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Mechanics of Protein-Mediated DNA Looping

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The formation of looped DNA-protein complexes in which a protein or protein assembly binds to multiple distant operator sites on the DNA is a common feature for many regulatory schemes on the transcriptional level. In a living cell, a multitude of mechanical forces and constraints act on these complexes, and it is imperative to understand their effects on biological function. For this aim, we study the lactose repressor as a model system for protein-mediated DNA looping in single-molecule experiments. Using a novel axial constant-force optical trapping scheme that allows us to manipulate sub-micron DNA fragments with well-controlled forces down to the 10 fN range, we show that mechanical tension in the substrate DNA of hundred femtonewton is sufficient to disrupt the loop formation process, which suggests that such mechanical tension may provide a mechanical pathway to controlling gene expression in vivo. From the force sensitivity of the loop formation process, we can also infer the topology of the looped complex; in our case an antiparallel conformation. In addition, we will present new tethered-particle microscopy data that shows lifetimes of the looped complexes that are two to three orders of magnitude shorter than those measured in biochemical competition assays and discuss possible interpretations, including the suggestion that operator binding of the lactose repressor tetramer leads to a destabilization of the dimer-dimer interface and that thus the loop breakdown process is mostly a dissociation of the tetramer into two dimers, instead, as widely assumed, an unbinding of the tetramer from the DNA.