Molecular dynamics simulations of α-Synuclein aggregation

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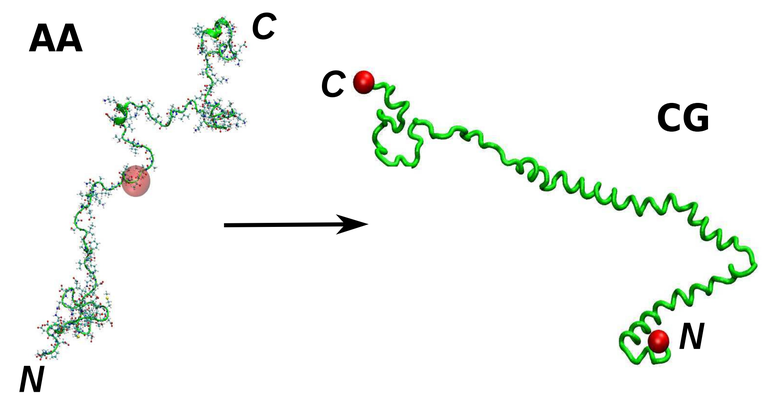
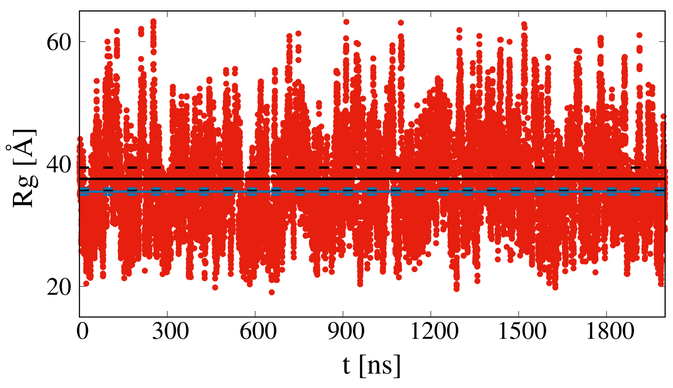
Abstract

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.

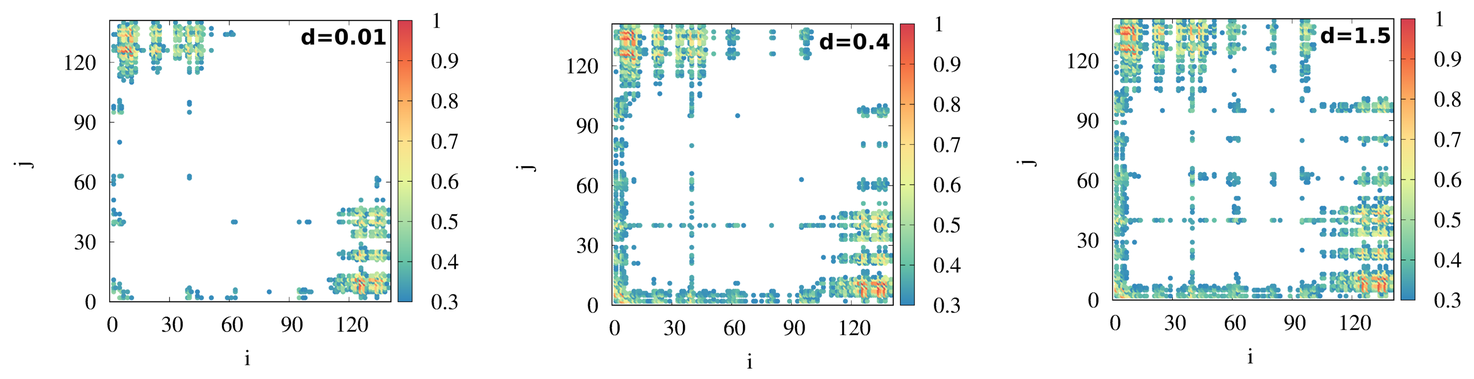
AA→CG



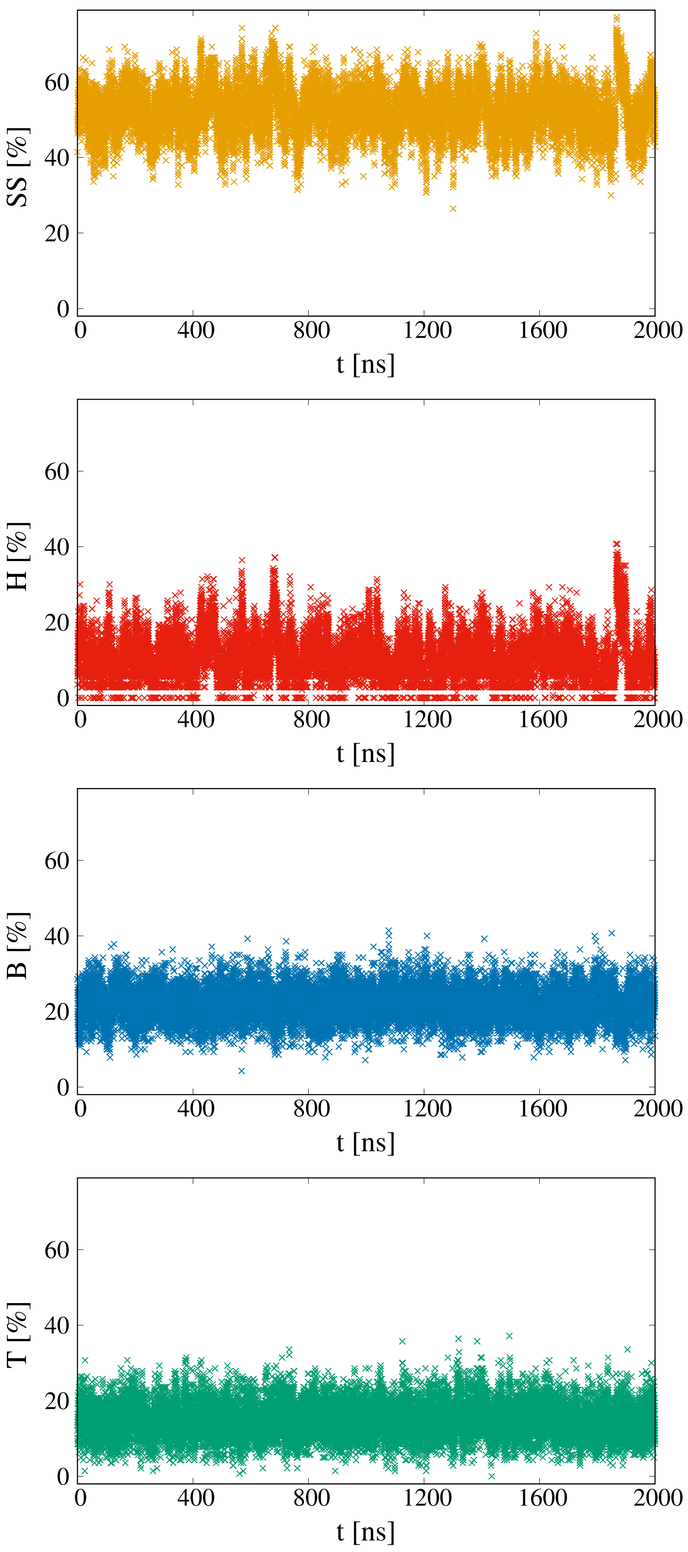
Radius of gyration (AA)



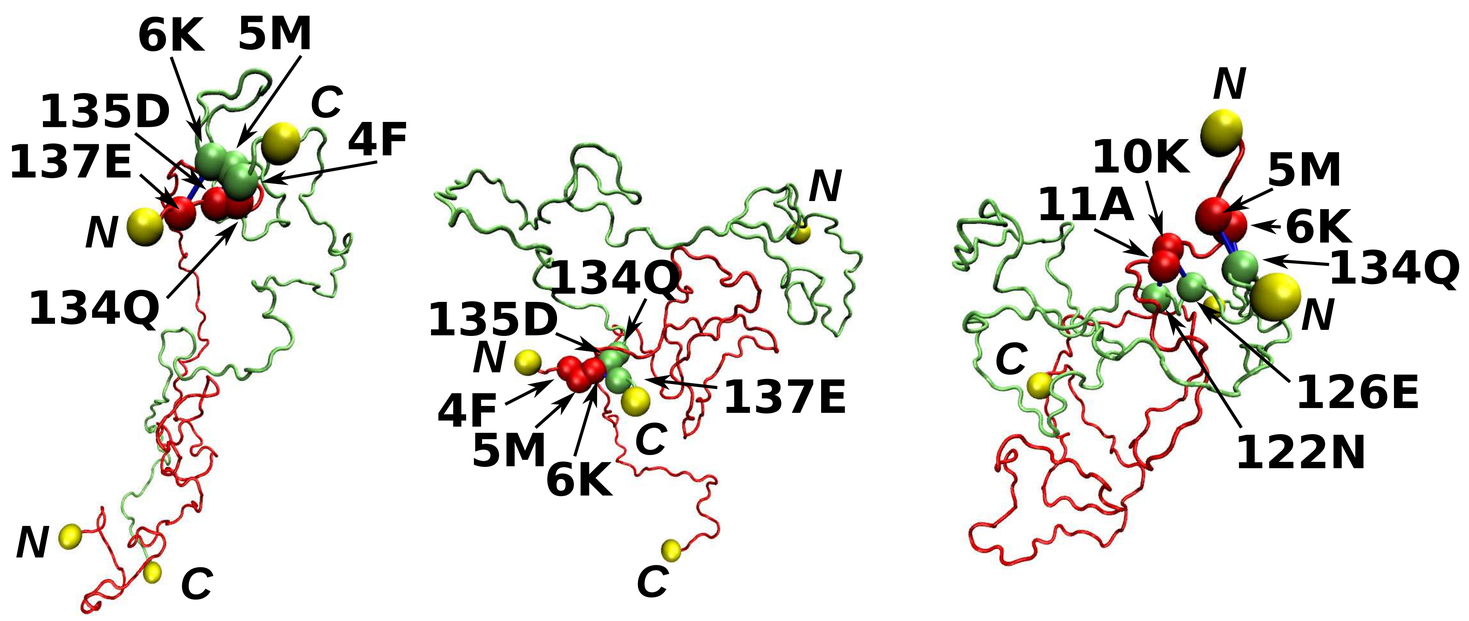
Contact map (CG)



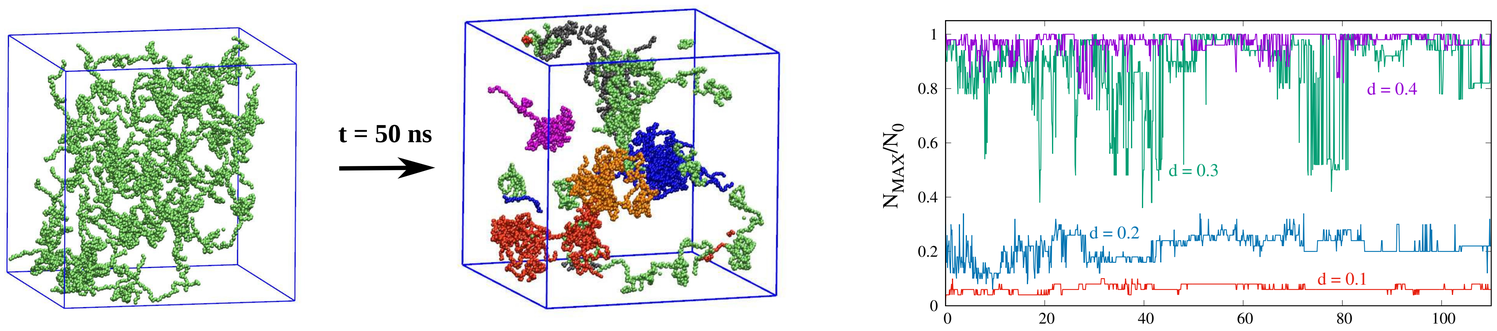
Secondary structures (AA)



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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