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Understanding the mechanism of DNA threshold elongation

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The mechanism of threshold elongation of DNA macromolecule (overstretching) is studied within the framework of phenomenological approach, accounting both external (stretching) and internal (conformational) displacement components. As shown, the overstretching of DNA under the action of an external force can occur in two stages. Firstly, due to the coupling between the components, at a some critical value of external force a conformational bistability is formed in the macromolecule structure. In turn, the appearance of bistability stimulates the formation of domains in the DNA chain with two different conformations (*B* and *S*). Secondly, under favorable boundary conditions, the conformationally induced deformation acquires the possibility to propagate along the macromolecule as domain walls. In this way the bistability occurrence in the macromolecule conformation provides a threshold effect of elongation. The calculated contributions in DNA overstretching show agreement with the observed data, and allow to explain the dependence of macromolecule threshold elongation on nucleotide content.

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87.15.La Mechanical properties;
87.15.hp Conformational changes;
63.20.Pw Localized modes.

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1. Introduction

Mechanical properties of DNA macromolecule are essentially important for understanding the mechanisms of biological processes in cells. To interpret the data on DNA mechanics, the macromolecule is often modeled as an elastic rod. Due to development of a single molecule manipulation techniques, the mechanical parameters of a DNA double helix (such as Young's module, bending and rotating stiffnesses) have been significantly refined [1–3]. But new results on DNA mechanics not always satisfy the elastic rod model. Sometimes, under the action of an external force, the deformation of double-stranded (ds) DNA occurs as a threshold process (see reviews [4–12]). Most clearly such effects manifest themselves in the experiments on DNA chain stretching. It was shown that at some critical value of applied force ($f_{cr} \sim$ 65 pN), the rotationally unconstrained macromolecule overstretches, i.e., elongates 1.5–1.7 times [2–6]. The constrained dsDNA passes to the overstretched state at a higher force [13,14]. Similar effects were observed for synthetic polynucleotides [15,16] and oligonucleotides [17–20], which have a DNA-type structure. It should be noted, that for dsRNA macromolecules the threshold elongation has not yet been observed [5,21].

The typical view of a dsDNA overstretching curve drawn according to data [3] is shown in Fig. 1. It is considered [1–6], that the deformation of DNA macromolecule occures in a few stages. On the interval of small forces ($\lesssim$5 pN), the force-extension curve describes the entropic extension of dsDNA to its contour length. For larger values of applying force, the elastic stretching of the double helix itself occurs (contribution *a* in Fig. 1). Further a deviation of the stretching curve from elastic course is observed (Fig. 1, contribution *b*). At certain critical value of external force the threshold elongation of the macromolecule is observed (Fig. 1, contribution *c*). The contributions of the entropic extension and the elastic stretching to dsDNA overstretching have been well understood, but the nature of the contributions *b* and *c* remains not clear still.

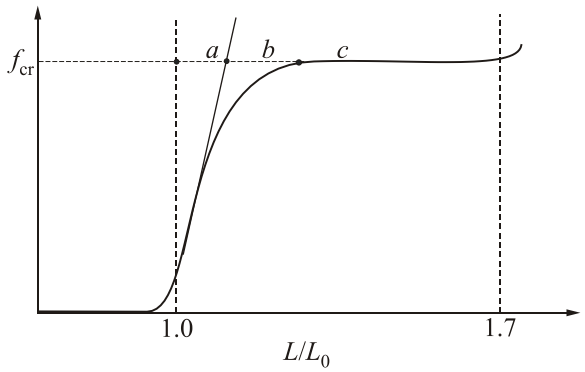

Fig. 1. Typical curve for dsDNA overstretching. The figure is drawn in accordance with the data [3], where overstretching of a λ-phage DNA is studied, f_{cr} = 65 pN. In the present paper the contributions to the dsDNA overstretching are distinguished as: (*a*) elastic stretching of the double helix, (*b*) deviation from the elastic stretching, (*c*) threshold elongation, as such.

Basically, two scenarios of dsDNA overstretching are discussed. First one is the force-induced internal melting of DNA with a transition of the double helix into a single-stranded state with destroyed base pairs [10,13,22–26]. The second scenario is the cooperative transformation of the macromolecule from its usual form (B) to stretched double helix (S-form) with preserved hydrogen bonded complementary pairs [2,3,15,27–29]. Thermodynamical analysis made in [30,31] and experiments [17–20,29,32,33] show that both internal melting and B–S transitions are possible for dsDNA. Their realization depends on temperature, concentration of counterions in solution, and DNA nucleotide content. An important result in understanding the effect is obtained in the work [19], where the appearance of bistability between B and S forms is observed during dsDNA overstretching occurrence.

Despite a rather large number of experimental results, the mechanism of the overstretching process in dsDNA is not yet clear (see discussions after the article [10], in book [12] (Ch. 3), and in the article [34]). In its turn the theoretical studies still have not come to an unequivocal answer, as well. Accordingly to the conformational analysis and molecular dynamics modeling [2,9,35–37], the probable structure of S-form is a narrow double helix, where the base pairs are strongly inclined with the preservation of hydrogen bonding and stacking interactions. The performed modelling demonstrates opportunity of dsDNA to transit to overstretched state, but no gives the explanation of the mechanism of effect. In theoretical works [38–40] it has been supposed that the coupling of a dsDNA stretching with twisting and bending can explain the dsDNA threshold elongation. Of course, it should be noted that the coupling of the displacement components could give a definite quantitative effect in dsDNA stretching, but this in itself can not be the origin of the threshold deformation. Authors of [29] consider that the overstretching deformation in dsDNA happens as a chemical reaction, due to gradual appearance of the domains with stretched form. But the authors, as well as the previous ones, do not give an explanation of how a gradual process can give a threshold effect. Using a polymer approach authors of the paper [41] have come to conclusion that for agreement with experiment it is necessary to suppose the change in the size of a DNA monomer link. That is, it is necessary to take into account the structural (conformational) changes within the macromolecule itself.

Just in the presented work the ability of DNA to change the double helix form under the influence of external factors is taken into account to explain the DNA overstretching. It is well known that the polymorphism of dsDNA structure is the key property of the macromolecule, that distinguish it from other molecules of the cell [42–46]. In the studying DNA overstretching in the present work the two-component approach is used, which takes into account both conformational rearrangement of a macromolecule and its deformation as well. It should be noted, that the two-component approach is a conventional method for description of structure mobility of the one-dimensional systems with the internal degrees of freedoms, such as one-dimensional molecular crystals [47,48 (and cited therein)]. In DNA investigations this approach has been used for the studding the conformational vibrations [49] and the conformational solitons [50–53] in DNA macromolecule.

In the present work, with the help of two-component approach the conditions of bistability of B and S forms realization in dsDNA under the action of an external force are defined. The contributions of different mechanical processes to the elongation of a polymorphic macromolecule are found, and the important role of conformationally induced deformation is shown. The mechanism of threshold overstretching in long DNA macromolecule is proposed and grounded. The calculated energies and characteristic parameters of dsDNA elongation accord to experiment.

2. Modeling the force action on a DNA macromolecule

As well known, dsDNA consists of two polynucleotide strands, which are formed by alternated groups of phosphates and deoxyribose (or sugar) rings. To the sugars the nucleic bases are attached. Under natural conditions, in ion-hydrate environment, DNA strands form a double helix, where the nucleic bases of different strands are bonded in complementary pairs (A·T and G·C) inside the helix [42]. Thus, dsDNA is a polymer, the monomer link of which includes two phosphate groups, two sugar rings and a complementary pair of nucleic bases (Fig. 2(a)).

The contour length of the macromolecule is calculated as $L = (N-1)l$, where N is a number of monomers in dsDNA chain and l — the length of base pair step in the double helix. The value of l is determined as a projection of a distance between the neighbouring base pairs (parame-

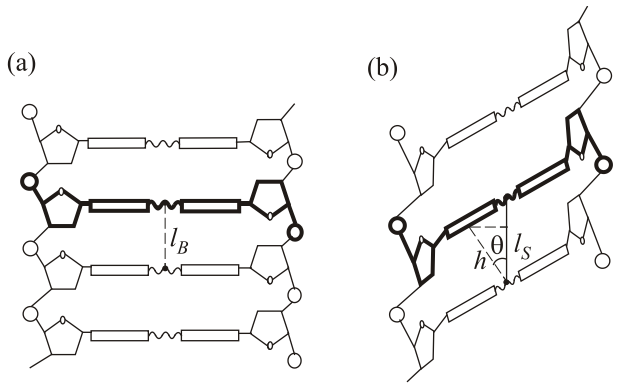

Fig. 2. Double-stranded DNA in B (left) and S (right) forms. The structure of the monomer units are shown in bold. (*a*) for B-form the distance between neighbouring base pairs corresponds to the value of the parameter rise, $l_B \approx h$; (*b*) for S-form the distance between neighbouring base pairs (l_S) is the sum of projections of rise on the helix axis and the value of monomer elongation under B–S transition, here θ is an inclination angle.

ter rise (h) [54] on the helix axis (Fig. 2). Note, that parameter rise remains unchanged in different forms of DNA double helix due to the preservation of van der Waals contacts between the atoms of nucleic bases in a step. In B-DNA the length of base pair step is practically equal to the rise value due to close to orthogonal position of the base pairs with respect to helix axis in B-DNA (Fig. 2(a)).

The analysis of the helix step extension in dsDNA during the overstretching process shows [2,35–37] that the macromolecule elongation is accompanied by a significant inclination of base pairs in the double helix and enlargement of base pairs slide (Fig. 2(*b*)). As follows from [55], such restructuring of the double helix allow to increase the projection of base pair step on helix axis and to enlarge the length of DNA step itself. It should be noted, that mentioned displacements occurs in the double helix without destroying the hydrogen binding in complementary pairs. So, it is fair to consider that the dominant component in the rearrangement of double helix structure under overstretching is the inclination of the base pairs as a whole. Note, these rearrangements in dsDNA can occur due to the changes in the conformation of the sugar rings and the sugar-phosphate backbone as well.

It should be underline, that DNA overstretching occurs with the anomalously large (in compare with the thermal fluctuations) amplitudes of the base pairs displacements. Thus, the effect of DNA overstretching can not be considered within the framework of elastic deformations, and is the subject of the nonlinear mechanics study.

To consider the mechanism of dsDNA threshold elongation in the present study, the model with two displacement components is used. One component (the external is R_n) describes a displacement of nth monomer from its equilibrium position in DNA chain under the force action. In fact, that component is the double helix stretching, the degree of freedom of DNA model as an elastic rod. Another model component (the internal is r_n), let it describe a displacement of the base pair in nth monomer relative to the backbone. Both components are considered as projections of the corresponding displacements on the axis of the double helix (OZ) and are scalar quantities. In the work the dynamics of deformation in DNA macromolecule will be studied also, and so it is assumed that both model components depend on time: $R_n(t)$ and $r_n(t)$. Under the investigation, it is assumed also that DNA macromolecule is already extended to its contour length, and the stretching of the double helix itself is studied.

Let us write the energy of a structural transformation of dsDNA macromolecule under the action of an external force:

$$E = \frac{1}{2}\sum_n \{M\dot{R}_n^2 + m\dot{r}_n^2 + k_R[R_n - R_{n-1}]^2 + k_r[r_n - r_{n-1}]^2 + \Phi(r_n) - \chi F(r_n)[(R_{n+1} - R_n) + (R_n - R_{n-1})]\} + A(R). \quad (1)$$

In expression (1) the summation is over all n monomers in DNA chain, $\dot{R}$, $\dot{r}$ are derivatives with respect to the time; k_R and k_r are the constants of stiffness, which describe the interactions along the macromolecular chain for the external and internal components; M means the mass of monomer link and m is the mass of base pair.

It is worth to note, that DNA is a heterogenic macromolecule due to the heterogeneity of its nucleic bases. But on the conformational pathways, when macromolecule remains in the double helix form with preserved base pairs, dsDNA can be considered as a homogenies polymer because the masses M and m have the same value for A·T and G·C pairs [50,51].

The potential function $\Phi(r_n)$ describes the conformational state of nth monomer itself on the pathway of conformational transition from ground to stretched state. In the absence of an external force polymorphic dsDNA is in a ground state (B-form under the physiological conditions [42]), and S-form should be considered as a metastable state. Thus, for describing B–S transition the function $\Phi(r)$ should be taken in the shape of a double well with two non-equivalent stable states: the ground B-form, and the metastable S-form (positions r_0 and r_2 in Fig. 3). Correspondingly, the conformation barrier (r_1) lies between two defined states.

The term with the coefficient χ in expression (1) describes the coupling between internal and external components under a macromolecule elongation. The presence of coupling term and its sign in expression (1) reflect the fact, that polymorphic macromolecule can reduce the energy needed for the deformation due to the change of its conformation. We will believe that: $\chi > 0$. The value of the

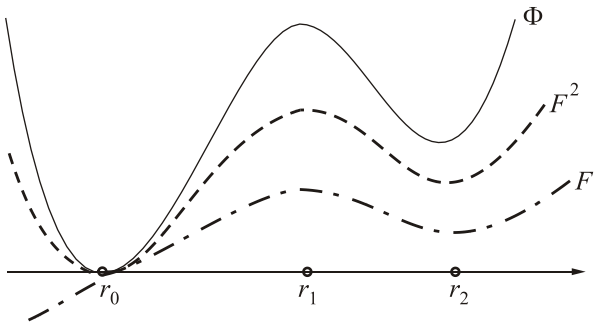

Fig. 3. The shapes of potential functions for nth monomer link in the model (1).

coupling depends on pathway of conformational transformation, and will determine by the shape of potential function $F(r)$.

The last term in expression (1) describes the action of an external force (f) on the macromolecule. Herewith we assume that the external force is applied to the external component, and is directed along the double helix axis. So,

$$A(R) = -f\sum_n (R_n - R_{n-1}). \tag{2}$$

In the present work, the model with only one external and one internal components of a DNA transformation is used, that are the dominant degrees of freedom of the modeled process. It is clear that, in such complex rearrangements as dsDNA overstretching, and other degrees of freedom of the double helix have to take place as well. But in this study, the simplest model with two dominant displacement components will be studied to understand the basic mechanism of threshold elongation of DNA macromolecule.

The model (1), (2) is a development of approach to modeling the DNA conformational transitions, in particular, $B-A$ transitions in dsDNA [50–53], where the DNA rearrangements were studied without the action of external force.

3. Deformation of the polymorphic macromolecule

To understand the impact of the conformation rearrangements in dsDNA deformation let us consider firstly the uniform deformations of macromolecule, assuming that $(R_n - R_{n-1}) \equiv \wp$, $r_n \equiv r$, $\dot{R} = 0$, $\dot{r} = 0$.

Using the model (1), (2), the energy density of the macromolecule that undergoes a uniform deformation can be written in the form:

$$\mathcal{E}(r,\wp) = \frac{1}{2}[k_R\wp^2 + \Phi(r) - 2\chi F(r)\wp] - f\wp. \tag{3}$$

Here $\mathcal{E} = E/N$.

As is clear, the macromolecule conformational state depends on the shapes of potential functions $\Phi(r)$ and $F(r)$. The explicit forms of these functions for dsDNA overstretching transition are not known by now, but their shapes can be determined accurately enough. So, in the ground state (r_0) it is correct to assume that:

$$\Phi(r_0) = F(r_0) = 0. \tag{4}$$

Then, it can be considered that functions $\Phi(r)$ and $F(r)$, by their definition, would increase on the pathway from the ground state of the system (r_0) up to the transition barrier (r_1), and then decrease nearby the metastable state (r_2), as is shown in (Fig. 3). Thus, it should be assumed that for the extrema of potential functions the following inequalities are fulfilled:

$$\Phi(r_0) < \Phi(r_2) < \Phi(r_1);\ F(r_0) < F(r_2) < F(r_1). \tag{5}$$

Under the action of an external force the equilibrium states of the system could be changed. New conformational states and the values of macromolecule deformation can be determined by solving the following equations:

$$\frac{\partial\mathcal{E}}{\partial r} = \frac{d\Phi}{dr} - 2\chi\frac{dF}{dr}\wp = 0, \tag{6}$$

$$\frac{\partial\mathcal{E}}{\partial\wp} = k_R\wp - \chi F(r) - f = 0. \tag{7}$$

From Eq. (7) the expression for the polymorphic macromolecule deformation can be written in the form:

$$\wp = \rho_{el} + \rho_\chi(r), \tag{8}$$

where

$$\rho_{el} = \frac{1}{k_R}f, \quad \rho_\chi(r) = \frac{\chi}{k_R}F(r). \tag{9}$$

As might be expected, the deformation of polymorphic macromolecule (8) is caused by the elastic properties of molecular chain, and the macromolecule conformational state. The term ρ_{el} in expression (8) describes an elastic stretching of a double helix as in the model of elastic rod. The second term in expression (8) appears due to the coupling between the external and internal components of a macromolecule transformation.

The conformational state of the macromolecule is described by equation (6). After substitution of expressions (8), (9) in (6), this equation can be written as:

$$\frac{d\Phi}{dr} - \frac{\chi^2}{k_R}\frac{d(F^2)}{dr} - 2f\frac{\chi}{k_R}\frac{dF}{dr} = 0. \tag{10}$$

Analysing Eq. (10), it is seen that in the absence of external force the functions Φ and F^2 have the same extrema points and depend on r similarly, accurate to constant. Moreover, when the condition for the ground state (4) is satisfied, this constant should be vanished. So, it can be concluded that for these functions the following relation fulfills:

$$\Phi(r) = \varepsilon_o F^2(r), \tag{11}$$

where parameter ε_o has the dimension of energy, and $F(r)$ is a dimensionless function. The value ε_o should be positive due to the positivity of the potential function in (11).

Under the force action, the positions of macromolecule stable states have to change, and new extrema points of the conformational energy (r_{0f}, r_{1f}, and r_{2f}) should appear. As is seen from (10), (11), new extrema can be determined by the equation:

$$\left[\varepsilon_\chi F(r) - \frac{\chi}{k_R} f\right]\frac{dF}{dr} = 0. \tag{12}$$

When writing an expression (12), it is accepted that

$$\varepsilon_\chi = \varepsilon_o - \frac{\chi^2}{k_R}. \tag{13}$$

The consideration of Eq. (12) shows that new extremum r_{0f} can be obtained by equating to 0 the expression in square brackets, that gives

$$F(r_{0f}) = \frac{\chi}{\varepsilon_\chi k_R} f = \frac{æ}{\chi} f, \tag{14}$$

here

$$æ = \frac{\chi^2}{\varepsilon_o k_R - \chi^2}. \tag{15}$$

Two other solutions follow again from the equation: $dF/dr = 0$, and they are $r_{1f} = r_1$, $r_{2f} = r_2$.

As can be seen from (14), the value $F(r_{0f})$ is positive if parameter ε_χ (13), and parameter æ (15) are positive as well. To fulfill these conditions, it is assumed that:

$$\varepsilon_o k_R > \chi^2. \tag{16}$$

A change of the macromolecule ground state position in the presence of an external force can be understood directly from Eq. (14). It is seen that, as $f > 0$, then $F(r_{0f}) > 0$ due to (14). Tacking into account assumed shape of function $F(r)$ (Fig. 3), it may be correct, if the macromolecule ground state shifts: $r_0 \to r_{0f}$, under the force action.

To fully determine the peculiarities of the deformation of polymorphic macromolecule, let us write the conformational deformation ρ_χ (9) in the following form:

$$\rho_\chi(r) = \rho_{o\chi} + \rho_{\rm tr}(r), \tag{17}$$

where the first term

$$\rho_{o\chi} = \frac{\chi}{k_R} F(r_{0f}) = æ\rho_{\rm el} \tag{18}$$

is a primary (before a conformation transition) deformation of the macromolecule due to a change of its conformation in the frame of ground state under the action of an external force. In deriving formulas (17), (18), expressions (9), (14) and (15) are used.

The second term in Exp. (17)

$$\rho_{\rm tr}(r) = \frac{\chi}{k_R}\mathcal{F}(r) \tag{19}$$

is the deformation accompanying a conformational transition as such, if it occur in the macromolecule.

In Exp. (19), the function $\mathcal{F}(r)$:

$$\mathcal{F}(r) = F(r) - F(r_{0f}), \tag{20}$$

describes the change of the conformation state of polymorphic macromolecule under the action of an external force.

In accordance with the defined contributions to the deformation of polymorphic macromolecule, let us rewrite the macromolecule energy. Integrating Exp. (12), one can obtain the expression for macromolecule conformational energy under the external force action:

$$\mathcal{E}(r) = \frac{1}{2}\varepsilon_\chi F^2(r) - \frac{\chi}{k_R} fF(r) + C_r, \tag{21}$$

where C_r is the constant of integration, which can be determined assuming that $\mathcal{E}(r_{0f}) = 0$. In this case

$$C_r = \frac{\chi}{2k_R} F(r_{0f})\, f. \tag{22}$$

Accounting Exps. (14) and (20), the view of the conformational energy (21) can be rewritten in the compact form:

$$\mathcal{E}(r) = \frac{1}{2}\varepsilon_\chi \mathcal{F}^2(r). \tag{23}$$

Accordingly, the energy of the macromolecule uniform deformation (3) can be presented as

$$\mathcal{E}(r, \wp) = \mathcal{E}(r) + A(\rho), \tag{24}$$

where the first term is the energy of deformation induced by the conformational rearrangements as such (23). The second term is conditioned by the appearance of elastic and primary conformational deformations of macromolecule as a reaction on the tension of an external force:

$$A(\rho) = \frac{1}{2} f(\rho_{o\chi} + \rho_{\rm el}). \tag{25}$$

4. Critical regime: the formation of conformational bistability

Let us consider the influence of an external force on the shape of macromolecule conformational energy. It is seen from Eqs. (21), (23), the shape of macromolecule conformational energy is determined by function $\mathcal{F}(r)$, in fact. With the growth of external force the position of ground state (r_{0f}) shifts, and the form of double well energy $\mathcal{E}(r)$ should be changed. Really, as is seen from expressions (14,20–23), the value of potential barrier (at r_{1f}) and the energy of the metastable state (at r_{2f}) will decrease proportionally under the external force increase.

At some critical value of an acting force, the values of $F(r_{0f})$ and $F(r_{2f})$ can become equal and the conformational energy should take the shape of double well function as shown in Fig. 4. Indeed, for some critical value of the external force, the macromolecule conformation can take a bistable form with two equivalent stable states, and with a reduced transition barrier between them. The conditions of such a macromolecule transformation can be found from an equality:

$$\mathcal{E}(r_{0f}) = \mathcal{E}(r_{2f}). \tag{26}$$

The realization of equality (26) means that the macromolecule transforms into bistable conformation (see Fig. 4, curve *3*). Such a state of the system we will call the critical regime.

Accounting (23), (26), and that $\mathcal{E}(r_{0f}) = 0$, for the critical regime it should be fair:

$$\mathcal{F}_{\rm cr}(r_{0f}) = \mathcal{F}_{\rm cr}(r_{2f}) = 0, \tag{27}$$

and, as follows from relation (20), $F(r_{0f}) = F(r_{2f})$.

Note that, in view of relations (26), (27), in the critical regime the expression for the macromolecule conformational energy can be approximated by analytical function. Really, on the interval (r_{0f}, r_{2f}) the function (20) can be written as:

$$\mathcal{F}_{\rm cr}(r) = \frac{1}{d^2}(r - r_{0f})(r_{2f} - r), \tag{28}$$

where $d = (r_{2f} - r_{0f})/2$.

Accordingly, in the critical regime the expression for conformational energy (23) can be presented in the form:

$$\mathcal{E}_{\rm cr}(r) = \frac{\varepsilon_\chi}{2d^4}(r - r_{0f})^2(r_{2f} - r)^2. \tag{29}$$

As is seen, function (29) has two minima and one maximum ($r_{1f} = r_{0f} + d$). Substituting the coordinate of the energy maximum in expression (29), the energy barrier in the critical regime can be determined as

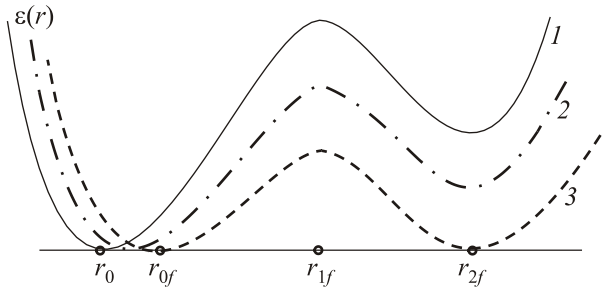

Fig. 4. Transformation of macromolecule conformational state under the action of an external force $f = 0$ (*1*); $0 < f < f_{\rm cr}$ (*2*); $f = f_{\rm cr}$ (*3*) (critical regime). It is seen the shift of the ground state of macromolecule conformation: $r_0 \to r_{0f}$.

$$\mathcal{E}_{\rm cr}(r_{1f}) = \frac{1}{2}\varepsilon_\chi = \varepsilon_{\chi b}. \tag{30}$$

Using expressions (14) and (27), we can write the expression for the value of external force under the critical regime realization as:

$$f_{\rm cr} = \frac{2\varepsilon_{\rm om}}{æ_{\rm cr}\rho_{of}}. \tag{31}$$

Here, $\varepsilon_{\rm om}$ is the energy difference between the ground and metastable (deformed) state of the macromolecule in the absent of force action:

$$\varepsilon_{\rm om} = \frac{1}{2}\Phi(r_2) = \frac{\varepsilon}{2}F^2(r_2), \tag{32}$$

and $\rho_{0f} = \rho_{\rm el} + \rho_{o\chi}$ is the uniform deformation of the macromolecule in the critical regime.

Note that using the formula (31), it is possible to determine the value of $\varepsilon_{\rm om}$ from the experimentally measured critical force and observed values of ρ_{0f} and $æ_{\rm cr}$.

As is seen, when the acting force approaches to its critical value, the contributions of the primary and elastic deformations of the macromolecule increase. Both these contributions create the uniform deformation of the macromolecule (ρ_{of}), but not constitute to the threshold process.

5. Conformationally induced deformation and threshold elongation in DNA macromolecule

Under the critical regime the macromolecule conformation transforms to a bistable form, thus the conformational transition becomes very likely and can induce the overstretching deformation in macromolecule chain. As is known [56], the realization of structural transitions in a macromolecule chain can occur through the formation of domains of monomer units with another (then initial) structural state. If the energies of both conformational states are the same, the boundaries of domains (domain walls) can move along the chain increasing (or decreasing) the domain area [57–60]. Under definite boundary conditions the induced in this case deformation can propagate along the macromolecule and lead to a threshold effect. Such mechanism can explain the process of dsDNA overstretching.

For understanding the process of dsDNA threshold elongation let us study the dynamics of B–S transition and induced by it deformation. Let us go to the continuum approximation, which is usually used when considering the structural transitions dynamics. It should be noted that in the case of studding B–S transition, the continual approximation is also valid. As molecular modeling [2,35,36] suggests, the stretched DNA retains pairs of complementary bases and stacking interactions between them up to the critical value of force. For dsDNA the preservation of its structural organization is sufficient to the use of the continuum approximation [51]. In the continuum approximation it is

considered $R = R(z,t)$, $r = r(z,t)$, and $(R_n - R_{n-1}) = hR'$, $(r_n - r_{n-1}) = hr'$, where R' and r' are the derivatives with respect to z, and h is the parameter rise, which accords to the base pair step in B–DNA.

The equations of motion for the external and internal components of a polymorphic macromolecule deformation can be written as

$$\ddot{R} = s_R^2 R'' - \frac{\chi h}{M}\frac{dF}{dr}r'; \tag{33}$$

$$\ddot{r} = s_r^2 r'' - \frac{1}{m}\left[\varepsilon F(r) - \chi h R'\right]\frac{dF}{dr}. \tag{34}$$

In Eqs. (33), (34) $s_R^2 = k_R h^2/M$, $s_r^2 = k_r h^2/m$, and the relation (11) between the potential functions is used also.

To consider the dynamics of conformational transition along the macromolecule chain, let us introduce a wave coordinate $\zeta = z - vt$ and will seek the solutions having the asymptotic of stable states. That are (r_{0f} or r_{2f}) of dsDNA conformation in the critical regime.

After the wave substitution and one-time integration of Eq. (33), we obtain the following expression:

$$(s_R^2 - v^2)R_\zeta - \frac{\chi h}{M}F(r) = C_R. \tag{35}$$

Equation (35) determines the dynamics of macromolecule deformation. In this equation R_ζ is the derivation with respect to ζ, C_R is the constant of integration. Considering $R_\zeta = \wp/h$, and that the initial condition for R_ζ is determined by the expression (7), we can obtain $C_R = fh/M$.

Introducing the wave coordinate in Eq. (34), and taking into account expression (35), after integration we obtain the equation for describing the dynamics of conformational component:

$$r_\zeta^2 + Q_f^2(r) = 0, \tag{36}$$

where $Q_f^2(r)$ is an effective potential energy of nonlinear oscillator (36).

The function $Q_f(r)$ itself is a cumbersome functions r, external force f and the model parameters. But Eq. (36) can be simplified, accounting that in experiments on DNA stretching the measured processes have the velocities not exceeding 10^{-5} m/s [2], which are much smaller than the value of velocity s_R, which can be estimated by formula $s_R = (k_R h^2/M)^{1/2}$. Using the value of stiffness constant k_R, which can be calculated from the experimental data on dsDNA Yong's module (see below), one can obtain: $s_R \sim 6\cdot 10^2$ m/s. The velocity s_r should have a close order, $s_R \le s_r$, according to our analysis in [51].

Thus, for the processes of dsDNA elongation the following inequality is true: $v^2 \ll s_R^2$, s_r^2. In this case, the effective potential function $Q_f^2(r)$ can be expressed in terms of the conformational energy in its critical view (23), and for the critical regime it can be written using expression (29). So, for the velocities of real experiment, it can be obtained the following:

$$Q_f^2(r) = -\frac{\varepsilon_\chi}{k_r h^2}\mathcal{F}_{\rm cr}^2(r). \tag{37}$$

The solution of equation (36) with potential (37) for the asymptotic of stable states (as $\zeta \to \pm\infty$, $r \to r_{0f}$ or r_{2f}, and $r_\zeta \to 0$) has the form of the domain wall [57–60]. After integration of Eq. (36) with the above-mentioned boundary conditions, we can obtain the following expression for the domain wall in the macromolecule:

$$r(\zeta) = r_{0f} + d\,[1 \pm \mathrm{th}(q_r\zeta)], \tag{38}$$

where

$$q_r = \sqrt{\varepsilon_\chi/k_r d^2 h^2} \tag{39}$$

has the dimension of inverse length.

In Exp. (38), the sign has been chosen in accordance to the boundary conditions: minus, if at the boundary (say, $\zeta \to -\infty$) r_{0f} state is realized (as $\mathrm{th}(-\infty) = -1$); and plus, if $r_{2f} = r_{0f} + 2d$ state. It is seen, solution (38) is a wave in the form of a step of $2d$ size — the transition from state r_{0f} to r_{2f} one, or the reverse process.

In a view of result (38), let us find the displacement of external component induced by the conformational transition. Using Eq. (35) and substitution (20) one can obtain:

$$R_\zeta = \frac{1}{hk_R}\left[f_{\rm cr} + \chi F(r_{0f}) + \chi\mathcal{F}_{\rm cr}(r)\right]. \tag{40}$$

According to expressions (9), (17), and using (40) the elongation of polymorphic macromolecule can be written as:

$$\delta L(\zeta) = N\rho_{of} + \rho_{\rm tr}(\zeta), \tag{41}$$

where ρ_{of} is the uniform deformation of the macromolecule chain, and $\rho_{\rm tr}$ is the wave of deformation induced by the wave of conformational transition (Fig. 5(a)).

The conformationally induced deformation can be expressed as

$$\rho_{\rm tr}(\zeta) = \frac{\chi}{hk_R}\int_0^\zeta d\zeta\mathcal{F}_{\rm cr}(r) = a_{\rm tr}[1 \pm \mathrm{th}(q_r\zeta)], \tag{42}$$

where $a_{\rm tr} = \chi/hk_R q_r$. Here, the solution for $r(\zeta)$ (38) and expression (28) for $\mathcal{F}_{\rm cr}(r)$ are used. To derive expression (42), it is supposed that states r_{2f} and r_{0f} are realized at different sides of the macromolecular chain. Thus, $\wp = \rho_{of} + 2a_{\rm tr}$ at one side of the domain wall (where $r = r_{2f}$), and $\wp = \rho_{of}$ at another side ($r = r_{0f}$) (Fig. 5(a)).

It should be noted that obtained solutions for the describing domain walls (38), (42) are the topological solitons. This type of solitons remains stable for unchanged boundary conditions in a macromolecule chain [57–60],

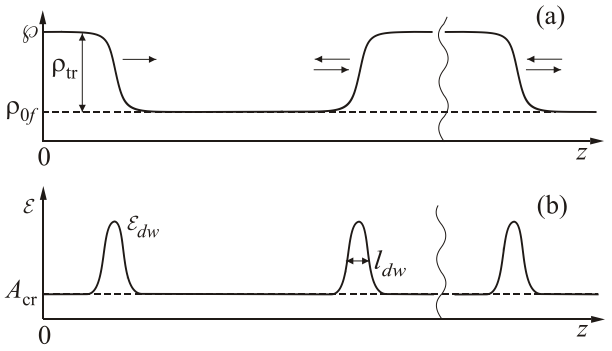

Fig. 5. Propagation of the wave of a conformationally induced deformation along the macromolecule chain under conditions of the critical regime: (*a*) macromolecule deformation comprises the deformation induced by the conformational transition (ρ_{tr}), and by the sum of elastic and primary deformations of the macromolecule ($\rho_{of} = \rho_{el} + \rho_{o\chi}$); (*b*) the energy distribution in the macromolecule chain under a threshold elongation, $\mathcal{E}_{dw}$ and l_{dw} are the energy and thickness of a domain wall, A_{cr} is the work of the external force to form a uniform deformation in the macromolecule.

and their appearance in the macromolecule happens at the end of the chain. The physical nature of these excitations is connected with the nonlinear character of the conformational energy and the existing of the coupling between the external and internal components in the macromolecule (1).

Besides, the Eqs. (36) and (40) have also two-soliton solutions, which describe the occurrence of the domains of another conformation inside the macromolecule with some different conformation. These solutions are shown in Fig. 5 as well. Note, that realization of one-soliton solution is more favorable energetically, because it requires the formation of only one domain wall at the end of macromolecule chain in this case.

The one- and two-soliton solutions differ from each other not only by the number of domain walls, but also by the boundary conditions for their realization. For the realization of one-soliton solution, it is important to have distinct stable states (r_{0f} or r_{2f}) at the different ends of the transition region. For the realization of two-soliton solution, it is necessary to have the same stable states (say, the ground state r_{0f}) at the domain boundaries.

6. Quantitative results

The developed approach allows us to study the properties of the overstretching process in dsDNA on the quantitative level. It is of interest to determine amplitude, thickness and energy of domain walls for the regime of dsDNA threshold elongation. For these purposes let us firstly get the expressions for estimations of these values and to determine the parameters used for calculations.

The choice of model parameters. As is seen from expression (42), the amplitude of macromolecule elongation induced by conformational transition has the value: $\rho_{tr} = 2a_{tr}$. Substituting q_r (39), in the expression for a_{tr} we can obtain $\rho_{tr} = 2d\sqrt{æk_r/k_R}$.

Hereinafter in this section we assume that the value of parameters æ and χ corresponds to their critical value.

Assuming that the constants k_r and k_R for DNA macromolecule are of the same order of values, the following simple formula for the estimation of the elongation amplitude can be obtained:

$$\rho_{tr} \approx 2d\sqrt{æ}. \tag{43}$$

It should be noted, that whereas d is a constant defined by a transition pathway, the amplitude of macromolecule elongation varies proportionally to the square root of æ.

The length of the double helix step in S-form should be calculated as a sum:

$$l_S = h\cos\theta + \wp, \tag{44}$$

where the first term is the projection of rise on the helix axis (here θ is the inclination angle, Fig. 2(b)), and the second term is the value of monomer elongation under B–S transition:

$$\wp = \rho_{el}(1+æ) + 2d\sqrt{æ}. \tag{45}$$

Here the expressions (8), (9), (18) and (43) are used.

The domain wall thickness should be determined as $l_{dw} = 2q_r^{-1}$ [57]. Using expressions (13), (15) and (39), the following formula for the domain wall thickness under the macromolecule overstretching can be obtained:

$$l_{dw} = hk_R\rho_{tr}/\chi. \tag{46}$$

The probable value of χ can be determined, using expression (15):

$$\chi^2 = \frac{æ}{1+æ}\varepsilon_o k_R. \tag{47}$$

As is seen, to estimate the parameter χ it is necessary to use the values of æ (which is observed), the known parameters of macromolecule stiffness and the energy ε_o.

The energy of domain wall can be determined as following:

$$\mathcal{E}_{dw} = \frac{1}{2h}\int_{-l_{dw}/2}^{l_{dw}/2} \varepsilon_{\chi b}\,\mathrm{ch}^{-4}(q_r\zeta)d\zeta. \tag{48}$$

To derive expression (48), the solution (38) and expressions (29), (30) are used.

After integration in (48), the resulting formula is:

$$\mathcal{E}_{dw} = 0.61\frac{l_{dw}}{h}\varepsilon_{\chi b}. \tag{49}$$

The obtained expressions allow us to determine the necessary parameters of the model.

In the calculation of the relative DNA elongation in S-form in compare with the same in B-form, the expression (44) is used. Accordingly, the DNA relative elongation is calculated as: $L/L_o = l_S/h$.

The estimation of the parameters values. For calculations of the characteristics of dsDNA overstretching process, the following values of model parameters are used: $k_R = s/h$, where dsDNA stretch module (S) has the value 1100±200 pN [39], and the rise h = 3.34 Å (in accordance to [61]). Thus, k_R =4.71±0.86 kcal/mol·Å^2. The value of parameter ε_o = 6 kcal/mol is adopted by the data of conformational analysis of DNA backbone [42,62] ε_{ob}.

From the observed overstretching data for dsDNA with an average nucleotide content and for the critical value of an external force (f_{cr} = 65 pN) [2,3,6,22,25,27] one can estimate the ratio: $\rho_{o\chi}/\rho_{el} \approx 1$. This evaluation allows to estimate the parameter æ as equal 1. Then, using formula (47) with known values of ε_o and k_R, one can obtain the value of coupling parameter: χ_{cr} = 3.76 kcal/mol·Å^2.

The determination the value of parameter d, that uses in (38), (43), (45), can be done from the data of [35]. By these results, under overstretching of dsDNA, the base pair inclination angle increases on ~ 34° in compare with B-form (our estimation by the data of [35], Fig. 3(b), structure 1.6). This gives the following estimate for the displacement of the base pair center in dsDNA (the middle point of the C_6C_8 line in DNA base pair [54]) along the double helix axis: 2.7 Å. The obtained value accords to the contribution of the conformational rearrangements in the elongation of the monomer link (17). Subtracting the primary deformation, that for dsDNA with the average value of the stretch module and value of the parameter æ = 1, is $\rho_{o\chi}$ = 0.2 Å, we obtain the following estimate for parameter d — 1.25 Å.

Dependence on nucleotide content. The parameters evaluated in such a way allow to calculate the characteristics of the overstretching process for dsDNA with an average value of the stretch module. The results of this calculations are presented in Table 1, in the 2nd row. But the DNA is a heteronomic macromolecule, and accordingly to results [15,16] the dsDNA overstretching depends strongly on nucleotide content.

To study the dependence of DNA overstretching process on nucleotide content the calculations of dsDNA elongation characteristics are performed also for double helix with stretch module, which differ from their average value by ±200 pN. Conditionally, in accordance with data [15,16], we will assume that dsDNA with lower stretch module will describe the dsDNA with A·T-rich content (1st row in Table 1), and the dsDNA with higher stretch module — the dsDNA with G·C-rich content (3*th* row in Table 1). In this case the values of parameter æ are calculated by formula (15) with different values of k_R, due to their deviations from the average value. The calculations of overstretching characteristics for dsDNA with different stretch modules are done with the same values of parameters ε, χ, and d, assuming that these parameters are not depend considerably from nucleotide contents. All values in the table are calculated with the accuracy up to the second decimal point and then are rounded to the first one.

As is seen from Table 1, the calculated values of dsDNA elongation per monomer correspond in order of their magnitudes to experimental data [1–6]. Over the range of DNA stretch module variation, the contribution of the elastic deformation ρ_{el} changes moderately, only in the second decimal point. In contrast, the contributions of the primary and transition deformations, and the value of parameter æ change significantly, and are larger for macromolecule with smaller stretch module (with A·T-rich content). The deformation ρ_{tr} gives the largest contribution to the value of macromolecule deformations in each case (more then 80%). The obtained results correspond with the data of the overstretching kinetics study in the force-clamp experiments [18,29], where it is shown that the macromolecule stretching amplitude increases by an order in the force interval of the DNA threshold elongation.

Note, the results presented in Table 1 show also that in conditions of the critical regime the transition barrier between unstretched and stretched DNA forms falls significantly (in compare with its initial value, ~ 3 kcal/mol).

It is seen also that the sizes of domain walls (l_{dw}) are practically unchanged on the interval of stretch module variation. Here, two processes (a decrease of the parameter æ and an increase of the macromolecule stiffness) proceed concurrently (43), (46).

Table 1. The calculated characteristics of dsDNA overstretching under the action of a critical force (f_{cr} = 65 pN): the values of parameter æ; the threshold elongation of the double helix per monomer link ($\wp$) and the contributions to it; the values of B–S transition barrier ($\varepsilon_{\chi b}$); the thicknesses of domain walls (l_{dw}), the energies of their formation, and the value of relative elongation. The data are presented for dsDNA with an average stretch module (2nd row), and the same for DNA with differ by ±200 pN stretch modules (1st and 3th rows).

S, pN	æ	$\wp$ (ρ_{el}, $\rho_{o\chi}$, ρ_{tr}), Å	$\varepsilon_{\chi b}$, kcal/mol	l_{dw}, h	A_{cr}; $\mathcal{E}_{dw}$, kcal/mol	L/L_0
900	1.6	3.7; (0.2; 0.4; 3.1)	1.2	3.2	0.9; 2.3	1.9
1100	1.0	2.9; (0.2; 0.2; 2.5)	1.5	3.1	0.6; 2.8	1.7
1300	0.7	2.4; (0.2; 0.1; 2.1)	1.7	3.1	0.4; 3.3	1.5

Note, the energies for initiating the appearance of domain walls are not so large in order to destroy a base pairs, in all cases the sum of the work (A_{cr}) and the domain walls themselves ($\mathcal{E}_{dw}$) is less then the denaturation energy of a pair.

7. Discussion.

According to the developed theory, the overstretching process in dsDNA takes place in two stages. At the first stage, at $f < f_{cr}$, under the external force action the uniform deformation appears in the macromolecule chain. The arising deformation consists of elastic stretching of DNA chain (ρ_{el}), and of the stretching caused by primary changes in the double helix conformation ($\rho_{o\chi}$) before conformational transition.

At the second stage, at $f = f_{cr}$, the macromolecule conformation transforms to a bistable state together with a decreasing of the energy transition barrier before the overstretching. The appearance of a bistable conformation in the double helix makes it possible to realize the cooperative B–S transition in a macromolecule chain, when the B–S boundaries propagate along macromolecule as domain walls. This scenario of the overstretching process in dsDNA is in accordance with the observation of the bistability of B and S forms in the range of the critical force action [19,20].

As is seen from developed theory, the propagation of the domain walls is strictly conditioned by boundary conditions and depends on the dsDNA state on the ends of the macromolecule under the force action. The predicted dependence of DNA overstretching on the boundary conditions is in a qualitative agreement with the results of the conformational analysis [35], and the experimental data [27].

Under constructing of dsDNA stretching model it was assumed that the macromolecule conformational rearrangement takes place as the displacement of the base pairs at the expense of the sugar-phosphates backbone transformations. This assumption can be confirmed by the observation of significant changes of the DNA Raman bands around 800–900 cm^{-1} and 1100–1200 cm^{-1} in single molecule experiments [63]. As known, these bands reflect the specific vibrations of DNA sugar rings and phosphate groups, respectively [42].

From the results of Table 1, it is seen that the overstretching deformation should be different for double helix fragments with different nucleotide content. According to the calculations made the overstretching deformation (and parameter æ) should be larger for dsDNA with smaller stiffness. So, because the stretch module for A·T-rich DNA is smaller than for G·C-rich DNA (as follows from the results of [15,16]), the overstretching deformation should be larger for A·T-rich DNA. Note, that this conclusion is in accordance with results of [19], where the larger amplitudes of the overstretching deformation are observed for A·T-rich DNA.

According to the conformational analysis [35,36], under overstretching the base pairs in S-DNA are greatly inclined with large uphill slide. These structural changes in DNA should lead to the losses in the base pairs stacking. As is known [64], the base stacking on a par with hydrogen bonding stipulate the base pairing in the double helix and dsDNA stability as a whole. Thus, the larger overstretching deformation of DNA with A·T-rich content should lead to disruption of base pairs and the subsequent internal melting. Hence, under overstretching of DNA with rich content of A·T pairs, or of DNA with reduced stability (due to temperature increasing, or counterions concentration decreasing), the overstretching process should lead to melting transition. Therefore, it can be concluded, the S-form is not stable for dsDNA with reduced helix stability. Such a conclusion agrees with the experiments [19,20], where some intermediate (between B and melted) state is observed under overstretching of A·T-rich oligonucleotides. As is shown in [19,20], this intermediate state is unstable under physiological conditions, and transmits to the melted state. So, it can be just the observation of unstable S-form for A·T-rich DNA.

It is important that the energy losses under propagation of B–S transition along dsDNA are considerably less than for the melting process. Really, under B–S transition the losses for internal component is minimal, because, in this case, the base pairs move as a unit, whose masses are the same [50,51]. In addition, under B–S transition propagation in dsDNA the losses for the external component due to the interaction with environment cannot be large, as well. This is so correct, because under B–S transition the double helix diameter is significantly reduced [28,35] in contrast with melting transition. The ability of the B–S domain walls to propagate in a heteronomic DNA is supported also by the results of quantitative estimations shown in Table 1, where is seen, that the size of domain walls remains sufficiently stable under the variability of the dsDNA stretch module.

Thus, there is every reason to believe that overstretching process in real dsDNA occurs as follows. Initially, at the critical value of acting force, B–S transition spreads across whole extended DNA chain, then in DNA sections with a rich A·T content the S-form, because of its instability, goes into the melted state.

Conclusions

It can be concluded that dsDNA as a polymorphic macromolecule has an additional mechanism of deformation that arises because of the coupling between stretching and conformation of the double helix. The elongation of dsDNA macromolecule can occur as a threshold effect due to the conformational bistability appearance and subsequent B–S transition propagation in the double helix as a domain wall. It should be noted that the absence of poly-

morphic properties in an RNA macromolecule can be the reason for not observing the overstretching effect for it.

As our analysis shows, the implementation of such a mechanism has definite differences for A·T-rich and G·C-rich dsDNA fragments. The overstretching for A·T-rich sequences, due to their lower stiffness, has a larger value of deformation, that leads to the larger losses in base pairs stacking. Therefore, the *S*-form in dsDNA is no stable for A·T-rich sequences, and a melting transition becomes more profitable here. Besides, *B*–*S* transition in G·C-rich dsDNA should occur very quickly, covering large fragments of the macromolecule due to the relatively small dissipation energy of the domain walls propagation.

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