Polymer translocation in solid-state nanopores: Dependence of scaling behavior on pore dimensions and applied voltage

Christopher M. Edmonds,1 Yeny C. Hudiono,2 Amir G. Ahmadi,2 Peter J. Hesketh,3 and Sankar Nair2, a)
1Interdisciplinary Bioengineering Graduate Program, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
2School of Chemical & Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
3Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA

(Received 14 November 2011; accepted 17 January 2012; published online 14 February 2012)

We investigate unforced and forced translocation of a Rouse polymer (in the absence of hydrodynamic interactions) through a silicon nitride nanopore by three-dimensional Langevin dynamics simulations, as a function of pore dimensions and applied voltage. Our nanopore model consists of an atomistically detailed nanopore constructed using the crystal structure of β-Si3N4. We also use realistic parameters in our simulation models rather than traditional dimensionless quantities. When the polymer length is much larger than the pore length, we find the translocation time versus chain length scales as $\tau \sim N^{2+\nu}$ for the unforced case and as $\tau \sim N^{(1+2\nu)(1+\nu)}$ for the forced case. Our results agree with theoretical predictions which indicate that memory effects and tension on the polymer chain play an important role during the translocation process. We also find that the scaling exponents are highly dependent on the applied voltage (force). When the length of the polymer is on the order of the length of the pore, we do not find a continuous scaling law, but rather scaling exponents that increase as the length of the polymer increases. Finally, we investigate the scaling behavior of translocation time versus applied voltage for different polymer and pore lengths. For long pores, we obtain the theoretical scaling law of $\tau \sim 1/V^\alpha$, where $\alpha \equiv 1$ for all voltages and polymer lengths. For short pores, we find that $\alpha$ decreases for very large voltages and/or small polymer lengths, indicating that the value of $\alpha = 1$ is not universal. The results of our simulations are discussed in the context of experimental measurements made under different conditions and with differing pore geometries. © 2012 American Institute of Physics. [http://dx.doi.org/10.1063/1.3682777]

INTRODUCTION

Nanopores of diameter 1–10 nm constructed in thin solid-state (e.g., silicon dioxide1 or silicon nitride2–8) or biological9–11 (e.g., protein) membranes are of significant current interest as single-molecule analysis devices possessing very high sensitivity, speed, and reversibility.9 One of the most-studied applications of nanopore devices is in the analysis of nucleic acids and other biopolymers. In addition to the technologically attractive possibility of eventually reading the sequence of nucleic acids with a single-molecule nanopore device, DNA (both double-stranded and single-stranded) is a well-characterized model biopolymer for understanding the mechanisms of molecular transport through nanopore devices. An example application with the aid of nanopore devices is the determination of DNA chain lengths by translocation time measurements.9,11,12 This is accomplished by driving negatively charged DNA molecules, dissolved in an aqueous salt solution, through the nanopore device with an applied voltage. Due to the ions in the salt solution, a current also flows through the nanopore device. When the DNA is outside of the pore, the ionic current is at a maximum, whereas when the DNA is inside the pore, the current is modulated at a minimum. Hence, one can determine the length of the DNA chain simply by measuring the time the current is at its minimum value. This technique of metering DNA length is orders of magnitude faster than traditional gel electrophoresis.9,13 Solid-state nanopores have many advantages over their biologically-derived counterparts, such as longer durability, wider range of operation, and controllable size.9,14 A number of experimental studies have reported the fabrication and operation of solid-state nanopore devices produced by a variety of techniques such as milling or ablation of solid-state membranes by focused ion beams and electron beams generated by transmission electron microscopes.15–19 Recent work has also addressed the development of wafer-scale processes for producing arrays of nanopores by combining electron-beam lithography and atomic layer deposition techniques.8 Furthermore, the incorporation of electronic measurement devices (such as tunneling detectors) within solid state nanopores has also been recently reported.20 Such a development may allow the direct reading of biopolymer sequence information during translocation.

In order to realize the technological potential of nanopore devices, a detailed theoretical and experimental
translocation through a nanopore is necessary. Computational studies of polymer translocation though nanopore devices are expected to provide valuable insight regarding the physics of translocation, as well as guidelines for better nanopore device design and operation. Previous studies have reported molecular dynamics (MD) simulations of events occurring during translocation of DNA through a solid-state nanopore. Although MD simulations provide atomistically detailed information, they typically describe phenomena occurring on time scales shorter than ~100 ns. To obtain physical insight into full translocation processes occurring on much longer time scales, “coarse-grained” simulation techniques are necessary. Such approaches, based upon Brownian or Langevin dynamics simulations, can address a number of important questions relating to the translocation process. In particular, this paper is targeted at understanding the dependence of polymer translocation mechanisms on the chain length, pore geometry (diameter and length), as well as the driving voltage. This is accomplished by means of Langevin dynamics calculations on polymer chains (up to 200–400 monomers in length) using a broad range of applied voltages (60–750 mV DC).

One of the most highly debated topics in polymer translocation through a nanopore is the scaling law behavior for translocation time versus chain length. Sung and Muthukumar found that the translocation time scaled as \( \tau \sim N^2 \) for the case of a small chemical potential difference \( \Delta \mu \) across a pore (in other words, unforced translocation), and as \( \tau \sim N/\Delta \mu \) for a large chemical potential difference (forced translocation), where \( N \) is the number of monomers in the polymer. Chuang et al. obtained a different lower bound on the scaling law behavior for a self-avoiding polymer obeying Rouse dynamics (the absence of hydrodynamic interactions) and diffusing through a nanopore without a driving electric field. If the distance traveled is approximated by the polymer’s radius of gyration, \( R_g \sim N^\nu \), the translocation time scales as \( \tau \sim N^{1+\nu} \), where \( \nu \) is the Flory exponent (\( \nu = 0.588 \) for a self-avoiding walk polymer in three dimensions). This expression was later modified by Panja et al. to \( \tau \sim N^{2+\nu} \) due to memory effects caused by tension in the polymer chain during the translocation process. Kantor studied and derived a scaling law for long polymer translocation through a short nanopore with the aid of a force, \( F \), acting only on one monomer in the chain at a time. By assuming the velocity scales as \( u \sim F/N \) and the distance the polymer travels is again approximated by the polymer’s radius of gyration, it was determined the translocation time will scale as \( \tau \sim N^{1+\nu}/F \). However, their theory assumes that the polymer on both the cis and trans side of the nanopore (Figure 1) are in equilibrium throughout the translocation process, which is not always a valid assumption especially when the applied force becomes large. Vocks et al. derived another expression, \( \tau \sim N^{1+2\nu}/(1+\nu)/F \), also based on memory effects due to the tension in the polymer that causes its velocity to vary during the translocation process. In addition, they derived a possible lower bound on the scaling law \( (\tau \sim \eta N^{2+\nu}/F \), where \( \eta \) is the viscosity of the solvent) based on the principle that the energy dissipated from the polymer into the solvent will be equal to the total energy provided by the applied force. When the length of the polymer is on the order of the length of the pore, the scaling laws mentioned above are no longer obeyed, often displaying exponents smaller than 1 and crossover behavior (curves with two different slopes). In order to gain a better understanding of the scaling law behavior, we report here a detailed Brownian dynamics simulation study, using nanopores of varying length and diameter, and Rouse polymer chain lengths in the range of \( N = 10–200 \) for short pore lengths and \( N = 1–400 \) for large pore lengths.

Scaling laws for translocation time versus voltage have also been investigated in previous work. As mentioned earlier, Sung and Muthukumar found that the translocation time scales as the inverse of an applied chemical potential difference \( \tau \sim 1/\Delta \mu \). Kantor also derived an expression for the translocation time, \( \tau \), through a nanopore with the aid of a pore force, \( F \), as \( \tau \sim N^{1+\nu}/F \), thereby indicating an inverse relationship between the driving voltage and the translocation time. This inverse relationship has been observed in many previous simulations as well as measurements using very long strands of dsDNA through a very wide (30 nm) silicon nitride nanopore. However, it has been observed in other simulation work that this scaling law breaks down when the applied force becomes large. In this report, we also investigate the effects of the applied force on the translocation for the important cases when the polymer length is much longer than the length of the pore length,
and when the polymer length is on the same order as the pore length.

SIMULATION METHODOLOGY AND MODELS

Nanopore model

Unlike many previous coarse-graining simulation studies that assume the nanopore is either a hole in a continuous solid or in a simple homogeneous lattice of atoms, we employ atomistically detailed nanopore models. The crystal structure of β-Si3N4 is used to construct membranes of different thicknesses, and approximately circular pores of different diameters are constructed by removing atoms from the membrane. An example of a nanopore with a diameter of 1.5 nm is shown in Figure 1. The simulation box size is 60 nm in the z direction, including reservoirs of water both above and below the nanopore.

Simulation methods

The dynamical simulation methodology integrates the Langevin equation of motion (1) in three dimensions.

$$m \frac{d^2 \vec{r}}{dt^2} = -\zeta \frac{d\vec{r}}{dt} + \vec{F} + \vec{R}. \quad (1)$$

Unlike MD simulations, which directly solve Newton’s equations of motion by explicitly modeling the interactions between monomers and solvent molecules, the stochastic Langevin equation of motion models the solute-solvent interactions by a random thermal force, which is defined by a Gaussian distribution, $\vec{R}$, and viscous drag force ($-\zeta d\vec{r}/dt$). At the beginning of the simulation, a polymer chain is positioned at random coordinates in the simulation volume with the distance between adjacent monomers resulting in a minimum potential energy value. To equilibrate the initial polymer conformation, a Metropolis Monte Carlo (MMC) simulation is carried out with 50,000 trials. The first monomer in the chain is then placed inside the nanopore, with the remaining chain outside the pore on the cis side of the water reservoir (see Figure 1). Each monomer is then assigned a random velocity from the same Gaussian distribution that defines the random thermal force, and the translocation time clock begins. A successful translocation occurs when the entire polymer chain moves from the cis side to the trans side through the nanopore under the applied electric field. The translocation time is defined as the time required for the entire polymer chain to move through the nanopore and exit at the trans side. Each simulation consists of 1000 trials and is performed at 298 K.

Calculation of forces

To solve Eq. (1), we compute the total force $\vec{F}$ acting on the polymer, including the electric force due to the applied voltage, the forces between the monomers, and the interactions of the polymer with the nanopore surfaces. The electric field due to the applied voltage is assumed to be zero outside the pore and constant inside the pore.29,35,36,39,40,56–59

The value of this force is computed using the relationship $F = qV/d$, where $q$ is the charge on each DNA monomer, $V$ is the voltage drop across the nanopore, and $d$ is the diameter of each monomer. Although the force due to the applied voltage varies as a function of ionic concentration, the force has been measured in previous experiments to be in the 10–30 pN range for voltages between 50 and 150 mV. Hence, in this paper, we varied the applied force from ~22 pN to 279 pN, which corresponds to a voltage range of 60–750 mV.

We model our polymer as a freely jointed chain Rouse polymer (no hydrodynamic interactions) with each monomer represented by a single bead. Each bead has a mass of 312 atomic mass units (amu)58 and a diameter of 4.3 Å,62 which are the corresponding values for single-stranded DNA. Adjacent beads are connected by spring models using a combination of two potential energy functions: (2) the Warner model (often referred to as the “finitely extendable nonlinear elastic” or FENE model)63 and the (3) Weeks-Chandler-Andersen potential,64 which prevents the beads from overlapping.

$$U_{\text{FENE}}(r) = \frac{1}{2}k_B R_0^2 \ln \left(1 - \left(\frac{r}{R_0}\right)^2\right), \quad r < R_0, \quad (2)$$

$$U_{\text{WCA}}(r) = \begin{cases} 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] + \varepsilon, & r \leq 2^{1/6} \sigma \\ 0, & r > 2^{1/6} \sigma \end{cases}. \quad (3)$$

In the above equations, we assign the values for the spring constant $k = 7.5 \varepsilon_{\text{poly}}/\sigma_{\text{poly}}^2$, the maximum allowed distance between beads $R_0 = 8.6$ Å, the Lennard-Jones energy well-depth $\varepsilon = \varepsilon_{\text{poly}} = k_BT$ (where $k_B$ is Boltzmann’s constant), and $\sigma = \sigma_{\text{poly}} = 4.3$ Å (where $\sigma_{\text{poly}}$ is the distance of the energy well depth). Using these values, the potential energy function is a minimum when the distance between beads is ~ 4.48 Å. The bead-to-bead energy for non-adjacent beads (excluded volume effect) is computed using the same Weeks-Chandler-Andersen potential in Eq. (3) with $\varepsilon = \varepsilon_{\text{poly}}$ and $\sigma = \sigma_{\text{poly}}$. Using these values for our polymer model permitted us to use a time step of 0.1 ps in our simulations.

The interaction between the polymer and the solvent, or the drag force, is determined by the friction coefficient $\zeta$ in Eq. (1). The friction coefficient is computed to be $\zeta = 40/(m\ell_{\text{LJ}})$, where $m$ is the mass of each monomer and $\ell_{\text{LJ}} = (m \sigma^2 \varepsilon)^{1/2}$ is the Lennard-Jones time step. Setting $\varepsilon = k_BT$ and $\sigma = 4.3$ Å, we obtain $\zeta = 4.2 \times 10^{-12}$ kg/s, which is approximately the same value found from Stokes’ law using a sphere with hydrodynamic radius of 2.15 Å.62 The energies and forces due to the interactions between the atoms in the nanopore and the monomers are computed using the same Weeks-Chandler-Andersen potential energy function given in Eq. (3), with the exception of different parameters $\sigma$ and $\varepsilon$, thus creating a very repulsive interaction between the polymer and the pore. The energy well depth for the interaction between a monomer and a nitrogen atom, $\varepsilon_{\text{poly-N}}$, is assigned a value of 0.1$k_BT$. This value was determined empirically through extensive trial simulations. From previous measurements using silicon nitride a ~63% increase was found between the van der Waals energy well depth parameter, $\varepsilon$, of silicon and nitrogen. Hence, in all of our simulations, we...
increase $\varepsilon_{\text{poly-N}}$ by 63% to determine the energy well depth for the interaction between a monomer and a silicon atom $\varepsilon_{\text{poly-Si}}$. To compute $\sigma_{\text{poly-N}}$ and $\sigma_{\text{poly-Si}}$, we use the measured values of $\sigma$ for silicon and nitrogen, $\sigma_{\text{Si}} = 4.3$ Å, and the Lorentz-Berthelot mixing rules. We employ a cutoff radius ($r_c$) of 9 Å in our simulations because the potential energy is very small beyond this distance and it also allows a significant decrease in the simulation time.

RESULTS AND DISCUSSION

Polymer model: Single-stranded DNA (ssDNA) or double-stranded DNA (dsDNA)?

The non-adjacent monomer model described in Eq. (3) has been used in many previous simulation methodologies to mimic a polymer with high excluded volume interactions which cause the polymer to swell. However, the question remains: does the polymer model resemble ssDNA or dsDNA in bulk solution or during a translocation process? To investigate this question, we first performed a simulation of the polymer in bulk solution (in the absence of a nanopore and applied electric field) and obtained the radius of gyration and the diffusion coefficient as a function of chain length as shown in Figure 2. In addition, we also performed a set of simulations in which we decrease the excluded volume interactions (“poor” solvent conditions) by changing the potential energy function to a full Lennard-Jones potential (Eq.(4)) and observed how the radius of gyration and diffusion coefficient change.

$$U_{\text{LJ}}(r) = \begin{cases} 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^6 - \left( \frac{\sigma}{r} \right)^{12} \right], & r \leq r_c \\ 0, & r > r_c \end{cases}$$

As shown in Figure 2(a), the radius of gyration for the polymer described by Eq. (3) scales as $\langle R_g^2 \rangle \sim N^{\alpha}$, which agrees with the theoretical prediction of $\langle R_g^2 \rangle \sim N^{2\nu}$, where $\nu = 0.588$. In addition, when the excluded volume interaction is removed, the radius of gyration decreases significantly as indicated by the much smaller slope. As shown in Figure 2(b), however, the diffusion coefficient, which scales as $D \sim 1/N$, does not change between polymer models. In fact, it is seen that both polymers diffuse as a Rouse polymer due to the absence of hydrodynamic interactions between the polymer and the solvent. From previous measurements for very long strands, ssDNA diffuses as $D \sim 1/N^{0.49}$ and dsDNA diffuses as $D \sim 1/N^{0.16}$ in bulk solution, indicating that hydrodynamic interactions are significant when describing the interactions between DNA and the solvent. It may be argued that hydrodynamic interactions between DNA monomers inside a narrow pore are negligible. On the other hand, hydrodynamic interactions between DNA monomers outside the nanopore will change the diffusivity of the polymer during the translocation process which, in turn, could alter scaling laws such as translocation time versus chain length. In this study, we will primarily focus on simulations involving Rouse polymers, as was done in previous investigations, with the understanding that future work will need to address the effects of hydrodynamic interactions on the translocation physics.

Translocation time vs. chain length: Scaling behavior for forced and unforced translocation

Figure 3 shows the translocation time as a function of polymer length, in an infinitesimally short (0.5 nm length, 0.96 nm diameter) pore with no applied voltage. To perform these simulations, the polymer was placed with its center monomer in the center of the pore with half of its remaining monomers on the cis side of the pore and the other half on the trans side of the pore. The polymer was then permitted to translocate in either direction. A successful trial was obtained once the polymer was out of the pore. The translocation time scales as $\tau \sim N^\alpha$, where $\alpha = 2.52$, a much stronger scaling behavior than predicted by Chuang et al. ($\alpha = 1+2\nu = 2.18$) and observed in some previous simulation results in which $\alpha$ varies between 2.2 and 2.33, but is in good agreement with that predicted by Panja et al. ($\alpha = 2+\nu = 2.58$) and observed very recently by Dubbeldam et al. ($\alpha = 2.5$).
Figure 3 shows the translocation time as a function of polymer length, in the same infinitesimally short pore, using an 80 mV applied voltage, for three different pore diameters (0.96 nm, 1.5 nm, and 3.0 nm). The translocation time scales as $\tau \sim N^{\alpha}$, where $\alpha = 1.35 - 1.40$, and changes very little with pore diameter. This behavior is in good agreement with the prediction of Vocks et al.\textsuperscript{26} for translocation through a nanoscale hole, i.e., $\tau \sim N^{1+2(0.588)/(1+(0.588))} = N^{1.37}$. This is also in good agreement with recent theoretical predictions by Sakaue,\textsuperscript{48} other simulation methodologies investigating this type of behavior,\textsuperscript{35, 36, 38, 46} and with measurements from Wanunu et al.\textsuperscript{3} who observed a crossover behavior with a scaling law exponent of $\alpha = 1.4$ for dsDNA between 150 and 3500 bp and $\alpha = 2.28$ for longer chains using a 4 nm diameter SiN pore. On the other hand, Storm et al.\textsuperscript{1} measured a scaling law exponent of $\alpha = 1.27$ for translocation through a 10 nm diameter SiO$_2$ pore and hypothesized this scaling law was due to the hydrodynamic forces acting on the “blob-like” structure of the DNA outside the nanopore (Figure 5). Interestingly, Fyta et al.\textsuperscript{71} observed a scaling exponent of $\alpha = 1.36$ in the absence of hydrodynamic interactions, which is in good agreement with our findings, and $\alpha = 1.28$ with hydrodynamic interactions. Because the scaling law in both our simulation results as well as the cited experimental results are smaller than the value predicted by Kantor\textsuperscript{31} ($\alpha = 1 + \nu = 1.588$) we can assume that the polymer is not in a state of equilibrium during the entire translocation process. We also note our scaling law results are smaller than those predicted from recent MD simulations ($\alpha = 1.47$)\textsuperscript{49} and previous works that solve the fractional Fokker-Planck equation and perform subsequent Monte Carlo simulations ($\alpha = 1.5$).\textsuperscript{27} However, as described later in this paper, by reducing the applied driving force, we can slow down the polymer flow through the nanopore, allowing the polymer to maintain an equilibrium configuration throughout the translocation process which results in larger scaling exponents that approach the above values.

From our simulations, and previous simulation and measurement results, dsDNA appears to behave like a Zimm polymer (with hydrodynamic interactions) as in the experiments of Storm et al.\textsuperscript{1} and like a Rouse polymer (without hydrodynamic interactions) for certain length ranges as in the experiments of Wanunu et al.\textsuperscript{3} A possible explanation for the discrepancy in the scaling law behavior could be due to electro-osmotic flow inside the nanopore during the translocation process. Recent computational studies\textsuperscript{72} have hypothesized that drag forces due to electro-osmotic flow inside a nanopore are more significant than hydrodynamic forces acting on the DNA blob outside the nanopore (see Figure 5). If the surface charge of the nanopore has the opposite charge of the polymer flowing through it, the electro-osmotic flow will be in the same direction as the translocation process (red arrow). If the surface charge of the nanopore is the same as the charge of the polymer, the electro-osmotic flow will be in the opposite direction (black arrow). The silicon nitride pore used by Wanunu et al.\textsuperscript{3} has a negative
surface charge density at high pH\textsuperscript{22} which, because DNA is also negatively charged, would result in an electro-osmotic flow in the opposite direction as the translocation process. This leads to an apparent decrease in the velocity of DNA in the nanopore and reduces the hydrodynamic force caused by the folded DNA chain outside the nanopore. In addition, the pore used by Wanunu \textit{et al.}\textsuperscript{3} is also much smaller in diameter than the pore used by Storm \textit{et al.}\textsuperscript{4} thereby increasing the effect of the electro-osmotic forces on the translocation process. This behavior is reflected in the translocation time measurements, where it was found that the translocation time through a narrow Si\textsubscript{3}N\textsubscript{4} pore was longer\textsuperscript{3} than the translocation time through SiO\textsubscript{2} pores,\textsuperscript{4} for DNA chains of similar length.

As mentioned earlier, the scaling law exponent for translocation time versus polymer length may vary depending upon how far the polymer is out of equilibrium during the translocation process. In order to test this, we performed translocation time simulations for several different values of applied voltage and monomer friction coefficient. Lowering the voltage and/or increasing the friction coefficient would slow down the translocation process providing more time for the polymer to equilibrate during the translocation process, which should change the scaling law behavior. As shown in Figure 6, increasing the friction coefficient from 1.5 to 8 times the value obtained from Stokes law leads to an increase in the translocation time, but does not affect the scaling law exponent. Hence, it appears that the force due to an applied voltage of 80 mV is still large enough to keep the polymer out of equilibrium during the translocation process even when the drag force per monomer is eight times larger than the value obtained from Stokes law. On the other hand, when we decrease the applied voltage to 40 mV the scaling law exponent increases from $\alpha = 1.35$ to $\alpha = 1.42$ and increases even more when the applied voltage drops to 10 mV ($\alpha = 1.74$). When the applied voltage is increased from 80 mV to 250 mV, the scaling law remains the same indicating that for our process, a lower limit $\alpha = 1.35$ is obtained. This trend of increasing scaling exponent due to lower applied forces has also been observed in other simulation methodologies.\textsuperscript{36,38} However, it has also been hypothesized that the scaling law exponent will increase with an increase in driving force.\textsuperscript{38,40,49} The differences in the two results remain unclear. Hence, further studies need to be performed in order to obtain an accurate and universal scaling law that correctly predicts measured results.

When the pore length is increased to 5 nm, the scaling law behavior changes substantially (Figure 7). For polymer lengths between 1 and 30 monomers, the scaling exponent is less than unity, whereas for chain lengths between 40 and 300 monomers the scaling exponent is greater than unity but still lower than the values observed in Figure 4. When the polymer length is increased to $N = 320–400$ monomers the scaling law exponent becomes 1.39, which is similar to the values observed in Figure 4. As shown, the scaling laws appear to be independent of the pore diameter. This trend of scaling law dependence on polymer length has also been observed in other simulation methodologies as well.\textsuperscript{37,44} A similar scaling law trend is also seen when the diameter and the length of the pore are increased to 4 nm and 10 nm respectively (Figure 8).

To understand why the scaling law exponents are fundamentally different in Figures 4 and 7, and 8, we examine the differences in the applied force. In the situation where the polymer length is on the same order as the pore length, the total force applied to the chain varies as a function of time. This force has its minimum value when only a single monomer is in the pore. The total force increases as more monomers enter the pore, reaching a maximum value when the pore is completely filled with monomers. Depending upon the length of the chain, the pore force will remain at this maximum value until the last monomer enters the pore. When the polymer has completely exited the pore, the total force returns to zero. This is quite different from the short-pore case in which the force experienced by the monomers remains constant throughout the translocation process. This force profile was also observed by Luo\textsuperscript{56} and Gauthier.\textsuperscript{44} In the latter work, a scaling behavior of $\tau \sim N$ was observed for chains much
smaller than the pore length, whereas $\tau \sim N^{1+\nu}$ was observed for chains much longer than the pore length. The discrepancy between our data and the work of Gauthier is probably due to the state of the polymer during translocation. As mentioned earlier, when the polymer is in equilibrium throughout the translocation process, the translocation time scales as $\tau \sim N^{1+\nu}$. However, as predicted by Vocks et al., the polymer is not in equilibrium, the translocation time scales as $\tau \sim N^{1+2\nu/(1+\nu)}$, which is the behavior seen in our simulations. Because our polymers are farther away from equilibrium during the translocation process for both short and long pores, we see different scaling law exponents. Vocks et al. used a conservation of energy approach to predict a lower bound on the translocation time scaling law given by the expression $\tau \sim \eta N^{2\nu}/F$, where $\eta$ is the viscosity of the solvent. In three dimensions, this would predict a translocation time dependence of $\tau \sim \eta N^{1.176}/F$ whose exponent is substantially larger than that obtained from Figure 7 for chain lengths between 1 and 200 monomers. However, as described earlier, in these simulations the force ($F$) is now a function of the chain length $N$, which reduces the scaling exponent to a value lower than $2\nu$, indicating an even lower bound when the chain length is on the order of the pore length. For the situation when the polymer length is much greater than the pore length (Figure 4), we have already seen from the scaling behavior that the polymer is not in equilibrium throughout the translocation process. This observation helps explain why the scaling exponent for intermediate chain lengths (5–30 monomers) in Figures 7 and 8 is much less than unity. Due to the longer pore length, the applied force is larger and, as a result, the translocation time is much shorter than the Rouse relaxation time. The polymer is therefore now farther from equilibrium during the translocation process. This phenomenon is also demonstrated by the increase in crowding of monomers at the exit of the pore as demonstrated in Figure 9.

As described by Sakaue and more recently in Dubbeldam et al., the total translocation time can be broken down into two individual time components: an initial period, $\tau_1$, where the tension caused by the applied force propagates down the polymer resulting in a decreasing chain velocity, and a second period, $\tau_2$, in which the tension propagation has reached the end of the chain and thus the velocity of the polymer remains constant throughout the remaining translocation process. Furthermore, Dubbeldam et al. described three possible formations (“trumpet,” “stem-trumpet,” and “stem”) of the polymer on the cis side of the pore, and two different translocation time versus chain length scaling law regions. Both the polymer shape and scaling law are dependent upon the strength of the applied force. For the force strengths used in this work (intermediate to strong), the scaling laws for the two different time regions are: $\tau_1 \sim N^{1+\nu}/F \sim N^{0.588}/F$ and $\tau_2 \sim N^{0.2}/F \sim N^{-1.76}/F$, which correspond to the “stem-trumpet” or “stem” polymer shapes. This can be seen in Figure 9(c), where a “stem” of four monomers is seen to exist at the pore entrance. In addition, the scaling law behavior—albeit with different scaling exponents—is demonstrated in Figures 7 and 8. When the length of the chain is very short, the time required for the tension to reach the end of the chain is very small, and thus the velocity during translocation is essentially constant, thereby resulting in small scaling exponents with the dominant time period being $\tau_2$. When the length of the chain is increased, the time required for the tension to reach the end of the chain increases, thus causing the chain velocity to decrease and resulting in a larger influence of $\tau_1$ and higher scaling exponents. Finally, when the length of the chain is long enough, a maximum scaling exponent is reached. Even though our scaling exponent in Figure 7 ($\alpha = 1.39$) is smaller than the exponent obtained by Dubbeldam et al. ($\alpha = 1.47$), the results in Figure 6 show that the applied voltage could be varied until the observed scaling law is reached, which occurs at $\sim 35$ mV.
Translocation time vs. applied voltage: Scaling behavior

Next, we investigate the scaling behavior of translocation time on the applied voltage (60 mV–750 mV) for several different chain lengths, through both a short (0.5 nm) and long (5 nm) nanopore. Figure 10 shows the voltage dependence of the translocation time for chains of different lengths in a very short pore (0.5 nm). For \( N = 1 \), the voltage scaling exponent is weak (about \(-0.3\) ), because the single monomer travels very quickly through the pore without being significantly accelerated by the applied voltage. As the chain length increases, the time required for the polymer to pass through the pore increases. This permits a longer duration for which the electrical force will be applied to the polymer chain. Because the force is applied for a longer period of time, the velocity of the chain now has ample time to increase during the translocation process. This increase in velocity is dependent upon the strength of the applied voltage. If the applied voltage is increased, the velocity is increased, which reduces the translocation time. Hence, when the length of the polymer is increased, the dependence of translocation time on voltage is increased as shown in Figure 10. The inverse proportionality \( \tau \sim V^{-1} \) sets in after \( N = 10 \). At higher voltages (\( \sim 500 \) mV), we begin to see a crossover behavior for all chain lengths. For example, in the case of \( N = 50 \), the scaling exponent changes from \(-0.96\) to \(-0.72\) as the voltage is increased from 400 mV to 500 mV. This behavior has also been observed in previous simulations\(^{36,38}\) and was hypothesized to be a manifestation of the polymer being far away from its equilibrium state.

An example of this phenomenon is given in Figure 11 which shows a snapshot of the translocation of a polymer chain with length \( N = 50 \) for: (a) \( V = 80 \) mV and (b) \( V = 750 \) mV. At (a) \( V = 80 \) mV, the chain at the trans side of the pore has a large radius of gyration with minimum folding whereas at (b) \( V = 750 \) mV there is a lot of monomer crowding indicating the polymer is far from its equilibrium state during the translocation process.

Figure 12 shows the scaling behavior of translocation time versus voltage for translocation through a long (5 nm) pore. Unlike the case of the short pore, the scaling exponents for all chain lengths are approximately \(-1\) and do not vary significantly with chain length. In addition, there are no voltages in which the slope changes from one value to another as seen in the short pore simulations. The key differences in voltage scaling between the short and long pores can be explained by remembering that the force due to the applied voltage is non-zero only inside the pore. For short pores and short polymer lengths, the polymer is present inside the pore briefly and therefore will only experience the applied force for a small amount of time, thus increasing the applied voltage only results in a slight increase in velocity and, as a
result, a small change in translocation time. When the polymer length becomes longer, even though each monomer only experiences the applied force for a short amount of time, the overall force on the polymer will increase because the time required for the polymer to fully translocate through the pore will increase. Similarly, when the length of the pore is increased, because more time is required for each monomer to translocate through the nanopore, the polymer will also experience the applied force for a greater period of time and, consequently, increases in the applied voltage result in increases in the polymer velocity and decreases in translocation time.

CONCLUSIONS

We have investigated the translocation time scaling laws, for both polymer length and applied voltage, for a Rouse polymer in atomistically detailed silicon nitride nanopores of varying diameter and length using realistic parameters rather than traditional dimensionless quantities. We found that in the case of short nanopores and long polymers, the translocation time versus chain length $N$ scales as $	au \sim N^\alpha$, where $\alpha = 1.35-1.40$, in good agreement with predictions by Vocks et al.

and Sakaue, and previous simulation results, and measurements of dsDNA with lengths between 150 and 3500 bp. Our results also clarify the dependence of the scalings upon the applied voltage. When the voltage is reduced below 80 mV, the scaling exponent increases and approaches the value for the unforced case, $\alpha = 2.52$, in good agreement with Panja et al. When the pore length increases, a continuous scaling law does not exist, but the scaling exponent increases as the length of the polymer increases which converges to the same value obtained in the short pore simulations for very long polymers. In addition, our simulation results mimic the theoretical predictions for translocation time dependence on applied voltage ($\tau \sim V^{-1}$) for the case of long pore lengths. When the pore length is very short, the scaling law is dependent not only on the polymer length, but also the applied voltage. The differences in the scaling laws can be attributed to the duration of the applied force on the polymer. In the case of the short pores, the duration of the applied force on the polymer is much smaller than the situation of long pores. This smaller duration, especially for the case of short polymers, results in smaller changes in velocity even for increased applied voltages. We found that when the polymer length ($N = 10$) is approximately 10 times the length of the short pore ($L = 0.5$ nm), the $\tau \sim V^{-1}$ scaling law is recovered. However, we found that in the case of short pores, a threshold voltage exists in which larger voltages result in smaller changes in translocation time. Finally, we found that using an atomistically detailed nanopore provided similar simulation results obtained from other simulation methodologies which modeled the nanopore as a simple homogenous lattice of atoms. This is probably due to the repulsive interaction between the polymer and pore (Eq. (3)) used in our and other simulation methodologies which guarantees the polymer will flow in a single file fashion (no folding) through the nanopore during the translocation process.

ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (Grant No. ECCS-0801829). We acknowledge Professor D. S. Sholl (Georgia Tech) for useful discussions.