



Comprendre le monde,
construire l'avenir



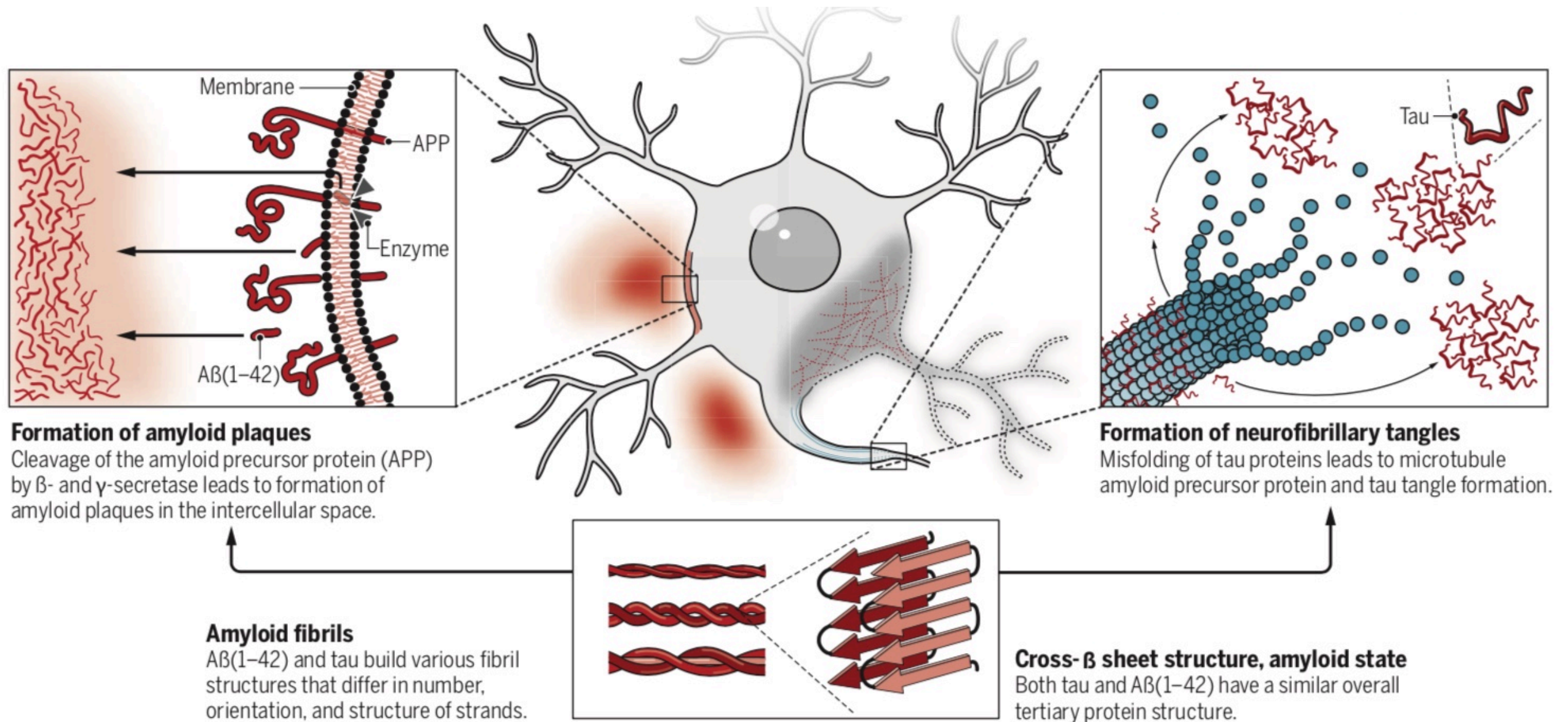
Integrative Model of Rhodanine Derivatives as Tau- aggregation inhibitors in AD

ligand-based (QSAR) and structure-based (docking, MD)
approaches

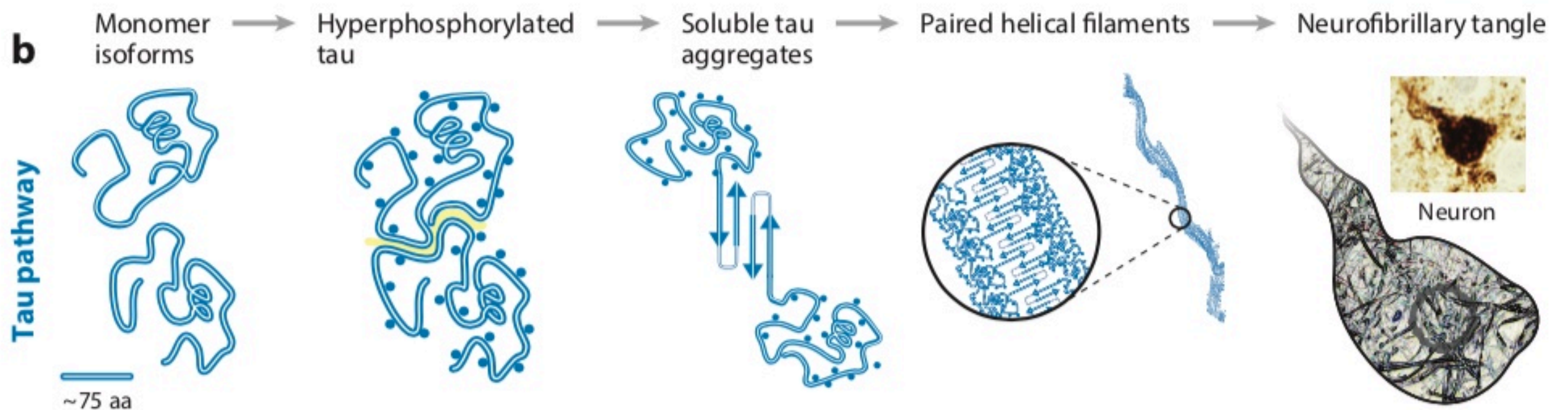
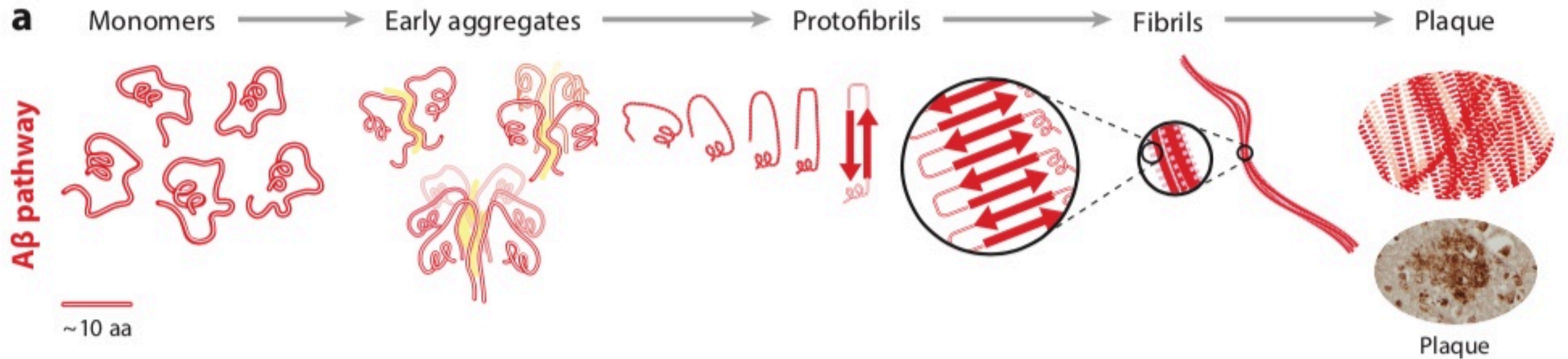
Fabrice Leclerc & Yoanna Álvarez Ginarte

Hallmarks for Alzheimer's Disease

Amyloid/Tau pathways

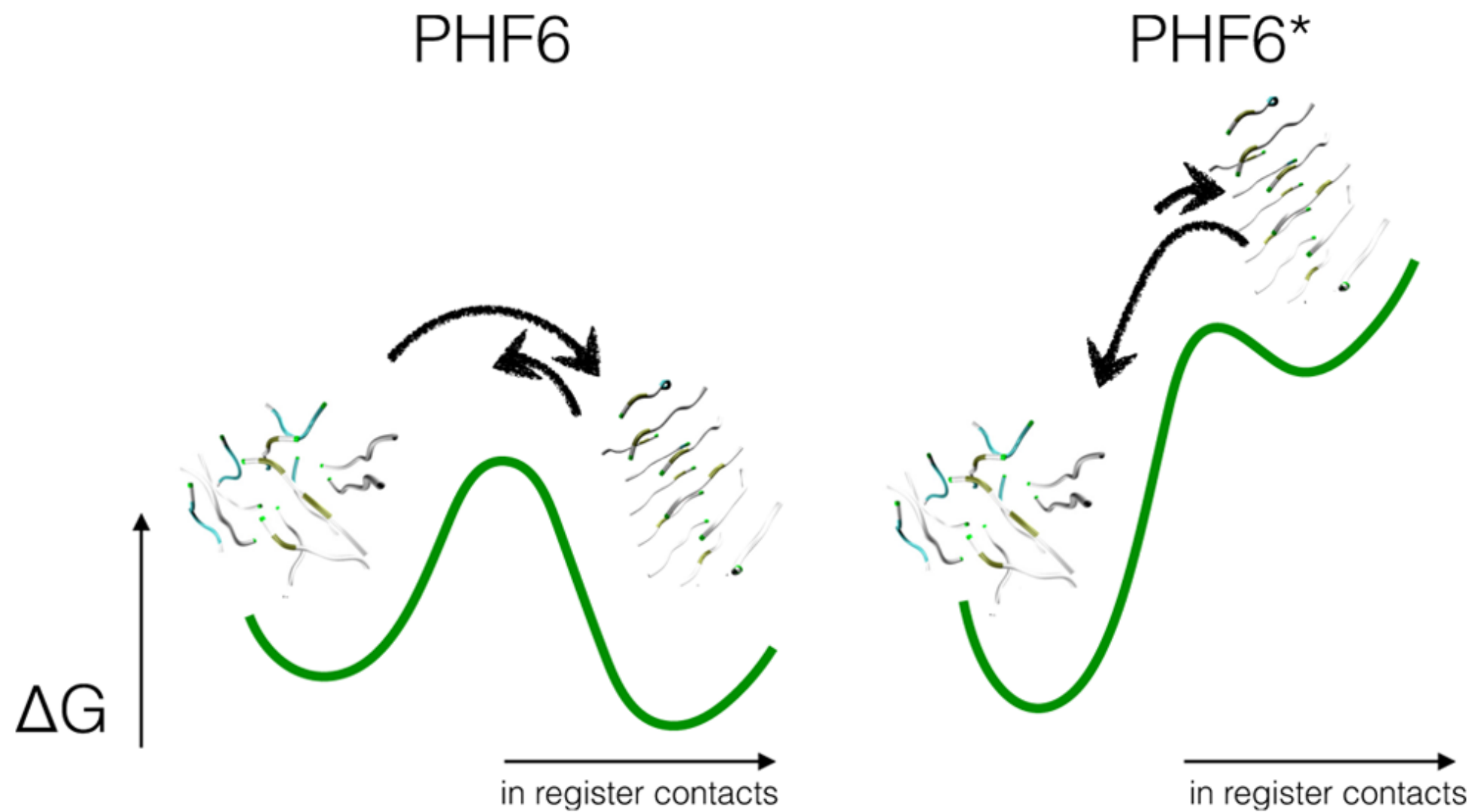


Molecular Basis of Alzheimer's Disease



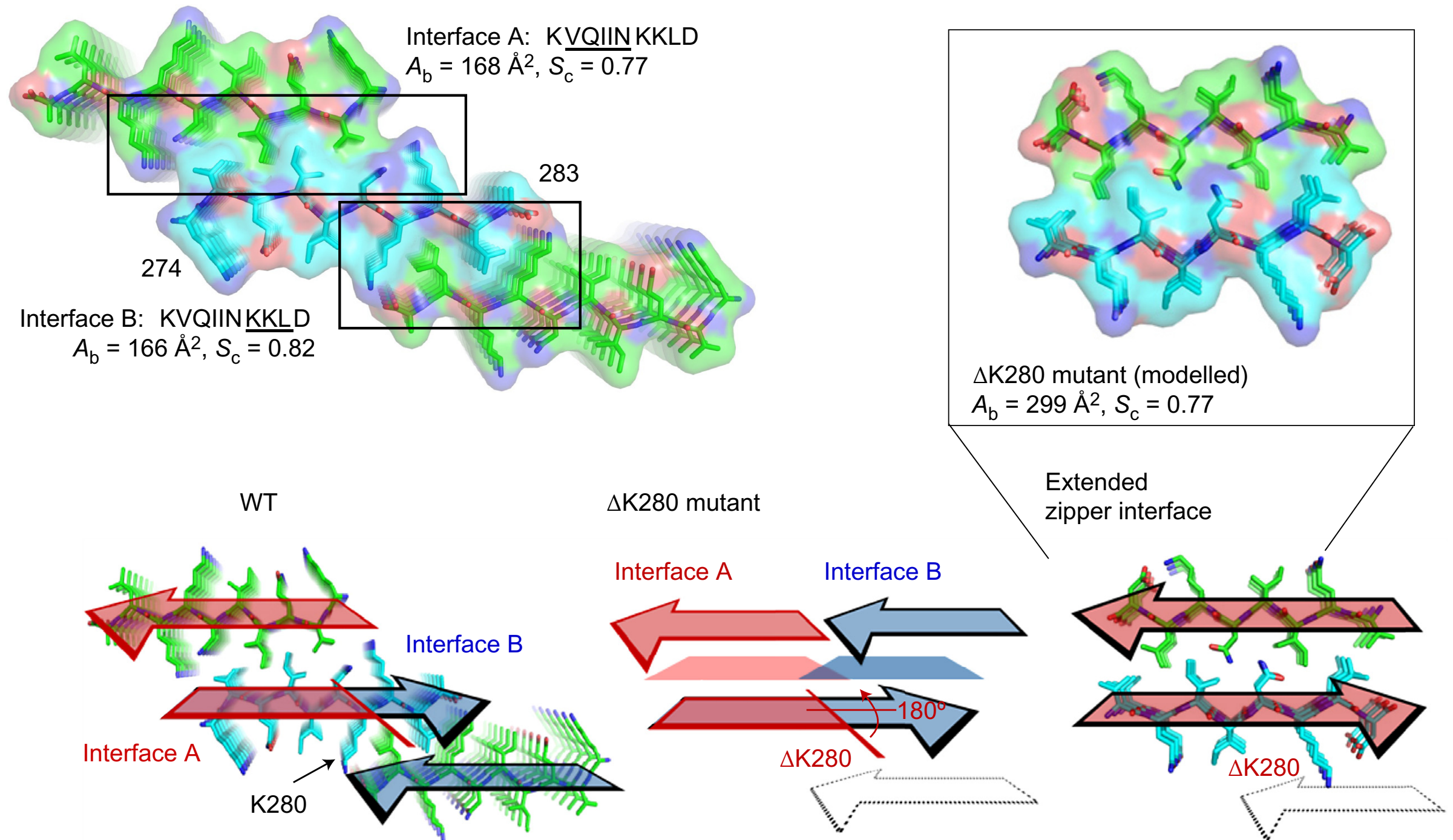
Graham *et al.*, Ann Rev Med, 2017.

Molecular Polymorphism of Tau aggregates: PHF6/PHF6*



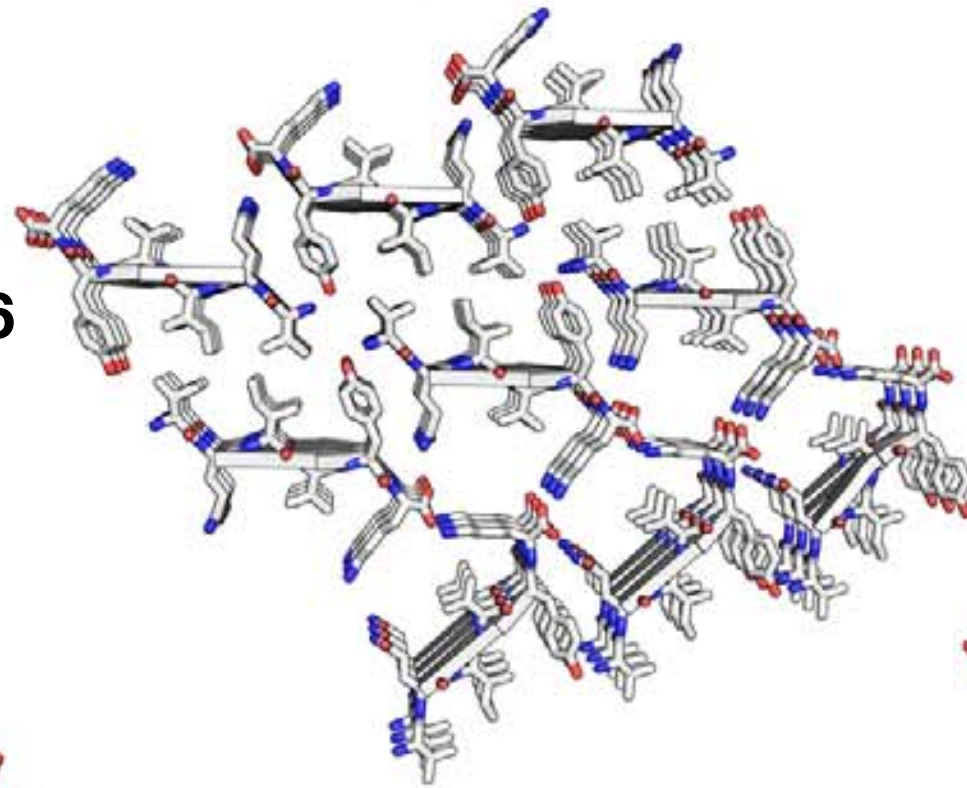
MD simulations

Variant Polymorphism of Tau aggregates: PHF6 wt/mutant

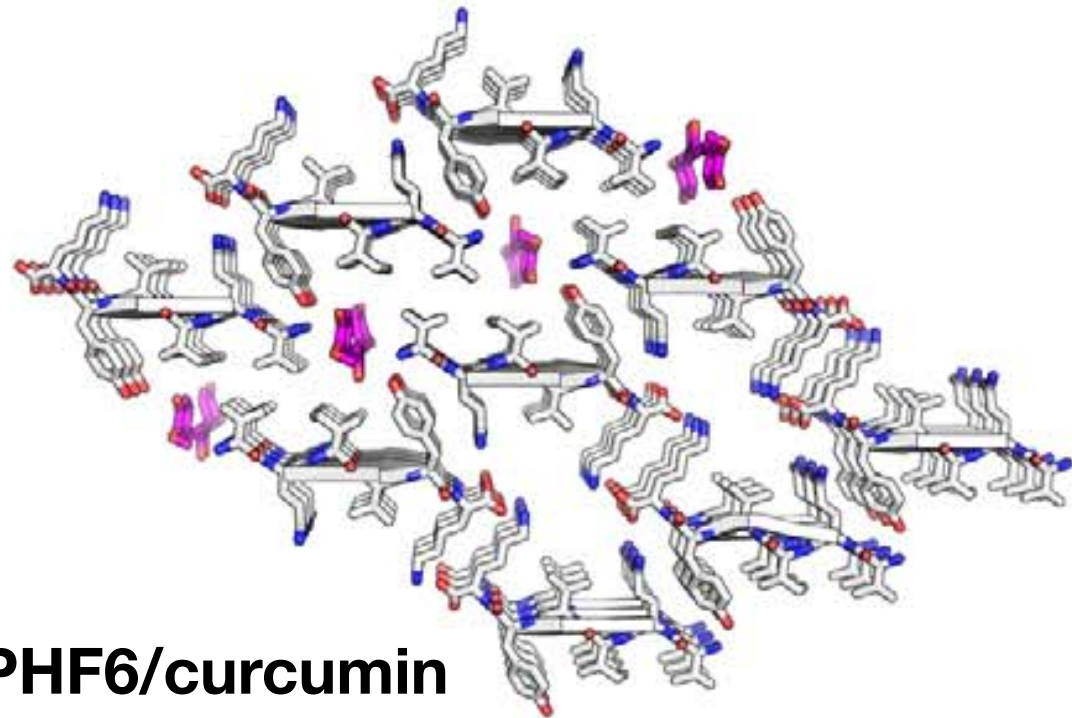


Induced Polymorphism of Tau aggregates: PHF6-ligands

PHF6

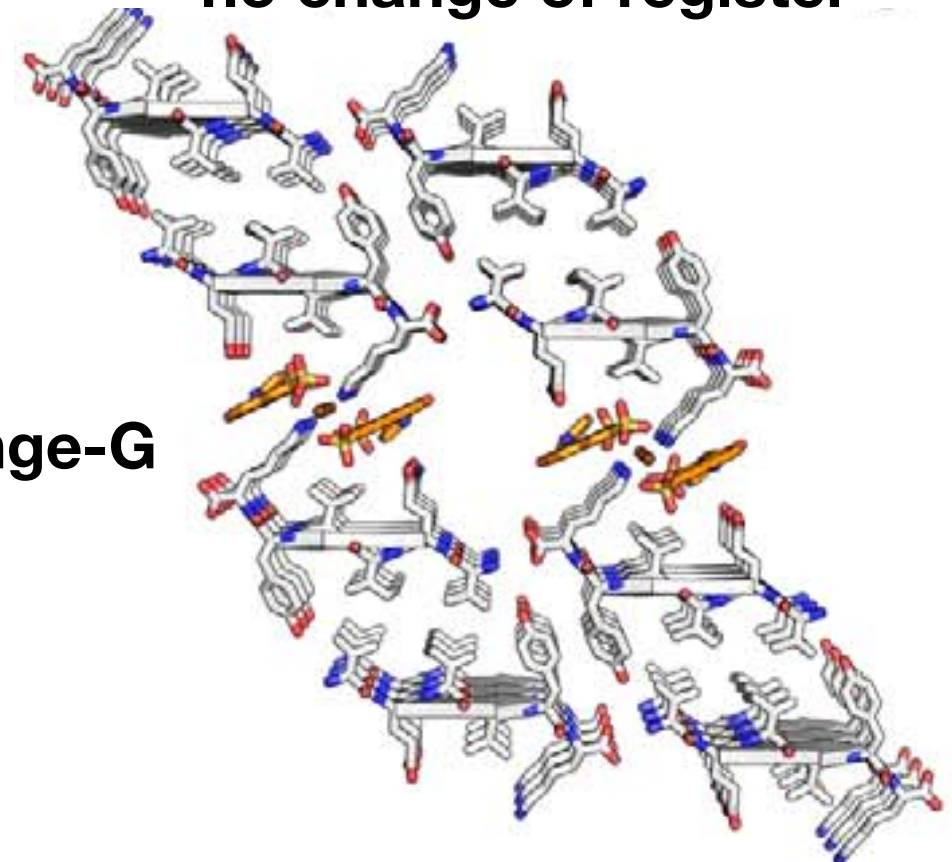


change of register



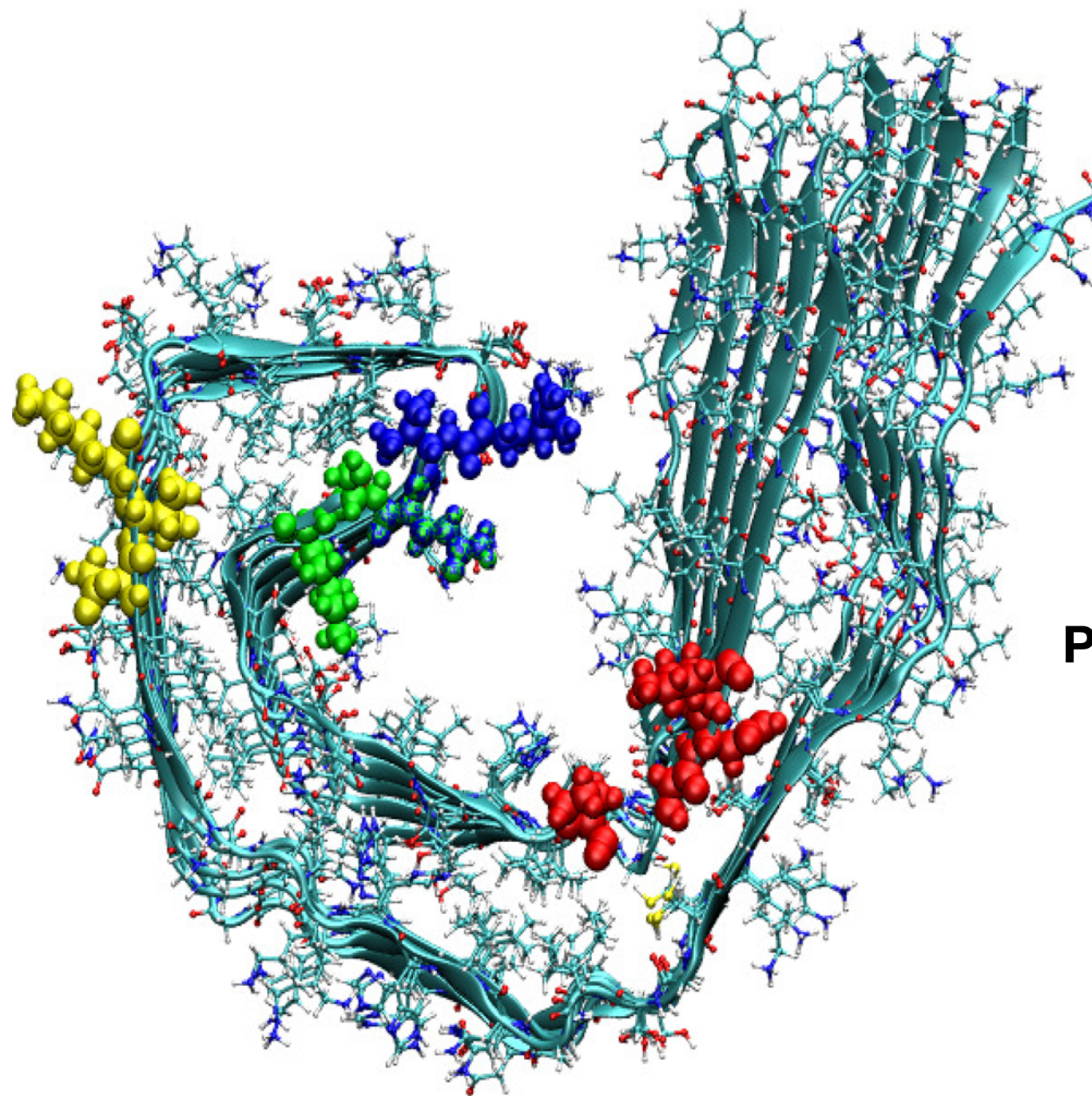
no change of register

PHF6/orange-G



PHF6/curcumin

Multiplicity of Ligand Binding sites in Tau Protofibrils

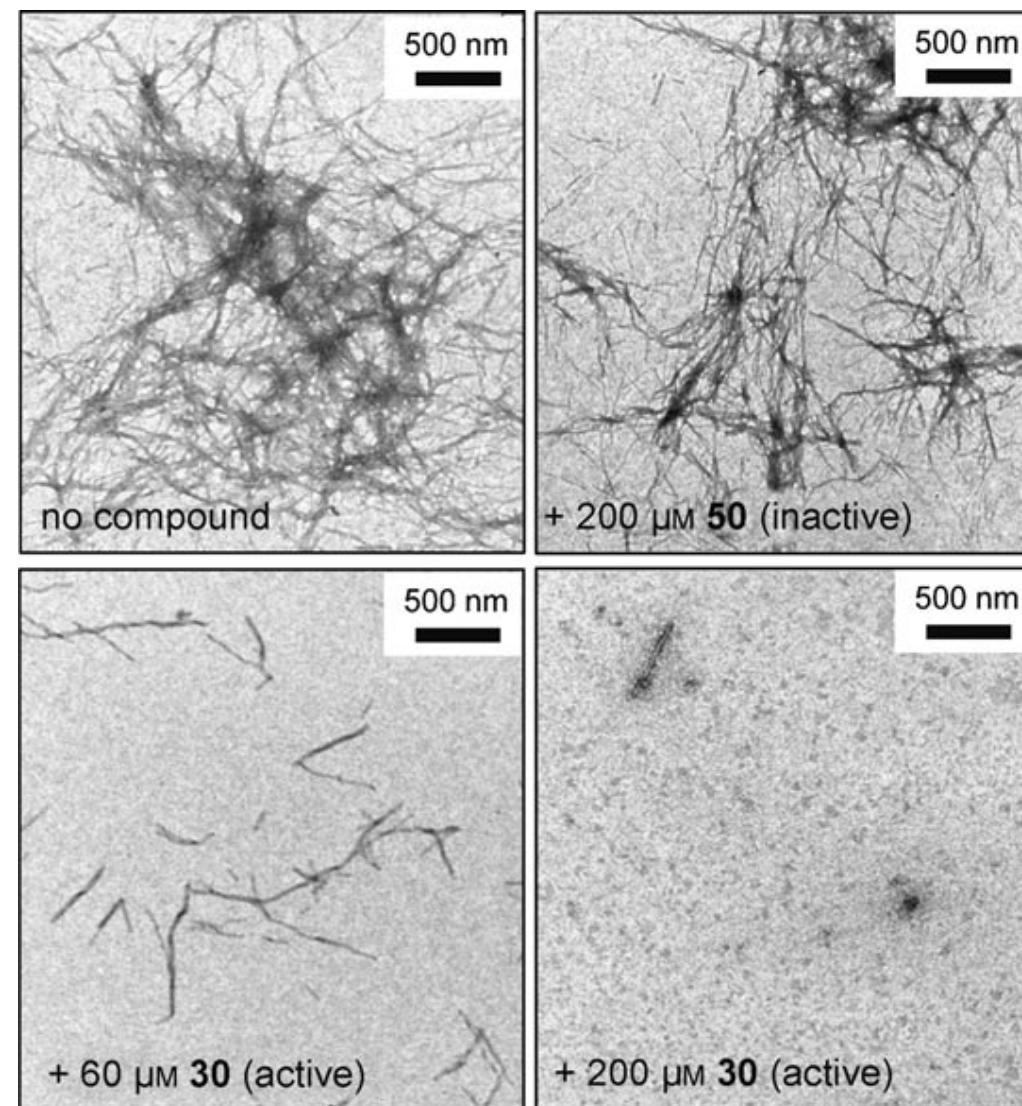
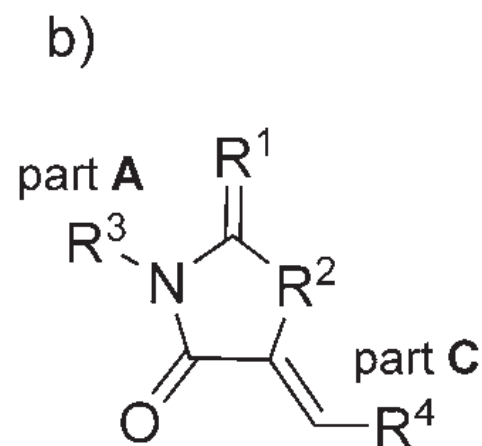
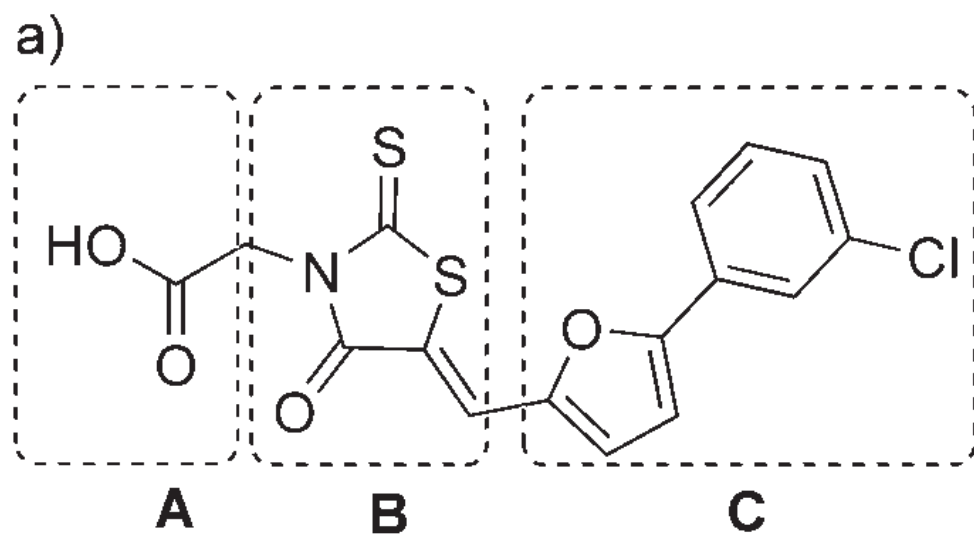


PET imaging tracers

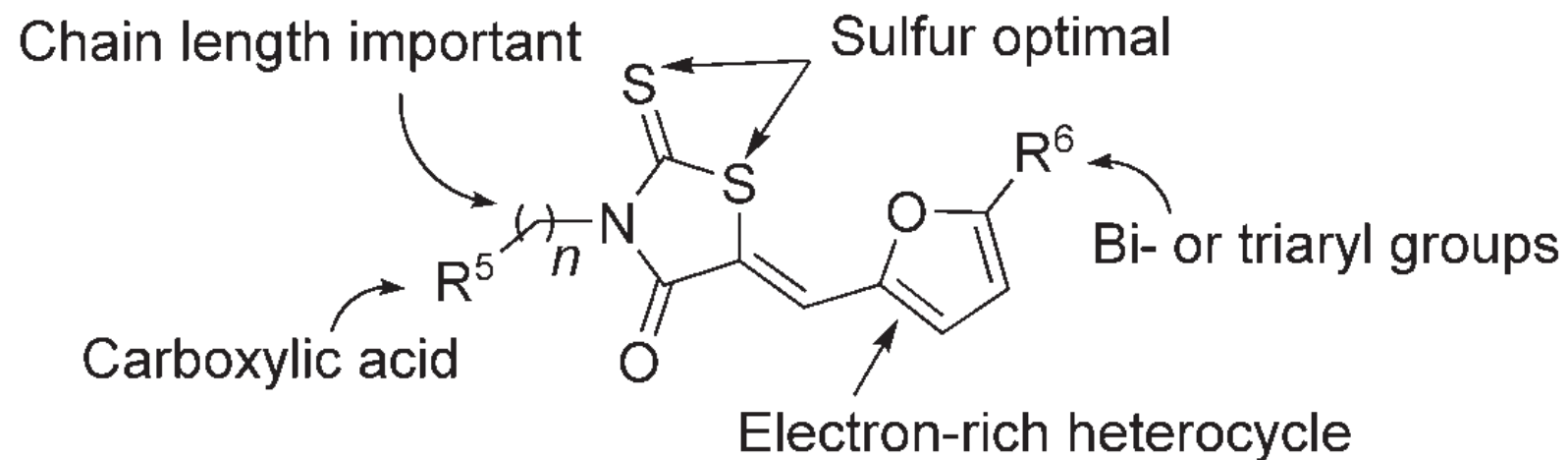
Integrative Modeling of Tau anti-aggregation agents

- **QSAR modeling**
 - inference of molecular properties associated with activity (*IC50*)
 - inference of molecular properties associated with cytotoxicity (*Log (LDH%)*)
- **Docking calculations**
 - binding modes of more active/less active compounds on PHF8 dimers
 - rebuilding of PHF8 tetramers from dimers of PHF8 docked complexes
- **MD simulations**
 - docking poses as initial configurations for simulations
 - evaluation of binding modes and stoichiometry (compound/PHF6 tetramer)

Rhodanines as Tau anti-aggregation agents



dissolution of PHFs (EM)



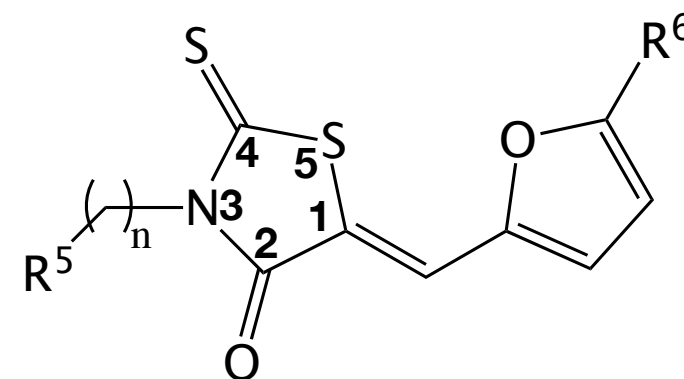
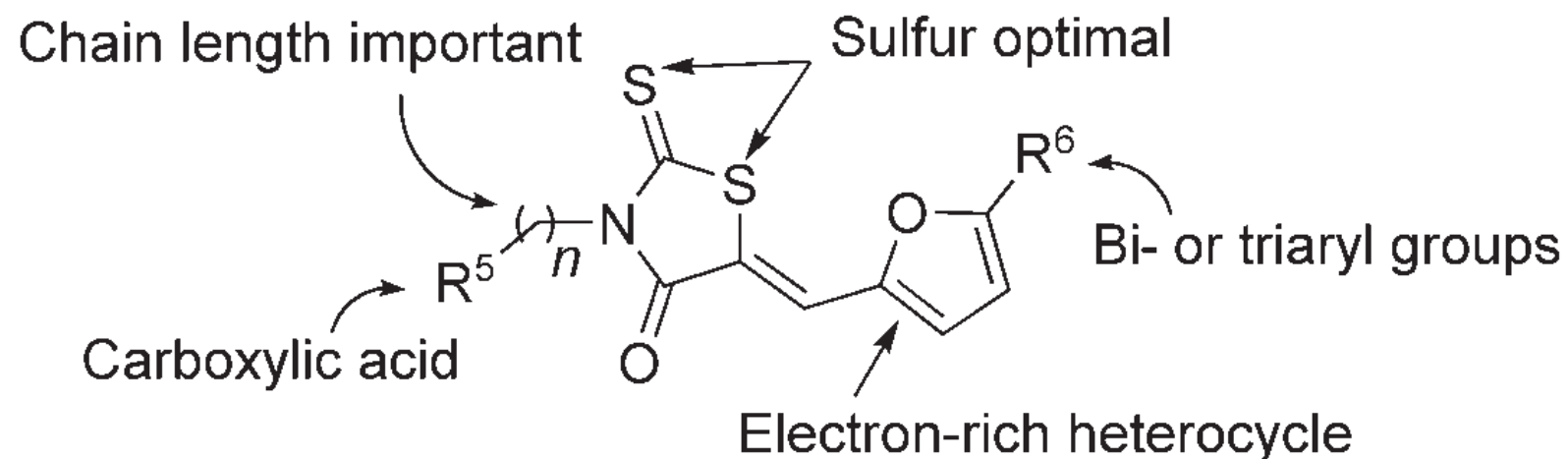
QSAR Study of Rhodanines: activity & cytotoxicity

Table 1: Compound structures, IC₅₀ and DC₅₀ values, PHF inhibition in cells, and cytotoxicity.

Entry	Compd	R ³ [^a]	R ⁴ [^a]	IC ₅₀ [μM] ^[b]	DC ₅₀ [μM] ^[b]	Inhibition in cells ^[c] [%]
1	1			0.82	0.10	20.40 ± 5.37
2	4			4.36	1.80	n.d.
3	14			0.67	0.94	70.47 ± 4.49
4	49			1.09	0.80	n.d.
5	16			0.47	0.30	21.55 ± 13.82
6	23			1.22	1.04	n.d.
...						
16	17			0.54	0.39	62.67 ± 4.08
17	19			0.17	0.13	16.49 ± 4.38

46 compounds

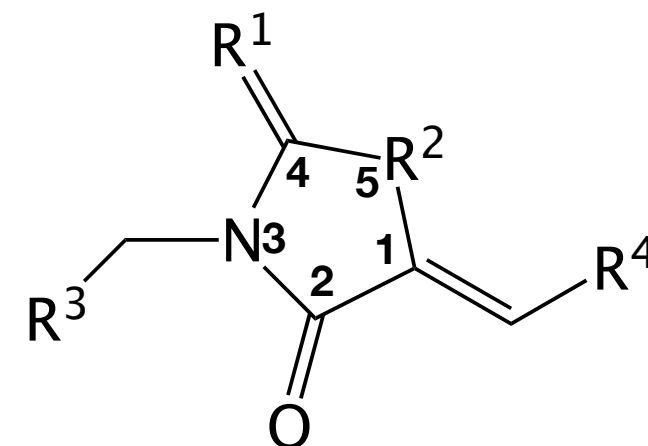
QSAR model of Rhodanine derivatives



$$pIC50 = -1.14MR + 45.43HOMO + 0.14\mu - 3.24q4 + 16.58$$

$$n=35; R^2 = 0.81; s=0.33; F=15.99; q^2 = 0.60; p < 0.01$$

$$\text{Test set: } n=9; R^2 = 0.60; s=0.57; F=5.86$$

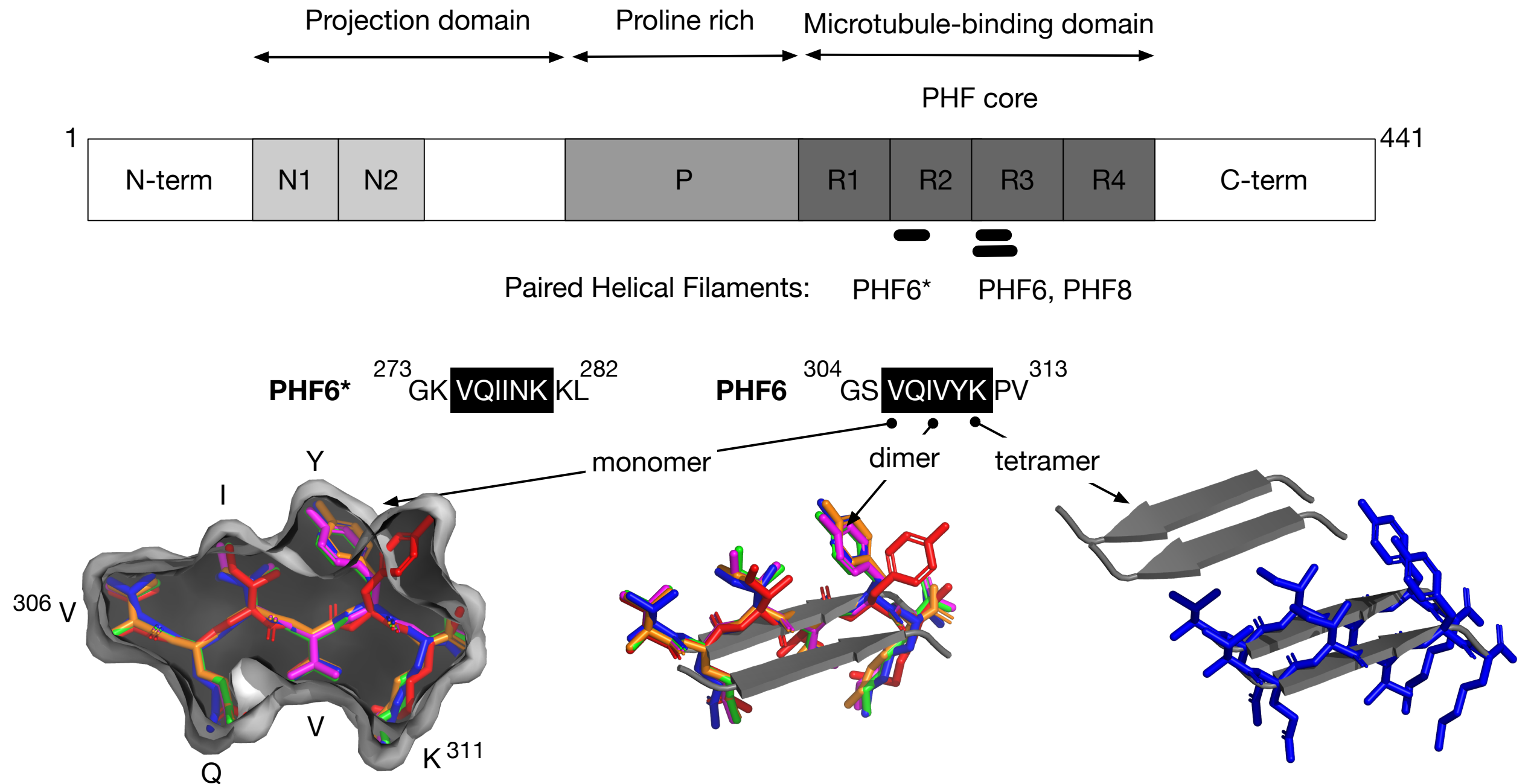


- global - steric: low value of molar refractivity (**MR**)

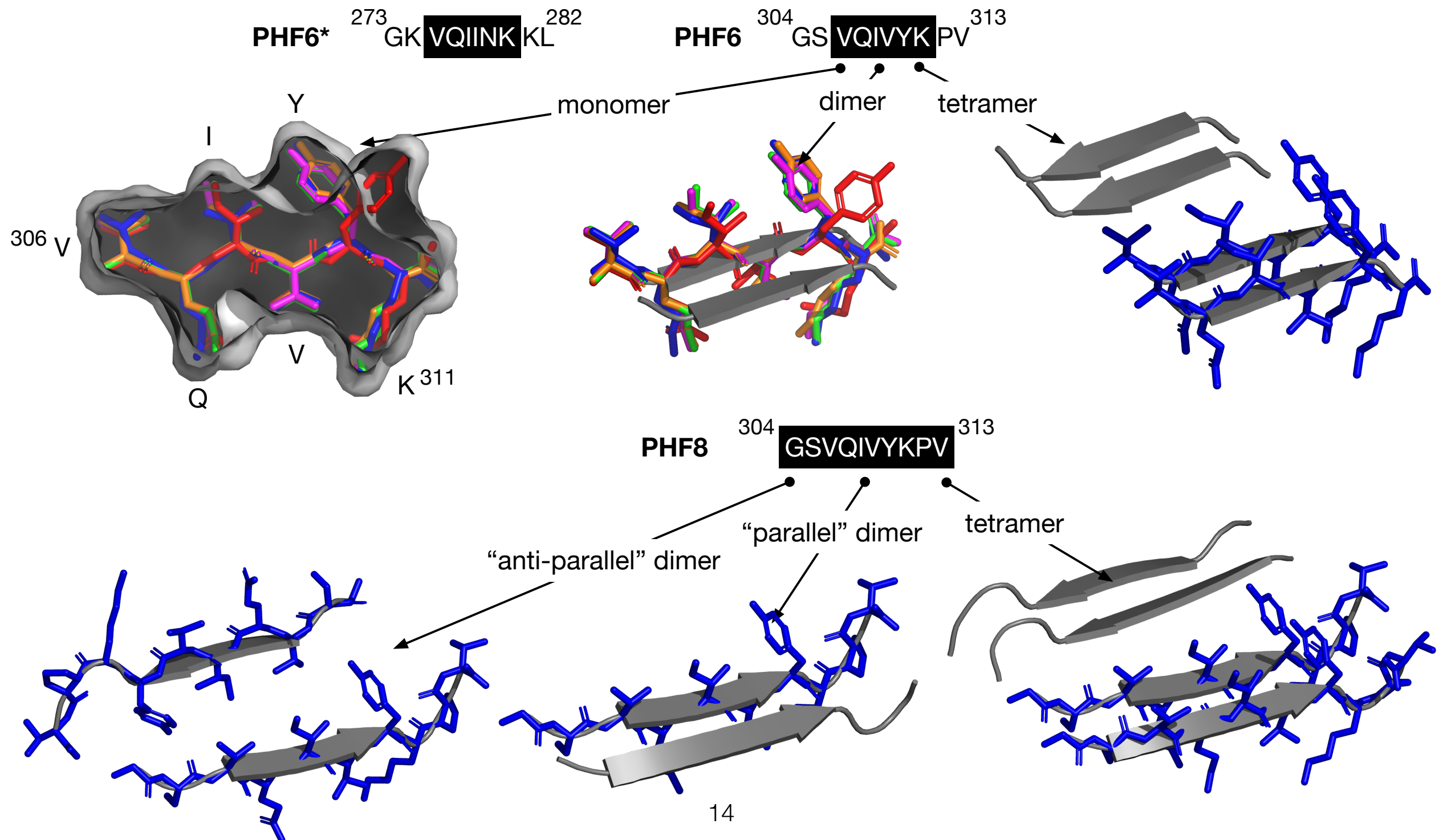
- global - electronic: high value of **HOMO** and dipolar moment (μ)

- local - electronic: negative **charge** on C4

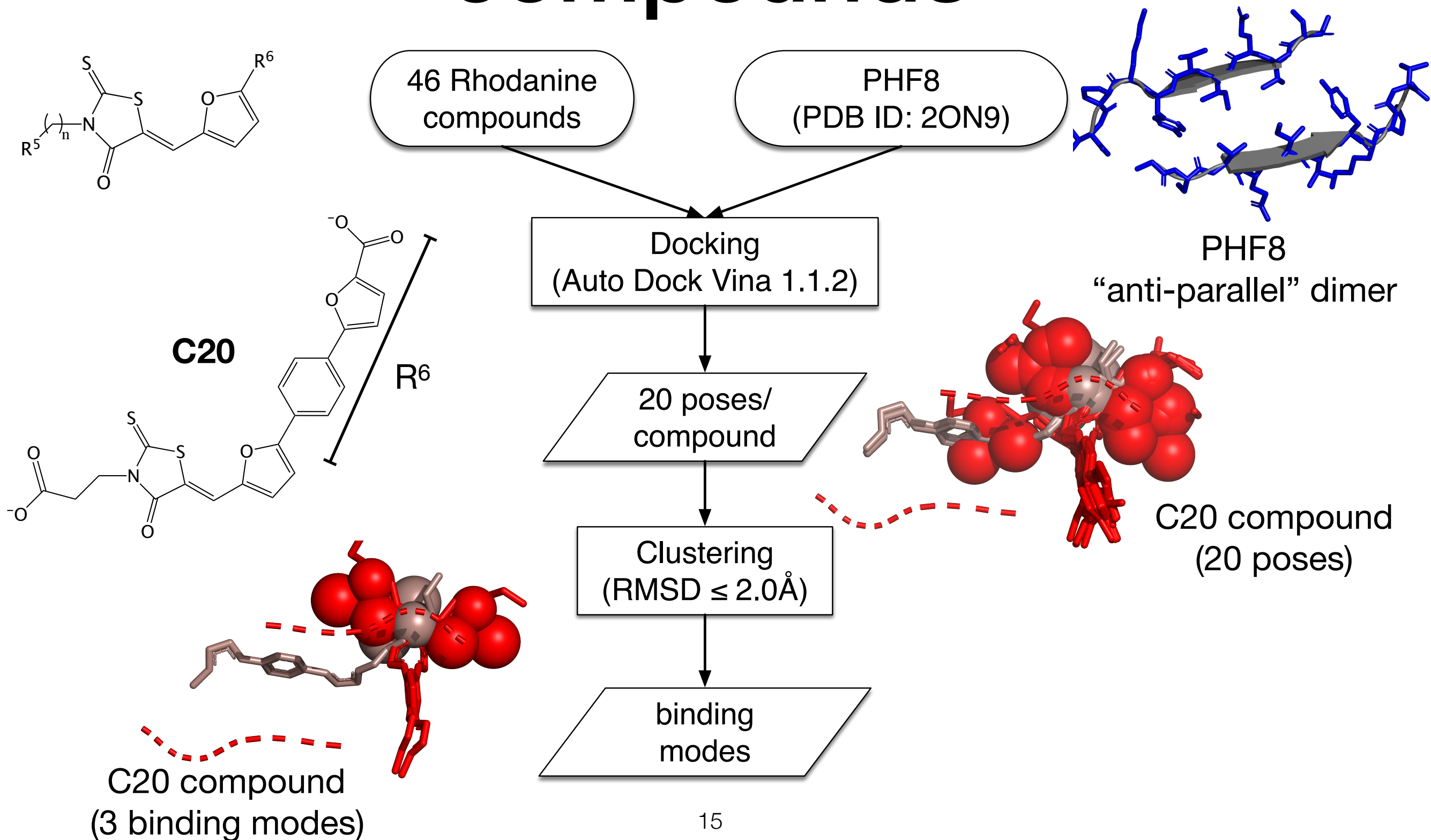
PHF6 Tau dimer and tetramer assemblies



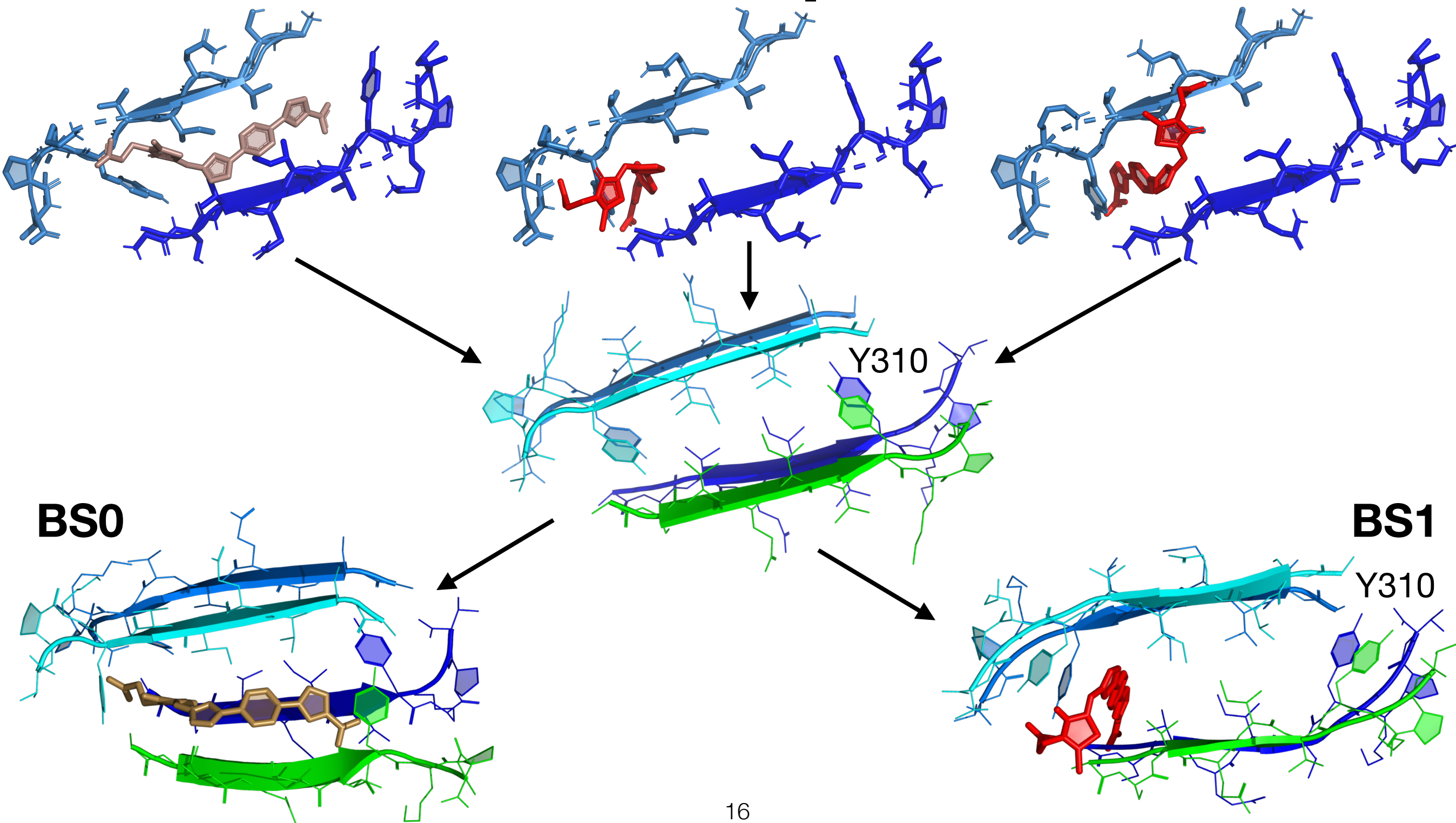
PHF8 Tau dimer and tetramer assemblies



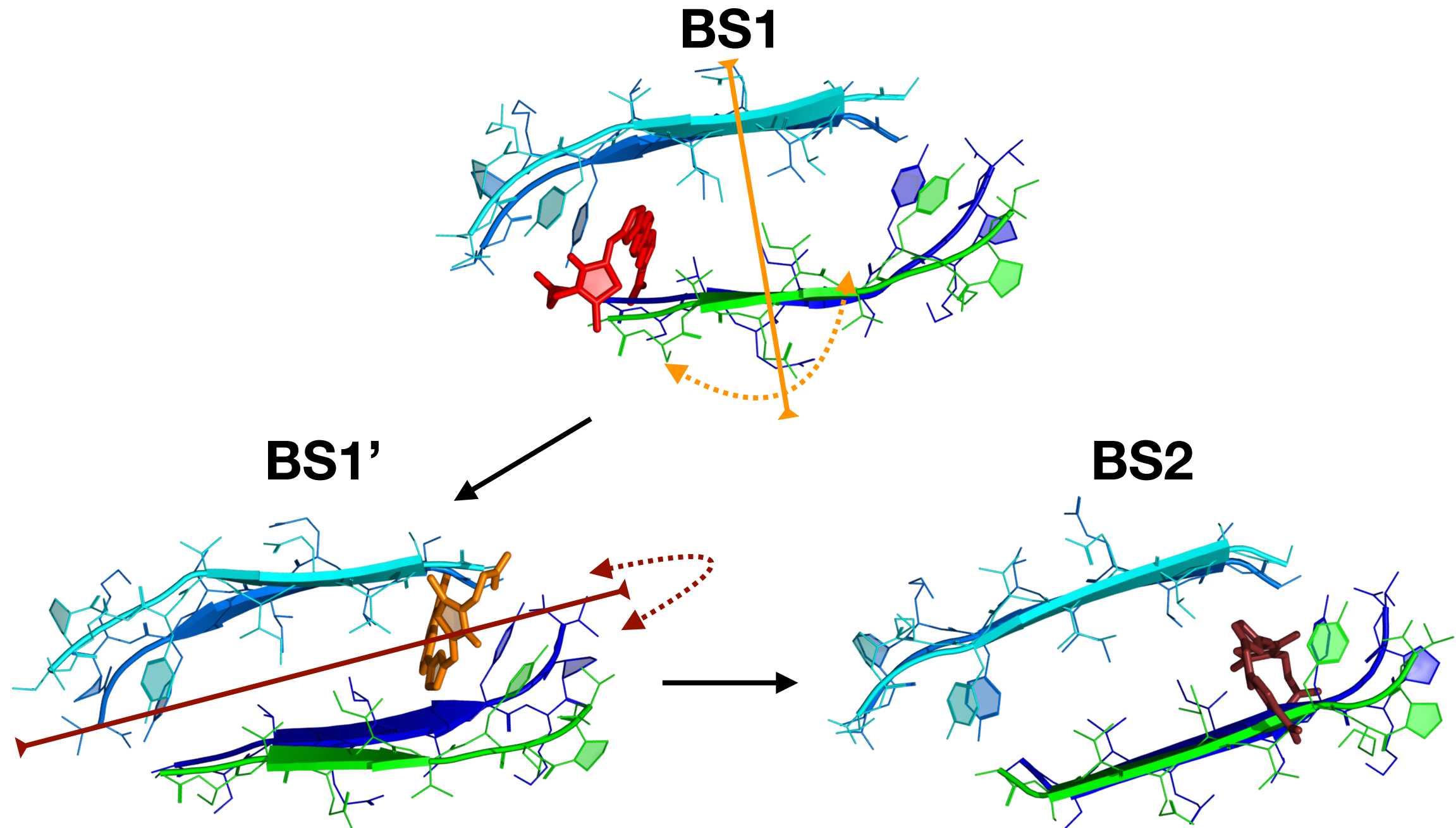
Docking of Rhodanine compounds



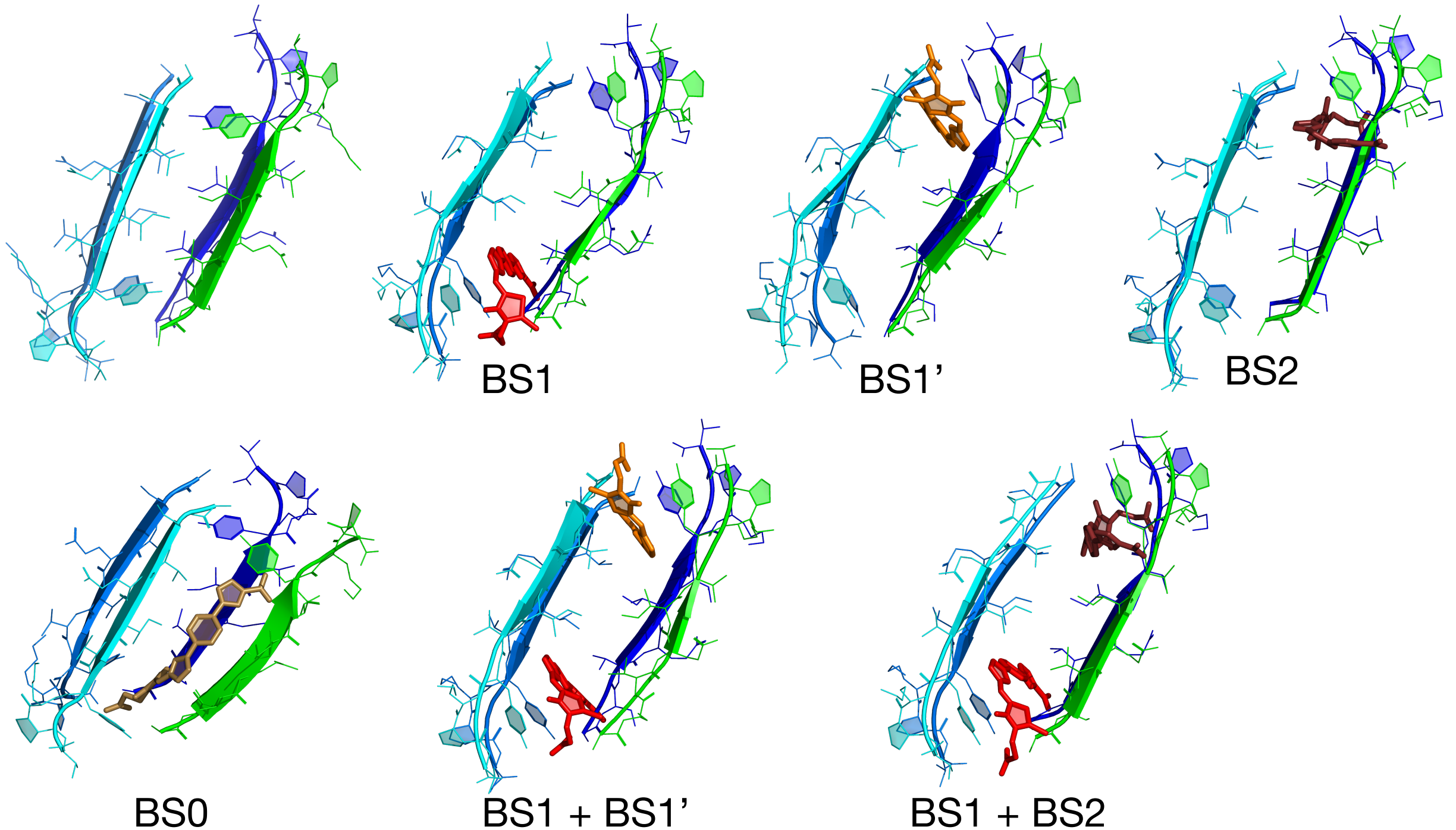
Tetramer “reconstruction” from PHF8 complexes dimer



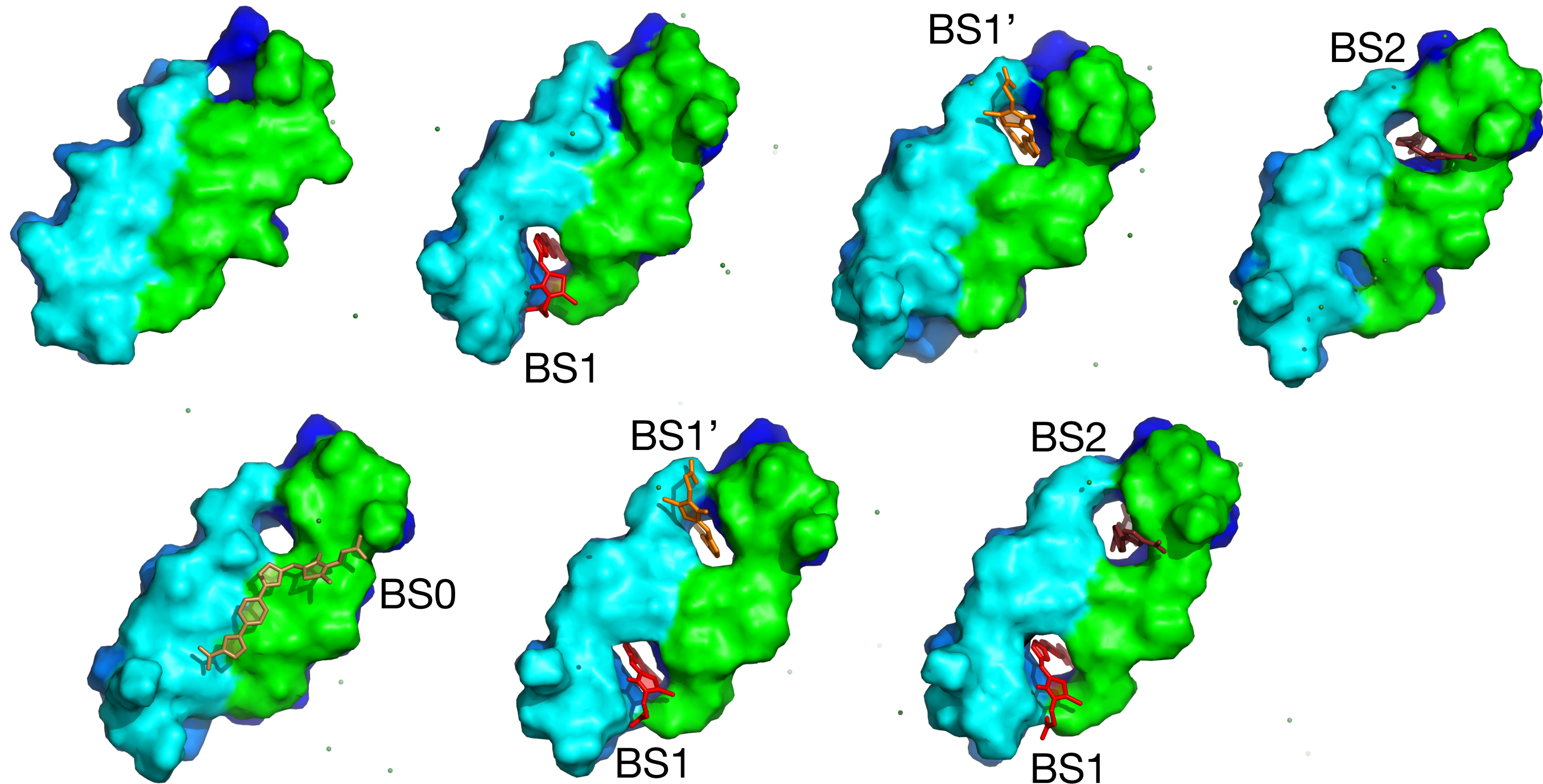
Symmetrical tetramers from PHF8 rebuilt complexes



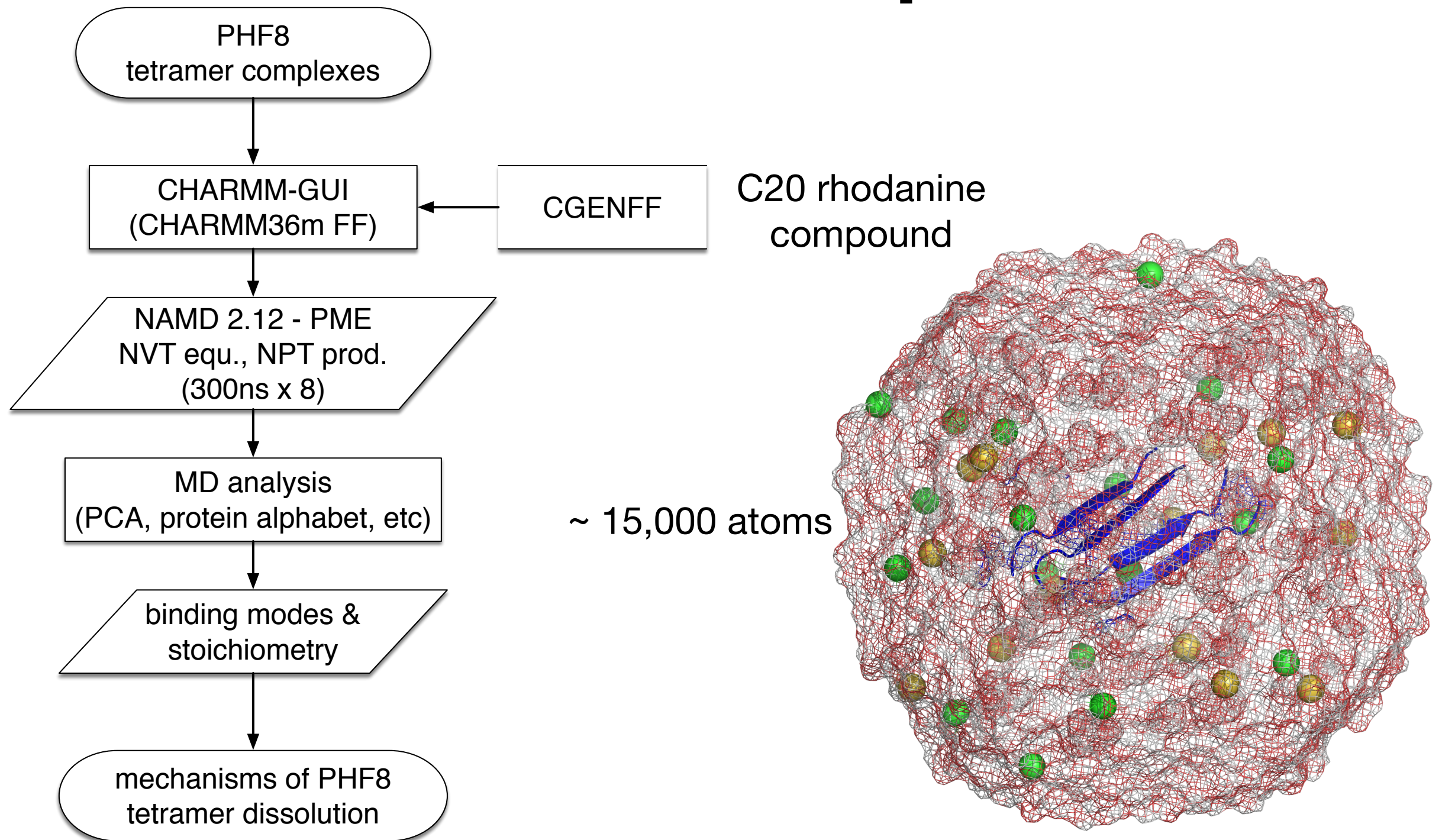
PHF8 tetramer complexes with 1:1/2:1 stoichiometries



PHF8 tetramer complexes with 1:1/2:1 stoichiometries



MD simulations of PHF8 tetramers complexes



Metrics for MD analysis

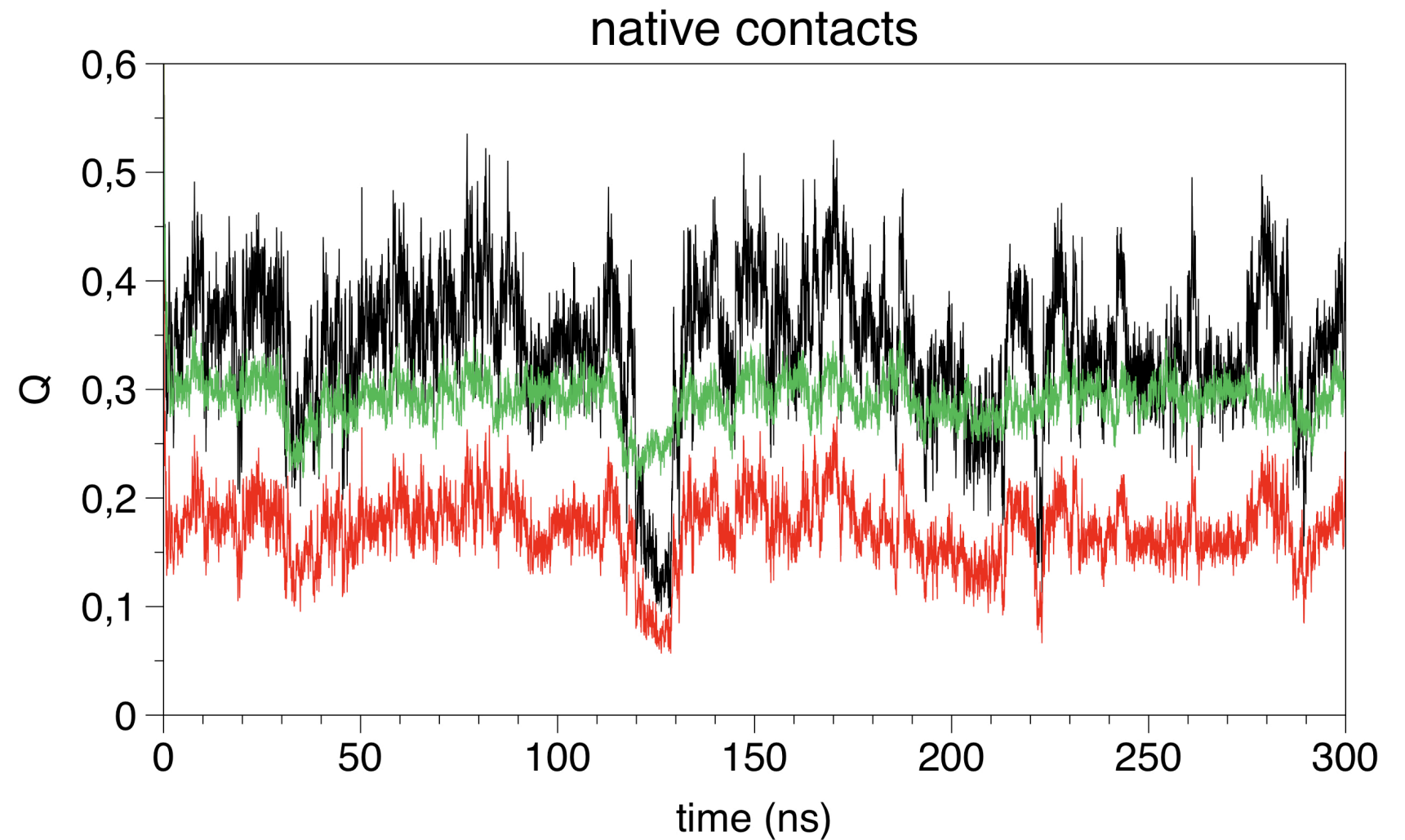
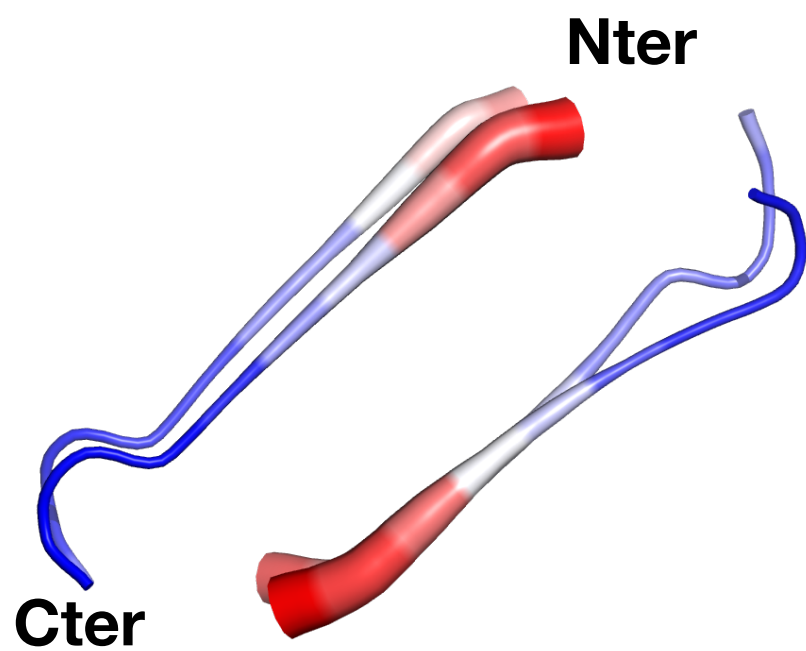
- native contacts
- radius of gyration
- low frequency motions (PCA analysis)
- conformational flexibility (protein alphabet)

Fraction of native contacts and radius of gyration

- native contacts are calculated for residues whose distance (\AA) is smaller than the number specified in 'Distance cutoff' (default: 8\AA), and which are at least as many residues apart as the number specified in 'Residue separation' (default: 2).
- mass-weighted radius of gyration of the selected atoms

PHF8 free tetramer native contacts

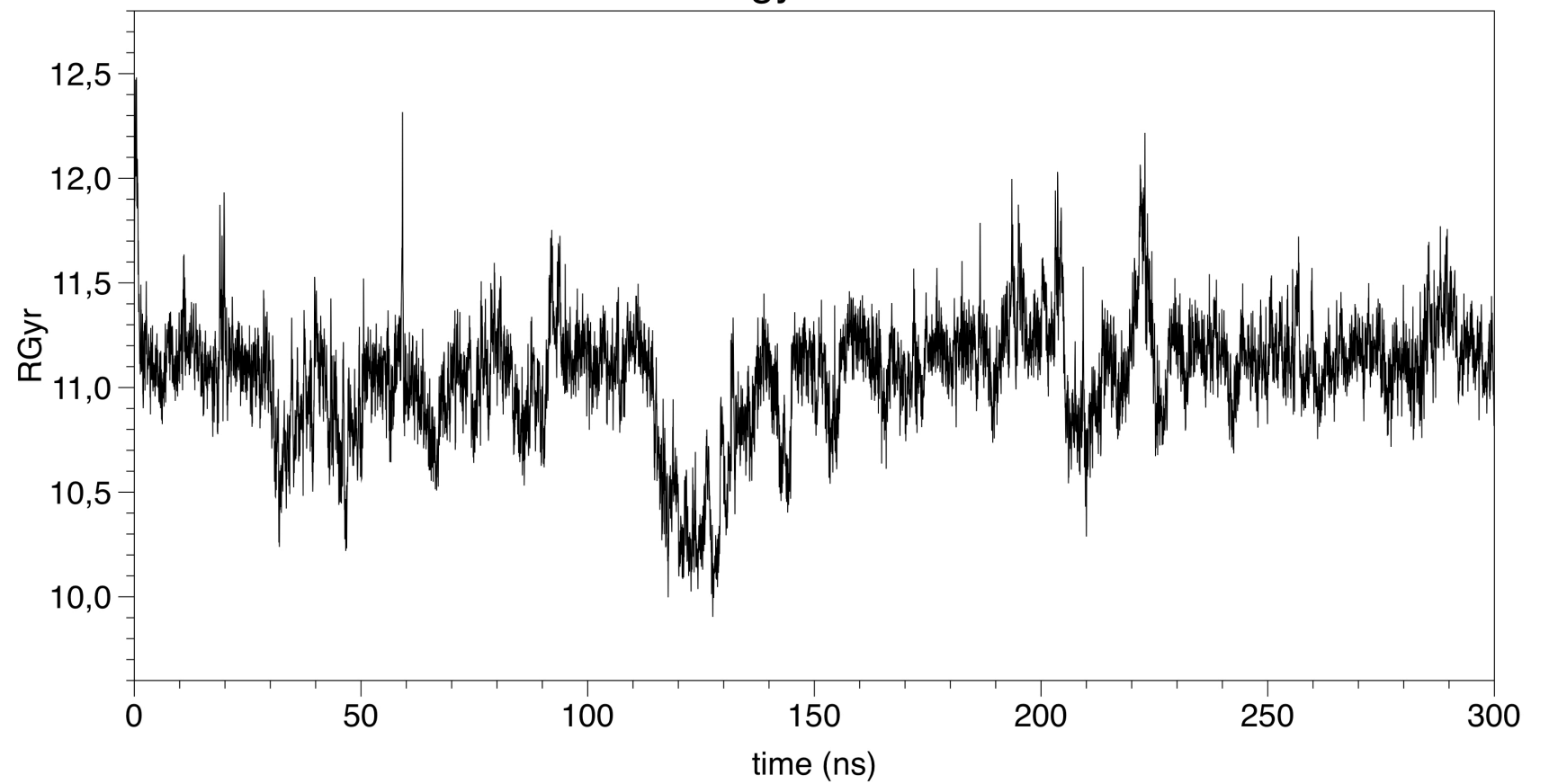
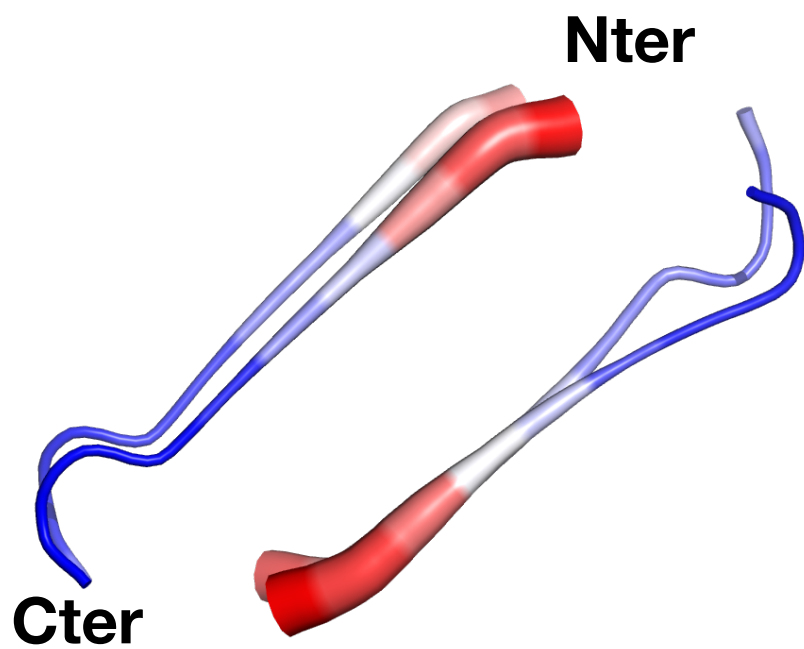
Q native contacts



PHF8 free tetramer radius of gyration

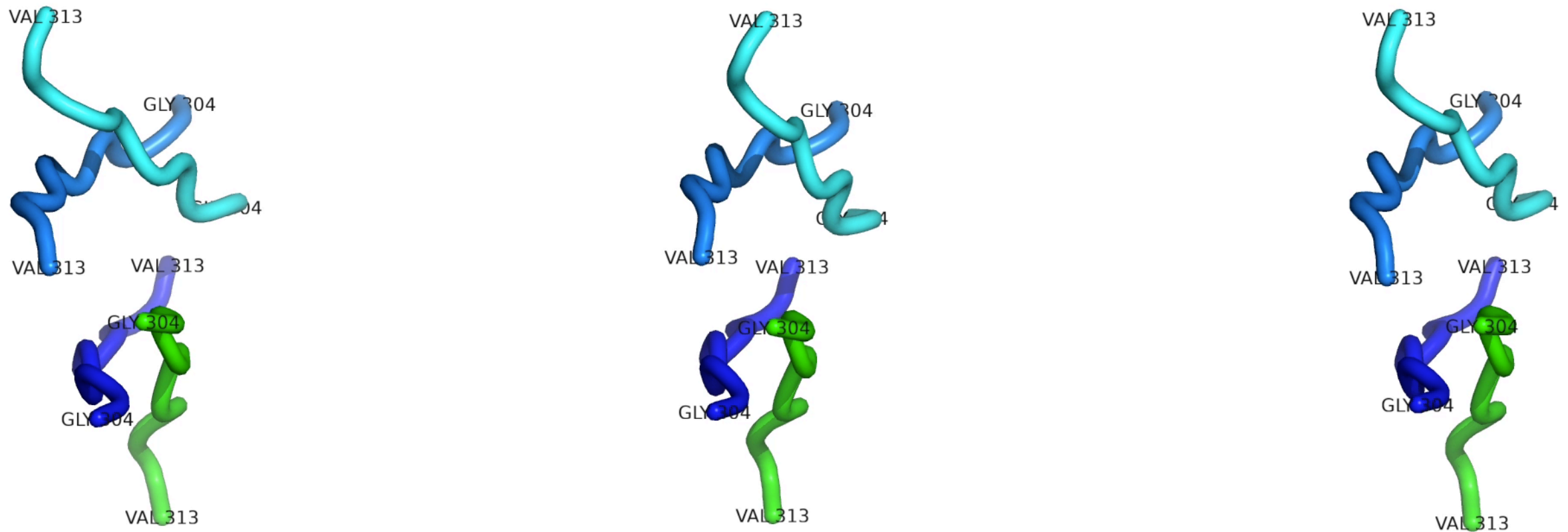
radius of gyration

radius of gyration vs time

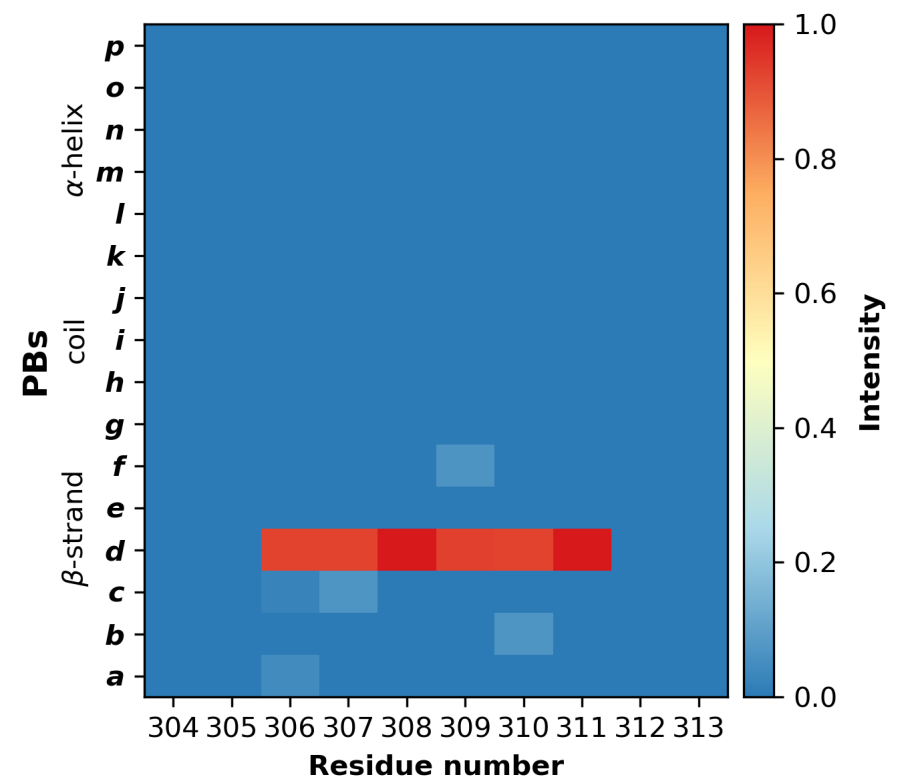
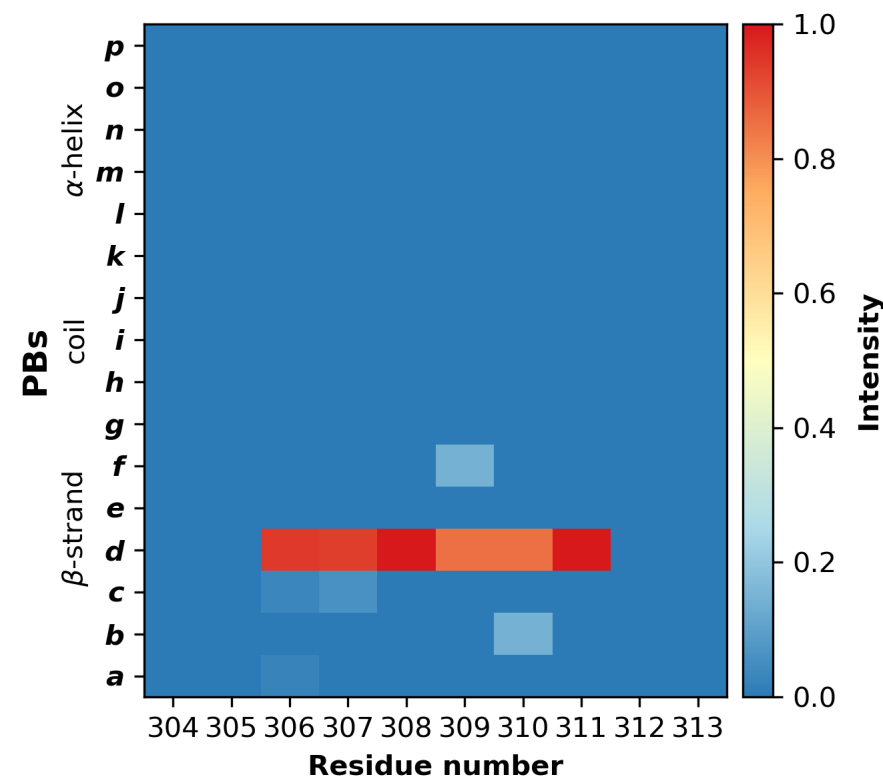
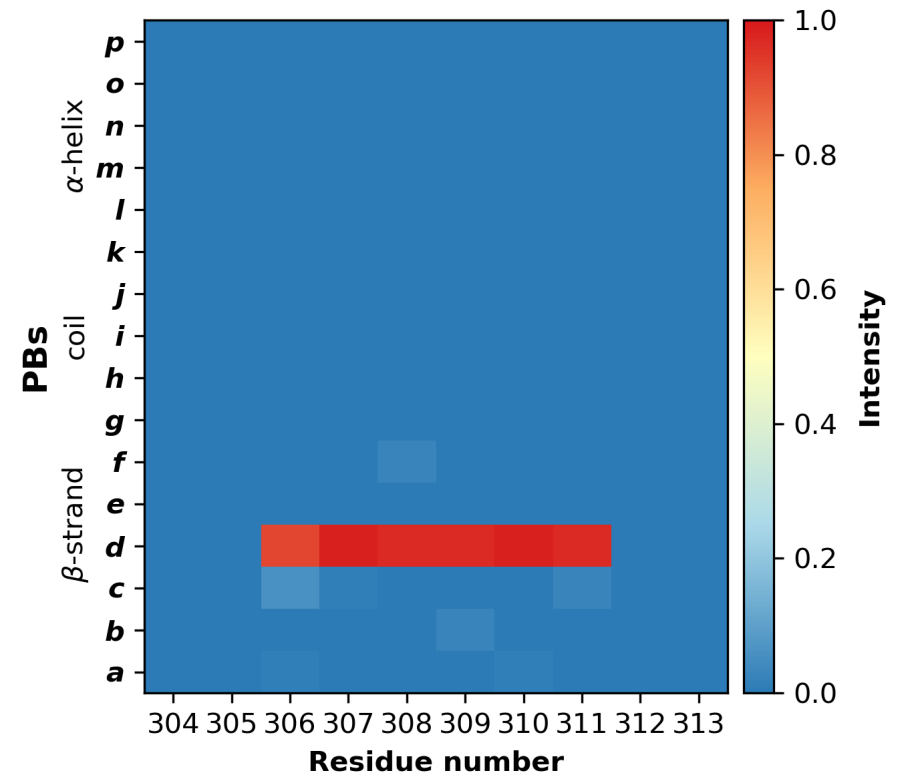
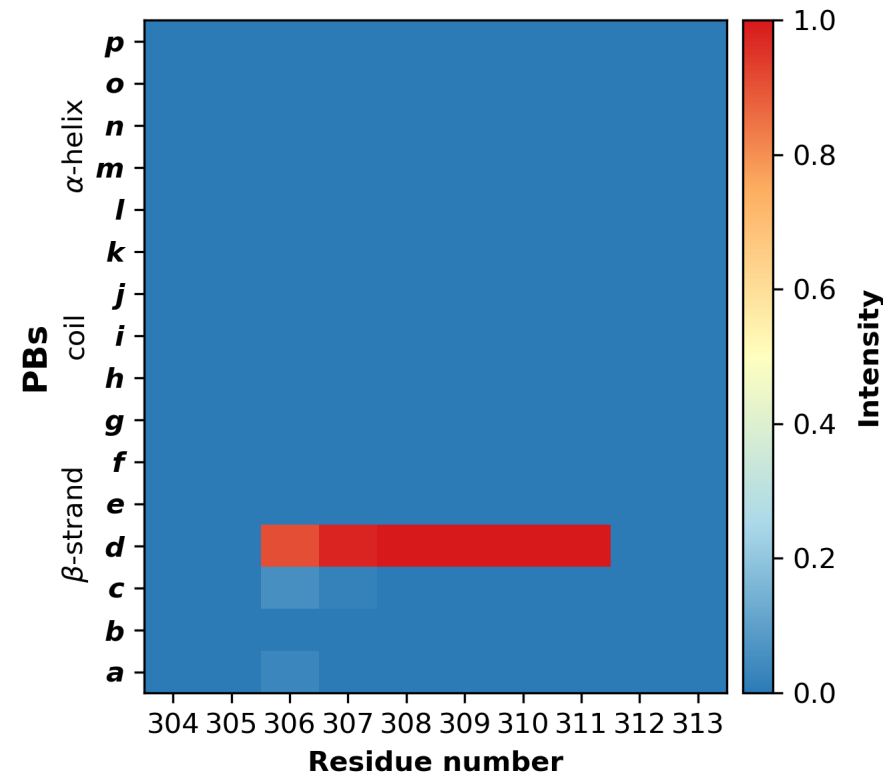
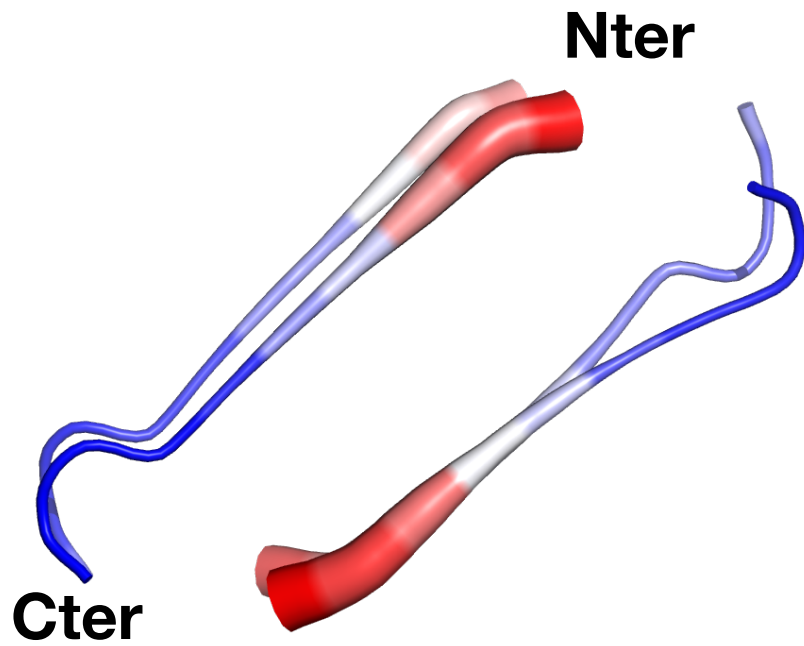


PHF8 free tetramer low frequency motions

PCA analysis

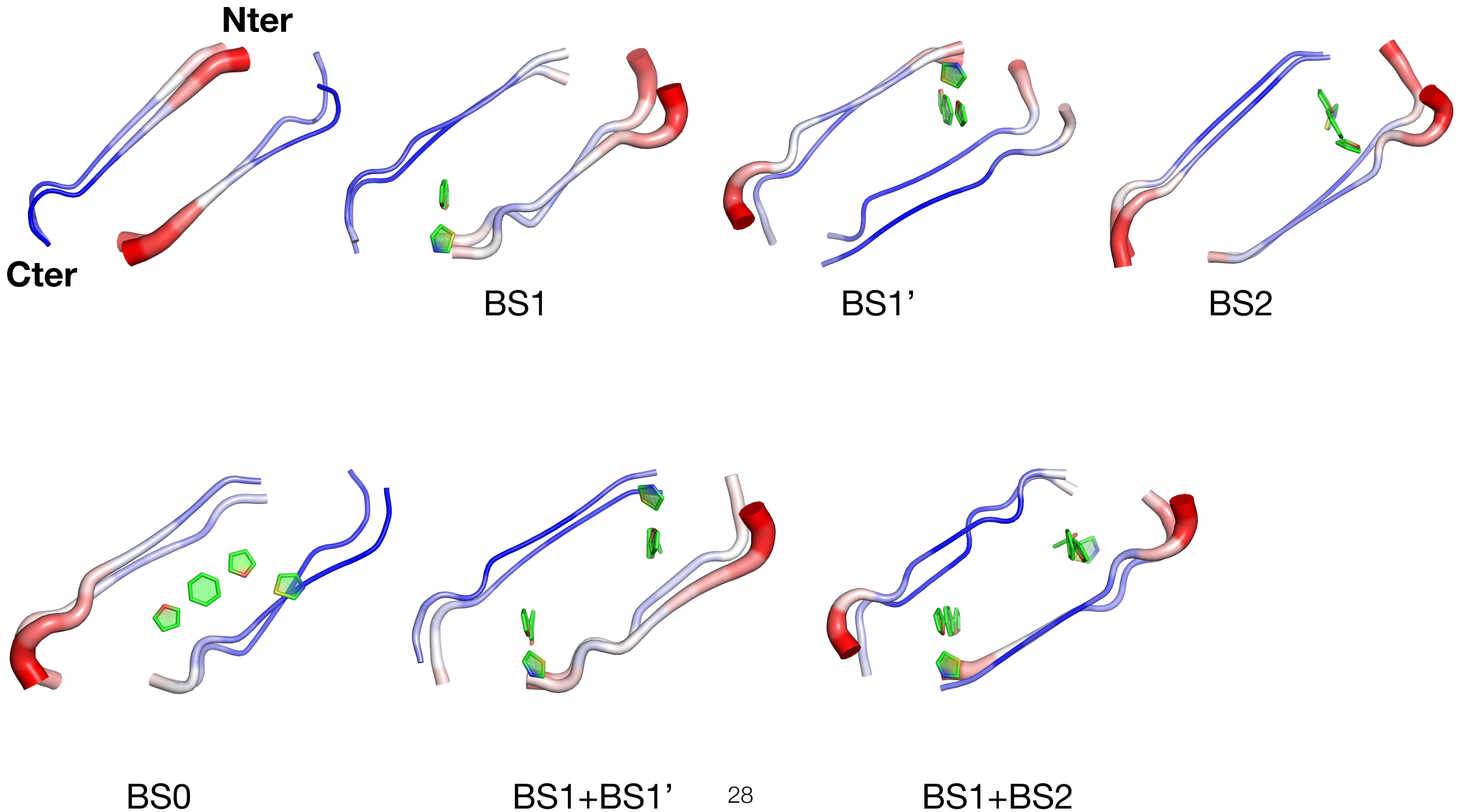


PHF8 free tetramer

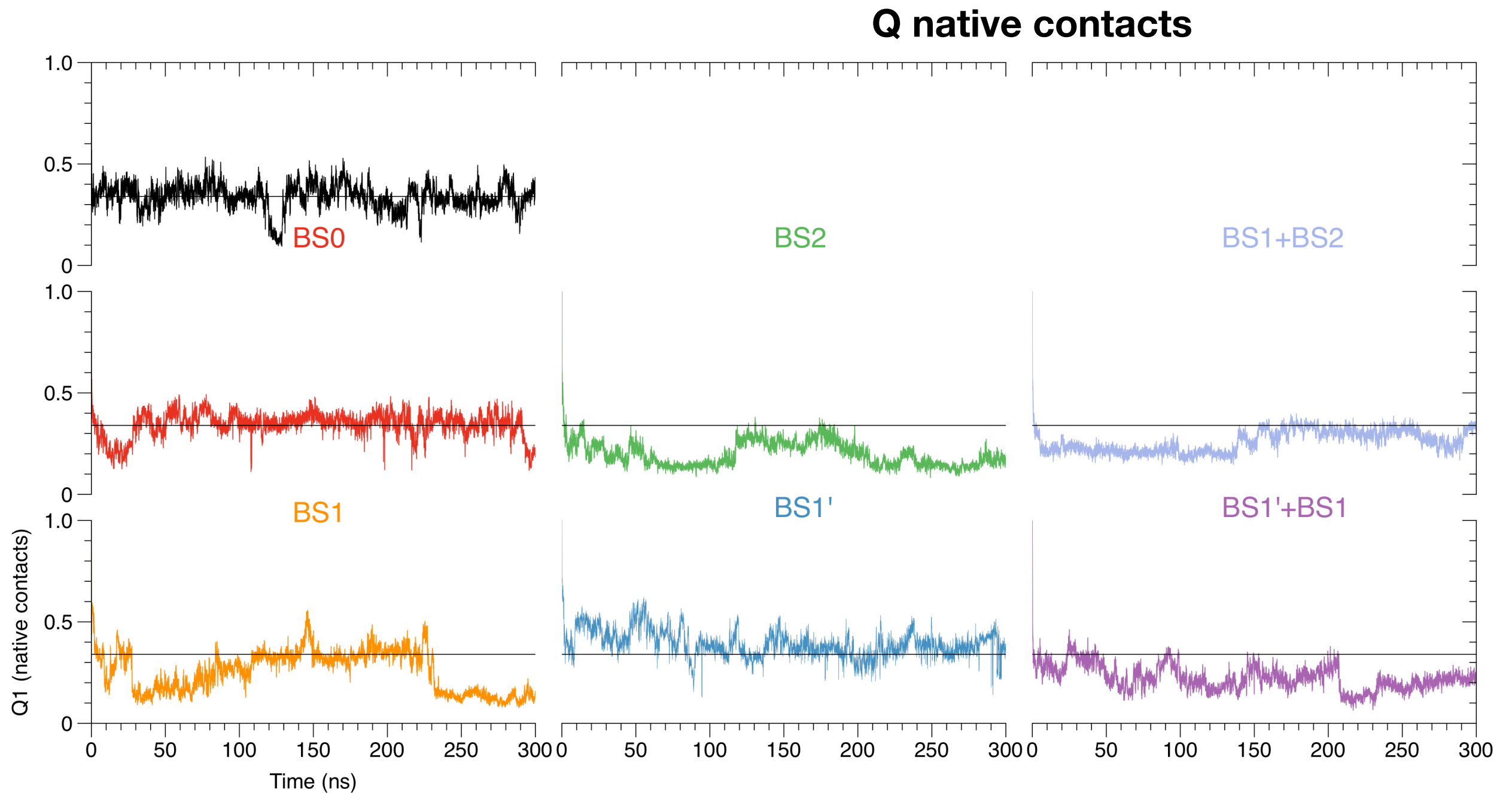


PHF8 tetramers

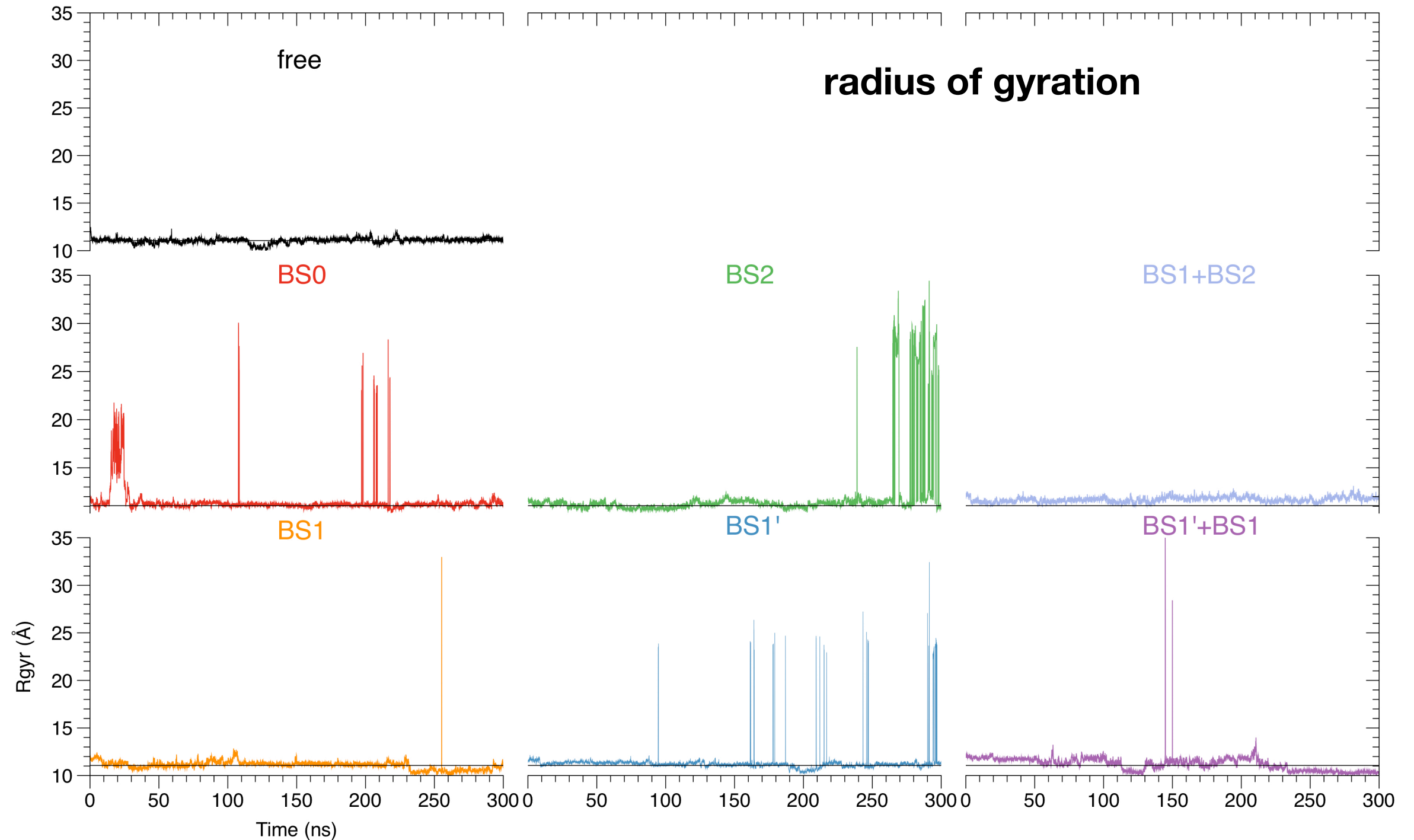
conformational flexibility



PHF8 tetramers native contacts



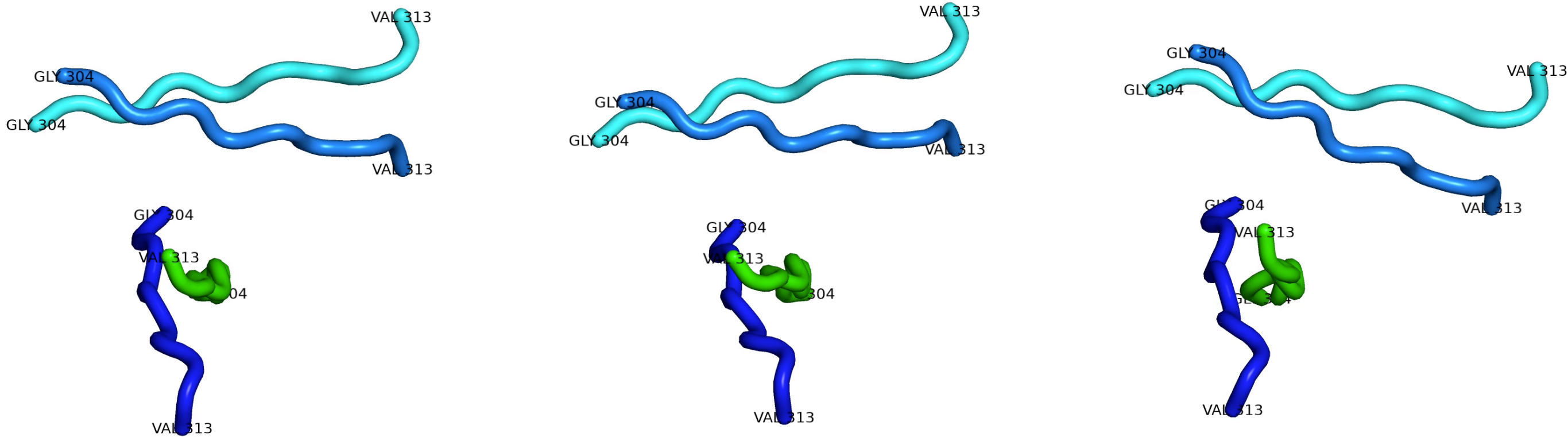
PHF8 tetramers radius of gyration



PHF8 tetramer BS1+BS1'

low frequency motions

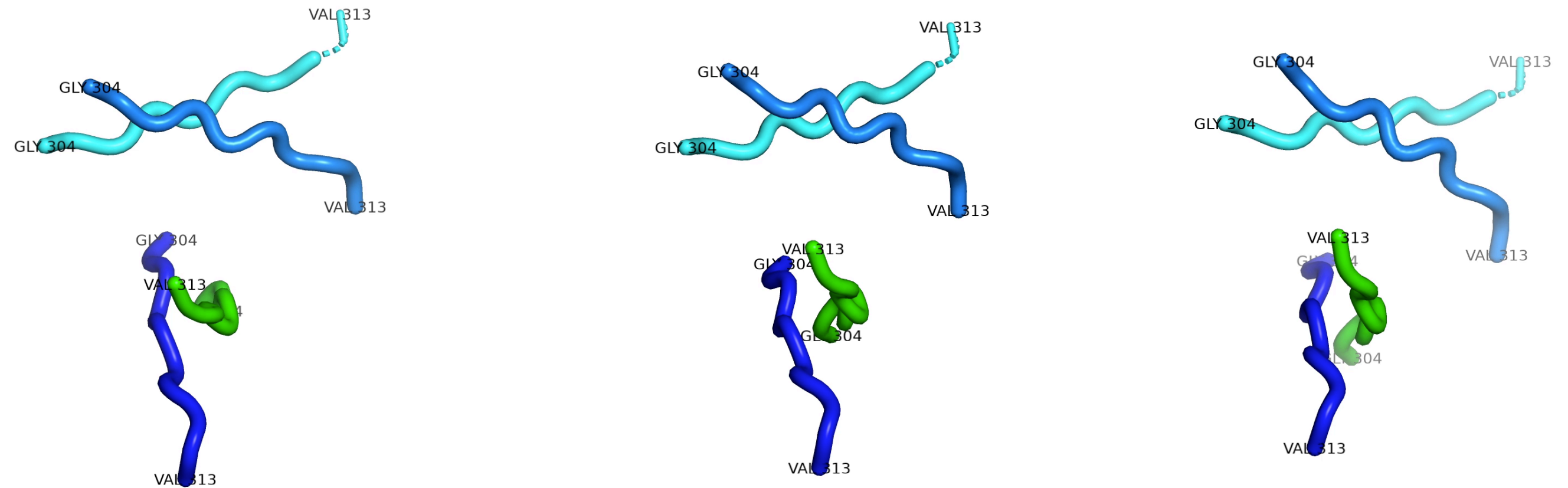
PCA analysis



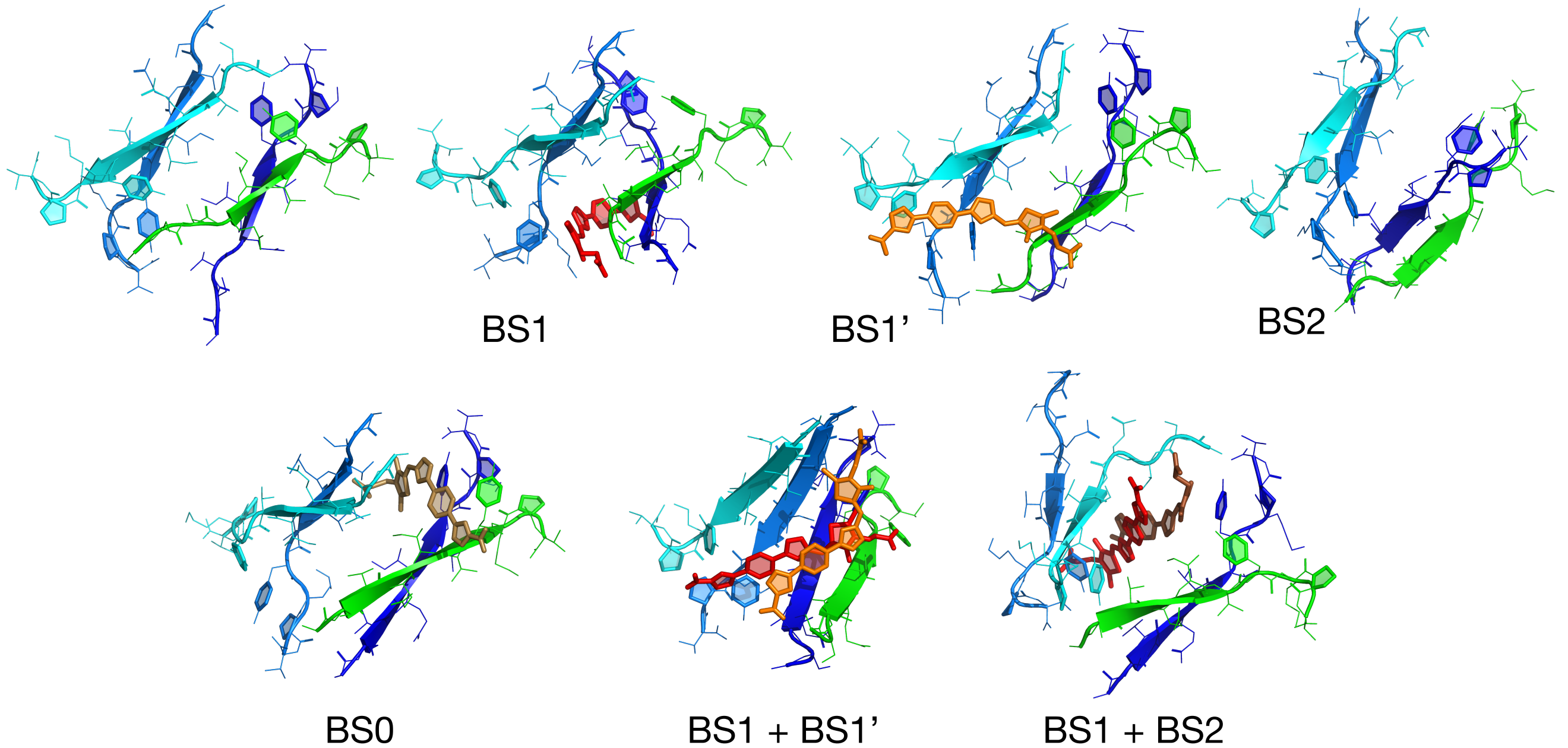
PHF8 tetramer BS2

low frequency motions

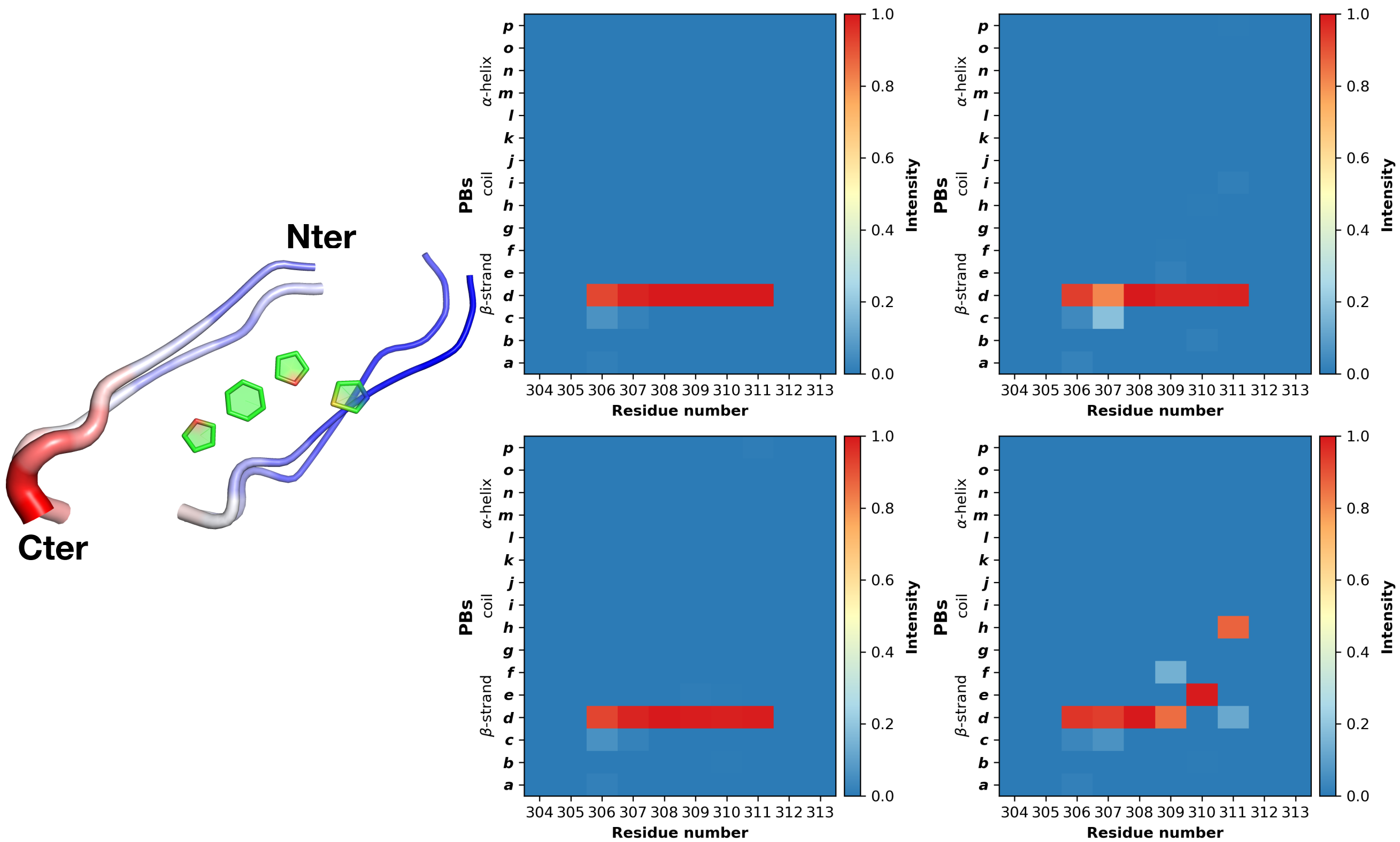
PCA analysis



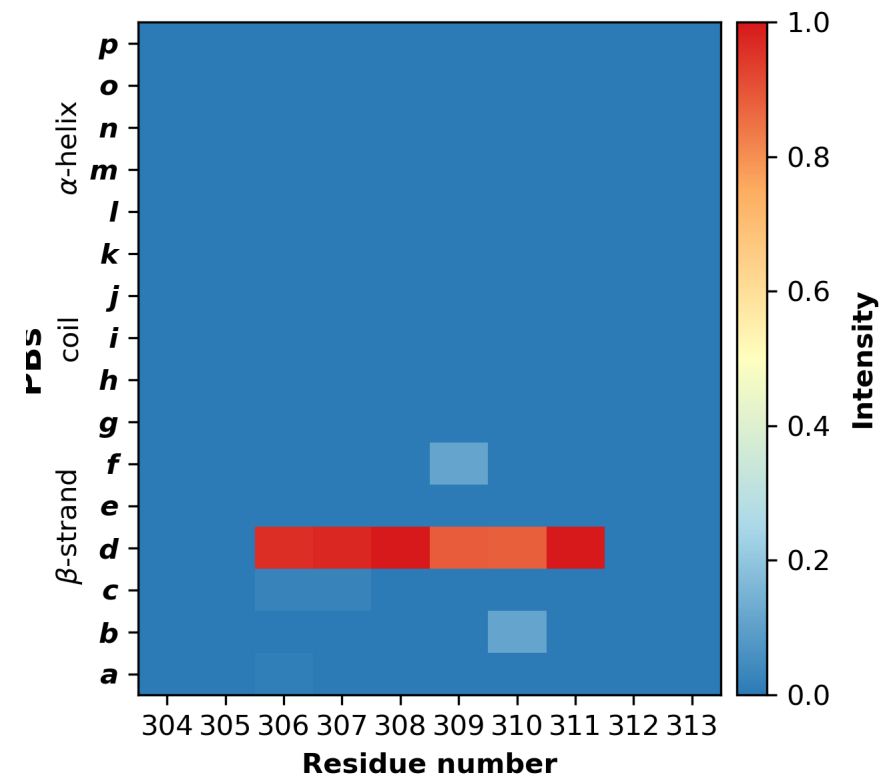
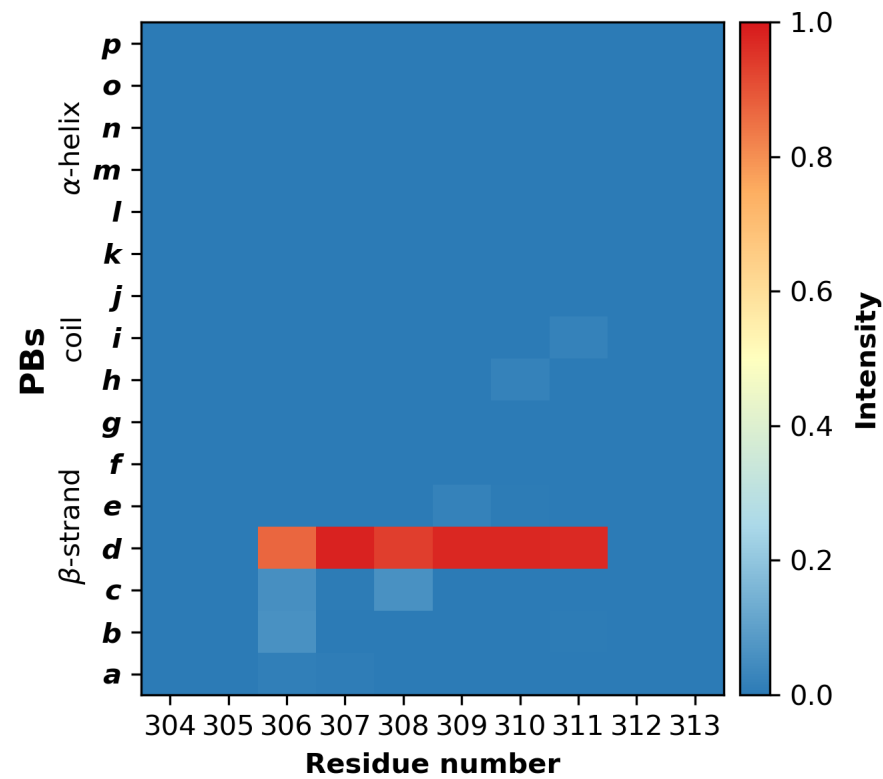
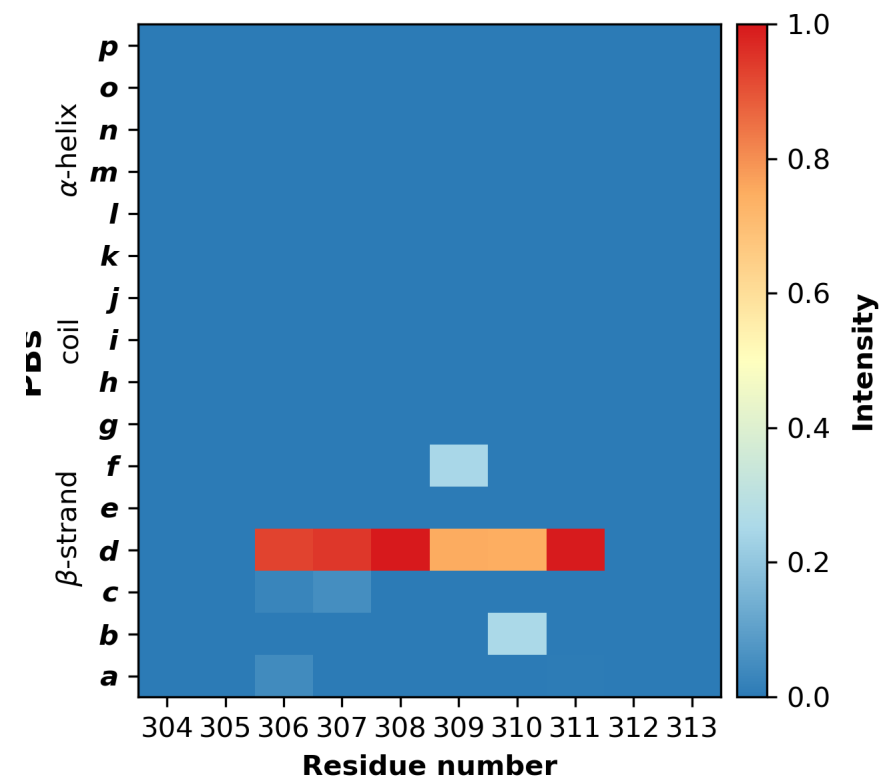
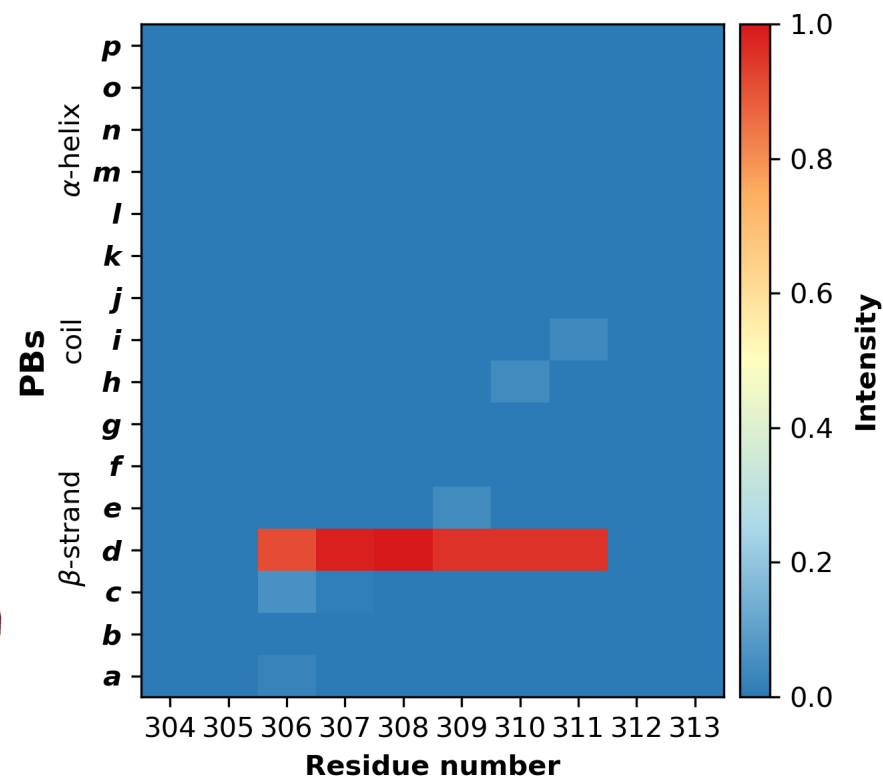
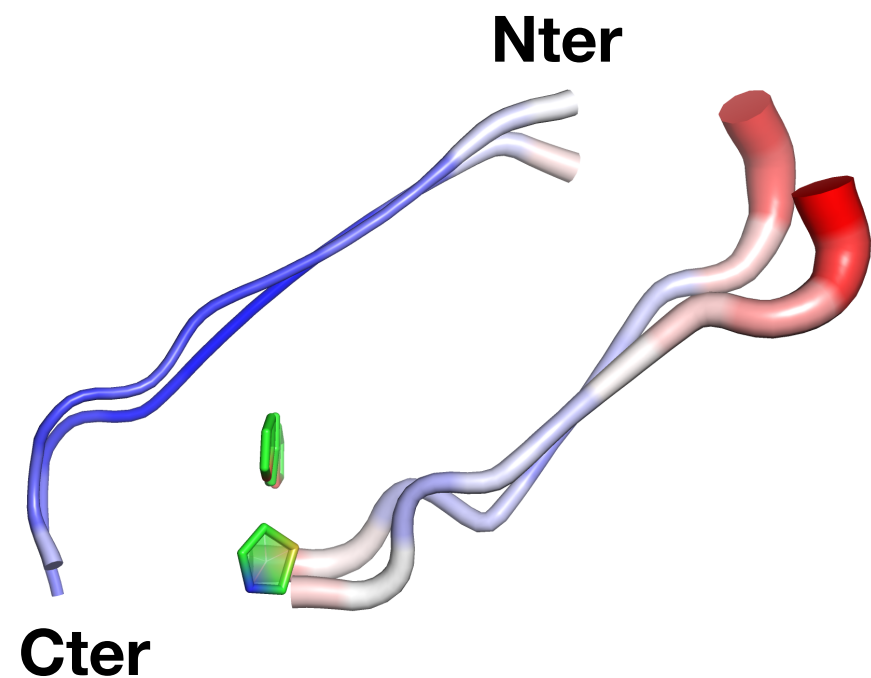
PHF8 tetramers binding modes



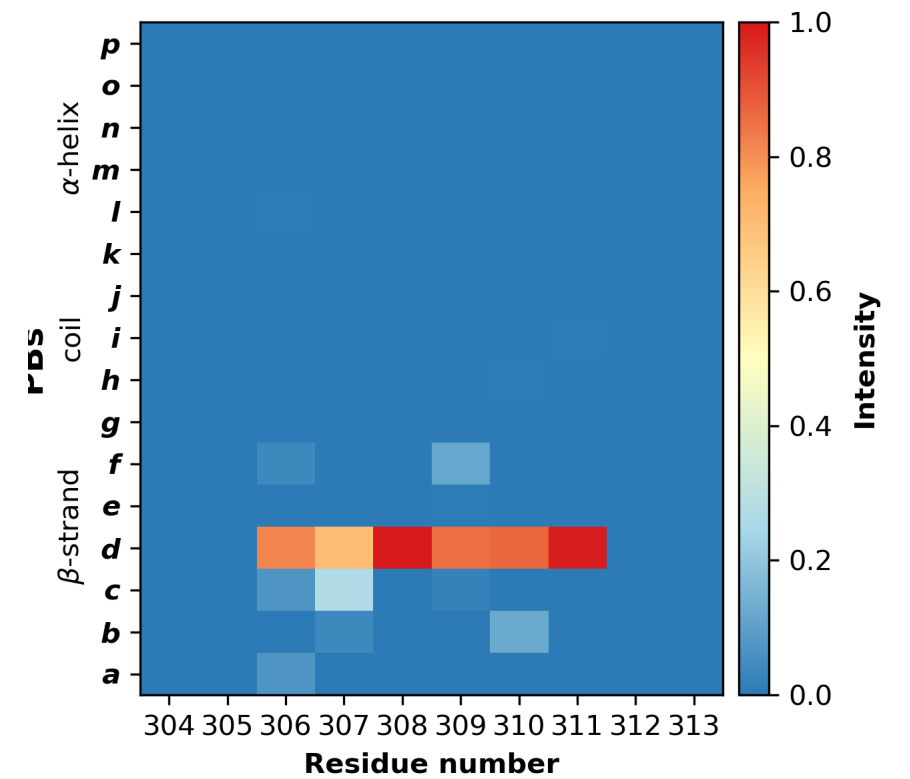
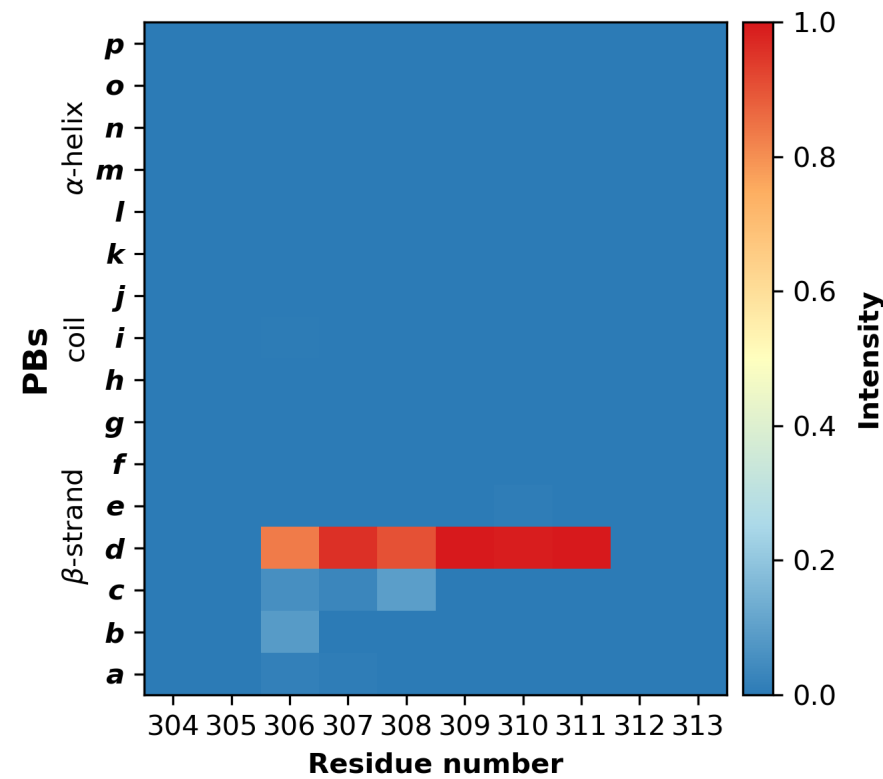
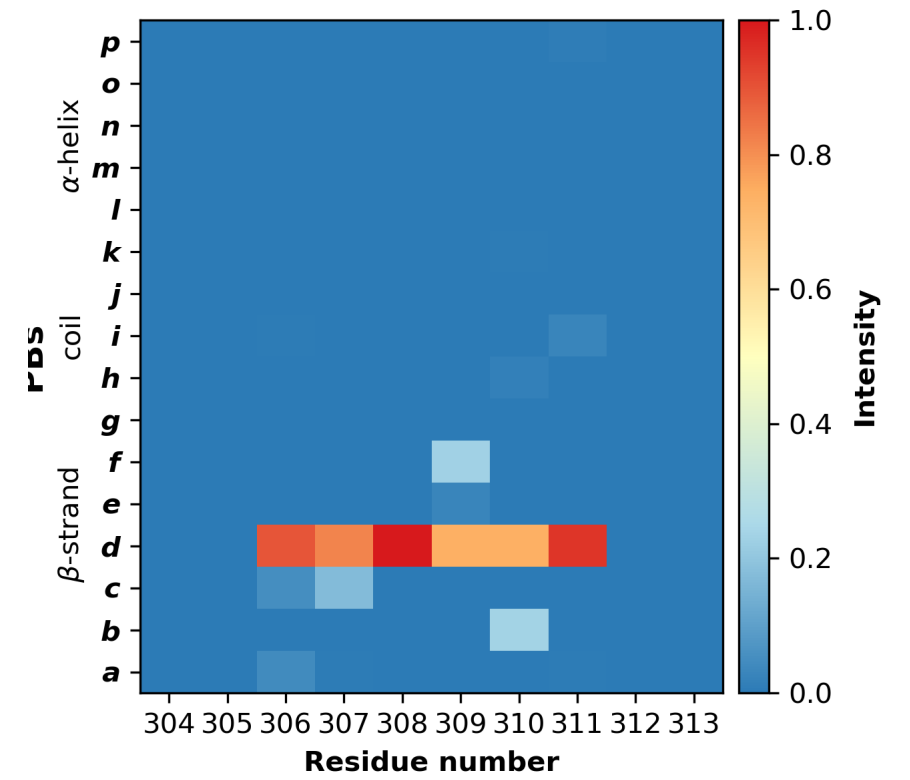
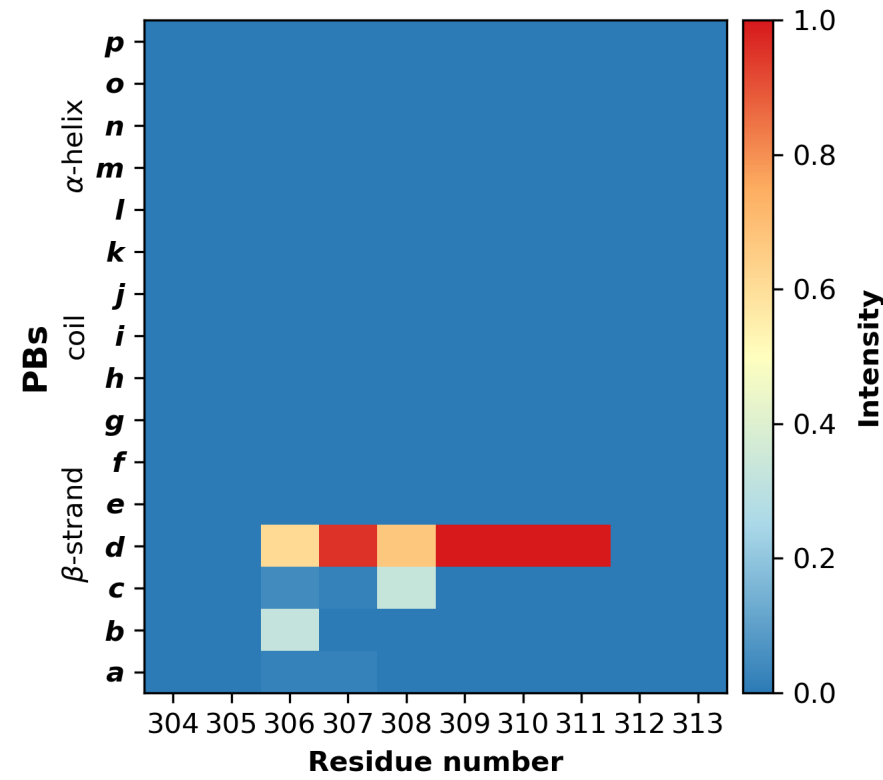
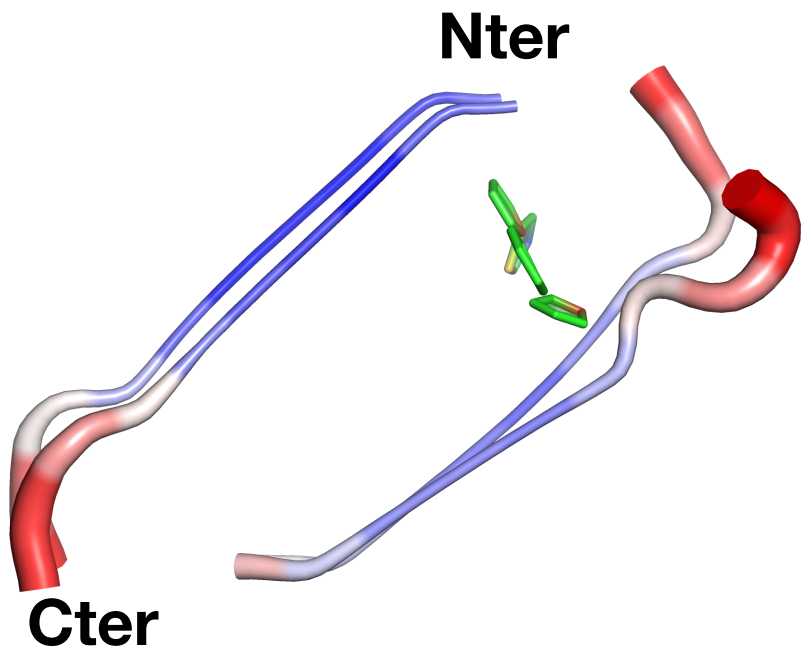
PHF8 tetramer BS0



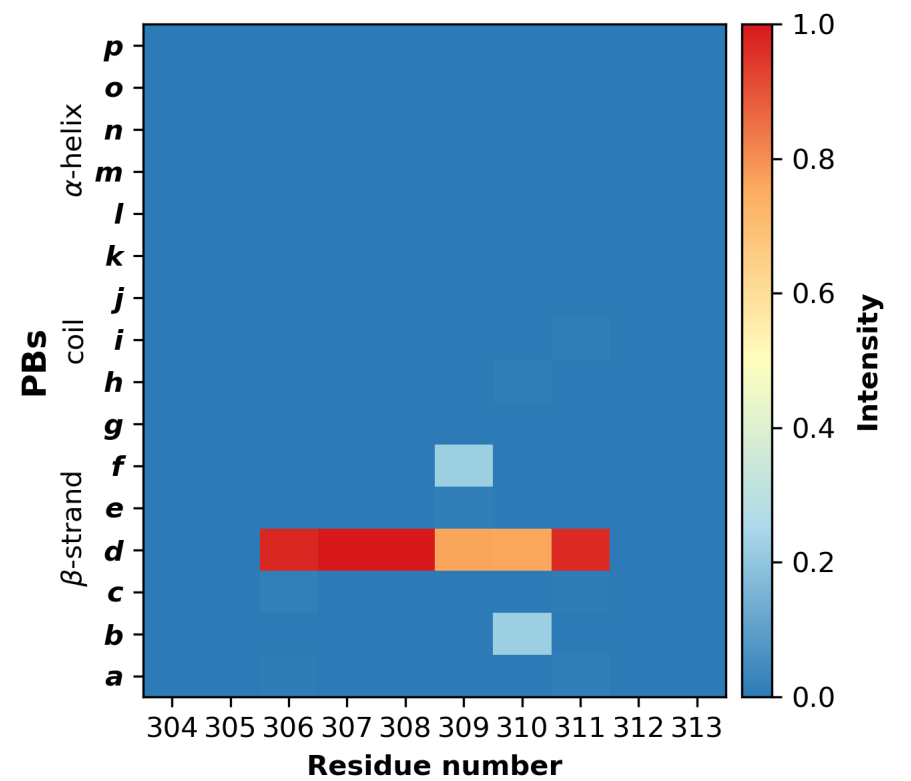
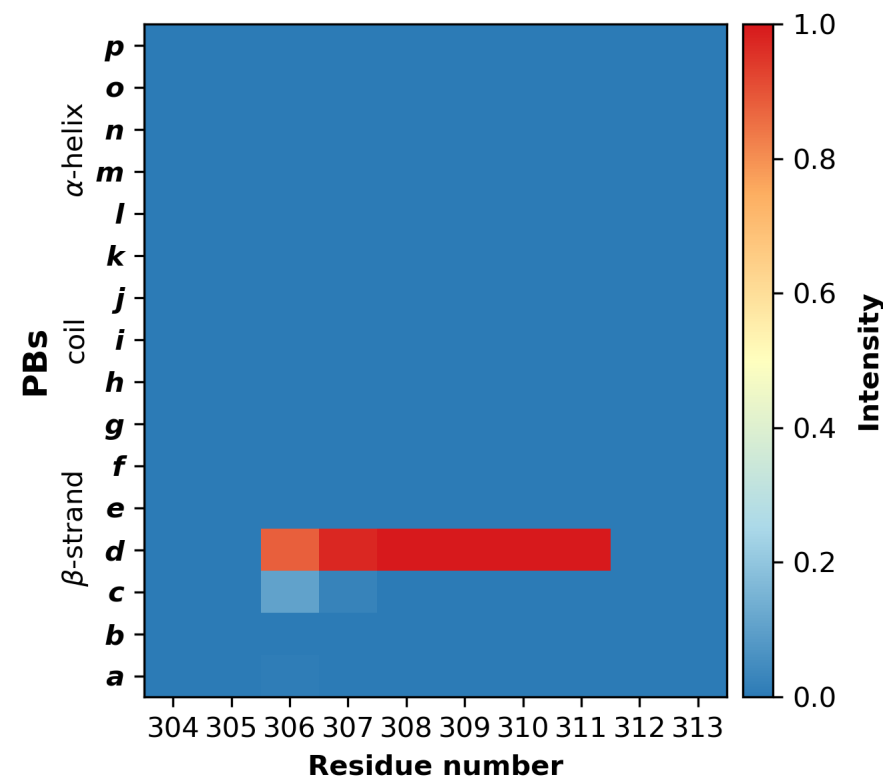
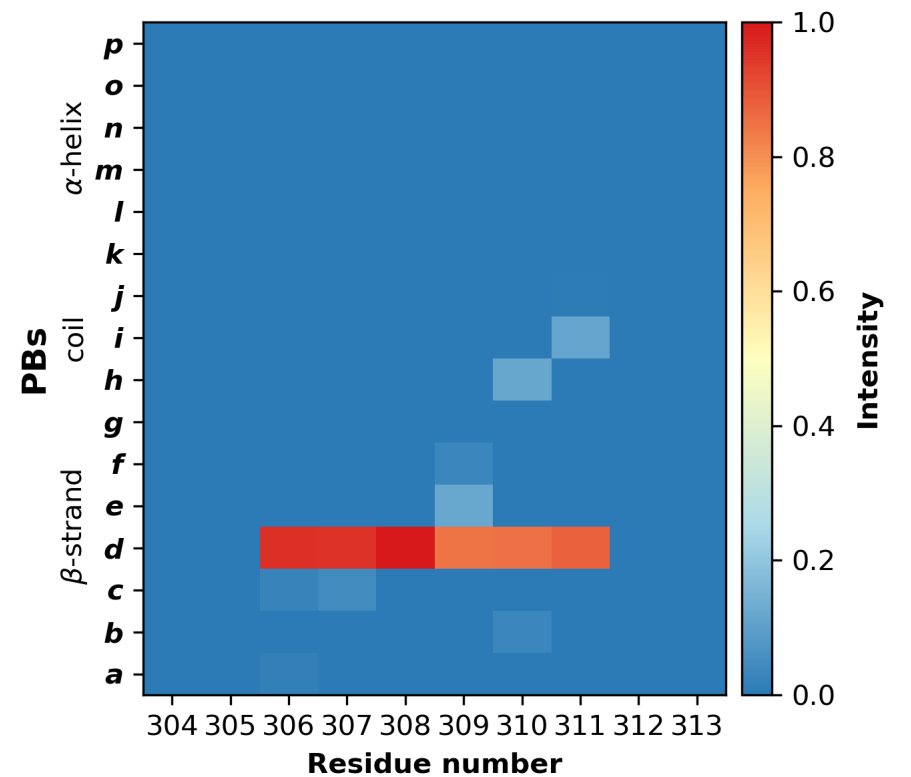
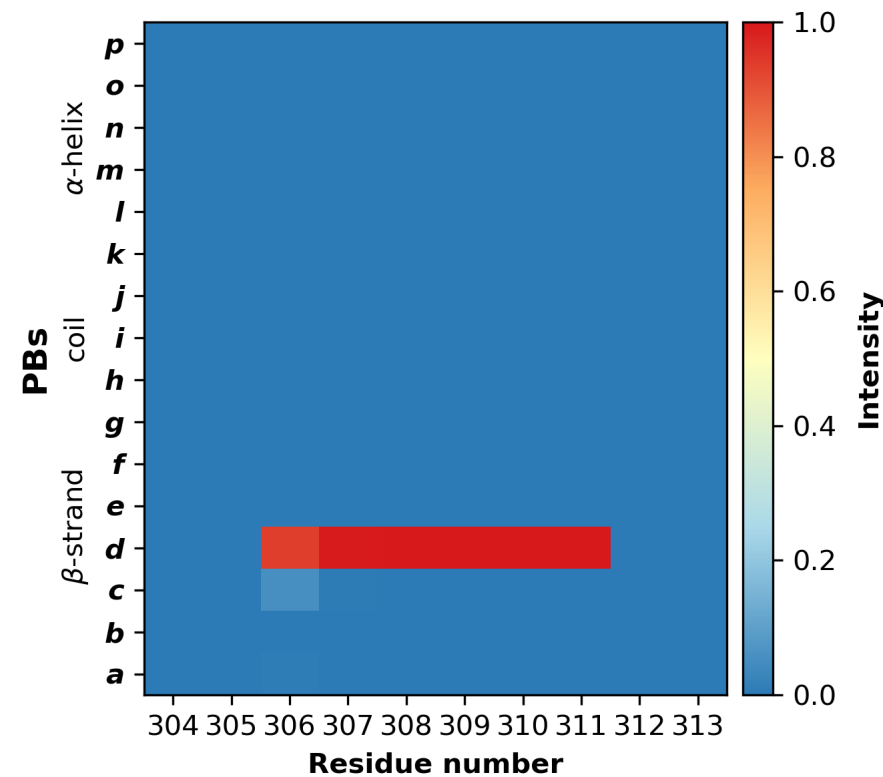
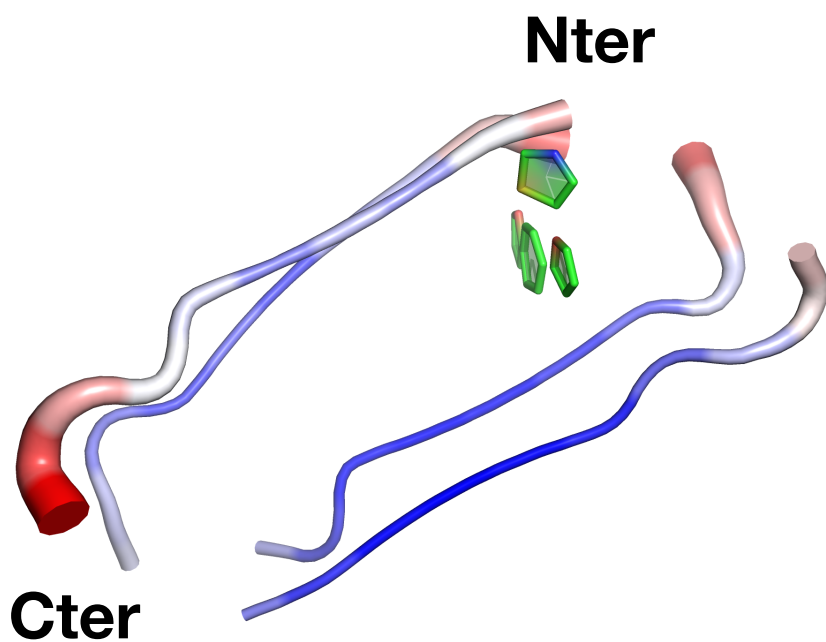
PHF8 tetramer BS1



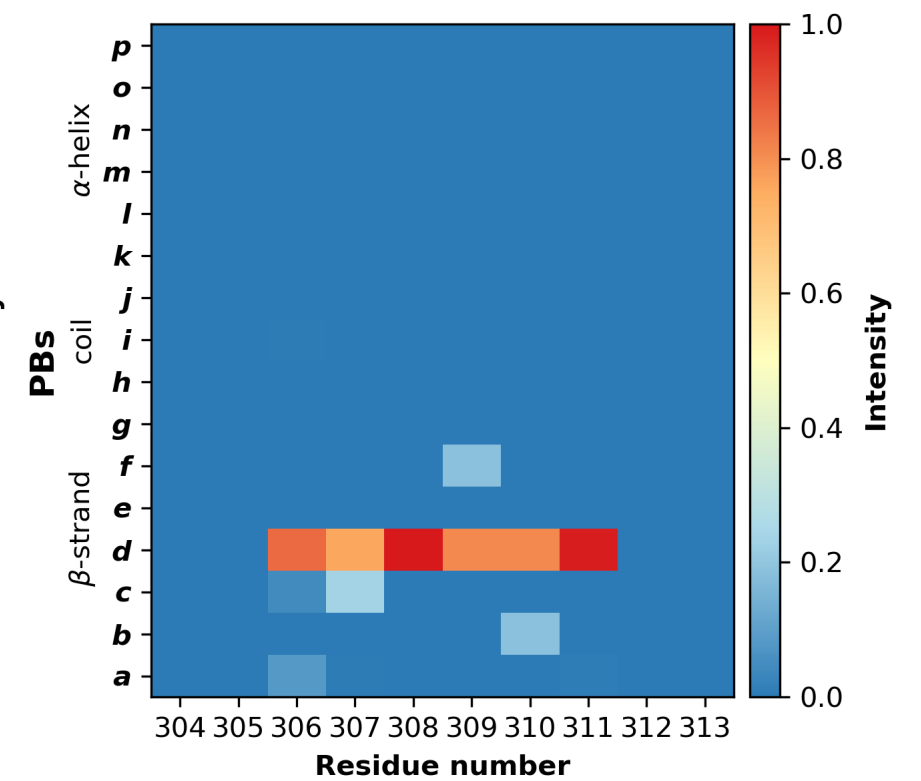
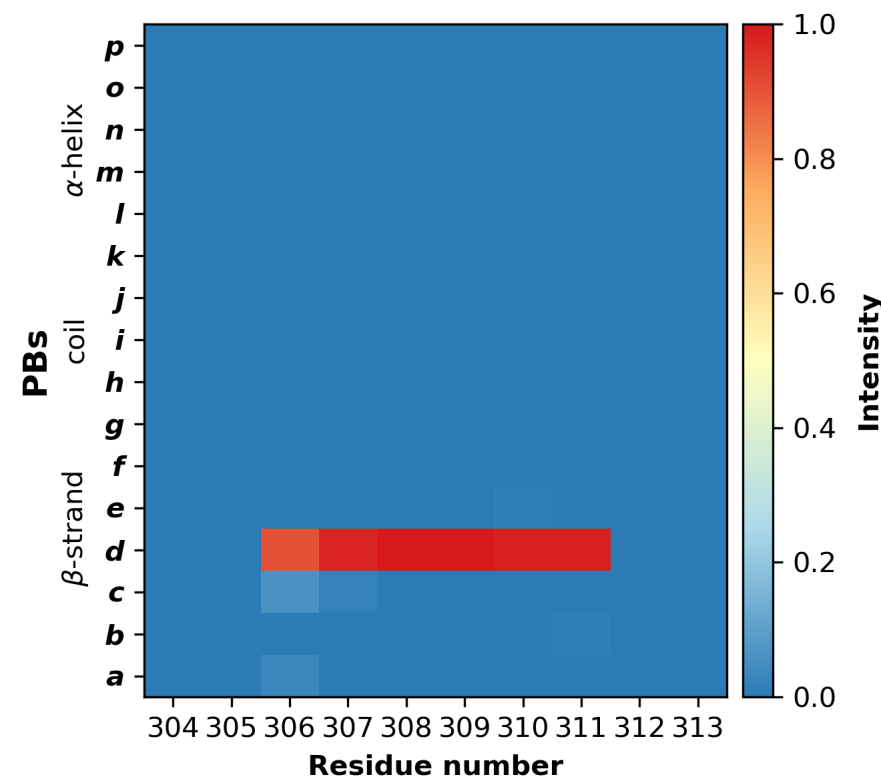
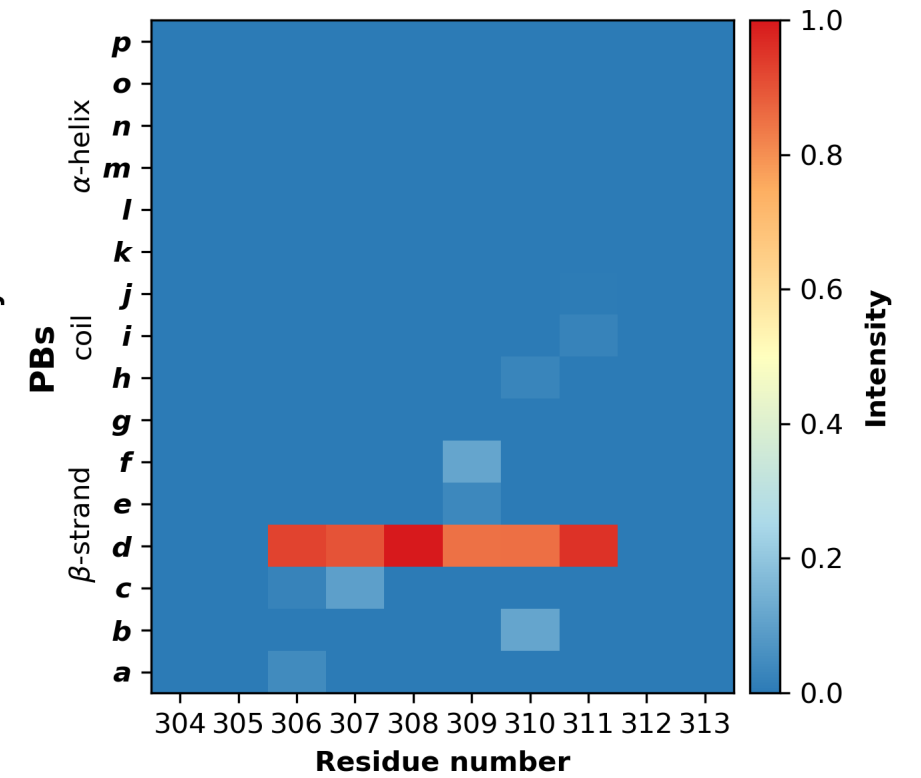
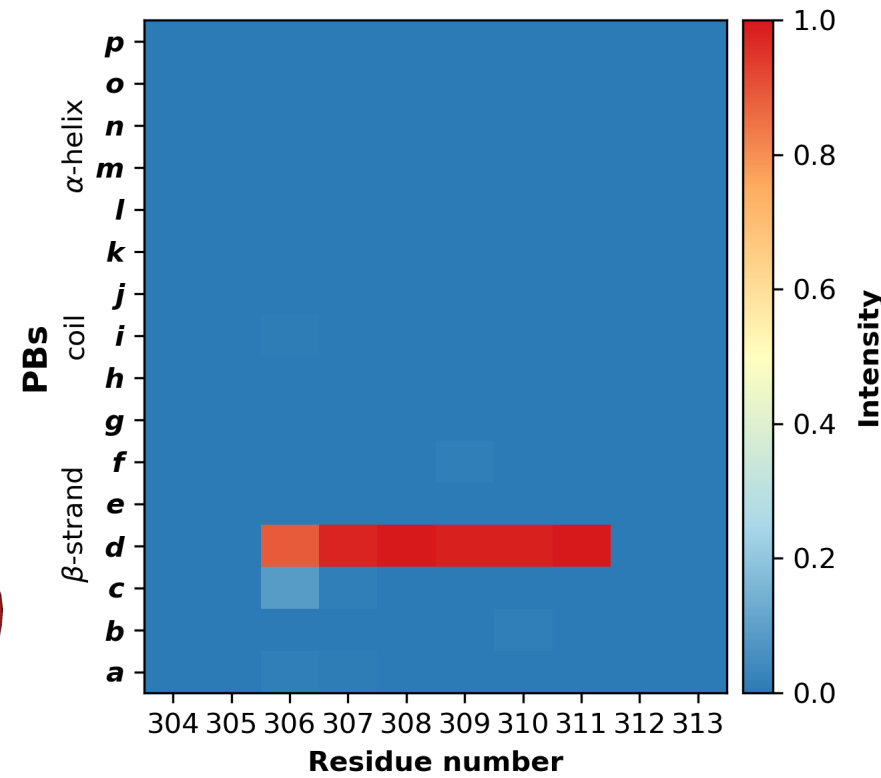
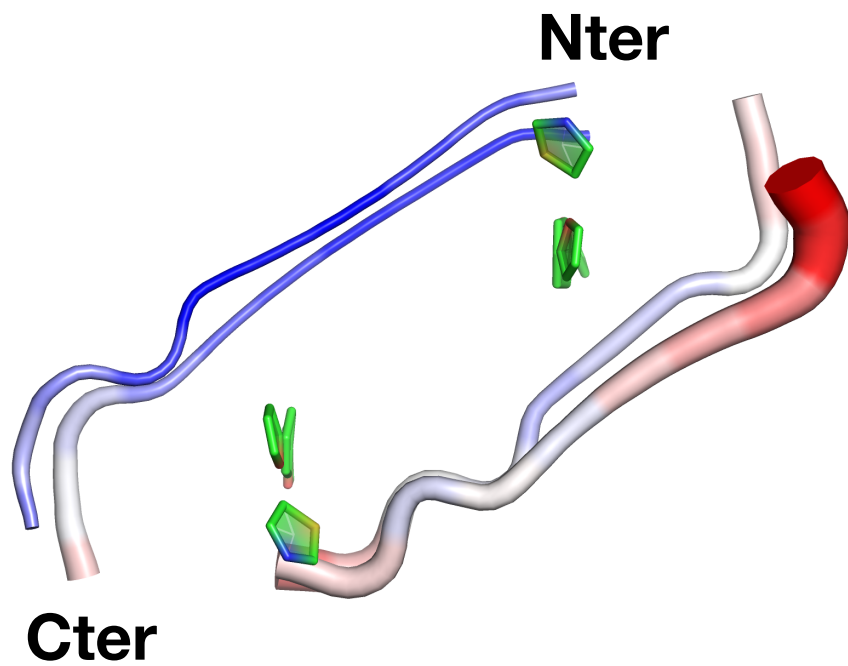
PHF8 tetramer BS2



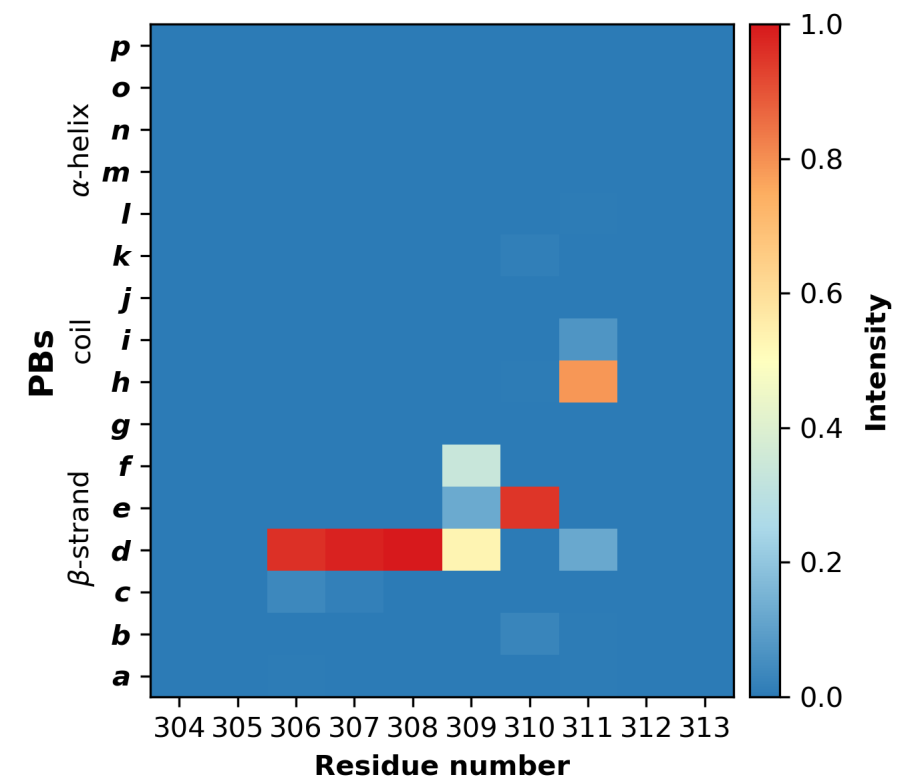
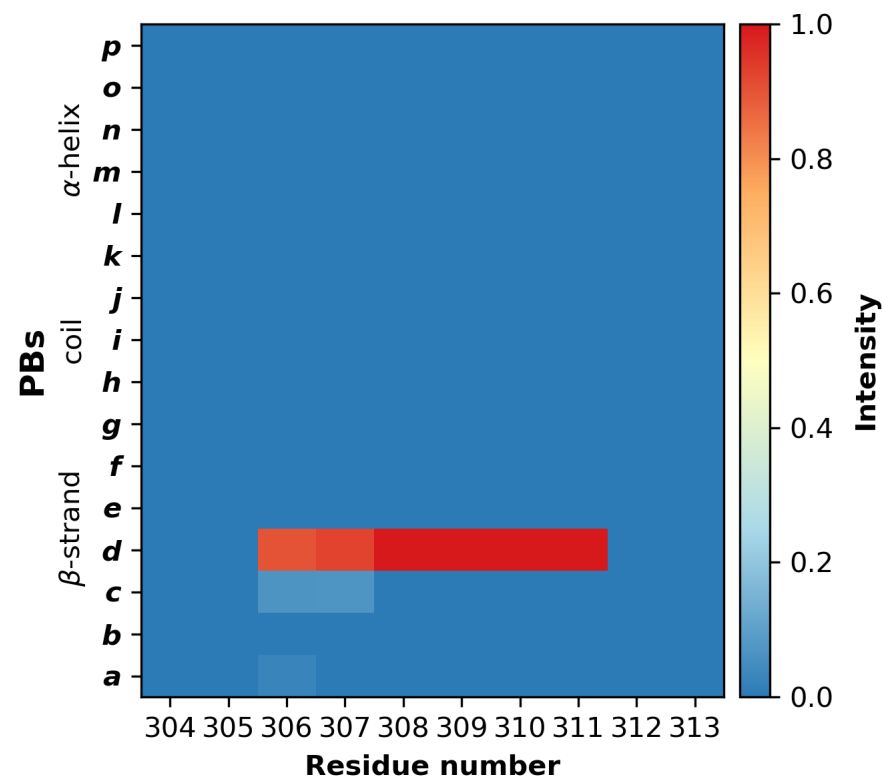
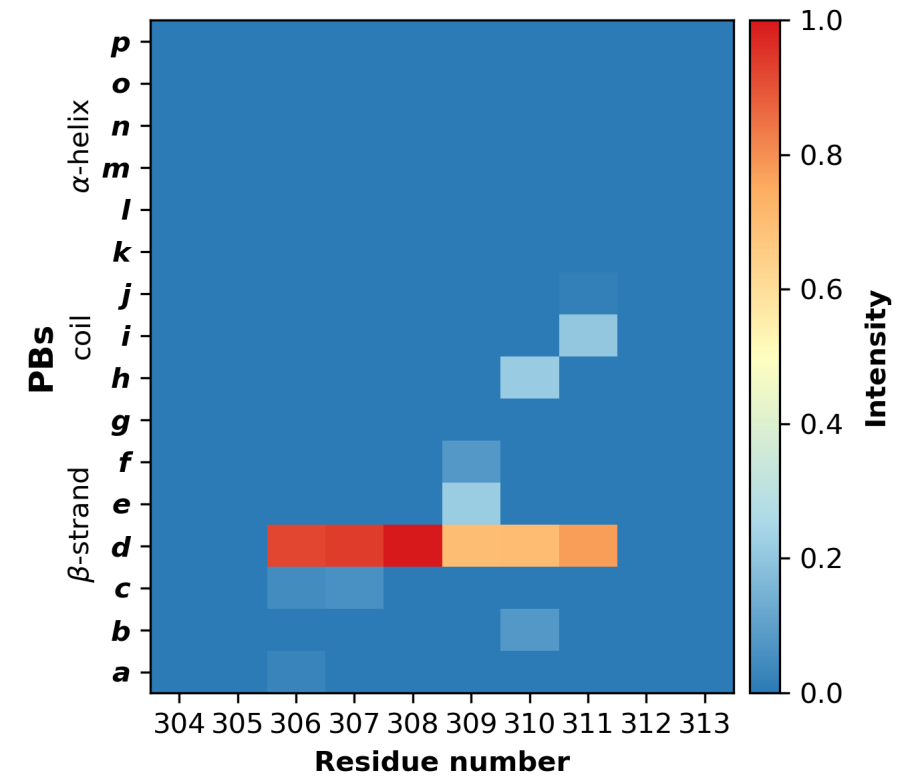
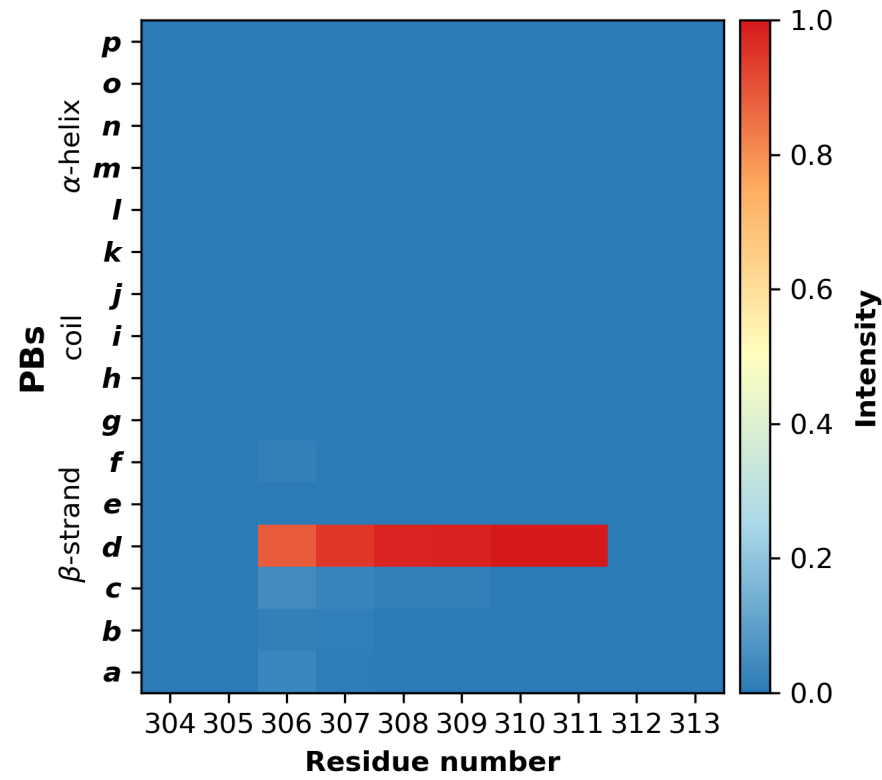
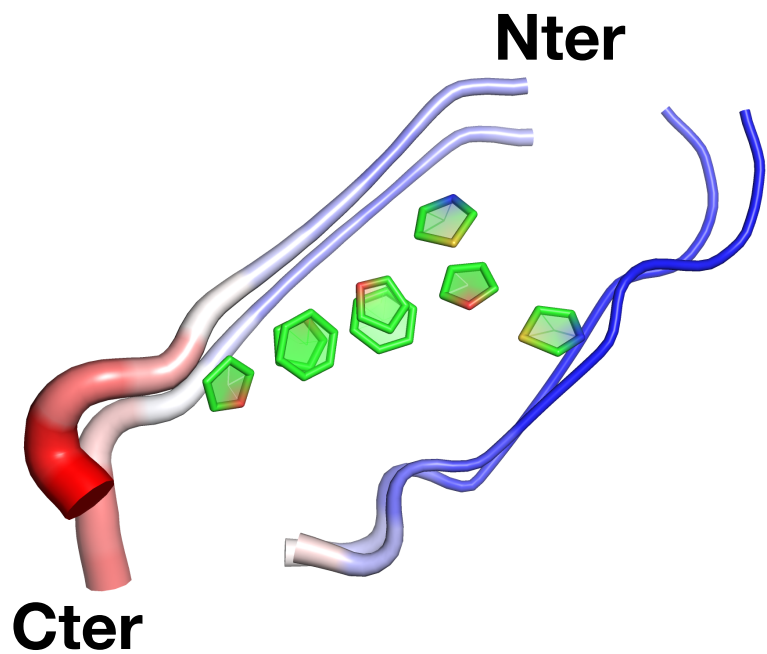
PHF8 tetramer BS1'



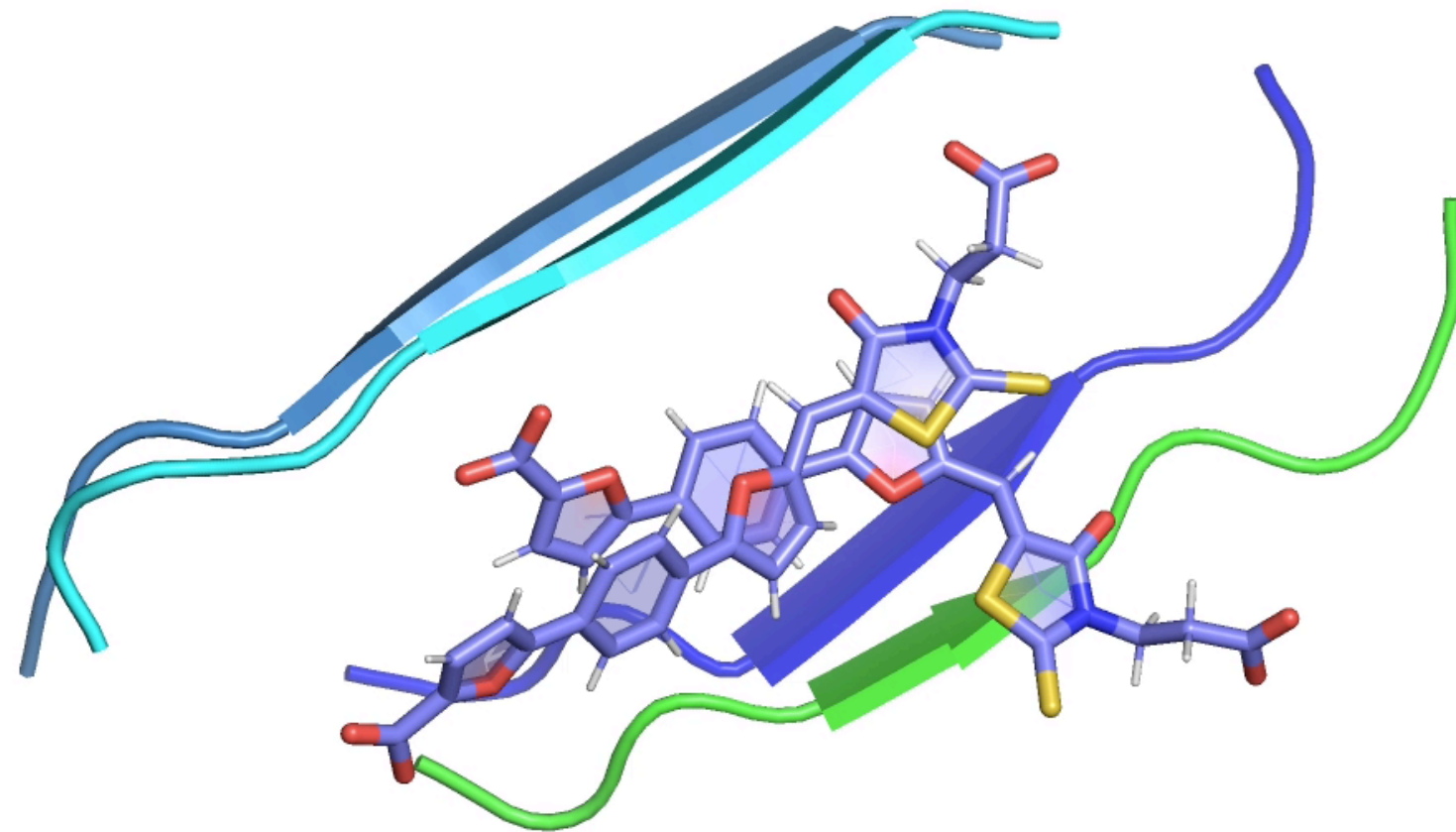
PHF8 tetramer BS1+BS1'



PHF8 tetramer (BS0)²



PHF8 tetramer (BSO)² trajectory



500ns

Conclusions

- loss of native contacts
- destabilisation of C-terminus
- transitions with increase of radius of gyration
- sizzling motion in anti-parallel dimers
- binding modes with shifting one (parallel) β -strand dimer
- stoichiometry 2:1 may facilitate inter-dimer insertion

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- Dr. Luis Montero Cabrera (UH)
- Dra Chryslaine Rodríguez Tanty (CNC)