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Resonant optimization in the mechanical unzipping of DNA

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received 16 January 2014; accepted in final form 12 March 2014
published online 27 March 2014

PACS 87.15.A– Theory, modeling, and computer simulation
PACS 87.15.-v – Biomolecules: structure and physical properties
PACS 05.40.-a – Fluctuation phenomena, random processes, noise, and Brownian motion

Abstract – The mechanical separation of the double-stranded DNA in single-molecule experiments is of fundamental importance in the understanding of the replication or transcription processes. Time-dependent forces can influence in different ways the dynamics of this separation. We study here this unzipping of DNA in the framework of the mesoscopic Peyrard-Bishop-Dauxois model under the influence of a periodic driving. Two different protocols, both of them feasible experimentally, have been studied under two modes of pulling: controlled force and controlled position. A strong resonant activation phenomenon has been observed in the magnitudes that characterize the mechanical unzipping such as the mean opening time, the mean opening force, and the mean critical opening force, all of them as a function of the frequency of the driving. This optimal frequency region has been observed for all the cases studied both in a uniform DNA of adenine-thymine nucleotides and in a real DNA sequence. Importantly, a well precise resonant frequency can be determined with the use of one of this protocols.

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Introduction. – Separation of the double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA) is an essential step in biological processes like replication and transcription. For this reason, the mechanical response of dsDNA under the action of an external force is of great relevance, and in this context the unzipping is one of the most useful and interesting single-molecule experiments \cite{1–3}. Mechanical unzipping has been conducted either with constant pulling velocity or with constant force. Nevertheless, the effect of alternate forces on the dynamical response of DNA and other biomolecules had become more and more relevant, and has been recently addressed both theoretically and experimentally. First, the linear and nonlinear resonances induced by radiation with frequency in the order of THz has been argued \cite{4–8}, and in ref. \cite{7} a reduction of the unzipping force was obtained due an inertial resonant mechanism at the frequencies of the normal modes of the dsDNA chain. Second, the use of mechanical alternate forces in some single-molecule experiments \cite{9–13} has been investigated. In \cite{9} a periodic pulling protocol is proposed for the folding and unfolding cycle of a protein. This periodic protocol presents interesting outcomes, as it allows a better resolution with respect to the standard linear pulling in the reconstruction of the free-energy landscape of the molecule. On the other hand, stochastic effects such as the stochastic resonance and resonant activation (RA) were observed during the folding/unfolding experiments of short DNA hairpins \cite{10}, and in numerical simulations in RNA \cite{11} and Ubiquitin unfolding \cite{12}. It is important to notice that the use of mechanical alternate forces is biologically relevant because many processes occur in a periodic way due to the periodic energy consumption inside the cell \cite{13}.

In this letter, we investigate a complementary aspect of the mechanical unzipping concerning the optimization of the escape rates with alternate forces. We found a RA in the mechanical unzipping, i.e. a big reduction of the opening time of the chain as a function of the frequency for a broad frequency range \cite{14}. This phenomenon has been widely studied both theoretically \cite{14–19} and experimentally \cite{20}. The RA has been also observed in a model of
the transport of a polymer in a metastable potential which oscillates periodically in time [21,22] and in the translocation driven by an active pore, which acts with a sinusoidal force in the polymer dynamics [23,24]. We study here the mechanical unzipping in a broad frequency interval of alternate forces, in the framework of the Peyrard-Bishop-Dauxois (PBD) model [25] modified to include the solvation barrier [26,27]. This model has been used for describing the mechanical DNA unzipping [28,29]. We found that a mechanism similar to the standard RA is obtained in the model under different ways in which the unzipping experiment is realized. We consider this result some important news involving both the theoretical background of the stochastic activations and the possibility to find optimized parameters (in waiting times and/or required force intensity) in the DNA unzipping experiments. Interestingly, and surprisingly in the thermal activation process, the presence of a quite precise resonant frequency can be observed. This novelty arises as a consequence of the consecutive ordered opening of the nucleotides of the chain which synchronize with the period of the driving.

Model and methods. – The PBD model describes the 1d dynamics of the strand separation of a dsDNA in a mesoscopic approach. We use a modified version of the model where a barrier is included to account for the mechanical DNA unzipping [28,29]. The potential energy of the system has two contributions: $V(y_n)$, that describes the interaction of the bases belonging to the same base pair (bp) and $W(y_{n-1},y_n)$, that accounts for the stacking interaction between consecutive bps. $V(y_n) = D(e^{-\alpha y_n} - 1)^2 + G e^{-(y_n - y_{n-1})^2/k}$ is the sum of the Morse potential and a Gaussian barrier. $D$ is the bp dissociation energy and $\alpha$ sets the width of the potential well. The parameters $G$, $y_0$ and $b$ are the barrier height, position and width, respectively. The stacking interaction reads $W(y_{n-1},y_n) = \frac{1}{2}K(1 + \rho e^{-\delta(y_n - y_{n-1})}(y_n - y_{n-1})^2$, with $K$ the coupling constant, $\rho$ sets the anharmonic character of the stacking and $\delta$ sets the scale length for this behaviour [25].

The mechanical unzipping is simulated in two modes that can be realized experimentally: controlled force (CF) and controlled position (CP). In the CF mode, one end of the chain is pulled apart from the other at a given force. In the CP mode, it is the separation of the two strands that is kept fixed or varied with a given law (generally constant velocity).

Here, we study both these modes under the two different protocols depicted in fig. 1, where a force $F(t)$ is differently applied as explained below. In the first one, called Protocol A, the first bp is pulled either by a constant and an alternate forces $F(t) = [F_c + A \cos(2\pi \nu t + \phi)]$ (CF mode) or an alternate displacement in the pulling force $F(t) = K_d Y(t-y_1)$ (CP mode), with $Y(t) = Y_0 + Y \cos(2\pi \nu t + \phi)$ the controlled position, and $K_d$ the stiffness of the experimental device. Here $\nu$ is the frequency of the alternate contributions, $A$, $Y$ are the amplitudes in the CF and CP modes, and $V$ is the constant pulling velocity. The harmonic contribution in the CP mode is necessary in order to check the value of the force which acts in the dynamics. This protocol is similar to those of [9,10], where unfolding and folding are performed with a periodic driving. In the second protocol, called Protocol B, the periodic driving $A \cos(2\pi \nu t + \phi)$ is applied uniformly to all bps, as in refs. [6,7]. In this case the non-oscillating forces $F_c$ and $[K_d (V t - y_1)]$ are added to the first bp Hamiltonian in the CF or the CP mode, respectively. An additional term of potential $U(y_n, y_{n+1}) = 0.5 K_s (y_{n+1} - y_n)^2$ is included in all cases in order to easily simulate the kinetics of the ssDNA once the chain is open ($y_n > y_0$). The dynamics is developed by solving the overdamped Langevin equations of motion,

$$\dot{y}_n = -V'(y_n) - W'(y_n, y_{n+1}) - W'(y_{n-1}, y_n) + F(t) + U'(y_n, y_{n+1}) + \xi_n(t),$$

with $\xi_n(t)$ the Gaussian white noise with zero mean and $\langle \xi_n(t) \xi_k(t') \rangle = 2k_B T \delta_n \delta(t - t')$, which is integrated with a stochastic Runge-Kutta algorithm of the 4th order with a $dt = 0.01$. The values of the potential parameters are the same of those of [27] for an homogeneous adenine-thymine (AT) chain: $D = 0.05185$ eV and $\alpha = 4 \AA^{-1}$ for the Morse potential; $G = 3D$, $y_0 = 2/\alpha$ and $b = 1/2\alpha^2$ for the Gaussian barrier; and $K = 0.03 eV \AA^{-2}$, $\delta = 0.8 \AA^{-1}$ and $\rho = 3$ for the stacking interaction. For simplicity, we use dimensionless units: length is given in units of $\alpha^{-1}$, mass in units of the nucleotide mass (300 u), and energy in units of $D$. The dimensionless temperature is defined as $\tilde{T} = k_B T/D$. With these transformations we get the following units for the force, the frequency and the temperature: $F_u = D\alpha = 332$ pN, and $T_u = 602$ K. The real time $t_R$ results rescaled according to $t_R \rightarrow t_1 = \frac{1}{\alpha} \sqrt{\frac{D}{2}} = 0.19$ ps. Moreover, the overdamped equation of motion (eq. (1)) requires a
time scaling $t_1 \to t = t_1/\tilde{\gamma} = 0.192^2 \gamma \text{ps}^2$. Where the dimensionless damping $\tilde{\gamma}$ has been used ($\gamma = \tilde{\gamma}/t_1$) (see footnote 1).

The dimensionless parameters of the model are then $D = 1, \alpha = 1, K = 0.0362$ and $\delta = 0.2$. We set $K_s = K_d = 1 (= 0.8296 \text{eV} \text{A}^{-2})$.

We use a homogeneous chain of 30 bps. All the bp separations are set to $y_n = 0$ at $t = 0$. Different driving frequencies have been spanned, and the outcomes have been averaged over $N$ realizations.

Results. — CF mode. In the CF mode, the following magnitudes are evaluated: the average opening time $t_{\text{op}}$, defined as the time needed to open a given number of consecutive bps of the chain starting from the first one (we use here 10 bps), the residence times $t_r$ of each bp, defined as the time that each base remains inside the Morse potential ($y_n < y_0$), and the critical force $F_{\text{cr}}$, defined as the critical value of the force that is able to open the chain after a certain waiting time $t_s$. The field phase $\phi$ is changed randomly in each realization in the interval $[0, 2\pi]$. We use $T = 0.5$ ($T = 301$ K), $A = 0.5$ and $\nu_c = 1.5$ for the temperature, field amplitude and constant unzipping force values, respectively.

Figure 2 shows the results of the simulation. The curves show a clear RA mechanism for both protocols, i.e. the behaviour of the unzipping times is quite similar to that of the mean first-passage time of a single Brownian particle crossing a fluctuating potential barrier [14–16]. This means that an evident signature of three different time scales is present, identified by the corresponding frequency regions: at high frequency (HF), for $\nu \gtrsim 10 \ (7.7 \ \text{THz})$, $\langle t_{\text{op}} \rangle$ presents a plateau that corresponds to the case where the effective escape barrier is given by an average potential constant in time. At low frequencies (LF), for $\nu \lesssim 10^{-3} \ (0.77 \times 10^{-3} \ \text{THz})$, there is a notable increase of $\langle t_{\text{op}} \rangle$ times because the period of the driving is much higher than any specific unzipping time, and the contribution to the average of the events with the potential in its higher barriers becomes dominant. The most interesting region appears at intermediate frequency values (IF), where there is a notable decrease in the $\langle t_{\text{op}} \rangle$, with a minimum value of the same order of magnitude of the period of the corresponding driving. This synchronization between time and period of the driving is the fingerprint of the RA mechanism. Such behaviour is observed in both the mean opening time and the mean residence time $\langle t_r \rangle$. In fact, the inset of fig. 2 shows the mean residence times for each base of the chain and it is evident that for each one of them the synchronization occurs in the same way than the total opening time $\langle t_{\text{op}} \rangle$. Differently than in other works [6,7], the resonant mechanism here does not depend on any inertial property of the chain, being the system overdamped.

The frequency resonant region is also evident in another important measure: the mean critical opening force $\langle F_{\text{cr}} \rangle$. We performed a set of calculations in order to find the dependence of $\langle F_{\text{cr}} \rangle$ on the frequency by fixing the amplitude of the oscillating term. Figure 2(b) shows the results for the two protocols for $t_s = 180$. We can see how the curves of $\langle F_{\text{cr}} \rangle$ exhibits a clear minimum in the resonant region, reproducing the same behaviour as $\langle t_{\text{op}} \rangle$.

Both the measures $\langle t_{\text{op}} \rangle$ and $\langle F_{\text{cr}} \rangle$ (and also the $\langle t_{\text{op}} \rangle$-equivalent $\langle t_s \rangle$) measure) provide the evidence of optimized conditions for the experimental execution of the unzipping in the two protocols.

Two main differences can be recovered in these plots. The first concerns the absolute values of the measures. As expected, at HF, results are independent of the protocol. At LF, $\langle t_{\text{op}} \rangle$ and $\langle F_{\text{cr}} \rangle$ of Protocol B are much higher than in Protocol A because the oscillation force acts with the same phase on all bps of the chain. A second difference concerns the resonant region, which in Protocol B is relatively much deeper than in Protocol A, and shows a well precise resonant frequency value instead of a large resonant plateau. This last property is related to the special way in which this protocol is defined and corresponds to a situation where the period of the force synchronizes with all the opening times of the different bases of the chain. To check this effect, a different number of opened bps $N_0$ have been simulated for this protocol, and are shown in fig. 3. For a small $N_0$ the opening times of the bases involve a wide region of periods. With increasing $N_0$, the opening time obviously increases, but also the synchronization of the simultaneous opening of all the bases with the period of the force at the same phase becomes more selective. The result is a narrow minimum able to select

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1 A possible estimation of the damping $\gamma$ of each bp is the following. We assume that each bp be a sphere of radius $R = 1$ nm and mass $m = 300$ uma immersed in water with viscosity $\mu = 1002 \mu \text{P} \text{A} \text{s}$. With these magnitudes we use the Stokes formula: $\gamma = 6\pi R \mu / m = 37.9 \text{ps}^{-1}$. With this value the time unit is then 1.3 ps.
Fig. 3: (Colour on-line) Mean opening time $\langle t_{op} \rangle$ as a function of the frequency for a different number of opening monomers $N_0$ (left). On the right: first column, probability distribution of $t_{op}$ at the minimum of frequency; second column, the cumulative resident times for the bases $\langle t_r \rangle$, and in the third column, the differential resident times of the bases as a function of the frequency (from top to bottom $N_0 = 5, 10, 15$).

Fig. 4: (Colour on-line) CP mode. (a) Average opening time at different frequencies. (b) Average opening force. In both cases $V = 0.05$, $Y = 5$, $A = 0.5$ and $T = 0.5$.

Fig. 5: (Colour on-line) Probability distribution of $t_{op}$ at different frequency values. (a) Protocol A-CF mode. (a) Protocol B-CF mode. (a) Protocol A-CP mode. (a) Protocol B-CP mode.

an optimum frequency value. In this way the repetition of the escape process with a uniform phase distribution of the oscillating driving forces, can give rise to a strict selection of the resonant frequency of the system. This feature is also visible in the right panel of fig. 3 where the $\langle t_r \rangle$ and the differential resident time for each base $\langle \Delta t_r \rangle$ are shown. $\Delta t_r$ is defined as the difference $t_r(n) - t_r(n-1)$, where $t_r(n)$ is the time spent by the $n$-th bp to open. In particular, the mean differential time $\langle \Delta t_r \rangle$ for both $N_0 = 10$ and $N_0 = 15$ presents a narrow vertical line at $\nu \approx 10^{-2.25}$ that shows that the resident times at that frequency are lower (and similar) for all the bases, while for $N_0 = 5$, the resident times are uniform in a large frequency region for quite all the bases opened. This feature is similar to the Protocol-A case. The probability distribution at the minima (1st column on the right of fig. 3) presents a second peak clearer and clearer with increasing the number of opening bases, indicating the selection of the opening times at the different periods of the driving.

**CP mode.** The average opening time $\langle t_{op} \rangle$ has been also computed in the CP mode. We determined the average opening force $\langle F_{op} \rangle$ defined as the force on the spring that pulls the first bp, $F_{op} = K_d(Y(t) - y_1)$, averaged on the time and on the $N$ realizations of the experiment. Figure 4 shows that the RA mechanism is similar to that observed in the CF mode: a minimum of both $\langle t_{op} \rangle$ and $\langle F_{op} \rangle$ is obtained as a function of the driving frequency. As in the previous mode, both protocols show the same HF behaviour. Again, Protocol B presents a well precise resonant frequency, as in the CF case.

Finally, we analyzed the probability distribution of $t_{op}$ for the two protocols and the two unzipping modes at different frequencies. The results are shown in fig. 5. At HF and IF the distributions are nearly Poissonian. For Protocol B two peaks are present in the distribution, corresponding to the main resonant exit at the two first semi-periods corresponding to the upper value of the force. As expected, for the LF range there is a great dispersion of $t_{op}$ and the distributions are highly asymmetric, with fast as well as very longly distributed opening times. The opening time distributions for CP (see panels (c) and (d)) show a more limited region of times, due to the particular way this protocol works, which obliges the opening to occur in a finite time, as the applied force progressively increases due to the increase of the probe distance in time.

**Concluding remarks.** – We have obtained an optimum frequency region of the mean opening times and the mean critical force for the DNA unzipping induced by force oscillating in time in the framework of the Peyrard-Bishop-Dauxois model, for all the cases studied in a short uniform DNA chain of adenine-thymine (AT). This simplification does not prejudice the generality of the outcomes. Longer non-homogeneous chains also give the same qualitative results. Figure 6 shows the mean opening time calculated
for a real piece of DNA of 69 bps, the P5 virus promoter, with the threshold of 10 bps open for our simulations using Protocol A in the CF mode. This DNA sequence (5’-GTGCCATTAGGTATATGCGGCGAGTGACGGAGCAGGATCTCCATTTTGACCGCAACAAATTGAACG-3’) has been largely studied in literature [6,27,32,33]. The heterogeneity is taken into account in the model with the values correspondent to the cytosine-guanine (CG) base pair ($D_{CG} = 1.5 \, D$, and $\alpha_{CG} = 1.5 \, \alpha$). It is evident in the figure that the resonant effect is always present, but with a longer mean opening time than for the AT chain presented before. This is because the CG bases have three hydrogen bonds (one more than the AT bases), so resulting stronger in their separation than the AT bps. In this way the mean resident times for the different bases clearly present higher values (see fig. 6(b)) according to the richness of the number of CG bases in the chain.

With the values of the parameters used in this study the resonant region involves many orders of magnitude. However, this range of frequencies depends on the characteristic opening times of the unzipping. In principle, any factor that leads to an increase of the opening time will cause the RA to occur at smaller frequencies. In fact, by decreasing the pulling force, or by decreasing the pulling velocity, or even by increasing the number of bps used to define the opening time, all these cases generate an increase of the opening times, and, consequently, the limit that we call low frequency will decrease. This is the reason for the broadening of the resonant region observed in the case of the P5 chain, and the displacement of the low-frequency limit to $10^{-4}$.

The different protocols used in this study correspond to different experimental implementations (already used or easily performable in future). Protocol A in the CF mode appears to be the closest to similar experiments already performed. Conversely, Protocol B can be useful for an experiment where the oscillating force is provided by an electromagnetic or electric field having the wavelength much longer than the dimension of the DNA chain. In this case all the bps experience the same oscillating force. Although to our knowledge these frequency optimization has not been observed experimentally yet, it can be checked at the actual development of single-molecule experiments.

Indeed, as mentioned in the introduction, a resonant activation mechanism similar to the one here presented has been already observed in DNA hairpins folding-unfolding (see sect. VI of ref. [10]).

This work is supported by the Spanish DGICYT Projects No. FIS2011-25167, co-financed by FEDER funds, and by the Comunidad de Aragón through a grant to the FENOL group. AEB-P also acknowledges the financial support of Universidad de Zaragoza and Banco Santander.

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