PPP - Potestio Prion Project

The creation of the prion

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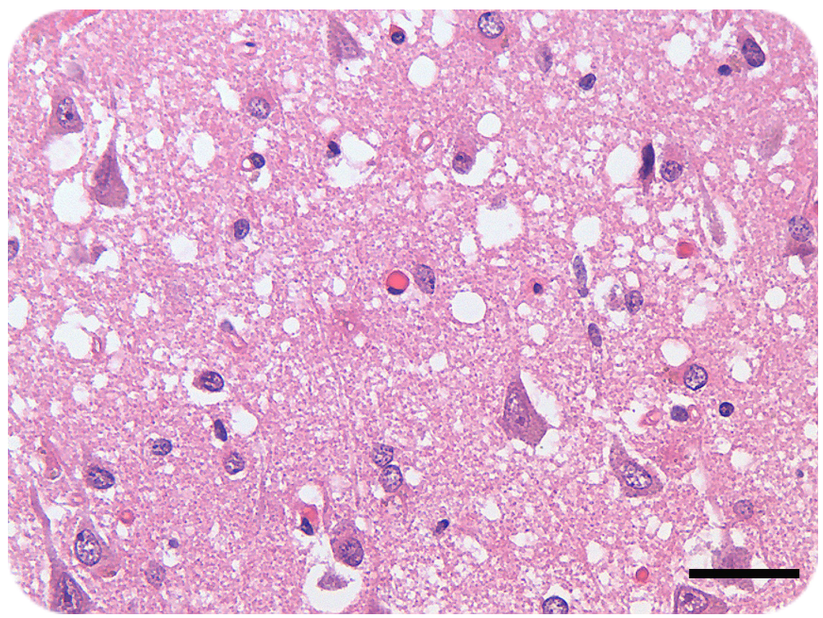
UNIVERSITÀ DI TRENTO

What are prions?

- IDP, self-replicative proteins
- Name coined by Stanley B. Prusiner in 1982
- Cause of TSEs
- Conformational change from PrP^{c} to PrP^{sc}
- **AIM** : study the conformational change from α-helix to β-sheet



OUR STRUCTURE

Our models for prion

CHI1

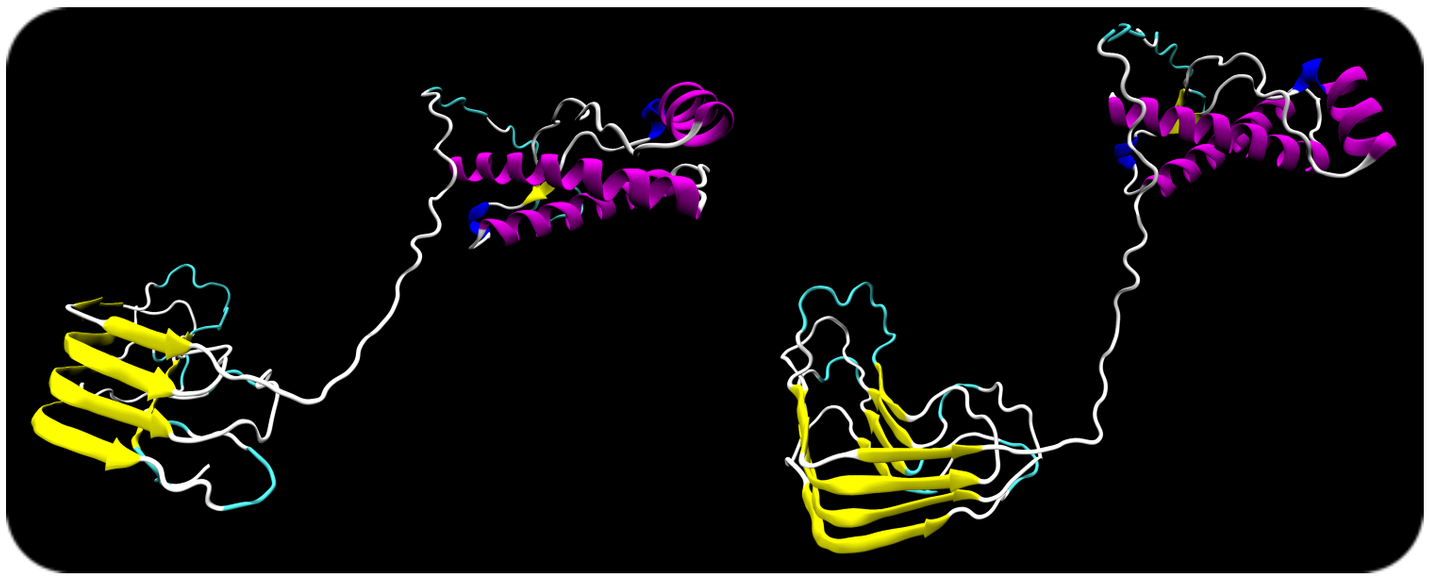
PrP^{c} from 1FKC (PDB)
PrP^{sc} from Spagnolli *et al.*

Bond : MP GLY 89 - 1FKC SER 231

CHI2

PrP^{c} from AlphaFold
PrP^{sc} from Spagnolli *et al.*

Bond : MP SER 230 - AF GLY 1

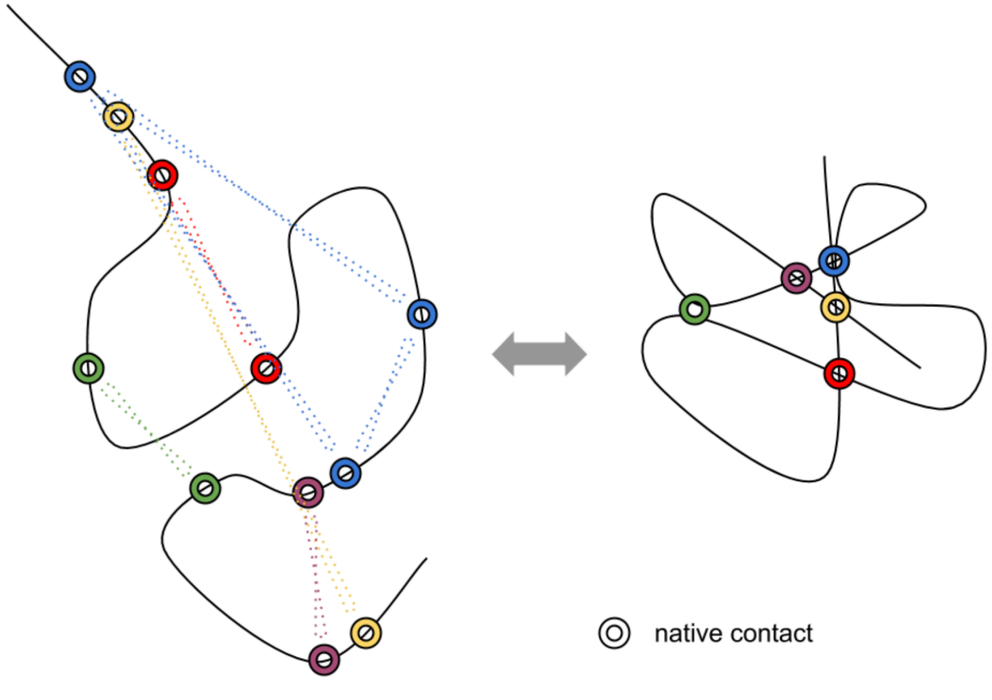


COARSE GRAINING METHODS

Coarse graining methods

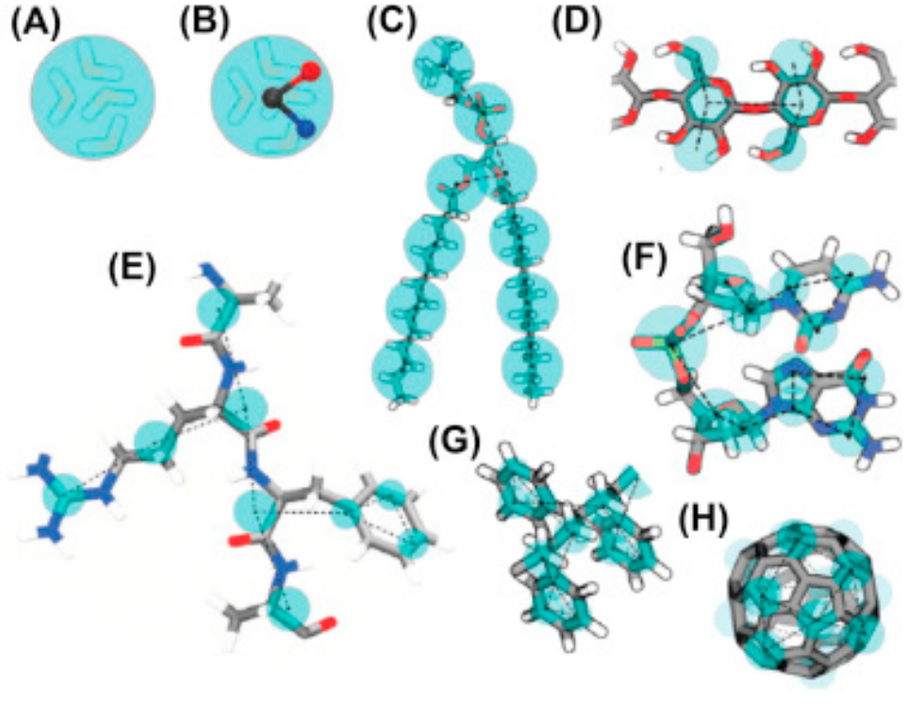
Gō model

- VdW and LJ approximated with native contacts energy function
- Funnel-shaped energy landscape



Martini model

- 4-to-1 mapping scheme
- Neutral beads interactions described by LJ
- Charged beads include also Coulomb forces

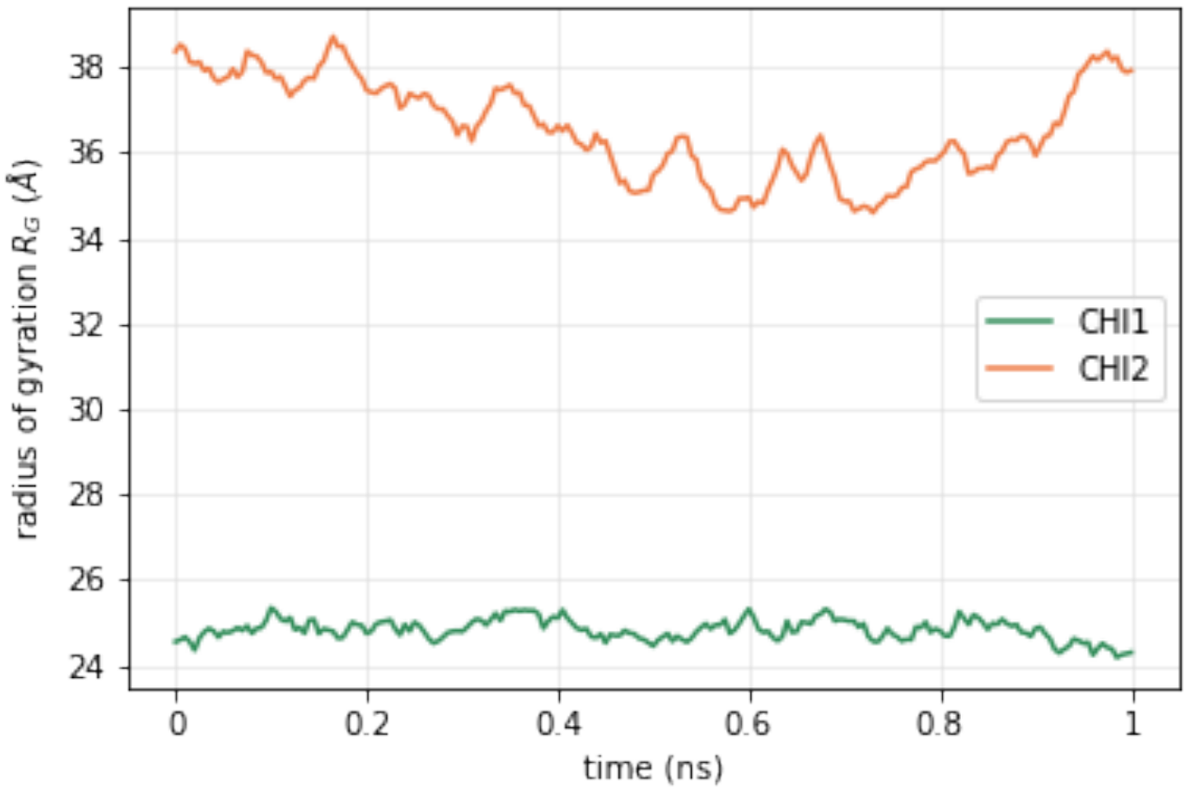


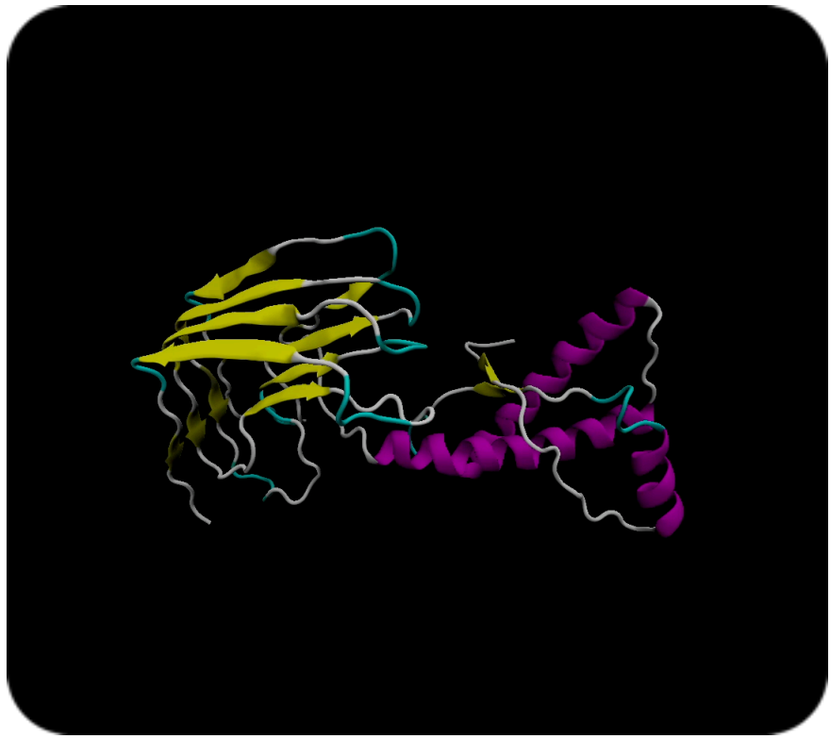
RESULTS

All-atom simulations

Radius of gyration

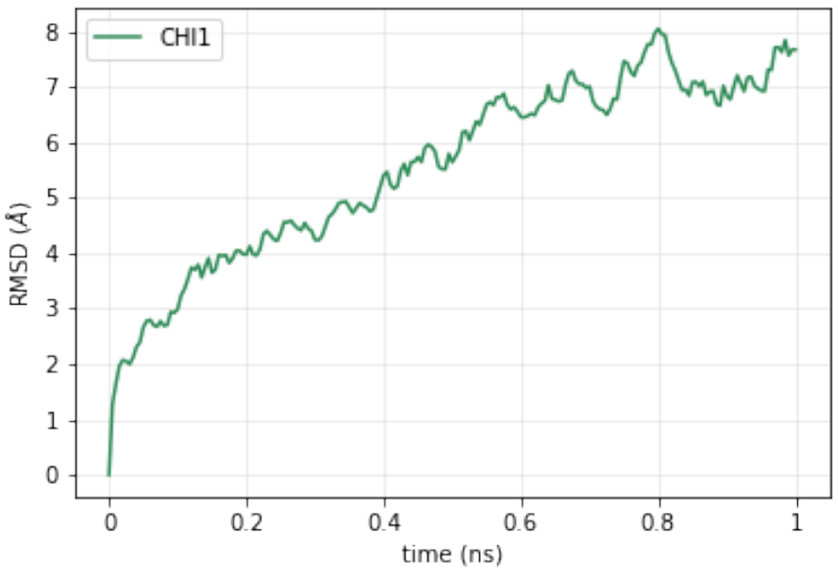
$$R_g^2 = \frac{1}{N+1}\sum_{i=0}^{N}\left\langle(\mathbf{r_i} - \mathbf{r_{cm}})^2\right\rangle$$

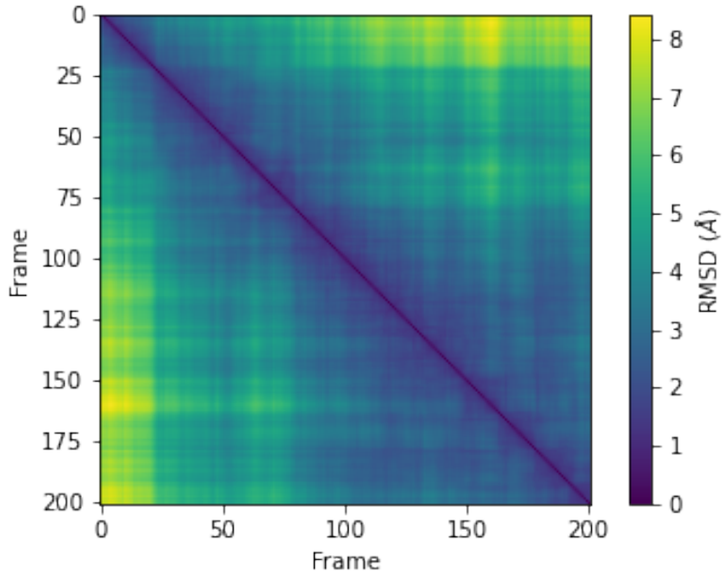


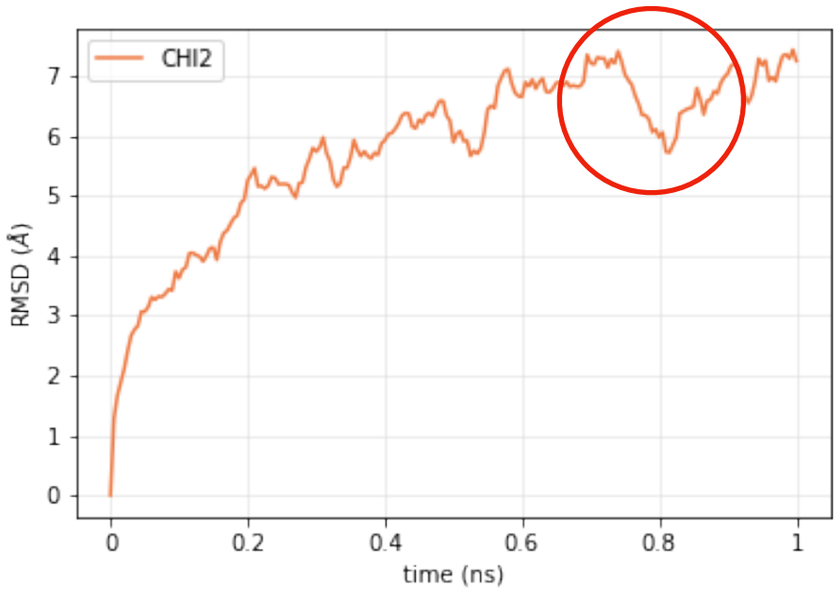


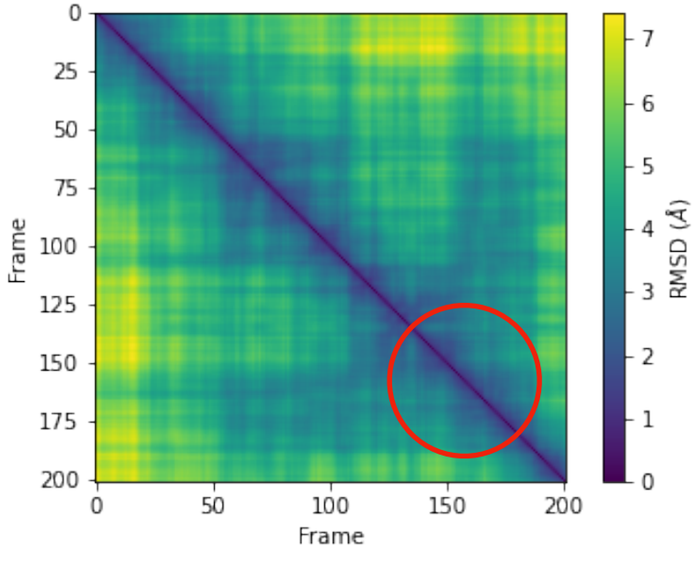
RMSD

$$\mathrm{RMSD}(t) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(\mathbf{r}_i(t) - \mathbf{r}_i(0))^2}$$



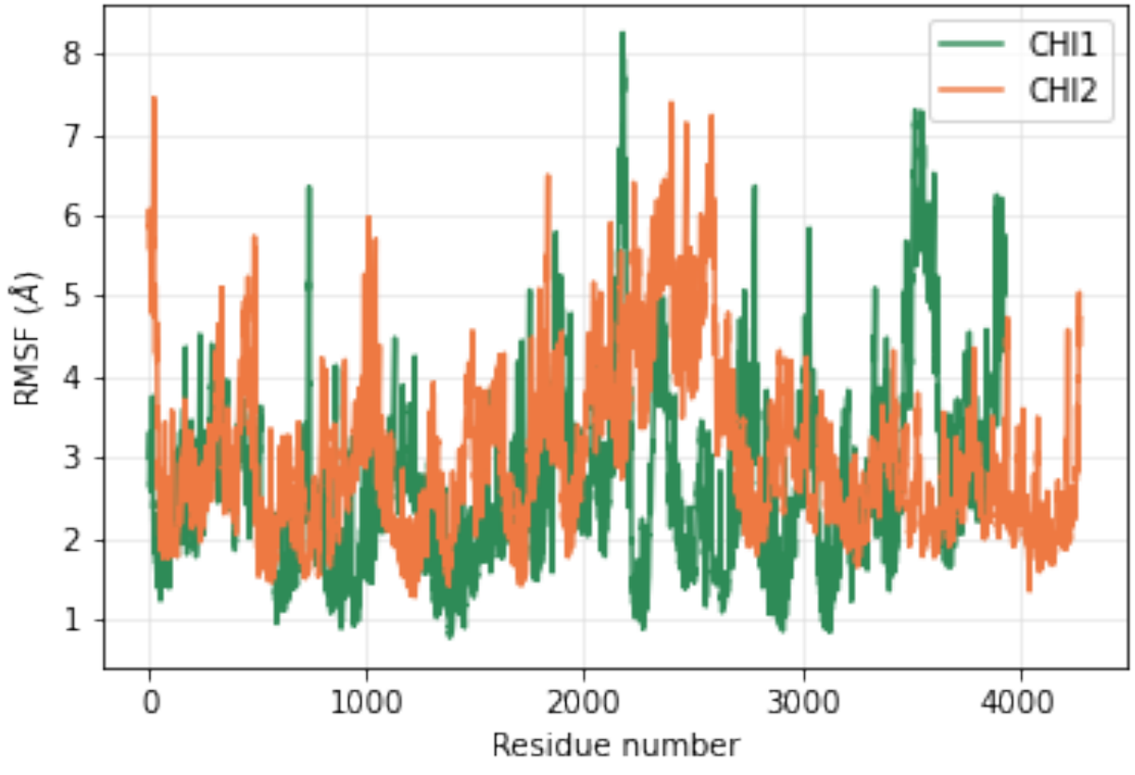






RMSF

$$\mathrm{RMSF}_i = \sqrt{\langle (\mathbf{r}_i - \langle \mathbf{r}_i \rangle)^2 \rangle}$$

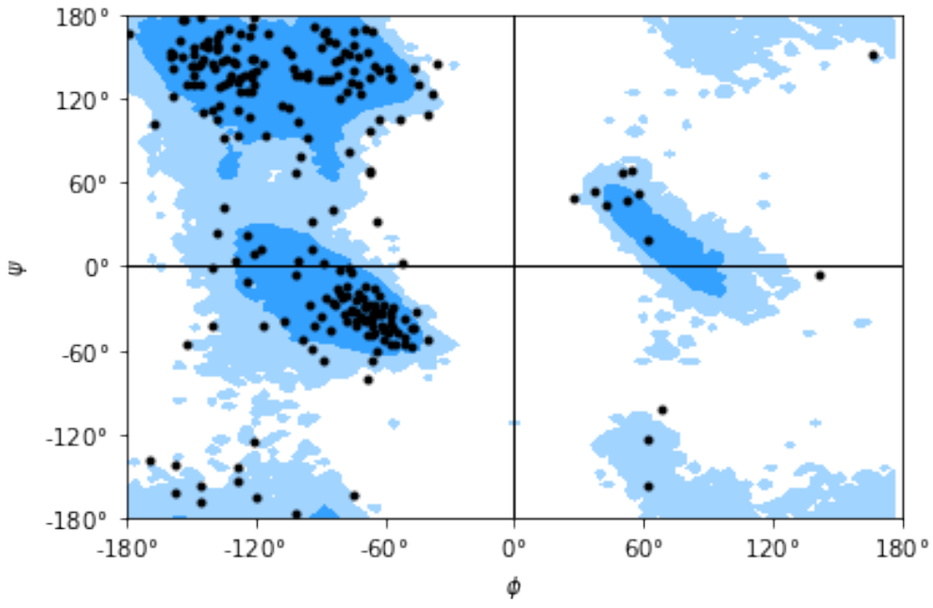


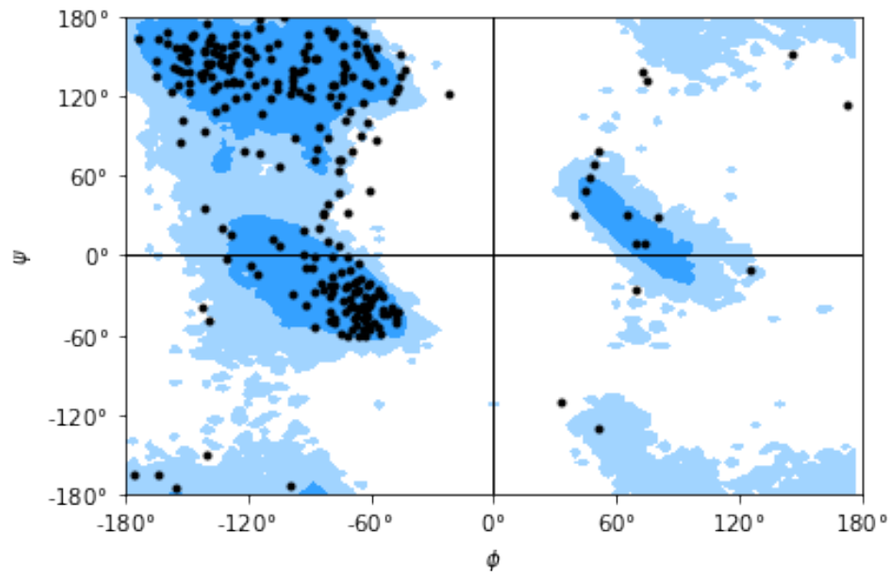
Ramachandran plot

CHI1

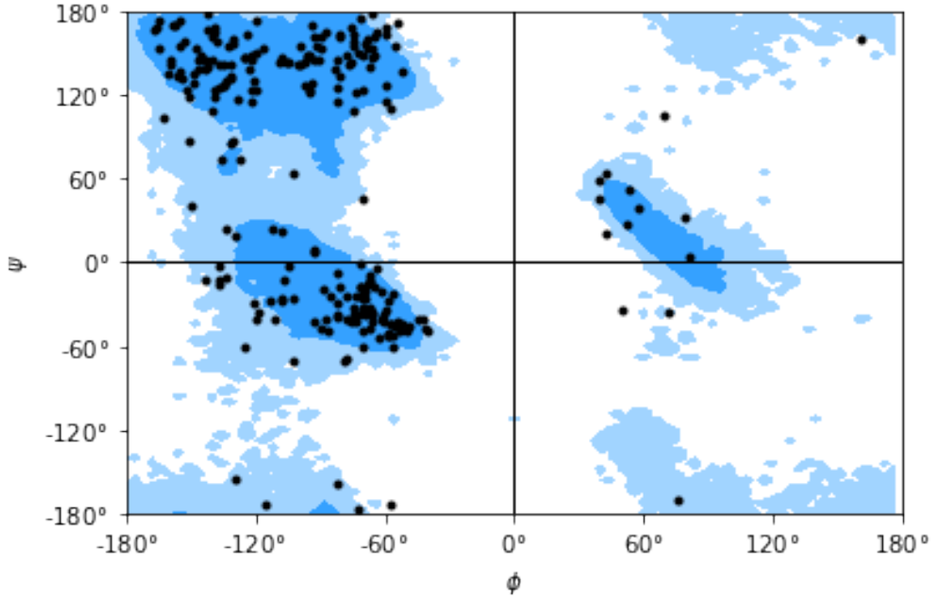
CHI2

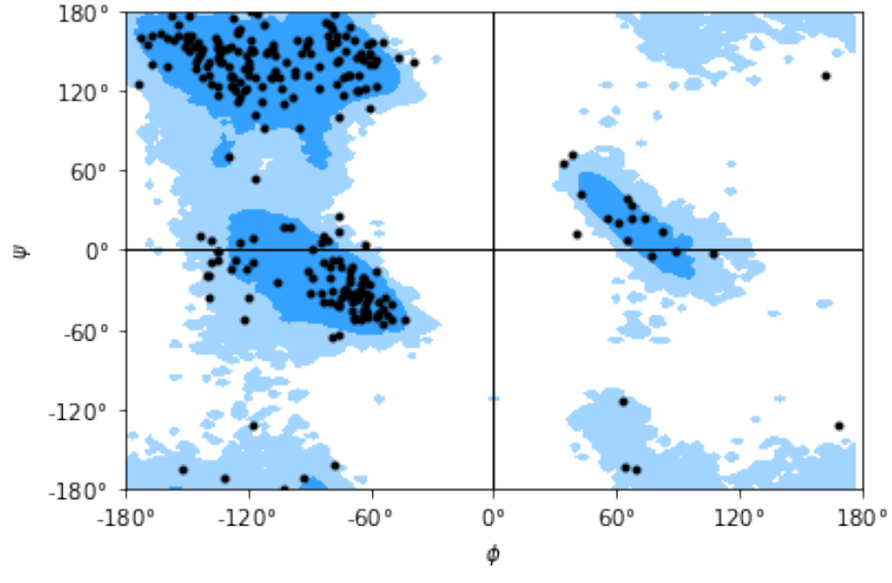
First frame





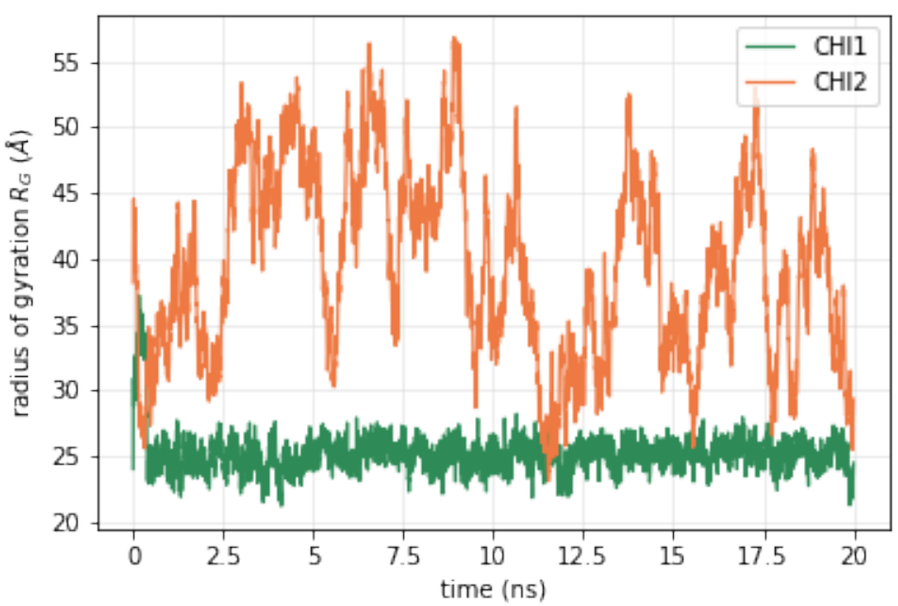
Last frame

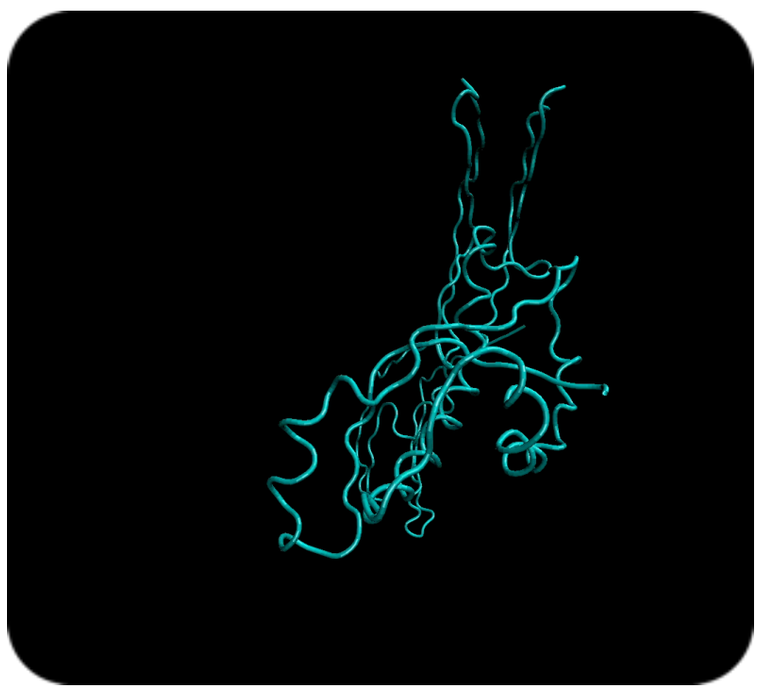




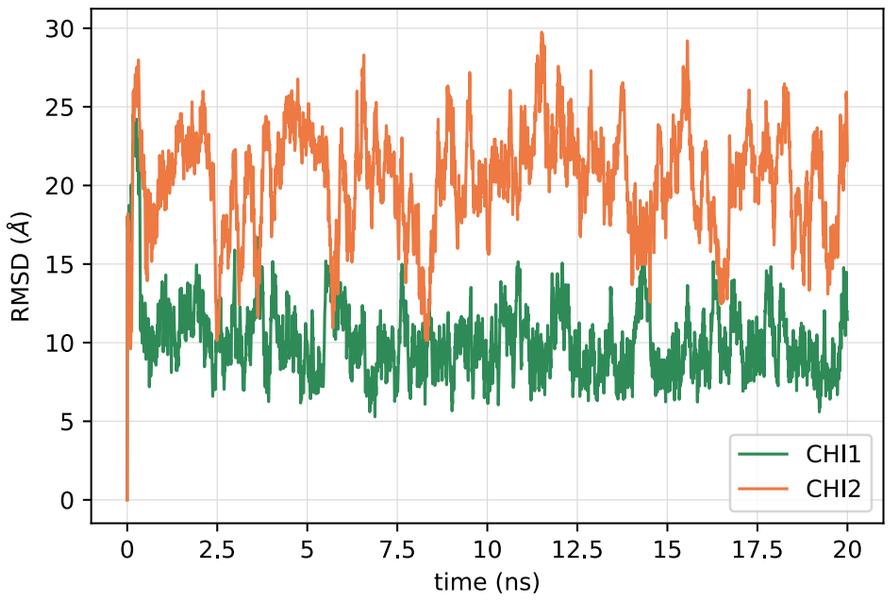
Gō model simulations

Radius of gyration

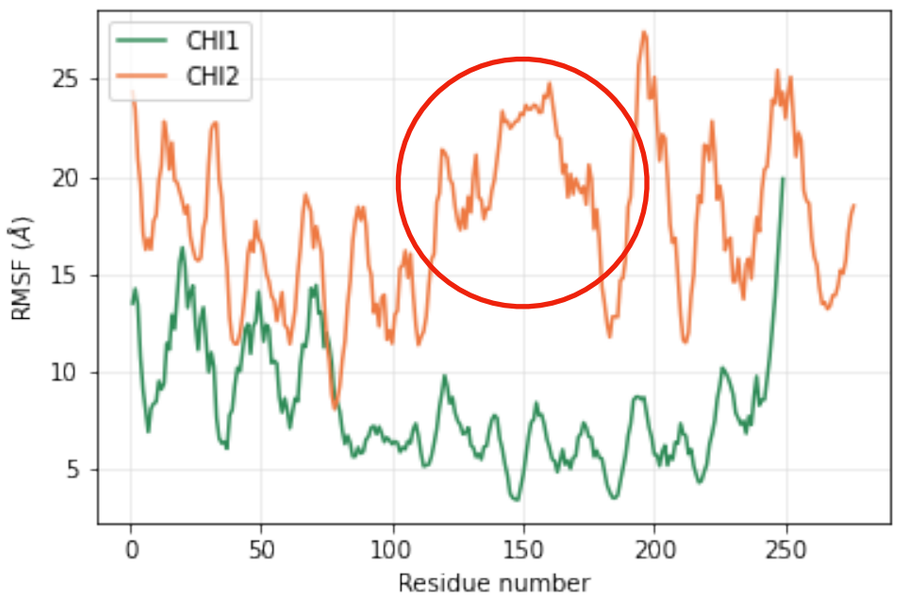




RMSD

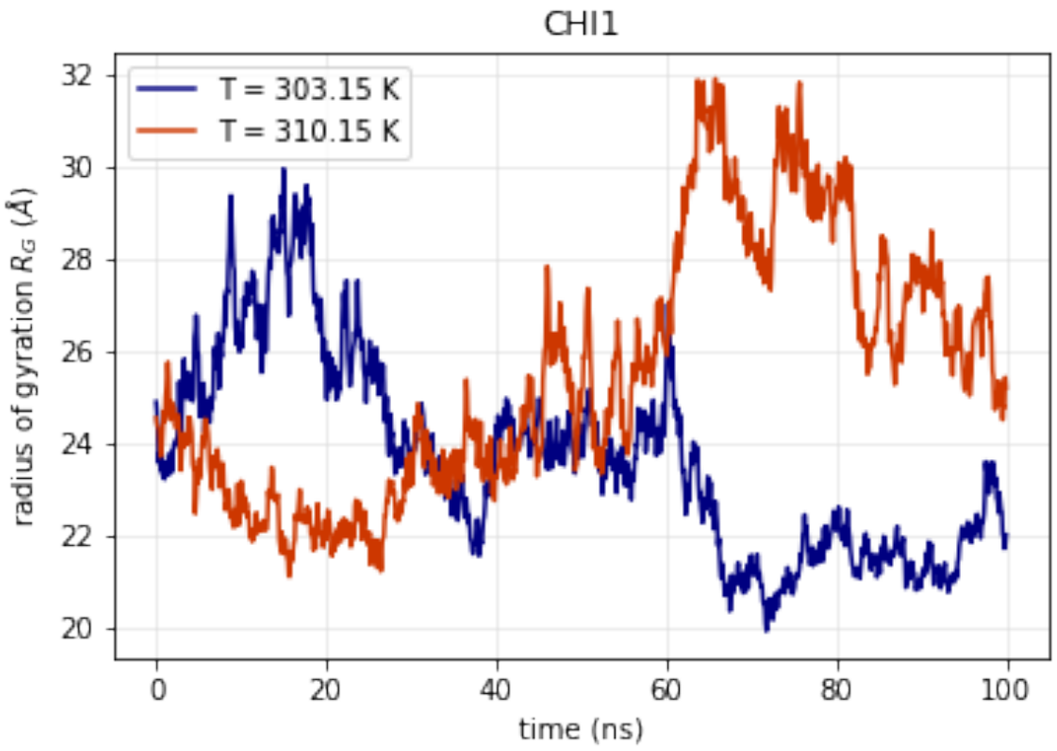


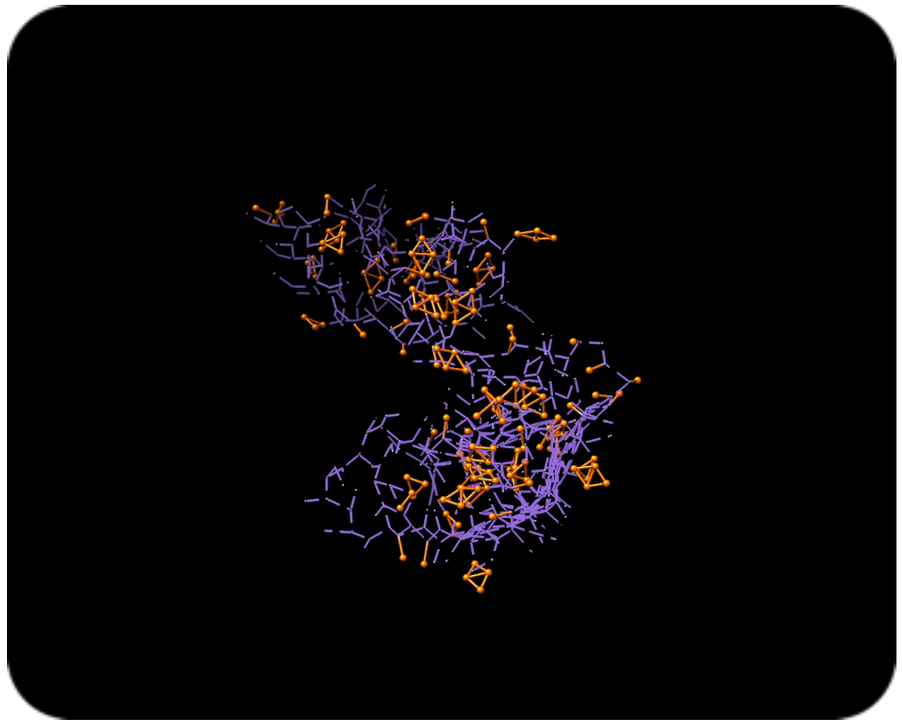
RMSF



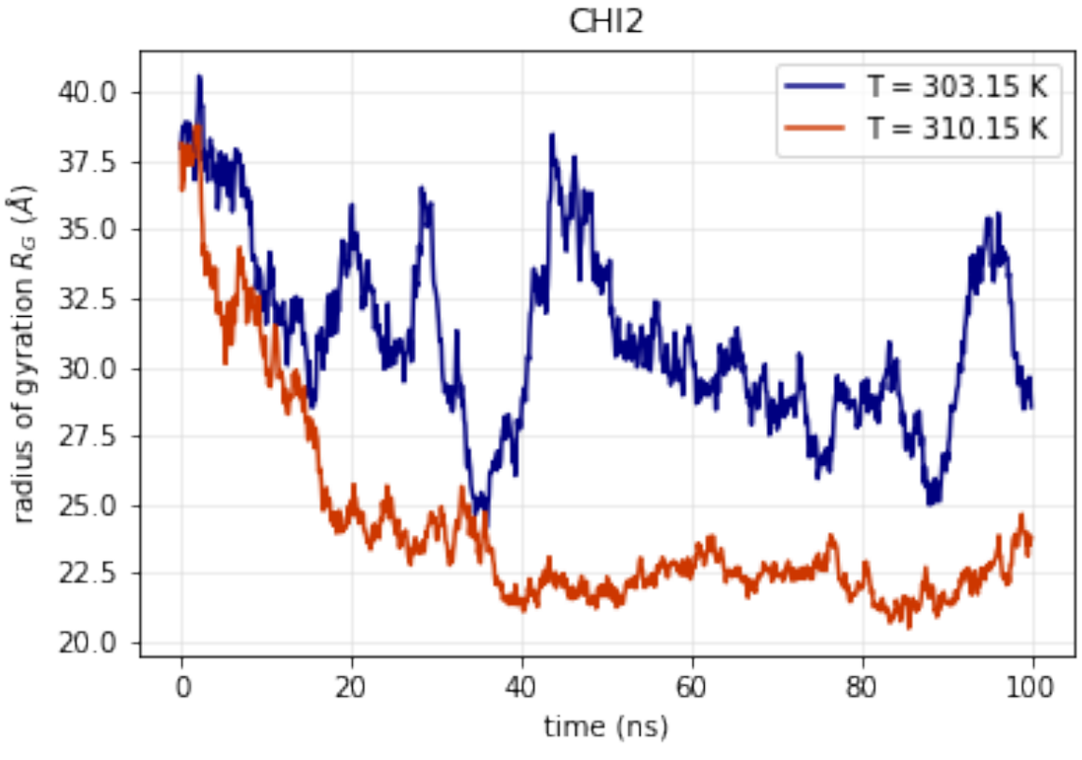
Martini 3 simulations

Radius of gyration

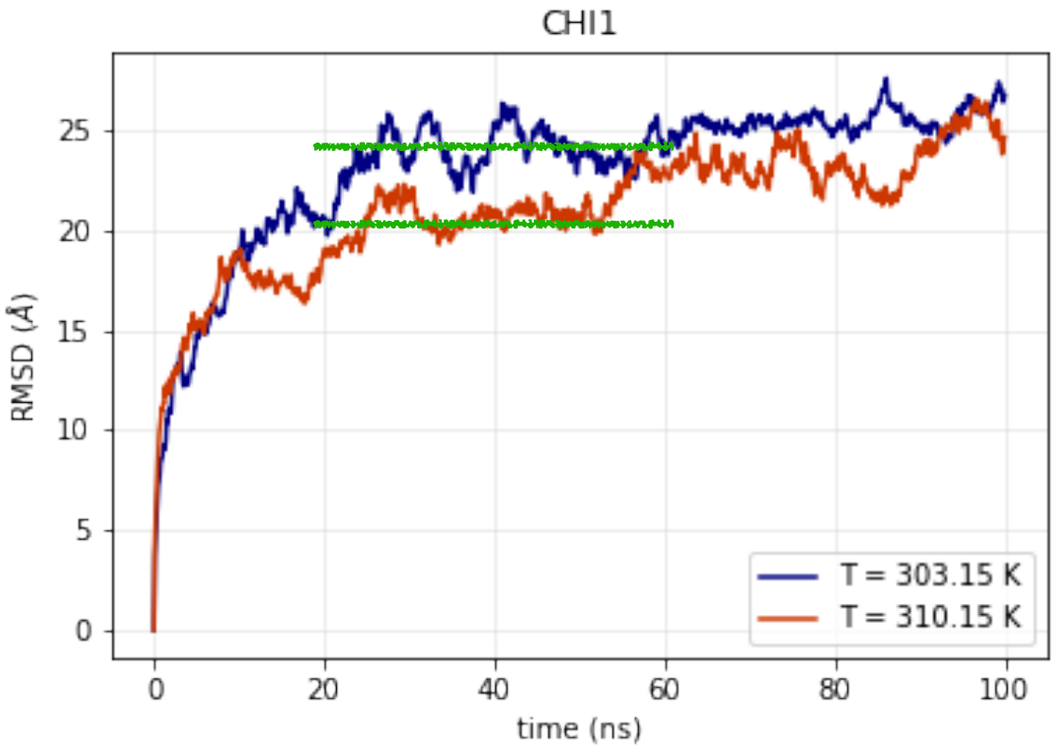




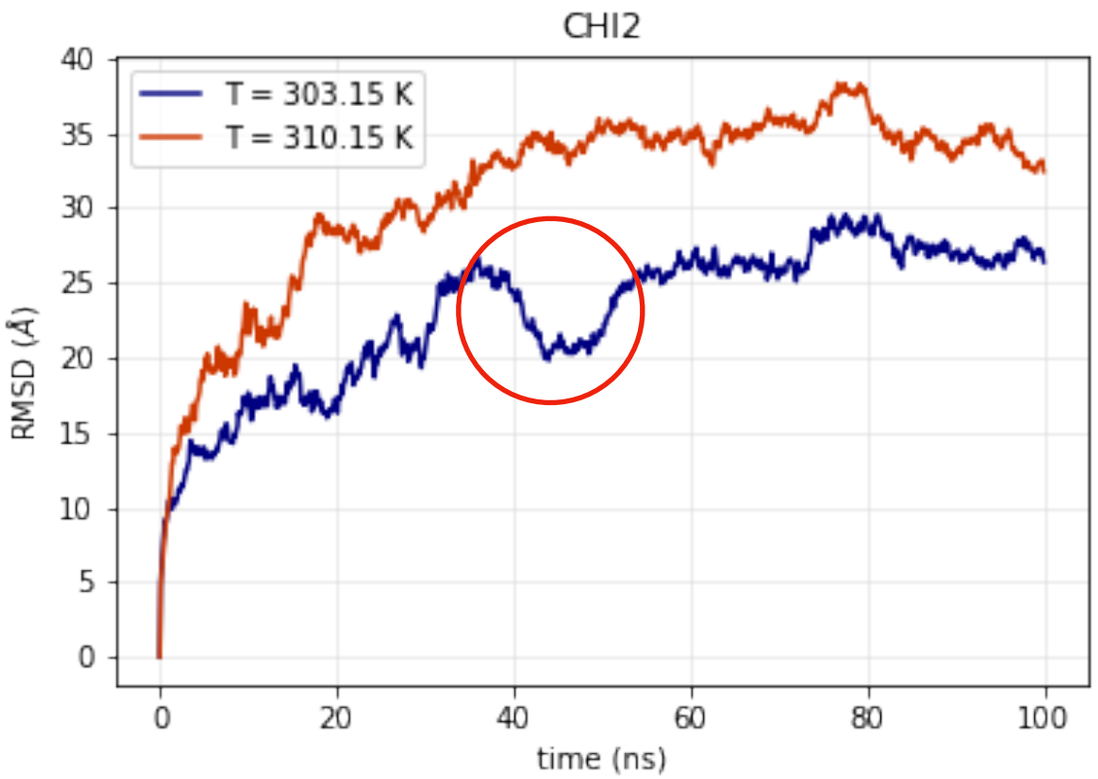
Odd behaviour: smaller R_g at higher temperature



RMSD

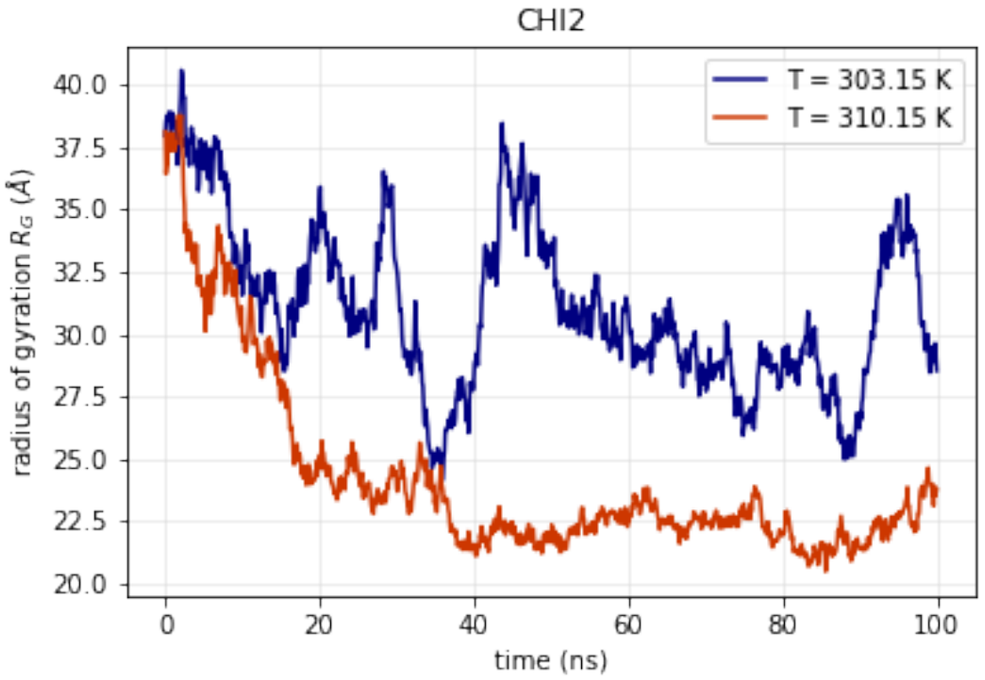


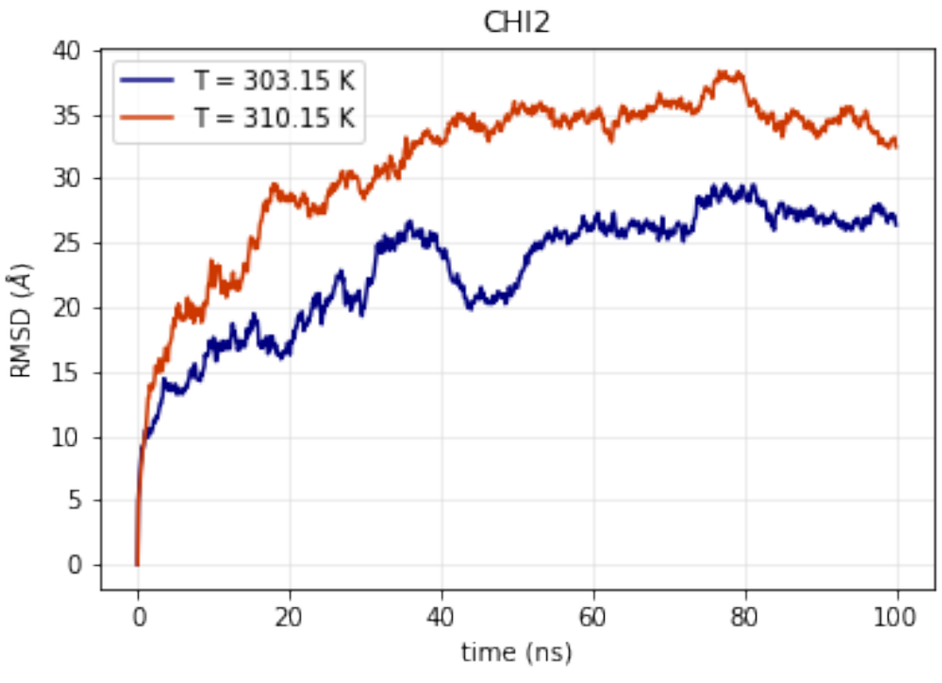
RMSD is lower at higher temperature. Is this wrong wrt R_g?



Martini 3 simulations

CHI2 “odd” behaviour explained

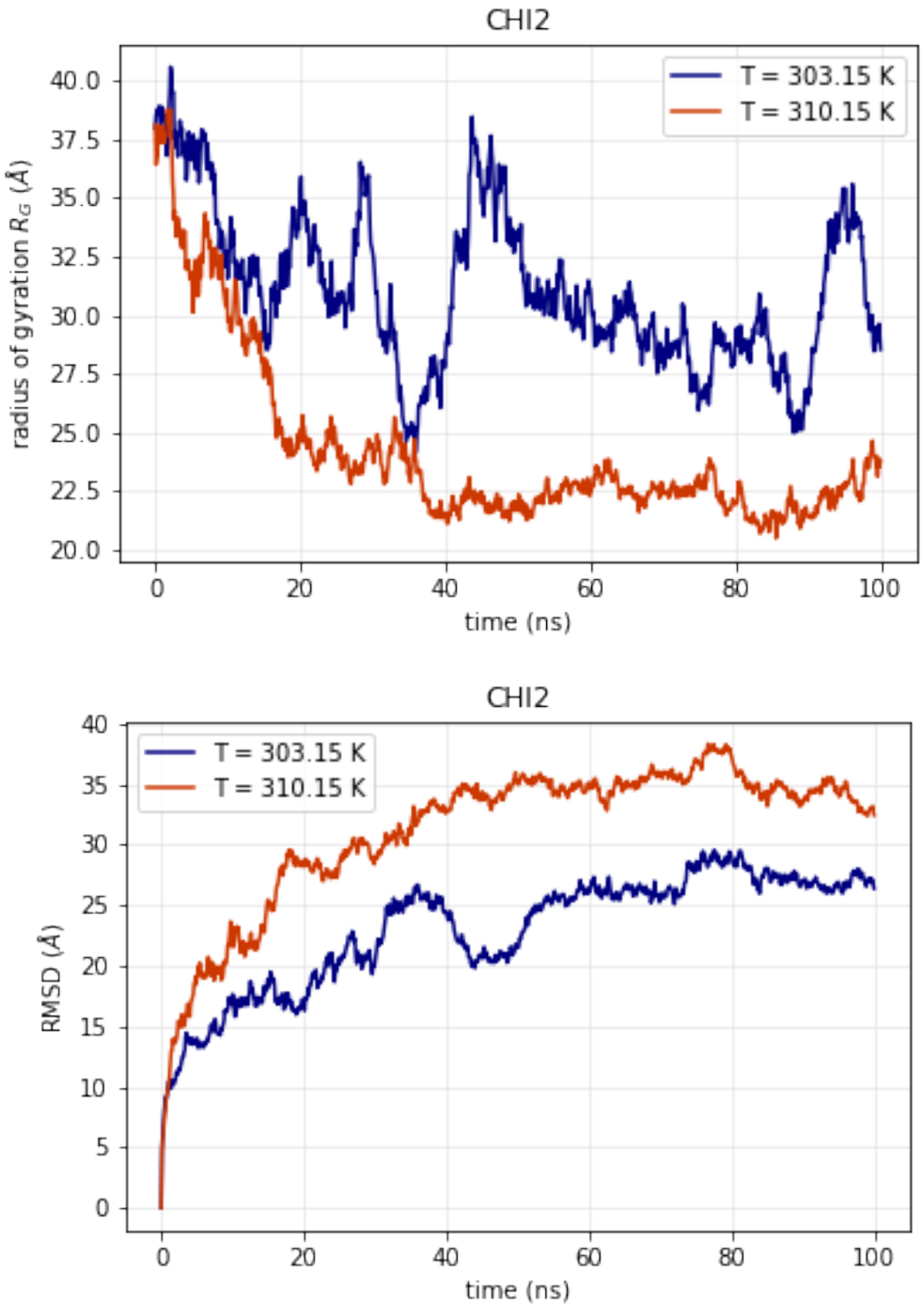


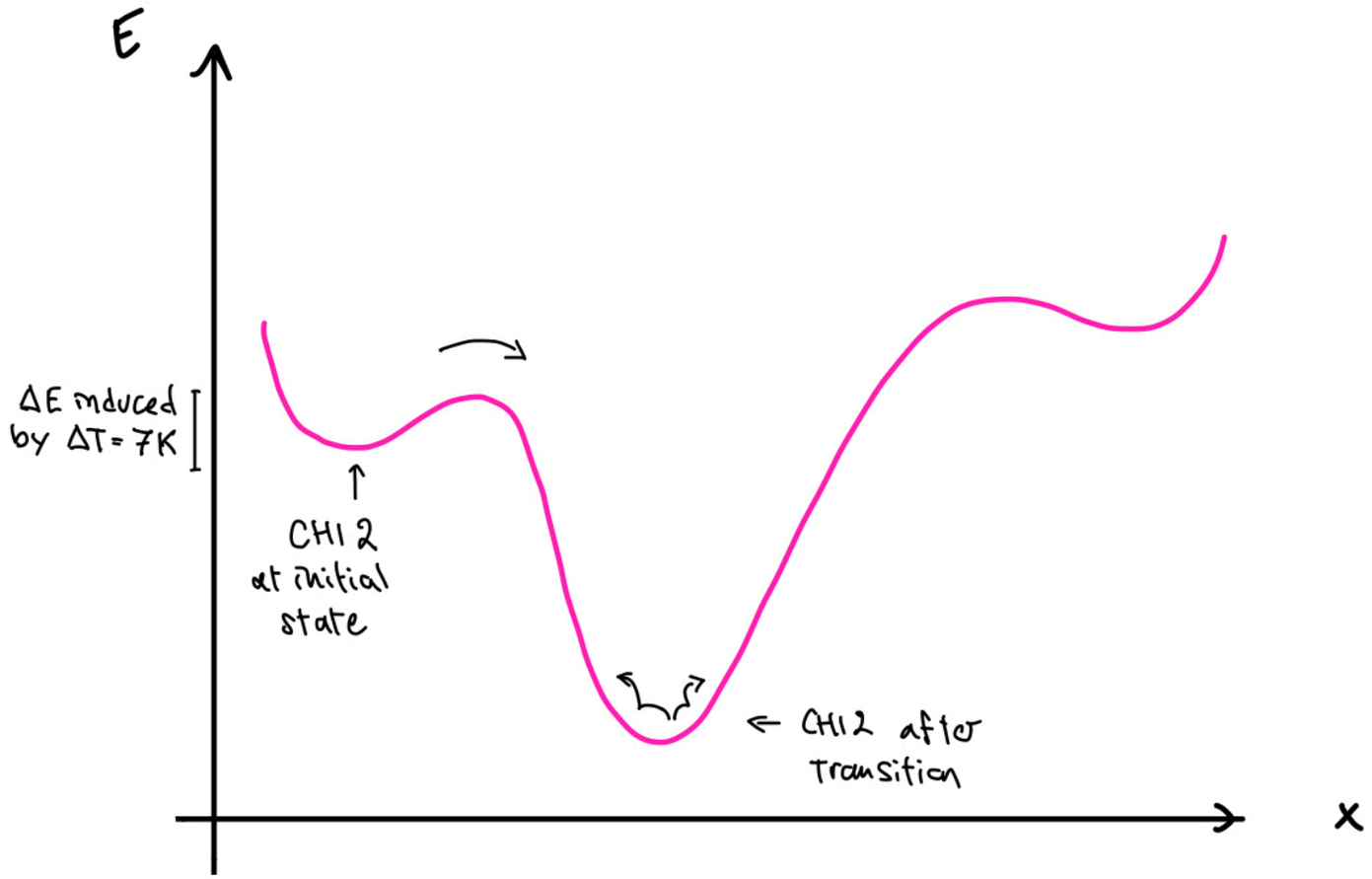


- Rg reaches equilibrium while RMSD has a variation at 40 ns
- Stronger interactions at higher temperature
- More compact structure

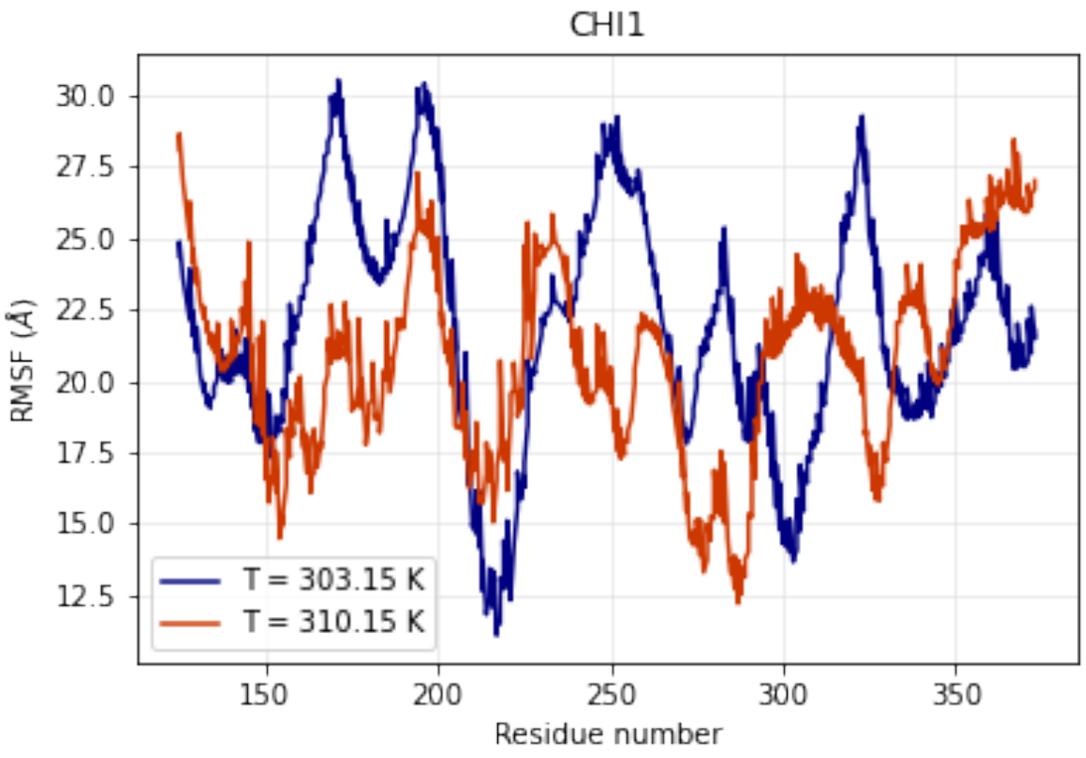
Martini 3 simulations

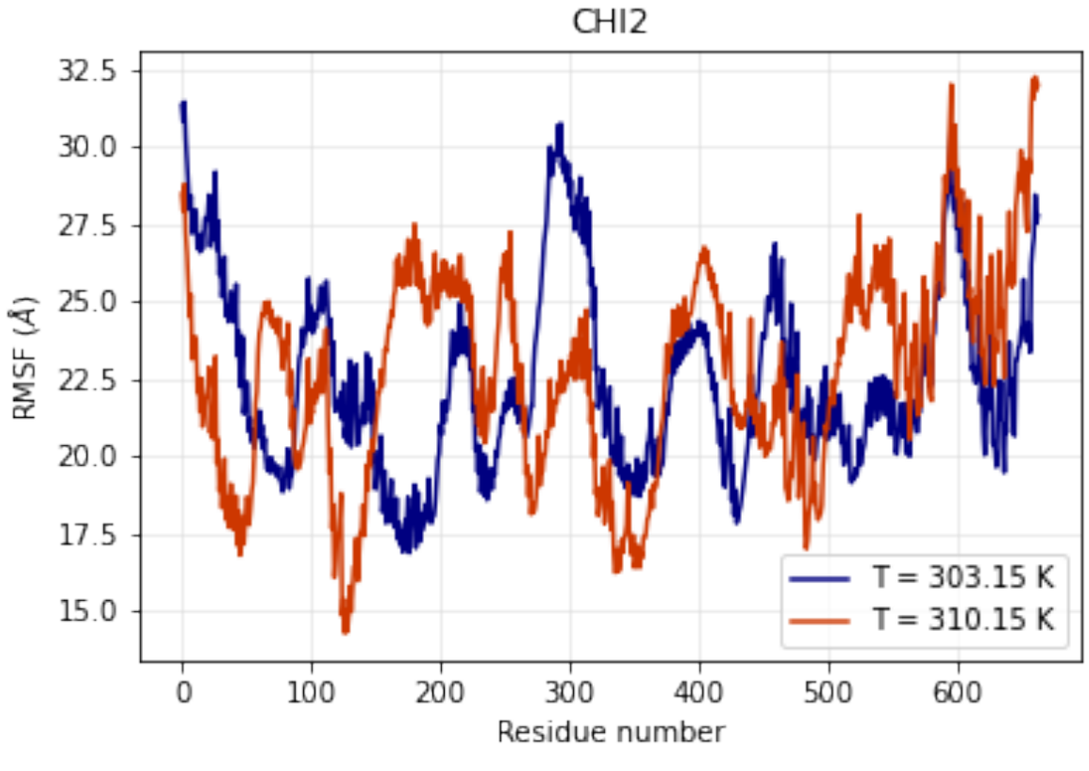
CHI2 “odd” behaviour explained





RMSF


CHI1
RMSF (Å)
30.0
27.5
25.0
22.5
20.0
17.5
15.0
12.5
T = 303.15 K
T = 310.15 K
150
200
250
300
350
Residue number


CHI2
RMSF (Å)
32.5
30.0
27.5
25.0
22.5
20.0
17.5
15.0
T = 303.15 K
T = 310.15 K
0
100
200
300
400
500
600
Residue number

Backmapping

CHI1

Conclusions

- AA ⟶ thermal fluctuations
- Gō model ⟶ ineffective for protein folding *(Karplus, 2013)*
- Martini 3 ⟶ insights about the energy landscape of the models

- CHI2 ⟶ transition to a stable state with Martini 3

The target transition did not occur

Conclusions

Springer Link

Review | Published: 12 November 2018

“Essentially, all models are wrong, but some are useful”—a cross-disciplinary agenda for building useful models in cell biology and biophysics

Julien Berro

Biophysical Reviews **10**, 1637–1647 (2018) | Cite this article

Thank you !