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A mesoscopic model for the DNA G-quadruplex stability analysis

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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 a quartets forming piled planes. They have been found both in vivo and in vitro cultures, and have important role in telomere end-protection, and chromosome stability. 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 used it extensively to analyze the mechano-chemical behavior of DNA and RNA. 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 structural G-quadruplex conformation, and the presence of a cation between each G4 planes.
To date, many experiments have been conducted, which want to finely analyze rupture profiles in single force-extension curves.
Although the increasing number of experiments on the subject, the theoretical predictions remain difficult, due essentially to the long computational time required by atomistic simulations, which, moreover, use parameter values (for example the velocity at which one extreme of the quadruplex is pulled to induce the rupture) some 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 effective potential 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, Dudko and Yoreo - permit the estimations of the potential barriers and positions that characterize the energy landscape of the unfolding process.

Some validation of the model with the results of experiments will be presented.

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