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SCREW MOTION OF DNA DUPLEX DURING TRANSLOCATION THROUGH PORE. I. INTRODUCTION OF THE COARSE-GRAINED MODEL

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Based upon the structural properties of DNA duplexes and their counterion-water surrounding in solution, we have introduced here a screw model which may describe translocation of DNA duplexes through artificial nanopores of the proper diameter (where the DNA counterion–hydration shell can be intact) in a qualitatively correct way. This model represents DNA as a kind of "screw," whereas the counterion-hydration shell is a kind of "nut." Mathematical conditions for stable dynamics of the DNA screw model are investigated in detail. When an electrical potential is applied across an artificial membrane with a nanopore, the "screw" and "nut" begin to move with respect to each other, so that their mutual rotation is coupled with their mutual translation. As a result, there are peaks of electrical current connected with the mutual translocation of DNA and its counterion–hydration shell, if DNA is possessed of some non-regular base-pair sequence. The calculated peaks of current strongly resemble those observed in the pertinent experiments. An analogous model could in principle be applied to DNA translocation in natural DNA–protein complexes of biological interest, where the role of "nut" would be played by protein-tailored "channels." In such cases, the DNA screw model is capable of qualitatively explaining chemical-to-mechanical energy conversion in DNA–protein molecular machines via symmetry breaking in DNA–protein friction.

Keywords: Screw; screw-jack; screw and nut; DNA; nanopore translocation.

1. Introduction

DNA translocation processes are of tremendous importance in many biological contexts and have attracted great attention from both experimentalists (Refs. 1, 2, 4, 5 and references therein), as well as theoreticians (Refs. 3, 6–12, 13–21 and references therein). For example, true translocation through pores takes place when a virus infects a cell, or there is transduction of DNA among bacteria, whereas translocation through an artificial nanopore has been proposed as a basis for DNA sequencing and gene therapy. In addition, DNA translocation or reptative sliding processes of DNA, as well as RNA, are crucial in solving various topological problems associated with the function of the cell machinery (translation, transcription, repair and folding/unfolding of DNA, chromatin remodeling, etc.).

Recently, systematical experiments have been carried out with single-stranded (ss) and double-stranded (ds) DNAs, by dividing the experimental vessels into two compartments with a membrane (typically, 10–30 nm thick) containing a pore (typically of up to 10 nm diameter). A water solution of DNA is placed into one of the compartments (called *cis*-side), whereas the opposite one contains the pertinent pure solvent (called *trans*-side), the voltage is applied across the membrane, so that the anode and the cathode are situated in the opposite compartments, and the electrolytic current is measured versus time. Driven by the chemical potential and the voltage differences, DNA polyanions are reaching the membrane on the cis-side, finding the nanopore and are translocated through the latter to the trans-side. This process is studied by observing specific blocades (dips) of the measured current, with the duration of every dip (typically, of millisecond order) being equal to the translocation time of a particular DNA polyanion.

For the present, it is experimentally well established[1–12] that (a) reducing voltage gives proportionally slower DNA translocation dynamics and vice versa; (b) DNA translocation time scales nearly linearly with the biopolymer length; (c) depending on the ratio of the DNA and nanopore diameters, the polyanion may translocate in a completely (or partially) unfolded state; (d) there is a critical value of the DNA solution ionic strength, above which DNA translocation causes decrease in the observed electrolytic current, whereas below it the current increases during DNA translocation. Meanwhile, many important mechanistic details of the DNA nanopore translocation are not yet clear, and this inhibits effective analytical-diagnostical applications of this process.

The theoretical studies range from the scaling models in the spirit of polymer physics to computer-aided molecular dynamics simulations.[3,13–21] Whereas ss-DNA nanopore translocation modalities are already rather well understood (see, for example, Refs. 6–12, 13–17), the relevant work on ds-DNA is still in its infancy.[3,16,18–21]

This is why, our present communication is devoted to ds-DNA nanopore translocation. We carefully scrutinize this process and propose a coarse-grained model based upon the helical symmetry and the polyanionic nature of the biopolymer

under study. The model proposed here considers a ds-DNA confined within a nanopore as a kind of "screw jack," where the role of the "screw" proper is played by the DNA duplex itself, and the "nut" driven by some external "electrical motor" should be the counterion-water environment. We write down equations of motion for this system, involving the longitudinal and torsional rigidity of the DNA duplex. Since the ds-DNA torsional rigidity is well known to be significantly dependent on the DNA nucleotide pair sequence,[22–29] whereas the longitudinal rigidity (for sufficiently low force-extension ranges ensuring the validity of the Hooke's law) is not,[30–35] we argue that using our model to explain the ionic current changes during voltage-driven ds-DNA nanopore translocation could be helpful for analytical DNA sequencing. Moreover, the DNA screw model could in principle be applied to DNA translocation in natural DNA–protein complexes of biological interest, where the role of "nut" would be played by protein-tailored "channels." In such cases, the model in question is capable of qualitatively explaining chemical-to-mechanical energy conversion in DNA–protein molecular machines via symmetry breaking in DNA–protein friction.

2. DNA Screw Model: A Qualitative Outline

In our modeling, we start from the proposal of Ref. 19 to consider the DNA duplex as a non-deformable charged cylider concentric with a cylidrical nanopore in an electroneutral rigid slab. Between the internal surface of the nanopore and the DNA surface there are counterions to saturate the total negative charge of the DNA polyanion, as well as water molecules.

Our first step would be to take into account that DNA duplexes are in fact deformable and possessed of definite longitudinal and torsional rigidities.[22–35] A similar guess was also done in Ref. 21, but, along with the longitudinal stiffness and intrapolymer excluded-volume interactions, these authors introduce bending stiffness and allow for no torsional rigidity at all.

Concerning the charge distribution on the surface of a DNA duplex, Ref. 19 assumes two *separate* possibilities: (a) homogeneous distribution and (b) linear distribution of double-helical symmetry, with the latter possibility studied under the assumption that a fixed probe charge is immobilized on the internal surface of the nanopore. The authors of Ref. 19 also consider the effects of Manning condensation on the DNA translocation, and find that, at low ionic strengths of the mother liquid, translocation is manifested in ionic current jumps, whereas at high ionic strengths it results in ionic current blocades, just in qualitative accordance with experimental observations.[5] Instead, Ref. 21 does not take into account explicit counterions and deals with the electrostatic interaction between DNA coarse-grained "beads," between the latter and the external field, as well as excluded volume interaction between the DNA and the internal surface of nanopores. Moreover, the authors of Ref. 21 make an unjustifiable assumption that the dielectric constant (in other words, relative dielectric permittivity) is $\varepsilon = 80$ everywhere in the system.

Meanwhile, there should in effect be noticeable differences in ε among the bulk solution, the surface of the membrane and the inside of the nanopore.[17]

Based upon earlier work, Refs. 36–40, we shall now scrutinize all the assumptions of the above-mentioned models. First of all, DNA duplex in water solution can be represented by three concentric dielectric media: DNA duplex itself (with the diameter about 2 nm), inserted into the so-called "Manning cloud" (which stands for the condensed couterion layer with the diameter about 4 nm), with these both being immersed into the bulk solvent (with an infinite diameter). The difference between the Manning cloud and the bulk solvent consists in that the former has anyway much higher counterion concentration than the latter. Specifically, the higher the ionic strength of DNA solution, the higher the mobile counterion concentration in the Manning cloud — and vice versa. Secondly, the effective decay length of the double-helical information in the local electric field of a DNA duplex is about 0.5 nm, so that beyond this length the charge distribution of the latter can be considered as a homogeneous one with cylindrical symmetry. This means that the spatial structure of the *internal* surface in the Manning cloud should also have double-helical symmetry mimicking that of the DNA duplex itself. Accordingly, to completely preserve the above electrostatic picture, nanopores should have diameters equal to or greater than 4–5 nm, otherwise the whole B-DNA conformation (which is conventional for bulk water solutions of DNA duplexes at moderate ionic strengths) could be unstable within nanopores, and some conformational transitions should take place (B-to-A transition, for example).

Now, let us consider collective dynamics of the DNA–counterion–water system in solution — at first in the absence of the externally applied electrostatic field. It is long known[41–46] that such a system will allow *acoustic plasmons* with longitudinal vibrations of DNA duplexes as a whole with respect to their Manning clouds as a whole. However, this *longitudinal* degree of freedom has been obtained assuming that the charge density of the DNA duplex surface is uniform and homogeneous. It is intuitively clear that, taking into account the double-helical symmetry of the DNA electrostatic field and potential, we shall also have the second degree of freedom in the acoustic plasmons — the *torsional* one. Indeed, double-helical symmetries of DNA duplexes and internal surfaces of their Manning clouds will perfectly match each other, and thus ought to convert the longitudinal and torsional degrees of freedom of the pertinent acoustic plasmons into screw-like modes (we will consider the detailed mathematical inferences elsewhere). In the latter representation, DNA duplexes themselves would play a role of the screws proper, with Manning clouds being "nuts," so that the whole DNA–counterion–water system within a nanopore can be considered a kind of nanoscopic "screw–jack" (see Fig. 1). To this end, the collective torsional modes of spatially confined polymers are known to be a generally important dynamical component[48] and, physically, can result from backflow effects during nanopore translocation. When every monomer of the translocated polymer is moving through a hole, it sets up a flow field which transfers momentum to neighboring monomers, thus helping them to move in the same direction.[47] Finally, the

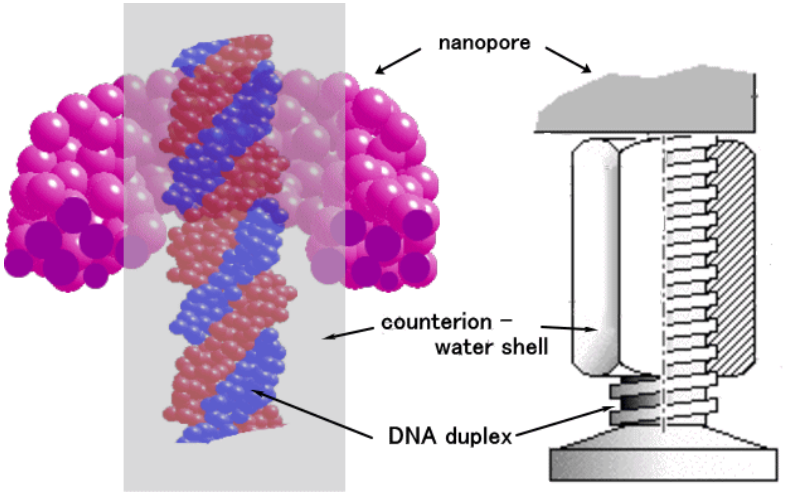

Fig. 1. Schematic respresentation of the physical essence of the DNA screw model.

possibility of cooperative screw-like dynamics for DNA duplexes was envisioned earlier on the basis of several X-ray structures of DNA–protein complexes,[49–52] and such motions had even been measured very recently using a sophisticated DNA–protein micromechanical setup.[53]

Finally, let us apply an external electric field to the DNA–counterion–water system. Then, one crucially important dynamical benefit of (*a relatively slow*) DNA screw motion would be coupling between the translational and rotational degrees of freedom, which renders the supra-molecular dynamical system *non-conservative* through the onset of *Coulomb friction*, with the friction force being dependent on the *direction* of the system's velocity vector, but *not* on its *magnitude* (see, for example, Ref. 54). Meanwhile, the latter dependence would instead result in the frictional *damping*, which ultimately tends to stop any dynamics and must anyway be present in molecular dynamical systems to render them thermodynamically consistent in view of the thermal (Brownian) motion. But, on the other hand, when a generalized dynamical system experiences *both* Coulomb friction *and* frictional damping, it can typically be much more unstable — and, thus, unpredictable and uncontrollable — than the same non-conservative system *without* damping.[55,56] We shall discuss this extremely interesting and important point in more detail below.

3. "Screw–Jack" Equations of Motion for DNA Translocation Through Nanopore

Bearing in mind all the above considerations, we can now cast a fresh look at the process of voltage-driven DNA duplex translocation through nanopores.

Specifically, we place DNA solution into the *cis*-compartment, the pertinent solvent into the *trans*-compartment of the vessel with the nanopore-bearing

membrane, apply the voltage and measure the resulting ionic current. DNA duplexes will move toward the membrane under the combined influence of the Brownian motion, electrostatic and hydrodynamic drag forces, before they reach the mouth of the nanopore. In the bulk water solution, DNA duplexes could have some folded tertiary structure, due to efficient electrostatic screening in the presence of high dielectric constant. However, on the membrane surface, near the nanopore mouth and within the nanopore, dielectric constant will be much lower than the bulk one. As a result, in these areas, DNA tertiary structure will tend to (at least partially) unfold — and the mobility of the polymer should moreover increase in general — the both facts are supported by the most recent experimental data.[57,58] If the nanopore diameter is small enough to prevent translocation of partially folded DNA tertiary structures, but large enough to ensure intactness of the Manning cloud around the translocated DNA duplex, then the process of translocation of a single unfolded DNA duplex in its B-DNA conformation will begin, as soon as one of the ends of the properly unfolded DNA duplex will be soaked into the nanopore.

As we have seen in the previous section, by screwing itself into the nanopore, the translocated DNA double helix will experience a *combined* action of load and torque, which should promote complete DNA duplex unfolding on the cis-side — and, at the same time, its refolding on the trans-side of the membrane. These joint unfolding–refolding effects ought to compensate each other both energetically and entropically, so that we shall not be interested in them from here on. We will just bear in mind that the only result of the DNA duplex screw-like translocation should be smooth and gradual transfer of the biopolymer mass from the cis-side to the trans-side.

Interestingly enough, the presence of the torque along with the load during the DNA translocation can be important even when nanopore diameter is large enough to accommodate partially folded tertiary structures of linear DNAs or cyclic DNAs as a whole (as detected in experiments[4] and simulations[21]). In such cases, being applied to the both tails of a linear DNA hairpin (or to the opposite strands of a cyclic DNA duplex) confined within the nanopore, the torques with respect to the relevant Manning clouds ought to promote some specific writhing — and thus refolding — of the DNA tertiary structure, to form a combination of balanced plies with end loops.[59–61] It is intuitively clear that, in turn, such compact tertiary superhelical structuresought to be effectively translocated through the nanopore at times much shorter — and will cause much deeper ionic current dips than those of the corresponding completely unfolded DNA tertiary structures, just as observed in experiments.[4] In contrast, linear DNA hairpins folded only partially (or cyclic DNA duplexes), that is, without plies, could in many cases clog the nanopore or even be rejected by the latter — just as revealed by computer simulations.[21]

But from now on, we shall only deal with the translocation of *completely unfolded* DNA tertiary structures, that is, intact B-DNA duplexes taken together with their Manning clouds. Our next step is to set up equations of motion for the DNA "screw–jack" described in the previous section in qualitative terms.

We shall start from the equations of motion for the true macroscopic *undamped* screw jack (consisting of a nut driven by some external forces and a screw interacting with the nut) with one translational and one rotational degrees of freedom, in a manner similar to that discussed in Refs. 62 and 63:

$$\begin{aligned} J_\phi \ddot{\phi} + k_\phi \phi &= T, \\ (m_v + m_1)\, \ddot{u} + k_g u &= -P - F, \end{aligned} \tag{1}$$

where ϕ: the rotational position of the screw, u: its axial displacement, J_ϕ: screw moment of inertia, m_v: screw mass, m_1: mass(es) clamped to the edge(s) of the screw, $k_\phi = EA_r/l$: screw torsional rigidity, E: screw Young modulus, $A_r = \pi r^2$: screw section area, r: screw radius (mean radius of the screw thread), l: screw length, $k_g = GI_p/l$: screw axial stiffness, G: screw modulus of rigidity, $I_p = (\pi/2)r^4$: screw polar moment of inertia, T: torque the nut exerts on the screw, P: load the nut exerts on the screw, F: the sum of all the external driving forces.

In our DNA translocation problem, the fragment of the B-DNA duplex currently situated within the nanopore plays the role of the "screw," whereas its intact Manning cloud within the nanopore should then be the "nut" (see Fig. 2). Hence, if the DNA "screw" is translocated from the cis- to the trans-compartment, the "nut" will move from the trans- to the cis-compartment of the experimental vessel. Here, we shall take the latter direction as the positive one and assume that the torque T is positive when rotation is counterclockwise — then the nut will be said to move in the positive direction if it rotates counterclockwise. This means that the screw is translated in the negative direction, with the mass of the screw being just the mass of the DNA duplex fragment situated in the nanopore at the given moment. Then, the screw moment of inertia is also defined by the latter fragment only, whereas the "mass(es) clamped to the edge(s) of the screw" stands just for the mass of the rest of the DNA duplex situated beyond the nanopore on the both sides of the membrane. This rest of the DNA duplex ought to be smoothly and gradually transferred from the cis- to the trans-compartment and does not participate in the rotational component of the screw motion — instead, it is involved into the unfolding–refolding processes on the opposite sides of the membrane, respectively. As already mentioned before, these unfolding and refolding events ought to compensate each other energetically and entropically, we shall assume that they do not influence the screw motion to a noticeable extent.

Further, the dynamics of the nut is in turn described by two degrees of freedom: u_f (translational) and ϕ_f (rotational), with the screw motion imposing a specific kinematical relationship between the screw and nut degrees of freedom[62,63]:

$$u_f = \phi_f r \tan\delta - \phi r \tan\delta + u, \quad \delta = \arctan(p/2\pi r), \tag{2}$$

where δ: the screw helix angle, p: screw pitch and r: screw radius (mean radius of the screw thread).

Now, to obtain DNA equations of motion in the closed form, we have to find the explicit expressions for the torque and load. In doing so, we need first to choose

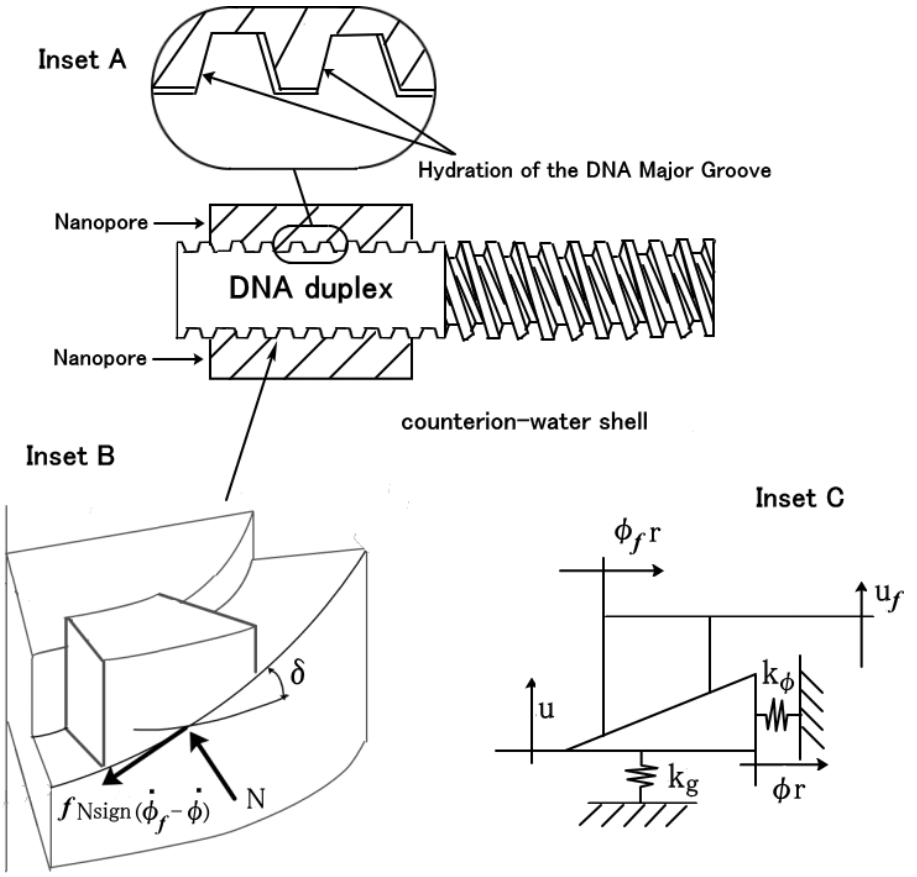

Fig. 2. DNA screw model in more detail. Inset A shows that the "threads" of the DNA "screw" are formed by the major groove of the DNA duplex, so that the reliable contact between the "screw" and "nut" is ensured by the hydration of the major groove. Inset B explains the force balance in the "screw–nut" system: **N** is the normal force exerted by the "nut" onto the "screw," whereas the corresponding "screw–nut" friction force is dependent on the sign of the relative angular velocity between the screw and nut, $\dot{\phi}_f - \dot{\phi}$, Coulomb friction coefficient f and the absolute value of the normal force **N**. Such a dependence of friction on the direction of velocity breaks the symmetry of the former and renders the whole system a *non-conservative* one (the total energy of such a system can not more be conserved, unlike in the conventional molecular systems whose dynamics is described by the Hamiltonian equations of motion). Remarkably, it is the non-conservativity of the "screw-nut" system that opens a possibility for rectifying its dynamics, thus creating prerequisites for chemical-to-mechanical energy conversion via Brownian ratchet mechanism.[80–82] Inset C depicts the degrees of freedom, as well as the rigidity parameters of the "screw-nut" model (confer Eq. (2) in the main text).

the form of the "thread" of the DNA "screw." We may arrive at the simplest DNA screw model, if we assume that the B-DNA duplex can be represented as a "square-threaded screw," with the "square-shaped crest" corresponding to the communion of the sugar–phosphate backbones separated by the B-DNA *minor* groove — and

the "square-shaped root" defined by the B-DNA *major* groove (see Fig. 2). In this case, the torque T can be cast as follows[62,63]:

$$\begin{aligned} &T = rP(\alpha+\beta)/(1-\alpha\beta), \\ &\alpha \equiv \tan\delta, \quad \beta \equiv f\,\mathrm{sgn}\omega_{\mathrm{rel}}, \quad \omega_{\mathrm{rel}} \equiv \dot{\phi}_f - \dot{\phi}, \end{aligned} \tag{3}$$

where f: friction coefficient, ω_{rel}: the relative angular velocity between the screw and the nut. Therefore, β is the frictional contribution to the torque. It is possible to simplify Eq. (3) by introducing the *friction angle* η, with $f \equiv \tan\eta$, thus $T = rP\tan(\delta \pm \eta) \equiv rP\Lambda$, with the plus sign (resp. minus sign) corresponds to the counterclockwise (resp. clockwise) rotation of the nut.

Now, we have to find the expression for the translational load P the nut exerts on the screw. If we take the nut mass to be m and use Eq. (2), the translational equation of motion for the nut reads: $P = m\ddot{u}_f + F = F - mr\ddot{\phi}\tan\delta + m\ddot{u}$. Bearing this in mind, we can rewrite Eq. (1) as

$$\begin{aligned} (J_\phi + \Lambda m r^2\tan\delta)\ddot{\phi} - (mr\Lambda)\ddot{u} + k_\phi\phi &= \Lambda rF, \\ -(mr\tan\delta)\ddot{\phi} + (m + m_v + m_1)\ddot{u} + k_g u &= -2F, \end{aligned} \tag{4a}$$

or in the matrix form:

$$\mathbf{M}\begin{Bmatrix}\ddot{\phi}\\ \ddot{u}\end{Bmatrix} + \mathbf{K}\begin{Bmatrix}\phi\\ u\end{Bmatrix} = \begin{Bmatrix}\Lambda rF\\ -2F\end{Bmatrix}, \quad \mathbf{M} \equiv \begin{bmatrix} J_\phi + \Lambda m r^2\tan\delta & -mr\Lambda \\ -mr\tan\delta & m + m_v + m_1\end{bmatrix}, \quad \mathbf{K} \equiv \begin{bmatrix} k_\phi & 0 \\ 0 & k_g\end{bmatrix}. \tag{4b}$$

Finally, we will discuss the physical nature of the external force F and the rigidity matrix $\mathbf{K}$ in our DNA translocation problem.

Indeed, the total external force should be sum of the driving force due to the voltage difference (its maximum possible absolute value is given by the expression $F_{\mathrm{driving}} = 2\mathrm{eV}/a$,[3] where e is the elementary charge, V is the applied voltage, $a = 0.34\,\mathrm{nm}$ is the spacing between neighboring nucleotide pairs in B-DNA) and a Langevin force owing to the thermal motion and the coarse-graining of the DNA molecular model (for example, it can be represented by an Ornstein–Uhlenbeck noise, or something alike). Here we have assumed, following the *macroscopic* considerations,[62,63] that the friction is dependent *solely* on the direction of the ω_{rel}, and *not* on its magnitude (Coulomb friction model), so that *there is no frictional damping contribution*. Most probably, this assumption ought to be quite reasonable for sufficiently slow translocation dynamics of spatially confined DNA duplexes.[64] On the other hand, to be thermodynamically consistent in the presence of the Langevin force, Eq. (4) must also contain a damping term (velocity-dependent friction) — only this way the fluctuation–dissipation theorem can be satisfied. We will revert to this very important discussion in the next section.

In effect, the rigidity coefficients of the DNA "screw" are the most interesting parameters of our problem. As concerns the coefficient of the DNA axial rigidity k_g, we can always safely take it to be constant, because at the typical voltages used in

the experiments[1–12] it is hardly possible that DNAs translocated through nanopores could be overstretched. Thus, the pertinent force-extension values ought to be insignificant enough to obey Hooke's law and exhibit rather weak dependence on the DNA nucleotide pair sequence.[28–35] In contrast, Young moduli of DNA duplexes — and, hence, their torsional rigidities — are well known to be appreciably dependent on DNA sequence.[22–27] With this in mind, we must recognize that the torsional rigidity coefficient of the DNA fragment translocated through the nanopore can in principle be a function of time. Specifically, only for DNAs with the homogeneous sequences like poly(dA)–poly(dT) or poly(dG)–poly(dC) can the torsional rigidity be constant — periodic, quasiperiodic or random DNA sequences would render this parameter periodic, quasiperiodic or random function of time, respectively.

To sum up, when considering homogeneous, periodic and even quasiperiodic DNA sequences, we are mainly interested in capturing just the *qualitative* effects. Therefore, in such cases, we shall consider the simplified nonconservative undamped model given by Eq. (4) and lay greater stress on the sequence dependence of the DNA torsional rigidity, with completely neglecting the former for the DNA axial rigidity. But for DNA duplexes with natural/chaotic sequences, a more realistic model should be worked out, because the *quantitative* effects are necessary for the practicable and meaningful DNA sequencing. Hence, in the latter case, we shall assume that *both torsional and axial* DNA rigidities are sequence-dependent, and render the equation of motion thermodynamically consistent by including the damping term.

All other mechanical parameters of DNA (masses, radii, lengths, moments of inertia) can be considered only weakly dependent on the sequence, since molecular masses and spatial dimensions of AT and GC Watson–Crick pairs are very close to each other.

The above conclusions turn out to be of crucial importance for application of our model to DNA sequencing with the help of the voltage-driven DNA nanopore translocation: by analyzing the ionic current response to the latter within the frame of our model, one can discriminate between different DNA sequences on the basis of the time-correlation functions of the torsional rigidity coefficients which are directly correspondent to the correlation functions of the relevant nucleotide pair sequences. To show the possible ways of embodying these ideas in practice, we shall analyze Eq. (4) for different types of DNA sequences in the next section.

4. Sequence-Dependent DNA Translocation Through Nanopores: A Qualitative and Quantitative Analysis

4.1. *Homogeneous DNA sequences (poly(dA)–poly(dT) or poly(dG)–poly(dC))*

In this case the stiffness matrix **K** in Eq. (4b) is independent of time, so that the stability analysis of Eq. (4) described in Refs. 62 and 63 is fully applicable. We shall make use of this fact below.

First, let us notice that Eq. (4) describes a *non-conservative undamped linear* dynamical system, because the energy gained from the driving force due to a voltage difference will be dissipated via Coulomb friction between the DNA duplex and its Manning cloud. Mathematically, the non-conservativeness of the system is manifested in that the mass matrix $\mathbf{M}$ is in general not a symmetrical one. It is convenient to reorganize Eq. (4) by premultiplying it by the following matrix:

$$\mathbf{M}_a = \begin{bmatrix} 1/J_\phi & 0 \\ 0 & 1/(m+m_v+m_1) \end{bmatrix},$$

to get

$$\begin{gathered} \tilde{\mathbf{M}} \begin{Bmatrix} \ddot{\phi} \\ \ddot{u} \end{Bmatrix} + \tilde{\mathbf{K}} \begin{Bmatrix} \phi \\ u \end{Bmatrix} = \begin{Bmatrix} \Lambda r F/J_\phi \\ -2F/M \end{Bmatrix}, \quad M \equiv (m+m_v+m_1)\,, \\ \tilde{\mathbf{M}} \equiv \begin{bmatrix} 1+(\Lambda m r^2 \tan\delta)/J_\phi & -(mr\Lambda)/J_\phi \\ -(mr\tan\delta)/M & 1 \end{bmatrix}, \quad \tilde{\mathbf{K}} \equiv \begin{bmatrix} \omega_\phi^2 & 0 \\ 0 & \omega_g^2 \end{bmatrix}. \end{gathered} \tag{5}$$

Now, the modified stiffness matrix contains squared natural torsional frequency of the DNA screw, $\omega_\phi = \sqrt{k_\phi/J_\phi}$, and its natural axial frequency including the masses of the DNA rest and the corresponding Manning cloud, $\omega_g = \sqrt{k_g/M}$.

Since Eq. (5) describes a system of two coupled oscillators each loaded with its own external force, to produce predictable effects it is important to ensure that the pertinent *unloaded* dynamical system be stable. Then, finite values of external forces should always cause some correspondingly finite response of the system. Under such conditions, dynamical systems are known to exhibit a so-called *weak stability* (in other words, dynamical systems of this kind are stable in the bounded-input–bounded-output (BIBO) sense). As shown in Refs. 62 and 63, solutions to Eq. (5) will be *stable* in the BIBO sense (independently of the physical nature of the external force F), if and only if the following conditions are simultaneously satisfied:

$$\begin{gathered} A \geq 0, \quad B \geq 0, \quad B^2 - 4AC \geq 0, \\ A \equiv 1 + \frac{\Lambda m r^2 \tan\delta}{J_\phi}\left(1 - \frac{m}{M}\right), \quad B \equiv \omega_\phi^2 + \omega_g^2\left(1 + \frac{\Lambda m r^2 \tan\delta}{J_\phi}\right), \\ C \equiv \omega_\phi^2 \omega_g^2. \end{gathered} \tag{6a}$$

Physically, if at least one of the above inequalities is not fulfilled, there would be no DNA translocation, and only torsional and axial vibrations of the DNA duplex with respect to its Manning cloud within the nanopore should be observed. This ought to noticeably diminish or even stop the observed ionic current during longer time periods than those usually observed[1–12] in the experiments. Here, it is also important to recall that Λ includes a contribution from the Coulomb friction between the DNA duplex and its Manning cloud in the nanopore, and thus might change its sign, depending upon what is the direction of the translocation (this can be checked in the experiments by changing the polarity of the applied voltage). Still, since the mass of the Manning cloud within the nanopore is definitely much

less than that of the whole DNA duplex, the first two inequalities will always be true, at least for all the positive values of Λ. The third inequality will then also be satisfied, if

$$\omega_\phi^2 \geq \omega_g^2 \left(1 + \frac{\Lambda m r^2 \tan\delta}{J_\phi}\right). \tag{6b}$$

In other words, to ensure BIBO stability in the both translocation directions, the torsional frequency must always be much higher than the axial one for sufficiently low absolute values of Λ. Otherwise, depending on the sign and magnitude of Λ, the inequality (6b) can be true when translocating DNA duplex in one direction, but would be false in the opposite one. Meanwhile, earlier estimates of the pertinent DNA normal mode frequencies show that the condition (6b) ought to be satisfied anyway.[65]

4.2. *Periodical DNA sequences (like poly(dAdT)–poly(dTdA), poly(dAdGdCdT)–poly(dTdCdGdA) or similar) vs "noisy" sequences*

In such cases, the torsional frequency in Eq. (5) will be a periodical function of time, with the time period reflecting the periodicity of the DNA sequence in question.

Mathematically, Eq. (5) can now be represented by a non-conservative undamped dynamical system consisting of two coupled linear oscillators, with the one of them being described by the Mathieu equation (parametrically driven oscillator with the frequency periodically dependent on time). The system is loaded by the sum of deterministic and stochastic external forces.

To investigate the BIBO stability of this system, we may use the conventional Floquet theory (see, for example, Ref. 66) for the system in the absence of the load. For this purpose, we first have to rewrite Eq. (5) in the following form:

$$\begin{Bmatrix} \ddot{\phi} \\ \ddot{u} \end{Bmatrix} + \tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} \begin{Bmatrix} \phi \\ u \end{Bmatrix} = \tilde{\mathbf{M}}^{-1} \begin{Bmatrix} \Lambda r F/J_\phi \\ -2F/M \end{Bmatrix} \equiv \begin{Bmatrix} \Lambda r F \\ -2F \end{Bmatrix},$$
$$\tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} \equiv A^{-1} \begin{bmatrix} \omega_\phi^2 & (m\omega_g^2 r\Lambda)/J_\phi \\ (m\omega_\phi^2 r\tan\delta)/M & \omega_g^2 + (m\omega_g^2 r^2 \Lambda \tan\delta)/J_\phi \end{bmatrix}, \tag{7}$$

where A is defined in Eq. (6a), $\omega_\phi^2 = \omega_{\phi 0}^2(1 + q\cos(\omega_m t))$, with some average torsional frequency $\omega_{\phi 0}$, amplitude of the modulation q due to the periodicity of the DNA sequence and modulation frequency ω_m.

The normal modes of Eq. (7) will in general be possessed of complex frequencies, $\omega_1 + i\Omega_1$ and $\omega_2 + i\Omega_2$, which should be some linear combinations of the initial average torsional and axial frequencies. The instability should occur near twice the real parts of the normal mode frequencies and their subharmonics, $2\omega_{1,2}/s, s = 1, 2, 3, \ldots$, as well as near the sum of and difference between the ω_1 and ω_2 and their subharmonics, $(\omega_1 \pm \omega_2)/s, s = 1, 2, 3, \ldots$.

Interestingly, if Eq. (7) is loaded by some additive force due to a colored (Ornstein–Uhlenbeck) noise, the critical value of the modulation amplitude q (from where on any increase of q would render the solutions to Eq. (7) unstable) should be independent of the strength and the correlation length of that noise.[67]

4.3. *Quasiperiodical DNA Sequences (periodically modulated periodical DNA sequences)*

In such cases, the torsional frequency in Eq. (5) should be a quasiperiodical function of time, with the number of incommensurate modes corresponding to the number of modulation modes in the DNA sequence involved.

For the BIBO stability analysis in this situation, the general form of Eq. (7) can be used again. Regretably, there are practically no analytical results for oscillators with quasiperiodically modulated frequencies. Numerical or perturbational analyses have mainly been carried out for some particular forms of the latter systems (see, for example, Ref. 68 and references therein). Summing up the available findings, one may conclude that quasiperiodical frequency modulations produce much richer choice of instabilities than the periodic ones, as can be anticipated from the viewpoint of general physics. Unlike with periodic modulations, the spectrum of the potentially unstable frequencies due to quasiperiodic forcing can even be quasi-continuum one in some frequency regions, instead of being clearly discrete in the whole frequency range. In contrast, resonances between special combinations of DNA torsional, axial and sequence modulation frequencies are possible at some discrete frequency values.

In application to our problem of DNA translocation through nanopore, unstable solutions to Eq. (7) would imply significant slowing down of the translocation process and some irregular shape of the ionic current dips/spikes, whereas resonances ought to promote the translocation acceleration.

4.4. *Thermodynamic consistency of the equation of motion*

Since the force F in Eq. (7) contains an additive noise due to Brownian motion, to make Eq. (7) thermodynamically consistent, we need to satisfy the requirements of the fluctuation–dissipation theorem and add a damping term $\mathbf{f}(\mathbf{x},\ \mathbf{v}) = \mathbf{B}\mathbf{v}$ on the left-hand side of Eq. (7), with $\mathbf{B}$ being a matrix of friction coefficients, $\mathbf{x}$, $\mathbf{v}$ — the vectors of the canonical coordinates and momenta, respectively — and, to ensure that the Newton's second law holds, $\mathbf{B}$ must be symmetrical and positively definite.[69] Moreover, $\mathbf{B}$ is usually considered diagonal, but this requires one to take into account some hydrodynamics[70] of hydrated biopolymers. Hence, in our case, we arrive at the following expression:

$$\begin{Bmatrix} \ddot{\phi} \\ \ddot{u} \end{Bmatrix} + \tilde{\mathbf{M}}^{-1}\mathbf{B} \begin{Bmatrix} \dot{\phi} \\ \dot{u} \end{Bmatrix} + \tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} \begin{Bmatrix} \phi \\ u \end{Bmatrix} = \begin{Bmatrix} \Lambda r F \\ -2F \end{Bmatrix}. \tag{7a}$$

Intuitively, when investigating the BIBO stability, the presence of the damping term ought to bring more stabilization into the whole system in question. But, on the other hand, it is well known[55,56,71,72] that the presence of both damping and non-conservative terms in equations of motion of Eq. (7) form may lead to intrinsic dynamical instabilities. In general physical terms, the destabilizing effect of damping is known to be due to the presence of the so-called "negative energy modes" in the undamped system, i.e. the modes that extract energy from the energy reservoir of the system. These modes can be supplied by the non-conservative term and need an energy sink in order to be excited — while damping often plays the role of such a sink, thus destabilizing the system. Similar phenomena were already described earlier in terms of negative energy waves in plasma physics[73] and in hydrodynamics.[74]

4.5. *Natural or stochastic DNA sequences*

This is the central part of our report, so that we consider here the more elaborate model described by Eq. (7a).

Indeed, Eq. (7a) is a two-dimensional stochastic oscillator equation with both additive and multiplicative noise. Specifically, both torsional and axial frequencies here can be recast in a general form as $\omega^2 = \omega_0^2(1 + qF(\xi(t)))$, where $F(\xi(t))$ is a function of some suitable random process with mean value zero, with $\xi(t)$ being either a white noise, colored noise, ergodic diffusion process, or even a Markov process with finitely many states. The latter case is called *real-noise-driven oscillator process*[75,76] and seems to be appropriate when speaking of DNA sequences.[77]

As a quick illustration, we shall consider some particular, highly idealized, but analytically tractable case. In accordance with this, we assume from here on that the noise $\xi(t)$ modulating the both frequencies in Eq. (7a) represents the simplest possible Markov process with two states and zero mean $\langle\xi(t)\rangle = 0$ (telegraph or dichotomous noise). It is well known (see, for example, Ref. 78) that such a process is a particular case of the Ornstein–Uhlenbeck noise with the two forms of correlators (time correlation functions):

$$\begin{aligned} &\langle\xi(t)\xi(t_1)\rangle = \sigma^2 \exp[-\lambda|t - t_1|], \quad \text{or} \\ &\langle\xi(t)\xi(t_1)\rangle = \frac{D}{\tau} \exp\left[\frac{|t - t_1|}{\tau}\right], \end{aligned} \tag{8}$$

where D is the noise strength and τ is the correlation time. The parameters σ and λ describe the telegraph process, with the random variable ξ taking only one of the values $\xi = \pm\sigma$ and $(\lambda/2)^{-1}$ being the mean waiting time in each of these two states.

Since for sufficiently long DNA duplexes $(m/M) \ll 1$, we obtain

$$A \cong 1 + \frac{\Lambda m r^2 \tan\delta}{J_\phi},$$

so that

$$\tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} \cong \begin{bmatrix} \dfrac{J_\phi \omega_\phi^2}{(J_\phi + mr^2\Lambda\tan\delta)} & \dfrac{\left(m\omega_g^2 r\Lambda\right)}{(J_\phi + mr^2\Lambda\tan\delta)} \\ 0 & \omega_g^2 \end{bmatrix}, \tag{9}$$

and, therefore, we may consider rotational and translational modes practically *independent* of each other. With this in mind, we shall first introduce a general analytical procedure to investigate the stability of each of the two oscillatory degrees of freedom.

For either of the latter, we may write down the equation of motion using non-dimensional time:

$$\ddot{Y} + 2[\zeta + \eta(t)]\dot{Y} + [1 + \xi(t)]Y = 0, \tag{10}$$

where ζ stands for the dimensionless damping coefficient, assuming in the most general case that (a) the normalized natural frequency is unity, (b) *both damping and frequency* are affected by the time-dependent multiplicative noise due to the DNA nucleotide sequence and (c) the noises are real non-white ergodic processes with zero mean and bounded variances. Moreover, the noises $\eta(t)$ and $\xi(t)$ should be correlated, because they are stemming from one and the same source. Then, applying the Infante's theorem, one can find[79] the following sufficient criterion of asymptotic sample stability (that is, Lyapunov asymptotic stability with probability one, or, almost sure asymptotic stability[79]) for the oscillator described by Eq. (10), if we know variances of the processes $\eta(t)$ and $\xi(t)(\sigma_\eta, \sigma_\xi)$ and their correlation coefficient ρ:

$$(1 - \rho^2\sigma_\eta^2)\sigma_\xi^2 - 4\zeta\rho(1 - \sigma_\eta^2)\sigma_\eta\sigma_\xi + 4(1 - \sigma_\eta^2)[(1 + \zeta^2)\sigma_\eta^2 - \zeta^2] = 0. \tag{11}$$

In effect, Eq. (11) describes the stability boundary for σ_η, if σ_ξ, or *vice versa*. An even stronger stability condition can be obtained, in case the joint probability for the noises $\eta(t)$ and $\xi(t)$ is also known, so that any additional information about the noises should further sharpen the stability criterion.[79]

Finally, it should be noted that a positive value of the effective squared rotational frequency has been assumed up to here. But, in principle, the latter can also be negative in some particular direction of motion, because Eq. (9) shows that it is in effect equal to $\omega_\phi^2(\frac{J_\phi}{J_\phi + mr^2\Lambda\tan\delta})$ and, thus, dependent on the difference between the DNA double-helical twist angle and the Coulomb friction. Interestingly, if the effective ω_ϕ^2 is positive in one direction but negative in the other one, the over-all screw motion ought to be rectified, so that we shall get a ratchet mechanically supported by the broken symmetry of friction, just as envisaged in Refs. 80–82. Besides, translocation through a nanopore of a single-stranded DNA *via* ratchet created by asymmetry of the external potential has been studied in detail in Ref. 14.

If the effective ω_ϕ^2 is negative, the noise can even stabilize the solution of the corresponding oscillator equation (see, for example, Ref. 83). To know which situation we are dealing with in every particular case, it is necessary to investigate the

stability of the averaged left-hand side of Eq. (7a) — then we shall deal with the *average* values of the frequencies and damping coefficients.

For this purpose, using the state space $\mathbf{z}^T = (\mathbf{y}^T,\ \dot{\mathbf{y}}^T)$, we rewrite the left-hand side of Eq. (7a) in the following block-matrix form:

$$\frac{d\mathbf{z}}{dt} = \begin{bmatrix} \mathbf{0} & \mathbf{I} \\ \tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} & \tilde{\mathbf{M}}^{-1}\mathbf{B} \end{bmatrix} \mathbf{z}, \tag{12}$$

where $\mathbf{I}$ stands for the 2×2 unity matrix and $\mathbf{0}$ is 2×2 zero matrix, whereas the structure of both frequency and damping submatrices is upper-triangular in our case (see Eq. (9))

$$\tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}} = \begin{pmatrix} -b & -b_1 \\ 0 & -d \end{pmatrix}, \quad \tilde{\mathbf{M}}^{-1}\mathbf{B} = \begin{pmatrix} -a & -a_1 \\ 0 & -c \end{pmatrix}. \tag{13}$$

Then, the characteristic polynomial of the matrix in Eq. (12) is of fourth order and can be cast in the following form:

$$\begin{gathered} \lambda^4 + \alpha\lambda^3 + \beta\lambda^2 + \gamma\lambda + \delta = 0; \\ \alpha \equiv a + c; \quad \beta \equiv b + ac + d; \quad \gamma \equiv bc + ad; \quad \delta \equiv bd, \end{gathered} \tag{14}$$

so that we may apply the Routh–Hurwitz theorem to derive the necessary and sufficient criteria for the matrix in Eq. (12) to have negative real parts in all of its eigenvalues, which is, in turn, indicative of the asymptotic stability of the solutions to Eq. (12). The desired criteria read as follows: $\beta > 0, \gamma > 0, \beta\gamma - \alpha\delta > 0, \beta^2 - 4\delta > 0$.[84] To apply this composite criterion, we must also take into account that in the matrices of Eq. (13) the translational frequency (d) is greater than zero (see Eq. (9)), and so must be the translational (c) and rotational (a) damping coefficients. Then, Eq. (12) will always be possessed of stable solutions, if the rotational frequency (b) in the matrix $\tilde{\mathbf{M}}^{-1}\tilde{\mathbf{K}}$ (see Eq. (13)) is greater than zero as well. But otherwise the system will in general be stable only if $|b| < |d|$. It should be noted that the both latter results are quite different from the stability conditions given by Eq. (6) for the corresponding non-conservative system without damping. This illustrates the well-known paradoxical changes[55,56,71,72] in non-conservative dynamical systems' stability upon addition of damping.

5. Sequence-Dependent DNA Translocation Through Nanopores: Numerical Simulations

As the main purpose of introducing here the DNA screw model is to describe the process of DNA sequencing, it is interesting to check whether our model can distinguish between different types of disorder due to DNA sequence. For this purpose, we have carried out two numerical simulations, using Eq. (7a) and assuming two different types of noise: white and the dichotomic ones. The results are shown in Figs. 3 and 4, respectively.

First of all, we may note that the calculated peaky electrical current patterns bear strong qualitative resemblance to those measured in the relevant experiments.[1–12]

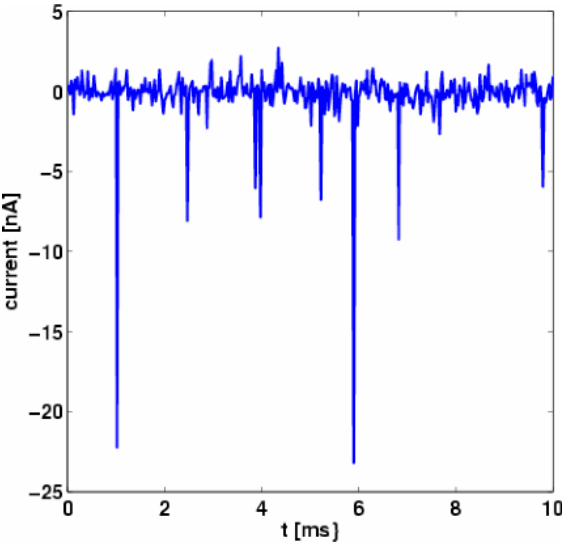

Fig. 3. Time dependence of the electrolytic current due to DNA translocation through a nanopore, as a result of numerical simulation with DNA screw model given by Eq. (7) with the frequencies and damping affected by time-dependent *white* noise. The current **j** was estimated using the relationship $\mathbf{j} = en\mathbf{v}$, where e is the electron charge, n is the concentration of charged particles (DNA monomers, counterions) and **v** is the translational velocity from the solution of Eq. (7). The DNA parameters used (see the main text for their definitions) are: $m = 1.4664\text{e+}7$ a.m.u., m_ν 3.72e+4 a.m.u., $m_1 = 2000 * m$, $r = 10$Å, $a = p = 3.4$Å, which corresponds to a B-DNA duplex with 7.9e+5 base pairs surrounded by water-counterion shell. This DNA molecule translocates through a nanopore of length 20 nm and diameter 10 nm, under the applied voltage of 200 mV.[1–12] For the DNA-counterion-hydration-shell system under study, the Coulomb friction coefficient turns out to be $f = 0.6$, the adopted velocity-dependent frictional damping coefficient is $\gamma = 0.02$ (the same for the rotational and translational degrees of freedom), the adopted value of the translational frequency is $\omega_g = 25\,\text{cm}^{-1}$,[41–46] and the torsional frequency is taken to be $\omega_\phi = 5 * \omega_g$.[65] The amplitude of the white noise is taken to be $q = 0.4$ and only the torsional frequency ω_ϕ was "noisy" in these simulations. Numerical integration was performed using two-step Heun method.

Further, Figs. 3 and 4 clearly demonstrate that our model is capable of feeling the difference between the various types of noise owing to DNA sequence. Indeed, according to our results, DNA with a random sequence described by white noise would translocate more quickly — and the current peaks would be more evenly distributed in time — compared to that with the random sequence described by the dichotomic noise.

Another check for the validity of our model would be the capability of the latter to explain the dependence of the translocation time on the length of the translocated macromolecule. In general, such a dependence obeys power law and may be appreciably influenced by the chemical nature of the translocating polymer, as well as by the external conditions of the translocation experiment (see Ref. 85 and references therein). To study the dependence of the translocation time on the length of the translocated polymer, Ref. 85 introduces a two-dimensional model of

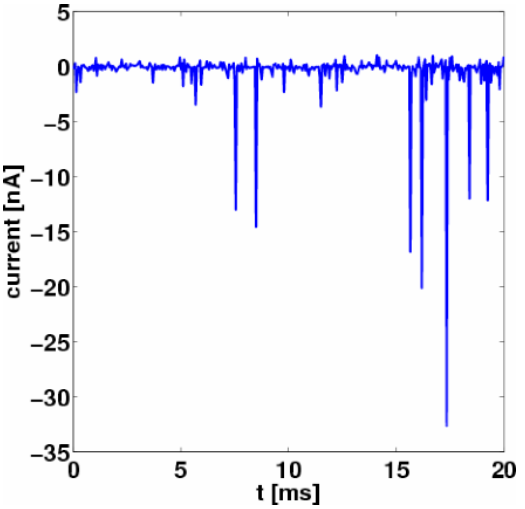

Fig. 4. Time dependence of electrolytic current due to DNA translocation through a nanopore, as a result of numerical simulation with DNA screw model given by Eq. (7) with the frequencies and damping affected by time-dependent *dichotomic* noise. The numerical integration method and the model parameters here are the same as presented in the legend to Fig. 3, except for the velocity-dependent friction constant, which is equal to 0.01 in this case. The telegraphic noise here assumes two values $+q$ and $-q$ at random, with the amplitude $q = 0.32$ and dimensionless correlation time $\tau = 1$ (correlated noise).

polymer translocation which is rather similar to ours. But there are significant differences between the former and the latter. Specifically, the model of Ref. 85 adopts the Rouse picture of a flexible polymer and neglects hydrodynamical effects (and, therefore, any possibility of rotational modes in the system), describing dynamics of every polymer segment by two overdamped nonlinear Langevin equations (whereas our model is instead linear and takes the inertial terms into account). Further, the nonlinearity of the model of Ref. 85 introduces potential barrier for one of the degrees of freedom to take into account posible quasi-equilibrium states of a polymer during its translocation. And our model takes the latter into account by assuming the possibility of the translocation stop via entering vibrational regime due to intrinsic instabilities in the system.

Following the model of Ref. 85, we may estimate the translocation (crossing) time as the Mean First Passage Time (MFPT). This is possible with our linear underdamped model given by Eq. (10), if we use the generalized Pontryagin theory (see Ref. 79, Chap. 8). To do so, we consider some diffusive Markov process $Z(t)$, and will look for the random time T, when $Z(t)$ reaches some critical value z_c. If $q(z, t|z_0, t_0)$ is transition probability for $Z(t)$, then the probability that $z_l \leq Z(t) < z_c$ at time t can be cast as follows:

$$R(z_c, t; z_0, t_0) = \int_{z_l}^{z_c} q(z, t|z_0, t_0)dz, \quad z_l \leq z_0 < z_c, \;\; t \geq t_0, \tag{15}$$

where z_l is the left boundary of the process $Z(t)$ and $R(z_c, t;\ z_0,\ t_0)$ is called reliability function. Then, the probability distribution F_T for MFPT is given by $(1 - R(\tau, z_c, z_0))$, with $\tau = t - t_0$. It is possible to derive the equation of motion for any $(n + 1)$th moment of distribution[79] F_T which is called generalized Pontryagin equation. Using Eq. (10) we can demonstrate the power law dependence of the first moment of F_T on the critical value of the corresponding amplitude process[79] $A(t) = \sqrt{Y^2(t) + \dot{Y}^2(t)}$ for the DNA screw translational degree of freedom. And the latter critical value is obviously dependent on the length of the translocated polymer, if we assume that the translational amplitude reaches its critical value when the whole translocation process of *one* DNA duplex is over, like it has been assumed in Ref. 85. We shall dwell on this very important point elsewhere.

6. Conclusions

Based upon the structural properties of DNA duplexes and their counterion-water surrounding in solution, we have introduced here a screw model which may describe translocation of DNA duplexes through nanopores of the proper diameter (where the DNA counterion–hydration shell can be intact) in a qualitatively correct way. This model represents DNA as a kind of "screw", whereas the counterion–hydration shell can be considered a kind of "nut." When an electrical potential is applied across the membrane with a nanopore, the "screw" and "nut" begin to move with respect to each other, so that their mutual rotation is coupled with their mutual translation. As a result, there are peaks of electrical current connected with the mutual translocation of DNA and its counterion–hydration shell, if DNA is possessed of some non-regular base-pair sequence. The calculated peaks of current strongly resemble those observed in the pertinent experiments. Interestingly, an analogous model could in principle be applied to DNA translocation in natural DNA–protein complexes of biological interest, so that the role of "nut" would be played by protein-tailored "channels". In such cases, our DNA screw model may demonstrate how symmetry breaking due to Coulomb friction may guarantee chemical-to-mechanical energy conversion in DNA–protein molecular motors.

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