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## Dynamics and deformability of $\alpha$ -, 310- and $\pi$ -helices

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# Dynamics and deformability of $\alpha$ -, $3_{10}$ - & $\pi$ -helices

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NICOLAS K. SHINADA

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

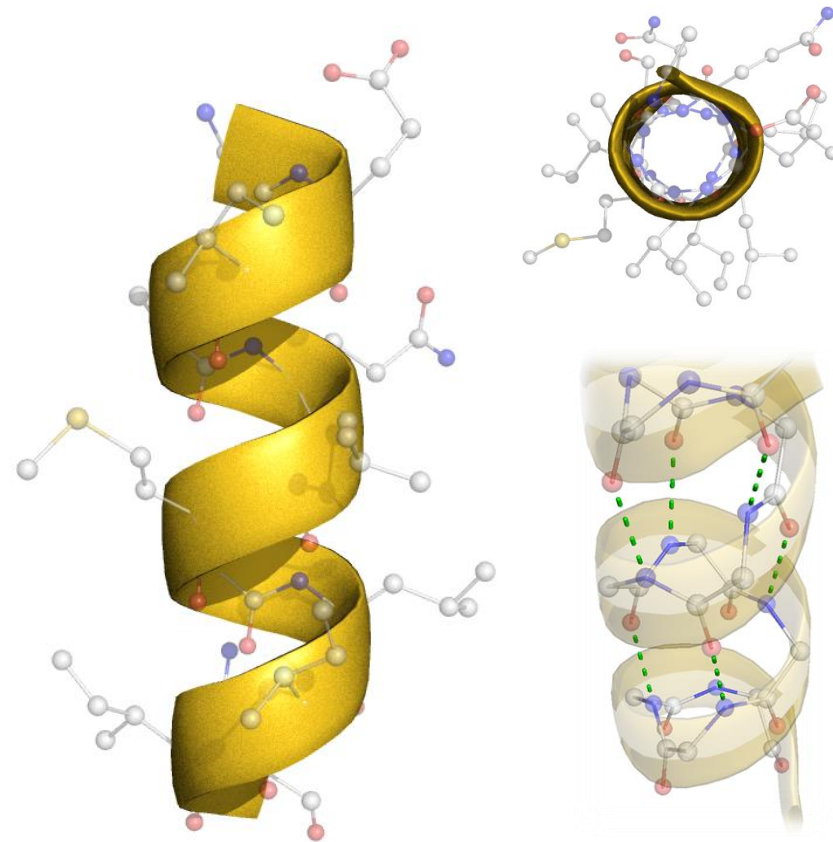
*Université Paris Diderot, Sorbonne Paris Cité, Institut National de Transfusion Sanguine (INTS)*

*GR-Ex laboratoire d'excellence, 6, rue Alexandre Cabanel, 75015 Paris – France*

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

# $\alpha$ -helix

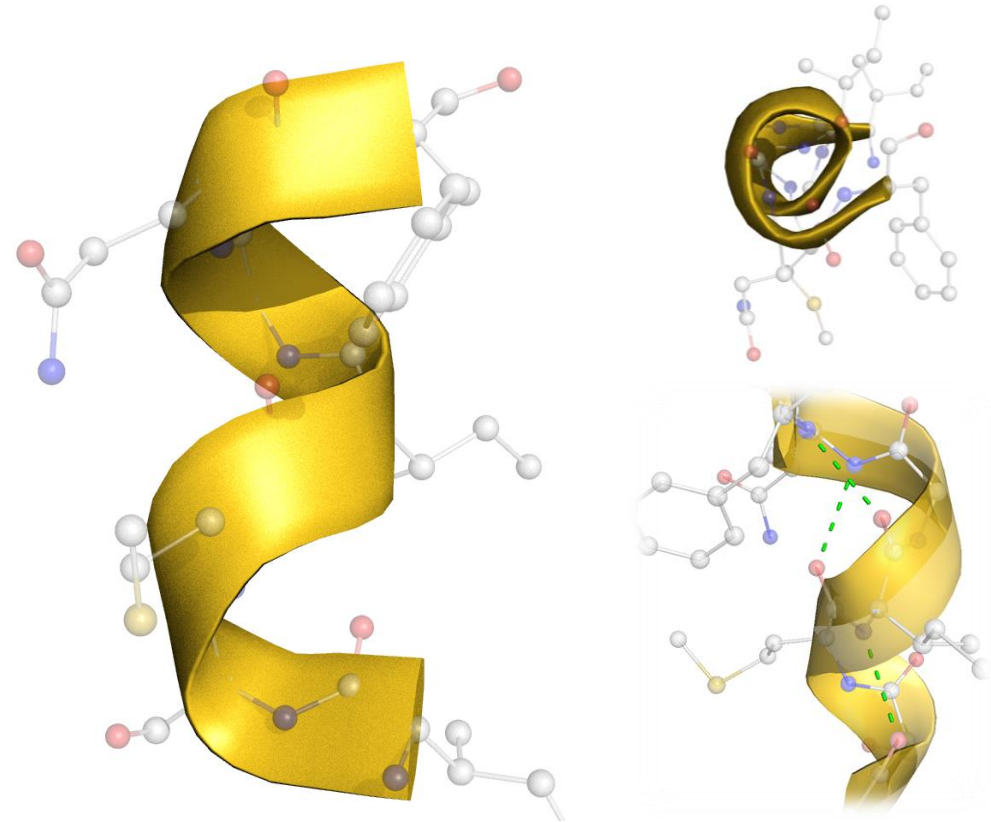
- $\alpha$ -helix (1/3 of protein residues): intramolecular H-bond between residues  $i$  and  $i+4$ .



$\alpha$ -helix (1uyd, A24-N35)

# $3_{10}$ -helix

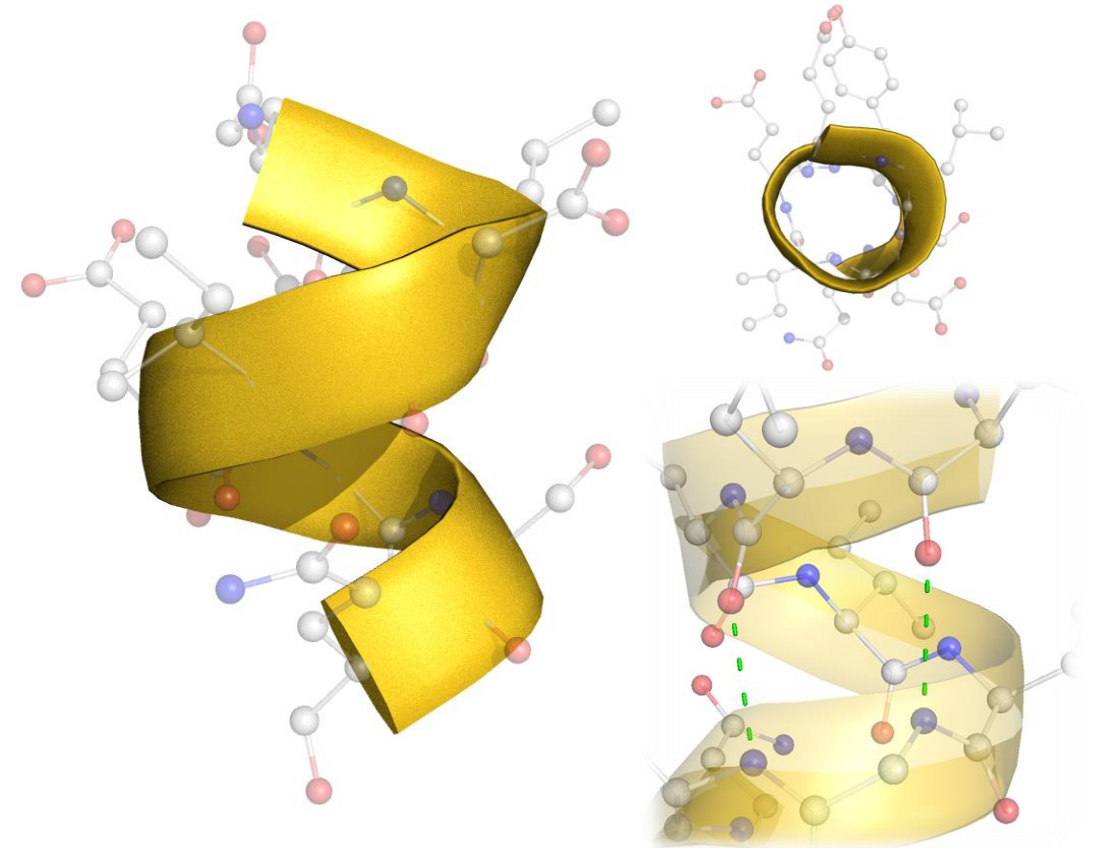
- $\alpha$ -helix (1/3 of protein residues): intramolecular H-bond between residues  $i$  and  $i+4$ .
- $3_{10}$  (4%): 3-4 residues long, H-bond ( $i, i+3$ ),  $\beta$ -hairpin or kink in helices...



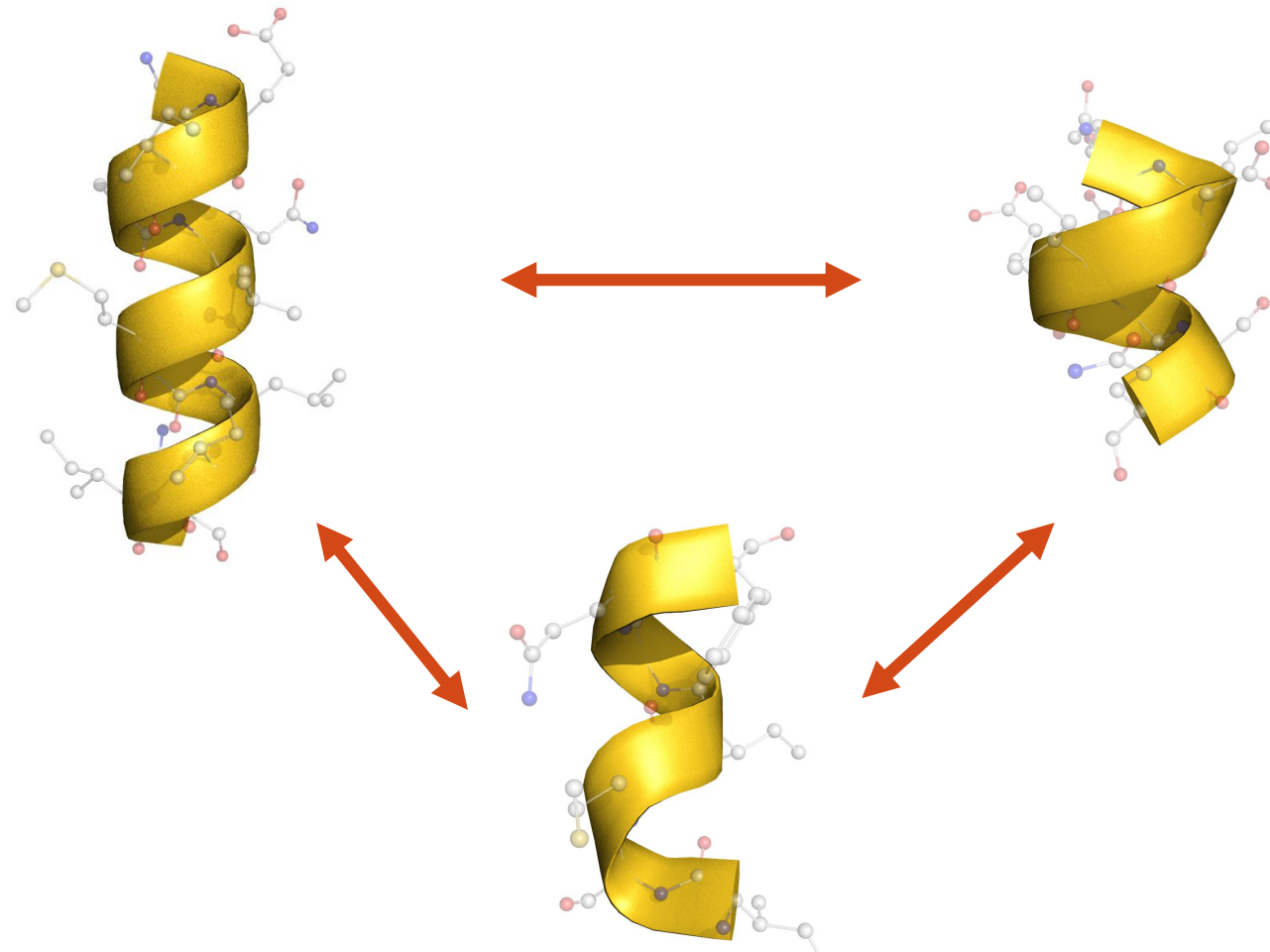
$3_{10}$ -helix (1uyd, I128-F134)

# $\pi$ -helix

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



$\pi$ -helix (2qd3, G347-V355)



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

# Local Movement

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## 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

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169 X-ray structures from PDB with good resolution.

- Normalized B-factor

3 independent MD using GROMACS4.5.7<sup>1</sup> and Amber99sb<sup>2</sup> FF of 50ns.

Conformations saved every ps:

- Secondary structures assignment using DSSP<sup>3</sup> (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

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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.

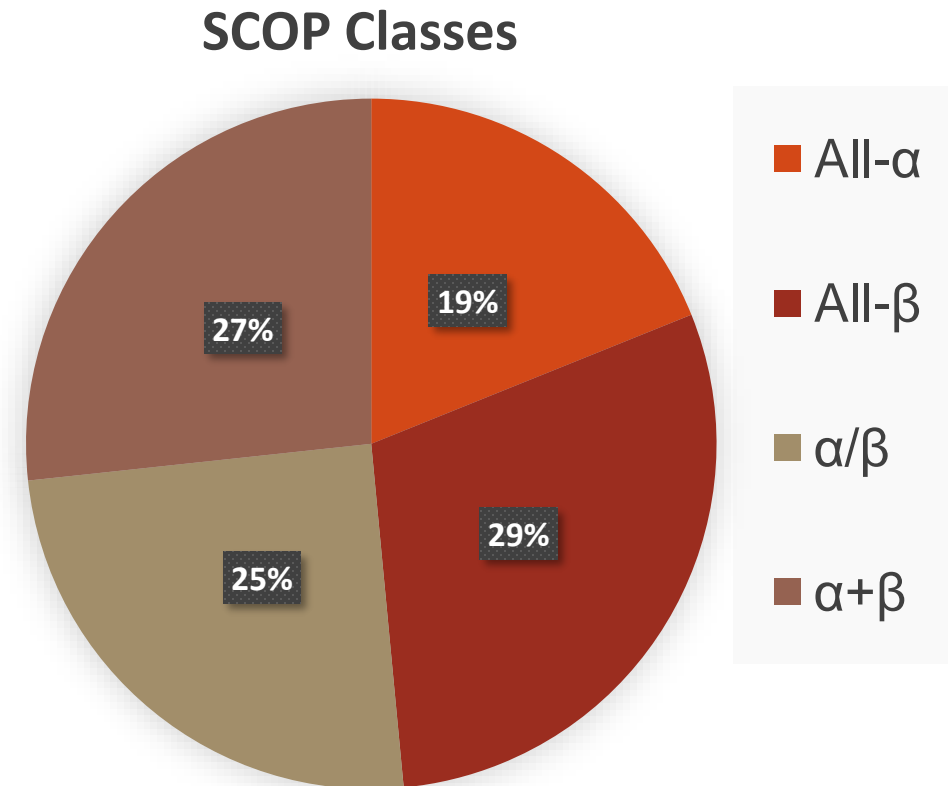
Vector clustering was performed with *K-means* ( $k = 5$ ) for each initial DSSP state assignment.

# Dataset Diversity

Equilibrated SCOP<sup>4</sup> distribution.

Helix distribution representative to the one observed in proteins.

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

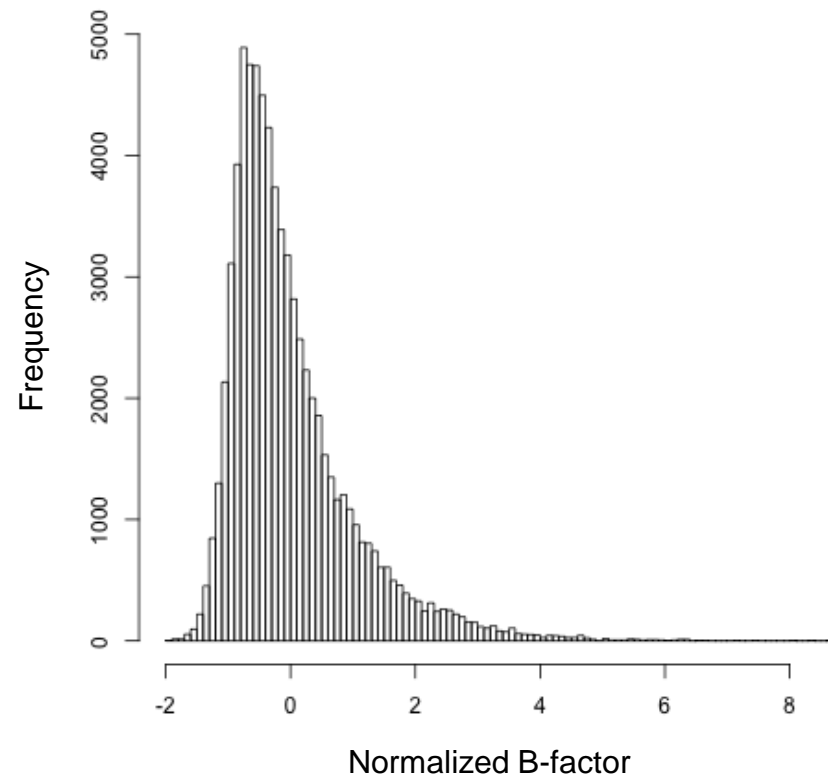


4. Murzin, Alexey G., et al. "SCOP: a structural classification of proteins database for the investigation of sequences and structures." Journal of molecular biology 247.4 (1995): 536-540.

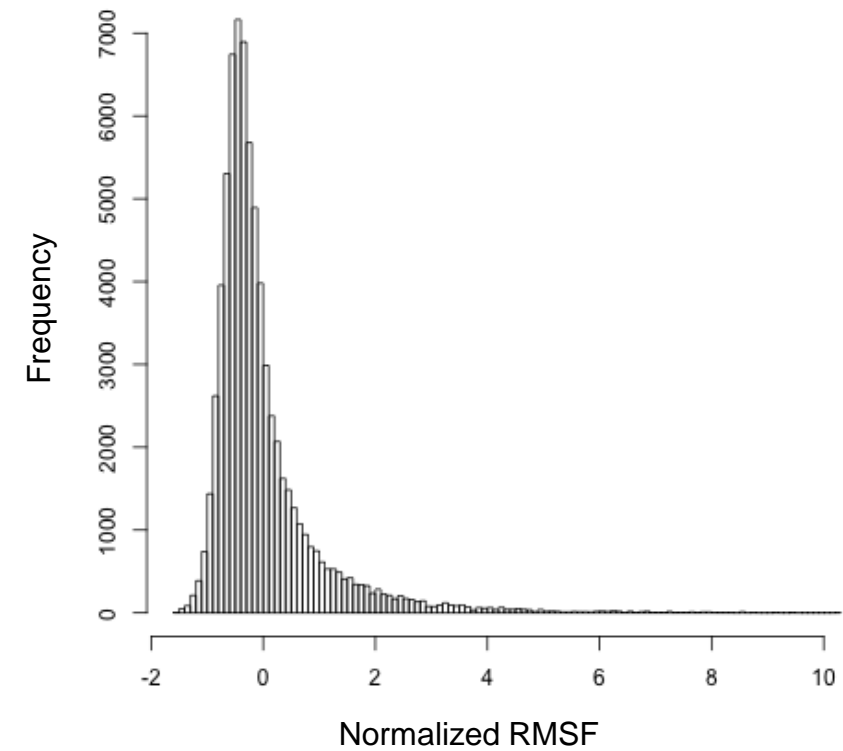
# MD Analysis

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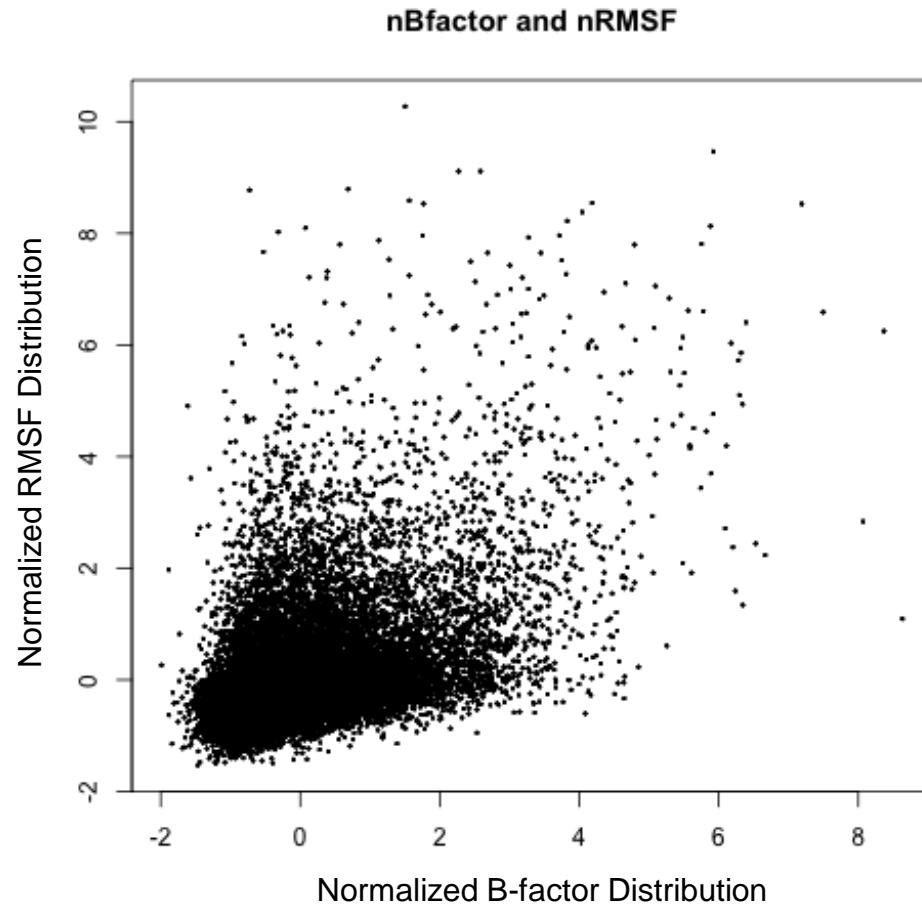
normalized B-factor distribution



normalized RMSF distribution



# MD Analysis



Correlation  $r = 0.49$

# $\alpha$ -helices behavior

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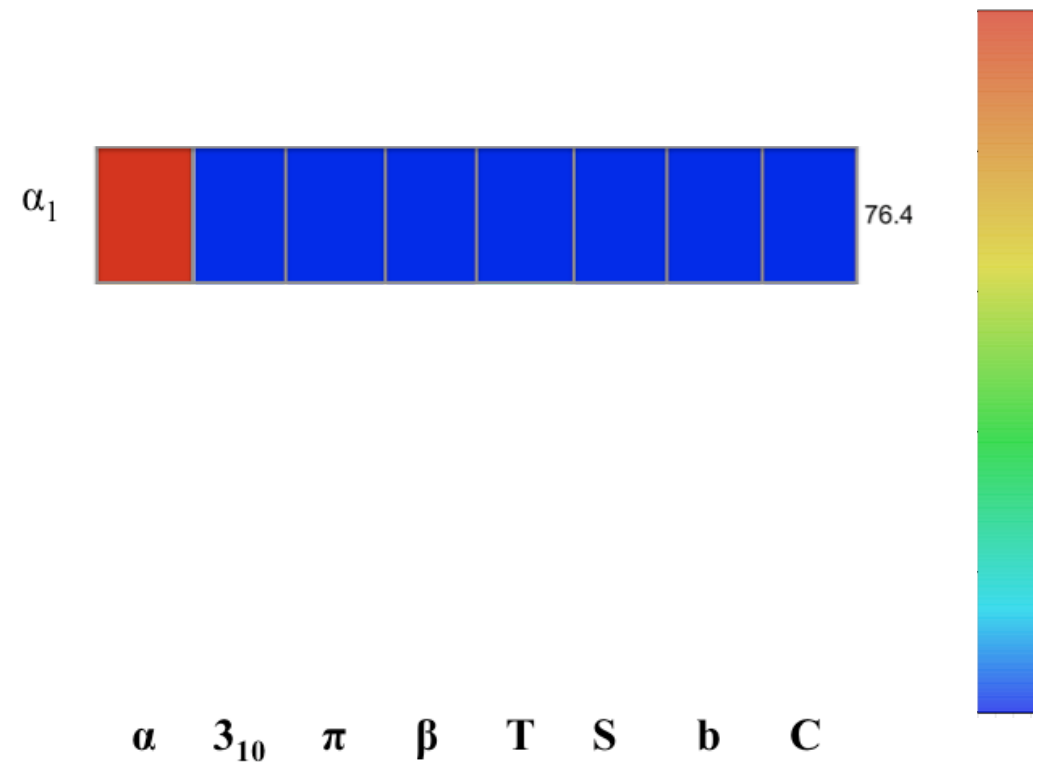
Stability: 90% remains in  $\alpha$ -helical state.

Initial state	100%	> 90%	> 50%	< 25%
$\alpha$ -helix	29.1	74.6	91.4	3.9
$3_{10}$ -helix				
$\pi$ -helix				

*Persistence of original helical state*

# $\alpha$ -helices behavior

Stability: 90% remains in  $\alpha$ -helical state.



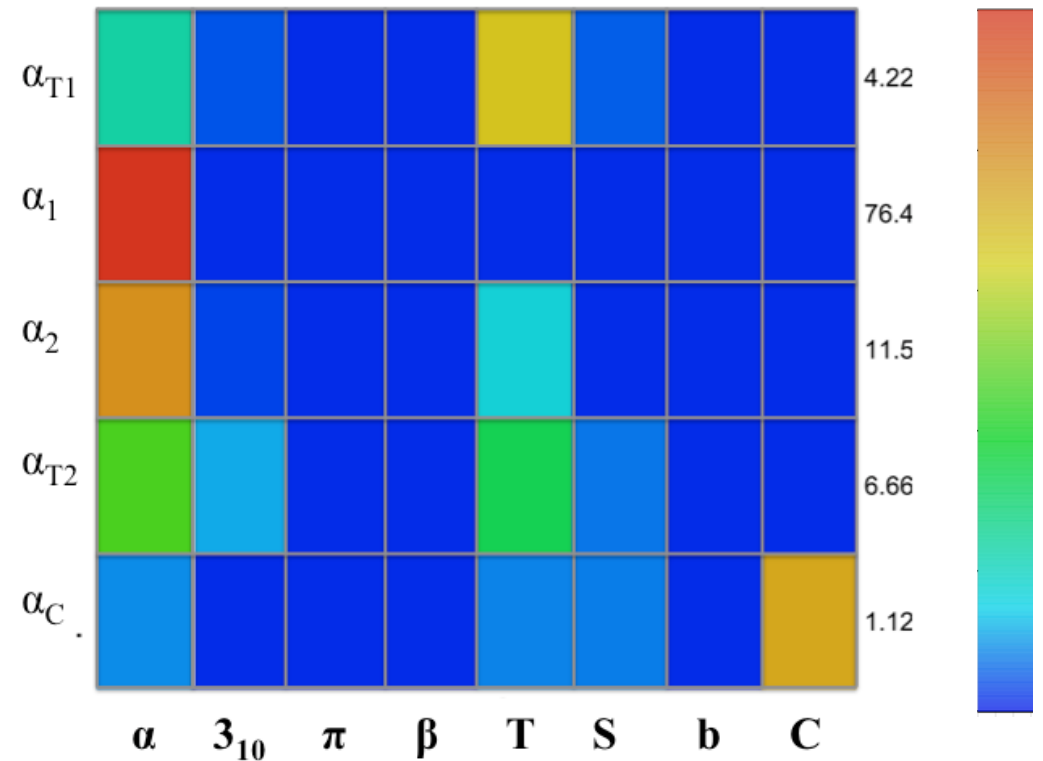
*K-means clusters of  $\alpha$ -helix behavior*

# $\alpha$ -helices behavior

Stability: 90% remains in  $\alpha$ -helical state.

$\alpha$ -helices to  $3_{10}$  very rare.

Otherwise tend to become  $\beta$ -turn.



*K-means clusters of  $\alpha$ -helix behavior*

# $3_{10}$ -helices behavior

---

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

Initial state	100%	> 90%	> 50%	< 25%
$\alpha$ -helix	29.1	74.6	91.4	3.9
$3_{10}$ -helix	<b>0.0</b>	<b>15.7</b>	<b>54.1</b>	<b>24.0</b>
$\pi$ -helix				

*Persistence of original helical state*

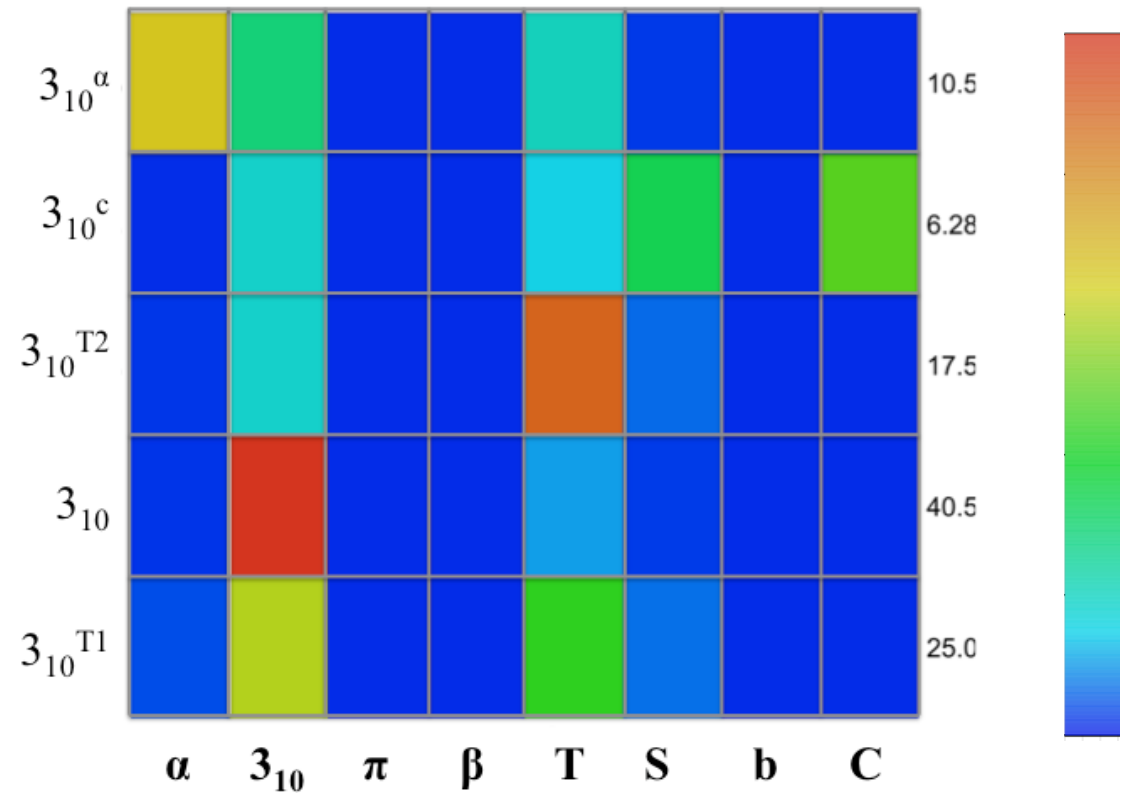


# $3_{10}$ -helices behavior

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

Evolve toward  $\beta$ -turn with flexibility increase.

Change to  $\alpha$ -helix rare.



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

# $\pi$ -helices behavior

---

No  $\pi$ -helices remains.

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

*Persistence of original helical state*

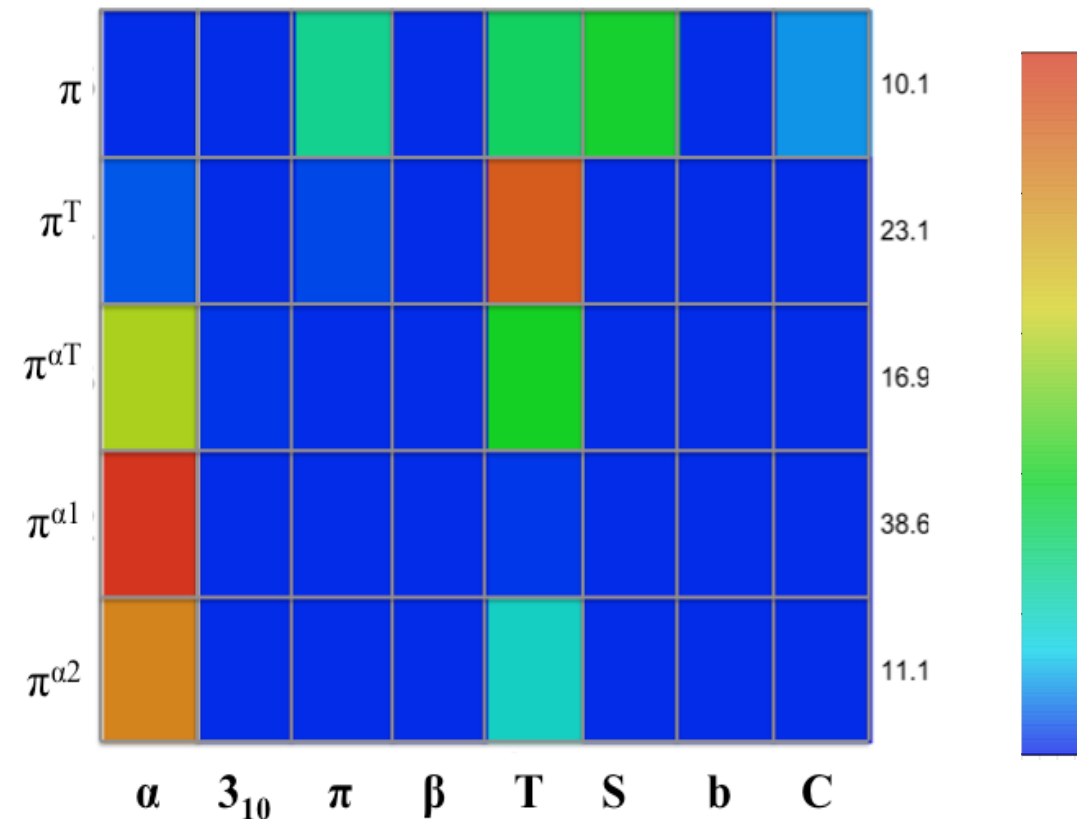
# $\pi$ -helices behavior

No  $\pi$ -helices remains.

$\pi$  to  $\alpha$  most recurring evolution.

$\pi$  to  $\beta$ -turn also frequent.

Fuzzy cluster  $\pi$ .



*K-means clusters of  $\pi$ -helix behavior*

# Conclusion

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$\alpha$ -helix structural behavior is very stable and conserved, adopt  $\beta$ -turn instead of other helical conformations.

$3_{10}$ -helix tend to show transitory behavior towards  $\beta$ -turn.

$\pi$  does not want to stay  $\pi$ -helices and adapt usually a  $\alpha$  or  $\beta$ -turn conformations.

# Discussion

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Questionable relevance of  $\pi$ -helices.

Molecular Dynamics effects:

- Simulation length
- Force Field

Impact of secondary structure assignment (DSSP) methodology.

# New DSSP<sup>5</sup>

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Change helix assignment priority:

- Before:  $\alpha \rightarrow 3_{10} \rightarrow \pi$
  - Now:  $\pi \rightarrow 3_{10} \rightarrow \alpha$
- 15 times more  $\pi$  (2/3 from  $\alpha$ , 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 DSSP<sup>5</sup>

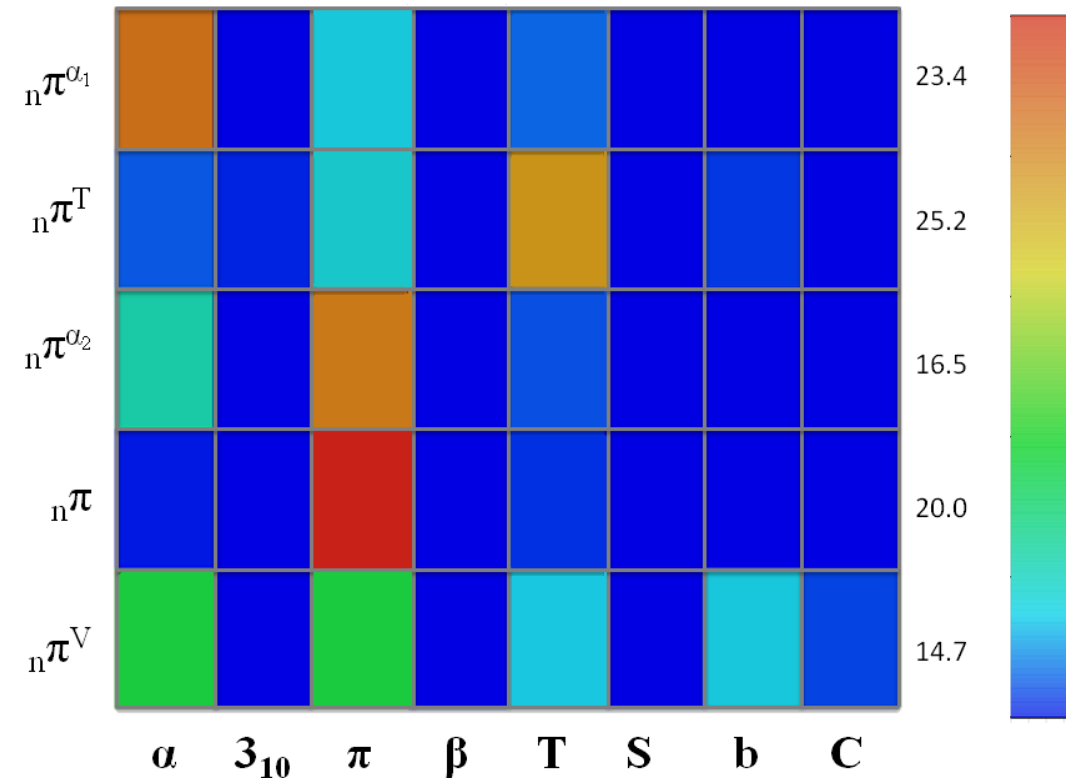
Change helix assignment priority:

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

One real  $\pi$  cluster.

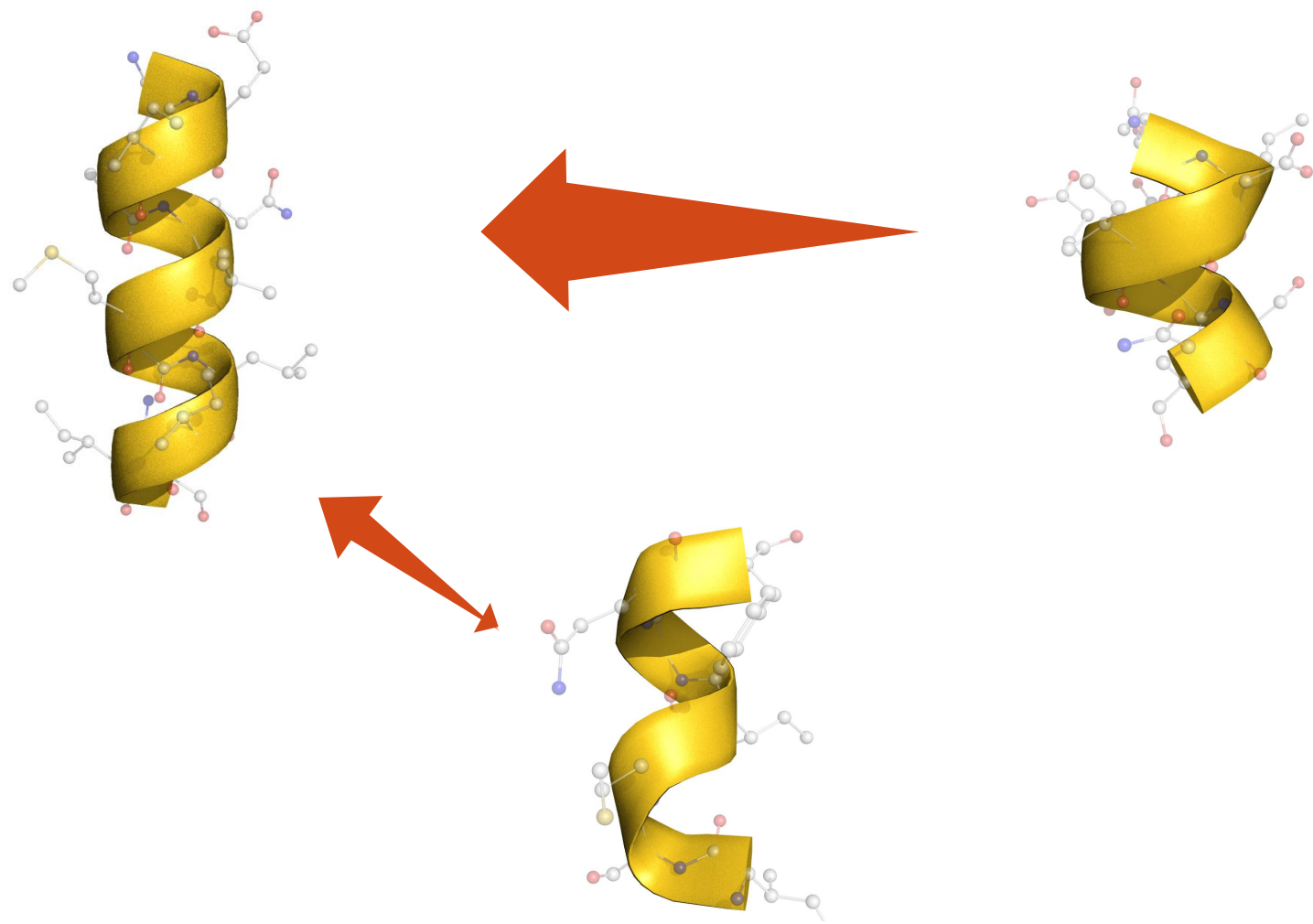
Expected transition to  $\alpha$ -helix &  $\beta$ -turn observed.

**Real impact of assignment leads to a more coherent behavior or  $\pi$ -helices.**



*K-means clusters of  $\pi$ -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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