Model of the splitting of DNA molecules

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A model is proposed for the splitting (i.e., doubling) of DNA molecules. This process is interpreted as clothing of a curve (describing the equilibrium conformation of the molecule) with a vector field **q** which models the hydrogen bonds between the two polynucleotide chains that form the double helix of DNA. Fluctuations of this field result in the renormalization of the torque that gives rise to the supercoiling of DNA (which actually occurs during replication). It is also shown that the local breaking of hydrogen bonds, which occurs under the action of temperature (or biochemical factors), results in delocalized deformation of the curve and a torque distributed on scales on the order of the persistent length. The expression derived for this torque makes it possible to relate the energy characteristics, measured in independent experiments, of the hydrogen bonds with the geometric parameters of the supercoil.

1. It is well known[1] that the DNA molecule consists of two polynucleotide chains that are twisted into a double helix. Both chains are coupled to one another by relatively weak hydrogen bonds (the interaction within each chain is much stronger). Such a structure can be characterized by three spatial scales: (i) microscale, not exceeding 10 Å (the distance between neighboring pairs of bases along the chain and the diameter of the double helix), which is mainly studied by methods of x-ray crystallographic analysis and molecular biology; (ii) macroscale on the order of the total length of the DNA molecule, which in the higher animals reaches 2 m; and, (iii) intermediate (meso) scale on the order of 1 or several persistent lengths (10^3 Å).

On the microscale level, the DNA molecule has a very complicated structure. It depends on the specific type of biological system and, in any case, a theoretical investigation on these scales must include numerical modeling. On the macroscale level, the DNA molecule is similar to an ordinary polymer and in this limit many details of the behavior are well described by known scaling laws[2] and are determined mainly by the entropy of the chain.

In the last few years (especially in connection with the impressive experiment[3] on direct measurement of the deformation of a DNA molecule by an external force) interest has arisen in the elastic properties of DNA which are associated with the mesoscales. A

model of the theory of elasticity of a DNA molecule was formulated in Refs. 4 and 5 and in the more general form in our work[6] (actually, the results of numerical modeling of the Brownian dynamics of a discrete model of DNA refers to the same range of mesoscales[7,8]).

Our objective in the present paper is to describe the process of splitting (i.e., decoupling of the two complementary nucleotide strands) of DNA molecules. This process is ordinarily regarded as an analog of a melting phase transition.[1] As the temperature increases (or the chemical conditions change correspondingly), the existence of a double helix becomes disadvantageous. The intermolecular bonds that keep the two complementary chains next to one another break and two single-strand molecules form from one double-strand molecule.

An important feature of the splitting (or melting) of a DNA molecule is that this process does not occur at a fixed point but rather is spread over a wide range of temperatures.[1] There also exists another problem associated with replication. After a DNA molecule splits, the two complementary strands must be separated and therefore at first they must "rotate" repeatedly around one another. Therefore, the model of the splitting process must describe both "melting" in stages and the appearance of a torque in the process.

2. As mentioned above, the physical properties of a DNA molecule on the intermediate scales of conformation are determined mainly by its elastic energy. This energy can be expanded in the standard manner in terms of the deformation tensor. It is convenient to represent this expansion in the following form,[4-6] which is a generalization of Kirchhoff's classical problem of the equilibrium of an elastic rod:[9]

$$F_0 = \int_0^L ds \left(\frac{1}{2} \sum_{i,j=1}^{3} a_{ij}\omega_i\omega_j + \sum_{i=1}^{3} b_i\omega_i \right), \tag{1}$$

where L is the length of the rod (the condition of applicability of the mechanical model limits this length to several persistent lengths), and s is the coordinate along the curve. The matrix a_{ik} is a symmetric but anisotropic ($a_{ij} \neq \delta_{ij}\, a$) matrix of the elastic moduli of the rod (the anisotropy a_{ij} models the double helix which exists on the microscales) and the vector $\mathbf{b}$ describes the spontaneous deformation of the stationary configuration of the molecule, which leads to the formation of a superhelix. The physical reason for spontaneous deformation can be, for example, adsorption of DNA molecules on nucleosomes (usually modeled by a cylindrical surface). The significance of introducing the vector $\vec{\omega}$ requires some explanation.

To describe the conformation of a DNA molecule, we can introduce a moving Frenet reference frame[10] $\mathbf{v}_1, \mathbf{v}_2$, and $\mathbf{v}_3$, where we choose $\mathbf{v}_1$ as a tangent vector ($\mathbf{v}_1 = \partial\mathbf{r}/\partial s$), and $\mathbf{v}_2$ and $\mathbf{v}_3$ are not necessarily the binormal and normal vectors. To simplify the calculations, it is more convenient to orient these vectors along the eigenvectors of the matrix a_{ij} in a plane perpendicular to $\mathbf{v}_1$. For DNA molecules the elastic moduli describing the torsion and bending deformations are several orders of magnitude[1,3-8] smaller than Young's modulus. To a very good approximation the DNA molecule can therefore be regarded to be nonextensible. consequently, the admissible deformations of the curve can be described by rotations of the Frenet reference frame, i.e.,

$$\frac{d}{ds}\mathbf{v}_j=\vec{\omega}\times\mathbf{v}_j, \quad j=1,\ 2,\ 3. \tag{2}$$

For the constants a_{ij} and $\mathbf{b}$ the minimum of the energy (1) corresponds to a constant value of ω:

$$\omega_i=\sum_{j=1}^{3} a_{ij}^{-1}b_j,$$

which describes the helical conformation of the molecule. We recall that we are talking here about a superhelix, since the initial double helix of DNA is important on the microscale level.

Kirchhoff's model (1) cannot describe the process of splitting, since only the axial line of the double helix enters into this model. However, a slight extension of this model, specifically, clothing the curve with a vector field $\mathbf{q}(s)$, gives a good picture of the splitting process. The field $\mathbf{q}(s)$ simulates the hydrogen bonds which couple the two strands together in the DNA molecule. The "melted" state which arises in the process of splitting can be characterized by the average $\langle|\mathbf{q}(s)|\rangle \neq 0$, which means that it is impossible to describe the conformation of the molecule by a single curve. We also note that the field $\mathbf{q}(s)$ clothing the curve can serve as a carrier of biological information along the curve, for example, during the spontaneous appearance of long-range order (i.e., a phase transition in this field).

Clothing the curve with the field $\mathbf{q}(s)$ also means that we must add to Kirchhoff's energy a contribution associated with the field $\mathbf{q}(s)$. In general, this part of the energy can represented as follows:

$$F_1=\int_0^L ds\left[\frac{1}{2}A\sum_{i=1}^{3}\left(\frac{\partial q_i}{\partial s}\right)^2+\frac{1}{2}Bq^2\right]. \tag{3}$$

Here the first term in Eq. (3) describes the deformation energy of the field $\mathbf{q}(s)$ (which simulates the deformation of the hydrogen bonds) and the second term describes the internal binding energy of the complementary strands of DNA.

At first glance, we have obtained two independent contributions to the energy (F_0 and F_1). However, this is not so, as can be easily verified by switching to a moving coordinate system. Here

$$\mathbf{q}=\hat{R}\vec{\pi}, \tag{4}$$

where $\hat{R}$ is the rotation matrix which is determined by $\vec{\omega}$, and $\vec{\pi}$ is the vector clothing of the curve in the stationary system. After some simple transformations we obtain from Eqs. (1), (3), and (4) the total energy

$$F=\int_0^L ds\left(\frac{1}{2}\sum_{i=1}^{3}a_{ij}\omega_i\omega_j+\sum_{i=1}^{3}b_i\omega_i+\frac{1}{2}(\partial_s\pi+\vec{\omega}\times\vec{\pi})^2+\frac{1}{2}\mathbf{Bq}^2\right). \tag{5}$$

Expression (5) gives the energy in the Kirchhoff model for an elastic curve clothed with a vector field. This model can serve as a basis for describing the splitting process.

3. To describe the process of splitting we must therefore use the Kirchhoff model clothed with a field $\vec{\pi}$ (or $\mathbf{q}$). In this model the vector $\vec{\omega}$ gives the configuration of the axial line of the double helix, and the field $\vec{\pi}$ gives the broken hydrogen bonds, i.e., the split state of the DNA molecule (the onset of the splitting process therefore implies that the Kirchhoff curve is clothed with a nonzero field $\vec{\pi}$).

We note that the process of splitting of a DNA molecule does not have the character of a phase transition (see, for example, Ref. 1), i.e., it does not arise spontaneously but rather under the influence of some local actions (including the temperature). The breaking of the bonds (the appearance of $\vec{\pi} \neq 0$) occurs if this external action exceeds some threshold value (of the order of the local hydrogen bond breaking energy). Under these conditions the energy of the external action which affects the hydrogen bonds

$$F_{\text{int}} = \int_0^L ds(\vec{\beta}\vec{\pi} + \vec{\pi}\hat{\gamma}\vec{\pi})\delta(s - s_0) \tag{6}$$

must be added to the energy (5). Here the vector $\vec{\beta}$ and the tensor $\hat{\gamma}$ fix the main terms of the energy of the external action which induces the splitting of the molecule and s_0 is the coordinate of the point at which this action is applied.

Minimizing $F + F_{\text{int}}$ leads to a system of Euler–Lagrange equations for $\vec{\omega}$ and $\vec{\pi}$. In general, the solution of this system can be found only numerically. Since we are interested only in a qualitative investigation of the onset of splitting, we shall simplify the problem by taking into account the fact that in this case $\vec{\pi}$ is small. Moreover, we shall examine the most important particular case, in which the seed value of the torque $\mathbf{b} = 0$ (i.e., before splitting starts the equilibrium configuration of the molecule is a straight line, $\vec{\omega} = 0$). In this approximation the equation for $\vec{\pi}$ is decoupled and has the form

$$\frac{\partial^2}{\partial s^2}\vec{\pi} - \Omega^2\vec{\pi} = \frac{\vec{\beta}}{A}\delta(s - s_0) + \frac{1}{A}\hat{\gamma}\vec{\pi}\delta(s - s_0). \tag{7}$$

Here we have introduced the notation $\Omega^2 = B/A$. The solution of Eq. (7) has the standard form

$$\vec{\pi}(s) = \int_0^L ds' G(s,s')\left(\frac{\vec{\beta}}{A} + \frac{1}{A}\hat{\gamma}\vec{\pi}(s')\right)\delta(s' - s_0),$$

where $G(s,s')$ is the Green's function of Eq. (7), which can be easily found by Laplace transforming

$$G(s,s') = \frac{1}{\Omega \sinh(\Omega L)}\{\theta(s' - s)\sinh(s\Omega)\sinh[(L - s')\Omega]$$

$$+ \theta(s - s')\sinh(s'\Omega)\sinh[(L - s)\Omega]\},$$

where $\theta(x)$ is the Heaviside unit step function. Substituting this solution into the Euler–Lagrange equation for $\vec{\omega}$, we find up to third-order infinitesimals

$$\nabla_s\vec{\omega} - A\nabla_s(\partial_s\vec{\pi} \times \vec{\pi}) = 0. \tag{8}$$

Here $\nabla_s = \partial_s + \vec{\omega} \times \ldots$ is the covariant derivative.

Equation (8) means that under conditions where the hydrogen bonds are broken locally as a result of an external action there automatically arises a torque $\mathbf{b}_d$

$$\mathbf{b}_d = -\frac{G^2(s,s_0)\partial_s G(s,s_0)}{A^2}(\vec{\beta} \times \hat{\gamma}\vec{\beta}). \tag{9}$$

Expression (8) is the main result of our work. It shows that the local external action (breaking of a hydrogen bond) results in delocalized deformation of the molecule, i.e., supercoiling. Indeed, the characteristic scale on which the torque $\mathbf{b}_d$ is different from zero depends on Ω, ranging from $1/\Omega$ for $\Omega L \gg 1$ to L for $\Omega L \ll 1$. This fact can be used as a unique Lindemann criterion for the splitting of a DNA molecule. The molecule can be regarded as split if the bond breaking induced by the local action results in deformation of the configuration of the molecule on scales of the order of the persistent length.

We note that our model contains parameters of different physical nature, which are measured by different physical methods (elasticity of DNA, energy of the hydrogen bonds, external actions). Therefore, expression (8) relates the energy characteristics of the hydrogen bonds and the geometric parameters of the supercoiling arising in the splitting process. The proposed model (5) is consistent with the experimental data of Ref. 1 on the diffuse melting of DNA. The point is that the energy (5) is valid only on intermediate scales on the order of several persistent lengths. On large (macroscopic) scales a DNA molecule is nonuniform and the conditions of splitting $\vec{\pi} \neq 0$ are therefore different in different sections of the molecule, which indicates that the melting of the molecule occurs in stages.

An additional torque $\delta \mathbf{b}$ also appears as a result of the thermal fluctuations of $\vec{\pi}$. The appearance of this torque, which is the analog of the classical Casimir effect in electrodynamics,[12] leads to the deformation of the initial conformation of the molecule, i.e., fluctuation supercoiling. In our model the field $\vec{\pi}$ is Gaussian, and we can integrate the distribution function over this field or, in other words, introduce the effective energy

$$\exp(-F_{\text{eff}}/T) = \int D\pi \exp(-F/T). \tag{10}$$

Switching in the standard manner to Fourier components, carrying out the simple integrations, and using the standard formula for an infinite product[13]

$$\prod_1^\infty \left(1 + \frac{z}{\pi^2 n^2}\right) = \frac{z}{\sinh z},$$

we obtain

$$F_{\text{eff}} = F_0 - T\sum_{i=1}^{3} \ln\left(\frac{z_i}{\sinh z_i}\right), \tag{11}$$

where

$$z_i = L\left(\frac{B + A(\omega^2 - \omega_i^2)}{A}\right)^{1/2}.$$

The second term in Eq. (11) is responsible for the above-mentioned fluctuation supercoiling. As an example, we present an expression for the fluctuation contribution to ω for large values of z_i:

$$\delta\vec{\omega} = -\hat{a}^{-1}\vec{\xi},$$

where

$$\xi_j = \frac{1}{2}T\sum_{i=1}^{3}\frac{\omega_{0j} - \delta_{ij}\omega_{0i}}{\sqrt{\frac{B}{A} + \omega_0^2 - \omega_{0j}^2}}.$$

The fluctuations of the field $\vec{\pi}$, which clothes the Kirchhoff curve, therefore lead to the renormalization of $\vec{\omega}$ or, equivalently, to the renormalization of the torque **b**.

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