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Colored noise in the fluctuations of an extended DNA molecule detected by optical trapping

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Abstract We studied fluctuations of an optically trapped bead connected to a single DNA molecule anchored between the bead and a cover glass or between two optically trapped beads. Power spectral densities of the bead position for different extensions of the molecule were compared with the power spectral density of the position fluctuations of the same bead without the molecule attached. Experiments showed that the fluctuations of the DNA molecule extended up to 80% by a force of 3 pN include the colored noise contribution with spectral dependence $1/f^{\alpha}$ with $\alpha \sim 0.75$.

Keywords DNA · Optical tweezers · Colored noise · Power spectral density

Introduction

Deoxyribonucleic acid (DNA) is an important biopolymer that contains genetic information and is found in all living cells. One of the most prevalent forms of DNA is a linear double-stranded DNA. The double helix provides both bending and twisting rigidity, making linear DNA a semi-flexible, charged polymer chain. Like any polymer in solution, DNA forms a random conformation that maximizes its entropy. The entropic force, which governs the mechanical flexibility of the DNA, plays a key role in all its cellular functions, and its experimental characterization is being actively developed (Bustamante et al. 2003).

A double-strand DNA molecule in solution bends and curves locally. Such fluctuations shorten the molecule's end-to-end distance, even against the applied force. The elastic behavior of DNA is thus purely entropic in origin. The entropic elasticity has been explored in the range from 0.01 to 10 pN (Smith et al. 1992). As the DNA extension reaches its B-form contour length, the force required to stretch it increases rapidly, because the double helix is straightened out and resists further increase in length. At extension force of 65 pN, very little additional force is required to increase the DNA length to 1.7 times its contour length. This is the so-called overstretching regime (Cluzel et al. 1996; Smith et al. 1996).

The dynamics of extended polymers is not fully understood and is in principle of great interest. The dynamics of a single DNA molecule have been studied previously for partially extended states. It was shown that the internal modes of a DNA extended up to 80% are related by a power law decreasing its intensity with the mode number (Quake et al. 1997; Gueroui et al. 2003). Internal hydrodynamic effects should raise the polymer friction coefficient as the molecule extends, causing the sequential increase of the polymer relaxation time (Gennes 1974; Pincus 1976). Extended DNA molecules are characterized by two different sets of relaxation times and spring constants (longitudinal and transverse), and the dynamics at high extensions points to yet unexplained nonlinear behavior (Meiners 2000). Particularly, the correlation functions have super-exponential relaxation that may indicate the presence of new physical effects.

Random conformations that a DNA molecule forms in solutions occur in the presence of the thermal noise with white spectrum of the forces, but also out-of-equilibrium mechanical activity plays an important role. These mechanical effects

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are directly related to biochemical reactions in the long polymer chain. The power spectrum of such force fluctuations is defined by processes that are different from the thermal noise and therefore may depend on the frequency of the fluctuations ("colored noise"). Recent detailed studies on the sources of fluctuations in some biological systems, in particular in bio-molecular motors (Gallet et al. 2009; Yoon et al. 2011), offer strong experimental indications that the noise signals in these systems include also the non-white component with a frequency-dependent power spectrum. The effect of colored noise is not restricted to destructive and thermodynamic effects, but also may change mechanical processes in biochemistry (Bustamante et al. 2004).

Force studies of single DNA molecules using single molecule force spectroscopy brought new insight into various DNA biological functions (Bustamante et al. 2003; Quake et al. 1997; Greenleaf et al. 2007; Ritort 2006). Questions still remain about the force spectrum of conformation fluctuations of DNA chemical structure in the low force regime where entropy is a driving factor. The DNA molecule acts as a platform for a host of critical biological functions such as transcription, replication, and other molecular motor-driven processes. During these processes, the DNA strand undergoes numerous mechanical entropic unfolding and extension events that are primarily supported by the polymer-like phosphate backbone, thus making it critical to have a full understanding of how the DNA structure responds to forces.

The aim of this work is to study experimentally the spectra of fluctuations of a single thermally excited DNA molecule in different states of extension in the regime of entropic elasticity. We explore well-known experimental schemes: the molecule is anchored between two optically trapped dielectric beads, or between an optically trapped bead and a surface (coverslip or pipette) (Smith et al. 1996; Ritort 2006; Wang et al. 1997; Perkins 2009). The time traces of the bead position are usually analyzed under a varied load applied to the molecule. In this work, the power spectral densities (PSD) of the bead fluctuations for different extensions of the molecule were compared with the power spectral density for the same bead without the molecule attached. We then subtracted the spectrum of thermally excited fluctuations of the molecule. To the best of our knowledge we demonstrated experimentally for the first time that in the regime of entropic elasticity the random fluctuations of the extended DNA molecule also include the contribution of the frequency-dependent power spectrum.

Experimental section

The main parts of the experimental setup are shown in Fig. 1. A dielectric bead with a DNA molecule attached to

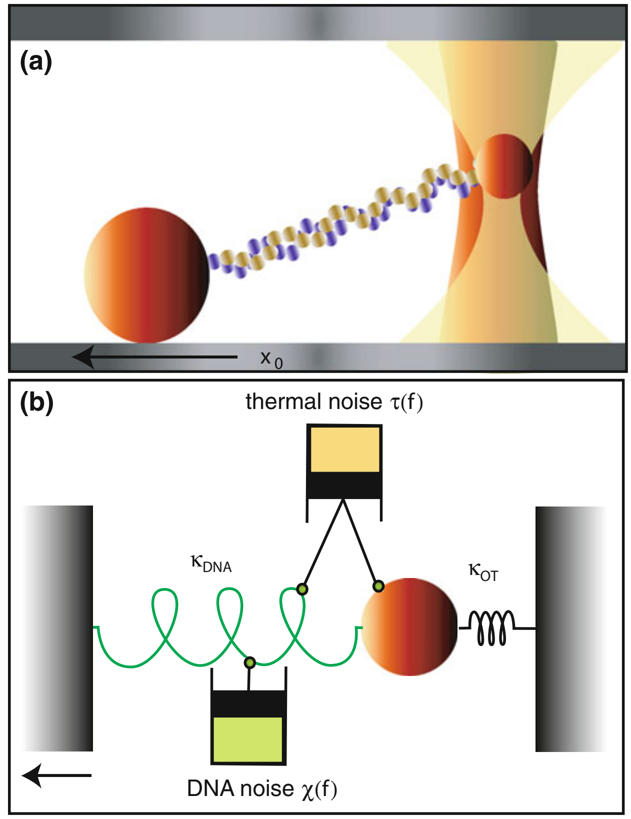

Fig. 1 **a** A DNA molecule between an optically trapped bead and a bead adhering to the coverslip of the fluid chamber. The optically trapped bead's position is monitored by a position detector via scattering of a detection beam. To stretch the molecule, the coverslip was moved at a distance x_0 by a given position of the trapping beam. **b** One-dimensional mechanical analog of **a**: the bead motion is governed by the trapping beam and the molecule, both considered as elastic strings with stiffnesses κ_{OT} and κ_{DNA}, respectively. The thermal noise with known power spectrum density $|\tau(f)|^2 = 2k_BT\gamma$ perturbs the motion of the bead and the molecule. The fluctuations of the DNA with unknown power spectral density $|\chi(f)|^2$ also affect the bead position

it is chemically connected to the surface of a movable coverslip. Another bead anchored to the opposite end of the DNA is trapped by a focused optical beam. An additional optical beam is coaxial to the propagation direction of the trapping beam. Its forward scattering intensity is characterized with a pinhole and a quadrant position detector in order to measure the bead position and calibrate the optical trap using well established procedures (Tolić-Norrelykke et al. 2006). The PSD of the bead position is calculated for different distances between the center of the optical trap and the center of the bead connected to the coverslip. Unlike previous publications, the optical trap's stiffness is kept similar to the DNA stiffness such that the fluctuations of the molecule become significant and control the measurements.

The studied molecule was a double-stranded λ-DNA from *Escherichia coli* amplified at 12 kbp using standard polymerase chain reaction (PCR) techniques with sample concentrations of 40 ng/µl. The molecules were tagged with biotin and digoxigenin (DIG) at each end to attach to streptavidin and anti-digoxigenin (anti-DIG)-coated polystyrene beads, respectively.

A 980-nm optical beam from a laser coupled in a single-mode fiber (Avanex, 1998PLM 3CN00472AG High Power 980 nm), expanded up to 10 mm and then focused by a 100 × NA = 1.3 objective (Nikon, CFI PL FL 100X AN 1.30 WD 0.16 mm), permitted the optical trapping. An additional 635-nm optical beam from a low-noise laser (Coherent, ultra-low noise diode laser LabLaser635, RMS noise <0.06 for bandwidths of 10 Hz to 10 MHz) was coaxial to the propagation direction of the trapping beam and was used as the position detection beam. The forward scattered light of the detection beam was collected by a 40× objective and analyzed by a position detector (Newport, 2931 position-sensitive detector). The forward-scattered light of the trapping beam was blocked by a short-pass filter (Thorlabs FES0700). The resulting signals were then transferred through an analog-to-digital conversion card (National Instruments PCI-6120) to computer software. The position detection system was used to calibrate the optical trap (i.e., to determine the stiffness of the optical trap κ_{OT} without the DNA molecule connected), to measure the molecule's extension curve and the PSD of the bead position with the molecule connected. In the second experiment we changed the experimental setup and used two optical traps to extend the molecule (see below inset in Fig. 7). The goal was to find how an additional isolation of the studied system from the instrumental noise and changes of the detection trap's stiffness (approximately 7 times) affect the spectrum of the measured fluctuations. Here, we introduced an expanded 1,060-nm optical beam from a laser coupled in a single-mode fiber (ManLight, ML10-CW-P-OEM/TKS-OTS, RMS noise <0.2, maximal power 10 W) into the optical trapping system. The position of this trap can be changed by a computer-controlled mirror. This mirror was optically conjugated with the input pupil of the trapping objective using two lenses.

DNA molecules were first incubated with the streptavidin-coated beads (1.87 µm diameter) for 45 min in phosphate buffer solution (PBS) at pH 7.4. Then the samples were washed and injected along with the anti-DIG-coated beads (3.15 µm diameter) into a fluid chamber. The final DNA bead constructs were assembled in situ (Rao et al. 2010): we trapped the streptavidin-coated bead by the optical trap, and then we moved the anti-DIG-coated bead, spontaneously attached to the surface of the fluid chamber, to the streptavidin-coated bead. After some time the binding between the DNA and the stuck bead can occur with a certain probability. This event was verified by moving the anti-DIG-coated bead and observing its

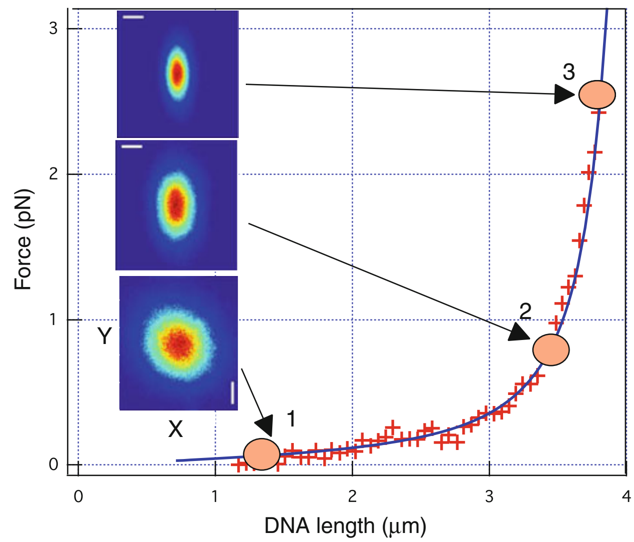

Fig. 2 Experimental extension curve data (*crosses*) fitted to the WLC model (*blue solid line*). The fitting gives the expected contour length (L_0) of 4.1 µm, and persistence lengths (P) that vary between 47 and 57 nm for different measurements. *Error bars* are calculated to be far less than the size of the plotting *symbols* and are therefore not shown. The PSD measurements were done for the free bead (*1*) and for two states of molecular extension (2) and (3). The *insets* show histograms of the bead position in the *xy* plane, perpendicular to the beam propagation direction, with *white lines* indicating the scale (25 nm). We studied the histograms of the free bead and then, obtaining the trapping potential, we found that it was parabolic in the range of ±400 nm

behavior. The motion of the surface caused the molecule's extension, and the dynamics of the optically trapped bead was measured by the position detection system.

To verify that a single DNA molecule was present between the beads, force-extension curves (Wang et al. 1997) were measured. Fitting the experimental data shown in Fig. 2 to a well-established worm-like chain (WLC) model (Marko 1995) $F_{\mathrm{DNA}} = \frac{k_B T}{4P}\left(\frac{1}{(1-L/L_0)^2} - 1 - \frac{4L}{L_0}\right)$ allows two basic parameters to be extracted: the contour length (L_0) and persistence length (P). (Here L is the equilibrium extension, k_B is the Boltzmann constant, and T is the absolute temperature). In all measurements, the measured contour length at 4.1 µm was consistent and verified our amplification protocol for this length as well as the rough length estimate found with electrophoresis and image analysis. (In the experimental data analysis, we neglected the bead's motion in z direction resulting from displacements of the coverslip.)

To calibrate the optical trap we acquired the time traces of the bead position without molecules connected to the bead. The data acquisition rate was 50 kHz; the acquisition time was 100 s. The bead was trapped 10 µm above the surface. Histograms of the bead position are shown in Fig. 2. The PSD for the motion along the load direction (x) and in the perpendicular direction (y) are shown in

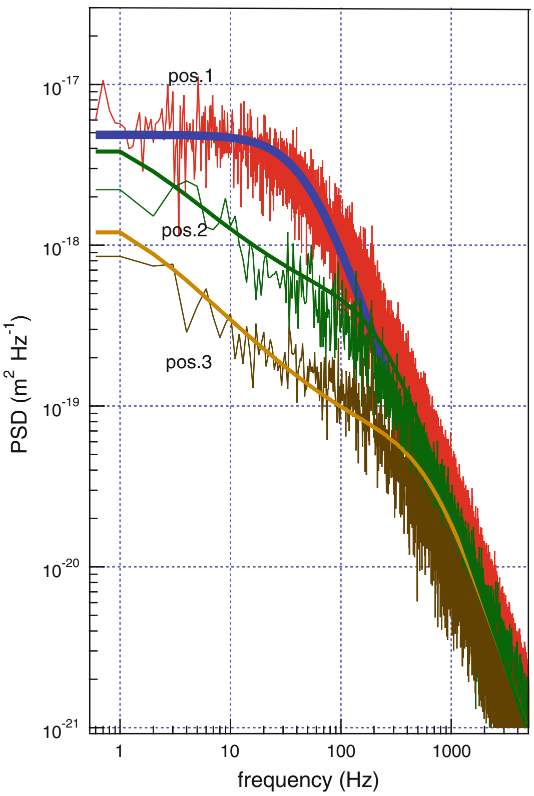

Fig. 3 PSD of the *x* position of the optically trapped bead for the free bead (pos.1) and for the bead connected to the molecule for two positions of the molecule extension (pos. 2) and (pos. 3) given in Fig. 2. The *solid lines* show the best fit to the Lorentzian function valid when only the random force with white spectrum acts on the free bead (pos.1), and the curves (pos. 2) and (pos. 3) that fit the experimental spectra of the bead position with the DNA noise included (see below). The experimental data for the free bead are well fitted to the Lorentzian curve even at frequencies below 1 Hz because of small level of instrumental noise

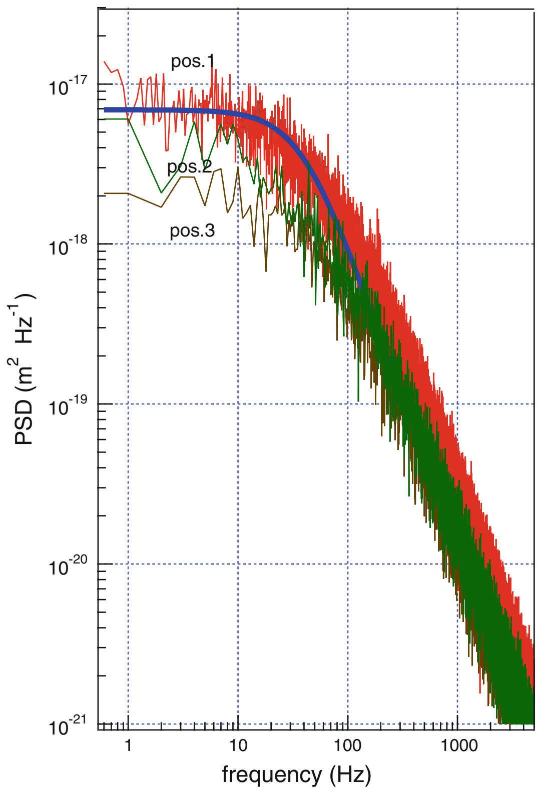

Fig. 4 PSD of the *y* position of the optically trapped bead for the same conditions as in Fig. 3. The *labels* of the *curves* have the same meaning as in Fig. 3

Figs. 3 and 4. For calibrating the optical trap we used a well-established procedure (Tolić-Norrelykke et al. 2006), fitting the experimental PSD of the free bead to a Lorentzian curve:

$$\mathrm{PSD}_0(f) = \frac{k_B T}{2\pi^2\gamma(f_c^2 + f^2)}, \quad (1)$$

where $\gamma = 6\pi\eta r$ is the drag coefficient, η is the viscosity, r is the radius of the bead, f is the frequency, and $f_c = \kappa_{\mathrm{OT}}/(2\pi\gamma)$ is the cutoff frequency. The stiffness was found to be $\kappa_{\mathrm{OT}}^x = 4.0 \pm 0.1$ pN/μm and $\kappa_{\mathrm{OT}}^y = 4.7 \pm 0.1$ pN/μm for the x and y directions, respectively. The difference in stiffnesses is due to the linear polarization of the trapping beam (Dutra et al. 2007). (In the case of the bead attached to the non-stretched molecule the calibration of the optical trap was not possible because the proximity of the stuck bead scattered the detection beam and interfered strongly with the scattering on the optically trapped bead.) The values of the stiffnesses were close to those found by using the equipartition theorem: $\kappa_{\mathrm{OT}} \langle x^2 \rangle = k_B T$, see below, Table 1.

We then measured the PSD of the bead position with the molecule connected. After confirming the presence of only one molecule between the beads as described above, we slowly extended the molecule up to the states of extension marked as 2 and 3 in Fig. 2. A flexible polymer coils randomly in solution (Bustamante et al. 2003). Therefore, the time traces by a given distance between the stuck bead and the optical trap center presented a stepwise behavior with a step duration usually within 10 s. We analyzed the position PSD during the intervals when no steps were observed. Figures 3 and 4 show the PSD obtained from raw data using this processing.

Results

When the mechanical load grows, the PSD of the *x* coordinate demonstrates changes, whereas the PSD of the *y* coordinate remains almost the same. However, in order to interpret the observed excess noise one has to consider many other sources of excess noise that exist in the optical trapping experiments with single DNA molecules (Lang et al. 2002; Carter et al. 2009). Special precautions were

Table 1 The values of the total stiffness $\kappa_{OT} + \kappa_{DNA}$ for two loads and for the free bead

Load	No load ($\kappa_{DNA} = 0$)	2	3
$\kappa^x_{OT} + \kappa^x_{DNA}$, pN/µm	3.99 ± 0.03	11.29 ± 0.06	30.50 ± 0.26
$\kappa^y_{OT} + \kappa^y_{DNA}$, pN/µm	5.06 ± 0.02	6.47 ± 0.04	10.25 ± 0.05

taken in our experiments to reduce the level of the instrumental noise affecting measurements. In particular, we shielded the optics with a plastic enclosure in order to minimize the airflow in the instrumental chamber. Also, we used an optical table levitated on pneumatic isolators, and all moving parts (translation stages and mirrors) were operated by motorized actuators controlled outside of the chamber. The detection laser was a stabilized diode laser (<0.1% power instability). The trapping beam was obtained from a low-noise (0.17% output power instability during 1 h) fiber coupled laser. The optically trapped bead's position fluctuations generated because of the laser instability were expected to be the same order of magnitude, and therefore the PSD changes due to the trapping beam instability had to be the same order.

In order to evaluate the drift and the low-frequency fluctuations in the microscope stage, we measured the PSD of the streptavidin-coated bead stuck on the coverslip. The stuck-bead spectrum provides an upper bound of the absolute noise detection. The low-frequency spectra of signals from the position detector are shown in Fig. 5 for the stuck bead (4) together with the spectra for the free optically trapped bead (1) and the bead connected to the molecule for the values of the molecule extension (3) (Fig. 2). As seen, the power of the instrumental noise at 1 Hz is 10^{-4} of that in the spectrum of the free bead. At a frequency of 30 Hz the difference is 5×10^{-6}. When the extended molecule is attached to the probe, the changes of the spectrum in the same frequency range are about 10^{-1}. If we assumed DNA is a pure elastic string that connects the probe with the coverslip surface and transmits 100% of its vibrations to the probe, the magnitude of the PSD changes for the free bead and for the bead with extended DNA would be insignificant in comparison with the changes observed in the experiments. We believe that the low stiffness of the optical trap (4 pN/µm) is crucial for our measurements with a single optical trapping. Previous results on the extended DNA dynamics were obtained for the trap stiffness of, for example, 100 (Lang et al. 2002), 530 (Carter et al. 2009) and 1,900 pN/µm (Abbondanzieri et al. 2005). Such high values of the stiffness permitted achieving a sub-nanometer resolution, but the isolation from the instrumental noise meets more stringent requirements. In fact, as follows from (1), at frequencies lower

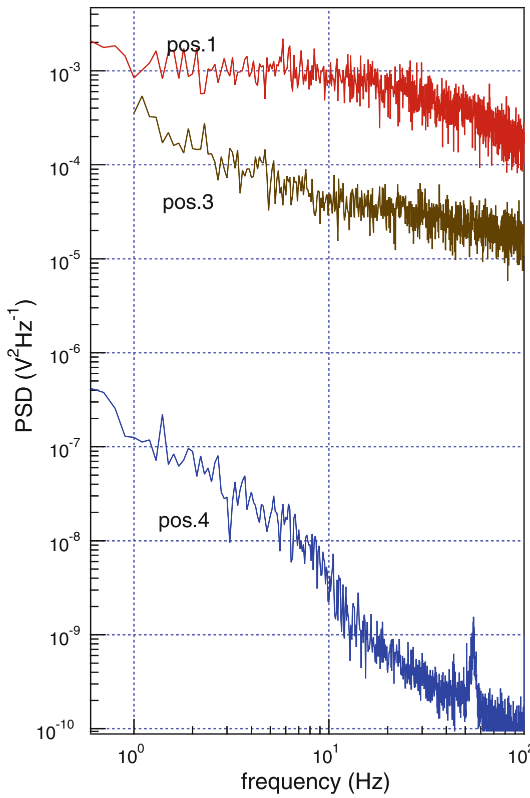

Fig. 5 PSD of the signals from the x position detector for the optically trapped free bead (pos. 1), for the bead connected to the extended molecule (pos. 3) (see Fig. 2) and for the stuck bead (pos. 4) within a frequency range of 0.6–100 Hz

than the corner frequency, the PSD is inversely proportional to the square of the trap stiffness. Using the optical trap with low stiffness, we increased the contribution of low frequency Brownian components of the trapped probe motion. The extended molecule connects the surface of the coverslip with the probe, but the observed changes in the PSD cannot be explained quantitatively by the instrumental noise keeping in mind its level measured with the stuck bead.

Discussion

We interpreted the results in terms of the hypothesis of thermally excited fluctuations of the DNA with unknown power spectral density $|\chi(f)|^2$ that also affect the bead position (Fig. 1b). Below we present a phenomenological description of the effect that permits us to subtract the spectral dependence of $|\chi(f)|^2$ from the measured spectrum of the probe motion.

As shown in (Meiners 2000) the measured longitudinal 7.6×10^{-9} $N \times$ s/m and transverse 17.3×10^{-9} $N \times$ s/m friction coefficients of the molecule are independent of extension over the range of extension <80%. Hence, the observed change of the PSD corner frequency is explained by higher effective stiffness of the system (the bead and the molecule) rather than changes of the molecule friction coefficients. Then dynamics of the optically trapped bead connected to the DNA molecule are given by

$$\gamma\dot{x} + \kappa_{\mathrm{OT}}x(t) + \kappa_{\mathrm{DNA}}(x(t) - x_0) = \tau(t) + \chi(t). \quad (2)$$

Solving Eq. (2) and supposing that $\tau(t)$ and $\chi(t)$ are not correlated, we have the PSD of the bead position when the molecule is connected to the bead as

$$\mathrm{PSD}_{\mathrm{DNA}}(f) = \frac{|\tau(f)|^2 + |\chi(f)|^2}{4\pi^2\gamma^2(f^2 + f_{\mathrm{cDNA}}^2)}, \quad (3)$$

where $f_{\mathrm{cDNA}} = (\kappa_{\mathrm{OT}} + \kappa_{\mathrm{DNA}})/(2\pi\gamma)$ is the corner frequency corrected for the elastic properties of the DNA.

The thermal noise spectrum does not depend on frequency $|\tau(f)|^2 = 2k_BT\gamma$. Hence, in order to find a spectrum of the molecule fluctuations using (3) we need to know the stiffness of the molecule κ_{DNA}. Experimental data (Figs.3 and 4) show that fitting of the PSD to the Lorentzian function cannot be used to find f_{cDNA}. As an approximation, we found the value of the total stiffness coefficient $\kappa_{\mathrm{OT}} + \kappa_{\mathrm{DNA}}$ by proceeding as follows. Supposing that the equipartition theorem is still valid even with the presence of the additional noise, we obtained the total stiffness using the histograms of the bead positions (insets in Fig. 2). Table 1 presents the results of the calculations. The obtained values of the DNA stiffness agree with those obtained in previous experiments (Meiners 2000; Lien et al. 2009).

With these values we used (3) to calculate the spectrum of the molecular noise $|\chi(f)|^2$. The results of the calculations are shown in Fig. 6.

Fitting the experimental power spectrum density $|\chi(f)|^2|$ to the dependence $1/f^{\alpha}$ shows that α changes from 0.8 for smaller value of loads to 0.7 for bigger loads, and the intensity of the noise increases with the load. However, the accuracy of our measurements does not permit us to draw conclusions about whether this difference is significant. The straight horizontal line in Fig. 6 shows the level of the thermal noise $|\tau(f)|^2|$ acting on the bead. As seen, the thermal white noise has less intensity than the colored noise of the molecule for frequencies below 30 Hz. For frequencies >30 Hz the colored noise interferes strongly with the thermal noise, making its detection difficult.

We also observed changes in the position PSD for the direction perpendicular to the load direction (see Fig. 4). These changes are much smaller because of a low transversal stiffness of the DNA molecule (Meiners 2000).

Let us consider now results obtained using two optical traps to extend the molecule (Fig. 7).

Using the procedure described above for the data presented in Fig. 7, we subtracted the additional noise. As

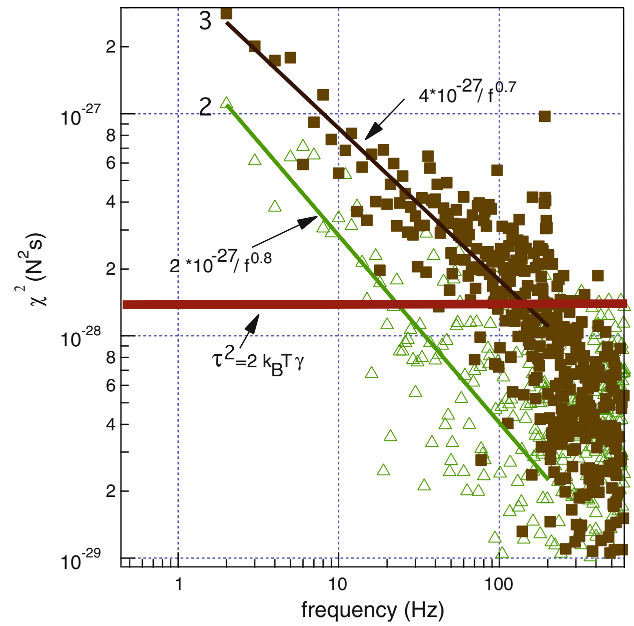

Fig. 6 The spectrum of the thermally excited noise of the extended DNA molecule for two loads (*2*) and (*3*) (see Fig. 2)

Fig. 8 shows, the additional noise signal with the spectrum $1/f^{\alpha}$ with $\alpha \sim 0.75$.

These new measurements confirm that the signal-to-noise ratio is independent of the trap stiffness at low frequencies. The ability to resolve fluctuations of the DNA molecule's length above the Brownian noise of the beads is independent of the trap stiffness. This result was proved previously by several groups (Carter et al. 2009; Abbondanzieri et al. 2005; Moffitt et al. 2006, 2008).

The noise behavior as $|\chi(f)|^2 \sim 1/f^{\alpha}$ with $\alpha < 1$ is characteristic of the system possessing so-called $1/f$ noise, which was previously observed in such distinct phenomena as vacuum tube voltage, resistance of semiconductors, traffic flow rate, economic data (Keshner 1982; Hoog 2002) and ionic current-voltage measurements of nano pores (Merchant et al. 2010). This noise is also present in statistics of DNA sequences (Vos 1992; Li 2005) and in temperature fluctuations during thermal denaturation of the DNA double helix (Nagapriya et al. 2006). The colored noise component is a measure of the memory existing in the system (Hanggi 1990).

In conclusion, our experiments showed that the fluctuations of the DNA molecule extended up to 80% by a force of 3 pN include the additional colored noise with spectral dependence $1/f^{\alpha}$ with $\alpha \sim 0.75$. Below we give an example that illustrates possible consequences of the presence of colored noise for the DNA functionality.

The effect of noise, which always accompanies all actual systems, is not restricted to destructive and thermodynamic effects, but the noise is also an integral part of

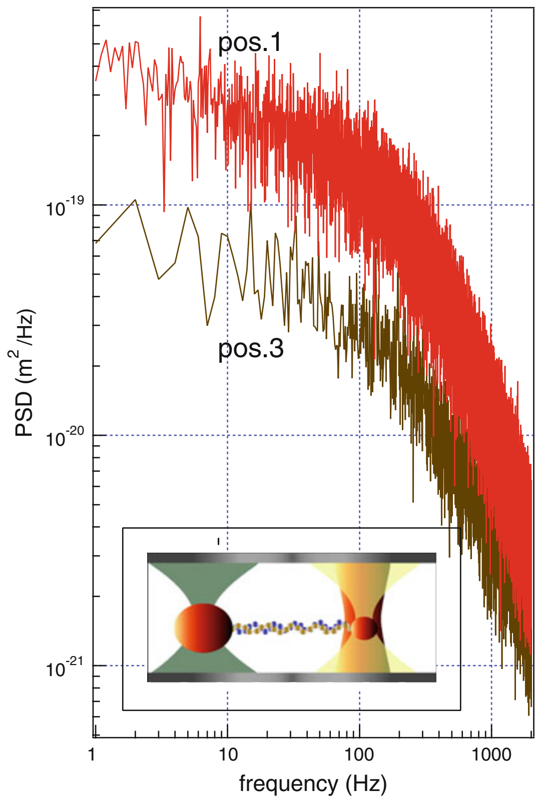

Fig. 7 PSD of the *x* position of the optically trapped unmovable bead for the free bead (pos. 1) and for the bead connected to the molecule extended with the force of 2 pN (pos. 3) (see the extension curve in this case in the inset Fig. 8). *Inset* shows the experimental setup with a DNA molecule between two optically trapped beads. The movable (*left*) trap that extends the molecule has stiffnesses $\kappa_x = 127$ pN/μm and $\kappa_y = 143$ pN/μm. The unmovable (*right*) trap has stiffnesses $\kappa_x = 27$ pN/μm and $\kappa_y = 30$ pN/μm. The detection beam is coaxial to this trapping beam

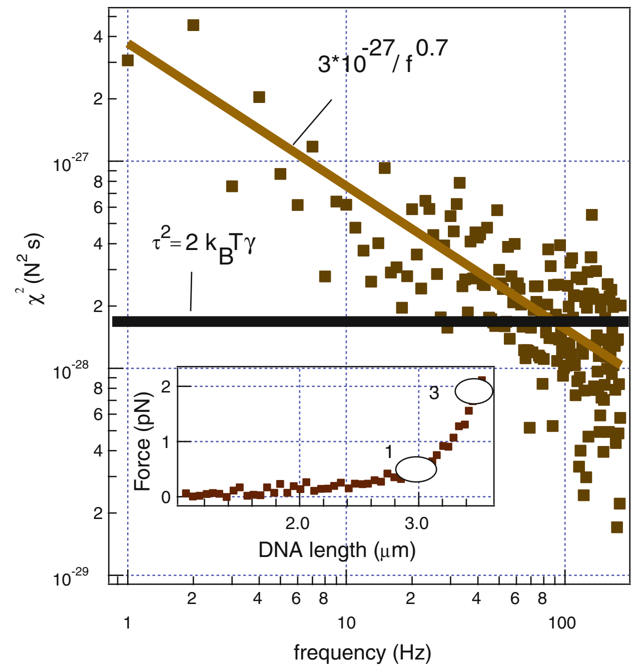

Fig. 8 The thermally excited noise spectrum of the extended DNA molecule for the load (pos. 3) (see Fig. 7). *Inset* shows the extension curve obtained with the dual-trap extended DNA molecule. The two positions labeled (*1*) and (*3*) correspond to the free bead and the bead connected to the molecule extended with the force of 2 pN

such effects as stochastic resonance and fluctuation-driven transport (Hanggi 1990; Leible 1994). Being mechanical in nature, many fundamental processes in DNA occur by discrete physical movements. The size of these displacements may be dictated by the inherent periodicity of the molecule. Such processes can be viewed as reactions of the energy landscape (Bustamante et al. 2004). The discrete motion in these processes originates from the fact that the states along these reaction pathways are highly localized minima within this energy landscape. The probability of the discrete mechanical steps depends on the ratio of the minima depth energy and the energy of the fluctuations acting on the molecule from the environment, and is described by Kramer's transition theory (Hanggi et al. 1990; Hanggi 1994). Also, an external deterministic force may change this probability because of the induced redistribution of the energy landscape. Recent experiments have shown that, for several proteins, the dependence of folding and unfolding rates on solvent viscosity does not obey Kramer's theory (Planxco 1998). For DNA in its natural conditions (in liquid), the Brownian noise stemming from fundamental thermal forces is the main contributor to the noise acting on the molecule. Kramer's transition theory is valid only when thermal noise with a white spectrum exists in the system. As we show here, the component with a colored noise spectrum exists in the molecule, and therefore these additional fluctuations may be added to the thermal noise, causing changes in the probability of noise-induced events. A theoretical attempt to explain the violation of Kramer's theory for the dependence of protein folding rates on viscosity showed that the presence of the correlated (colored) noise may be needed (Bag et al. 2010). The knowledge of the spectral dependence of the colored noise is therefore important for a deep insight into biophysics of the DNA molecules.

One may expect considerable changes in the spectrum of the colored noise of the fluctuations of a DNA extended up to the enthalpic and overstretching regimes, where a force-induced melting of the two strands is achieved. These measurements require stiffer optical traps and, therefore, the use of optical setups with eliminated stage drift through, for example, a laser-based detection and feedback (Carter et al. 2007, 2009), and/or dual-optical trap designs (Moffitt et al. 2006; Shaevitz et al. 2003), that circumvent stage drift. The comparison of the noise spectra of single stranded and double stranded molecules is one of our future aims.

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