

Polymer Translocation Through a Nanopore: A Geometry Dependence Study

James O’Keeffe, Ioana Cozmuta and Viktor Stole
NASA Ames Research Center,
Moffet Field, CA

jtok@nas.nasa.gov

James O’Keeffe,
Dept. of Electrical Engineering,
Stanford University,
Stanford, CA

Abstract—The translocation of a single stranded nucleic acid polymer through a nanopore, by an external electric field applied across the pore, may be well described by a 1-D drift-diffusion model. Translocation times and velocities are calculated for a homopolymer driven through a nanopore, where the polymer-pore interaction dominates the polymer dynamics. In this model a purely electrostatic polymer-pore interaction is introduced, based on atomic charges on the polymer and pore. Simulation results show that the peak repulsion force occurs on the polymer during entry into the pore. In addition, the peak polymer-pore interaction is shown to decrease with polymer length for strands less than 20 nucleotides in length. The modeling results offers an explanation for the enhanced drift velocities experimentally observed for such short polymers. The dependence of the polymer translocation time on the pore geometry is investigated. For increasing pore radius the translocation velocity approaches the free space drift velocity for the surrounding ionic solution.

I. INTRODUCTION

In recent years experiments have shown that single stranded RNA and DNA can be driven by an external electric field through organic nanopores with a minimum internal diameter is 1.5nm [1]. Furthermore, the current reduction and blockade duration associated with translocation have been used to distinguish between different single homopolymer strands [2]. Such experiments offer the tantalizing prospect of using biological membranes and pores for rapid DNA sequencing or filtering. Two problems in achieving this goal are ion current resolution and the complex nature of the polymer-pore interaction, when multiple different bases occupy the pore. To date ion current resolution and sampling rates make single nucleotide resolution difficult. Increasing the DNA translocation time offers one possible solution to this problem. The complex nature of the polymer-pore interaction makes real-time identification of nucleotides, based on blockade duration very challenging. In the case of DNA we must consider interference between adjacent bases as several bases interact with the pore concurrently. Any solution to this problem would involve a detailed physico-chemical understanding of how the polymer velocity is influenced by interaction with the pore.

An ideal model for polymer translocation would involve atomic-scale simulation of polymer, pore and ion dynamics in the presence of an applied electric field. While attractive from an accuracy standpoint, such a full MD approach is computationally very expensive, particularly when one considers that such a simulation must be conducted over microsecond timescales to capture blockade current events. Van Der Straaten [3] employed a hybrid modelling approach to determine potassium-chloride (KCl) dynamics in a trimeric porin channel. Ionization states and ion diffusion coefficients were calculated using molecular dynamics simulations. A coarse-grain drift-diffusion model was then used to calculate current-voltage relations for the ionic solution. Muthukumar considered voltage driven Gaussian chain motion through a nanopore with a length of M Kuhn steps, where the polymer length N was always greater than M [4]. The transport was dominated by the entropy barrier posed by the pore up to a threshold pore length M_c . Beyond M_c the polymer-pore interaction determined the translocation time. Lubensky and Nelson [5] simulated 1-D voltage driven polymer translocation through a pore, and assumed strong interaction with the pore walls, such that the dynamics of the polymer outside the pore were much faster when compared with dynamics inside the pore and were therefore neglected. The distribution of passage-times for uniform length poly[U] strands was simulated and found to be more narrow than the experimental values of KBBB [1]. It was concluded that the driving force was overestimated, based on unscreened electrostatic interaction of the polymer and the pore. The pore was represented as a single interaction site with the polymer, giving an effective pore thickness $d=0$. In reality nanopores have a well defined length and in particular α -hemolysin has a length approximately 11nm. In order to model experimentally observed enhanced translocation velocities [6] for polymer lengths on the order of the pore length it is necessary to account for multiple interactions along the finite pore length.

To date, DNA transport simulations have not included a detailed model of the physico-chemical interaction of the polymer with pore walls. A more detailed description of the atomic scale polymer-pore interaction potential would allow

for the tailoring of inorganic pores and enable better differentiation between individual subunits. In this paper, a hybrid modeling approach is used to calculate voltage-driven translocation velocities in the presence of strong interactions with the pore walls. The existing formalism of Lubensky and Nelson is extended to include multiple interaction sites within the pore. The interaction potential acts as an entropy barrier by reducing the degrees of freedom for the polymer and thus slows the diffusion process across the pore. An atomistic model of the polymer-pore potential is developed, based on the electrostatic interaction of charges on both the polymer and nanopore. The interaction potential is used in a coarse-grain drift-diffusion model [7] to calculate translocation times and velocities for single stranded DNA translocation through an α -hemolysin nanopore. In experiments, an external voltage is typically applied across the nanopore to introduce a significant drift component into the polymer dynamics. Because a 1-D drift-diffusion model neglects any motion perpendicular to the pore axis it is generally only accurate in cases where the external voltage causes the drift velocity to dominate the polymer dynamics. This results when the translocation length L_t is much larger than the characteristic diffusion length $l_d = D_0/v_0$, where D_0 is the free space diffusion coefficient and v_0 is the drift velocity.

II. METHODS

Assume a 1-D diffusion model for the polymer translocation through a nanopore, governed by a Smoluchowski equation,

$$\frac{\partial P}{\partial t} = D_0 \frac{\partial}{\partial z} \left[\frac{\partial P}{\partial z} + \frac{U'(z) - F}{k_B T} P \right], \quad (1)$$

where $P(z,t)$ is a measure of the probability that a length z of the polymer backbone has passed the midpoint of the pore at a time t . The separation between the polymer center and the pore center is denoted by the variable z , where the origin of the z axis is at the center of the pore. Alternatively $P(z,t)$ can be thought of as the normalized probability density of finding the first monomer of a polymer along the z axis at time t . $D_0 = 10^{-12} \text{m}^2/\text{s}$ is the bare diffusion coefficient [8]. In experiments a driving voltage $V \approx 120 \text{mV}$ is applied to overcome the entropy barrier created by the membrane and pore. The driving force is approximated as $F \approx eV/a$, where $a = 8 \text{\AA}$ is the nucleotide spacing, measured between adjacent phosphates. $U(z)$ is the total interaction energy resulting from polymer interaction with the pore and counterions. Ideally, $U(z)$ includes components from Van Der Waals interactions with atoms in the pore as well as coulombic interaction with ions and the pore. Here the analysis is limited to the coulombic interaction between the polymer and pore atoms.

U combines potential energy contributions from several nucleotides inside the pore as well as the finite polymer lengths outside the pore. Here we consider the scenario for

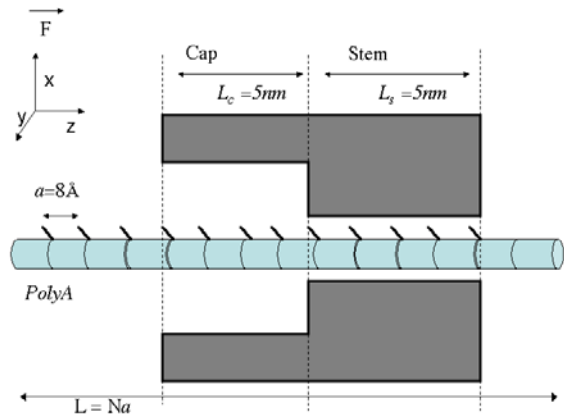


Figure 1: Schematic diagram of single stranded DNA transport through an α -hemolysin nanopore. Each monomer of the uncoiled polymer has a length $a = 1 \text{nm}$. The wide cap section and narrow stem section of the pore are both approximately $5a$ in length. The polymer has a total length $L = Na$.

short homopolymer strands < 100 nucleotides, where the interaction potential does not have translational invariance with the periodicity of the nucleotides. For a polymer chain with n atoms the interaction energy has $(n+M)^2/2$ contributions and is given by,

$$U_{(z)} = \sum_i^{n+M} \sum_j^{n+M} \frac{q_i q_j}{4\pi\epsilon(R_{ij})^2}, \quad (2)$$

where q_i and q_j are charges on the i th and j th atoms. $R(i,j)$ is the distance between atoms i and j when the center of the polymer is located at z . The dielectric constant is $\epsilon = 80$, corresponding to the solvated environment. For the polymer dynamics described by (1) we are primarily interested in the friction force $U'(z)$ resulting from the interaction energy. The friction force is given by $U'(z) = \delta U / \delta z$. Only those atoms that change their relative separation as the polymer moves contribute to $U'(z)$, making this a much less computationally expensive ($n \times M$) calculation.

$$U'_{(z)} = \sum_i^n \sum_j^M \frac{q_i q_j}{4\pi\epsilon(R_{ij})^2} \cdot \frac{(z_i - z_j)}{|R_{ij}|}. \quad (3)$$

The translocation time is measured from the time that the first nucleotide enters the pore until the last nucleotide exits the pore. We consider that for translocation to occur, the first nucleotide in the polymer must move a total contour length $L_t = L + L_p/2$, relative to the pore center, where L is the polymer length and L_p is the pore length. The translocation time t' and velocity v are calculated according to:

$$\int_{L_t}^{\infty} P(z, t') dz = 0.5 \quad (4)$$

and

$$v = (L + L_p) / t'. \quad (5)$$

III. RESULTS AND DISCUSSION

In this section we use equations (3), (4) and (5) to calculate:

- Translocation velocity as a function polymer length for different driving forces, both greater and less than the peak repulsion force.
- Velocity versus pore radius, where the minimum internal pore radius is increased.
- Translocation times versus pore length where the pore length is increased by multiplying the pore along the axial direction

The first step in each case is to determine the polymer-pore interaction based on (3). Fig.2a. illustrates that the maximum of $U'(z)$ occurs as the first nucleotide is about to enter the pore. At this location the pore repels the polymer most strongly. Fig.2a. also illustrates that once the polymer moves into the pore, the interaction force decreases, thereby repelling the polymer less strongly. For the short $N=6$ polymer the peak repulsion is significantly lower than in the case of the $N=32$ strand. Fig2b. shows how the peak repulsion increases with polymer length. One obvious reason for this behavior is that the effect of the hydrogen terminated ends is more important for short

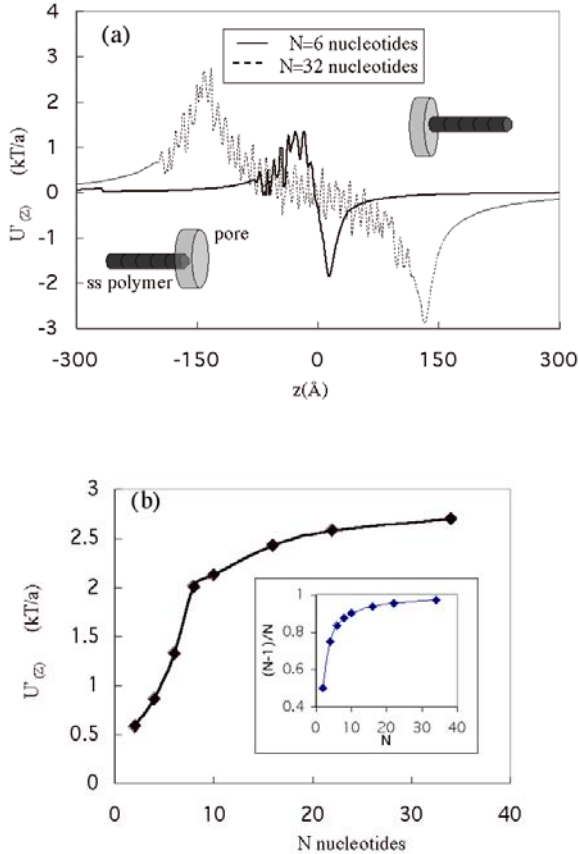


Figure 2: (a) Plot of the interaction force U' for $N=6$ bases solid line and $N=32$ dashed line. The maximum of each curve represents the peak repulsion between the negatively charged polymer and pore. (b) Plot of peak repulsion as a function of polymer length. The peak height is significantly reduced for $N<10$ bases. The insert shows how the average charge per nucleotide $(N-1)/N$ is significantly reduced for short polymers ($N<10$) as a result of the hydrogen terminations.

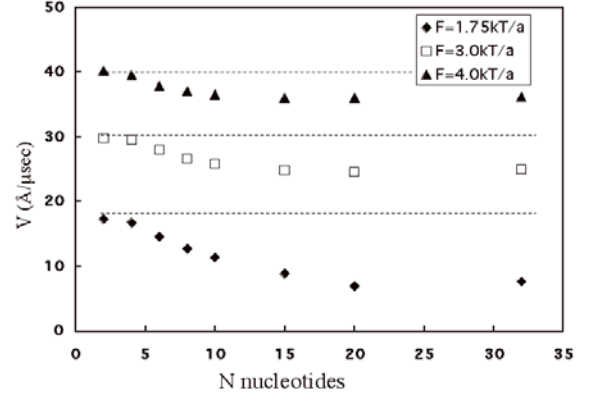


Figure 3: Translocation velocity v as a function of polymer size N for different driving forces F . The dashed lines represent the free space drift velocity $v_0 = D_0 F / k_B T$, where D_0 is the bare diffusion coefficient for the polymer in water

polymers ($N<10$). The total charge averaged over all nucleotides is $N-1/N$ electrons. The insert in fig.2b. illustrates how this average charge increases with polymer length. For $N<10$ the average charge per nucleotide is significantly lower than 1 electron. This offers a possible explanation for the sharp roll-off in peak repulsion observed for such short polymers. In contrast, the average charge per nucleotide approaches 1 electron for long polymers. Beyond $N=40$ nucleotides the peak repulsion appears to saturate. In this regime the contribution to $U'(z)$ from nucleotides far from the pore entrance approaches zero as the polymer length tend to infinity.

The translocation velocity corresponding to three different driving forces are shown in Fig.3. For comparison the free space drift velocity v_0 given by,

$$v_0 = D_0 F / k_B T \quad (6)$$

corresponding to each F is also shown. In each case short polymers exhibit an enhanced translocation velocity that approach v_0 . The maximum translocation velocity for short polymers increases linearly with F . For $N>20$ the velocity reaches a limiting value v_{sat} . The non-linear relation between the F and v_{sat} is particularly interesting. One possible explanation for the smaller values of v_{sat}/v_0 obtained for lower F is the increased importance of the peak repulsion as the polymer enters the pore. For $F=1.75kT/a$ the peak repulsion is larger than the driving voltage, resulting in negative instantaneous drift velocity at the pore entrance. In such cases where the repulsion exceeds the driving force, the polymer diffuses across the entropy barrier at the pore entrance, before experiencing voltage driven translocation within the pore.

For all values of driving force F used in this analysis the simulated translocated velocities are approximately 2 orders of magnitude greater than experimental results [6]. This is similar to results of [3]. One possible reason is that the driving force F on the polymer is given by,

$$F = e(V/d)I; \quad I = \int_{-d/2}^{d/2} q(z) dz, \quad (7)$$

where I is the total net charge on the section of the polymer that occupy the pore. In this work, each nucleotide inside the pore contributes 1 electron to I . When the pore is completely filled with m nucleotides $I = m$ electrons. However charges on both the polymer and pore are screened by the surrounding water and counterions. In reality therefore the net charge for a nucleotide inside the pore is significantly less than 1 electron. Another explanation for lower experimental translocation velocities is that the peak repulsion occurs when the pore is empty and I approaches zero.

Artificial nanopores are not limited by the same shape constraints as biological pores. In particular both the pore length and radius can be varied. In order to gain an understanding of how the pore radius affects the translocation velocity we simulated the effect of uniformly expanded the pore in the (x,y) plane. Fig.4a illustrates the increase in translocation velocity as the pore radius is increased. As expected intuitively, the translocation velocity increases with pore radius. For $R/R_0 > 4$ ($R_0 = 7\text{\AA}$) the translocation velocity approaches the free space drift velocity v_0 . This suggests that a small radius pore would be better able to differentiate between nucleotides based on blockade duration. Fig.4b illustrates that the translocation time increases monotonically with the pore length. This shows that the polymer motion is dominated by the polymer-pore interaction over the entire length of the pore

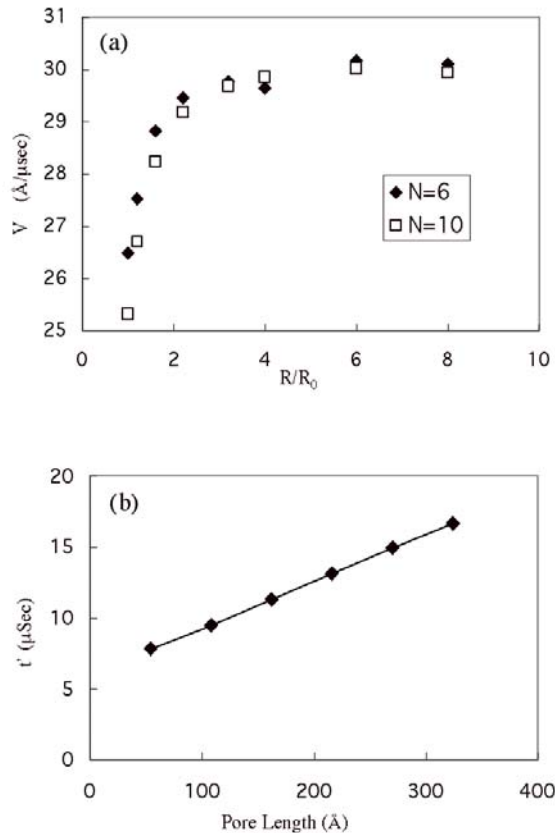


Figure 4: (a) Plot of translocation time t' as a function of increasing pore radius R/R_0 where R_0 is the equilibrium α -hemolysin pore radius.(b) The translocation time t' increases monotonically with the pore length where $N=10$ bases and $F=3kT/a$

and not the entropy barrier at the entrance, a point also noted by [4]. In summary, the dynamics of short homopolymers were investigated, using a 1-D Nerst-Plank model. The enhanced drift velocity, experimentally observed for short polymers, was successfully accounted for using a using an atomic scale description for coulombic polymer-pore interaction. Future work will involve extending the polymer-pore interaction potential to include the effect of charge screening in the surrounding ionic solution.

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