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First-principles Calculation Of DNA Looping In Tethered Particle Experiments

PHILIP NELSON, University of Pennsylvania

We show how to calculate the probability of DNA loop formation mediated by regulatory proteins such as Lac repressor, using a mathematical model of DNA elasticity. Our approach has new features enabling us to compute quantities directly observable in Tethered Particle Motion (TPM) experiments; e.g. it accounts for all the entropic forces present in such experiments. Our model has no free parameters; it characterizes DNA elasticity using information obtained in other kinds of experiments. It can compute both the "looping J factor" (or equivalently, looping free energy) for various DNA construct geometries and repressor concentrations, as well as the detailed probability density function of bead excursions. We also show how to extract the same quantities from recent experimental data on tethered particle motion, and compare to our model's predictions. In particular, we present a new method to correct observed data for finite camera shutter time. The model successfully reproduces the detailed distributions of bead excursion, including their surprising three-peak structure, without any fit parameters and without invoking any alternative conformation of the repressor tetramer. However, for short DNA loops (around 95 bp) the experiments show more looping than is predicted by the linear-elasticity model, echoing other recent experimental results. Because the experiments we study are done in vitro, this anomalously high looping cannot be rationalized as resulting from the presence of DNA-bending proteins or other cellular machinery. We also show that it is unlikely to be the result of a hypothetical "open" conformation of the repressor.

Ref: KB Towles et al, accepted for publication in Physical Biology.