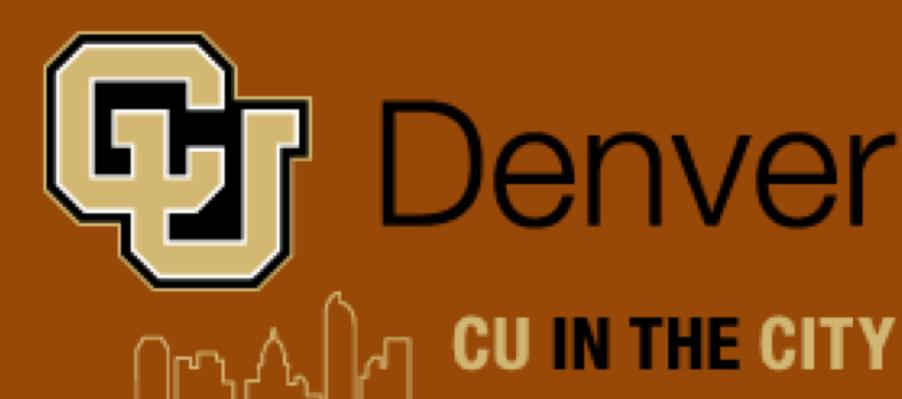


Investigating the Dynamics of F58 within HP36 via Umbrella Sampling : A Computational Analysis



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Introduction

- Hydrophobic side chain interactions are a major force in the folding of globular proteins and aggregation of many non-globular proteins.
- HP36 is a villin headpiece subdomain of 36 residues that form 3 tightly packed α -helices.
- The dynamics of core hydrophobic residues of HP-36 are suspected to share similarities with those of β -amyloid plaques related to Alzheimer's disease.[1]
- Molecular modeling is used to probe the molecular basis of the motions of these residues in this hydrophobic core.
- **Hypothesis:** Based on experimental observation, we hypothesize that the dynamical rotations of the residue F58 sidechain within the hydrophobic core of HP36 depends on temperature and hydration level.

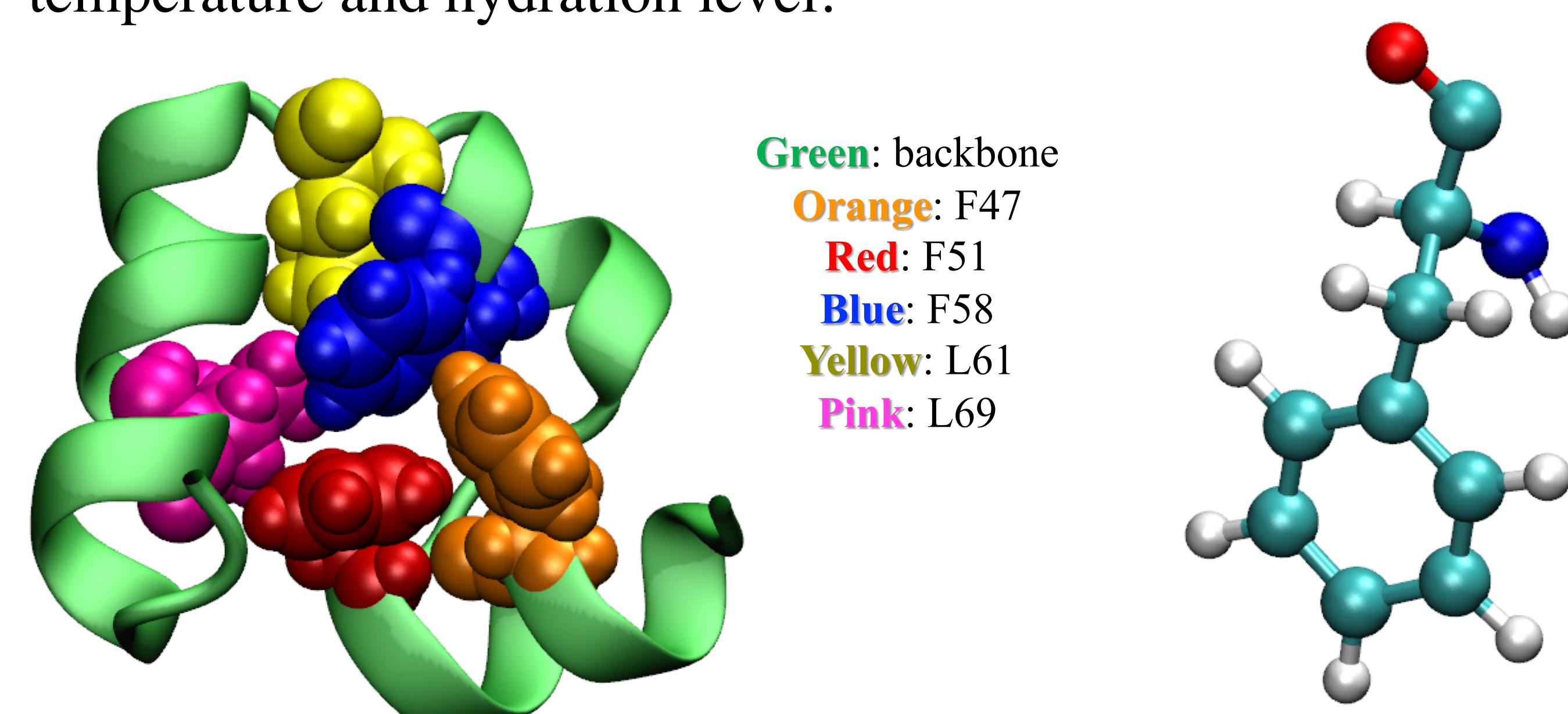


Figure 1. Left: HP36 hydrophobic core in VMD Right: Phenylalanine in VMD

Model

- **Protein:** PDB code 1YRF
- **Cluster model:**
 - 8 proteins in primary cell
 - Periodic Box: 50x50x50 \AA^3
 - Temperature:
300 K, 275 K
 - Hydration level:
140%
(water mass vs. protein mass)

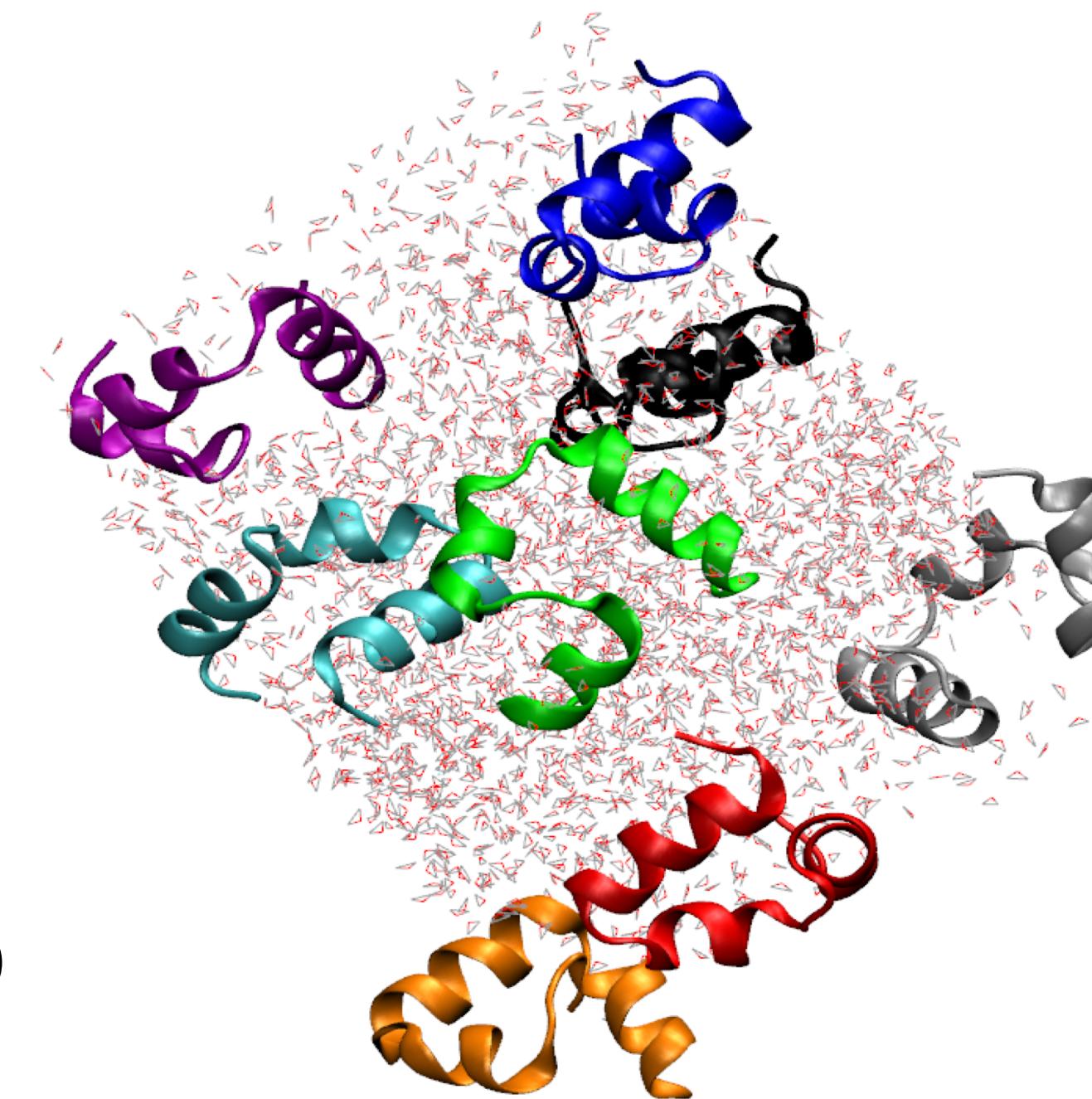


Figure 3. Hydrated cluster model & water molecules in VMD

Results

Figure 4. Potential of Mean Force of χ_2 rotation for F58 at 300K

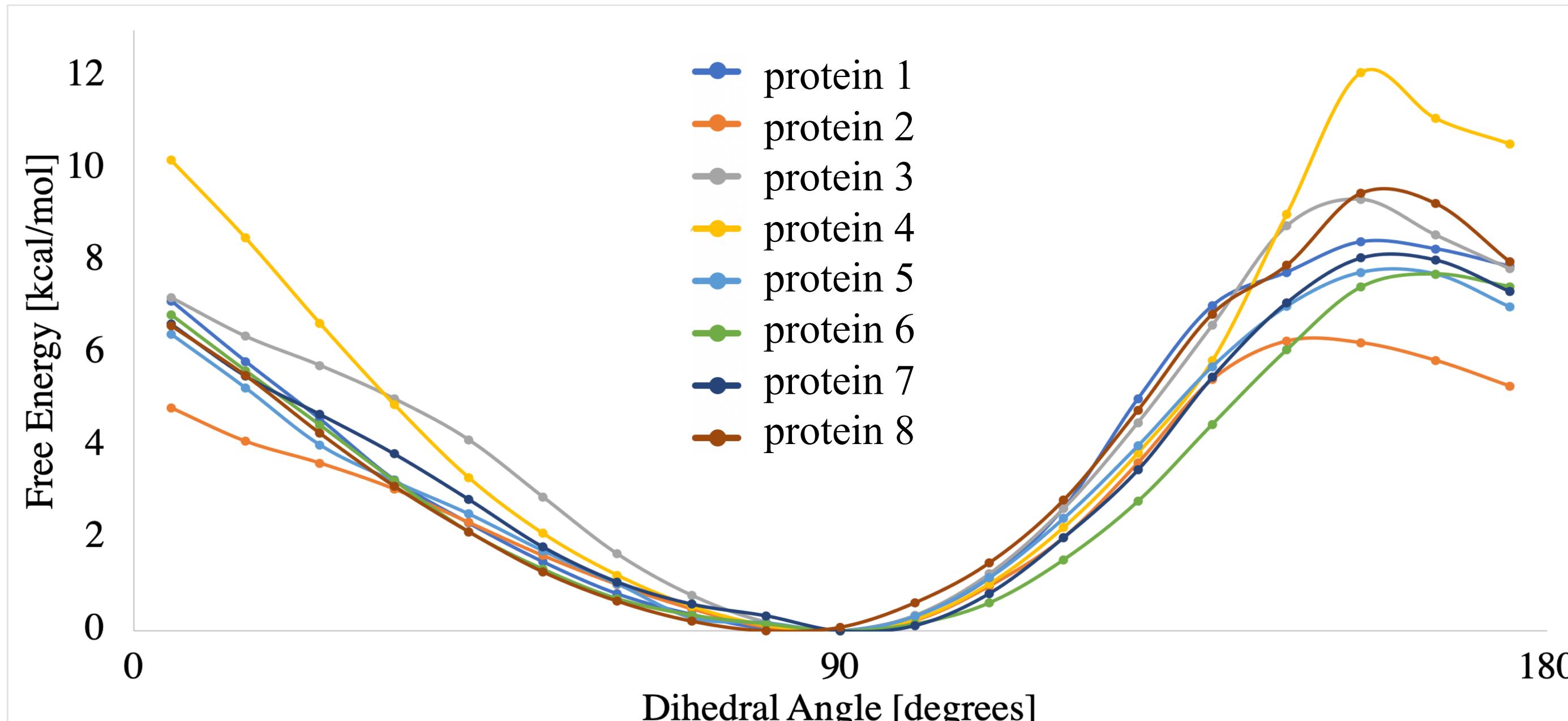


Table 1. Location and the Height of Rotation Barrier for F58 at 300K

	1	2	3	4	5	6	7	8
$\chi_{2,\max}$	156°	147°	156°	156°	166°	166°	166°	156°
ΔE_{\max} [kcal/mol]	8.4	6.3	9.3	12.1	7.8	7.7	8.1	9.5

Figure 5. Potential of Mean Force of χ_2 rotation for F58 at 275K

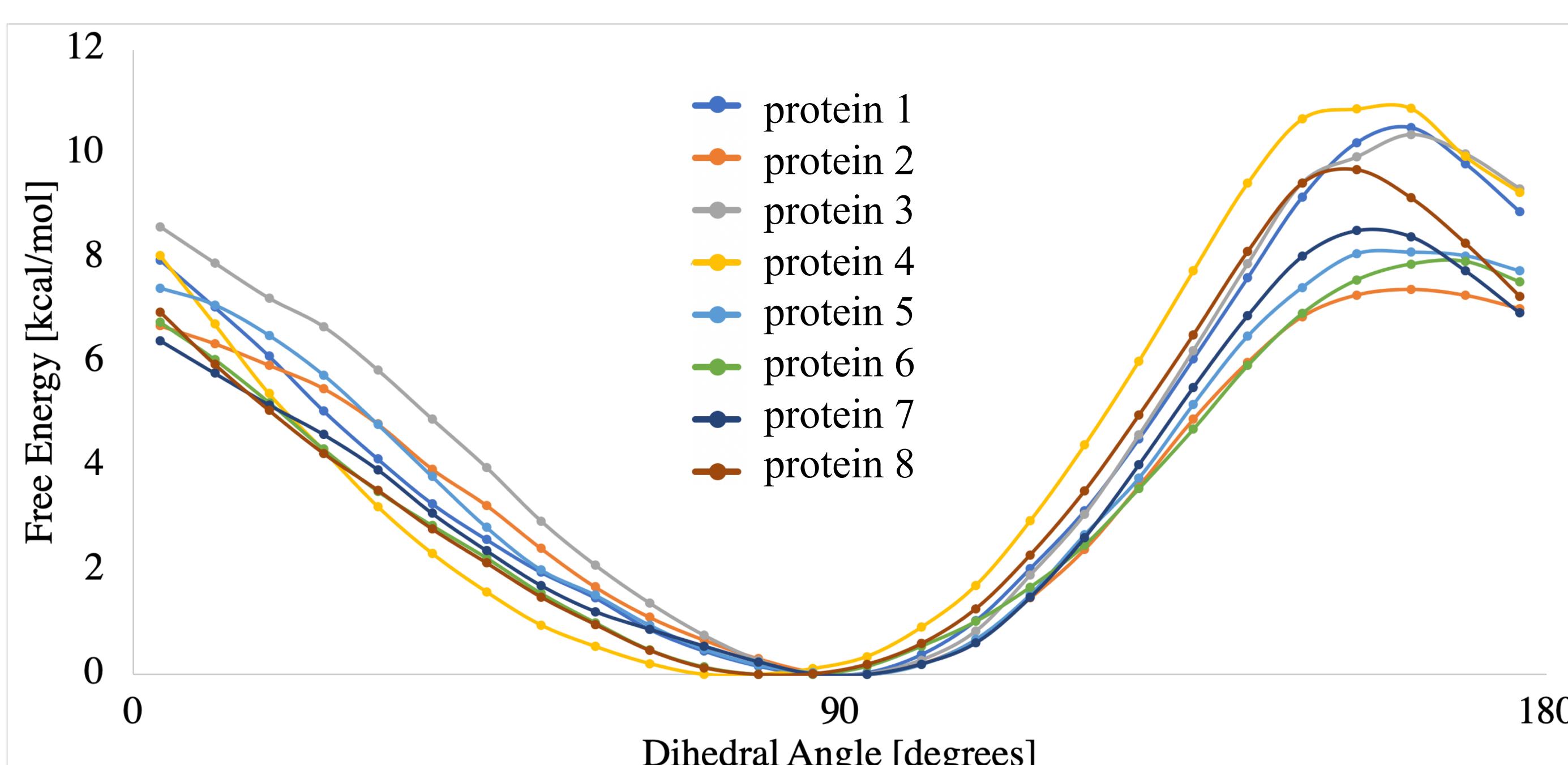


Table 2. Location and the Height of Rotation Barrier for F58 at 275K

	1	2	3	4	5	6	7	8
$\chi_{2,\max}$	163°	163°	163°	163°	163°	170°	156°	156°
ΔE_{\max} [kcal/mol]	10.5	7.4	10.4	10.9	8.1	7.9	8.5	9.7

Computational Details

- **Program:** VMD and NAMD 2.10/2.11
- **Force fields:** CHARMM36 (protein) and TIP3P (water)
- **Umbrella Sampling:**
 - Artificial harmonic bias potential imposed on χ_2
 - χ_2 scanned from -180° to 0° with 10° step size for all 8 proteins independently
 - 2-ns NPT production at each dihedral angle
 - Potential of mean force determined using the WHAM analysis

Summary

Conclusion:

- Free energy barrier for F58 χ_2 rotation is 8.7 ± 1.7 kcal/mol at 300 K
- 9.2 ± 1.4 kcal/mol at 275 K
- The barrier height varies modestly across all proteins: max/min
12.1 / 6.3 kcal/mol at 300 K
10.9 / 7.4 kcal/mol at 275 K
- The barrier slightly increases as the temperature drops from 300K to 275K

Future work:

- Calculate barriers at additional [40% & 10%] hydration levels
- Identify correlations between protein conformations and rotational barriers

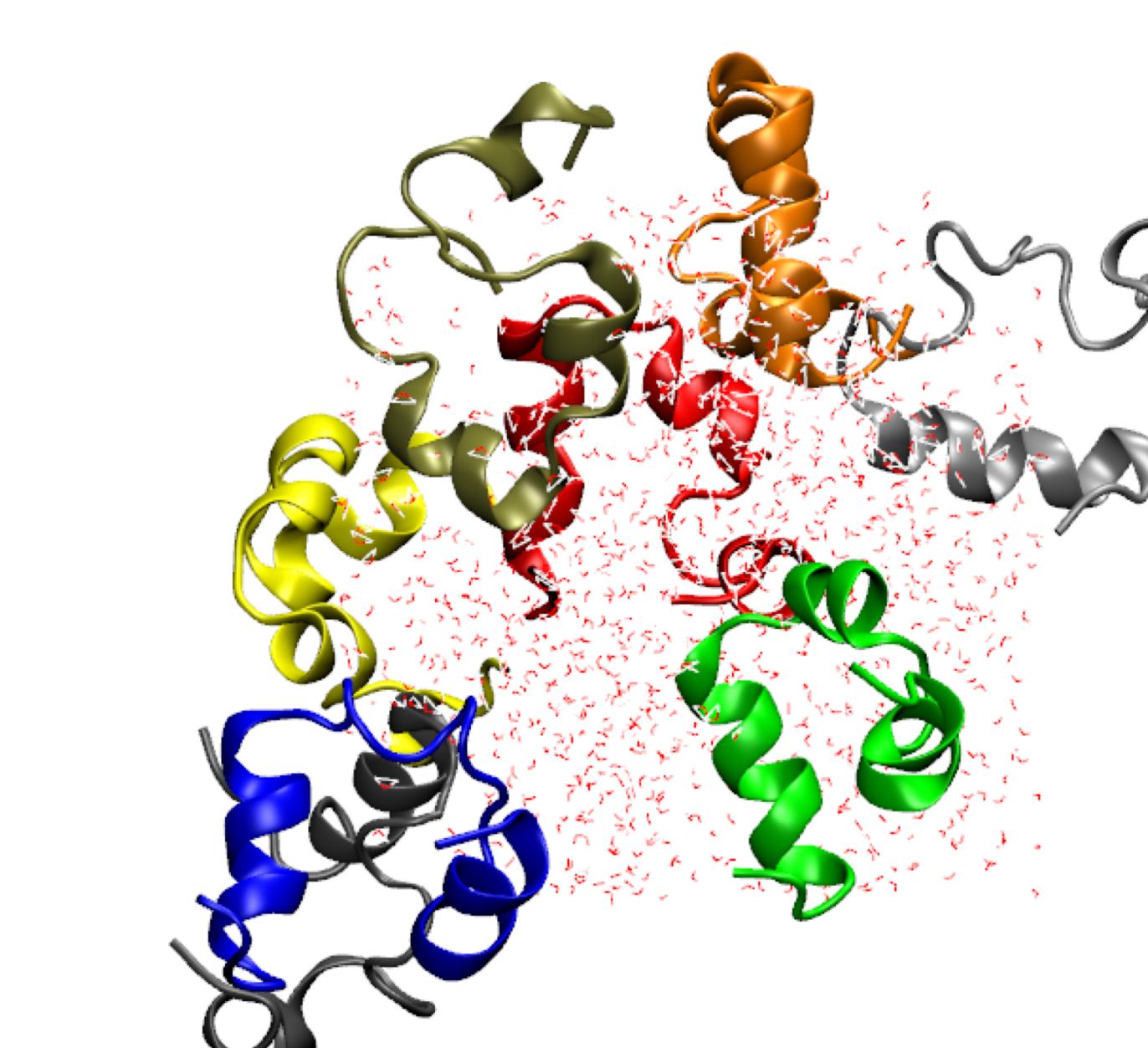


Figure 6. 40% hydrated cluster model & water molecules in VMD

Lowering the hydration is achieved by a step-wise removal of water molecules that are associated with largest (top ~25%) RMSD values at each step. In total there are 4 steps.

Acknowledgements & References

[1] Mukherjee, A.; Bagchi, B. The Journal of Chemical Physics 2004, 120 (3), 1602–1612.

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