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RESEARCH ARTICLE

Sensing DNA–DNA as Nanosensor: A Perspective Towards Nanobiotechnology

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Based on modern single molecule techniques, we devise a number of possible experimental setups to probe local properties of DNA such as the presence of DNA-knots, loops or folds, or to obtain information on the DNA-sequence. Similarly, DNA may be used as a local sensor. Employing single molecule fluorescence methods, we propose to make use of the physics of DNA denaturation nanoregions to find out about the solvent conditions such as ionic strength, presence of binding proteins, etc. By measuring dynamical quantities in particular, rather sensitive nanoprobes may be constructed with contemporary instruments.

Keywords: DNA, DNA Breathing, Single Molecule Spectroscopy, Nanosensors, Fluorescence Correlation Spectroscopy, Fluorescence Resonance Energy Transfer.

1. INTRODUCTION

Single molecule techniques allowing both the manipulation and probing of single molecules, have come of age. Optical tweezers, atomic force microscopes, or single molecule tracking and optical detection methods (for instance, fluorescence correlation spectroscopy, FCS, or fluorescence (Förster) resonance energy transfer, FRET) have become standard methods in laboratories. By means of these techniques having access to scales in the nanometre domain allows us to obtain quantitative information about the physical properties of molecules without being masked by the inevitable ensemble averaging inherent in bulk measurements. Even though typical single molecule data are more noisy than bulk signals, the gain of individual molecular behaviour by far outweighs this disadvantage. In certain cases, single molecule experiments can reveal information, that is not accessible to bulk measurements, for instance, the recent experiments on the characteristics of single-stranded DNA-binding proteins,[1] or the measurements of the passage of single biopolymers through nanopores.[2,3] Moreover, one may even extract information from the single molecule noise; for example, on the nature of such known phenomena as Brownian motion.[4] This progress is essential to recent advances in a number of fields like biological and soft matter physics, or nanobiotechnology. The small system sizes also make it possible to test fundamental physical theories such as the Jarzinsky relation connecting measurements of the nonequilibrium work needed, e.g., to stretch an RNA segment,[5] to the difference in the corresponding thermodynamic potential;[6] or the entropy production along single trajectories exposed to stochastic forces.[7]

In what follows, we devise a number of potential experimental setups probing on scales down to the nanolevel, both the physical behaviour of DNA itself as well as different ways to employ DNA as a nanosensor. A certain emphasis is put on methods where theoretical models are available so the physical parameters of the DNA and its surroundings may be *quantitatively* extracted from experimental data. These setups should be well within reach of the state of the art techniques and may be used to obtain important new information on DNA, or prompt new technologies based on DNA. As the DNA molecule is the main ingredient for our exposition, we start with a primer on the physical properties of DNA, before embarking for setups to probe (some of) these properties on the single molecule level and propose several possibilities to use DNA as a sensor.

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2. DNA-PHYSICS

DNA has a number of remarkable properties. Made up of two chemically very stable individual molecules that wind around each other to produce the double-helix, it carries, embedded in its core, the entire genetic code of an organism. Modern gene technology is able to produce custom-designed DNA molecules with any given sequence. There exists proteins ("biological glue") by which DNA can be attached to microbeads, that, in turn, can be manipulated by optical tweezers or microbeads. These properties make DNA an ideal object for single molecule experiments.

DNA consists of a backbone of sugar and phosphate molecules suspending the base-pairs in its core, see Figure 1. This ladder structure in 3D forms the spiral staircase structure (see Fig. 1 on the right) originally predicted by Watson and Crick.[8] The Watson-Crick double-helix, or, more precisely, its B-form, is the thermodynamically stable configuration of a DNA molecule under physiological and a large range of *in vitro* conditions. This stability is effected first by Watson-Crick H-bonding, that is essential for the specificity of base-pairing ("key-lock principle"). Base-pairing therefore guarantees the high level of fidelity during replication and transcription. The second, major, contribution to DNA-helix stability comes from base-stacking between neighbouring base-pairs, through hydrophobic interactions between the planar aromatic bases, that overlap geometrically and electronically.[9, 10]

The relevant length scales of DNA span several orders of magnitude.[10–13] The distance between neighbouring base-pairs is approximately 3.4 Å, while the hard core diameter of DNA is 2 nm. One full turn of the double-helix is made up of 10.5 base-pairs. The persistence length, i.e., the distance over which the tangent–tangent correlations decay, is of the order of 50 nm (340 base-pairs), more than an order of magnitude larger than the diameter. Locally, double-stranded DNA (dsDNA) therefore appears stiff. In contrast, single-stranded DNA (ssDNA) has a persistence length of a few nm, depending on solvent conditions and sequence. Finally, the overall length of naturally occurring DNA ranges from several μm in viruses, over some mm in bacteria, to tens of centimetres in higher organisms. The South American lungfish hosts 35 m of DNA per cell.[10]

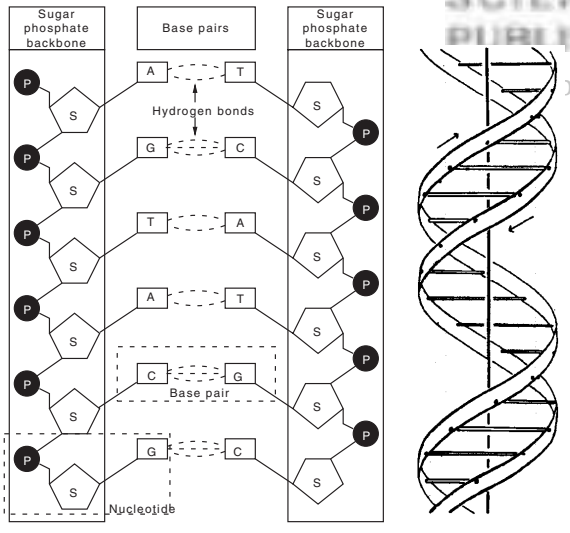

Fig. 1. Left: Schematic view of the chemical structure of the DNA molecule, showing the bases suspended by the outer Sugar-Phosphate scaffold. Right: Reproduction of the original graph of the proposed double-helical structure of DNA. Reprinted with permission from [8], J. D. Watson and F. H. C. Crick, *Nature* 171, 737 (**1953**). © 1953, Nature.

An important feature of dsDNA is the ease with which its component chains can come apart and rejoin, without damaging the chemical structure of the two daughter-strands. This unzipping of the H-bonds between base-pairs is crucial to many physiological processes such as replication and transcription. Classically, the melting and reannealing behaviour of DNA has been studied in solution *in vitro* by increasing the temperature, or by titration with acid or alkali. Such equilibrium measurements are described by the Zimm-Poland-Scheraga model based on the following physical parameters of DNA:[14–17] (i) the statistical weight $u = \exp(-\beta\epsilon)$ (with $\beta = 1/(k_B T)$, where k_B is the Boltzmann constant, and T the temperature), associated with the free energy ϵ of breaking a single base-pair. Note that ϵ is smaller for AT than for GC bonds.[9, 10, 18] u also depends on ambient salt concentration, applied torques and forces; (ii) the non-universal prefactor $\sigma_0 \ll 1$ that measures the loop initiation energy associated with breaking the stacking interactions;[15, 16, 18, 19] (iii) and the loop closure exponent c that stems from the entropy loss due to the closed loop structure of the ssDNA bubble, compare.[15, 17, 18]

While the double-helix is the thermodynamically stable configuration of the DNA molecule below the melting temperature (or at non-denaturing pH), even at physiological conditions there exist local denaturation zones, so-called DNA-bubbles, predominantly in AT-rich regions of the genome.[15, 16] A DNA-bubble is a dynamical unit, whose size varies by thermally activated zipping and unzipping of successive base-pairs at the two zipper forks where the ssDNA-bubble meets the intact double-helix. This DNA-breathing is possible due to the fact that on bubble formation the enthalpy cost and entropy gain, despite each being significant amounts in terms of $k_B T$, almost cancel and the unzipping of a base-pair involves a free energy cost of the order of a $k_B T$.

We will in the subsequent sections discuss different possible experimental setups that allow for the measurement of the properties of DNA and its surroundings.

3. SENSING DNA: NANO-SETUPS MEASURING THE PHYSICAL PROPERTIES OF THE MOLECULE OF LIFE AND ITS ENVIRONMENT

In this section, we propose a number of arrangements by which physiological processes and the fundamental physical properties of DNA can be monitored. Apart from

measuring the characteristics of DNA itself, micro- and nanosetups are suggested for obtaining information about its topological state or the solution conditions.

3.1. Melting and Monitoring a Nanoregion of DNA

The local stability of DNA can be probed as sketched in Figure 2. Here, a linear stretch of DNA is held in place by two microbeads, and a local denaturation zone is monitored by fluorescence of a fluorophore at the bubble position, for instance, by fluorescence correlation spectroscopy.[20] Recent developments in the theoretical description of DNA breathing dynamics[21, 22, 24, 25] relate measurable dynamical quantities to the Zimm-Poland-Scheraga physical parameters discussed in the previous section, as well as to the properties of the surroundings.[21, 22] In particular the fluorescence correlation could be quantified and shown to depend on (i) the local statistical weights u, i.e., temperature, salt concentration, twist, as well as the local DNA sequence; (ii) the bubble initiation parameter σ_0; (iii) the loop exponent c; (iv) the concentration and binding constants of single-stranded binding proteins; (iv) the rate constant for unzipping and unbinding, respectively. In addition, the presence of double-stranded binding proteins could be detected through the relaxation time spectrum.[25]

Alternatively to probing spontaneous DNA-breathing due to thermal fluctuations, a bubble can also be induced by mechanical stretching of the DNA, and then the fluorescence traces along the DNA could successively reveal regions of high and low AT-content. It could also be measured how occasional multiple bubble states develop, for instance, how bubbles coalesce across a GC-rich barrier between two AT-rich bubble domains. Finally, bubbles might be induced at a selected location observed by microscope through a strong laser beam or with confocal light of a different wavelength. This technique may in fact be employed to DNA-sequencing, distinguishing AT-rich regions from GC-rich, analogously to bulk melting experiments on the basis of which coding regions of the DNA could be identified.[26]

We also mention a potential measurement of DNA-mechanics based on the different persistence length between dsDNA and ssDNA connected to this setup. Namely, by inducing a larger region of DNA to denature, one reduces the local stiffness, and by this also the average resistance of the DNA to longitudinal tension. A change in temperature or the presence of a denaturing agent should, in principle, be visible through an increase of the extension between the two microbeads.

3.2. Denaturation Beacon as Sensor

Unclamped DNA preferentially opens up at the ends (see Fig. 3), as this does not involve the typical energy barrier for bubble initiation in the middle of the DNA.[15] Having a DNA construct that is rich in AT at one end and rich in GC at the other end (or that has a closed loop at that end) could then serve as a molecular beacon sensing the solvent conditions in small volumes, for example, in gene microarrays. The dynamics of an ionic fluorophore-quencher pair depends on the statistical weight u, and one would thereby have a rather sensitive probe for measuring (i) the presence and concentrations of (multivalent) ions in solution; (ii) the presence of single-stranded binding proteins; or (iii) local temperature gradients. A detailed study of the dynamics of such a denaturation beacon and its dependence on the physical parameters has just been reported.[23]

3.3. Monitoring Replication and Transcription Progress

Figure 4 displays a DNA-molecule that is being replicated by action of DNA helicase and polymerase.[10, 27] The DNA molecule is lined with fluorophore-quencher pairs. Close together in intact double-strand, fluorescence is quenched; once separated during the replication or transcription processes, fluorescence occurs.[28] The position of the replication fork along the DNA can be monitored similar to a radar trace either by microscope or digital camera. Using dyes that bleach out on an appropriate timescale, the observed fluorescence occurs only in close vicinity of the helicase molecule. To enable a reference

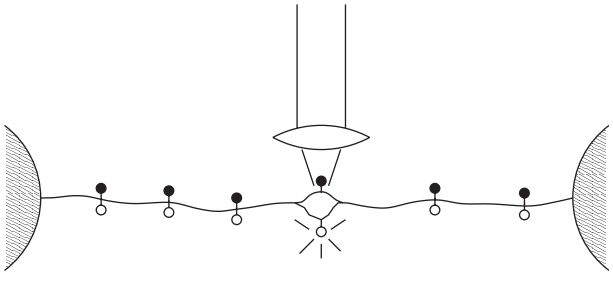

Fig. 2. A local denaturation zone can be detected by a microscope through the fluorescence of a dye. Conversely, the DNA being closed at the position of a fluorophore-quencher pair, the close proximity of the dye to the (black) quencher prevents fluorescence. Various ways of externally inducing the bubble are discussed in the text.

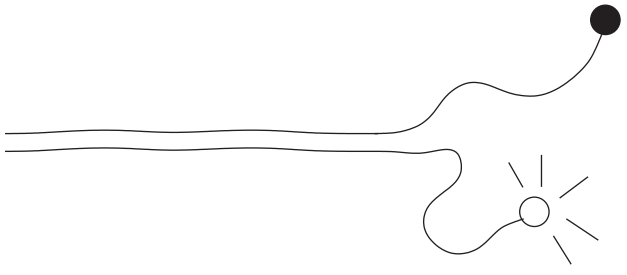

Fig. 3. Denaturation beacon setup. The right part of the DNA is designed to be rich in AT, and preferentially opens up from its ends. The left part, rich in GC or equipped with an end-loop, stays closed. Once open, the fluorophore-quencher pair is separated, and fluorescence starts.

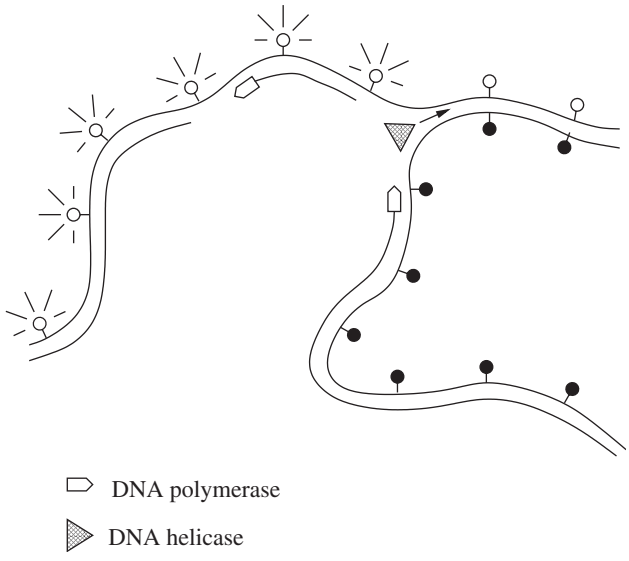

Fig. 4. DNA during replication by DNA helicase and DNA polymerases. The DNA molecule is lined with fluorophore-quencher pairs that start to fluoresce once they are separated spatially.

frame for the motion, the molecule can be held in place by optical tweezers, as used in some of the other setups in this study.

The setup in Figure 4 may be used to measure the *local* transcription/replication speed. The local speed will depend on (i) the energy needed to break a bond, i.e., the local statistical weight u (which in turn depends on, for instance, salt concentration); (ii) the presence of a knot or a kink in the DNA, which would decrease the local speed (compare 29); (iii) the presence of double-stranded binding proteins would slow down or completely halt the opening at the replication fork; (iv) single-stranded binding proteins would possibly help in the unzipping process and thereby increase the local speed. Furthermore, in combination with twisting by magnetic tweezers, over- or underwound states can be created, and the interplay of transcription or replication speed with twist or twist-induced superstructure studied.

3.4. Locating a DNA Knot and Measuring its Size

DNA-knots are created physiologically, and can be detected and removed by certain enzymes.[30] A number of questions about such knotted states of DNA are still unresolved, for instance, how a knot can be detected by topoisomerases; how a knot reduces the transcription speed; how much it decreases the rupture strength of DNA; or, whether knots at sequence-determined or chemically stabilized positions are relevant in gene regulation by bringing segments of the DNA that are distant in the chemical coordinate along the DNA backbone, close to each other in physical space.

The setup shown in Figure 5 allows for the measurement of the local brightness of fluorescence labels along the

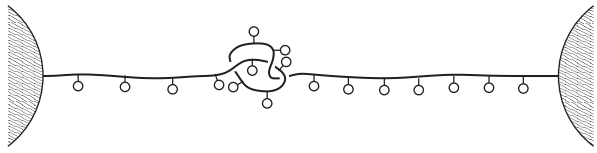

Fig. 5. Fluorescent labels along a knotted DNA will show increased local intensity at the knot position. By monitoring the size of the brighter spot, and its position, important information can be obtained about the effects caused by the knot state. In particular, sequence dependence and the influence of stabilising ligands can be studied.

DNA, which in turn allows for the determination of: (i) the position of the knot; experimentally, a knot in a DNA lined with fluorophores can be monitored through increased local fluorescence where the knot entangles a portion of the DNA-molecule; a first knot observation study using homogeneous staining of the DNA was reported recently.[31] (ii) the local properties of the knot; by releasing or increasing tension along the DNA, it can, for instance, be monitored, whether the size of the knot changes, or whether it is always tight. Again, effects of additional twist, sequence, and solution conditions can be probed.

One might replace the fluorescent labels by plasmon resonant nanoparticles[32] or quantum dots.[33] Such particles have the advantage of not photobleaching. Furthermore, plasmon resonant particles, that are in close proximity to each other, couple (through induced dipole-coupling) such that their resonance frequencies shift compared to well-separated particles. Thus, the presence of a tight knot is expected to show up as a shift in resonance frequence for the particles in the knot region. Plasmon particles can be manufactured with different resonant scattering wavelengths. Different parts of the DNA may therefore be labelled by particles with different resonance wavelength, allowing for detection not only of the presence of a knot (through a shift in resonance frequency) but also its rough location (through the absolute value of the resonance frequency).

We point out that FRET labels could improve the knot size resolution, and potential size changes of the knot as a function of time. Moreover, combination of the above setup with the locally induced DNA-denaturation as discussed in Section 3.1, it should be possible to observe a decrease in the knot size when temperature or solvent conditions are changed, due to the considerably smaller persistence length of ssDNA compared to dsDNA.

3.5. Target Search of Proteins on a DNA

Figure 6 shows a possible way to obtain information about the target search process of DNA-binding proteins on a DNA. This is connected to the important question about the dynamical details of how transcription factors, that regulate gene expression, find the specific target sequence they are supposed to bind to as efficiently as they are known to. In the Berg-von Hippel model for target

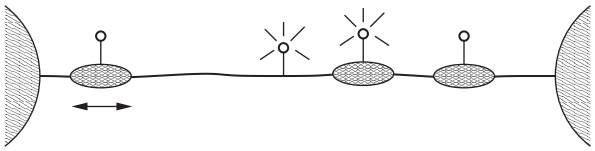

Fig. 6. An acceptor dye placed in the microscope focus on the DNA emits FRET signals once a protein, that is equipped with a donor dye, comes in close contact.

search,[34] this could be explained by a combination of volume diffusion and one-dimensional sliding of the proteins along the DNA while being non-specifically bound. A quantitative study of this model has not been achieved up to date. A large fraction of binding proteins are non-specifically bound to DNA;[35] in that state, sliding motion is their only means of propagation. There have even been identified cases when each binding protein remains on the DNA during the entire target search process.[36]

The setup from Figure 6 provides a possibility to obtain quantitative single molecule information about the targeting process. By labelling the protein with a donor dye, which has a corresponding acceptor dye on the DNA molecule, that is held in place by the optical tweezer, one can measure by FRET single events when an individual protein comes within a few Å of the DNA-dye. The obtained time series can then be converted into the desired dynamical information such as sliding diffusion constant etc, as function of solution conditions, protein types, or DNA sequence. In addition, the effects of DNA-knots on the target search may be studied.

Alternatively, one might dress the binding proteins by plasmon resonant nanoparticles (compare to Subsection 3.4). Possible clustering effects may then be detected as shifts in the resonance frequency spectrum of these particles. Moreover, from such measurements there is hope to extract the local concentration of binding proteins as a function of time, as well as interactions between the proteins (cooperativity effects).

3.6. Measuring Protein Binding Using DNA Translocation

Above discussion shows that by use of single DNA setups, DNA itself can be probed, or used to probe its environment on the micro- and nano-scale. Here, we suggest one possible experiment, in which DNA (and binding proteins) can be employed to create small, controllable forces. The results here also allow for the measurements of equilibrium binding properties and binding kinetics.

Our example relates to binding proteins, that by reversible binding (partially) rectify the passage of a biopolymer through a membrane nanopore.[37] The experimental setup we have in mind is depicted in Figure 7: once an end of the biopolymer is threaded through the pore, binding proteins on the trans side can (reversibly) bind. While bound, a protein prevents backsliding through

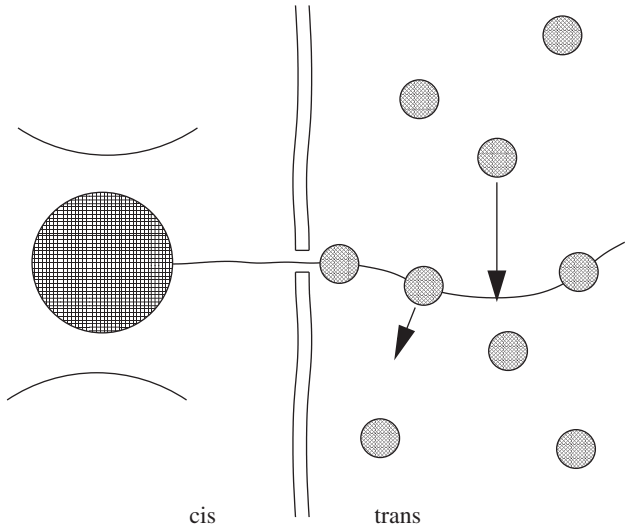

Fig. 7. Binding proteins that adsorb to and unbind from the part of the biopolymer to the right of the membrane partially rectify its translocation through the pore. Held in a quasistationary mode by an optical tweezer bead to the left of the membrane, the small forces exerted by the binding proteins can be monitored.

the pore such that the diffusive motion of the biopolymer through the pore becomes (partially) rectified. A microbead attached to the end of the biopolymer that is on the cis side of the pore, experiences a net drag force towards the pore that can be measured, for instance, by monitoring the displacement of the bead in an optical trap. The typical force exerted onto the connected microbead in such a setup can be approximated as a few pN, and below; compare the analysis in Ref. [38], and the experiments reported in Ref. [39], for which binding protein-mediated ratcheting was proposed as the most likely mechanism. The advantage of such a force transducer may be in the possibility of a slow build-up of a small force, in comparison to optical tweezers or similar single molecule tools that are typically run with constant force or constant velocity protocols. The setup connected to a sensitive force-meter such as an optical tweezer could measure (i) the concentration of binding proteins; (ii) the protein binding constants (iii) the size of the proteins.[38] An alternative to the binding proteins could be a molecular motor such as polymerase progresses along a DNA that is threaded through the nanopore, and thus create a relatively constant pulling speed.

When the translocating biopolymer is a flexible single-stranded DNA the force exerted on the microbead additionally depend on: (iv) entropic forces, which in turn depend on the persistence length; (v) interactions between the surface and the biopolymer.[40]

One may measure (vi) the unbinding rate in the following way: one moves the bead "backwards" slowly until it stops (due to the presence of a bound binding protein). When the binding proteins unbinds the bead can again move. The average stopping time is a measure of the unbinding rate constant.

4. PERSPECTIVE NANOBIOTECHNOLOGY

During the last decade or so, single molecule methods have taken root in disciplines like soft matter and biological physics, and it was demonstrated in numerous experiments the basic potential and feasibility of these techniques. By now, the time appears to be ripe to explore new possibilities for the applications of these methods. In the present work, we collected a number of potential experimental setups that can be employed to both explore the physical properties of DNA and its interaction with other molecules, as well as to utilize DNA as sensitive probe of its environmental conditions. These setups mainly concern the micro- and nanometre range, and may therefore be particularly useful in small volumes such as the microdishes of gene arrays, in microreactors, or as monitors or micromachines that are introduced in cells.

The potential applicability of these experiment designs, as far as they involve fluorescence techniques, relies crucially on the quality of the dyes. Whereas typical fluorophores bleach out within rather short timescales, the quantum dots and plasmon resonant nanoparticles we mentioned earlier provide a robust alternative, that will doubtlessly boost fluorescence techniques in small systems.

Our proposed setups are all based on the physical properties of DNA and the interactions dynamics with its environment; in particular, entropy and free energy effects. In this sense, the characteristics studied here are similar to previously suggested designed chemical molecules, whose functionality is based on entropic units such as sliding rings.[41, 42]

Various of the proposed setups involve the fixation of the DNA molecule by an optical tweezer. A few words on this methods are therefore in order. Firstly, it should be kept in mind that the typical size of such beads is of the order of a μm. For short DNA to be investigated, surface effects due to the beads may therefore come into play that obviously decrease with increasing chain length. Secondly, there is a tradeoff between the positional fixing of the chain and the magnitude of the applied pulling force. Whereas for very small forces the chain is only marginally affected and a statistical segment close to its centre still has a large amplitude of motion, a very large pulling force can keep the same segment almost still but changes the statistical properties of the DNA significantly (for instance, it can become close to force-induced denaturation). In between these two regimes, the blob picture is a good description of the DNA chain at lower to intermediate forces:[43] the pulling force f then gives rise to blobs of size $\xi = k_B T/f$ in which the DNA is undisturbed; the blobs themselves align parallel to the force vector. At intermediate to higher forces, the worm-like chain model applies.[44] Depending on the effects intended to probe, different of these regimes may be chosen.

We point out that many of the "old" single macromolecular techniques measure quantities which are equilibrium averages over the macromolecule, for instance by DNA pulling experiments one obtains the average behaviour of the entire molecule. Many of the methods presented here allow for the study of *local* (nanometre to subnanometre) and *dynamical* behaviour of DNA and its local environment, thereby providing new opportunities in the studies of subcellular behaviour and biotechnology. In that sense, the proposed setups represent a continuation of recent experiments such as the pulling of small RNA hairpins by optical tweezers[5] and their opening and closing dynamics (molecular beacon) as measured by fluorescence,[28] the polymer dynamics of dsDNA versus ssDNA,[45] or the persistent length and its sequence dependence of ssDNA measured by fluorescence methods.[46, 47]

We hope that the this study will inspire the design of novel DNA-based single molecule experiments.

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