Coarse-grained molecular dynamics of intrinsically disordered proteins

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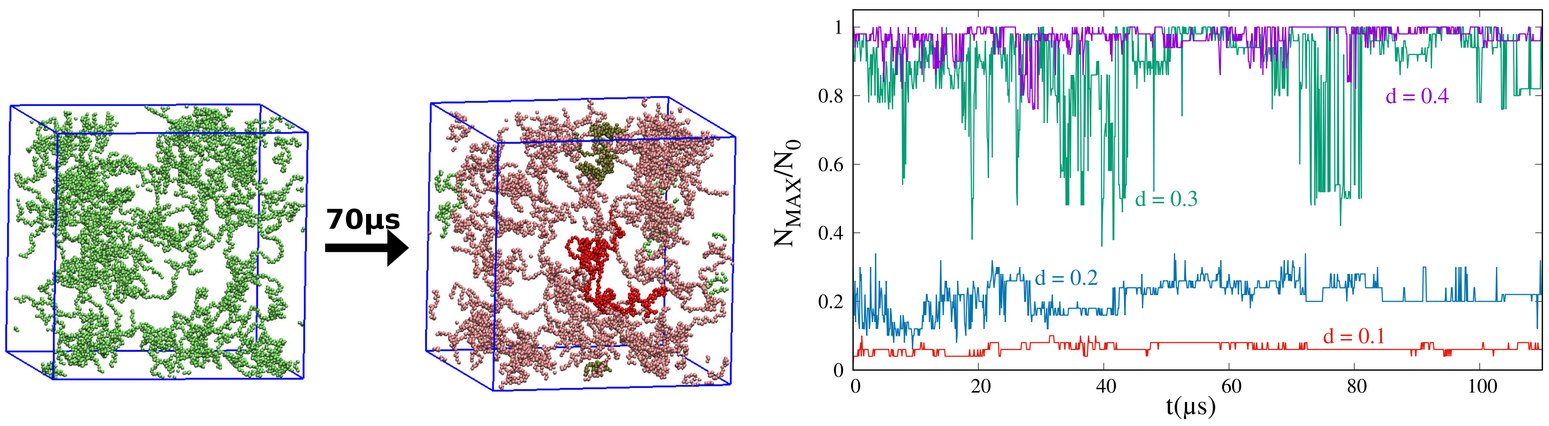
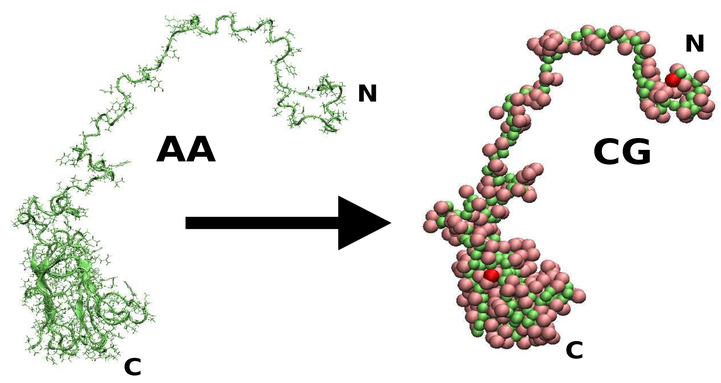
Abstract

We employ molecular dynamics (MD) and coarse-grained (CG) methods to study intrinsically disordered proteins and their assemblies. Firstly, we use the CG pseudo-improper-dihedral model that we have developed recently [1,2] to study α-synuclein in a broad range of concentrations and temperatures. Our simulation results show that α-synuclein assembles into network structures that percolate at sufficient protein concentrations. We discuss the role of particular contacts in the α-synuclein networks, and show that the majority of them are based on electrostatic interactions between the N- and C-termini. We also investigate how the density of α-synuclein clusters depends on protein concentration and temperature. Secondly, we employ the Martini 3 model [3] to characterize conformations of galectin-3, which is mixed-folded protein comprising an intrinsically disordered N-terminal tail and a carbohydrate recognition domain. We follow the methodology of Thomasen et al. [4] to rescale protein-water interactions, and obtain a conformational ensemble fully consistent with data from small angle X-ray scattering experiments [5]. Our simulation results show that galectin-3 exhibits large-scale fluctuations between compact and extended conformations.

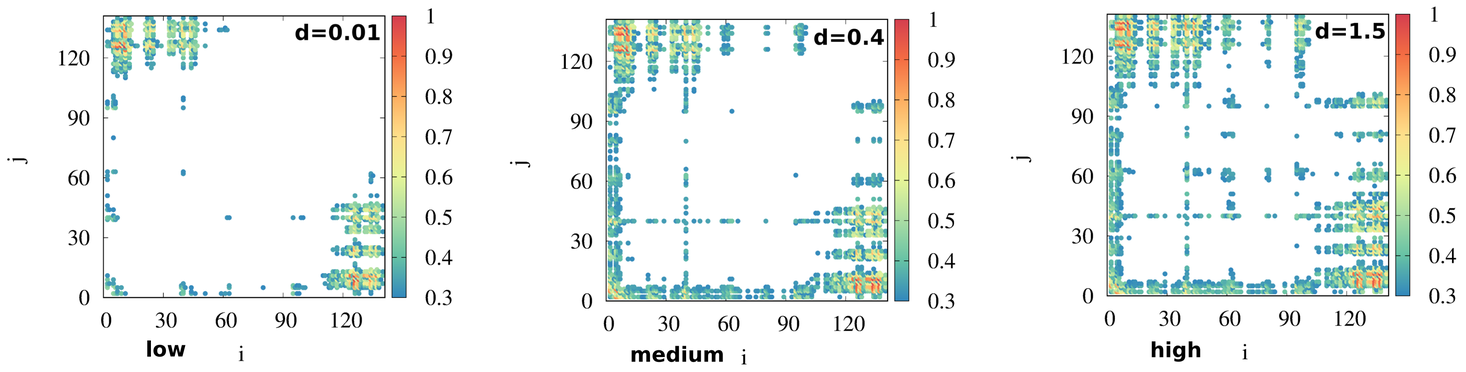
α-syn clusterisation



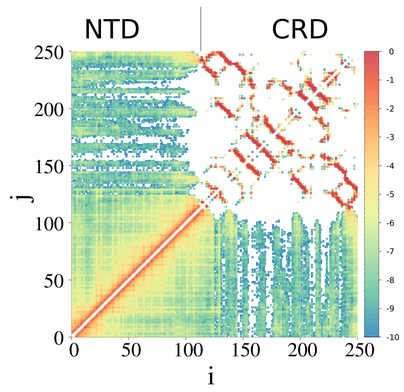
gal-3 AA→CG



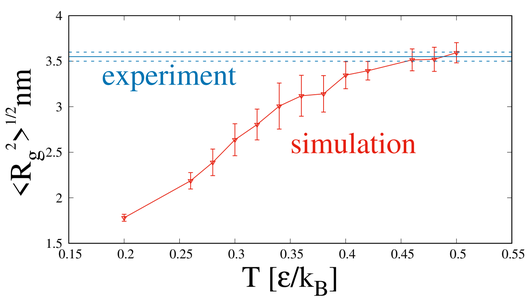
α-syn contact map



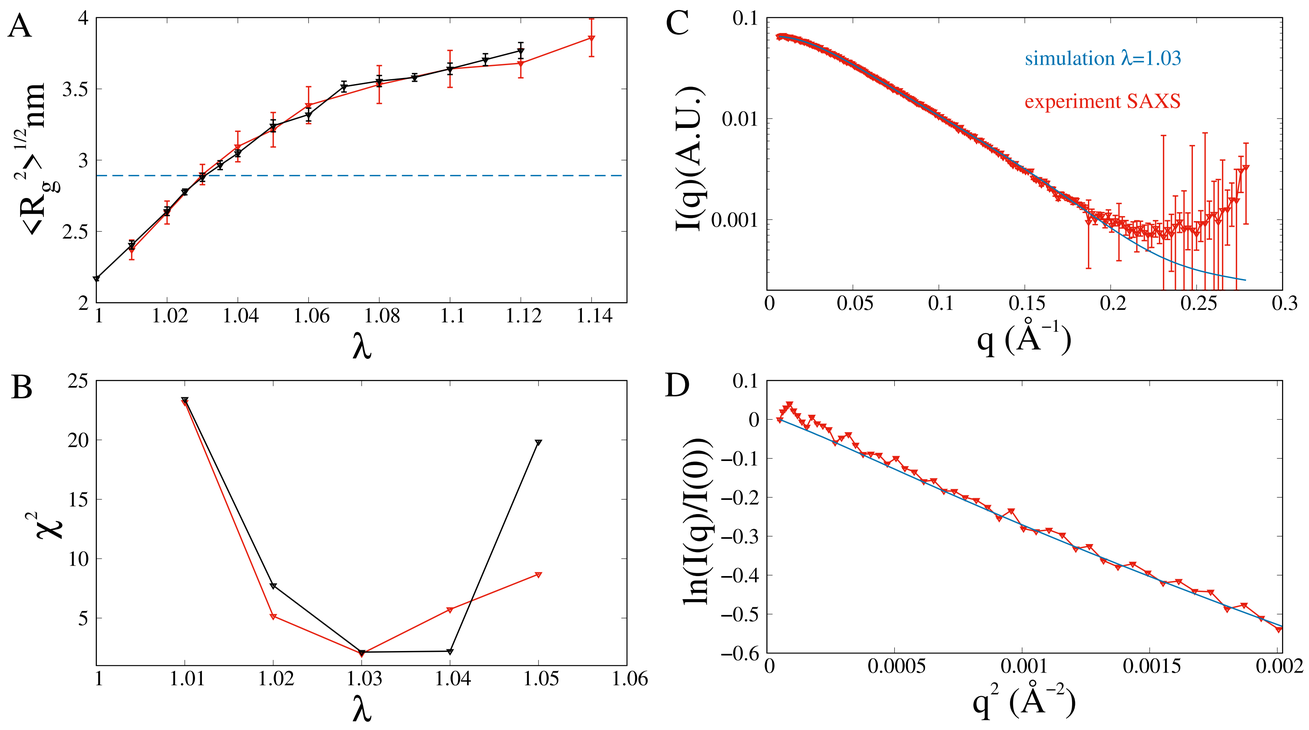
gal-3 contact map



α-syn single peptide



gal-3 comparison to SAXS



Conclusion

We have identifed groups of amino acid residues that mediate aggregation of α-synuclein. The aggregation turns out to be caused mainly by electrostatic interactions. In addition, we note that the aggregation is very senstive to changes in protein concentration. By rescaling interactions between water and galectin-3, we obtain a conformational ensemble consistent with SAXS data. Our simulations show that galectin-3 exhibits large-scale conformational fluctuations.

Acknowledgements

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References

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gal-3 fluctuations