Asociación Argentina
de Mecánica Computacional

Mecánica Computacional Vol XL, págs. 867-867 (resumen)
F.A. Avid, L.C. Bessone, P. Gamazo, J.J. Penco, M.A. Pucheta, M.A. Storti (Eds.)
Concordia, 6-9 Noviembre 2023

MULTISCALE SIMULATION OF DNA CRYSTALS

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Keywords: Computational Chemistry, Quantum Mechanics, Molecular Mechanics, Crowded systems.

Abstract. Macromolecular crowding is an important factor that influences the behavior of biomolecules in cellular environments and their stability and folding capability in new nano-materials. Molecular simulations by means of atomistic Molecular Dynamics (MD) strongly complement experiments (NMR, X-ray crystallography, CryoEM) in elucidating the structure and dynamics of molecules. However, until recently, these simulations were restricted in the case of DNA to single molecules of small sizes immersed in boxes with explicit solvent. In such systems, timescales of several dozens of microseconds are typically reached. These spatial/temporal limitations are more critical when simulating DNA crystals, where multiple DNA molecules are packed together generating strongly crowded conditions as in the cellular nucleus or new Origami DNA-based materials. Since crystallographic structures have been historically used as the golden standard to compare and validate MD force-fields, crystal simulations were being attempted for long time but with little success. Given recent advances in computer speed, MD algorithms, and force-fields, crystal simulations of more realistic systems have begun to emerge. Nevertheless, in the latest and most extensive study of DNA crystal simulations published in 2015, the authors concluded that the integrity of the crystal lattice was slowly degraded in MD simulations, disrupting the crystal structure in the microsecond timescale. With the help of millions of CPU hours and our new force-field (derived from QM calculations) for the simulation of DNA (PARMBSC1), we were finally able to obtain stable crystal simulations, expanding the actual limits of the field. This allowed us to understand with unprecedented level of detail the nature of the intermolecular forces that participate in the formation of crystals in various symmetry groups and under different ionic environments, and to decipher the crucial role that chemical additives (small molecules or specific cations that are added experimentally to obtain crystals) play in the stability of crowded crystal structures.