Detailed atomistic molecular dynamics study of the conformation and diffusion of small circular and linear DNA molecules in dilute solution

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ABSTRACT

Essential to all fundamental life processes, DNA molecules can be found in a multitude of molecular conformations, a prime example being topologically constrained circular conformations, frequently found within the cytoplasm, reaching molecular lengths up to thousands of base pairs. Much smaller DNA circles and, in addition, short linear DNA fragments of molecular length of no more than two hundred base pairs, are also becoming increasingly relevant, in applications such as targeted drug delivery and in establishing novel biomarkers related to circulating tumour-shed DNA (ctDNA). Advances in microfluidics and micro-rheology have offered appreciable new insights into the dynamics of single DNA molecules of both ring and linear architecture. Despite the significant progress, though, inherent experimental difficulties in accurately studying the detailed structure of DNA at an atomistic level persist and pose limitations to the consistent and unambiguous determination of conformational and dynamic properties. In this case, molecular simulations offer therefore an appealing alternative route for the study of these systems at the atomic and molecular scale.

The objective of the work presented here is to demonstrate the use of molecular simulations as a tool for the elucidation of the structural and dynamic properties of solvated linear and circular DNA molecules, and their dependence on parameters such as the concentration and their molecular length. Detailed atomistic molecular dynamics (MD) simulations of dilute aqueous solutions of short DNA circles (also called minicircles) and of short linear DNA fragments of similar length and base sequences are performed. Last generation force fields of the AMBER family have been implemented [1] and the resulting MD trajectories from relatively long simulations are thoroughly analyzed for the calculation of local conformational properties and (segmental and terminal) dynamics. In the case of linear DNA fragments, the qualitative effect of the molecular length increase on the onset of a rigid-rod to semi-flexible chain conformation is observed well below the experimentally inferred persistence length limit of 50nm (~150 base pairs). The rotational and translational components of the diffusion coefficient of linear DNA fragments are also calculated and very good agreement is observed compared to relevant experimental data at the limit of very dilute concentrations, as well as to theoretical models developed for rod-like molecules.

REFERENCES

[1] Ivani I, Dans P.D., Noy A., et al. 2016. *Nature Methods*, **13**(1):55-61.