Modelling the DNA G-quadruplex unfolding

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The G-quadruplexes (G4) are non-canonical secondary DNA and RNA structures composed of four guanine basis bonded each other in quartets forming planes eventually piled in two, three or four layers. They are present both in vivo and in vitro cultures, and have important role in telomere end-protection, chromosome stability, aging control. Their folding patterns and structures are also found in eukaryotic promoter regions of oncogenes, making them increasingly recognized among chemists and biologists due to their potential applications in Nanomedicine as therapeutic targets in cancer treatments.

In the last years, single-molecule techniques have attracted much attention between the scientific community and a number of groups have extensively used them to analyze the mechano-chemical behavior of DNA and RNA chains. Optical and magnetic tweezers, as well as Atomic Force Microscopies, are employed to characterize not only the mechanical stability and unfolding dynamics of G-quadruplexes, but also to unveil structural intermediates not accessible to ensemble-average techniques due to their relatively low occurrence.

The stability of the G-quadruplex structure is related, among the others, to the specific G-quadruplex conformation, and the presence of a cation between each of the G4 planes. Although an increasing number experiments have been conducted with the purpose to finely analyze rupture profiles in single force-extension curves, the theoretical predictions remain difficult, due essentially to the long computational time required by atomistic simulations, which, moreover, use parameter values –specifically the velocity at which one extreme of the quadruplex is pulled to induce the rupture– orders of magnitude far away from the experimental values.

With the aim to bridge the gap between experiment and theoretical expectations, we build a mesoscopic physical model of the G-quadruplex structure with a reduced number of degrees of freedom and a few effective potentials that permits to study the mechanical unfolding in a wider interval of time scales than those allowed in all-atom simulations, in particular under different pulling velocities. The subsequent analysis on the light of the most recent stochastic theories for rupture force –as those of Bell-Evans-Richie, Evans-Hummer-Szabo, and Friddle-Noy-DeYoreo– permit the estimations of the potential barriers and positions that characterize the energy landscape of the unfolding process.

In this communication the model will be presented together with its validation against the results of an unfolding experiment on RNA G-quadruplex pulled by an optical tweezer.

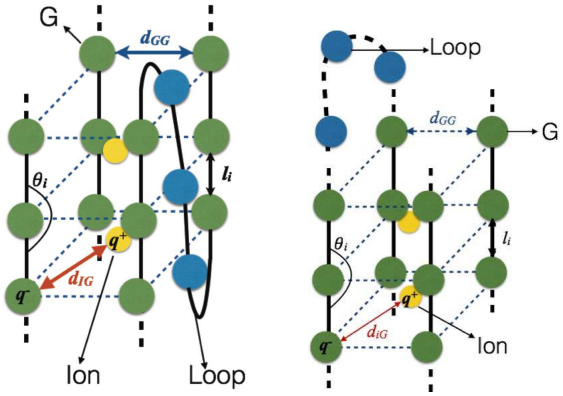

Fig. 1. Mesoscopic model for the G-quadruplex. Scheme of a parallel G4 assembly where each nucleotide is represented by a single bead. The G-tetrad plane are twisted between each other (not represented). (Left) Parallel configuration. (Right) Anti-parallel configuration.

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