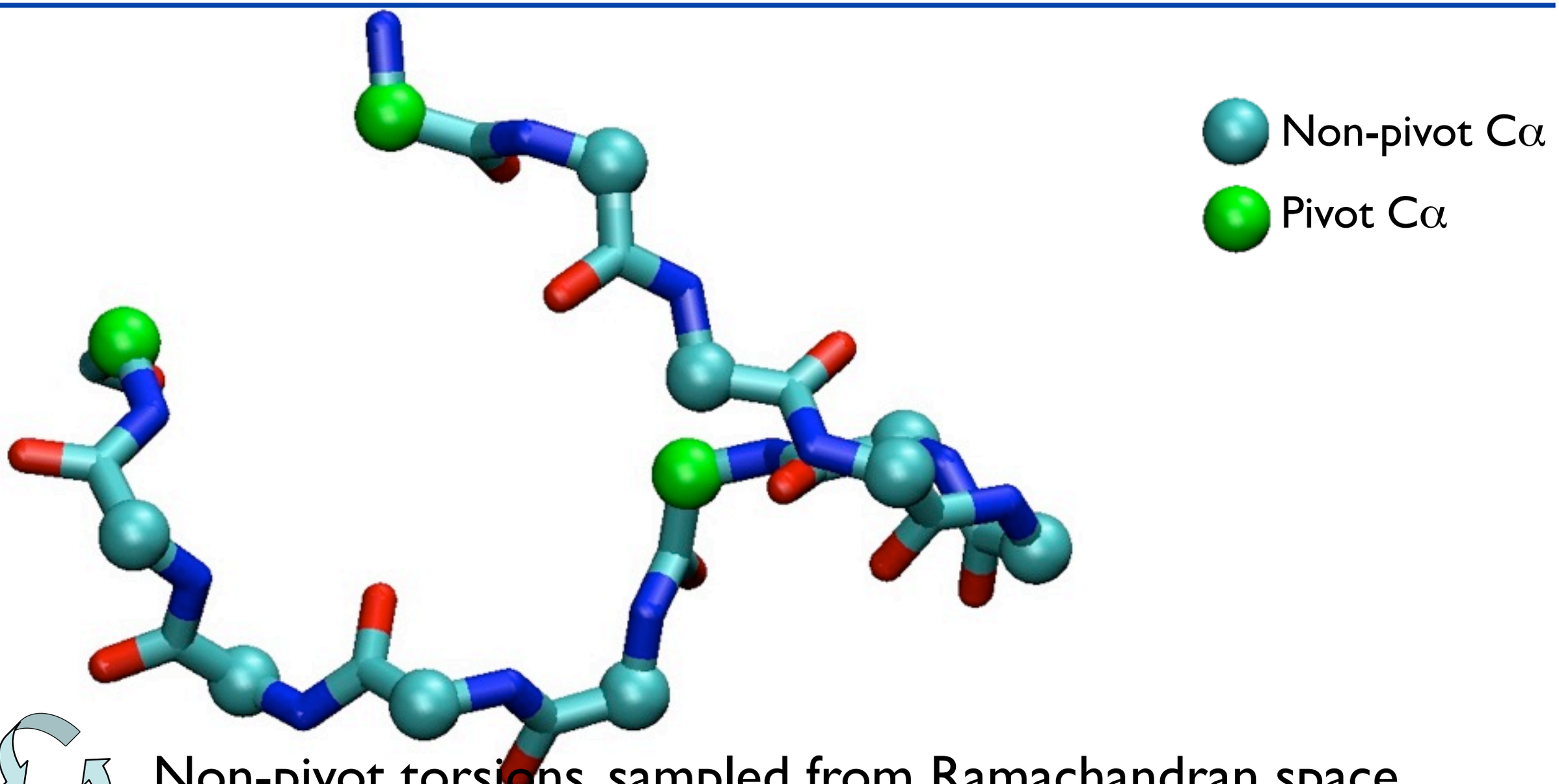

Non-pivot torsions, sampled from Ramachandran space

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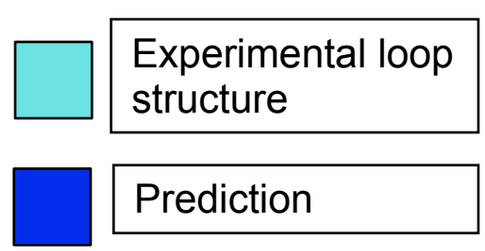
KIC explores a broad range of possible conformations, and reconstructs loops with high accuracy

- integrated in a Monte-Carlo minimization protocol in Rosetta
- side chains within 10A of the remodeled region are repacked
  - no native rotamers



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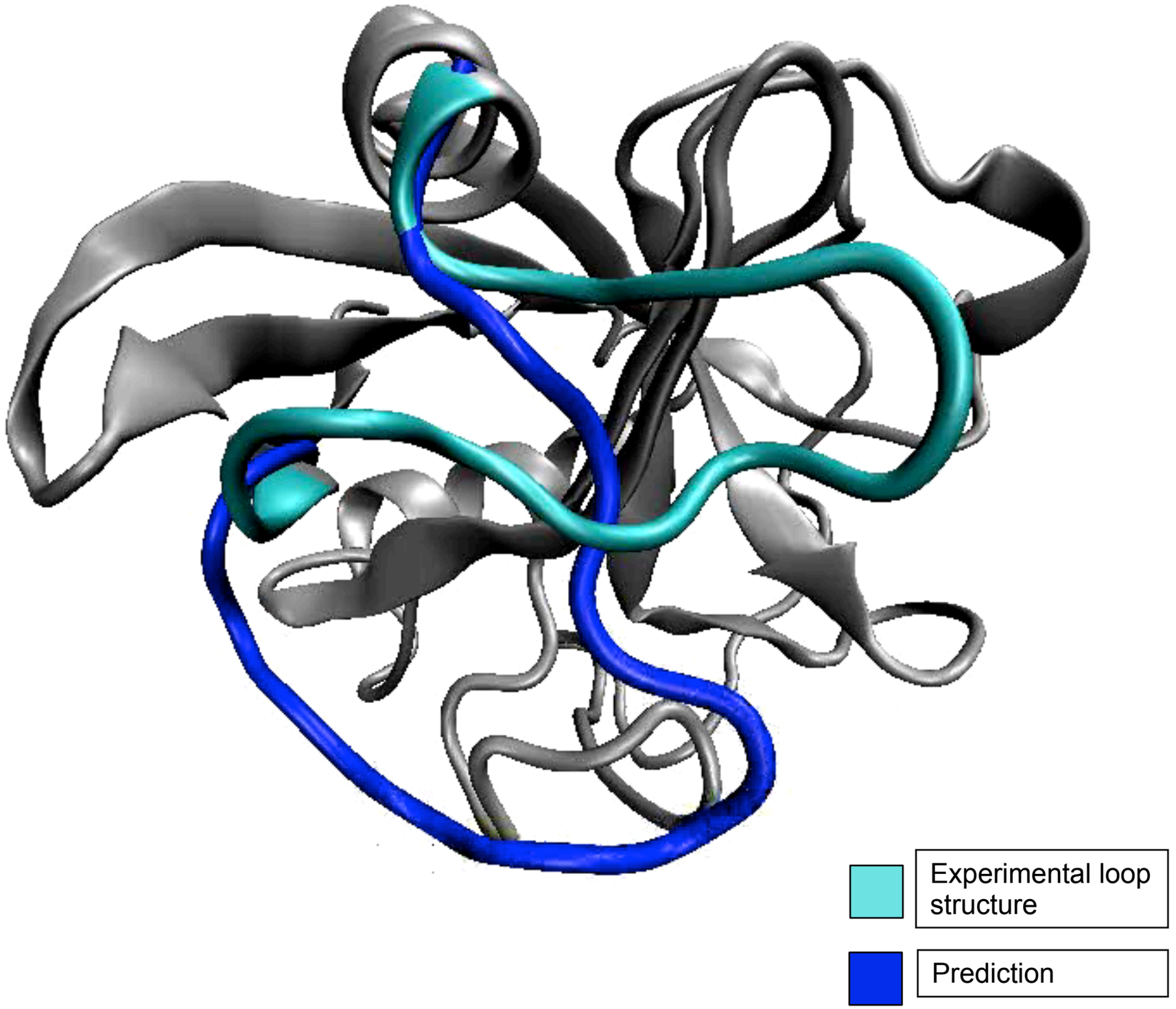
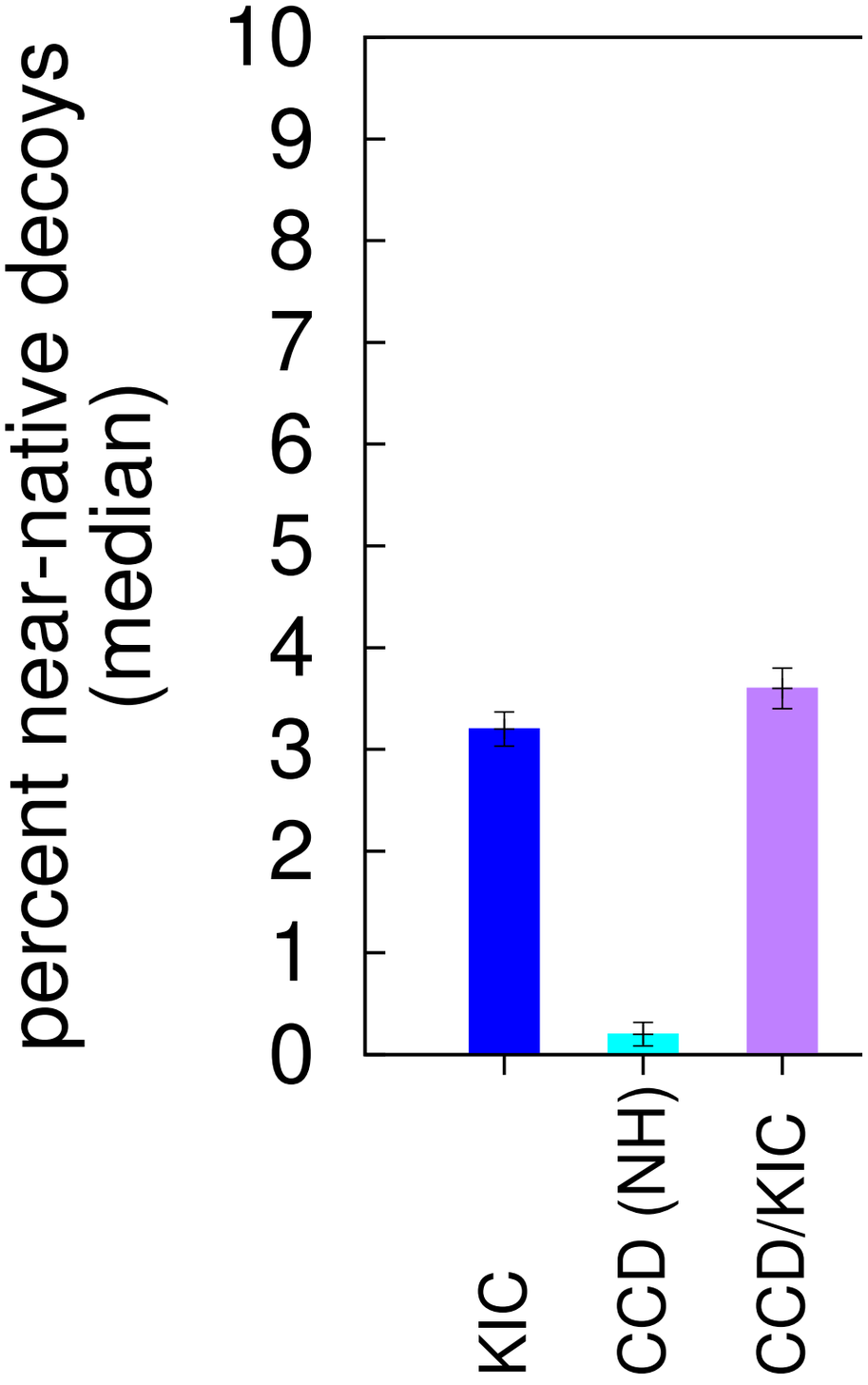
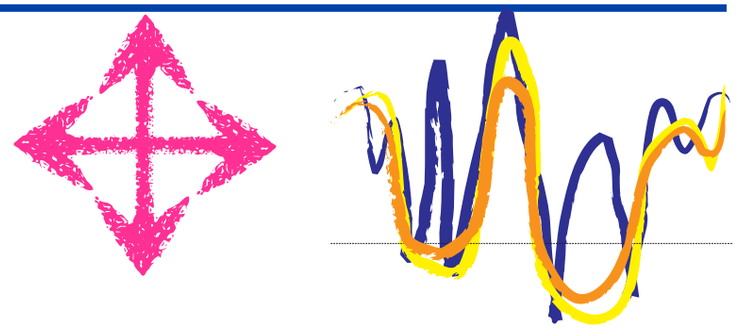


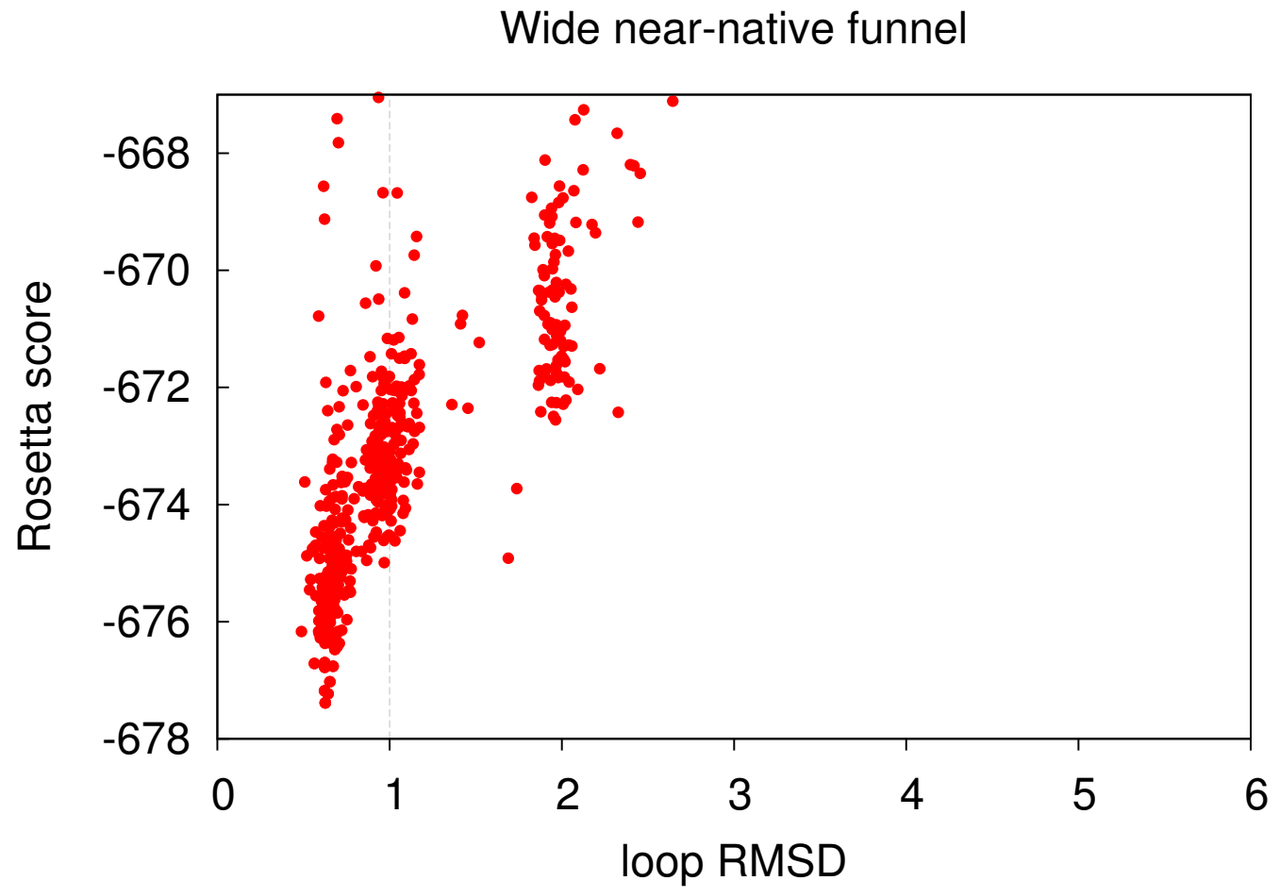
Near-native conformations are rarely sampled across the benchmark set (12-residue loops in 45 structures)

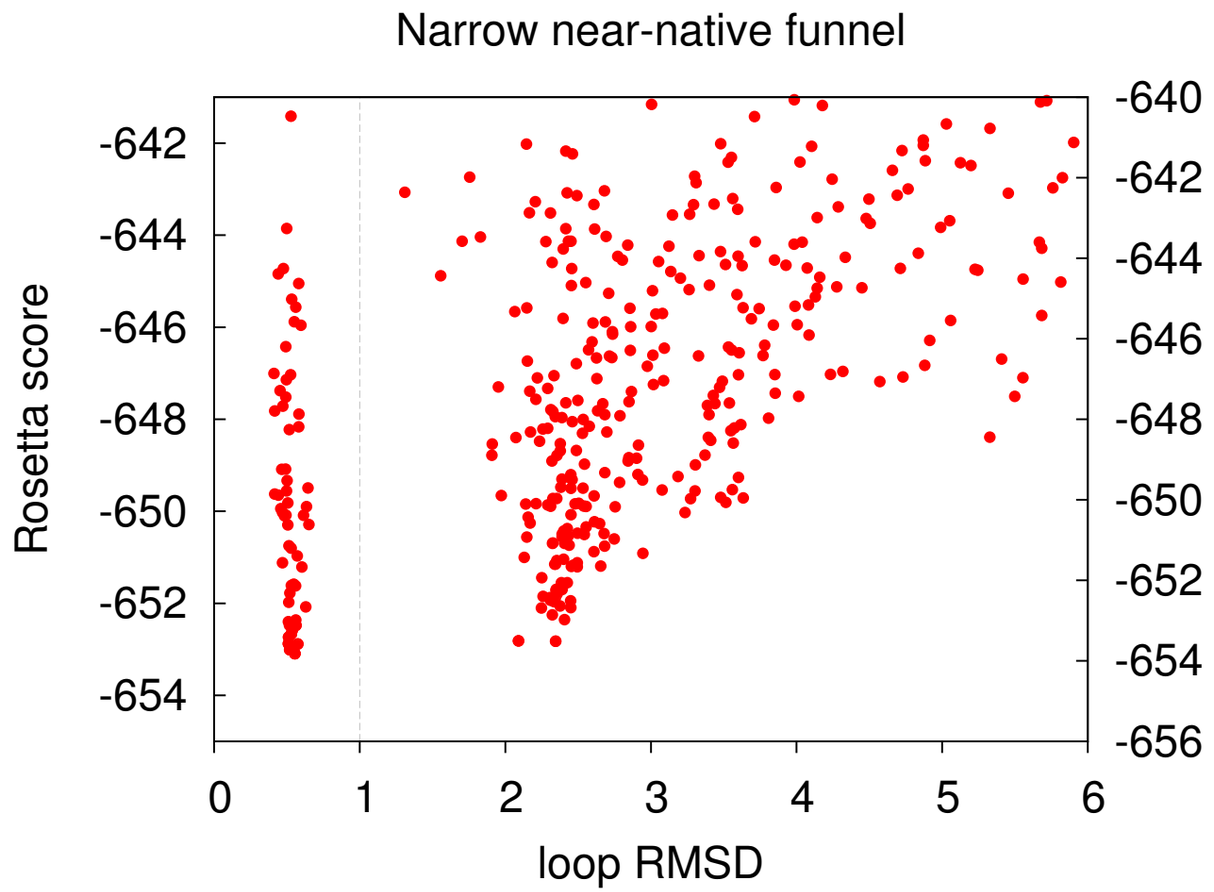


- Metric: median percentage of near-native (<1A) conformations across the benchmark set

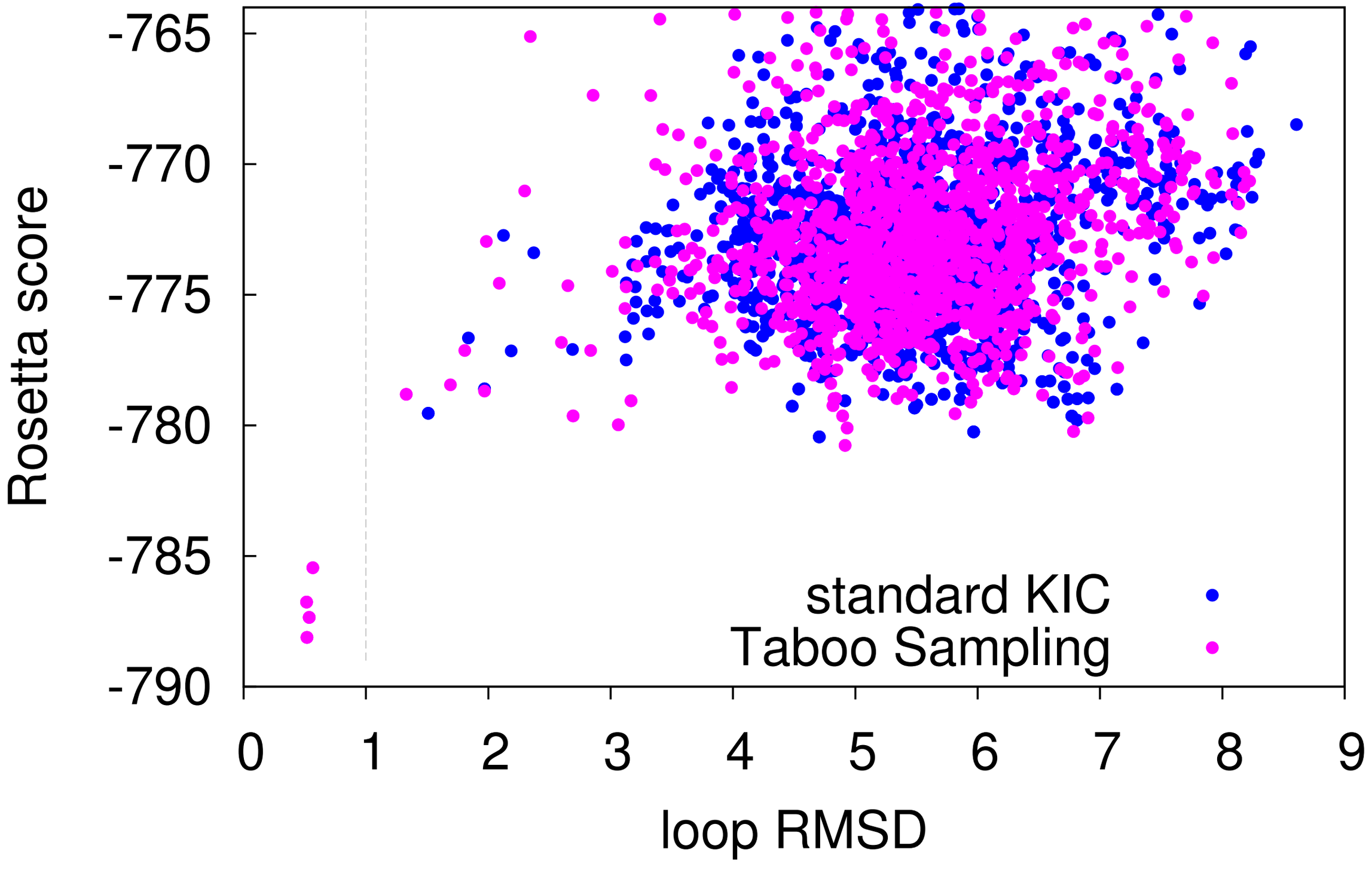
Narrow minima are difficult to sample



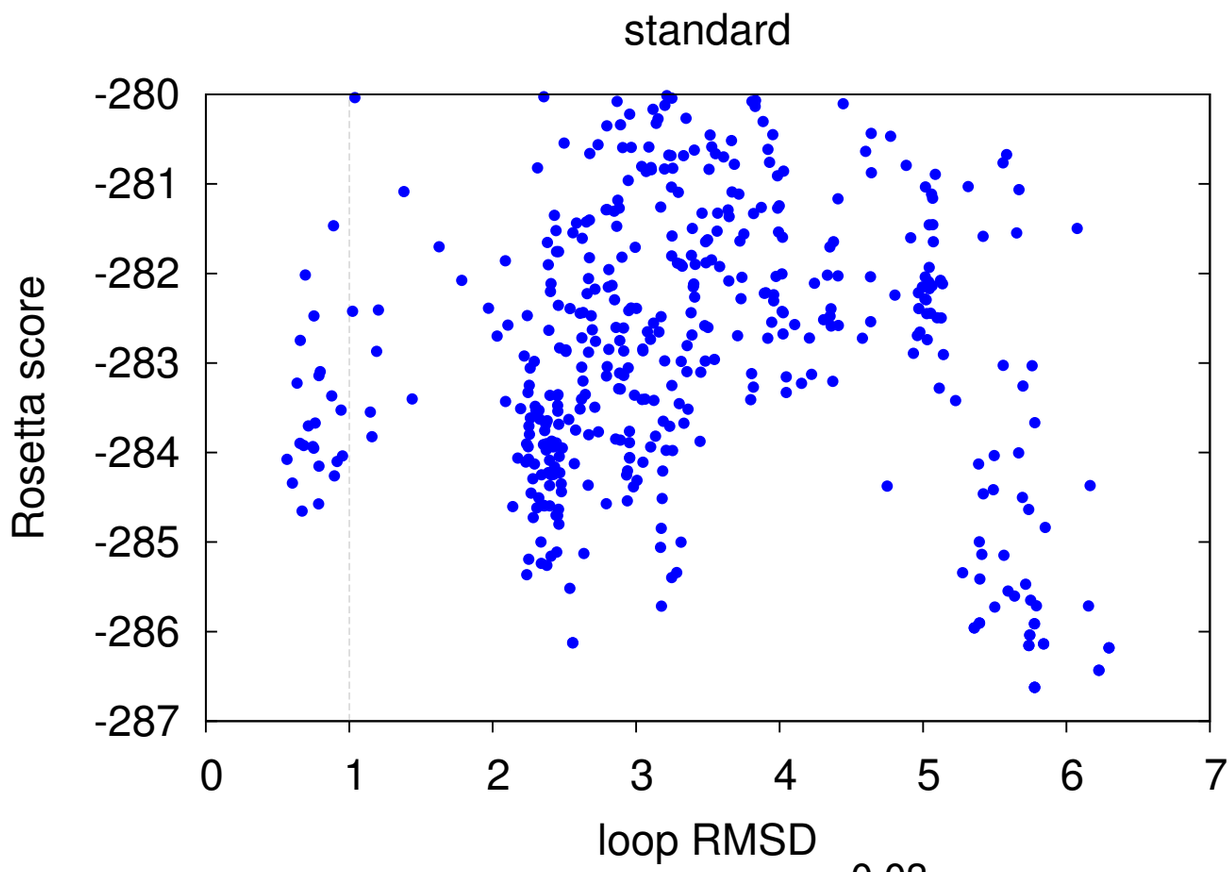


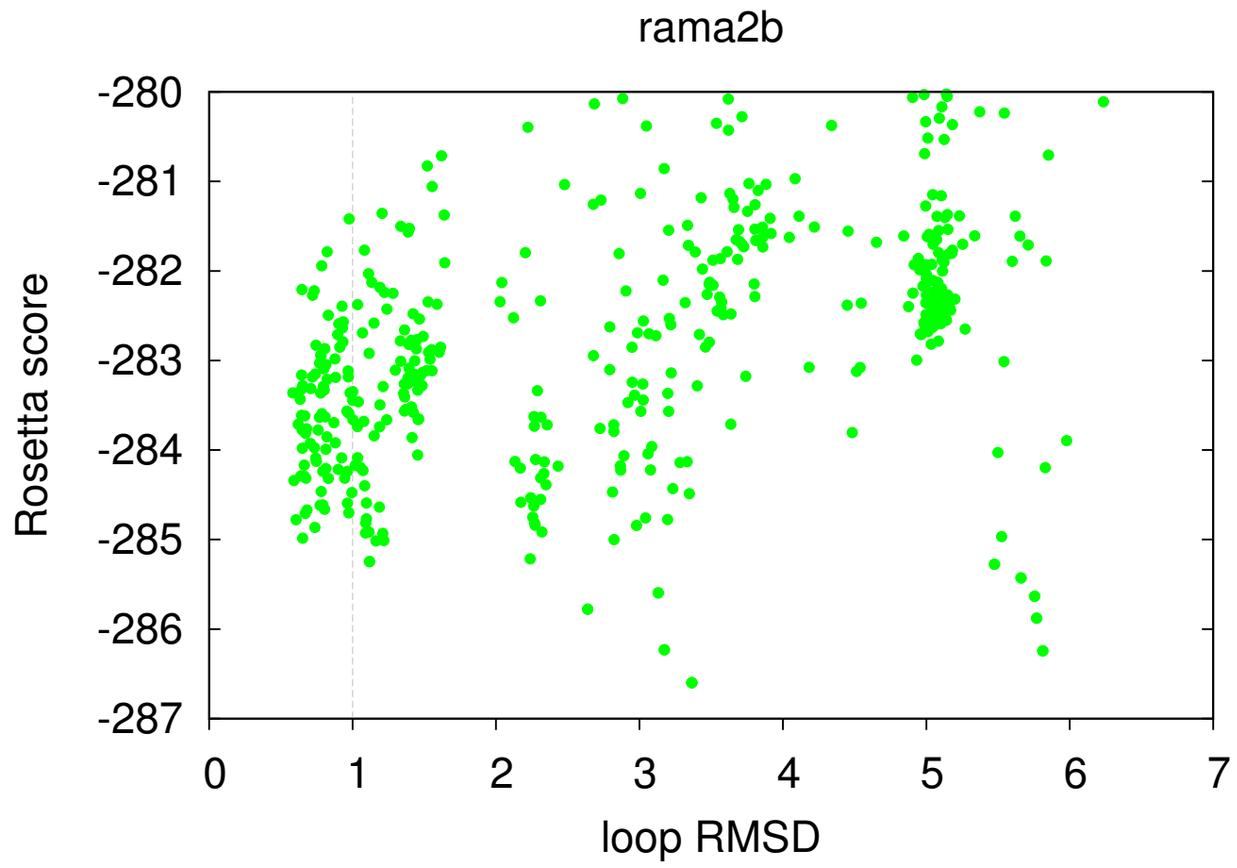


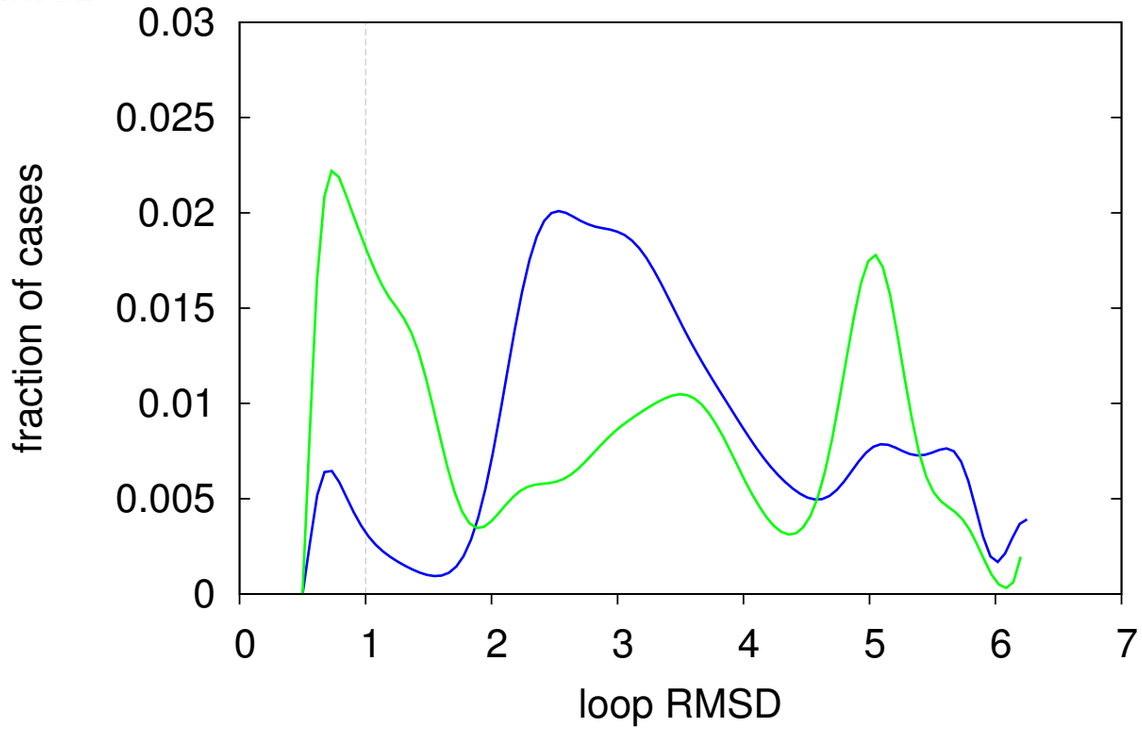
Taboo Sampling increases diversity among sampled conformations



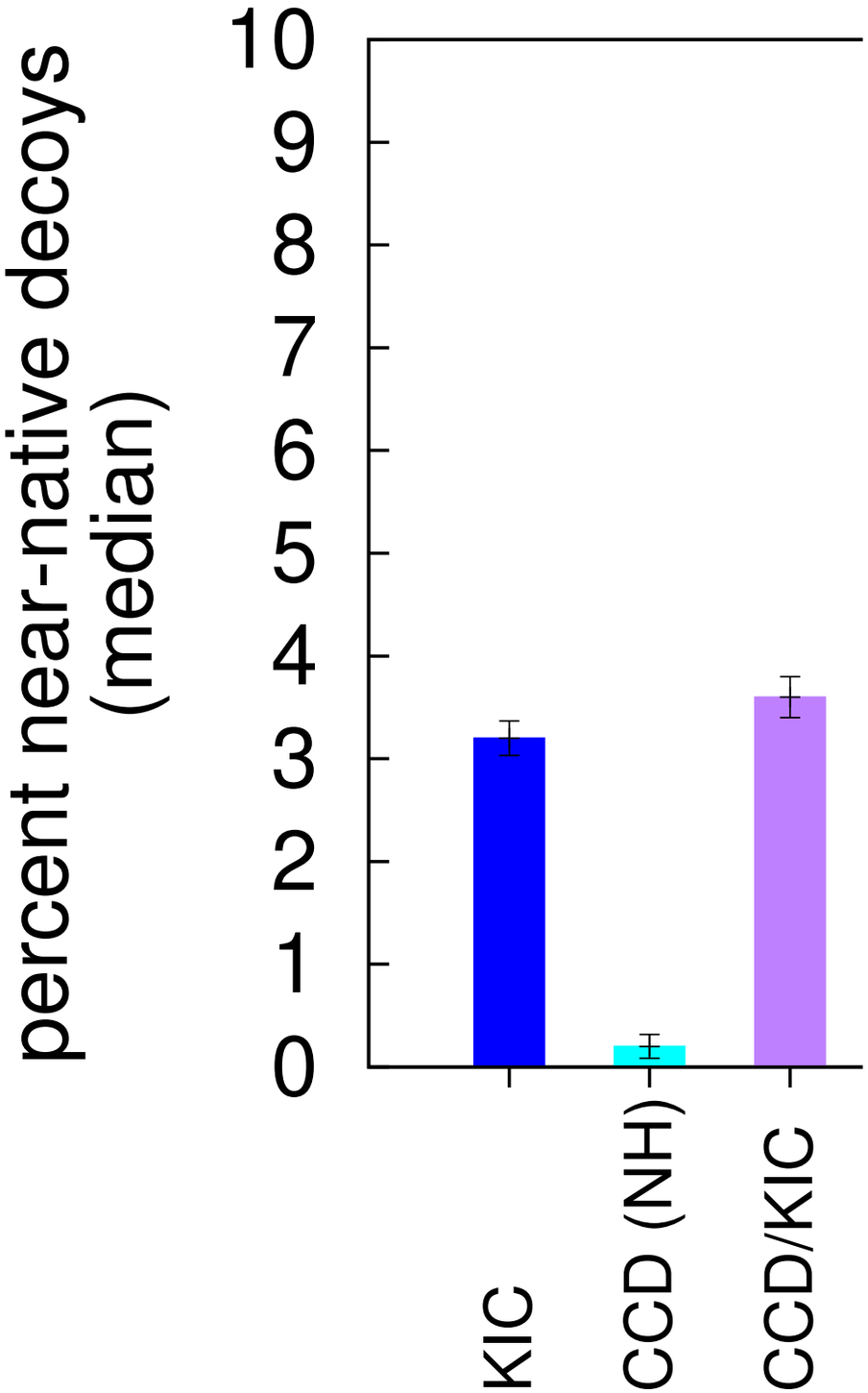
Neighbor-dependent phi/psi sampling enriches near-native conformations despite scoring problems







Individual changes only have moderate effects on the overall benchmark performance



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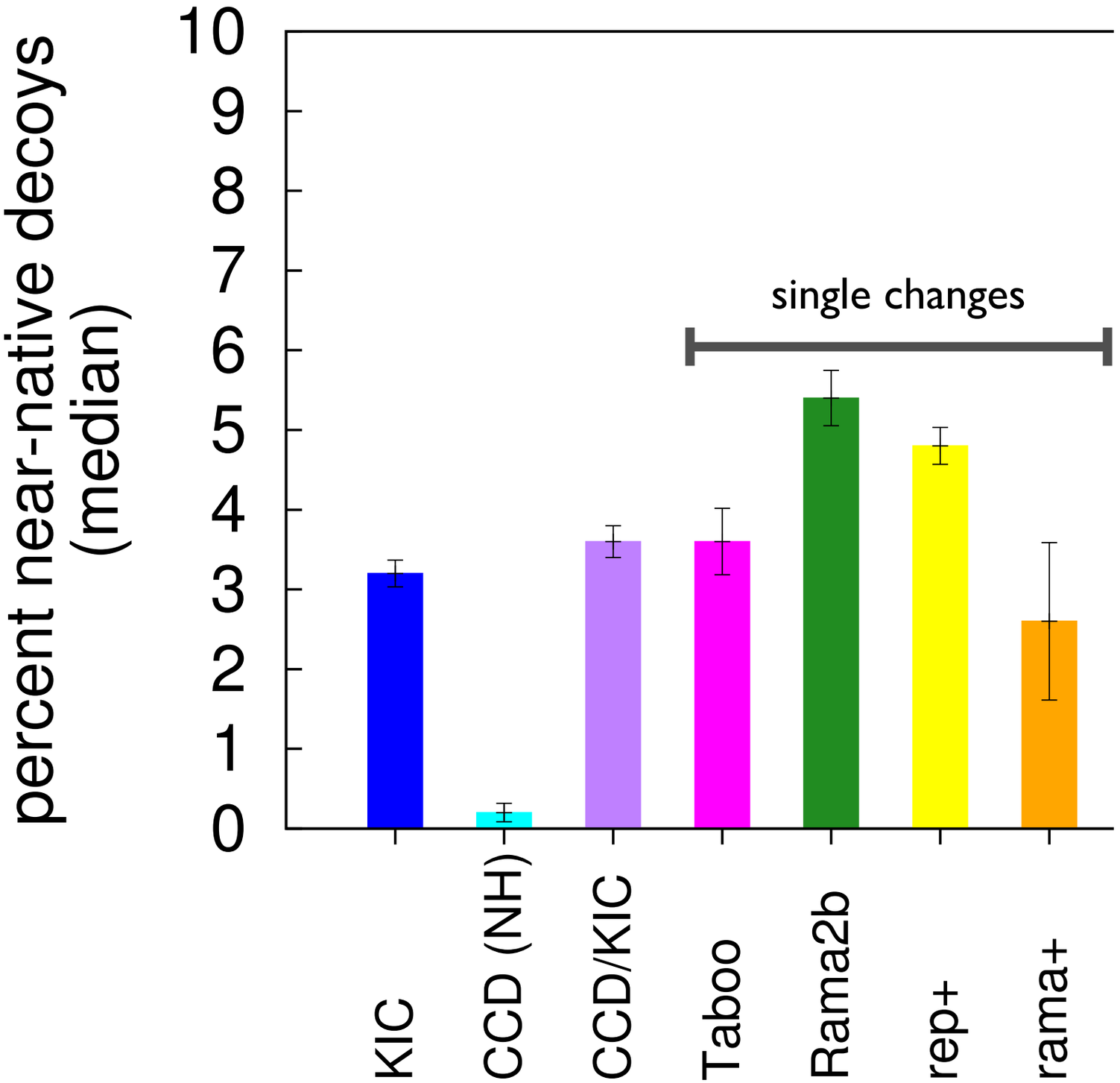
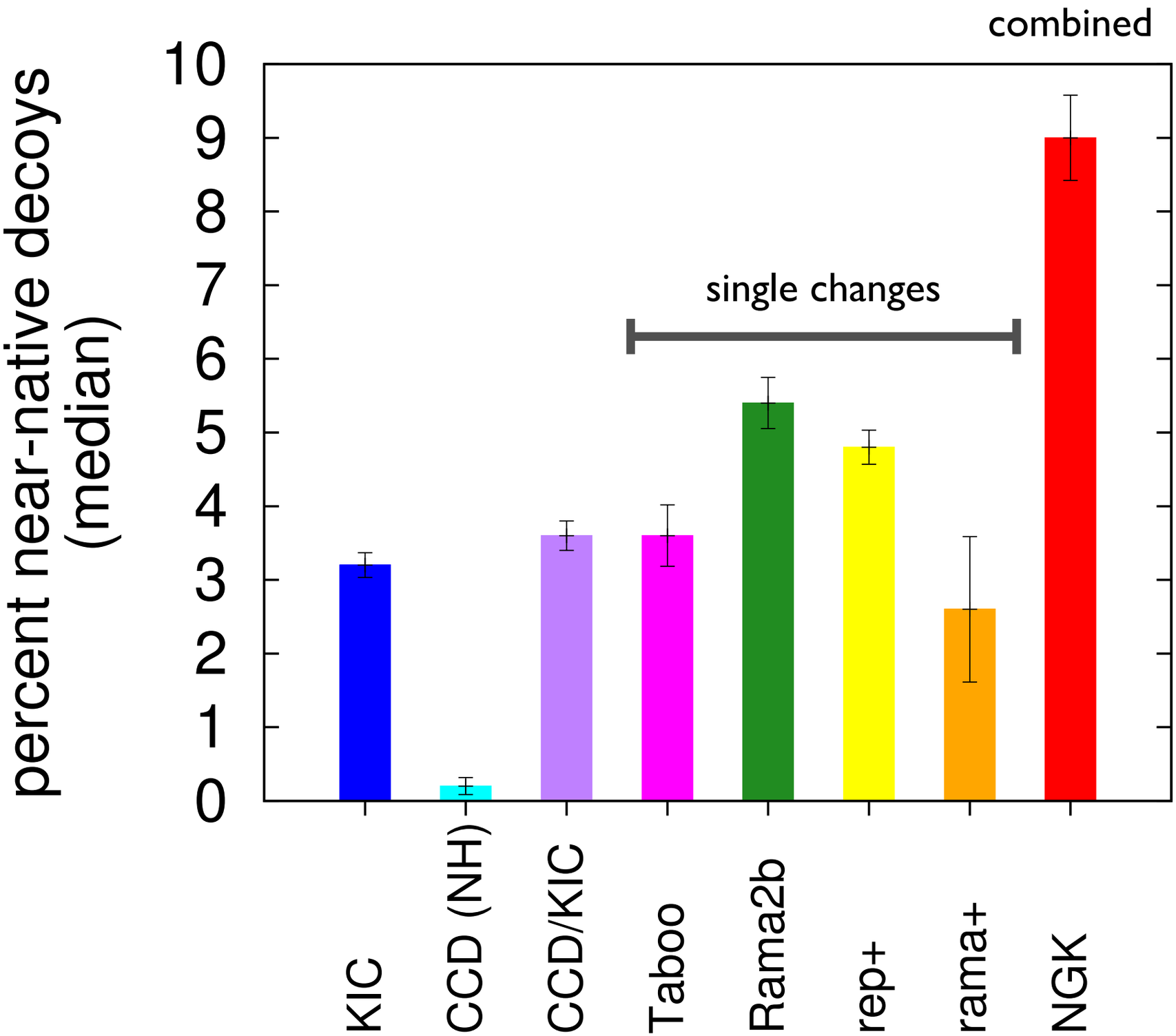


Synergy between the individual strategies leads to considerable improvement in sampling near-native conformations



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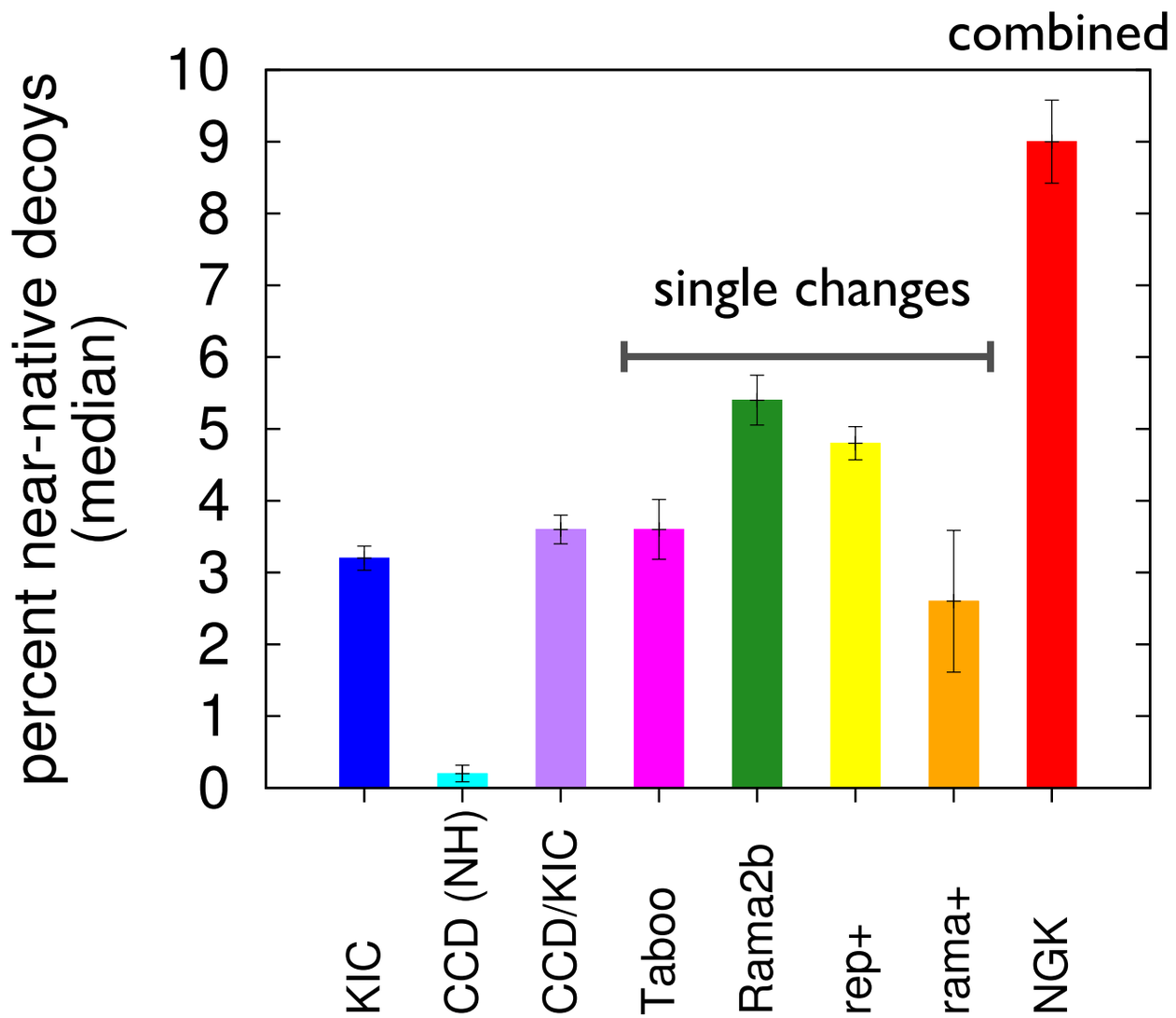

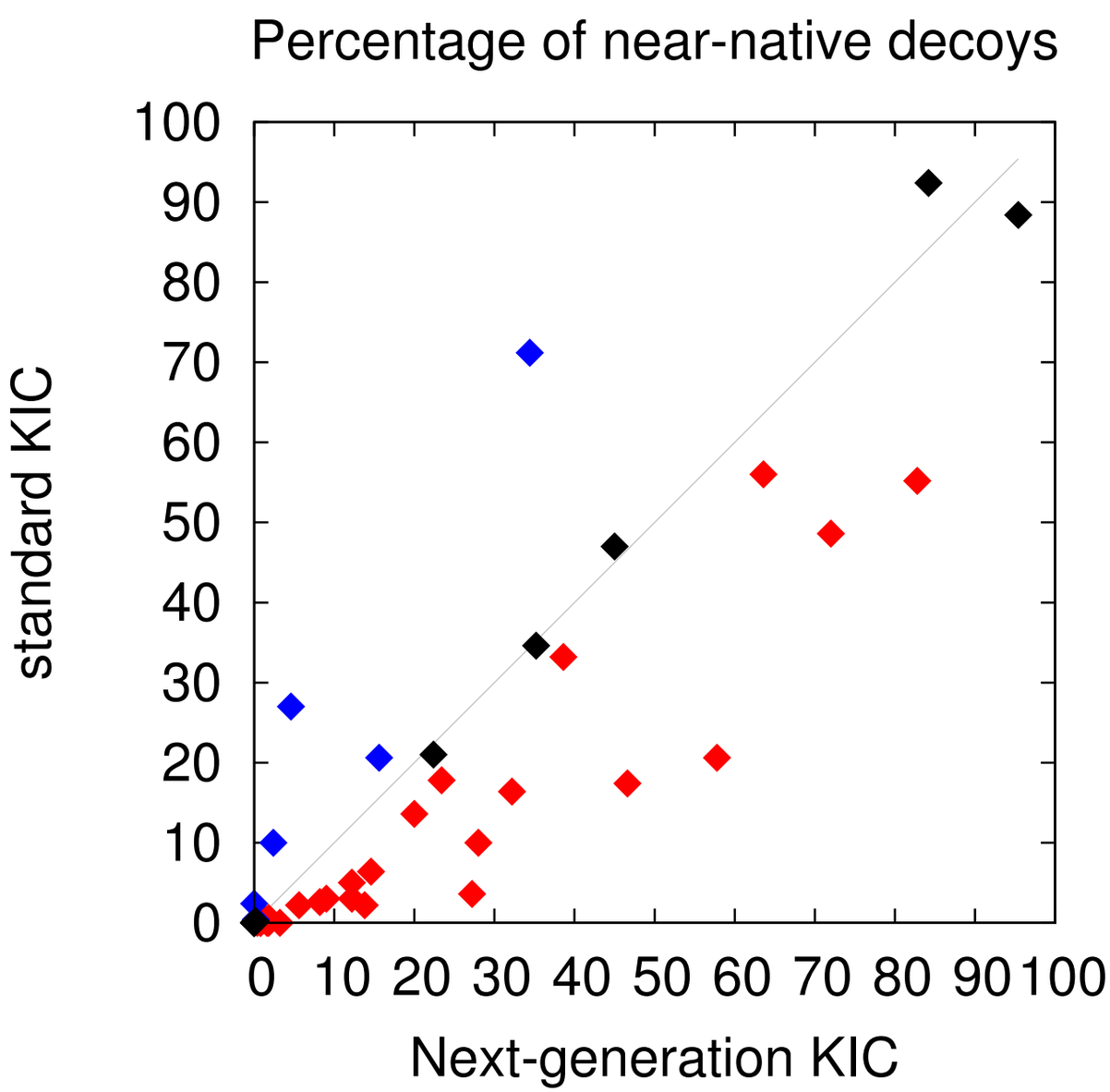

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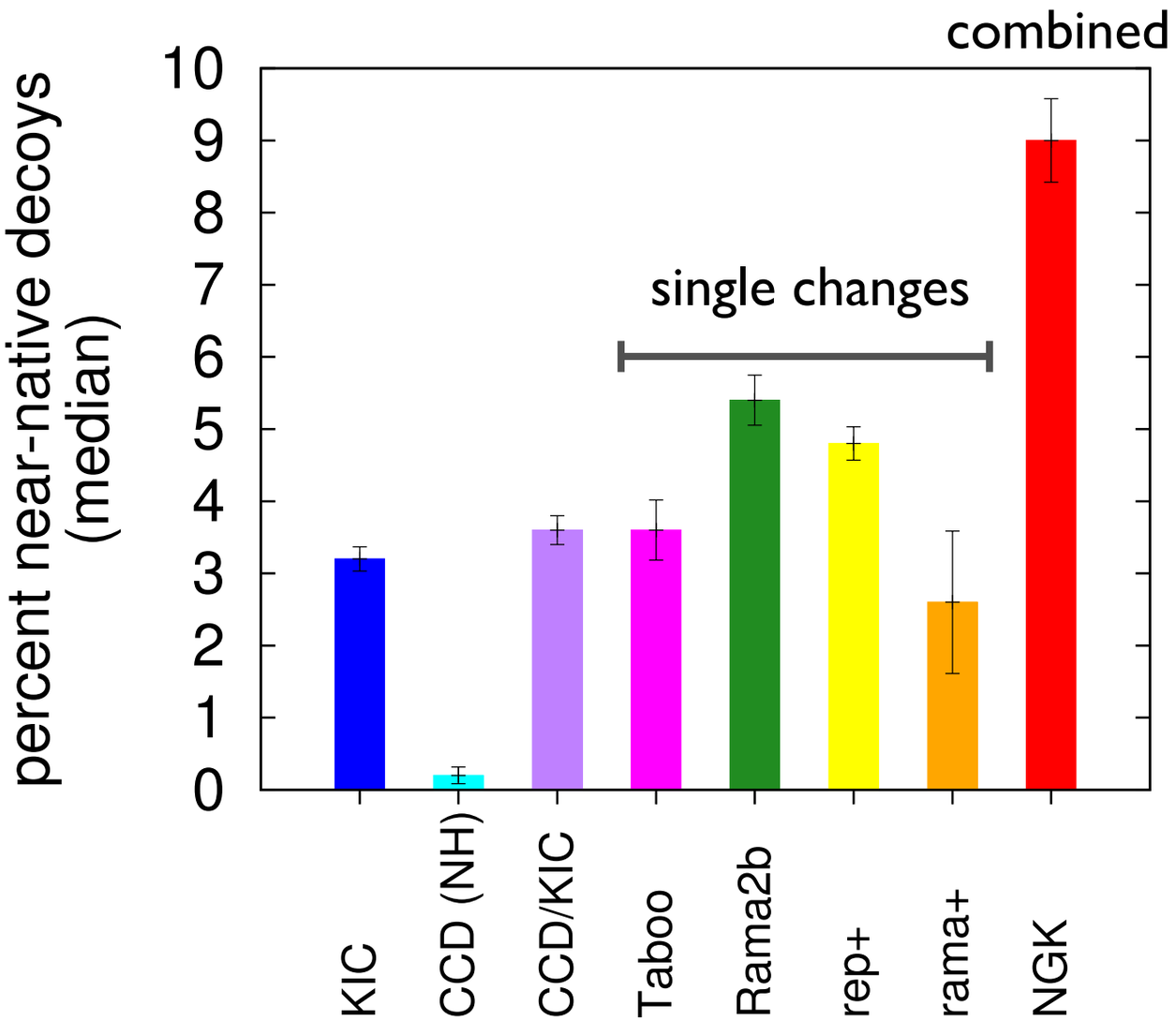
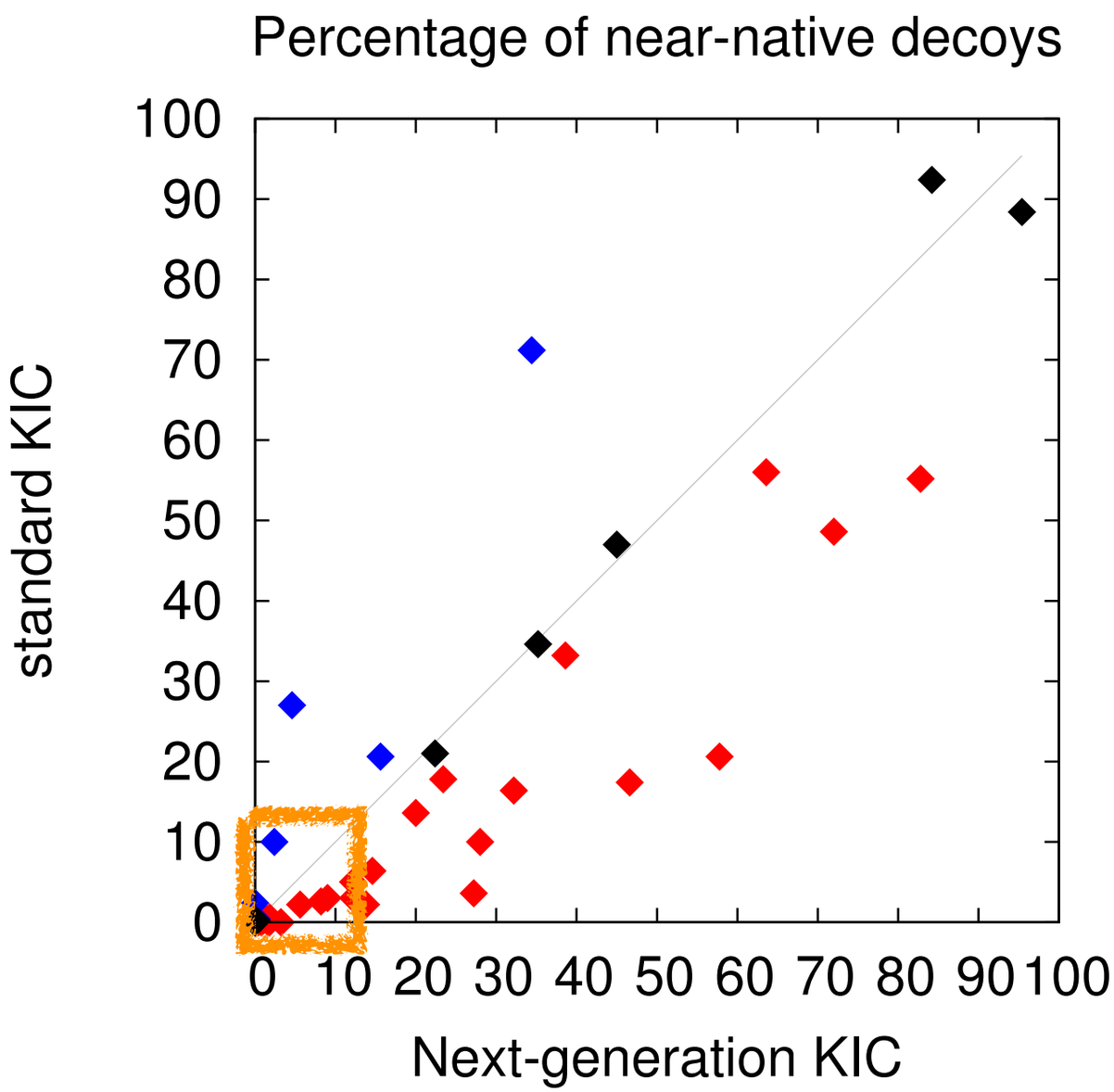
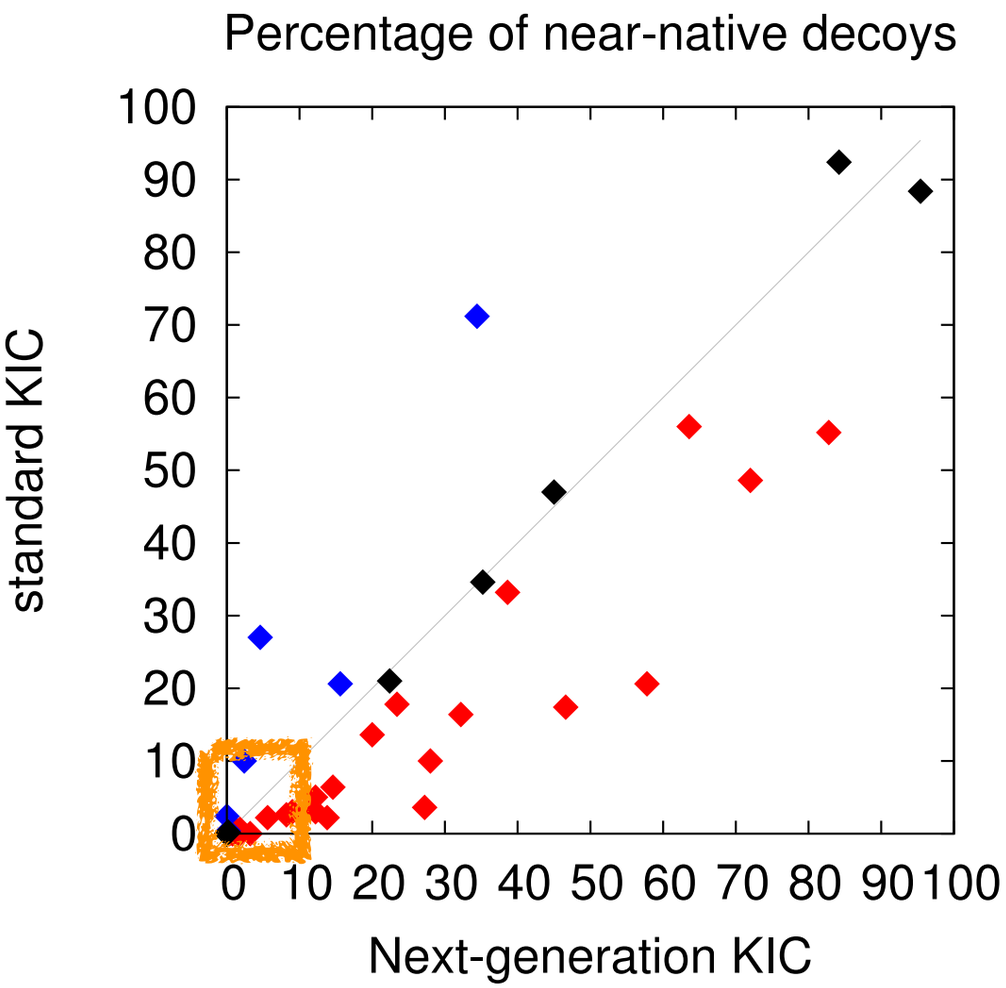
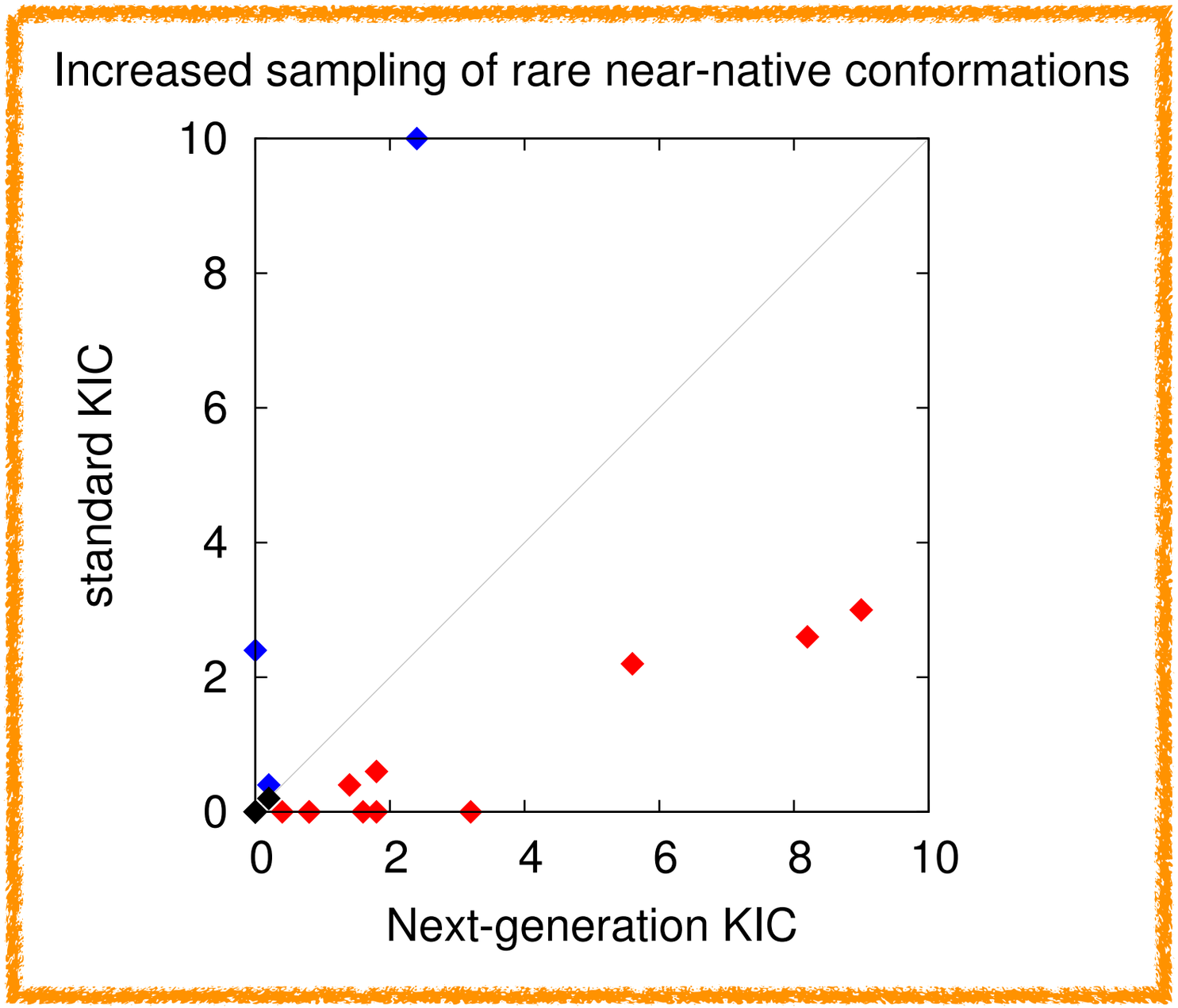




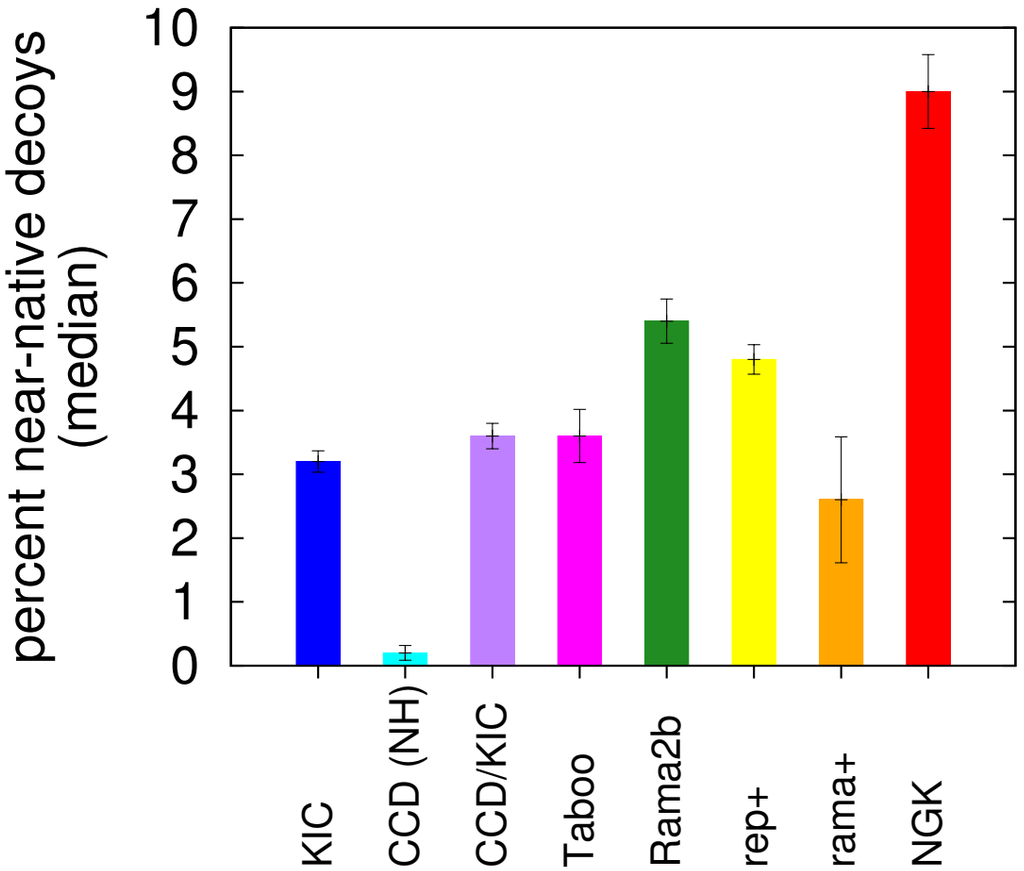
The percentage of near-native decoys increases for most cases in the benchmark set

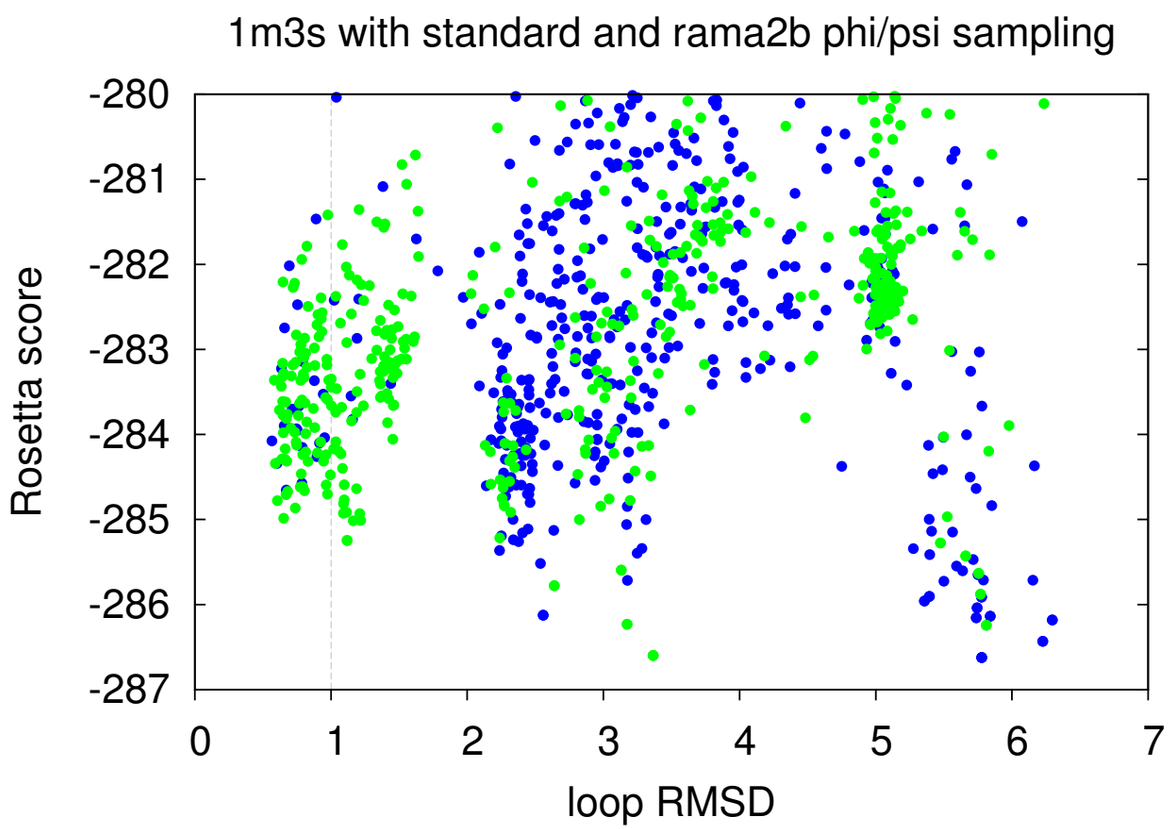




Conclusions

- Significant improvement in sampling of near-native conformations
- Synergy is key - combining different modifications led to considerable improvements overall
- Ideal testing ground for energy function improvements
  - orbitals with Steven Combs (Meiler Lab)





Outlook

- KIC with fragment insertion
- Add sampling of omega angles as well as bond lengths & angles

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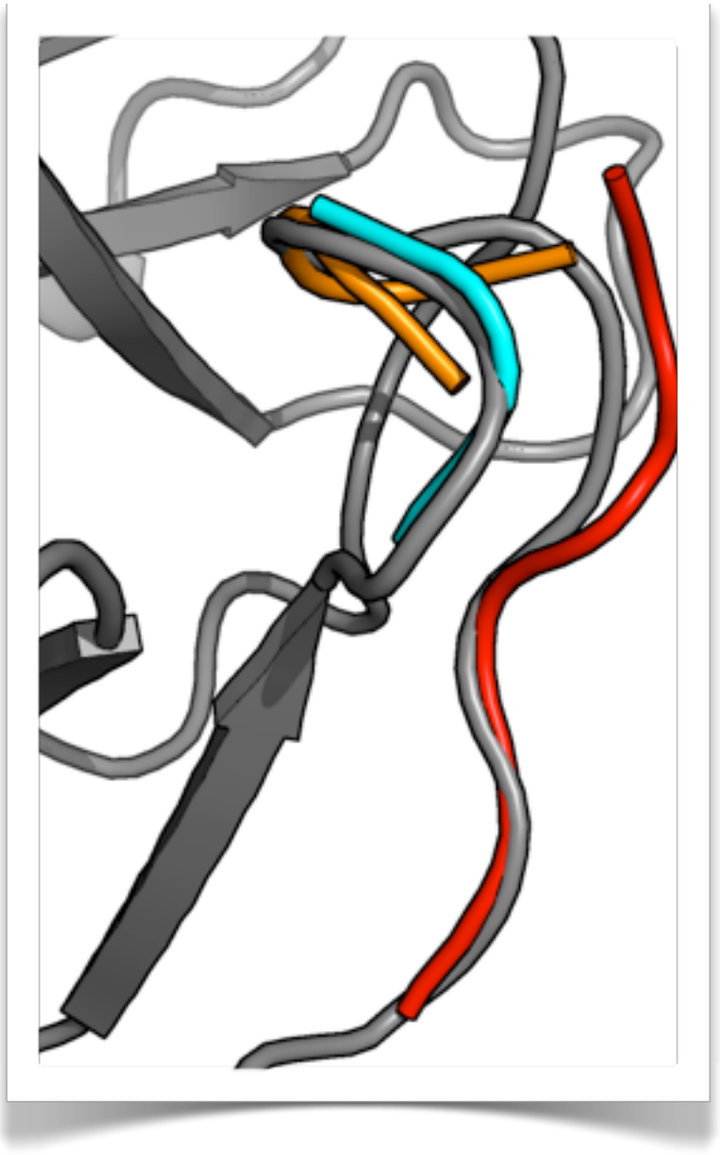
- Conformational space annealing
- Replica exchange



Outlook

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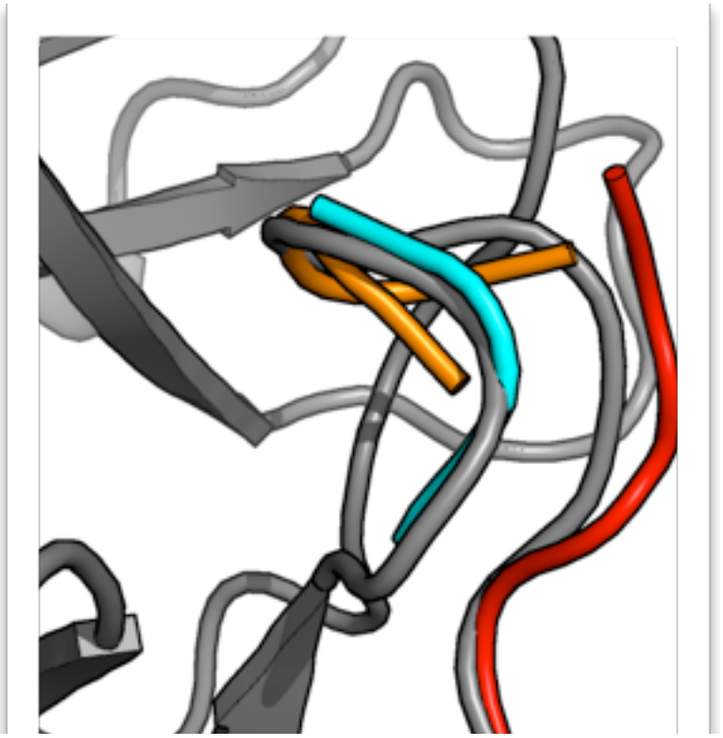
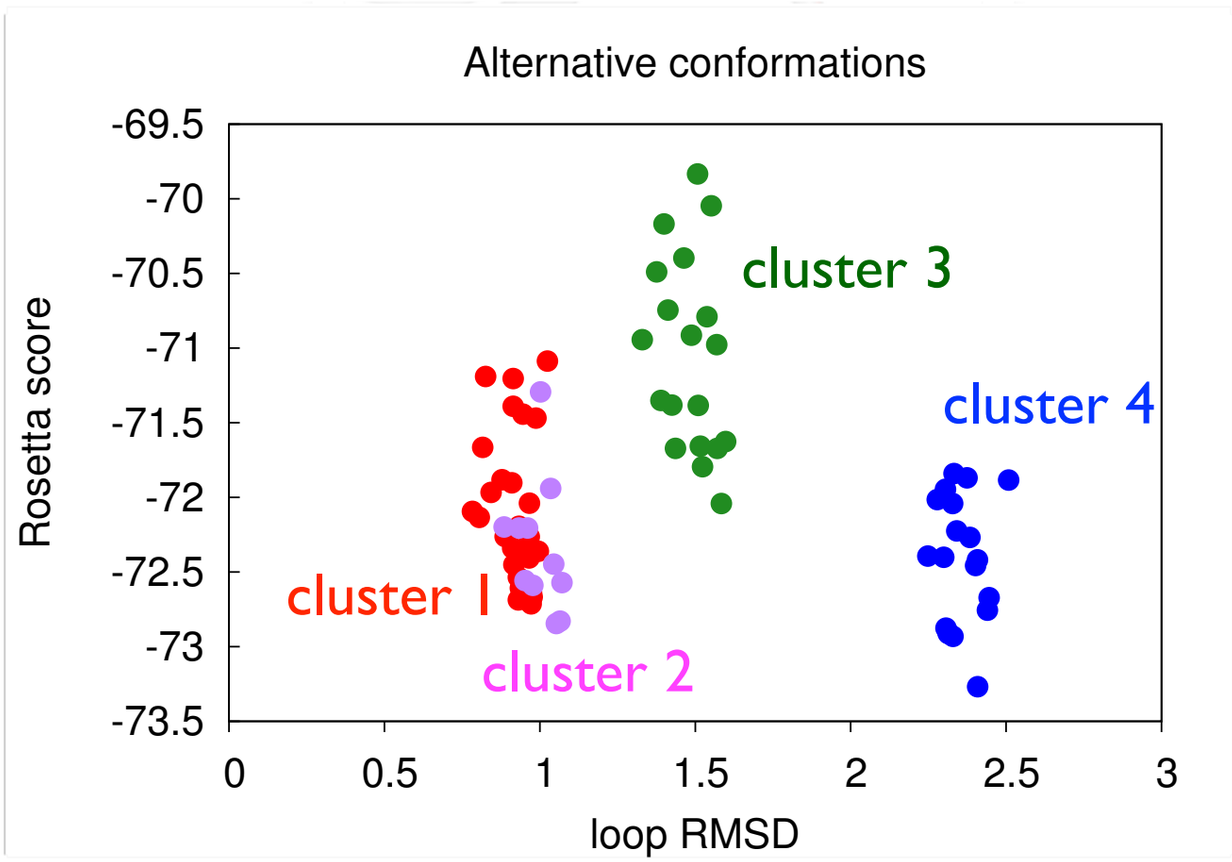
- Add sampling of omega angles as well as bond lengths & angles
- Conformational space annealing
- Replica exchange
- Alternative conformations & switch loops
- Dynamically determining flexible regions during design





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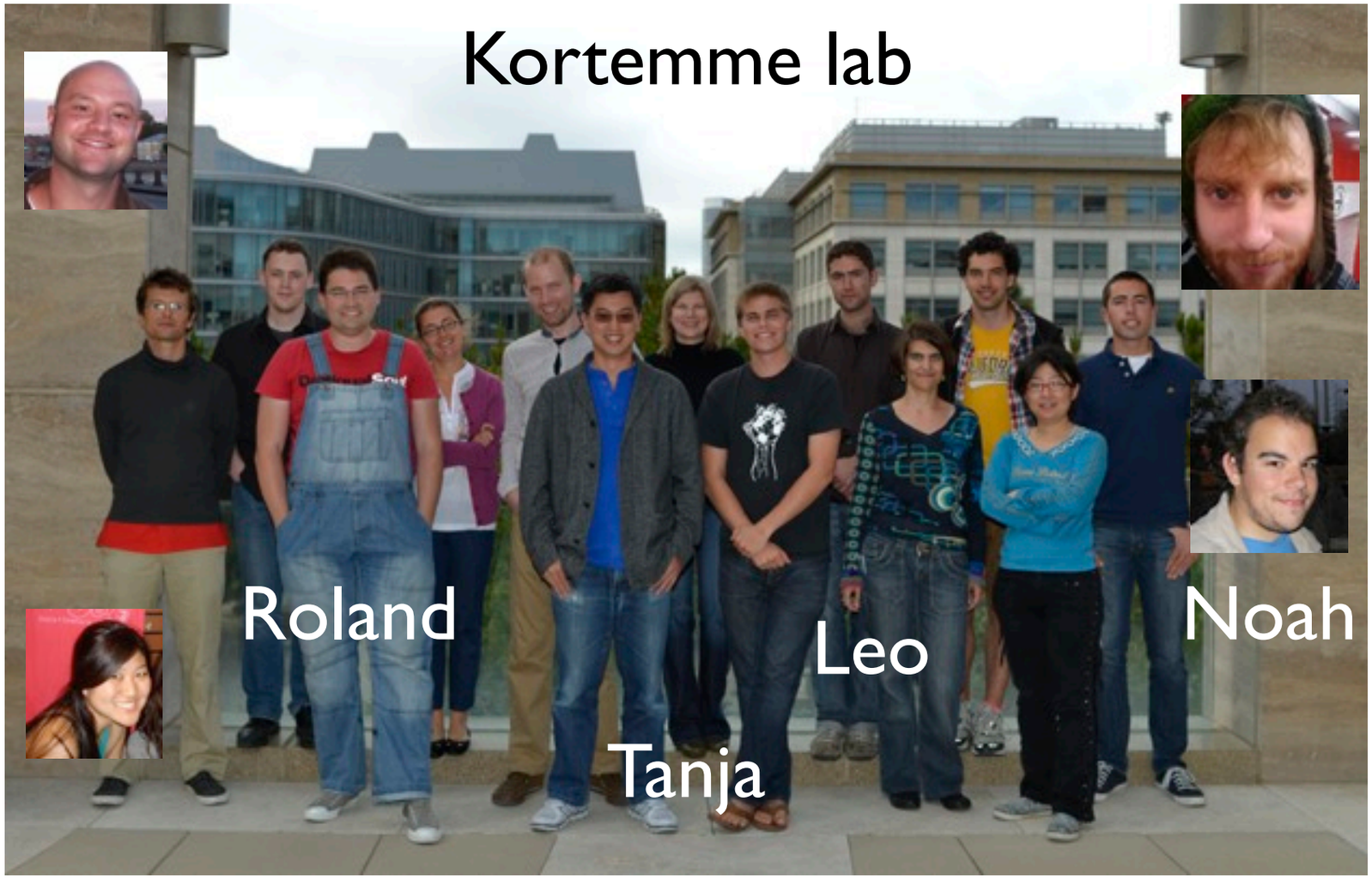

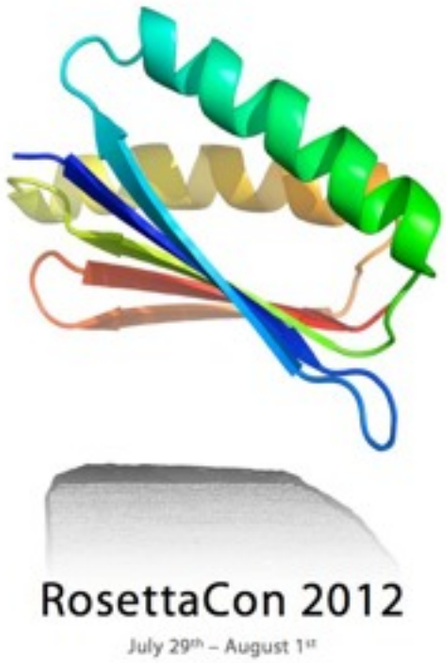

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