Molecular dynamics simulations of α-Synuclein aggregation

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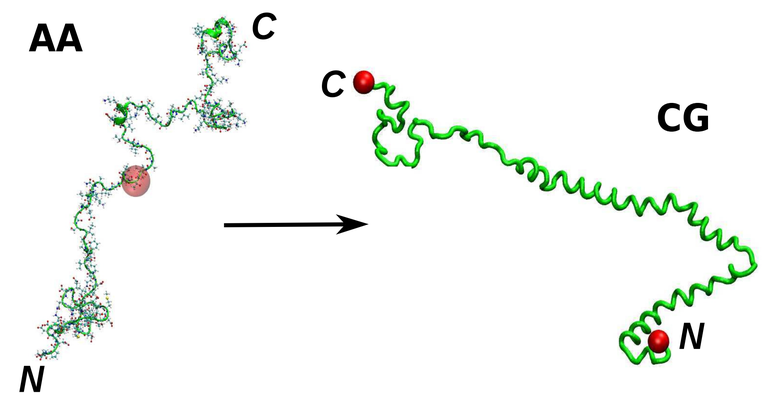
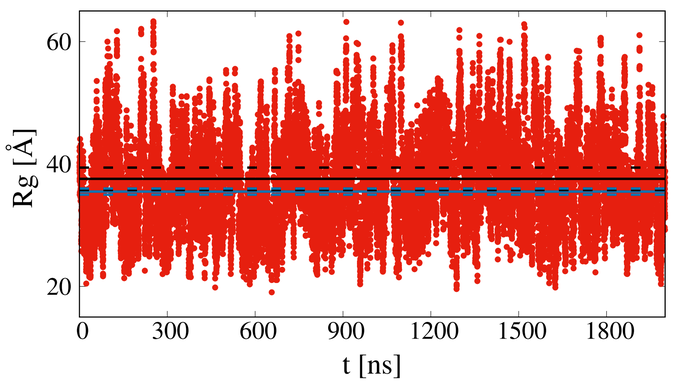
Abstract

Intrinsically disordered proteins lack a well-defined structure in extended parts of their sequences. Despite the lack of stationary structure under physiological conditions, they play important functional roles in the cell, including signalling, cell-cycle regulation, and initiation of translation. They are often involved in neurodegenerative disorders such as in Alzheimer, Huntington and Parkinson diseases. The toxicity often arises through aggregation into pore-like annular structures and amyloid fibers [1]. Here, we present results of our computational studies on α-synuclein. We performed molecular dynamics simulations within our locally developed coarse-grained Cα-based model [2,3] and an all-atom model with implicit solvent [4]. We discuss the role of transient secondary structure elements and specific contacts in the aggregation process. Moreover, we present the aggregation process dependence on the protein concentration and temperature.

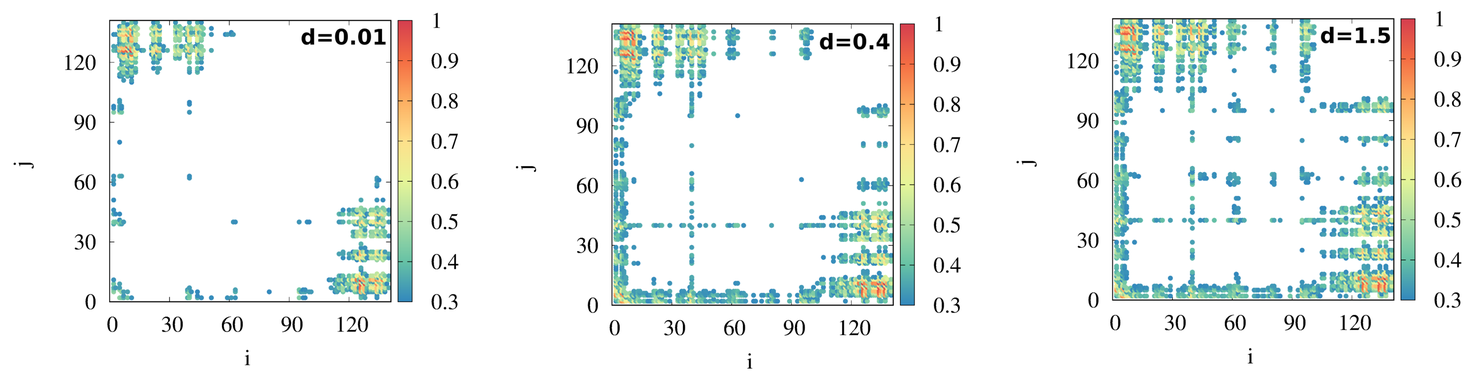
AA→CG



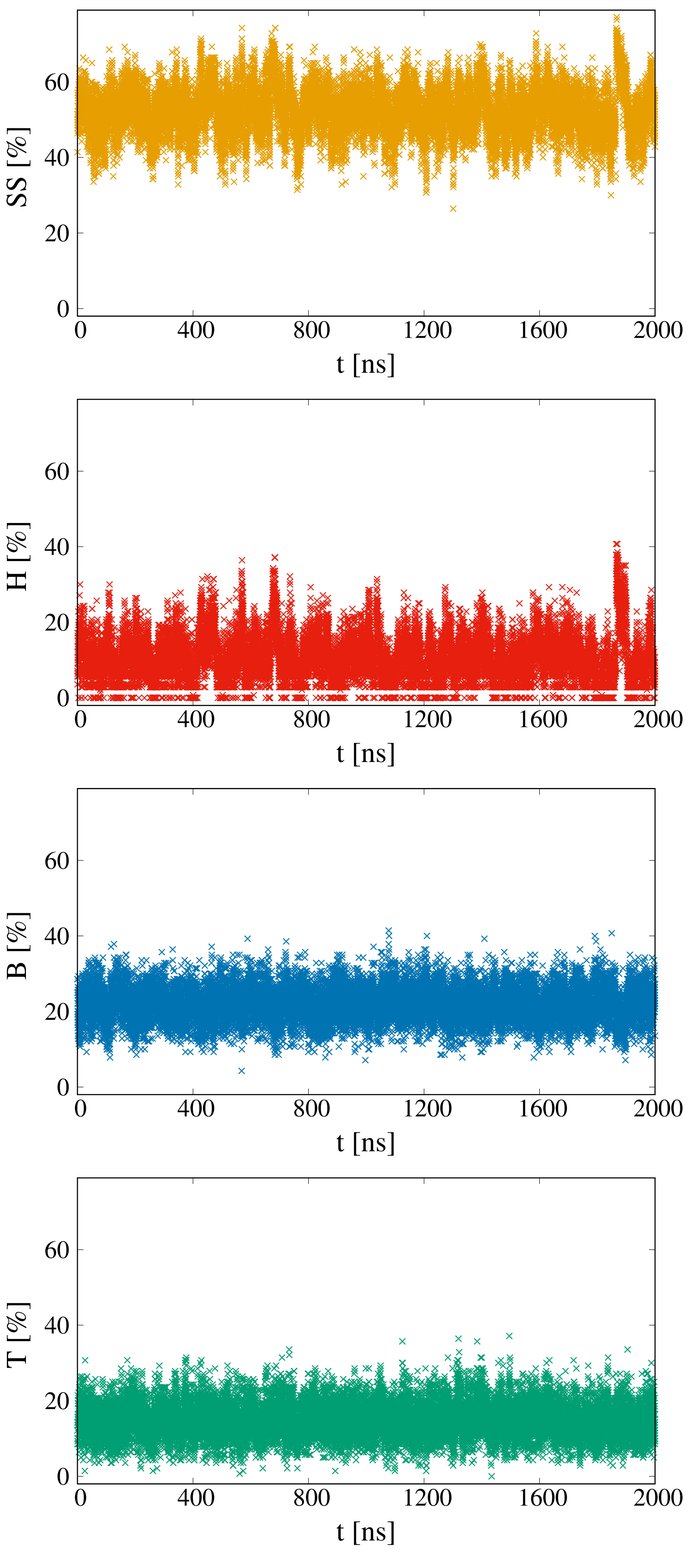
Radius of gyration (AA)



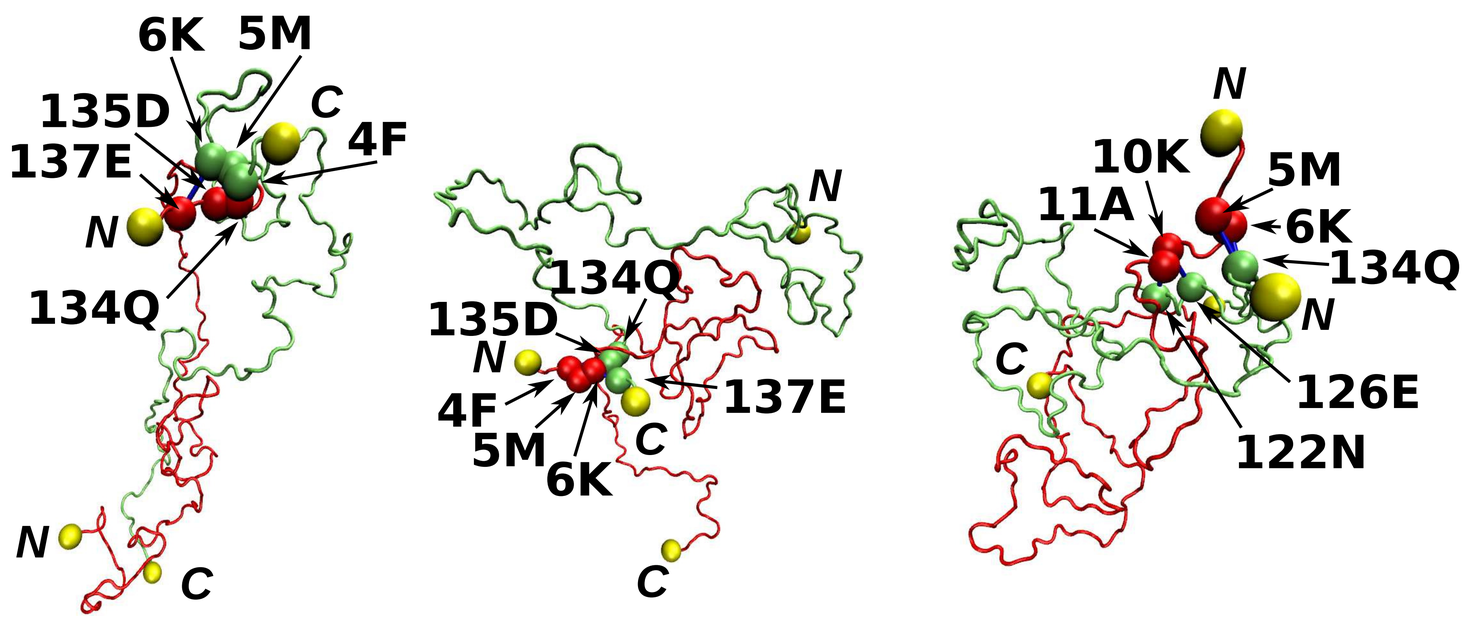
Contact map (CG)



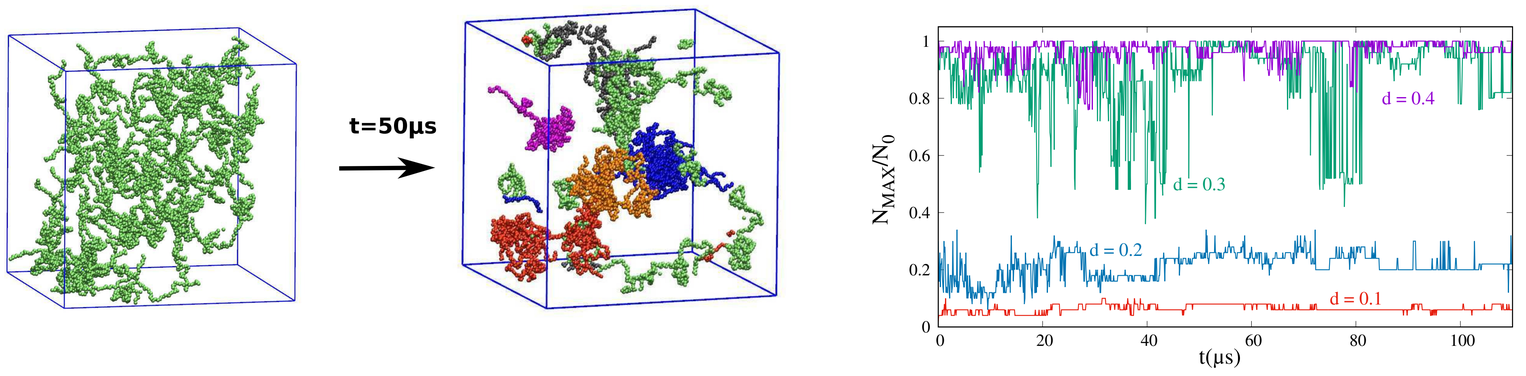
Secondary structures (AA)



Chains aggregation (CG)



Clusterisation (CG)



Conclusion

We have identified groups of amino acid residues that mediate aggregation of α-Synuclein. The aggregation turns out to be caused mainly by electrostatic interactions between the N- and C-terminal regions. In addition, we note that the aggregation is very senstive to changes in protein concentration.

Acknowledgements

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References

[1] M. Chwastyk, M. Cieplak (2020) Conformational Biases of α-Synuclein and Formation of Transient Knots, J. Phys. Chem. B 124 (1), 11-19.

[2] Ł. Mioduszewski, B. Różycki, M. Cieplak, (2020) Pseudo-Improper-Dihedral Model for Intrinsically Disordered Proteins, J. Chem. Theory Comput., 16, 7, 4726-4733.

[3] M. Cieplak, Ł. Mioduszewski, M. Chwastyk, (2022) Contact-Based Analysis of Aggregation of Intrinsically Disordered Proteins. In: M.S. Li, A. Kloczkowski, M. Cieplak, M. Kouza (eds). Computer Simulations of Aggregation of Proteins and Peptides. Methods in Molecular Biology, vol 2340. Humana, New York, NY.

[4] J. Huang, S. Rauscher, G. Nawrocki, T. Ran, M. Feig, B. L. de Groot, H. Grubmueller, A. D. MacKerell, (2017) CHARMM36m: an improved force field for folded and intrinsically disordered proteins. Nature Methods 14, 71-73.