CONFORMATIONAL BIASES OF α-SYNUCLEIN AND FORMATION OF TRANSIENT KNOTS

MATEUSZ CHWASTYK, MAREK CIEPLAK

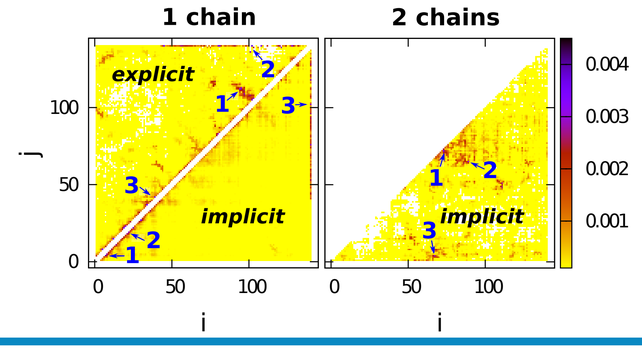
Institute of Physics, Polish Academy of Sciences, Warsaw, Poland

e-mail: chwastyk@ifpan.edu.pl

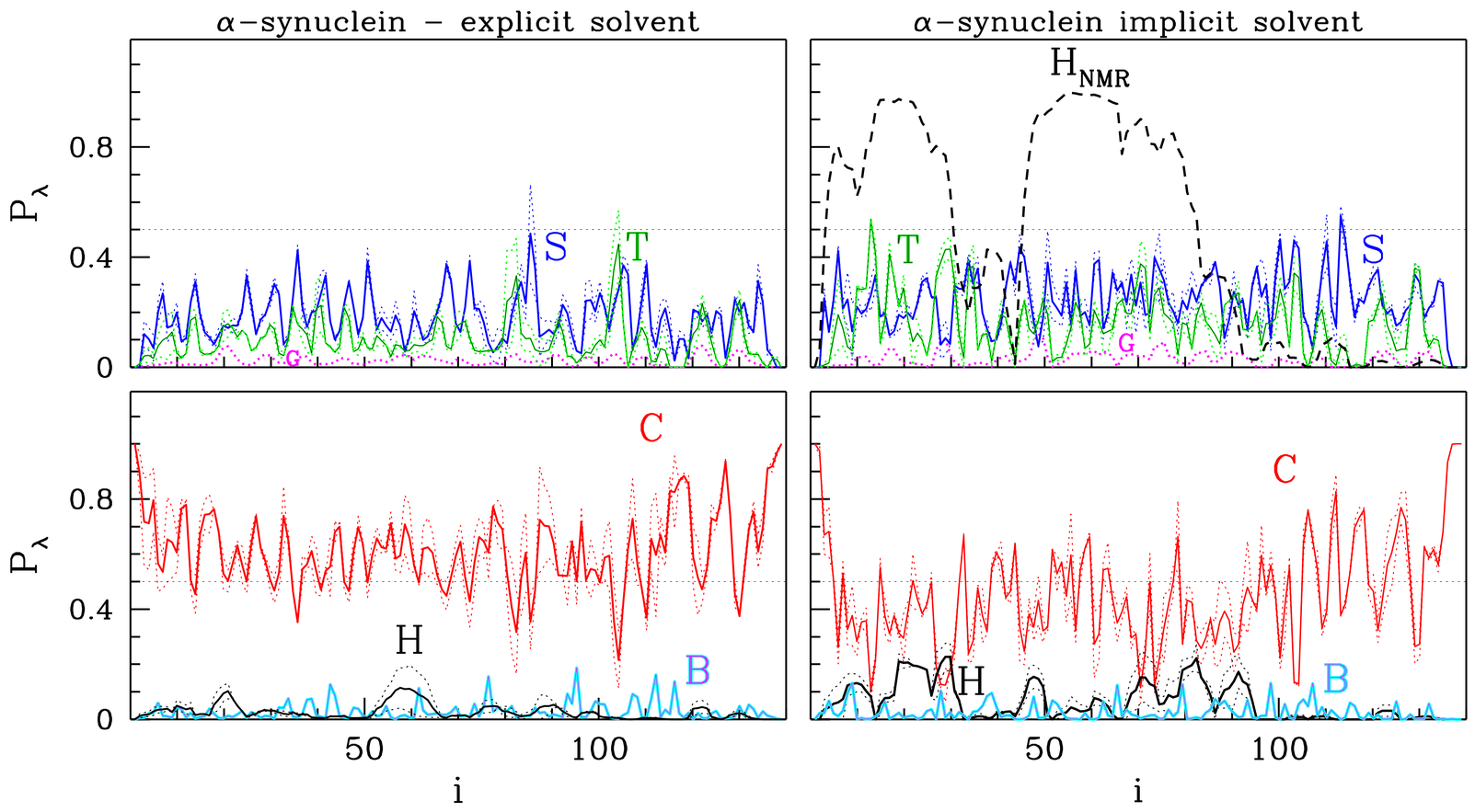
ABSTRACT

We study local conformational biases in the dynamics of α-synuclein by using all-atom simulations with explicit and implicit solvents. The biases are related to the frequency of the specific contact formation. In both approaches, the protein is intrinsically disordered, and its strongest bias is to make bend and turn local structures. The explicit-solvent conformations can be substantially more extended which allows for formation of transient trefoil knots, both deep and shallow, that may last for up to 5 μs. The two-chain self-association events, both short- and long-lived, are dominated by formation of contacts in the central part of the sequence. This part tends to form helices when bound to a micelle.

THE TIME-AVERAGED CM

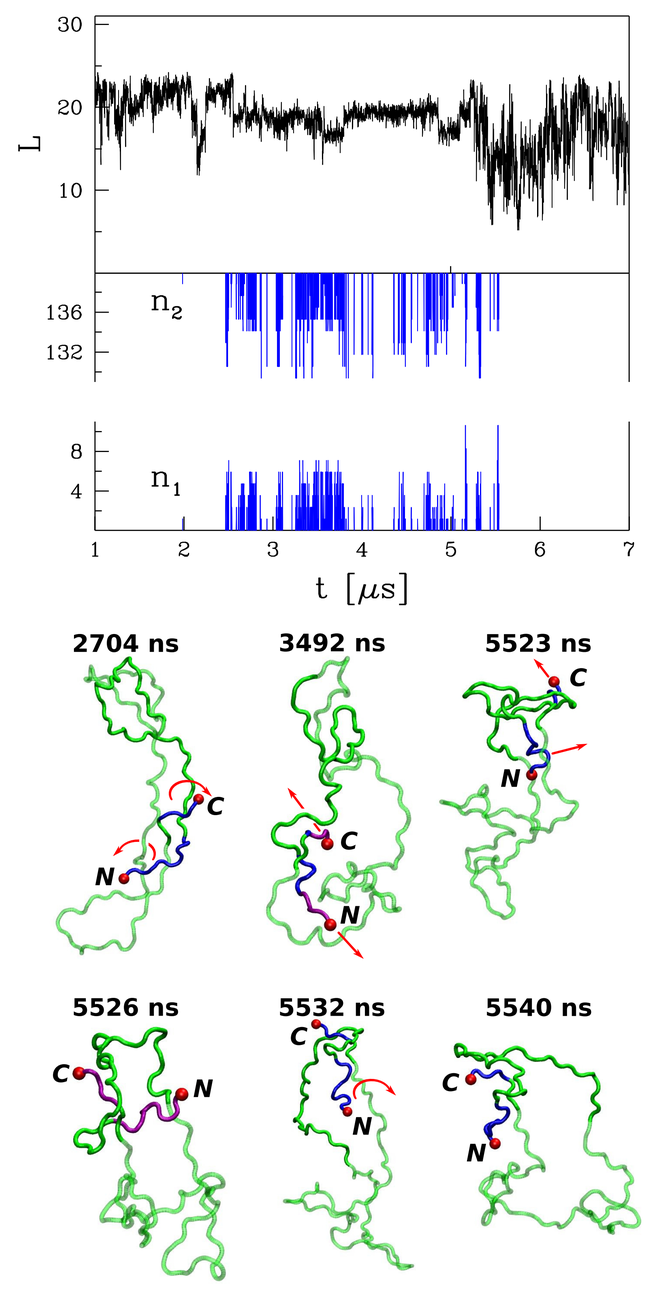


RESULTS



Probabilities P_λ for the monomer of α-synuclein to adopt the local secondary structures λ at residue i. The structures shown are T and S (upper panels; green and blue, respectively) and H, B, G, and C (lower panels; black, purple, magenta, and red, respectively). The dotted lines (not shown for G and B for clarity of the presentation) indicate the size of the error bars. They were obtained by splitting the whole trajectory into two halves. The data points in the left panels have been obtained by using the C22*/TIP4P-4D force field with the explicit solvent. The panels on the right correspond to the NAMD-derived implicit solvent simulations. The black broken line shows the helical content if the starting conformations is the PDB:1XQ8 structure.

THE KNOTTING PROCESS



CONCLUSIONS

- When analyzing the structural propensities, we have found, not surprisingly, that the solvent increases the disorder substantially, which shows as an enhancement in the C-content.
- The types of the transient secondary structures that are detected are the same indicating that for most computational purposes the implicit-solvent approach is sufficient.
- The nature of the solvent may be important when assessing the topological features. This appears to be the case of α-synuclein. This protein supports formation of knots in the explicit-solvent case but not in the implicit-solvent one or there is a reduction in the probability of making a knot.

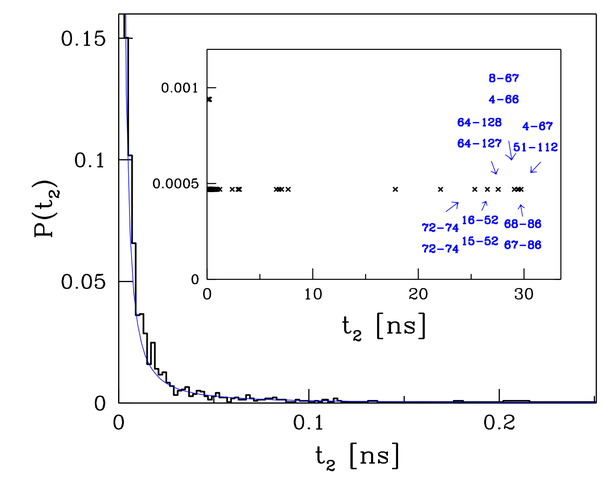
REFERENCES

[1] Chwastyk, M., Cieplak, M. J. Phys. Chem. B 124, 1, 11-19 (2020).

[2] de Aquino, B. R. H., Chwastyk, M., Mioduszewski, Ł., Cieplak, M. Phys. Rev. Res. 2, 013242 (2020).

[3] Cieplak, M., Chwastyk, M., Mioduszewski, Ł., de Aquino, B. R. H. Progress in Mol. Biol. And Translational Sci. 174, 79-103 (2020), ed. V. N. Uversky, book: Dancing Protein Clouds: Intrinsically Disordered Proteins in Health and Diseses, Elsevier.

THE DURATION TIMES



Distribution of the duration times, t_2, of dimers (the solid black line). The thinner blue line corresponds to the power law fit $(t_2/t_{2p})^{-3/2}$ with $t_{2p} = 0.002$ ns.