MM Part: MD Simulation of Chignolin

Advanced Practical in Theoretical Chemistry

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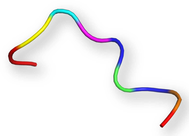
Introduction & Overview

The aim of the practical course was to study and analyse the dynamic properties of the fast-folding miniprotein CLN025 [1].



Residue	Residue
Y (darkred)	T (Blue)
Y (darkred)	G (Green)
D (Yellow)	T (Blue)
P (Cyan)	W (Orange)
E (Magenta)	Y (Red)

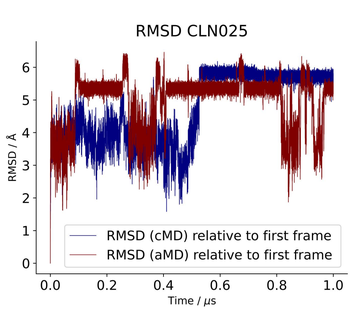
Figure 1: *(Left)* Starting Structure of CLN025 obtained from the DESRES Simulation; *(Right)* Color coding of the aminoacids

Force Field: ff14SB [2] **Water Model:** TIP3P WM
1 μs cMD + 1μs aMD (Total Energy and Dihedral Boost)

Root Mean Square Deviation

By calculating the root-mean-square deviation in respect to the atomic coordinates, dominant structural changes are visualized

$$RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{n}\delta_i^2}$$



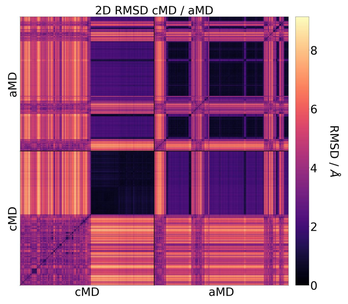


Figure 2: *(Left)* 1D RMSD of cMD (colored in blue) and 1D RMSD of aMD (colored in red); *(Right)* 2D RMSD respective simulations cMD / aMD are compared

Clustering Analysis

In order to obtain characteristic structures a hierarchical agglomerative clustering is performed. The clustering is based on the RMSD of the C_α atoms.

Figure 3: *(Left) cMD : In lightblue Cluster 1 with 49.8 %; In coral Cluster 2 with 29.3 %*
(Right) aMD: In lightblue Cluster 1 with 71.7 %; In coral Cluster 2 with 16,1 %

Detail Question: Periodic Boundary Conditions

- Simulation box is periodically expanded
- Influences of bulk solvent can be included

Principle of Minimum Image Convention

- Cut-off radius r_{cutoff} is introduced
- Truncation of Potential Energy
- **VdW:** r_{ij}^{-6} switching functions
- **Electrostatic:** Ewald Summation

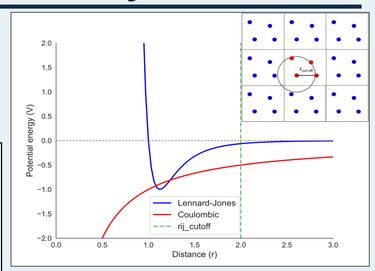


Figure 4: Potential Energy Curve for the Van-der-Waals (Lennard-Jones) (12,6) and the Coloumb interaction.

Secondary Structure Analysis

Secondary structure elements were analyzed with the DSSP algorithm

- CLN025 populates β-hairpin state at room temperature [3]
- cMD unfolded in beginning of simulation, finds local minimum at ~ 600 ns
- aMD shows more diverse structural motives

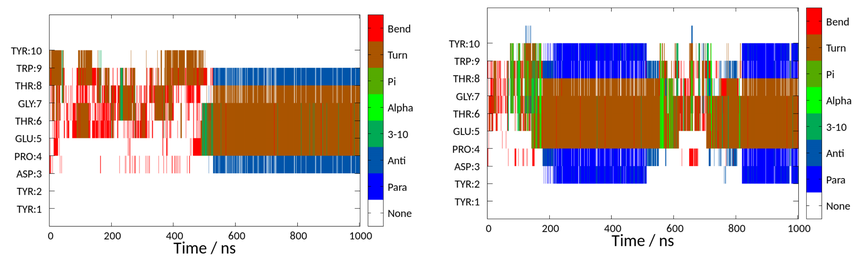


Figure 5: Time dependent evolution of secondary structure elements for *(Right)* cMD, *(Left)* aMD

Principal Component Analysis (PCA)

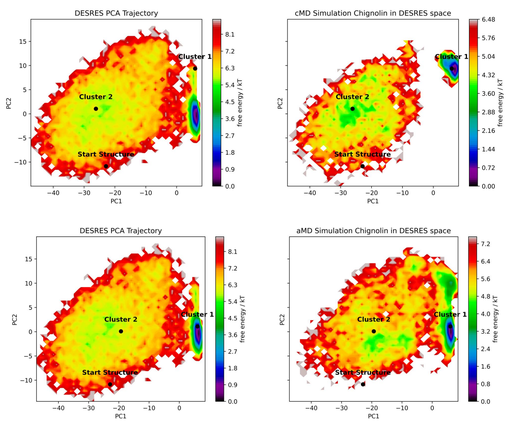


Figure 6: (*Top Left, Bottom Left*) PCA of DESRES trajectory with clusters of cMD/aMD visualized.
(*Top Right, Bottom Right*) cMD/aMD trajectory projected into the DESRES space

PCA was applied to the coordinates of the atoms obtained from the simulation.

- aMD shows more diverse sampling of configurational space
- cMD cluster 1 in local minimum

tICA and MSM States

tICA is a linear transformation that maximizes the autocorrelation of transformed coordinates. Backbone atom distance was selected as a dominant feature, $\Delta t = 50\ ns$ was chosen.

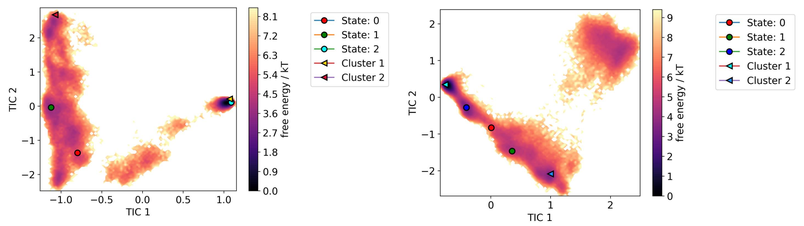


Figure 7: (*Left*) tICA analysis for cMD simulation with MSM states (circles) and clusters (triangles)
(*Right*) tICA analysis for aMD simulation with MSM states (circles) and clusters (triangles)

MSM was build on tICA analysis visualizing conformational states and transition probabilities

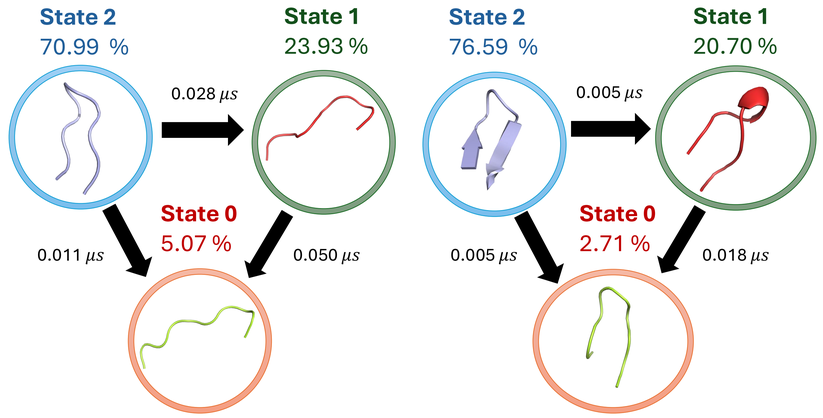


Figure 8: MSM states for both the cMD (*left*) and aMD (*right*) with the probability and the transition time visualized.

X-Ray Crystallography

By applying FT to a diffraction pattern a electron density map is obtained. METTL16 was used as a search model.

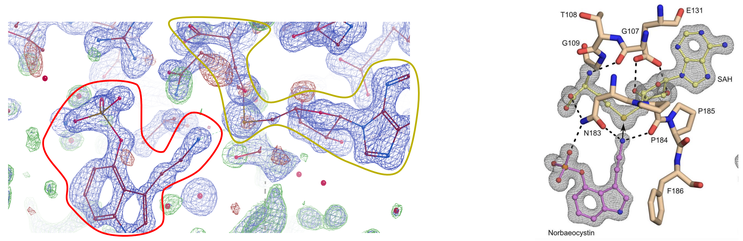


Figure 9: *(Left)* Active Site of PsiM, circled in red, the norbaeocystin, circled in gold, the coenzyme SAH, (*Right*) Visualization of Coordination Mechanism [4]

References:
[1] Kamenik AS, Handle PH, Hofer F, Kahler U, Kraml J, Liedl KR. Polarizable and non-polarizable force fields: Protein folding, unfolding, and misfolding. J Chem Phys. 2020 Nov 14;153(18):185102. doi: 10.1063/5.0022135. PMID: 33187403.
[2] ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. JCTC 2015 Jul, James A. Maier et al. Doit 10.1021/acs.jctc.5b00255
[3] McKiernan KA, Husic BE, Pande VS. Modeling the mechanism of CLN025 beta-hairpin formation. J Chem Phys. 2017 Sep 14;147(10):104107. doi: 10.1063/1.4993207. PMID: 28915754; PMCID: PMC5597441.
[4] Hudspeth, J., Rogge, K., Dörner, S. *et al.* Methyl transfer in psilocybin biosynthesis. *Nat Commun* **15**, 2709 (2024). https://doi.org/10.1038/s41467-024-46997-z.