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TO THE UNDERSTANDING OF PHASE DIAGRAM OF DNA DOUBLE HELIX UNZIPPING

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Interpretation of phase diagram (temperature-force) of the mechanical melting of the DNA double helix in the temperature range from 15 to 50 °C is suggested. The double helix unzipping is modelled taking into account the probable pathway of the mechanical strands separation under external force, the formation of metastable states of the base pairs in DNA at high temperature, and the possibility of the macromolecule transition to the condensed state at low temperature. It is shown that the DNA unzipping in the different temperature intervals may be considered as a first order phase transition induced by applied force. The expression for the critical force is obtained and the dependence of force on temperature is calculated. A reasonable agreement of our theory with experiment is reported for the temperature range 24-35 °C. Possible reasons for the origin of plateaus above 35 °C and below 24 °C are suggested.

KEY WORDS: DNA macromolecule, mechanical melting, double helix unzipping, DNA metastable states.

The transition of DNA macromolecule from the double-stranded (ds) state to the single-stranded (ss) configuration occurs under a temperature increase (> 60-90 °C), change of ion concentration in solution or humidity, interaction with proteins and under the action of some external forces. Under such processes the H-bonds in complementary pairs of dsDNA break out and the nucleic bases become open. In these transitions the opening of the pairs in the double helix is a cooperative process that induces the separation of the two DNA strands. Under native conditions the DNA opening is a key element of essential biological processes, such as the DNA transcription and replication. The understanding of mechanisms of double-helix separation is one of the main problems of DNA physics. Complete resolving of the problem is not reached still because of insufficient knowledge on DNA helix micromechanics.

During the last decade there appeared a number of new experimental techniques for probing single-molecule mechanics which have been used for studying the process of DNA double helix opening. The important advances were achieved with the use of atom force microscopy, optical and magnetic tweezers [1,2]. There was developed a special, so called, Bockelmann system for the investigation of mechanical separation of the DNA strands (unzipping) [3-5]. The unzipping of the DNA helix was studied under the action of external force acting on a paramagnetic bead chemically connected with one of the strands of the double helix. The second strand of the dsDNA is tethered to a massive surface through a special spacer – another dsDNA, see Fig.1. After stretching of a spacer to its counter length by comparatively small force (2pN) the unzipping of the dsDNA begins. In the experiments [3-5] the DNA from lambda phage was used for the stretched macromolecule and for the spacer. This DNA had the known base pair sequence (48502 bp) and the counter length of 16.5 μm

Recently, the experiment on dsDNA mechanical separation was supplemented with measurements of the temperature dependence of DNA unzipping within the temperature interval from 15 up to 50 °C [6]. It was measured the force needed to unzip the first 1500 base pairs in λ-DNA. The results obtained were presented as the force-temperature phase diagram of DNA unzipping. The experiment shows that the base pair opening by external force depends on temperature nontrivially [6]. The unzipping force decreases steadily with the temperature growth only within the range of temperatures 24-35 °C. Beyond this range, i.e. at 18-24 °C and at 35-40 °C, the force-temperature diagram of DNA unzipping possesses the plateaus. In these temperature ranges the unzipping force drops without significant temperature rise. The observed plateaus cannot be explained within the frame of traditional thermodynamic approach [6], and are not seen in the Monte-Carlo simulations based on a simple DNA model [7].

In the present work the DNA unzipping is considered as a process of probing of dsDNA state by applied force at a fix temperature. It is important to take into account that under mechanical unzipping the DNA macromolecule is in a double-stranded configuration in the studied temperature interval. As known the DNA double helix exists in the double-stranded state up to temperatures of 60-70°C [8,9]. The process of DNA melting is observed with the use of the hypochromic effect in UV spectra which is directly connected with keeping up of the stacking interactions of bases along the DNA chain [9,10]. The absence of significant changes in DNA hypochromism implies that the observed structural transformations in the double helix under temperature <50 °C occur without disruption of double-stranded ordering. This point of view coincides with results of the DNA melting study utilizing electronic microscopy [11] and computation analysis [12].

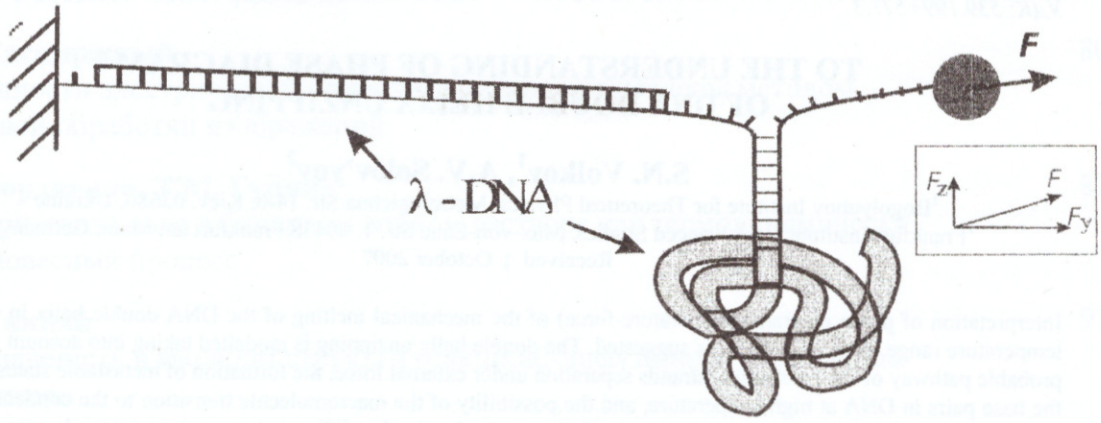

Fig.1 The process of ds λ-DNA unzipping by external force in the experiments [4-6]. In the inset the force decomposition is shown.

So, in our approach we will consider that the DNA helix in the experiments [6] in the temperature interval of 15-50 °C does exist in the ds configuration before unzipping. At the same time for the interpretation of the phase diagram of DNA unzipping it is necessary to take into account the possible premelting changes in the double helix such as the change in the helix angle when the temperature increases from 0 to 40 °C [13,14], the appearance of thermally induced metastable states above 35 °C as it was observed in the circular dichroism experiments [15] and in the fluorescent correlation spectroscopy [16].

As known [4], the λ-DNA has about 40% A·T pairs in the first 1500 bp that are being unzipped in the experiment [6] and about 60% A·T pairs in remaining part of the DNA sequence. The DNA A·T-rich regions are less stable then G·C-rich regions. Therefore the metastable states of A·T pairs may play a definite role in the force-temperature dependence of DNA unzipping.

It should be noted that in accordance with the known phenomenon of DNA condensation [17] in the Bockelmann system the aggregation of single DNA molecule is very probable under relatively low temperature and in the environment of definite number of paramagnetic beads (see the conditions of experiments in [6]).

All these factors are taken into account under consideration of the DNA unzipping process in the present work.

Mechanism of DNA unzipping process

Under applying the external force the DNA chain divides on to two parts: double-stranded, with closed base pairs, and unzipped, with opened base pairs. Between these parts of the DNA chain only one boundary (so called "fork") occurs. During the DNA unzipping the fork moves along the chain as dynamically stable atomic cluster. The form and stability of fork cluster determines the character of phase transformation in the chain.

To understand the unzipping of dsDNA let us consider the pathways of base pair opening in double helix. As known there are two possible pathways of base pair opening in double helix: "opening" and "stretching". Under pathway "opening" the nucleic bases in the pair move in the direction of double helix grooves, and under pathway "stretching" the nucleic bases in the pair move in the direction of backbone strands. Usually from the large rigidity of backbone only the "opening" pathway is considered as probable for DNA opening in natural conditions [18]. But under directed mechanical melting (unzipping) the pathway of dsDNA "stretching" have take place due to the construction of Bockelmann system.

Taking into account the experimental conditions for DNA unzipping and the results of the modeling of the conformational pathway of base pair stretching in dsDNA [19] the energy of unzipping process may be write as the following expression:

$$E = \int \frac{dz}{2h}\left[\mu\left(\frac{\partial y}{\partial t}^2 + s^2\frac{\partial y}{\partial z}^2\right) + \Phi(y) + \mathrm{A}(y)\right], \qquad (1)$$

where μ - the reduced mass of bases in the complementary pair, s – the elastic constant of interaction along the chain (sound velocity), Φ(y)) – the potential energy of base pair stretching in direction OY (Fig. 1). From our estimations [19] the values μ are not influence on base pair type, but the constant s depends on nucleotide sequence in DNA. The last term in expression (1) – A(y), denotes the work of external force. In a simple case

this work may be written as $A = (y_0 - y)F$. The preliminary view of the functions $\Phi(y)$ and A(y) is shown on the Fig.2, where y_0 and y_2 are the stable states corresponding to the closed and opened states of the base pairs in DNA. As seen from Fig.2 under some critical value of force at $y = y_2 > y_0$, both states become equally alike and the unzipping may realize.

The equation of motion of unzipping fork has the following view:

$$\mu\left(\frac{\partial^2 y}{\partial t^2} - s^2 \frac{\partial^2 y}{\partial z^2}\right) + \frac{\partial \Pi}{\partial y} = 0 \ . \qquad (2)$$

In expression (2) $\Pi(y)=\Phi(y)+A(y)$.

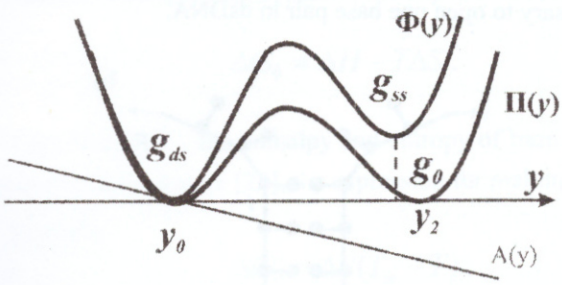

Fig. 2 A sample view of the potential of the base pair opening in dsDNA under applying of the external force.

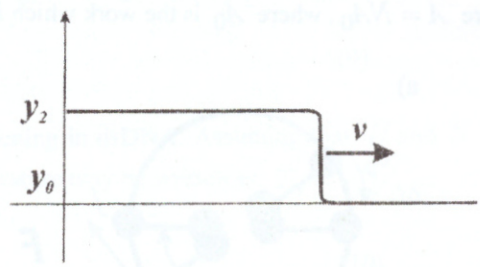

Fig. 3 The view of the propagating transition of the dsDNA unzipping.

Taking into account that the unzipping process occurs with the definite velocity v, let us find the view of the solution of (2) in the form of the wave: $y = y(u)$, and $u = z - vt$. Here z – the coordinate along the chain, t - the time. In this case the equation (2) has the form:

$$\mu(v^2 - s^2)\frac{\partial^2 y}{\partial u^2} + \frac{\partial \Pi}{\partial y} = 0 \ . \qquad (3)$$

But because of low speed of strand puling by optic or magnet tweezers (20-40 nm/sec [4,5]) in compare with the value of sound velocity in DNA (~10^3 m/sec [20]) the relation has to be fulfilled: $v^2 << s^2$, and the equation (3) may be resolved as for the static state in condition of invariable force action.

So the solution of equation (3) for the case of state equilibrium ($\Pi(y_0)=\Pi(y_2)$) give the form of a step – the transition from closed to opened DNA state:

$$y(z) = a + b\,\mathbf{th}(qz) \ , \qquad (4)$$

where $a = (y_2 + y_0)/2$, $b = (y_2 - y_0)/2$ and q is coefficient which depends on the system parameters (mass, constant s and the potential form).

The view of the solution is presented on Fig.3. It is necessary to take into account also that at the room temperature the transition from close to open state is no cooperative process [21,22]. For our model that is mean that the potential barrier of $\Phi(y)$ is larger then the stacking interactions and the transition can not propagate along the macromolecule chain without the external force. Therefore the transition has the form of sharp step with the very narrow wide (one step only), and the velocity of it propagation is the speed of pulling of the single strand by external force (Fig.1,3).

According the evaluation made the unzipping fork moves with the velocity of external force and no conformational excitations propagate forward along the dsDNA. So, as a common view at the temperature much less then the melting temperature the dsDNA unzipping has the character of first order phase transition induced by external force. This conclusion may be true up to the some higher temperatures until the DNA safe the ds form.

Critical force of DNA unzipping

Taking into account the results of previous section let us write the free energy of the base pair opening in the double helix under action of external force:

$$\Delta G = \Delta G_0 + A, \qquad (5)$$

where ΔG_0 - the free energy difference between ds- and ss-states of the double helix. The free energy of the helix chain depend on the number of the base pairs in dsDNA: $\Delta G_0 = N g_0$, $g_0 = g_{ds} - g_{ss} < 0$ is the free energy difference between the closed and opened states of base pair in the double helix.

The term A in expression (5) is the work of applied force F on pulling apart of the double helix strands. Here $A = NA_0$, where A_0 is the work which is necessary to open one base pair in dsDNA.

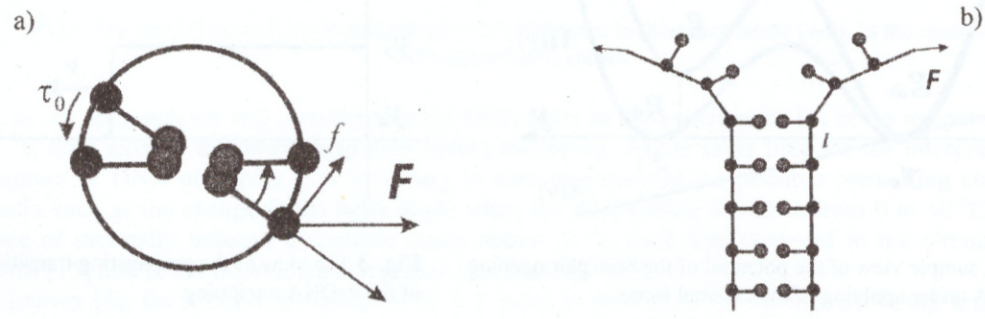

Fig.4. a)The base pair rotation under DNA unzipping, τ_0 -helix step angle; b) DNA helix is divided on two parts on the pathway "stretching", l – step of dsDNA;

In according with the construction of Bockelmann system for DNA unzipping the process of n-th base opening in DNA has to consist from the rotation of n-th pair on angle τ_0, that determine the helix step in the definite DNA form, and following pulling apart the bases in the pair along the pathway "stretching" (Fig. 4). So the work to open base pair by external force consists of two parts:

$$A_0 = 2lF + \tau_0 M = 2lF + \tau_0 r_0 f, \qquad (6)$$

Where l - the distance between the bases along the dsDNA, $2l$ – the increasing of the length of unzipped DNA, M - the rotation moment of the pair, r_0 - the distance from the helix axis to the atom of nucleic base to which the external force applied, and f is the component of the external force applying to rotate the base pair (see Fig. 4). From the geometry of the system (Fig. 4a) the expression for this force component may be written as: $f = F\cos(90 - \tau_0)$.

Note that in the expression (6) the work on unwrapping of the ssDNA after breaking off the hydrogen bonds in the base pair is not taken into account. This part of work is very small (it have to be smaller then the work on unwrapping of dsDNA, i.e. < 2pN [6]).

Thus the work of unzipping of N base pairs in dsDNA may be written as:

$$A = NF(2l + \tau_0 r_0 \sin\tau_0). \qquad (7)$$

For some critical value of $F = F^{cr}$, the equality fulfills: $A = -\Delta G_0$, $\Delta G = 0$ and the transition from DNA double-stranded state to single stranded one occurs. The value of the critical force may be calculated by expression:

$$F^{cr} = -g_0 / (2l + \tau_0 r_0 \sin\tau_0). \qquad (8)$$

It is also clear, that the value of g_0 depends on kind of base pair (A·T or G·C). But this dependence is not important for the considered full force of unzipping of the sequence of 1500 base pairs in dsDNA.

Note that from the view of equation (8) the conclusion follows, that the unzipping force is decreased when the angle τ_0 increased, i.e. when the DNA helix untwisted.

Thermodynamics of unzipping

It is clear that in common case the value ΔG_0 is depended on temperature. Really, when $T \to T_m$, where T_m is a melting temperature, $\Delta G_0 \to 0$.

From traditional thermodynamics the expression for free energy of unzipping may be written as:

$$\Delta G_0 = \Delta H - T\Delta S. \qquad (9)$$

Here H and S – the enthalpy and entropy of base pair opening in dsDNA. Assuming that H and S do not depend on temperature [23], the expression for melting temperature may be written as: $T_m = {\Delta H}/{\Delta S}$.

Therefore:

$$\Delta G_0 = \Delta S(T_m - T). \qquad (10)$$

Tacking (10) into account the dependence of critical unzipping force on temperature may be obtained in the following form:

$$F^{cr} = \frac{-S_0}{(2l + \tau_0 r_0 \sin\tau_0)}(T_m - T), \qquad (11)$$

where $S_0 = {\Delta S}/{N}$.

So, $F^{cr} \sim (T_m - T)$, and when $T \to T_m$, $F^{cr} \to 0$.

The dependence (11) qualitatively agrees with the known experiments on joint action of the temperature and external force on DNA unzipping [6].

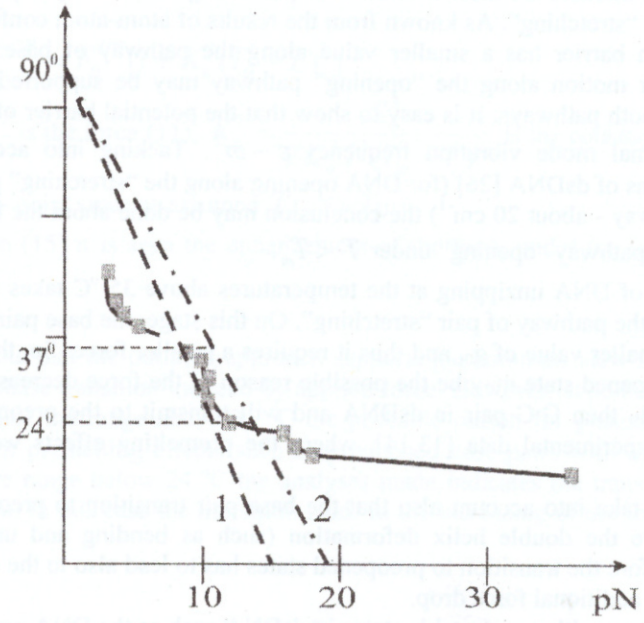

Fig.5 The view of the force-temperature dependence of DNA unzipping. The squares –the experiment of [6]. The line 1 is our calculation without accounting of the effect of base pair rotation. The line 2 is the calculated force-temperature dependence on expression (11).

Using the expression (11) the dependence of critical force on temperature may be calculated for definite parameters of dsDNA. From the geometry of dsDNA it follows that $l = 3.4$ Å, $\tau_0 = 36°$ (B-form), and $r_0 \approx 4.5$ Å - the averaged distant from the helix axis to the N_1 or N_9 - atom of nucleic base (pirimidine or purine, accordingly). For the entropy S_0 there was used the value taken in the paper [6]. This value $S_0 = -20.6\, cal/mol\,\mathrm{K}$ was obtained by averaging over the first 1500 bp using the data of [23].

The calculation of the dependence (11) with the presented parameters gives the results shown on Fig.5. The line 1 is the force-temperature dependence for the dsDNA without accounting of the effect of base pair rotation. The line 2 on Fig.5 is the calculated dependence (11) as a whole. In the calculations it was taken into account the known effect of double helix unwinding under temperature increase [6,7], but the value of effect was very little in compare with a inaccuracy of calculations.

As seen from Fig.5 the developed approach leads to linear force-temperature dependence of DNA unzipping and it is in agreement with the experiment at the temperature interval 24-35 °C [6], with the thermodynamic estimations [6] and Monte-Carlo simulations [7]. Our results are consistent with experiment for the interval 24-35 °C (see Fig.5), but do not describe the strong deviations of critical unzipping force from linear law (11) in the temperature ranges below 24 °C and above 35 °C.

Nature of the plateaus on the force-temperature diagram of DNA unzipping

In the frame of the model an explanation of the plateaus appearance on the force-temperature diagram of DNA unzipping can also be done. Firstly let us consider the nature of significant drop of the unzipping force above the temperature of 35 °C and then the effect of force increasing below the temperature of 24 °C.

In the temperature range above 35 °C the DNA double helix remain in the double-stranded state as follows from the results of UV-spectroscopy [8,9], only the metastable states in the configuration of base pairs with the preservation of the stacking interactions may realized. Particulary, at temperature of 37 °C it is known the effects of premelting of dsDNA in A·T rich regions [15,16].

A mechanism of DNA unzipping at the range above 35°C may be treated as two-stage process. On the first stage, due to temperature increase the closed base pairs in dsDNA transmit to the metastable state. The quantum-mechanical analysis of base pair opening shows that the nearest (to closed) excited state of the base pair is preopened configuration [24,25]. This state of base pairs is known as intermediate between close and open states. It is characterized by partial destruction of hydrogen bonds and by insertion of a water molecule between the bases in the pair [24]. The transition of base pair to the preopened state occurs as the displacement of the pair center of mass on the distance of about 0.5Å.

Under temperature increase the motion of the base pair along the pathway "opening" is more appropriate in compare of the pathway "stretching". As known from the results of atom-atom conformational analysis [18], the corresponding transition barrier has a smaller value along the pathway of base pair "opening". The larger probability of base pair motion along the "opening" pathway may be supported also by estimations of the transitions barriers for both pathways. It is easy to show that the potential barrier of transition is proportional to the square of the normal mode vibration frequency: $\varepsilon \sim \varpi^2$. Tacking into account the known values of conformational vibrations of dsDNA [26] (for DNA opening along the "stretching" pathway it is about 100 cm^{-1}, and for "opening" pathway - about 20 cm^{-1}) the conclusion may be done about the larger probability of the base pairs motions along the pathway "opening" under $T < T_m$.

The second stage of DNA unzipping at the temperatures above 35 °C takes place as the phase transition induced by force along the pathway of pair "stretching". On this stage, the base pair unzipping happens from the preopened state with smaller value of g_0, and thus it requires a smaller force. So, the transition of the base pairs from the closed to preopened state may be the possible reason of the force decrease above 35 °C. Note that the A·T pairs are less stable then G·C pair in dsDNA and will transmit to the preopened state firstly. That is in accordance with the experimental data [13,14], where the premelting effects were seen for A·T rich DNA regions.

It is necessary to take into account also that the base pair transition to preopened state along "opening" pathway has to involve the double helix deformation (such as bending and unwinding) as was shown in experiment [27]. Therefore the transition to preopened states has to lead also to the deformation of the spacer (ds λ-DNA) also and to the additional force drop.

The formation of premelting metastable states in dsDNA such as the DNA preopening explains the plateau appearance on force-temperature phase diagram of DNA unzipping at 35 °C.

Let us consider now the range of 24-15 °C where the plateau on the force-temperature diagram is seen also. In this temperature range the increasing of unzipping force is observed (Fig.5). For the understanding of the

plateau appearance in this temperature range it is necessary to take into account that the dsDNA macromolecule does not undergo significant changes in its conformation and in the configuration of complementary pairs. Due to the construction of Bockelmann system and in accordance with the known phenomenon of DNA condensation [17,28] it is very probable the aggregation of single DNA molecule under relatively low temperature and in the environment of synthetic polymer materials (large number of paramagnetic beads in the experiment [6]). On the assumption of DNA condensation the transition from condensed state to string configuration of dsDNA have to occur. Such transition is very close to the globule-coil transition well known for proteins that realized under sufficiently high temperature [29,30]. It is also correspond closely with the ball-string transitions for single polymers [31]. If the DNA condensation occurs the additional force has to be applied to transmit the DNA from condensed to free state before unzipping.

Let us consider the possible influence of effect of condensation on the value of unzipping force. In this case the expression for unzipping force may be written as:

$$F^{cr} = \sqrt{F_z^2 + F_y^2}\ , \tag{12}$$

here F_z and F_y are the components of the unzipping force (see inset in Fig. 1). For F_y it is true the expression (11), and for F_z it may be written:

$$F_z = \frac{S_c}{l_z}(T_\theta - T)\ . \tag{13}$$

Here S_c - the entropy of condensed state of the double helix, $l_z \approx l$ - the distance in one step of the helix, and T_θ -the temperature of the transition of DNA from the condensed state to string.

Let us write the whole expression for the unzipping force:

$$F^{cr} = \sqrt{K_0^2(T_m - T)^2 + \frac{S_c^2}{l^2}(T_\theta - T)^2}\ , \tag{14}$$

where $K_0 = \dfrac{-S_0}{(2l + \tau_0 r_0 \sin\tau_0)}$ is the combination of parameters of dsDNA.

As seen from expression (14) for the range near T_θ temperature the dependence of unzipping force may be written as:

$$F^{cr} \approx F_0^{cr}[1 + K_c^2(T_\theta - T)^2]. \tag{15}$$

In expression (15) F_0^{cr} is the force (11), $K_c^2 = \dfrac{S_c^2}{2K_o^2 l^2 (T_m - T)^2}$ is the constant that very weak depend on temperature around of θ - point since as assumed $T_m >> T_\theta$.

So form the expression (15) it is seen the enhancement of the force under the temperature reduction for $T < T_\theta$.

As a conclusion we note that the outlined approach supports the common view that the process of DNA unzipping is the first order phase transition induced by applied force. However, at some stages this process may have a different character. For the range above 35 °C the probable reason for plateau existence in the phase diagram is the appearance of premelting effects such as preopened base pairs with lower free energy of pair opening. For the temperature range below 24 °C the analyses made indicates the transition from condensed to string state of the DNA chain. In this case the transition leads to the increasing of the force needed for the DNA unzipping.

Acknowledgements

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ДО РОЗУМІННЯ ФАЗОВОЇ ДІАГРАМИ МЕХАНІЧНОГО РОЗКРИТТЯ ПОДВІЙНОЇ СПІРАЛІ ДНК

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Дано інтерпретацію фазовій діаграмі (температура-сила) механічного плавлення подвійної спіралі в температурному інтервалі від 15 до 50 °С. Змодельовано процесс розкриття подвійної спіралі з урахуванням імовірної траєкторії механічного розділення тяжів під дією зовнішньої сили, формування метастабільних станів пар основ в ДНК при високих температурах та можливості переходу макромолекули в конденсований стан при низьких температурах. Показано, що відкриття подвійної спіралі в різних температурних інтервалах можна розглядати як фазовий перехід першого роду індукований зовнішньою силою. Одержано вираз для критичної сили розкриття подвійної спіралі та розраховано залежність сили від температури. Продемонстровано згоду теорії та експерименту для температурного інтервалу 24-35 °С. Запропоновано механізми появи плато на фазовій діаграмі залежності сили від температури для інтервалів вище 35 °С та нижче 24 °С.

Ключові слова: макромолекула ДНК, механічне плавлення, розкриття подвійної спіралі, метастабільні стани ДНК.