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Dynamics and deformability of α -, 3_{10} - & π -helices

NICOLAS K. SHINADA

INSERM UMR-S 1134 - Dynamique des Structures et Interactions des Macromolécules Biologiques (DSIMB)

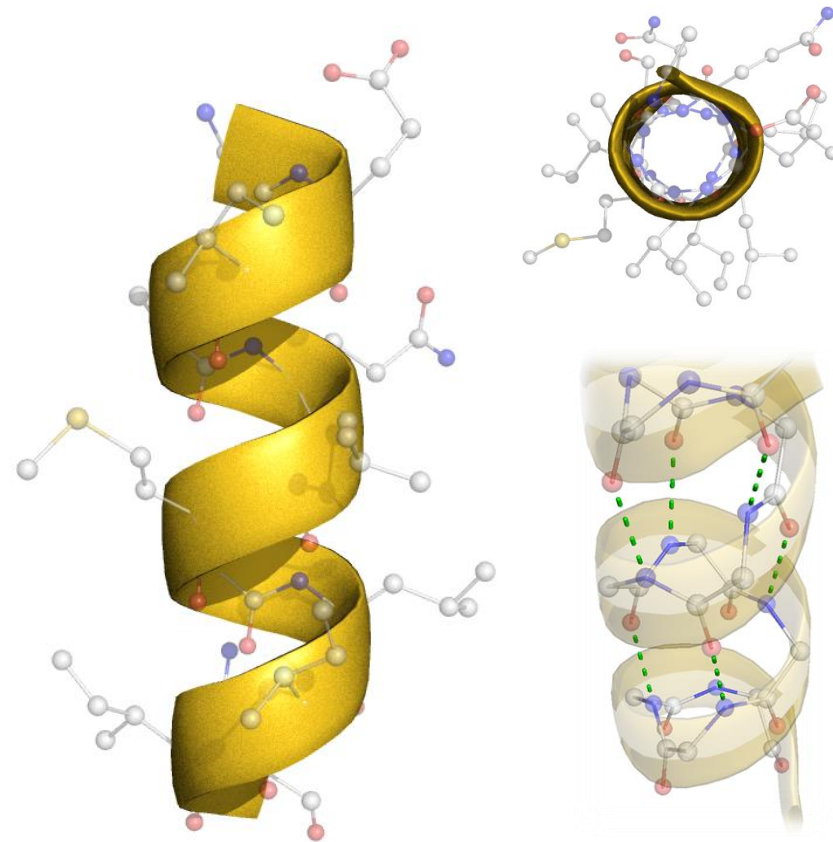
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Discngine – 79 Avenue Ledru Rollin, 75011, Paris – France

α -helix

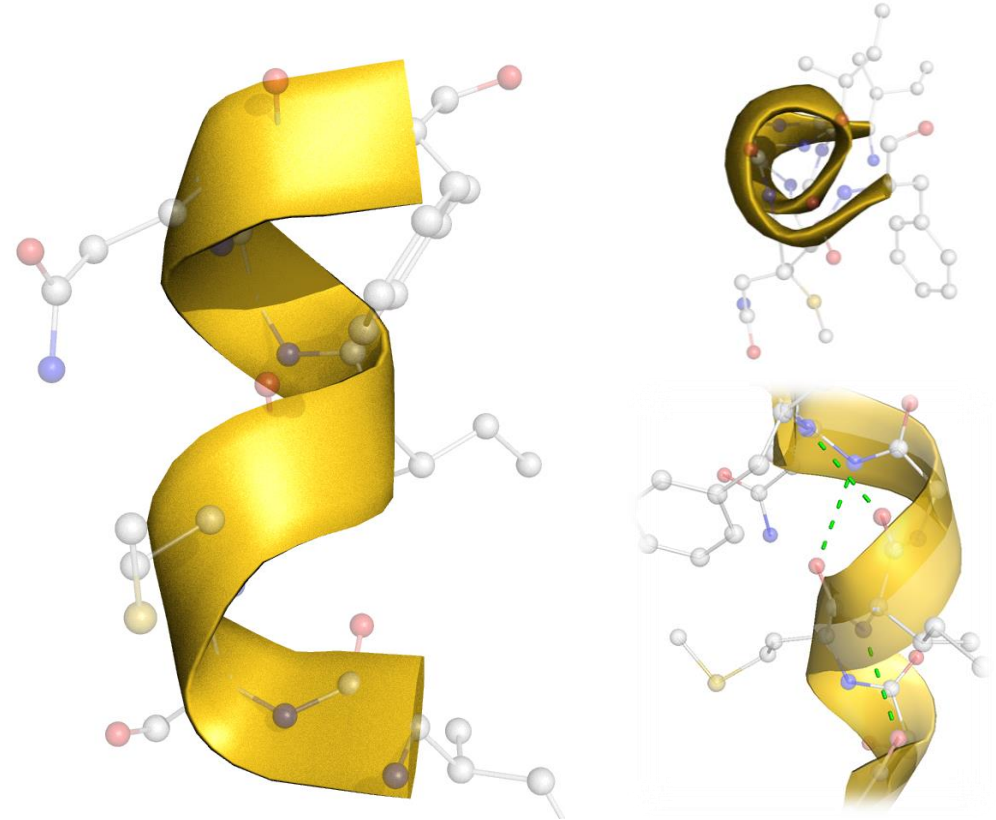
- α -helix (1/3 of protein residues): intramolecular H-bond between residues i and $i+4$.



α -helix (1uyd, A24-N35)

3_{10} -helix

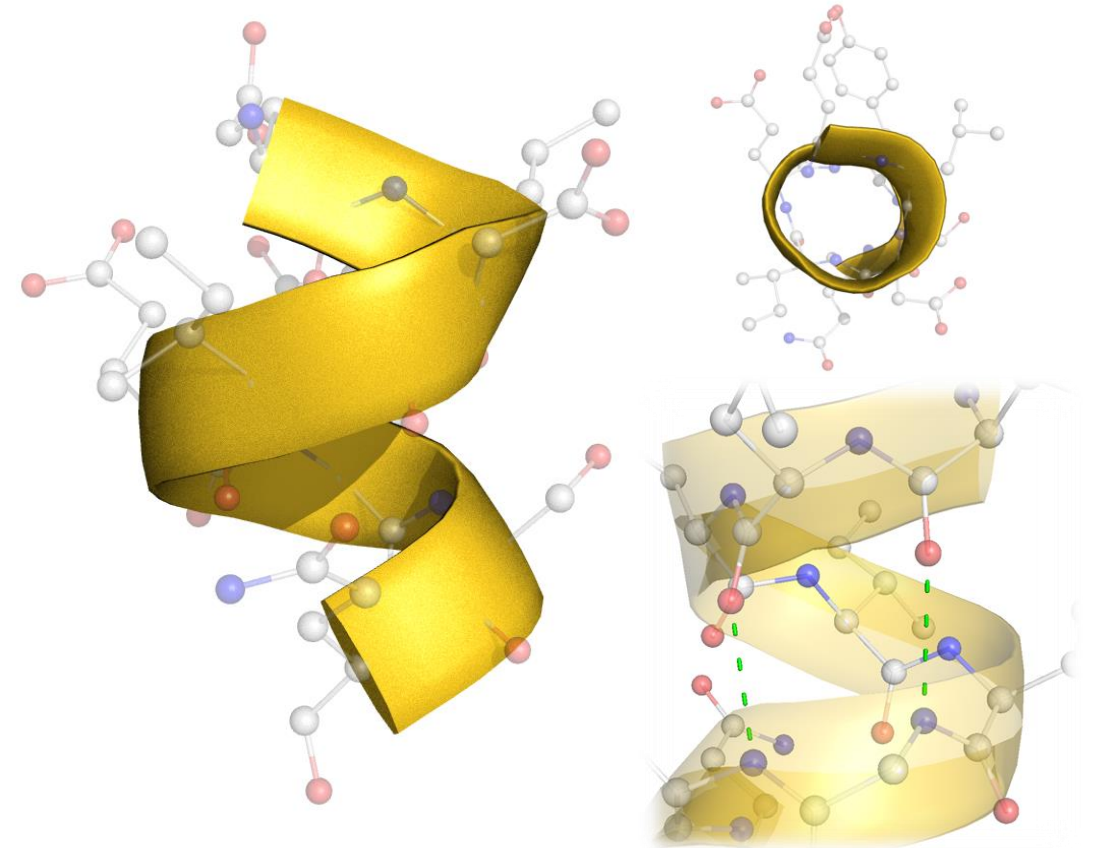
- α -helix (1/3 of protein residues): intramolecular H-bond between residues i and $i+4$.
- 3_{10} (4%): 3-4 residues long, H-bond ($i, i+3$), β -hairpin or kink in helices...



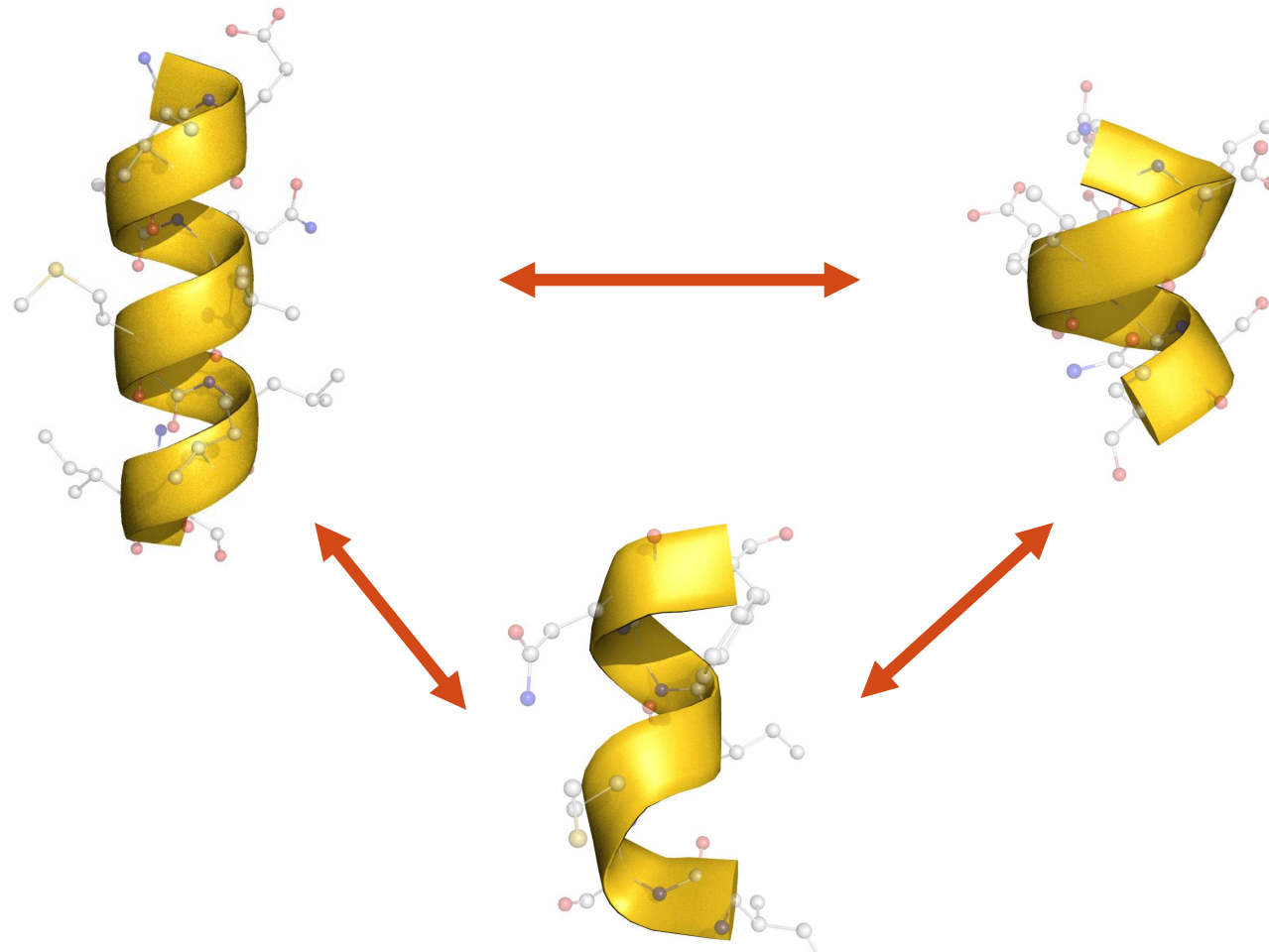
3_{10} -helix (1uyd, I128-F134)

π -helix

- α -helix (1/3 of protein residues): intramolecular H-bond between residues i and $i+4$.
- 3_{10} (4%): 3-4 residues long, H-bond ($i, i+3$), β -hairpin or kink in helices...
- π -helix (0.02%): H-bond between residues ($i, i+5$), role in binding sites.



π -helix (2qd3, G347-V355)



Study helices structural behavior in different protein families through Molecular Dynamics.

Local Movement

Crystal Structure:

- B-factor: electronic density scattering of an atom (high = disorder).

Molecular Dynamics to simulate behavior (structural movement) in biological environment:

- RMSF: root mean square fluctuation of a residue/atom between its initial position and its average position.
- Protein Blocks: local deformation.

Dataset & Tools

169 X-ray structures from PDB with good resolution.

- Normalized B-factor

3 independent MD using GROMACS4.5.7¹ and Amber99sb² FF of 50ns.

Conformations saved every ps:

- Secondary structures assignment using DSSP³ (CMBI ver. 2000)
- Normalized RMSF computation

1. Pronk, Sander, et al. "GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit." *Bioinformatics* (2013): btt055.
2. van Gunsteren, Wilfred F., et al. "Biomolecular simulation: the {GROMOS96} manual and user guide." (1996).
3. Kabsch, Wolfgang, and Christian Sander. "Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical features." *Biopolymers* 22.12 (1983): 2577-2637.

Clustering

Evolution of DSSP assignment for each residue was computed.

→ Each residue is defined by a vector of size 8 (all DSSP types) representing its secondary structure assignment evolution throughout MD.

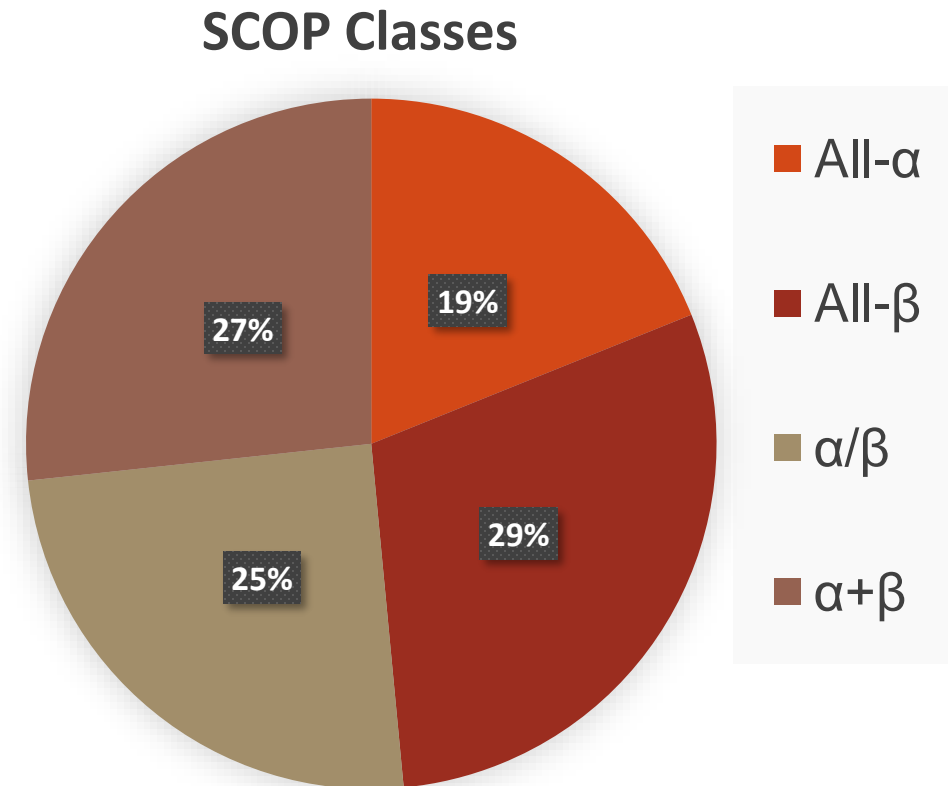
Vector clustering was performed with *K-means* ($k = 5$) for each initial DSSP state assignment.

Dataset Diversity

Equilibrated SCOP⁴ distribution.

Helix distribution representative to the one observed in proteins.

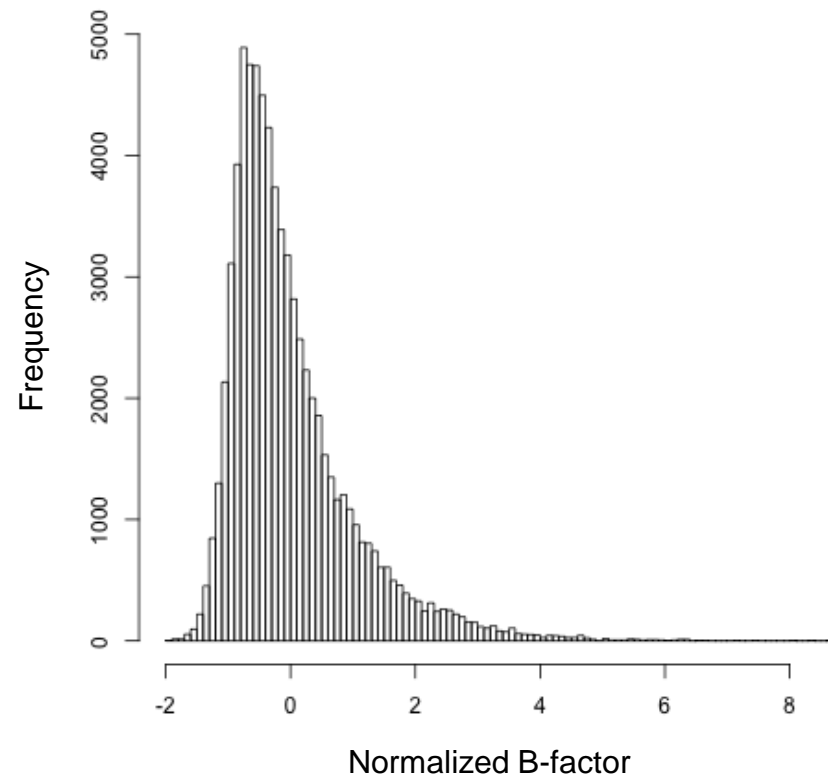
Average B-factor shows $3_{10} > \pi > \alpha$.



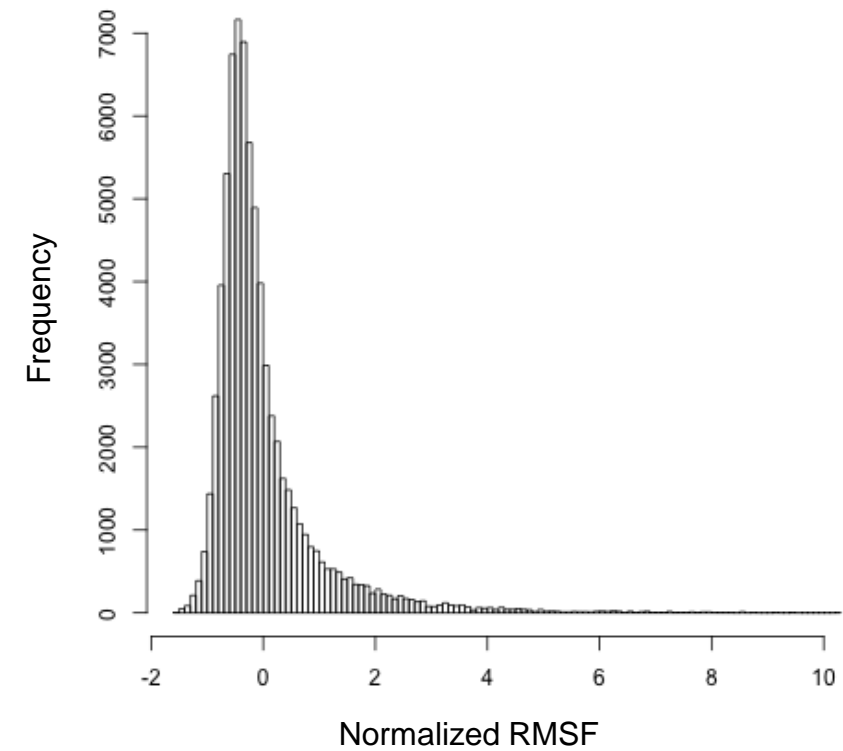
4. Murzin, Alexey G., et al. "SCOP: a structural classification of proteins database for the investigation of sequences and structures." Journal of molecular biology 247.4 (1995): 536-540.

MD Analysis

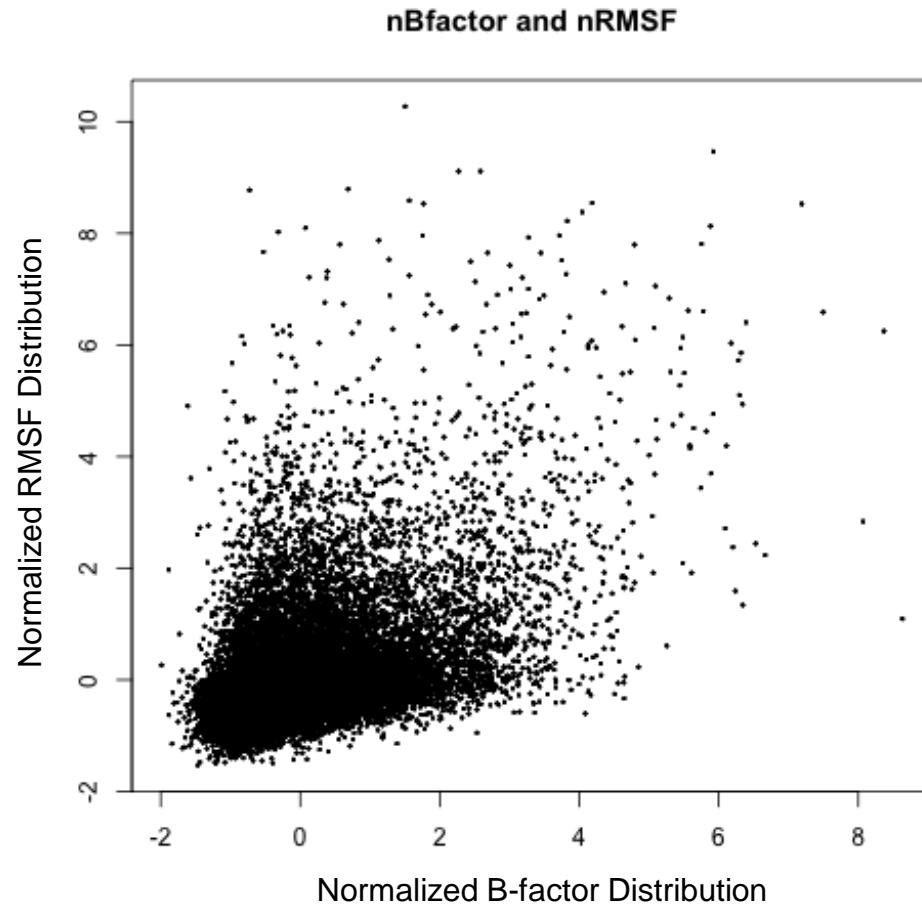
normalized B-factor distribution



normalized RMSF distribution



MD Analysis



Correlation $r = 0.49$

α -helices behavior

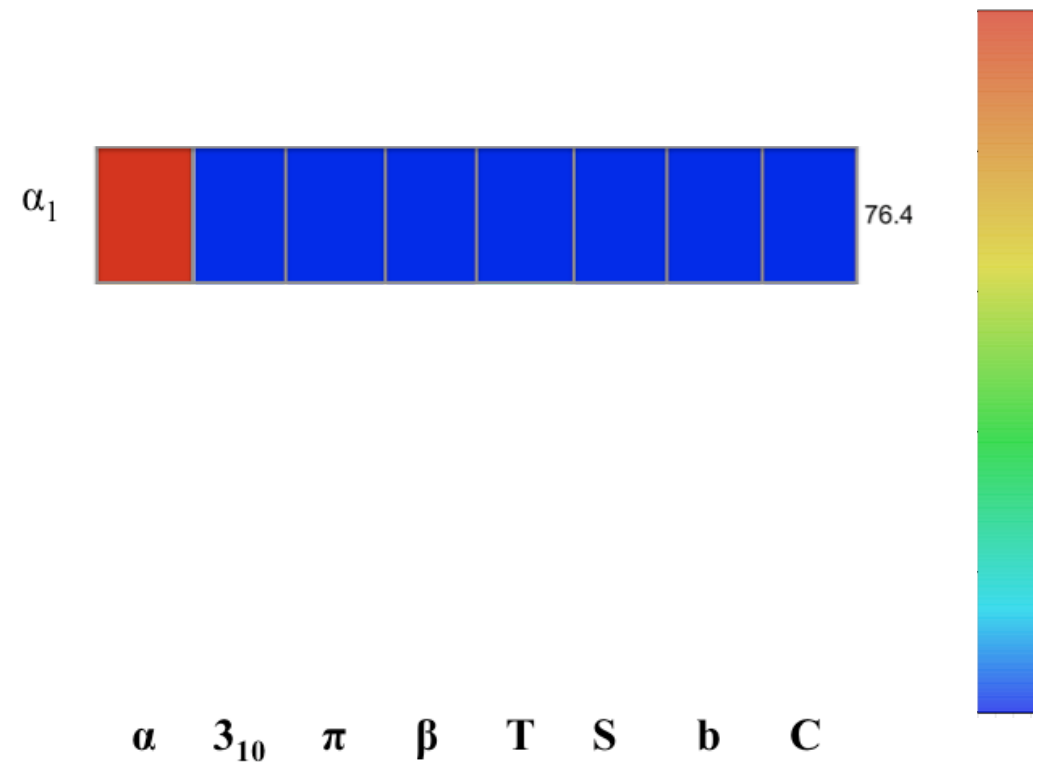
Stability: 90% remains in α -helical state.

Initial state	100%	> 90%	> 50%	< 25%
α -helix	29.1	74.6	91.4	3.9
3_{10} -helix				
π -helix				

Persistence of original helical state

α -helices behavior

Stability: 90% remains in α -helical state.



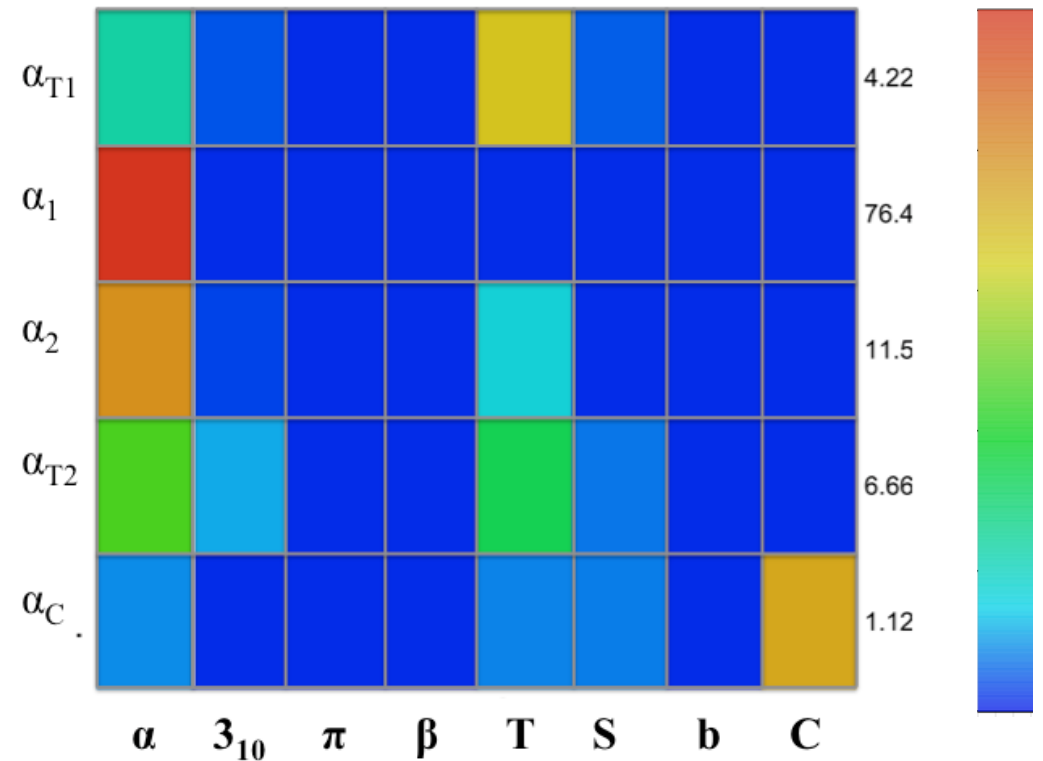
K-means clusters of α -helix behavior

α -helices behavior

Stability: 90% remains in α -helical state.

α -helices to 3_{10} very rare.

Otherwise tend to become β -turn.



K-means clusters of α -helix behavior

3_{10} -helices behavior

Transitory: none of 3_{10} remains in same helix state.

Initial state	100%	> 90%	> 50%	< 25%
α -helix	29.1	74.6	91.4	3.9
3_{10} -helix	0.0	15.7	54.1	24.0
π -helix				

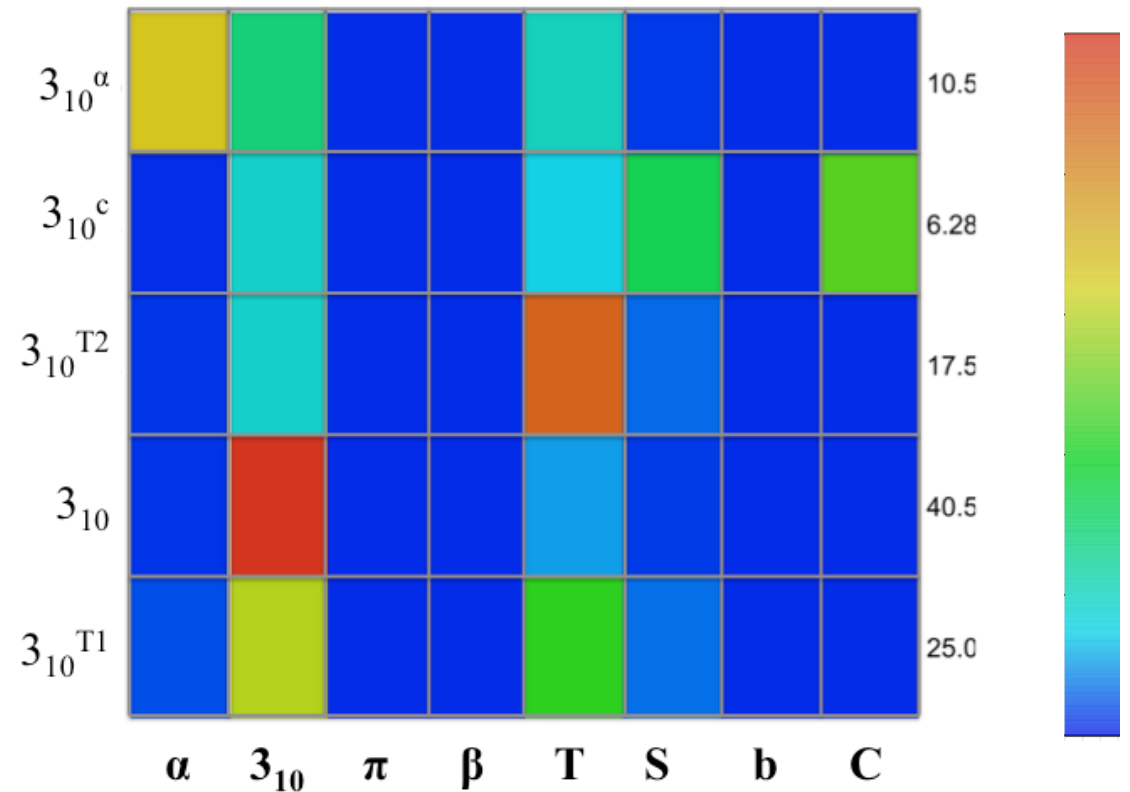
Persistence of original helical state

3_{10} -helices behavior

Transitory: none of 3_{10} remains in same helix state.

Evolve toward β -turn with flexibility increase.

Change to α -helix rare.



K-means clusters of 3_{10} -helix behavior

π -helices behavior

No π -helices remains.

Initial state	100%	> 90%	> 50%	< 25%
α -helix	29.1	74.6	91.4	3.9
3_{10} -helix	0.0	15.7	54.1	24.0
π -helix	0.0	0.0	2.4	97.6

Persistence of original helical state

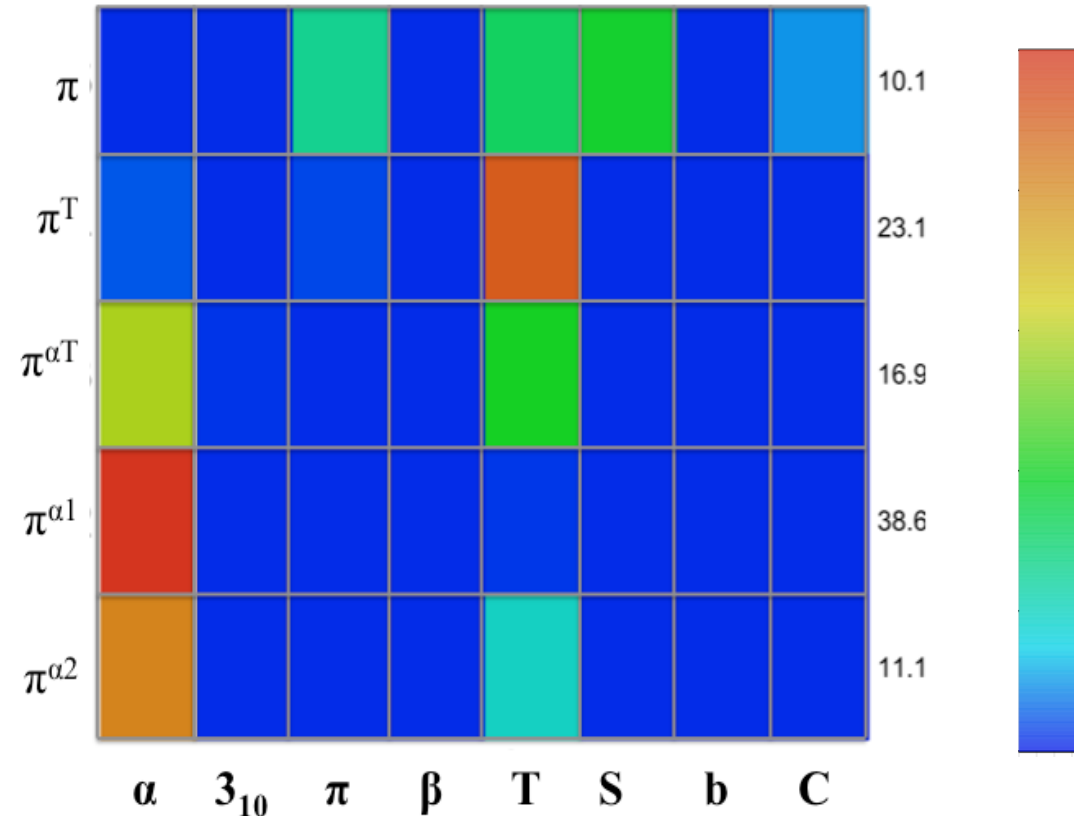
π -helices behavior

No π -helices remains.

π to α most recurring evolution.

π to β -turn also frequent.

Fuzzy cluster π .



K-means clusters of π -helix behavior

Conclusion

α -helix structural behavior is very stable and conserved, adopt β -turn instead of other helical conformations.

3_{10} -helix tend to show transitory behavior towards β -turn.

π does not want to stay π -helices and adapt usually a α or β -turn conformations.

Discussion

Questionable relevance of π -helices.

Molecular Dynamics effects:

- Simulation length
- Force Field

Impact of secondary structure assignment (DSSP) methodology.

New DSSP⁵

Change helix assignment priority:

- Before: $\alpha \rightarrow 3_{10} \rightarrow \pi$
 - Now: $\pi \rightarrow 3_{10} \rightarrow \alpha$
- 15 times more π (2/3 from α , 1/3 from turn).

5. Touw, Wouter G., et al. "A series of PDB-related databanks for everyday needs." *Nucleic acids research* 43.D1 (2015): D364-D368.

New DSSP⁵

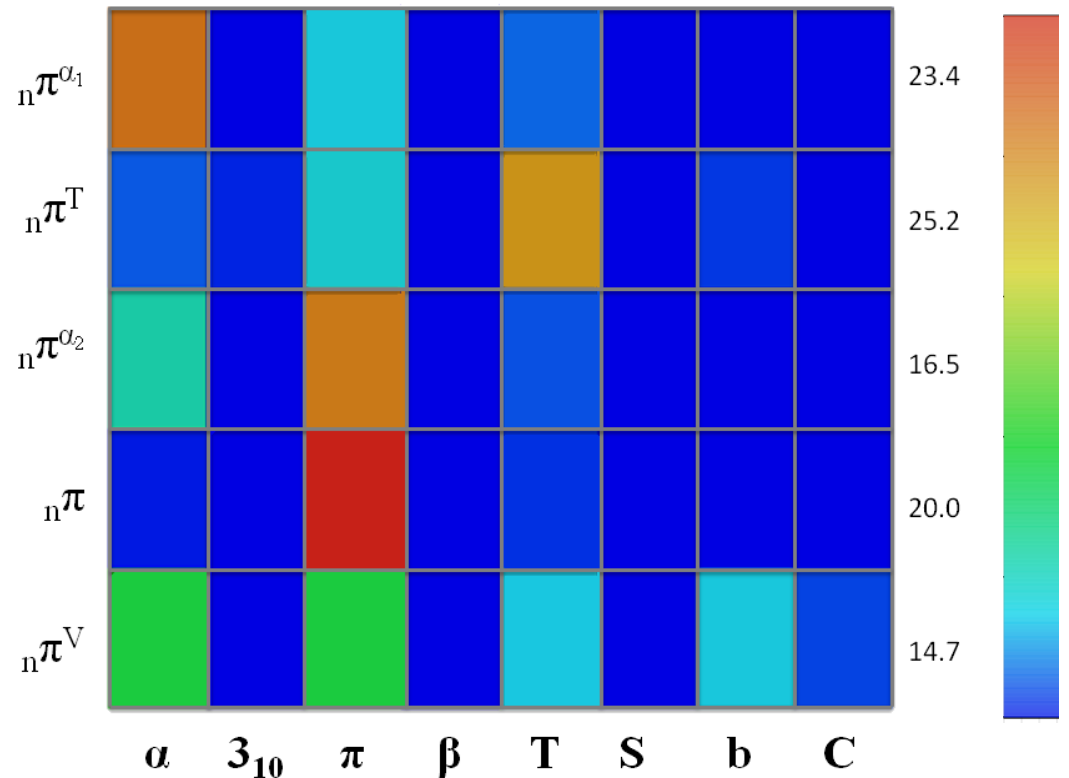
Change helix assignment priority:

- Before: $\alpha \rightarrow 3_{10} \rightarrow \pi$
 - Now: $\pi \rightarrow 3_{10} \rightarrow \alpha$
- 15 times more π (2/3 from α , 1/3 from turn).

One real π cluster.

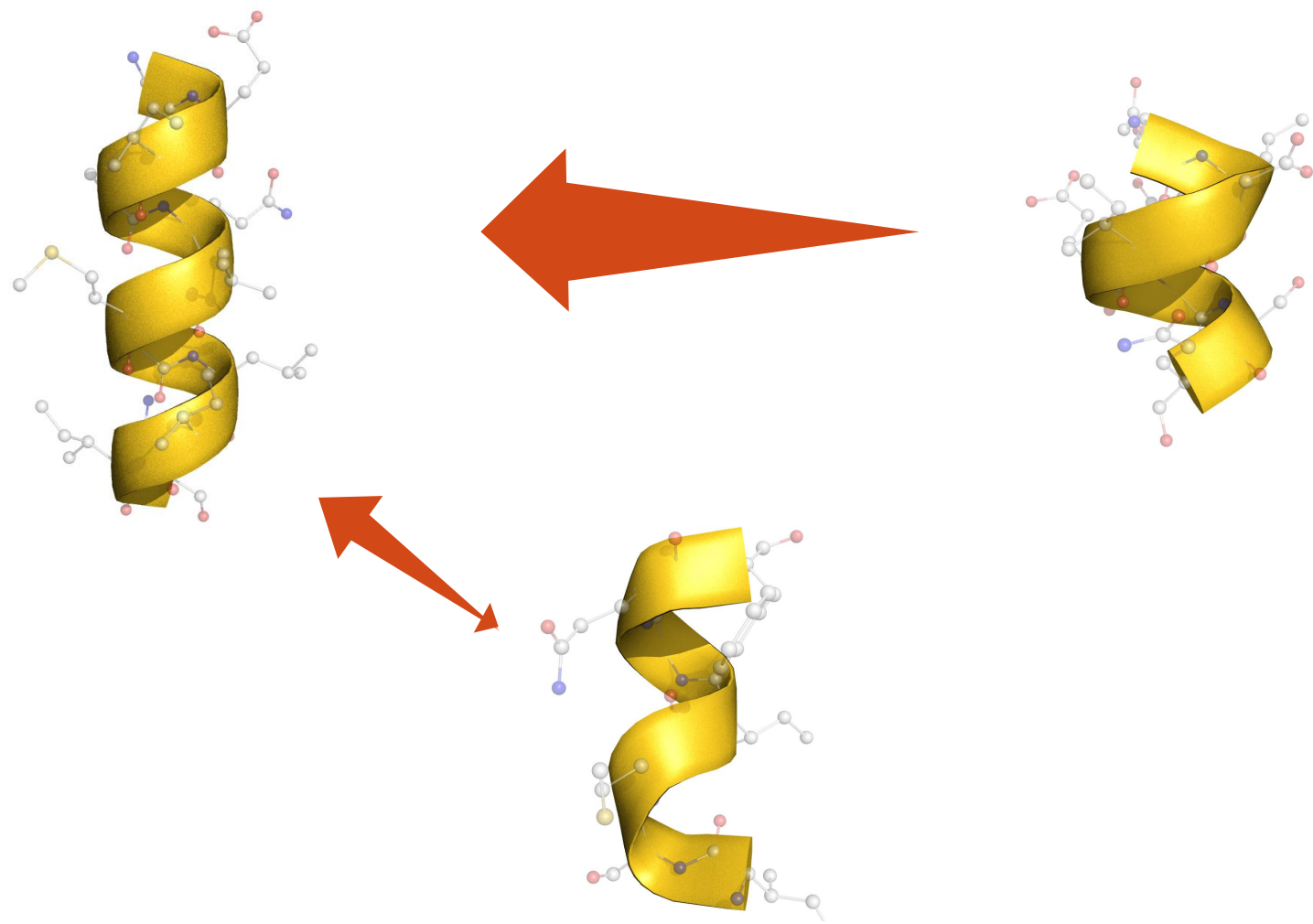
Expected transition to α -helix & β -turn observed.

Real impact of assignment leads to a more coherent behavior or π -helices.



K-means clusters of π -helix behavior with new DSSP

5. Touw, Wouter G., et al. "A series of PDB-related databanks for everyday needs." *Nucleic acids research* 43.D1 (2015): D364-D368.



Acknowledgments



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