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S. A. Pikin [a]

[a] Shubnikov Institute of Crystallography RAS, Moscow, Russia

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On the DNA Cleavage by Restriction Enzymes – Molecular Motors with Polarization Properties

S. A. Pikin
Shubnikov' Institute of Crystallography RAS, Moscow, Russia

In the paper, on the general physical basis, the attempt was done to explain the operation of restriction enzymes of different types. The physical model lies in the DNA deformation in the protein zone which is caused by catalytic processes taking place here. It is shown that some phenomena are similar to liquid-crystalline effects. The DNA molecule either forms locally a chiral kink moving together with a protein (the II type enzymes) or realizes the translocation through protein (the I and III type enzymes). The velocity of linear motion of the enzymes was estimated on the basis of proper kinetic equations which include the action of a longitudinal stalling force, the role of this force in DNA cleavage being different for different enzymes. The supercoiling of DNA during its translocation is discussed.

Keywords: DNA cleavage; molecular motor; restriction enzyme

PACS Numbers: 87.16.Nn; 87.16.Dg; 64.70.Md

I. INTRODUCTION

Restriction endonucleases are parts of restriction–modification (RM) systems which comprise an endonuclease and a methyltransferase activity. RM systems serve to protect bacterial cells against bacteriophage infection, because incoming foreign DNA is highly specifically cleaved by the restriction enzyme if it contains the recognition sequence of the endonuclease. The cellular DNA is protected from cleavage by a specific methylation within the recognition sequence. RM systems are divided into different types according to the subunit composition and the cofactor requirement [1–4]. In the I-type enzymes,

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Address correspondence to S. A. Pikin, Shubnikov' Institute of Crystallography RAS, Moscow, Russian Federation. E-mail: pikin@ns.crys.ras.ru

one subunit (S) binds to the unmethylated DNA recognition sequence and serves as a core to which the others bind. The M-subunits (usually two M) determine the methylation status of the target sequence and produces methylation of adenine bases. The R-subunits (usually two R) produce the DNA translocation and create the DNA loop behind these subunits (Fig. 1). The III-type enzymes contain the R- and M-subunits which exert similar modification and restriction activities. Type II RM systems comprise two separate enzymes [3,4].

The I- and III-type enzymes require ATP hydrolysis and Mg^{2+} for restriction [1]. ATP is hydrolyzed in large amounts following DNA cleavage. The behaviour of such enzymes differs from the occasional motion of the more symmetric II-type enzyme. During the translocation through the R subunits, the DNA acquires an additional twisting [2]: for each helical turn, one positive supercoil is created ahead of the motor and one negative supercoil in the DNA loop behind. As a rule, the I-type enzymes cleave linear DNA roughly half way between two successive target sites (sometimes several thousand bases away). A strong block to translocation appears to be a trigger for DNA cleavage. The mean translocation rate was found to be 550 bipartite per sec (bp/s) for single R subunit [2]. The III-type enzymes cleave DNA 2–3 tens bp downstream of the recognition sequence. A huge quantity of experiments in the II-type enzymes [3–10], indicate on large contribution of electrostatic interactions between protein and phosphate groups of the DNA. The II-type restriction endonucleases operate without an energy-consuming mechanism. They distort the DNA upon binding to its specific site: the DNA is kinked in the base sequence. Overall, the DNA is bent by about 10° [8].

The enzymes have the active places which are rich with the residues of amino acids. Full hydration layer of water separates the protein and the DNA [5]. The tightly bound water molecules form an extensive network of hydrogen bonds that interconnects all structural

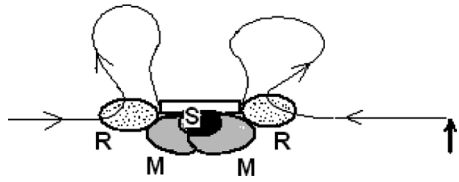

FIGURE 1 Conditional image of the I type enzyme which realizes the DNA thread translocation (thin line). The direction of motion is marked by thin arrows; the target sequence (light rectangle), basic subunits (see text), DNA loops are shown; the place of cleavage is marked by bold arrow.

elements involved at the protein–DNA interface, including those directly responsible for catalysis [6,7]. There are of importance the changes in the protein–DNA interface, from which solvent molecules and ions have to be expelled. Water and cation release is a major driving force for the recognition process in the II-type enzymes [9]. The specific binding to the DNA and cleavage of the DNA occurs within a relatively small region, but a general feature of the restriction endonucleases is that interactions between protein and DNA extend beyond the boundaries of the recognition sequence [4].

In general, the actual mechanism of phosphodiester bond cleavage by restriction enzymes states many questions. In the present paper, we consider the operation of R- subunits in the framework of the model of chiral kink movement under the action of transverse electric field, and the model of proper kinetic equations. The both models assume the existence of director **n** characterising the DNA orientation, as in liquid crystals, which allows to describe phenomena under consideration. The energy released during catalytic reactions due to participation of certain metal-ions and ATP is used for the production of bending and twisting of the director, its angular motion, and the linear movement of the enzyme along the DNA chain. The DNA cleavage is discussed as a result of stalling effects.

II. General Kinetic Equations for the Enzymes

It is suggested that the work of such molecular motors is induced by generalised "forces" [11,12]: the rotary velocity **N** of the DNA chain inside the motor, the chemical potential difference Δ that measures the free energy change per catalytic process, and the linear force **F** acting on the DNA chain. The action of the forces **N**, **F**, and Δ leads to the generalised "currents": the mechanical turning force **g**, the rate of catalytic process u, and the linear chain velocity **v**.

The currents and forces are related by linear equations [11,12] if the whole system is operating not far from its equilibrium. This results in a qualitative description of happening processes:

$$\mathrm{v} = \nu'[\mathbf{nN}] + \eta\mathbf{F} + \mathbf{k}\Delta \tag{1a}$$

$$u = -(\mathbf{wN}) - (\mathbf{kF}) + \lambda\Delta \tag{1b}$$

$$\mathrm{g} = \gamma\mathbf{N} - \nu'[\mathbf{nF}]/V + \mathbf{w}\Delta/V \tag{1c}$$

Here, γ is the rotational viscosity for the DNA chain inside the enzyme, η is the linear chain mobility, ν' is the chirality coefficient for the

construction protein–DNA, V is the volume of the complex enzyme–DNA, coefficients η, λ, and γ are positive. Other kinetic coefficients are vectors $\mathbf{k}$, and $\mathbf{w}$. In such a case, the dissipation rate $T\dot{S} = (\mathbf{gN}) + (\mathbf{vF})/V + (u\Delta)/V = \lambda\Delta^2/V + \gamma N^2 + \eta F^2/V$, related to unit volume, is obviously positive.

The director $\mathbf{n}$ characterises the possible local small deviation of the double-stranded DNA from the initial linear chain orientation (the z axis). In general, the distribution $\mathbf{n}(z)$ can describe the spatial bending and twisting of the DNA chain. In such a case, we have

$$\mathbf{n}_\perp \mathbf{n}_\perp = n_x^2 + n_y^2 = \theta^2, n_z^2 \approx 1. \tag{2}$$

The velocity $\mathbf{N} = d\mathbf{n}/dt = [\Omega\mathbf{n}]$, where Ω is the angular velocity of the director, it is the angular velocity of the deformed DNA chain, $\Omega_x = \Omega_y = 0$, but $\Omega_z \neq 0$.

We assume that the enzyme groove for the DNA has numerous contacts with the DNA, which induce the pointed DNA deformation. Namely this fact allows, as in chiral smectics with polar axis C_2, the deviation ξ, whose modulus $\sim\theta$, to arise cooperatively, and these deviations are twisted due to the chirality properties of the protein–DNA complex. The vector ξ has the two components [13]

$$\xi_x = n_z n_y, \xi_y = -n_z n_x. \tag{3}$$

The corresponding polar vector $\mu\xi$ is directed in the xy plane along the axis which is perpendicular to the plane formed by $\mathbf{n}$ and axis z (Fig. 2). The polar vector $\mu\xi$, where μ is the special chirality coefficient ("piezocoefficient"), inevitably must present in this chiral electrostatic system.

The magnitude Δ is caused by the catalytic processes. For the II-type enzymes, Δ is governed by electrostatic interactions arising due to the presence of amino acid residues, cations, and anions. For the I- and III-types enzymes, Δ is governed by the hydrolysis of ATP.

The electrostatic interactions, possibly, result in the transverse electric field $\mathbf{E}$. Thus, we can expect that magnitudes Δ and E are mutually related in some extent. Inside the groove, at the respective chain point, the transverse electric field $\mathbf{E}$ effects on the chain polarization $\mu\xi$.

Kinetic coefficients $\mathbf{k}$, and $\mathbf{w}$ describe the interactions whereby catalytic processes induce the mechanical motion of the DNA chain. We should underline that these interactions disappear without the θ-deviations of the DNA chain. For the mentioned kinetic coefficients, we supposed [11] that the factor of importance is the orientation of the

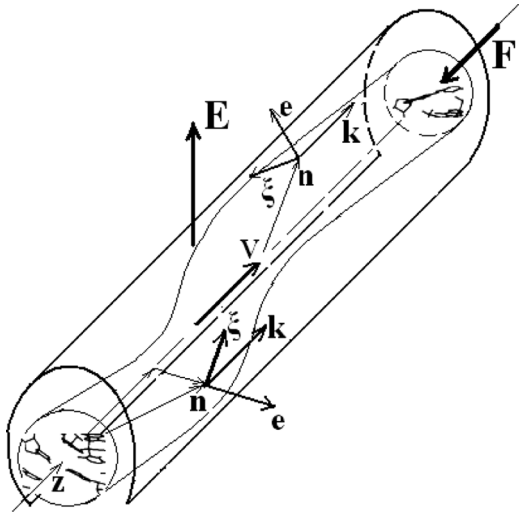

FIGURE 2 Bending and twisting of the DNA chain inside the enzyme groove. The transverse electric field **E**, normal to the DNA chain/groove interface **e,** inclined director **n**, vectors ξ, and **k**, and the enzyme contour (thin lines) are conditionally shown. The torque (parallel to the z axis), acting on the DNA chain, induces the kink motion or the DNA translocation with velocity **v**; the stalling force **F** is acting in the opposite direction. The bipartite contours are shown.

normal to the DNA chain/groove interface **e** (Fig. 2). Since the physical quantities must not depend on the **n** direction, the polar vector **k** must be related to **e** and **n** by an expression of the type $\mathbf{k} = c[e\xi]$, where $\mathbf{e} \perp \xi$, c is a constant. For simplicity and clearness, we suppose that **k** is parallel to the z axis, but the vectors **E** and **e** are perpendicular to the z axis, i.e.,

$$k_x = k_y = 0,\ k_z = -cn_z(\mathbf{en}_\perp) = -c\theta n_z\, sgn(\mathbf{en}), \tag{4}$$

$$\mathbf{w} = \nu''[\mathbf{nk}] \tag{5}$$

with an additional chirality coefficient ν''.

Vector $\mathbf{k} = c[\mathbf{e}\xi]$, directed along the z axis, can form the $\mathbf{k}\Delta$-type pushing force (see Eq. (1)) which induces the enzyme motion along the linear chain of the DNA. For the I- and III-types enzymes, such a pushing force provides the translocation of the DNA through the enzymes. This phenomenon has a simple physical sense: at the hydrolysis of ATP molecules, relatively massive DNA fragments (nucleotides) take favorable places with respect to amino acid residues and other elements of the enzyme structure, and they are reoriented

and shifted inside the enzyme due to pointed polar interactions activated by catalytic reactions. In this case, the deformed parts of DNA compare with the enzyme fragments, and this results in forces which are proper for rotary and longitudinal motions of nucleotides.

III. THE MOTION OF THE ENZYMES AND DNA

The interaction of $\mu\xi$ with the transverse field **E** (in the II-type enzyme) results in so called kink motion along the z axis, as in polar smectics [11]. The kink has a certain width h in the spatial azimuth distribution of $\mu\xi$ in the xy plane, which has a twist shown in Figure 2, and moves with the constant velocity

$$v_z = \frac{h\mu E\theta}{\gamma}. \tag{6}$$

The kink arises inside a relatively small region whose length is of the enzyme size. The enzyme creates and pushes the kink along the DNA chain. So, the complex protein–DNA kink is moving along the DNA backbone. The direction of this movement is occasional and depends on the initial mutual orientation of vectors $\mu\xi$ and **E**. For the I- and III-types enzymes, the translocation of the DNA through them occurs due to the formation of such a kink inside the enzyme groove [14] because of its specific interior twisted structure, and the direction of this movement is not occasional.

If stalling force **F** is sufficiently small, the described motion occurs with the constant velocity v_z, and the $\mu\xi$ vector rotates (by jumps) in the space with an average angular velocity Ω_z. This phenomenon can occur when the torque $[\mathbf{gn}] = 0$, i.e., the slightly deformed DNA chain can freely rotate around the z axis, and, respectively, the enzyme-motor does not produce a mechanical rotary work, since the product $(\mathbf{gN}) = 0$ in such a case, but $\theta \neq 0$. At these conditions, we obtain by Eqs. (1)–(5) the values v_z and Ω_z:

$$\gamma\Omega_z \approx (\nu'/V)F_z - c(\nu''/V)n_z\theta\Delta\, sgn(\mathbf{en}), \tag{7a}$$

$$v_z \approx \eta F_z + \nu'\Omega_z\theta^2 - cn_z\theta\Delta\, sgn(\mathbf{en}). \tag{7b}$$

For simplicity, we suppose that $\Omega_z \approx 2\pi h^{-1}v_z$, and such a concordance of velocities v_z and Ω_z superposes an additional condition for F_z, v_z and Δ [11].

The enzyme-motor generates the linear motion along the DNA chain if the vectors **k** and **F** have opposite directions. For small values

of θ, the critical value for this force, when the linear velocity v_z is equal to zero accordingly to Eq. (7b), is

$$F_{cr} \approx \frac{|c|\theta\Delta}{\eta} \tag{8}$$

If the magnitude $F_z = F_{cr}$ in Eq. (7a) then the angular velocity $\Omega_z = 0$ at $\theta = 0$ only.

It was shown in [11] that such motors can work with a different efficiency

$$\Xi = -\frac{v_z F}{u\Delta} \approx \frac{F(|c|\theta\Delta - \eta F)}{\Delta(\lambda\Delta + |c|F\theta)} \tag{9}$$

which is determined by material parameters of the enzymes and the force F. The most low efficiency values exist at $F \to 0$ and $F \to F_{cr}$.

IV. THE ESTIMATE OF PARAMETERS OF DIFFERENT ENZYMES

The II-Type Enzyme Motion

Since typical pitch h in the DNA helix is of 10 bp or 3.5 nm, and it is assumed that the kink width h is of the same order, after substitution the values $\mu \sim 10^{-3}$ C $\cdot$ m^{-2}, $\gamma \sim 10^{-3}$ Pa $\cdot$ s, which are typical for good ferroelectric liquid crystals with high μ and low γ, $\theta \sim 0.1$, and assumed field $E \sim 10^7$ V/m, we obtain the velocity value for the II-type enzyme [11]:

$$v_z = \mp\frac{h\mu E\theta}{\gamma} \approx -c\theta\Delta \sim 10^6 \text{ nm} \cdot \text{s}^{-1}. \tag{10}$$

This estimate of linear velocity has the order of the experimental one $v_z \sim 10^7$ bp/s [15]. Eq. (9) shows that, if no ATP, the energy Δ is proportionally related to the moderate transverse electric field acting in the complex when the water layer separates the protein and the DNA.

Accordingly to kinetic equations (1) and relations (8)–(10) for the motor with sufficiently high efficiency ($F \sim F_{cr}/2$), where, for simplicity, all the added terms are supposed to be of the same order, and the rate of catalytic process u is of 1 s^{-1}[4], the $\Delta \sim 10\, k_B T \sim 10^{-19} J$, we obtain the following estimates:

$c \sim 10^{17}$ m $\cdot$ s^{-1} J^{-1}, $\eta \sim 10^{13}$ m^2 s^{-1} J^{-1}, $\lambda \sim 10^{19}$ s^{-1} J^{-1}, $v^n/V \sim v'/\eta$ $V \sim 2\pi\gamma/h \sim 10^7$ m^{-1} Pa $\cdot$ s. So for the considered II type motors with

high mobility η, $F_{cr} \sim 10^{-4}$ pN is very small. It means that the motor stops often and occasionally what is the experimental fact.

At large forces $F >> F_{cr}$, linear velocity v_z becomes zero, but torque (related to unit volume) $[\mathbf{gn}] \neq 0$ at $\theta \neq 0$. The torque trying to turn director $\mathbf{n}$ around axes x and y, is

$$M_{x,y} \sim [\mathbf{gn}]_{x,y} \sim \nu' V^{-1} F_z n_z n_{x,y} \propto \nu' V^{-1} F \theta \tag{11}$$

During the θ–angle relaxation, torque $M_{x,y}$ creates mechanical tensions and deformations in the DNA chain, which can promote the chain cutting. In the case of the action of torque (11), we obtain "cutting" torque $M_{x,\ y} \sim 10^9\,\mathrm{N \cdot m^{-2}}$ if $F \sim 100$ pN [11]. Such a big force locally can be related to the interaction between charged residues and DNA bases which are in the surroundings with very low dielectric constants. These surroundings arise when the solvent molecules and ions have to be expelled from the protein-DNA interface during the recognition process accompanied with a highly cooperative restructuring of this interface and a mutual induced fit of enzyme and DNA [4]. The work of corresponding torque in molecular volume $V \sim 10^{-28}\,\mathrm{m^3}$ is of $10^{-19}\,\mathrm{J}$ (the molar equivalent is $\sim 25\,\mathrm{kcal/mol}$), i.e., of the order of bond energy per molecule. The action of this force creates energy conditions to produce the DNA cleavage.

The DNA Translocation by the I- and III-Type Enzymes

The Equations (8)–(11) are valid for the I- and III-type enzymes too (excluding the expression with field E). The experiments show [2] that forces F_z of the order of several pN do not influence on velocity v_z (at $F_z < F_{cr}$). If $F > F_{cr}$ then the DNA stops. Now we assume that $\Delta \sim 10^{-19}\,\mathrm{J}$, $F_{cr} \sim 10$ pN, $\theta \sim 0.1$, and $v_z \sim c\theta\Delta \sim 10^3\,\mathrm{nm/s}$, $u \sim 10^{-3} \div 10^{-2}\ \mathrm{s^{-1}}$ in accordance with experimental data [2], then,

$$c \sim 10^{14}\,\mathrm{m \cdot s^{-1}\,J^{-1}}, \eta \sim 10^6\,\mathrm{m^2\ s^{-1}\,J^{-1}}, \lambda \sim 10^{16} \div 10^{17}\,\mathrm{s^{-1}\,J^{-1}},$$

$$\nu''/V \sim v'/\eta V \sim 2\pi\gamma/h \sim 10^5 \div 10^6 \sim \mathrm{m^{-1}\,Pa \cdot s}.$$

We see that mobility η and parameter λ are much less in the I and III type enzymes which appear to be more viscous with $\gamma \sim 10^{-1}\,\mathrm{Pa \cdot s}$. The torque $M_{x,\ y} \sim 10^7 \div 10^8\ \mathrm{N \cdot m^{-2}}$ if $F \sim 100$ pN. This torque is not enough to produce the DNA cleavage inside the enzyme groove, and a more strong force F is necessary with respect to one for the II-type enzyme. The effective DNA cleavage by the I- and III-type enzymes

demands (in experiments) such a powerful factor as the collision of two complexes bound to the same DNA molecule [1].

The made estimates underline the essential difference of cleavage conditions for the II-type and I- or III-type enzymes. In the I- and III-type enzymes, the DNA has more viscous properties, a smaller mobility, and weaker "piezoelectric" properties. These peculiarities result in the velocity of the DNA translocation which is less than the velocity of the II-type enzyme on several orders. The DNA cleavage by I-type enzyme seems to be much more occasional than in the case of the II-type enzyme. It should be noted that here the mechanical work for the deformation of DNA and enzyme is considered as a basic stimulus, but, in the final stage, the DNA cleavage consists in the break of chemical bonds in its chain at the expense of the introduced energy.

V. DISCUSSION

Supercoiling of the DNA in the I and III Type Enzymes

The additionally twisted parts (screw-like) of the DNA shown in Figure 3 appear as loops after translocation of the DNA molecule with constrained ends through the I and III type enzymes. We suppose that the DNA entering into the enzyme (in its R–unit) is effected to similar orientation changes (bending and twisting) to correspondent to the enzyme structural peculiarities. One can speculate that the supercoils have to possess the additional μ ξ–effect and corresponding interactions with ionic coats which prevent to specific chemical agents from doing attacks on phosphodiester bonds of the DNA outside the enzimes. Torsion stresses in the supercoiled DNA, like a phone cord [16,17], are released by plectonemes when the DNA duplex forms the helices with terminal loops without supertwist (Fig. 3). In plectoneme areas, the disappearance of supertwist results in changing of ionic coats and screening conditions.

It is quite possible that the screening conditions are different in the vicinity of different enzymes, for example the ionic conditions are

FIGURE 3 Supercoiled sites of the DNA chain. Positive and negative supertwists, and the elimination of supertwist in the plectoneme with a chain writhe are shown. The helical nature of the DNA duplex is omitted for clarity.

lower in the case of enzymes III (μ is less), but they are higher in the case of enzymes I (μ is larger). In such a situation, the negative supercoils behind the I- and III-type enzymes possess different quantities of weak places for the DNA cleavage. In the case of enzymes I, negative supercoils are more stable. Large-scale plectonemes (without a supertwist) on the DNA loops near to enzymes III are more exposed for the attacks on phosphodiester bonds.

In positively supercoiled DNA (ahead of the enzymes), the weak places are the local regions where a strong molecule's overwinding is stored. At a certain *F*-force regime, the torsion deformation excess is concentrated into regions with the overwound phosphate backbone inside [17]. This effect should strengthen the attacks of specific chemical agents on phosphodiester bonds that can be a reason for the DNA cleavage by enzymes I statistically far from them, ahead of the motor.

VI. CONCLUSIONS

It was shown that the necessary conditions for the action of molecular motors under consideration are the chirality of protein–DNA complex, the presence of polar axis C_2 in large atomic groups in this complex, and its polarization properties. In the paper, the attempt was done to explain the operation of restriction enzymes of different types which make the DNA cleavage under certain circumstances. The physical model lies in the DNA deformation in the protein zone which is caused by catalytic processes which occur here. The velocity of linear motion of the II-type enzyme was estimated on the basis of plausible electrostatic characteristics of the described complex. The velocity estimates were done also on the basis of proper kinetic equations which include the action of a longitudinal stalling force on the motor. When this force is sufficiently strong then, after the protein stop, the powerful torque carries on doing to deform the DNA, and this effect can promote cutting the DNA chain due to proper chemical attacks on the molecular bonds.

The similar kinetic equations were applied to describe the I- and III-type enzymes which translocate the DNA molecule. In these enzymes, the ATP hydrolysis helps to the forward and rotary motion through the groove during translocation, but the model of transverse electric field is unfit here. The appearance of supercoils ("screw-like") outside theproteins is related to the situation of constrained ends of the DNA molecule. The supercoiled DNA behind the I- and III-type enzymes has non-identical stability conditions. For the DNA cleavage by these enzymes, a more strong stalling force is necessary with respect to one for the II-type enzyme. In the case of the I-type enzyme,

the DNA cleavage near to the enzyme is difficult, and it occurs statistically far from the enzymes.

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