

# Single stranded DNA translocation through a nanopore: A master equation approach

O. Flomenbom and J. Klafter

School of Chemistry, Raymond &amp; Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

(Received 10 April 2003; revised manuscript received 26 June 2003; published 14 October 2003)

We study voltage driven translocation of a single stranded DNA through a membrane channel. Our model, based on a master equation approach, investigates the probability density function of the translocation times, and shows that it can be either double peaked or mono peaked, depending on the system parameters. We show that the most probable translocation time is proportional to the polymer length, and inversely proportional to the first or second power of the voltage, depending on the initial conditions. The model recovers experimental observations on heteropolymers when using their properties inside the pore, such as stiffness and polymer-pore interaction.

DOI: 10.1103/PhysRevE.68.041910

PACS number(s): 87.14.Gg, 87.15.Aa, 87.15.He

## I. INTRODUCTION

Translocation of biopolymers through a pore embedded in a membrane is a fundamental step in a variety of biological processes. Among the examples are the translocation of some species of mRNA through the nuclear membrane, which is the first stage of gene expression in eucaryotic cells [1], and the attack of cells by viruses that occurs by injecting the genetic information through a hole in the cell membrane [2]. The translocation importance in biosystems, and the possibility for developing fast sequencing methods, have been the motivation for recent experiments, in which a voltage-driven single stranded DNA (ssDNA) is translocated through  $\alpha$ -hemolysin channel of a known structure [3]. In these experiments one measures the time it takes a single ssDNA molecule to pass through a membrane channel [4–7]. Since ssDNA is negatively charged [each monomer has an effective charge of  $zq$ , where  $z$  ( $0 < z < 1$ ) is controlled by the solution pH and strength], when applying a voltage the polymer is subject to a driving force while passing through the membrane from the negative (*cis*) side to the positive (*trans*) side. Because the presence of the ssDNA in the transmembrane pore part (TPP) blocks the cross-TPP current, one can deduce the translocation times probability density function (PDF) from the current blockade duration times [4–7]. It has been found that the shape of the translocation times PDF is controlled not only by the voltage applied to the system, the temperature, and the polymer length but also by the nature of the homopolymer used: poly-*dA* (*A*, adenine), poly-*dC* (*C*, cytosine), poly-*T<sub>nu</sub>* (*T<sub>nu</sub>*, thymine), and the sequence of heteropolymers [4–7].

The translocation process can be roughly divided into two stages. The first stage is the arrival of the polymer in the vicinity of the pore and the second stage is the translocation itself. Several models have been suggested for describing the translocation stage. In Ref. [8] an equation for the free energy of the translocation, obtained from the partition functions of the polymer parts outside the TPP, was derived and used to calculate the mean first passage time (MFPT). Other investigators used similar ideas with improved free energy terms by taking into consideration effects such as the membrane width [9,10], or assumed that only the part of the ssDNA inside the TPP affects the dynamics of the translocation rather than the polymer parts outside the TPP [11,12].

In this work we present a theoretical approach that allows to consider both the polymer parts outside the TPP and within the TPP. Using the master equation (ME) we are able to map the three-dimensional translocation onto a discrete space one-dimensional process. Based on the ME we compute the PDF of the first passage times (FPT) of the translocation,  $F(t)$ , and the MFPT, as a function of the system parameters. We relate our theoretical results to recent experimental observations and by analyzing them using our model, we come up with physical understanding of these observations.

## II. THE MODEL

An  $n (= N + d - 1)$ -state ME is used to describe the translocation of an  $N$ -monomer long ssDNA subject to an external voltage  $V$ , and temperature  $T$ , through a TPP of a length that corresponds to  $d$  ( $= 12$ ) monomers. A state is defined by the number of monomers on each side of the membrane and within the TPP. A change in the state of the system (only nearest states' transitions are allowed) is assumed to be controlled mainly by the behavior of the polymer within the TPP in the presence of the applied voltage. In addition, it is assumed to be influenced by entropic and interaction factors of the polymer outside and within the TPP. Absorbing ends are used as boundary conditions, which are the natural choice for this system because the polymer can exit the TPP on both sides. The state  $j = n$  represents the arrival of the first monomer into the TPP from the *cis* side, and the state  $j = 0$  represents the departure of the far end monomer from the *trans* side of the TPP. Let  $P_j(t)$  be the PDF to occupy state  $j$  that contains  $m_j$  nucleotides within the TPP according to

$$m_j = \begin{cases} j, & j \leq d \\ d, & N > j > d \quad \text{given } N \geq d \\ n + 1 - j, & j \geq N \end{cases} \quad (1a)$$

$$m_j = \begin{cases} d, & N > j > d \quad \text{given } N \geq d \\ n + 1 - j, & j \geq N \end{cases} \quad (1b)$$

$$m_j = \begin{cases} j, & j \leq d \\ d, & N > j > d \quad \text{given } N \geq d \\ n + 1 - j, & j \geq N \end{cases} \quad (1c)$$

and a similar set of equations for a short polymer,  $N \leq d$ , which is obtained by exchanging  $N$  and  $d$  in Eqs. (1a)–(1c). The governing equations of motion are

$$\begin{aligned} \partial P_j(t) / \partial t = & a_{j+1,j} P_{j+1}(t) + a_{j-1,j} P_{j-1}(t) \\ & - (a_{j,j+1} + a_{j,j-1}) P_j(t), \quad j = 2, \dots, n-1, \end{aligned}$$

$$\begin{aligned} \partial P_y(t)/\partial t = & a_{y+1,y} P_{y+1}(t) \delta_{y,1} + a_{y-1,y} P_{y-1}(t) \delta_{y,n} \\ & - (a_{y,y-1} + a_{y,y+1}) P_y(t), \quad y=1,n. \end{aligned} \quad (2)$$

Equation (2) can be written in matrix representation  $\partial \vec{P}/\partial t = \mathbf{A} \vec{P}$ . The propagation matrix  $\mathbf{A}$  is a tridiagonal matrix that contains information about the transitions between states in terms of rate constants. We assume that the rate constants can be decoupled into two terms,

$$a_{j,j+/-1} = k_j(T) p_{j,j+/-1}(V, T). \quad (3)$$

The first term provides the rate to perform a step, while the second term gives the probability to jump from state  $j$  in a given direction, and obeys  $p_{j,j+1} + p_{j,j-1} = 1$ . To obtain  $k_j$ , we first consider the bulk relaxation time of a polymer [13]  $\tau_b \propto \beta \xi_b b^2 N^\mu$ , where  $\beta^{-1} = k_B T$ ,  $b$  is a monomer length,  $\xi_b$  is the Stokes bulk friction constant per segment,  $\xi_b = 6\pi b \eta$  (where  $\eta$  is the solvent viscosity),  $N$  is the number of monomers in the polymer, and the dimension dependent  $\mu$  represents the effect of the microscopic repulsion on the average polymer size. In three dimensions  $\mu = 3, 9/5, 3/2$  for rodlike, self-avoiding, and Gaussian (Zimm model) chains, respectively. To compute the relaxation time inside the TPP, the confined volume of the TPP must be taken into account. For a rodlike polymer the restricted volume dictates a one-dimensional translocation, whereas for a flexible polymer the limitations are less severe. We implement this by taking  $\mu$  as a measure of the polymer stiffness inside the TPP that obeys  $0 \leq \mu \leq 1.5$ . The expression for the relaxation rate of state  $j$  is therefore,

$$k_j = 1/(\beta \xi_b b^2 m_j^\mu) \equiv R/m_j^\mu. \quad (4)$$

From Eq. (4) it is clear that as  $\mu$  becomes smaller the rate to perform a step becomes larger, namely,  $k_j$  for a rodlike polymer increases. This feature appears, at first sight, to be in contradiction to the relaxation time behavior of a bulk polymer, where a rodlike polymer has a larger relaxation time than that of a flexible polymer. This contradiction is resolved by taking into account the different dimensional demand for a rodlike polymer relative to a flexible polymer inside the TPP. Because  $\mu$  is a measure of the polymer stiffness inside the TPP, it is controlled by the interaction between the monomers occupying the TPP, e.g., base stacking and hydrogen bonds, and therefore is affected by the monomer type and the sequence of the ssDNA.

The friction constant per segment inside the TPP,  $\xi_p$ , represents the interaction between the ssDNA and the TPP. The physical picture is that during translocation there are few or no water molecules between the polymer and the TPP. Consequently the water molecules inside the TPP can hardly be viewed as the conventional solvent and the Stokes friction constant is replaced by  $\xi_p$  representing the ssDNA-TPP interaction.

To calculate  $p_{j,j-1}$ , the second term on the right-hand side of Eq. (3), we assume a quasiequilibrium process and use the detailed balance condition for the ratio of the rate constants between neighboring states:  $a_{j,j-1}/a_{j-1,j}$

$= e^{-\beta \Delta E_j}$ , where  $\Delta E_j = E_{j-1} - E_j$ . We then use the approximation  $a_{j,j-1}/a_{j-1,j} \approx p_{j,j-1}/(1-p_{j,j-1})$ , and deduce the jump probabilities by computing  $\Delta E_j$ . To compute  $E_j$  the contributions from three different sources are considered: electrostatic  $E_j^p$ , entropic  $E_j^s$ , and an averaged interaction energy between the ssDNA and the pore,  $E_j^i$ .

For the calculations of the electrostatic energy difference between adjacent states,  $\Delta E_j^p$ , we assume a linear drop of the voltage along the TPP and write for  $m_j$  monomers occupying the TPP penetrating from the cis side of the membrane for a length of  $i_j b$ ,

$$E_j^p = zq(V/d) \sum_{n=i_j}^{m_j+i_j-1} n = zq(V/2d) m_j (m_j + 2i_j - 1). \quad (5)$$

The effective charge per monomer in the TPP is taken to be the same as of the bulk. For states that contain monomers at the *trans* side of the membrane,  $zqV$  should be added to  $\Delta E_j^p$ . This contribution represents the additional effective charge that passed through the potential  $V$ . Accordingly, the expression for  $\Delta E_j^p$  is (see Appendix A)

$$\Delta E_j^p = zqV(m_j + \alpha_j)/d. \quad (6)$$

Here  $\alpha_j$  takes the values  $\alpha_j = \{-1; 0; 1\}$  for cases described by Eqs. (1a), (1b), and (1c), respectively ( $\alpha_j = 1$  and  $\alpha_j = -1$  correspond to the entrance and exit states of the translocation, whereas  $\alpha_j = 0$  corresponds to the intermediate states of the translocation). For a short polymer,  $\alpha_j$  has the same values as for a large polymer.

The contribution to  $\Delta E_j$  from  $\Delta E_j^s$  is composed of two terms. One term is the entropic cost needed to store  $m_j$  monomers inside the TPP, and the second term originates from the reduced number of configurations of a Gaussian polymer near an impermeable wall. Combining these terms leads to (see Appendix B)

$$\Delta E_j^s = \gamma_j / \beta, \quad (7)$$

where  $\gamma_j = \{-1 + g_j; g_j; 1 + g_j\}$ , for cases described by Eqs. (1a), (1b), and (1c), respectively.  $g_j$  is given in Appendix B in terms of  $N_{j,cis}$  and  $N_{j,trans}$ , which are the number of monomers on the *cis* and *trans* sides, correspondingly. For a short polymer  $\gamma_j$  behaves similarly but for intermediate states  $\gamma_j = 0$ .

For computing  $\Delta E_j^i$  we focus on the average interaction between the ssDNA and pore (not only its transmembrane part). Due to the asymmetry of the pore between the *cis* and the *trans* sides of the membrane [3], the ssDNA interacts with the pore on the *cis* side of the membrane and within the TPP but not on the *trans* side of the membrane. Assuming an attractive interaction,  $E_j^i = -\varepsilon(N - N_{j,trans})$ , we obtain by setting  $\varepsilon = k_B T$  in the relevant temperature regime

$$\Delta E_j^i = \zeta_j / \beta, \quad (8)$$

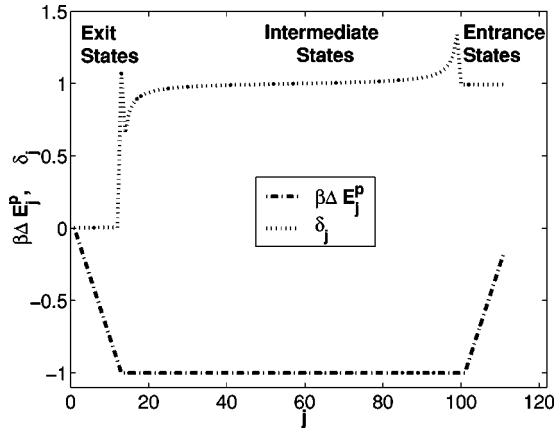


FIG. 1. The components of the  $\beta\Delta E_j$ ,  $\beta\Delta E_j^p$  ( $\beta z|q|V=1$ ) and  $\delta_j$ , are shown for  $N=100$ . For states  $j>d$ , voltages fulfilling  $V/V_C < 1$  lead to  $\beta\Delta E_j > 0$ , and accordingly to a *cis* side bias.

where  $\zeta_j = \{1; 1; 0\}$ , for the cases described by Eqs. (1a), (1b), and (1c), respectively, and for a short polymer  $\zeta_j = \{1; 0; 0\}$ .

Using the above relations, and defining  $\delta_j = \gamma_j + \zeta_j$ , we obtain

$$p_{j,j-1} = (1 + e^{\beta\Delta E_j^p + \delta_j})^{-1}. \quad (9)$$

For the system to be voltage driven  $-\beta\Delta E_j^p > \delta_j$  must be fulfilled, which translates into the condition  $V/V_C > 1$ , where a characteristic voltage is introduced,  $V_C^{-1} \equiv (1 + 1/d)\beta z|q|$ . This inequality ensures that there is a bias towards the *trans* side of the membrane. Otherwise the polymer is more likely to exit from the same side it entered than to traverse the membrane. Under experimental conditions [6]  $V_C = 46$  mV, when using  $z \approx 1/2$ .

In Fig. 1 we show the different contributions to  $\beta\Delta E_j$ :  $\beta\Delta E_j^p$  (for  $\beta z|q|V=1$ ) and  $\delta_j$ .  $\beta\Delta E_j^p$  decreases for the entrance states of the translocation, increases at the exit states of the translocation, and is a negative constant for intermediate states. Clearly  $\beta\Delta E_j^p \leq 0$  reflects the field directionality. On the other hand,  $\delta_j$  opposes the translocation for the entrance and intermediate states. For the entrance states  $\delta_j > 0$  due to both entropic terms, but approaches zero (from below) for the exit states of the translocation, due to the cancellation of  $\Delta E_j^t$  against the entropic gain of storing less monomers within the TPP. At intermediate states  $\delta_j \approx 1$ , where its shape near the crossover between the different situations is controlled by  $g_j$ .

### III. RESULTS AND DISCUSSION

#### A. The FPT PDF

In this subsection we compute the FPT PDF,  $F(t)$ , and examine its behavior as a function of the system parameters.  $F(t)$  is defined by

$$F(t) = \partial(1 - S(t))/\partial t, \quad (10)$$

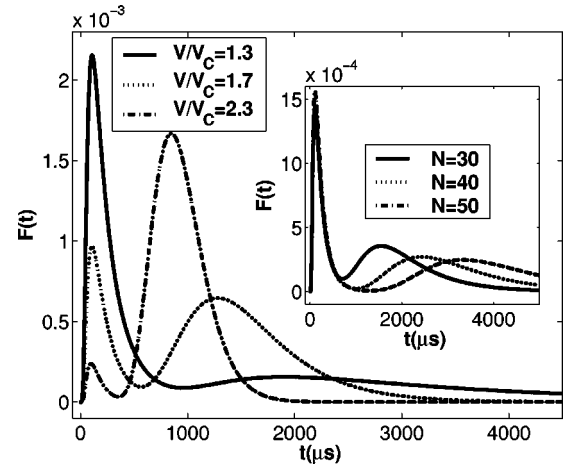


FIG. 2.  $F(t)$ , for several values of  $V/V_C$ , with  $N=30$ ,  $x=N+d/4$ ,  $z \approx 1/2$ ,  $T=2$  °C,  $V_C=46$  mV,  $\mu=1.14$  and  $R=10^6$  Hz. The left peak represents the nontranslocated events, whereas the right peak represents the translocation. Inset:  $F(t)$  as a function of  $N$ , with  $V/V_C=1.5$ , and the other parameters as above. The non-translocation peak remains unchanged when increasing the polymer length, while the translocation peak shifts to the right with  $N$ .

where the survival probability, namely, the probability to have at least one monomer in the TPP,  $S(t)$ , is given by

$$S(t) = \vec{U} C e^{\mathbf{D}t} C^{-1} \vec{P}_0. \quad (11)$$

Here  $\vec{U}$  is the summation row vector of  $n$  dimensions,  $\vec{P}_0$  is the initial condition column vector,  $(\vec{P}_0)_j = \delta_{x,j}$ , where  $x$  is the initial state, and the definite negative real part eigenvalue matrix,  $\mathbf{D}$ , is obtained through the transformation  $\mathbf{D} = \mathbf{C}^{-1} \mathbf{A} \mathbf{C}$ .

Substituting Eq. (11) into Eq. (10),  $F(t)$  is obtained. Figure 2 shows the double-peaked  $F(t)$  behavior as a function of  $V/V_C$  and  $N$  (inset), for starting at  $x=N+d/4$ . The left peak represents the nontranslocated events. Its amplitude decreases as  $V/V_C$  increases but remains unchanged (along with the position) with the increase in  $N$ , because only the “head” of the polymer is involved in these events. As  $x$  decreases, namely, when the translocation initial state shifts towards the *trans* side, the nontranslocation peak and the translocation peak merge and for  $x=n/2$ , namely, for an initial condition for which  $N_{j,cis} = N_{j,trans}$ ,  $F(t)$  has one peak (data not shown) independent of  $V/V_C$ .

For a convenient comparison to experimental results, we calculate and examine the behavior of the most probable average translocation velocity,  $v = xb/t_m$ , where  $t_m$  is the time that maximizes the translocation peak.

Figure 3 shows  $v(N)$  behavior, for  $V/V_C=2.60$ .  $v(N)$  is a monotonically decreasing function of  $N$  for  $N \leq d$ , but is independent of  $N$  for  $N \geq d$ . This agrees with the experimental results [6]. The origin for  $v(N)$  behavior stems from Eqs. (1) and (4), according to which the minimal  $k_j$  is a decreasing monotonic function of  $N$  for  $N \leq d$ , but is independent of  $N$  for  $N \geq d$ .

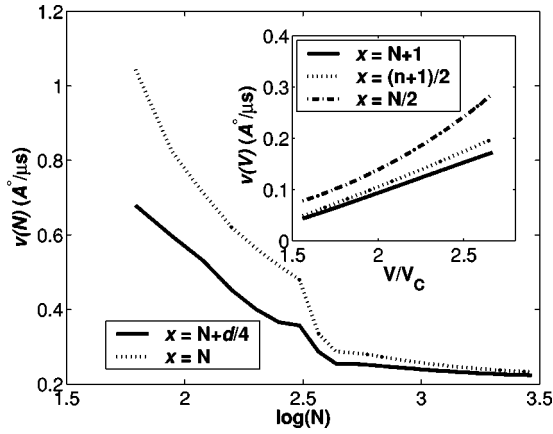


FIG. 3. The velocity as a function of the polymer length, for the same parameters as in Fig. 2, various initial conditions (linear-log scales), and  $V/V_C=2.6$ .  $v(N)$  tends towards a length independent behavior for large polymers, but displays a sharp decrease for short polymers. Note the step feature of  $v(N)$  when  $N$  becomes larger than the TPP length  $d$ . Inset:  $v(V)$ , for  $N=30$ , showing linear and quadratic scaling depending on the initial condition,  $x$ .

The velocity  $v(V)$  depends on  $x$ ,  $v(V)=v_x(V)$ , and changes from a linear to a quadratic function of the voltage when changing  $x$ , as shown in the inset of Fig. 3, for  $N=30$ .

Starting at  $x=N+1$ , a linear scaling is obtained:  $v_{N+1}(V)=b_1(V-b_2/b_1)$ . The coefficient  $b_2/b_1$  can be identified as an effective characteristic voltage:  $\bar{V}_C^{-1}\equiv(1+1/d)\beta\bar{z}|q|=b_1/b_2$ . From the last equality  $\bar{z}$  can be extracted.

Starting at  $x=N/2$ , i.e., when the initial state is close to the exit states, a square dependence is obtained:  $v_{N/2}(V)=c_1(V-c_2)^2+c_3$ , with  $c_1=o(10^{-5})$ ,  $c_2=40$  mV, and  $c_3=o(10^{-2})$ . These coefficients are similar to the measured values [6].

We note that both linear and square scaling behaviors have been observed experimentally [4,6]. A possible explanation for the different functional behavior of  $v(V)$  might originate from different data analysis that can be interpreted as having a different initial condition.

To get numerical values for  $\xi_p$  and  $\mu$ , we use the experimental data in Refs. [6,7], and obtain  $\mu(C)=1$ ,  $\mu(A)=1.14$ ,  $\mu(T_{nu})=1.28$ , and  $\xi_p(A)\approx 10^{-4}$  meV s/nm<sup>2</sup>,  $\xi_p(C)=\xi_p(T_{nu})=\xi_p(A)/3$ . From these values we find the limit in which the relaxation time of the polymer parts outside the TPP can be neglected. We estimate the maximal bulk number of monomers,  $N_{max}$ , for which the bulk relaxation time is much shorter (5%) than the TPP relaxation time. For a poly-*dA* bulk Zimm chain we get  $N_{max}\approx 271$ , by taking for the viscosity the value for water at 2 °C,  $\eta\approx 1.7\times 10^{-3}$  N s/m<sup>2</sup>. Using this value,  $\xi_b$  can be calculated from the Stokes relation to be  $\xi_b\approx 10^{-7}$  meV s/nm<sup>2</sup>, which is three orders of magnitude smaller than  $\xi_p$ .

### B. The MFPT

Additional information about the translocation can be obtained by computing the MFPT,  $\bar{\tau}$ . To compute an analytical

expression for  $\bar{\tau}$ , we consider a large polymer,  $N>d$ , and replace  $p_{j,j-1}$  and  $k_j$  by state independent terms  $p_+=[1+e^{(-V/V_C+1)}]^{-1}$ , valid for  $x\approx N$ , and  $k=1/(\beta\xi_p b^2 d^\mu)$ . This leads to  $a_+=p_+k$  and  $a_=(1-p_+)k$ , which define a one dimensional state invariant random walk. The MFPT is obtained by inverting  $\mathbf{A}$  [14]:  $\bar{\tau}=\int_0^\infty tF(t)dt=-\vec{U}\mathbf{A}^{-1}\vec{P}_0$ . The calculation of the elements of the state independent  $\mathbf{A}^{-1}$  yields (see Appendix C)

$$(-\mathbf{A}^{-1})_{s,x}=\frac{\Delta(p^s)\Delta(p^{n+1-x})}{\Delta(p)\Delta(p^{n+1})}\frac{p_+^{x-s}}{k}, \quad s<x, \quad (12)$$

where  $\Delta(p^m)=p_+^m-p_-^m$  and  $(-\mathbf{A}^{-1})_{s,x}$  for  $s\geq x$  is obtained when exchanging  $s$  with  $x$  and  $p_+$  with  $p_-$  in Eq. (12). Summing the  $x$  column elements of  $(-\mathbf{A}^{-1})$  we obtain  $\bar{\tau}$  (see Appendix C),

$$\bar{\tau}=\frac{\Delta(p^{n+1-x})p_+^{x-x}-\Delta(p^x)p_-^{n+1-x}(n+1-x)}{k\Delta(p)\Delta(p^{n+1})}, \quad (13)$$

which in the limit of a weak bias,  $V/V_C\geq 1$ , can be rewritten as (see Appendix C)

$$\bar{\tau}\approx\frac{2x\xi_p b^2 d^\mu}{z|q|(1+1/d)}\frac{1}{V-V_C}. \quad (14)$$

Although  $\bar{\tau}$  and  $t_m$  are different characteristics of  $F(t)$  and differ significantly when slow translocation events dominate, Eq. (14) captures the linear scaling with  $N$  and  $1/V$ . The quadratic scaling of  $t_m$  with  $1/V$  is obtained when using Eq. (9) rather than its state invariant version, for starting at, or near, an initial state for which  $\delta_{j=x}\leq 0$ .

### C. The sequence effect

Under the assumptions that are presented below, we now construct  $\xi_p$  and  $\mu$  for every ssDNA sequence and thus examine the sequence effect on  $t_m$ . For a given ssDNA sequence occupying the TPP in the  $j$  state, we write an expression for the average friction of that state,  $\xi_{p,j}$ , assuming additive contributions of the monomers inside the TPP:

$$\xi_{p,j}=(1/m_j)\sum_{s=1}^{m_j}\xi_p(nu_s). \quad (15)$$

Here  $nu_s$  stands for the nucleotide  $s$  occupying the TPP. To construct a compatible state dependent stiffness parameter,  $\mu_j$  we first argue that only nearest monomers can interact inside the TPP, e.g., base stacking [15] and hydrogen bonding, and thus contribute to the rigidity of the polymer, which in turn increases  $k_j$ . We then examine the chemical structure of the nucleotides and look for ‘‘hydrogen-like’’ bonds between adjacent bases. The term ‘‘hydrogenlike’’ bonds is used because the actual distance between the atoms that create the interaction may be larger than that of a typical hydrogen bond. The pairs *AA* and *CC* can interact but not the pairs *T<sub>nu</sub>T<sub>nu</sub>* and *CA*. For the pair *CT<sub>nu</sub>* the interaction is orientation dependent; namely, for the  $l$  pairs sequence, poly-

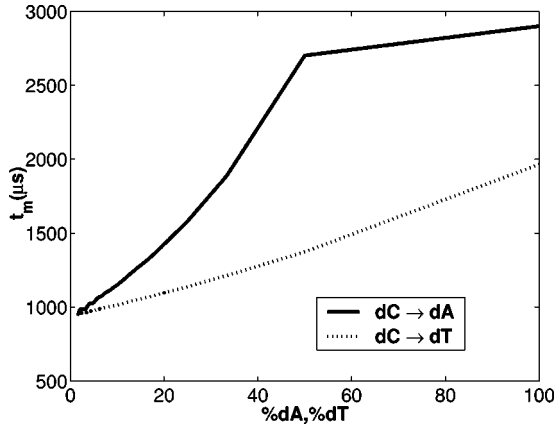


FIG. 4.  $t_m$  as a function of the percentage of equally spaced monomers substitutions  $C \rightarrow A$  and  $C \rightarrow T_{nu}$ , for  $N=60$ ,  $x=N$ ,  $z \approx 1/2$ ,  $V/V_C=1.63$ , and  $T=19^\circ\text{C}$ . The curves emphasize the effects of the rigidity and the friction on the translocation dynamics. See text for discussion.

$d(CT_{nu})_l$ , the interaction is within each of the pairs but not between the pairs. Accordingly we have  $\mu(nunu) = \mu(nu)$ ,  $\mu(CA) = \mu(AC) = \mu(T_{nu})$ ,  $\mu(CT_{nu}) = \mu(C)$ ,  $\mu(T_{nu}C) = \mu(T_{nu})$ , which allow the calculation of  $\mu_j$  following the definition

$$\mu_j = \frac{1}{m_j - 1} \sum_{s=1}^{m_j-1} \mu(nu_s nu_{s+1}) \quad (16)$$

with  $(\mu_j)_{m_j=1} = 0$ . Fig. 4 shows  $t_m$  as a function of equally spaced substitutions  $C \rightarrow T_{nu}$  and  $C \rightarrow A$ . The linear scaling of  $t_m(C \rightarrow T_{nu})$  is due to the linear scaling of  $\mu_j(C \rightarrow T_{nu})$ . The saturating behavior of  $t_m(C \rightarrow A)$  is a combination of two opposing factors: the linear scaling of  $\xi_{p,j}(C \rightarrow A)$  and the nonmonotonic behavior of  $\mu_j(C \rightarrow A)$ . Our model also predicts that for sufficiently large  $l$ ,

$$t_m[(CA)_l] > t_m(C_l A_l). \quad (17)$$

This feature is explained by noticing that  $2t_m[(CA)_l] > t_m(C_{2l}) + t_m(A_{2l})$ , see Fig. 4, which follows from the expression for  $\mu_j$ , Eq. (16), and then using  $2t_m(C_l A_l) \approx t_m(C_{2l}) + t_m(A_{2l})$ , which follows from the linear scaling of  $t_m$  with  $N$ , for  $N \geq d$  in addition to Eq. (15). The above findings regarding the behavior of  $t_m$  for hetro-ssDNA fit the experimental results [7].

#### IV. CONCLUSIONS

In the presented model, the translocation of ssDNA through  $\alpha$ -hemolysin channel is controlled, in addition to the voltage, by the interaction between the polymer and the pore ( $\Delta E_j^i$  and  $\xi_p$ ), and between nearest monomers inside the TPP ( $\mu$ ), as well as by entropic factors originating from polymer segments outside and within the TPP. Based on the model, we showed that  $F(t)$  can be mono peaked or double peaked depending on  $x$  and  $V/V_C$ . We calculated the MFPT to be  $\bar{\tau} \sim N/(V - V_C)$ , for  $N > d$  and  $V/V_C \geq 1$ , and  $t_m$

$\sim N/v_x(V)$  for  $N \geq d$ , where  $v_x(V)$  changes from a linear to a quadratic function of  $V$  with  $x$ . In addition, we estimated that  $\xi_p \approx 10^3 \xi_b$ , and by constructing  $\xi_p$  and  $\mu$  for hetro-ssDNA explained experimental results regarding the various behaviors of  $t_m$  for hetro-ssDNA.

An extended version of this model that describes translocation through a fluctuating channel structure can be used to describe unbiased translocation, which displays long escape times [16]. Translocation of other polymers through protein channels can be described using the same framework by changing  $\mu$ ,  $\xi_p$ , and  $\Delta E_j$ .

#### ACKNOWLEDGMENTS

We acknowledge fruitful discussions with Amit Meller and with Ralf Metzler. O.F. thanks Olga Dudko for a critical reading of the manuscript. This work was partially supported by the U.S.-Israel Binational Science Foundation and the Tel Aviv University Nanotechnology Center.

#### APPENDIX A:

We wish to calculate the electrostatic energy difference between states,  $\Delta E_j^p$ . There are three cases during translocation, which are described by Eqs. (1a)–(1c). For any polymer length, Eq. (1a)(exit states) describes a case for which  $N_{j,cis} = 0$  and Eq. (1c) (entrance states) describes a case for which  $N_{j,trans} = 0$ . For the case described by Eq. (1b) (intermediate states), there are monomers on both sides of the membrane for a large polymer, or no monomers on both sides of the membrane for a short polymer. Starting from Eq. (5) we have for the entrance states

$$\Delta E_j^p = \frac{zqV(m_j+1)}{d}. \quad (A1)$$

For the exit states  $\Delta E_j^p$  is composed of two contributions. One contribution stems from the passage of a monomer with an effective charge of  $zq$  through the potential  $V$

$$\Delta E_{j,1}^p = zqV. \quad (A2)$$

The second contribution calculated from Eq. (5) is

$$\Delta E_{j,2}^p = \frac{-i_j zqV}{d}. \quad (A3)$$

Combining the two contributions, we find

$$\Delta E_j^p = \frac{(d-i_j)zqV}{d} = \frac{(m_j-1)zqV}{d}, \quad (A4)$$

when using  $m_j = d + 1 - i_j$ .

For the intermediate states and a large polymer, we have only the contribution given by Eq. (A2) (the number of monomers within the TPP is constant), which can be written as

$$\Delta E_j^p = \frac{m_j zqV}{d}, \quad (A5)$$

when using  $m_j=d$  which holds for the intermediate states. For a short polymer, we have to consider only the contribution given by Eq. (5), which leads again to Eq. (A5). Equation (6) is obtained from adding the above contributions.

### APPENDIX B:

For calculating  $\Delta E_j^s$ , we start by writing an expression for the entropic energy that consists of two terms,

$$E_j^s = E_{j,1}^s + E_{j,2}^s. \quad (\text{B1})$$

$E_{j,1}^s$  represents the entropy cost of storing  $m_j$  monomers within the TPP and is a linear function of  $m_j$  [10].  $E_{j,2}^s$  originates from the reduced number of configurations of a Gaussian polymer near an impermeable wall, and can be approximated by [8]

$$E_{j,2}^s = \begin{cases} \frac{1}{2} k_B T \ln(N_{j,trans}), & j \leq d \\ \frac{1}{2} k_B T \ln(N_{j,trans} N_{j,cis}), & N > j > d \\ \frac{1}{2} k_B T \ln(N_{j,cis}), & j \geq N. \end{cases} \quad (\text{B2})$$

Separating the translocation into three regimes, described by Eqs. (1a)–(1c), we find that for the entrance states  $\Delta E_{j,1}^s$  is given by

$$\Delta E_{j,1}^s \propto k_B T, \quad (\text{B3})$$

while for the exit states

$$\Delta E_{j,1}^s \propto -k_B T, \quad (\text{B4})$$

with a proportional constant of  $o(1)$ .

For the intermediate states  $\Delta E_{j,1}^s = 0$  because the same number of monomers occupy the TPP between adjacent states.  $\Delta E_{j,1}^s$  for a short polymer has the same values as for a large polymer, when adjusting the conditions for the three cases [exchanging  $N$  and  $d$  in Eqs. (1)].

Computing  $\Delta E_{j,2}^s$  from Eq. (B2) results in  $k_B T g_j$ , where

$$2g_j = \begin{cases} \ln[1 + 1/(N-j)], & j \leq d \\ \ln[1 + 1/(N-j)][1 - 1/(j-d)], & N > j > d \\ \ln[1 - 1/(j-d)], & j \geq N. \end{cases} \quad (\text{B5})$$

For a short polymer,  $g_j$  is similar to Eq. (B5) for the entrance and exit states, but  $g_j = 0$  for the intermediate states because  $N_{j,cis} = N_{j,trans} = 0$  for these states. Note that  $|g_j| < 1$  for all  $j$ . Special care is needed when computing  $g_j$  for states that belong to the crossover between the three situations. For these states a combination of Eqs. (B2) was used. From the above contributions we obtain Eq. (7).

### APPENDIX C:

To compute  $\bar{\tau}$  which is given by

$$\bar{\tau} = \sum_{s=1}^{x-1} (-\mathbf{A}^{-1})_{s,x} + \sum_{s=x}^n (-\mathbf{A}^{-1})_{s,x}, \quad (\text{C1})$$

we have to calculate the elements of the general inverse Toeplitz matrix  $(-\mathbf{A}^{-1})_{s,x}$  [17]

$$(-\mathbf{A}^{-1})_{s,x} = \frac{\Delta(\lambda^s) \Delta(\lambda^{n+1-x}) p_+^{x-s}}{\Delta(\lambda) \Delta(\lambda^{n+1})} \frac{p_+^{x-s}}{k}, \quad s < x, \quad (\text{C2})$$

where  $\lambda_{+/-} = [1 + / - \sqrt{(1-4p_+p_-)}]/2$ . Substituting the expression for  $p_+$  and  $p_-$  into the expressions for  $\lambda_{+/-}$ , we obtain  $\lambda_{+/-} = p_{+/-}$ , which when used in Eq. (C2) results in Eq. (12). The summation of each of the terms in Eq. (C1) is straightforward. The first term yields

$$\sum_{s=1}^{x-1} (-\mathbf{A}^{-1})_{s,x} = \alpha \sum_{s=1}^{x-1} (1-y^s) = \alpha \left( x - \frac{1-y^x}{1-y} \right), \quad (\text{C3})$$

where  $y = p_-/p_+$  and

$$\alpha = \frac{p_+^x \Delta(p^{n+1-x})}{\Delta(p) \Delta(p^{n+1}) k}. \quad (\text{C4})$$

The second term in Eq. (C1) is

$$\begin{aligned} \sum_{s=x}^n (-\mathbf{A}^{-1})_{s,x} &= \tilde{\alpha} \sum_{s=x}^n \Delta(p^{n+1-s}) p_-^{s-x} \\ &= \tilde{\alpha} p_-^{n+1-x} \left[ y^{x-n-1} \frac{1-y^{n+1-x}}{1-y} \right. \\ &\quad \left. - (n+1-x) \right], \end{aligned} \quad (\text{C5})$$

where

$$\tilde{\alpha} = \frac{\Delta(p^x)}{\Delta(p) \Delta(p^{n+1}) k}. \quad (\text{C6})$$

Combining the right-hand sides of Eqs. (C3) and (C5) and rearranging terms results in Eq. (13).

Rewriting Eq. (13) as

$$\bar{\tau} = \frac{x}{k \Delta(p)} - \frac{(n+1)(1-y^{-x})}{k \Delta(p)(1-y^{-n})}, \quad (\text{C7})$$

we find that for  $V/V_C \geq 1$ , the second term in Eq. (C7) vanishes as  $y^{n-x}$ . Keeping the first term in the expression for  $\bar{\tau}$ , Eq. (C7), and expanding to first order in  $V/V_C$  the explicit form of  $\Delta(p)$ ,

$$\frac{1}{\Delta(p)} = \frac{1 + e^{-V/V_C + 1}}{1 - e^{-V/V_C + 1}} \approx \frac{2}{V/V_C - 1}, \quad (\text{C8})$$

Eq. (14) is obtained.

- [1] B. Alberts *et al.*, *Molecular Biology of The Cell* (Garland, New York, 1994).
- [2] M. T. Madigan, J. M. Matinko, and J. Parker, *Biology of Microorganisms* (Prentice-Hall, Englewood Cliffs, NJ, 1997).
- [3] L. Song *et al.*, *Science* **274**, 1859 (1996).
- [4] J. Kasianowicz, E. Brandin, D. Branton, and D.W. Deamer, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 13770 (1996).
- [5] S.E. Henrickson, M. Misakian, B. Robertson, and J.J. Kasianowicz, *Phys. Rev. Lett.* **85**, 3057 (2000).
- [6] A. Meller, L. Nivon, and D. Branton, *Phys. Rev. Lett.* **86**, 3435 (2001).
- [7] A. Meller, and D. Branton, *Electrophoresis* **23**, 2583 (2002).
- [8] W. Sung and P.J. Park, *Phys. Rev. Lett.* **77**, 783 (1996).
- [9] M. Muthukumar, *J. Chem. Phys.* **111**, 10371 (1999).
- [10] T. Ambjornsson, S.P. Apell, Z. Konkoli, E.A. Di Marzio, and J.J. Kasianowicz, *J. Chem. Phys.* **117**, 4063 (2002).
- [11] D.K. Lubensky and D.R. Nelson, *Biophys. J.* **77**, 1824 (2001).
- [12] A.M. Berezhkovskii and I.V. Gopich, *Biophys. J.* **84**, 787 (2003).
- [13] M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics* (Clarendon Press, Oxford, 1986).
- [14] A. Bar-Haim and J. Klafter, *J. Chem. Phys.* **109**, 5187 (1998).
- [15] N.L. Goddard, G. Bonnet, O. Krichevsky, and A. Libchaber, *Phys. Rev. Lett.* **85**, 2400 (2000).
- [16] M. Bates, M. Burns, and A. Meller, *Biophys. J.* **84**, 2366 (2003).
- [17] Y. Huang and W.F. McColl, *J. Phys. A* **30**, 7919 (1997).