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Thermodynamics and Kinetics of DNA in Hydrophilic Nanopores

Enhanced sampling techniques spanning a sub-μs timescale reveal that, under the presence of an electric field acting upon single-walled carbon nanotubes (SWCNTs), complete encapsulation of a Dickerson B-DNA dodecamer[1] occurs with fast kinetics (≤ 4.3 ns) and is thermodynamically spontaneous, as demonstrated by a ≈ 40 kJ/mol decrease in the system's Gibbs free-energy.[2] Encapsulation is driven by strong electrostatic attractions between the nucleic acid and the solid, which in the early stages of confinement accounts for at least 80 % of the total interaction energy. The encapsulated DNA end-to-end length is similar to that of the canonical B-form (*ca.* 3.8 nm) in the two solid topologies under consideration, (51, 0) and (40, 0); however, consecutive free-energy minima occur in the thermodynamical landscapes, located within the endohedral volume, and corresponding to a 0.25 – 0.5 nm deviation away from the canonical form (Fig. 1). Very interestingly, and contrary to what happens with the (40, 0) hydrophobic analogue, the existence of an electric field on the walls induces biomolecular confinement. Furthermore, and by contrast with the larger (51,0) topology, the ϕ_2 phase space spans a broader range now including non-stable (transient) DNA forms with highly compressed double-strand lengths (ϕ_2 < 3 nm); these observations are corroborated by independent atomically detailed techniques.

The effects exerted by the confining solid upon the nucleic acid exhibit a marked dependence on nanopore diameter, and this is attributed to entropic reasons arising from free-volume considerations. Nonetheless, DNA maintains translational mobility inside the nanotube and is able to translocate within a cylindrical volume comprised between *termini,* according to a (*x*, *y*, *z*) anisotropic self-diffusion mechanism that also involves molecular translation caused by a self-rotation of the double-strand axis.[3] The nanoscopic picture obtained for the single-strand individual axes *ensembles* (Fig. 2) indicate that the biomolecule favours positioning in close contact with the nanopore walls in the (51, 0) topology, in contrast with what is observed for the (40, 0) nanotube where the DNA's c.o.m. is preferentially located along the pore central axis, (*x*, *y*) ≈ (0,0).

Precise physiological conditions (310 K, [NaCl]=134 mM) allow the extrapolation of results to *in vivo* systems and constitute a novel and thorough contribution to nanotube technology in the areas of nucleic acid encapsulation/delivery and personalized therapeutics.

References

[1] H.R Drew et al, *Proc. Nat. Acad. Sci.* 78 (1981) 2179

[2] F.J.A.L. Cruz, J.P.B. Mota *J. Phys. Chem. C* 120 (2016) 20357

[3] F.J.A.L. Cruz, J.J. de Pablo, J.P.B. Mota *Biochem. Eng. J.* 104 (2015) 41

Figures

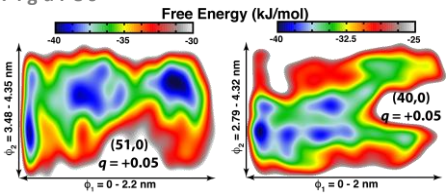

Figure 1: Gibbs free-energy maps of encapsulated DNA. ϕ_1 is the distance between centres of mass of DNA and the SWCNT, projected along the nanopore's main axis (*z*), and ϕ_2 corresponds to the DNA end-to-end length measured between opposite (GC) *termini*. Low-lying free-energy valleys, evidenced as dark blue regions, are always distributed along the nanopore internal volume, ϕ_1 < 2 nm, and linked amongst themselves via a thermodynamical highway with a free-energy penalty ≤ 5 kJ/mol.

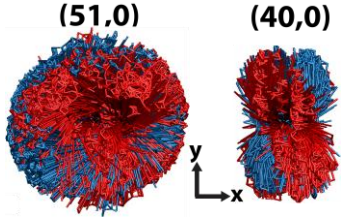

Figure 2: ***Ensemble*** **space of single-strand individual axes for confined DNA.** Each strand individual axis runs from a terminal Phosphorus atom to the last one located on the same corresponding strand, thus each strand axis is represented by a different colour: strand A (blue) and strand B (red). Note that the carbon nanotubes are parallel aligned along the z-axis with diameters $D^{(51,0)}$ = 4 nm and $D^{(40,0)}$ = 3 nm.