Polymer Translocation through a Nanopore: DPD Study

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Supporting Information

ABSTRACT: Translocation of a polymer chain through a narrow pore is explored using 3D explicit solvent dissipative particle dynamics simulation. We study the dependence of the translocation dynamics and translocation time $\tau$ on the chain length $N$, driving force magnitude $E$, and solvent quality. Two types of driving forces are considered: uniform hydrostatic force, which is applied equally to the chain and solvent particles, and uniform electrostatic force, which is applied selectively to the charged particles in the chain and oppositely charged counterions in the solvent. We concluded that the scaling correlations $\tau \sim E^{-\xi}$ and $\tau \sim N^{\beta}$ are valid only for coil-like chains. For globular chains, the exponents $\xi$ and $\beta$ could not be identified with a reasonable accuracy. While the found value of $\xi$ agrees with published experimental results and does not depend on the driving force type, the exponent $\beta$ depends on the driving force and solvent quality. This is explained by nonequilibrium effects, as in the systems considered, the time of translocation is comparable with the time of chain relaxation. These effects, manifested in the changes of chain conformation in the process of translocation, were analyzed on the basis of the variation of the gyration radii of segments of the chain in normal and lateral directions. A prominent chain expansion was observed for coils and was insignificant for globules. This work demonstrates the feasibility of the 3D dissipative particle dynamics modeling of translocation phenomena and accounting for the electrostatic interactions with explicit counterions, as well as for the solvent quality, in a computationally efficient manner.

1. INTRODUCTION

Translocation of polymers through nanoscale pores is a complex physical process, which is of great importance for various biological phenomena such as injection of viral DNA, RNA transfer across nuclear pores, and protein transport through membrane nanopores, as well as for chromatographic separation and purification of natural and synthetic polymers and biomolecules on nanoporous substrates. In order to thread through an opening that is much smaller than its radius of gyration, the polymer chain has to assume an elongated conformation that is entropically unfavorable. This entropy toll on the chain free energy creates a barrier, which can be overcome by an external driving force. Polymer translocation has attracted a great deal of attention in the literature. Experimental studies typically deal with penetration of polymer coils dissolved in a good solvent through nanopores of biological or solid state membranes driven by a constant electrostatic force. In their pioneering paper, Kasianowicz et al. reported experimental investigations of translocation of single-stranded RNA and DNA molecules through a lipid bilayer with $\alpha$-hemolysin pores of $\sim 2.6$ nm in diameter. The translocation event was detected as a prominent drop of the ionic current due to a partial pore blockage by the moving chain. The duration of the current drop was associated with the translocation time. The authors distinguished “short-time” and “long-time” blockages, which may be related, in fact, to failed and successful translocation attempts. In later experiments, similar setups were employed with various single- and double-stranded DNA translocating through nanopores in biological and solid state membranes. The relationships between the translocation time $\tau$ and the key system parameters, such as the chain length $N$ and driving force magnitude $E$, are traditionally interpreted in terms of scaling correlations, such as $\tau \sim N^{\beta}$ and $\tau \sim E^{-\xi}$, with the scaling exponents $\xi$ and $\beta$ that are commonly assumed to be independent of each other. Experimental data for globular proteins, for which water is a poor solvent, is limited. In the process of translocation, the globule should open up as suggested by Talaga and Li, who explored translocation of $\beta$-lactoglobulin through a pore in a silicon nitride membrane (see also a comprehensive review in ref 8).

A number of simulations and theoretical calculations have been performed using various models of polymer chain dynamics. It is worth noting that atomistic level simulations, in particular molecular dynamics (MD), which are very impressive and demonstrative, are still prohibitively expensive, e.g., ref 9. Indeed, even with specially designed high performance algorithms, it takes 24 h for thousands of CPUs to compute one all-atom trajectory of translocation of just 10 nucleotides through a nanopore. Taking into account that we deal here with a stochastic process, it is necessary to perform multiple runs to collect statistically meaningful data. This
The same group studied the dependence of translocation and relatively wide channels and obtained the scaling exponents polymer translocation driven by electrostatic solvent quality on the studied the chain translocation driven by a contrast in the DPD simulation of translocation phenomenon. The authors modeling polymer translocation; however, all but two is worth noting that the DPD method was shown e enables comparison with the earlier simulations, where the computational e account. Most importantly, the DPD method, which operates with soft quasi-particles, provides a significant improvement of computational efficiency compared to the MD and other methods that employ hard-core interaction potentials of Lennard-Jones type (e.g., recent ref 33). Also, the size of the bead of the coarse-grained polymer chain can be chosen commensurate with the pore opening, thus ensuring that the pore cross section can accommodate only one bead. This natural coarse-graining helps simplify the simulation setup and enables comparison with the earlier simulations, where the condition of one bead in the pore cross section was implied. It is worth noting that the DPD method was shown efficient in modeling polymer translocation; however, all but two previously published works were limited to 2D models. The 2010 work of Kapahnke et al. was the first attempt of 3D DPD simulation of translocation phenomenon. The authors studied the chain translocation driven by a contrast in the solvent quality on the cis and trans sides of the membrane that is equivalent to the application of the local force inside the pore. Several very recent papers employed the hard-core interaction potentials with the 3D DPD simulation scheme to avoid particle overlap. In particular, Li et al. explored polymer translocation driven by electrostatic field through relatively wide channels and obtained the scaling exponents \( \beta \) and \( \xi \) for different solvent quality and driving force magnitude. The same group studied the dependence of translocation dynamics on the length of the channel between cis and trans compartments. Feng et al. reported different scaling exponents depending on the choice of the range of dissipative interactions. Another just published paper employs LJ hard-core potentials with the Langevin thermostat; this paper considers different features of the translocation process, such as the translocation time dependence on channel length. Note-worthy, the use of soft potentials is the most attractive feature of the DPD method that makes it computationally efficient compared to the MD and BD models with hard-core interactions between beads.

The methodological novelty of this work is in the demonstration of the feasibility of the 3D DPD method for modeling the translocation phenomena and accounting for the electrostatic interactions with explicit counterions, as well as for the solvent quality, in a computationally efficient manner (compared with hard-potential models). We performed 3D DPD simulations with two different types of driving forces: (i) a spatially uniform hydrostatic-type force, which equally acts on polymer and solvent beads, and (ii) a spatially uniform electrostatic-type force, which acts only on the charged beads within the polymer chain and on the counterions in solution. In the latter case, we consider explicitly, for the first time in the translocation literature, the electrostatic interactions between charged fragments of the polymer and counterions in the solution. In doing so, the charges are either equally distributed between the beads of the chain, as is done in modeling uniform electrolytes such as sulfonated polystyrene or DNA (this model will be referred to as "uniform charge model") or assigned to the selected beads to mimic a heterogeneous charge distribution in proteins (this model will be referred to as the "heterogeneous chain model"). These models were chosen for their simplicity and qualitative difference; in the uniform chain model, the force is proportional to the chain length, while in the heterogeneous chain model, the force is independent of the length. We analyze the dependence of the translocation time on the chain length, the driving force magnitude, and the solvent quality. Special attention is paid to the alteration of chain conformations in the process of translocation in good and bad solvent, which has only been briefly discussed in the literature. An analysis of polymer conformation is especially important for studies of translocation of globular proteins.

The rest of the paper is structured as follows. In section 2, we briefly present the DPD methodology employed to simulate the translocation process and describe the interaction parameters, as well as the simulation system setup. In section 3, we demonstrate that the adopted simulation model provides a proper description of the coil—globule transition, and thus is suitable for studies of the effects of solvent quality. In section 4, we study the effect of the driving force magnitude for the case of good solvent. In section 5, we present results of the influence of the solvent quality, which was varied from good to bad conditions, on the translocation time for different driving forces. In section 6, we consider chain conformations during the translocation process. The conclusions are summarized in section 7.

### 2. SIMULATION SETUP AND TECHNIQUES

We used a standard version of the DPD technique, as summarized in ref 35. The polymeric molecule is presented by a chain of quasi-particles, or beads of equal diameter \( R_b \). The interactions between beads \( i \) and \( j \) include soft conservative repulsion force, random force, and velocity dependent friction drag force: \( F_{ij} = F^{BC}_{ij} + F^{RB}_{ij} + F^{VD}_{ij} \). We applied the standard
260 charged solvent beads were added to the solvent. The charged counterions (positive and negative) modeled as bead charge. The sum of bead charges along the chain equaled on the level of coarse-graining, each bead contained a certain presented in the Supporting Information, Figure S1. Depending of coarse-grained beads. The charge pro consider a particular example, we location of proteins, which can be di
249 This manner of applying the driving force, which we will call total charge is di
241 equilibrium bond length. We set neighboring beads: the chain beads is ensured by a spring force acting between the chain is relaxed with the driving force turned o
281 the simulation cell had a cylindrical shape with periodic boundary conditions applied in the axial x-direction (Figure 1). The sizes of the cylinder were 30R in length and 20R in diameter. The cylinder walls were composed of implicit immobile DPD beads “smeared out” over the outer space 303
283 The simulation cell had a cylindrical shape with periodic boundary conditions applied in the axial x-direction (Figure 1). 300 βLGa (like many other proteins) is inhomogeneous. Most of the negative charges are concentrated in the tail of the chain (that is, the beads that are the last to enter the opening), while the head section, which enters the opening first, is slightly positively charged and therefore experiences force opposite to the translocation direction. The central section of the polymer also bears a positive charge. Second, the interactions between explicit charges of the chain, as well as with the hydrophilic counterions, affect the conformations of the translocating protein, especially in bad solvent, effectively making it more hydrophilic. Since the polymer charge remained constant and the chain length varied, polymer beads were allowed integer charges stronger than ±e, but all counterions were assigned ±e or −e charge, and each charged bead was neutralized by one or more counterions. Accordingly, the number of counterions changed from 10 (all positive) at N = 1 (single bead) to a maximum of 29. Assuming that each solvent bead effectively models three water molecules, the concentration of counterions varies approximately from 0.02 to 0.08 M, which is sufficient to affect substantially the conformations of the translocating chain 282 as well as the translocation time.
283 (ii) In the second model, each bead carried a fixed amount of charge, which is independent of the chain length. In this case, the total charge and, correspondingly, the driving force acting on the chain are proportional to the chain length N. This model is referred to below as the “uniform chain model”. In the uniform model, electrostatic repulsion interactions between the polymer beads and counterions were omitted, which meant they do not affect conformations of the translocating polymer. 289 The uniform chain model is therefore similar to one under the hydrostatic driving field, but the driving force is only applied to the polymer beads rather than to all beads. The absence of intrachain electrostatic interactions and the uniformity of the driving field make our setup different from that in current blockage experiments 285 where the driving force depends strongly on the bead location.

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Figure 1. Simulation setup. In the initial configuration, the polymer is placed in the cis compartment (shown on the left side of the membrane) with the first three beads located within the pore. The chain is relaxed with the driving force turned off and the second bead fixed at the pore center. At time zero, the driving force is applied.

The Journal of Physical Chemistry B
outside the cylindrical system. The density of implicit beads had
354 a density \( \rho R^3 = 3 \) (equal to the average density of the main
355 system) which was constant for polymer and solvent with
356 the parameter \( \Delta \nu \). As we proceeded further, the three
357 subscript indices refer to the polymer, \( \nu \) to solvent, \( W \) to
358 the wall, and \( M \) to the membrane). The cylindrical cell was
359 separated into cis and trans compartments by a membrane that
360 consisted of three layers of repulsive beads (4314 beads in
361 total). By using three layers of repulsive beads, we make sure
362 that the probability of penetration of solvent and polymer beads
363 through the membrane is negligible. The membrane had a pore
364 of circular cross-section of 2.2Rc in diameter (counted as the
365 distance between the centers of immobile beads that form the
366 membrane), as shown in Figure 1. The positions of the membrane
367 beads were fixed throughout the simulation.
368
369 In the initial configuration of each simulation, the polymer
370 molecule was placed in the cis compartment with the three end
371 beads already in the channel (Figure 1). The chain was relaxed
372 with the driving force turned off. Coordinates of the second
373 bead were fixed at the center of the pore throughout the
374 relaxation process. No restrictions were applied to other mobile
375 beads such as solvent and counterions. The counterions were
376 dissociated with practically no ion pairs observed. They tended
to spread throughout the system. At time zero, the driving force
377 was applied, the chain was released, and the translocation
378 process began. If the entire chain exited the opening to the
379 trans compartment, the translocation was considered successful.
380 The time at which the last chain bead crossed the plane formed
381 by the centers of the rightmost layer of membrane beads was
382 recorded as the translocation time \( \tau \). If the entire chain exited
383 the channel to the cis compartment, the translocation is
384 counted as “failed” and the simulation stopped. The duration of
385 the fail translocation event was recorded as well.

3. CONDITIONS OF THE COIL–GLOBULE TRANSITION

To show that the model chosen is capable of describing polymer behavior in good and bad solvent, we determined the
389 conditions of the coil–globule transition. For this purpose, we
390 simulated free uncharged polymer chains in a large solvent bath
391 under 3D periodic boundary conditions with solvent–solvent
392 and polymer–polymer repulsive parameters \( a_{SS} \equiv a_{pp} \equiv 25kT / R_c \)
393 and polymer–solvent repulsive parameter \( a_{ps} \) being varied.
394 The state of the polymer chain was detected using the
correlation between the chain length and the radius of gyration
396 in the form of the power law \( R_g \sim N^\nu \) and is quantified with the
397 Flory exponent \( \nu \). The results are presented in Figure 2. When
398 the solvent is poor (that is, \( a_{ps} \) is high), the chain collapses into
399 a globule with the volume proportional to the chain length \( \nu \approx 1 / 3 \). As the solvent–polymer interactions become less
400 repulsive, the polymer exhibits a continuous transition to a
401 random coil signified by the increasing \( \nu \). We could see that the \( \Theta \)
402 solvent conditions (\( \nu \approx 1 / 2 \)) correspond in the DPD model to
403 \( a_{ps} = 27.25 kT / R_c \) see Figure 2. This result agrees within the
404 accuracy of these calculations with data reported recently.\(^{15} \)
405 Using a widely adopted linear correlation between the
406 interaction contrast \( \Delta \alpha = a_{ps} - a_{ss} \) and the Flory–Huggins
407 parameter, \( \chi = 0.286 \alpha \), we estimate the \( \Theta \) point value of \( \chi \nu \)
408 = 0.63. As the solvent–polymer interactions improve further, \( \nu \)
409 stabilizes in the 0.56–0.64 interval, which includes the values
410 obtained previously for self-avoiding polymer chains using
411 different methods, including similar 3D DPD simulations.\(^{40–2} \)
412 In further simulations of translocation, most of the simulations
413 were performed with \( a_{ps} = 25kT / R_c \) (\( \chi = 0 \), good solvent,
414 unconstrained polymer chain adopts a coil configuration) and \( a_{ps} = 40 kT / R_c \) (\( \chi = 4.29 \), bad solvent, polymer chain assumes a
415 globular state).

4. DRIVING FORCE EFFECT IN GOOD SOLVENT

The scaling between the translocation time \( \tau \) and the driving
419 force magnitude \( E \) was extensively studied in the literature both
420 experimentally and with simulations for coil-like chains at the
421 good solvent conditions. Assuming the standard power law
422 scaling, \( \tau \sim E^\xi \), Kasianowicz et al.\(^3 \) obtained an inverse
423 proportional dependence with the scaling exponent \( \xi = 1 \). This
424 intuitively plausible result, the stronger the force the shorter the
425 time, was confirmed by later studies of single-stranded and
double-stranded DNA translocation through solid and \( ^{36} \)
426 hemolyssin pores.\(^{5,43,44} \) Meller et al.\(^39 \) found strongly nonlinear
427 dependence of the polymer velocity on the applied voltage. On
428 the theoretical front, numerous kinetic MC and LD/BD
429 simulations in 2D and 3D with the “local” driving force
430 confirmed the inverse proportional correlation \( \xi \approx 1 \).\(^{25,45–48} \)
431 Ilonen et al.\(^36 \) in their MD and theoretical study of polymer
432 translocation found a nonuniform correlation between \( \tau \) and \( E \)
433 with \( \xi \approx 0.9 \) for weaker driving forces and \( \xi \approx 1 \) for stronger
434 forces. They concluded that translocation time could not be
435 described with a universal set of scaling exponents and stressed
436 the importance of pore–polymer interactions that contributed
437 substantially to the nonuniversal polymer behavior. There is
438 also a significant dissent. He et al.\(^32 \) modeled polymer
439 translocation by 2D DPD with a uniform hydrostatic force
440 applied to all beads, polymer, and solvent, and obtained \( \xi \approx 1 \).
441 Kantor and Kardar\(^16 \) in their 2D MC simulations obtained
442 the scaling exponents of \( \beta = 1.875 \) and \( \xi = 1.45 \) when the
443 polymer was pulled from one end and driven by a chemical
444 potential difference, correspondingly. \( \beta = 2.0 \) correlation was
445 observed in 2D dynamic MC simulations of Chen et al.,\(^50 \)
446 and 3D explicit solvent MD simulations of Matysiak et al.\(^3 \). Later,
447 Luo et al.\(^31,52 \) reported a complex picture with several intervals
448 of the driving force characterized by different values of \( \xi \)
449 including \( \xi = 1 \) at sufficiently strong forces.

For examination of the driving force influence on \( \tau \), we
450 consider polymer chains of 80 beads driven by uniform
451 hydrostatic and electrostatic driving forces at the good solvent
452 influence
453

\[ a_{ps} = 25kT / R_c (\chi = 0, \text{good solvent}), \]

\[ a_{ps} = 40 kT / R_c (\chi = 4.29, \text{bad solvent}), \]

\[ a_{ps} \text{ is the parameter of solvent–polymer interaction.} \]

\[ \chi = 0 \text{ for weaker driving forces and } \chi \approx 1 \text{ for stronger forces.} \]

\[ \tau \sim E^\xi \text{ for good solvent conditions.} \]

\[ \xi \approx 1 \text{ for weaker driving forces and } \xi \approx 1 \text{ for stronger forces.} \]

\[ \beta = 1.875 \text{ and } \xi = 1.45 \text{ when the polymer was pulled from one end and driven by a chemical potential difference.} \]
conditions. The range of driving field magnitude for each force type was chosen so the driving force acting on one bead in a polymer chain was substantially weaker compared to the mean conservative repulsion force acting between the soft beads in DPD simulation but strong enough to yield reliable statistics. The magnitude of the driving force acting on a bead varied from 0.05 $kT/R_c$ to 0.9 $kT/R_c$ for hydrostatic force and from 1.0 $kT/R_c$ to 9.0 $kT/R_c$ for electrostatic force. This means that the strongest driving forces were comparable to the typical repulsive forces between the individual beads in our DPD system, while the weakest driving forces were much weaker than the interparticle forces. Generally, when the electrostatic force is applied, the beads move through the resisting viscous solvent. The oppositely charged counterions add to this resistance. Contrary to that, the hydrostatic force affects all beads, and as such, both the chain and the solvent form a driven flow through the pore. Note that the hydrostatic force employed here does not correspond to the pressure driven flow considered in MD studies of water ultrafiltration through nanopore.

Despite the different nature of the flow, the correlation between the force magnitude $E$ and $t$ is very similar for both driving force types (Figure 3). Here and further on, each point shown is obtained as an average of at least 1000 successful translocations. The weaker the driving force, the longer is the translocation time, and the more expensive the simulations are. That is why the statistical error is greater for weaker forces. The ranges of magnitudes of driving forces acting on the entire chain were approximately the same for all field types: 0.4−80$kT/R_c$ for the hydrostatic field and 0.6−90$kT/R_c$ for the electrostatic field. However, the translocation times obtained with the electrostatic field were substantially slower. In both cases, there is a reliable linear correlation between the logarithms of the translocation time $t$ and the force magnitude $E$ with the slope of $\xi \approx 0.9$. This result is close but not equal to the trivial inverse proportional scaling, $\xi = 1$, observed in experiments and simulations reported previously, and rather coincides with the MD result obtained in ref 49 for weaker driving force and a recent DPD simulation. This finding is likely to indicate the importance of an explicit solvent model when translocation phenomena are considered.

**Figure 3.** Translocation time dependence on the driving force magnitude for $N = 80$ in good solvent: (a) uniform hydrostatic driving force; (b) uniform electrostatic driving force, heterogeneous chain model. Each point shown is the average of at least 1000 successful translocation events. The slopes of the linear fit are $-0.89 \pm 0.02$ (a) and $-0.88 \pm 0.01$ (b), correspondingly. Uncertainties are given at 90% confidence level.

5. **CHAIN LENGTH DEPENDENCE. INFLUENCE OF THE SOLVENT QUALITY**

A linear increase of the translocation time with the chain length ($\tau \sim N^\beta$, $\beta = 1$) was reported for single-stranded DNA by Kianianowicz et al. and later by Meller et al., Storm et al., experimented with much stiffer double-stranded DNA and solid silicon oxide pore, and reported a higher scaling exponent, $\beta = 1.27$, that was also obtained in a number of theoretical and simulation studies, which employed 2D DPD, MD, BD, LD, and 3D dynamic MC, and a complex 3D multiscale methodology combining constrained MD for the polymer motion with a lattice-Boltzmann treatment of the solvent hydrodynamics. However, in other works, higher values of $\beta$, ranging up to 2.5, were obtained. Some authors found different scaling exponents for different chain lengths and driving force magnitudes. There were also several attempts to establish correlations between scaling exponent $\beta$ and Flory exponent $\nu$ for translocation in 2 and 3 dimensions. For example, Sung and Park studied translocation of ideal chains by using self-consistent field theory (SCFT) and obtained $\beta = 2 + \nu$ at very weak driving forces; as the driving force became stronger, the translocation time encountered a crossover in the scaling behavior from $\beta = 2 + \nu$ at very weak driving force to $\beta = 1 + \nu$ at stronger driving forces. The same correlation, $\beta = 1 + \nu$, was suggested by Dubbeldam et al. and Tsuchida and Matsuyama. Later, Park and Sung studied the temperature dependence of translocation driven by polymer adsorption on the trans side of the membrane. They found that the correlation between $\tau$ and $N$ differed above and below $T_c$, the temperature of adsorption−desorption transition, for ideal polymer chains on the trans side: $\beta = 2$ at $T > T_c$ and $\beta = 3$ at $T < T_c$. Using SCFT calculations, Muthukumar studied translocation of polymer chains with excluded volume interactions and obtained $\tau \sim N$. Matsyuk et al., Wei et al., and Bhattacharya et al. reported $\beta = 2\nu$, while the relationship $\beta = 1 + 2\nu$ was reported by Milchev et al., Romiszowski and Sikorski, and Lehtola et al. Very recently, Qian et al. obtained $\beta = 2.35$ for a partially charged polymer under uniform electrostatic driving field. And last, Feng et al. obtained in 3D DPD simulation with LJ interactions between the particles the scaling exponents $\beta \approx 1$ that are significantly smaller than all other reported values. In addition, disagreement between the value of $\beta$ determined with...
the explicit-solvent\textsuperscript{28,49} and implicit-solvent models shows the importance of accounting for explicit solvent in simulations of polymer dynamics.

We explored the dependence of the translocation time $\tau$ on the chain length $N$ under the uniform hydrostatic and electrostatic driving forces in good and bad solvents. The results for chains ranging from $N = 20$ to $N = 120$ are presented in Figure 4 in double logarithmic coordinates. The power law correlation between $\tau$ and $N$ seems applicable to the systems considered under good solvent conditions (Figure 4a), for which $\beta$ was determined with a reasonable accuracy at $N > 20$. For the uniform hydrostatic force, the scaling exponents were determined as $\beta \approx 1.44$, which is generally consistent with the $\beta = 1 + \nu$ correlation based on the chi-square criterion, in contrast to other possible correlations ($\beta = 1$, $\beta = 2\nu$, $\beta = 1 + 2\nu$, $\beta = 2$).

With electrostatic driving force, both uniform and heterogeneous models produced a higher scaling exponent that is inconsistent with the previously reported values of $\beta$. The steepest increase of $\tau$ with $N$ is observed for the heterogeneous model, which is natural because the overall driving force in this case is constant and does not depend on the chain length. Under bad solvent conditions (Figure 4b), a reasonable scaling was found only for the heterogeneous model. In this case, the value of $\beta$ obtained was nearly identical to that in good solvent. This unexpected result can be explained by the fact that the chain due to the strong electrostatic charges did not comprise into a globule but generally assumed open configurations. This is confirmed by the analysis of configurations of \textit{cis} and \textit{trans} subchains discussed below (section 6). The difference in the translocation process for coils and globules is illustrated in Figure 5, where we present a series of snapshots taken at the different degrees of translocation (0, 25, 50, 75, and 100%) in real simulation time. Typical snapshots of a chain simulated with the heterogeneous chain model are shown in Figure 5b. Despite the fact that apparent local compaction of fragments of the chain is observed, the chain generally maintains a stretched, coil-like configuration.

In the uniform chain model, where the electrostatic forces between the beads are weak and do not affect the polymer conformation, the chain under bad solvent conditions remained in a well-defined globular conformation (Figure 5a) throughout the translocation process, in \textit{cis} and \textit{trans} compartments alike, similarly to the chain under hydrostatic field. The translocation mechanisms for coil and globular polymers are inevitably different, especially at large $N$. Indeed, both the work needed to transfer the center of mass of the tethered chain from the \textit{cis} to \textit{trans} compartment and the friction coefficient are proportional to the chain effective diameter, which is smaller for the globule and scales as $N^{0.6}$ for coils. As such, the time for the globule translocation should be smaller than the time for the coil translocation at the same driving force, as seen from Figure 4. We also should expect a smaller $\beta$ exponent for globules compared to that for coils. This is confirmed qualitatively by the data in Figure 4, especially for the hydrostatic force, when the chain transformation is not affected by electrostatic repulsion and the difference between the coil in good solvent and the globule in bad solvent is well pronounced. However, the time—length relationship for globular chains does not show a power law scaling with reasonable accuracy, at least for the chain lengths considered here. One of the possible explanations is that translocation of globules occurs much faster than translocation of coils and the statistics was insufficient even though the data was collected over 1000 successful translocation events.

From the comparison of the scaling exponents for translocations in good and bad solvents for the hydrostatic force, we concluded that the translocation time increases with chain length faster under good solvent conditions. This conclusion is supported by the simulations, in which the solvent—polymer/ solvent—solvent interaction contrast $a_{PS}$ was varied. For example, Figure 6a shows the correlation between $\tau$ and $a_{PS}$ for $N = 30$. It is obvious that the better the solvent, the larger the translocation time is. A similar result was obtained by He \textit{et al.}\textsuperscript{32} in 2D DPD simulation with the hydrostatic driving force.

The translocation time decreases roughly linearly with $a_{PS}$, and respectively, it increases linearly with the Flory—Huggins parameter $\chi$. However, given the different scaling exponents $\beta$ in $\tau(N)$ dependences for coil and globule polymers, one cannot expect a universal scaling relationship between the translocation time and the solvent quality. In particular, Figure 6b shows that the solvent quality has a greater influence on longer chains compared to shorter chains.

The influence of the driving force magnitude on $\beta$ may be explained by a nonequilibrium nature of the process: if the
translocation is slow, polymer conformational relaxation is much faster compared to penetration through the pore. The two fragments of the chain located in the cis and trans compartments behave as tethered subchains. These configurations may be deformed as the driving force becomes stronger and the translocation process faster.48 β increased with the driving force magnitude well beyond the statistical error.48 However, Kapahnke et al.15 actually observed a monotonic decrease of β as the driving force strengthened. Lower β ∼ 1 for stronger driving force was also obtained by Li et al.28 The detailed analysis of the τ−N dependence in the process of adsorption driven translocation showed that the linear dependence with β = 1 holds for strong driving force and gradually deteriorates as the driving force decreases.60 The dependence on the driving force may also explain the difference between the higher value of β obtained in this work and experimental results obtained for electrostatically driven translocation of single-stranded DNA through membrane nanopores.4,39 Because of the different opening sizes, channel lengths, and potentials applied, a direct comparison is, unfortunately, problematic.

6. EVOLUTION OF CHAIN CONFORMATION DURING THE TRANSLOCATION PROCESS

Configurations of polymer on the cis and trans sides have been considered in the literature. Most theoretical studies considered translocating polymer as quasi-static, assuming that chain relaxation is much faster compared to the translocation process itself, as described above. In our simulations, as well as in earlier works reviewed below, the translocations scale is longer but comparable to relaxation scale and these processes cannot be separated. Fyta et al.61 observed that for N > 100 the transverse component of Rg follows a dynamic scaling law of 0.6, close to the Flory exponent of a 3D self-avoiding random walk. Guo et al.29 found an increase in the mean-square radius of gyration of polymer by the DPD method, which indicates that the polymer elongates in the flow direction during translocation. Feng et al.25 observed in 3D DPD simulation that, during the translocation process, the size of the trans fragment is larger than the size of the cis fragment. Luo et al.62 observed that the cis fragment was more stretched than the trans fragment due to significant nonequilibrium effects. However, a straightforward comparison with the DPD results is somewhat problematic, since in refs 25 and 26 the polymer beads interacted attractively instead of repulsively.

Figure 5. Sample snapshots of the translocating chain at different solvent conditions and degrees of translocation. Column A, uniform chain model, bad solvent; column B, heterogeneous chain model, bad solvent; column C, hydrostatic driving force, good solvent. Top to bottom: varying degree of translocation: 0, 25, 50, 75, and 100%.

Figure 6. Translocation time dependence on the solvent quality: (a) translocation time dependence on the solvent quality characterized by the solvent–polymer/solvent–solvent interaction contrast, hydrostatic driving force; (b) translocation time dependence of the chain length in good and bad solvents, electrostatic driving force.
613 via Lennard-Jones interactions between the particles, and
614 scaling relationships obtained depended on the ratio between
615 the Lennard-Jones particle radius and the radius of dissipative
616 forces. For example, the gyration radius $R_g$ of the trans
617 fragment determined in ref 25 fulfilled the scaling relationship
618 $R_g \sim N_{trans}^{0.79}$ for smaller dissipative radius and
619 $R_g \sim N_{trans}^{0.64}$ for larger dissipative radius. Even in the case of unbiased
620 translation, nonequilibrium effects were evident.63
621 To study how the chain conformation changes during the
622 translocation process, we considered conformations of cis and
623 trans fragments of the translocating chain separately as a
624 function of degree of translocation, here defined as $N_{trans}$ the
625 number of monomers that has moved to the trans side. Figure 7
626 demonstrates the evolution of the cis and trans radii of gyration
627 in the normal and lateral direction during the translocation
628 process. The data points presented are averaged over series that
629 include no less than 1000 successful translocations each. The
630 results of events with failed translocation are also included in
631 the average $R_g$ presented in Figure 7. The plots of $R_g$ vs $N$
632 are more instructive in normal, rather than logarithmic, coor-
633 dinates. Since the chain length was limited to 60 or 53 beads,
634 the scaling analysis cannot be performed and, indeed, the log
635 log plots did not contain well-defined linear regions in any
636 reasonable length intervals.
637 Under good solvent conditions, translocation starts from an
638 asymmetric coil-like cis chain (Figure 5b,c). As the trans
639

![Figure 7. The evolution of lateral ($x$ direction, parallel to the driving field) and normal ($yz$ plane projection, perpendicular to the driving field) radii of gyration of the entire chain, cis segment, trans segment; $N = 60$ for the hydrostatic force and the homogeneous model $N = 53$ (heterogeneous model). Upper panels: uniform hydrostatic force at good (a) and bad (d) solvent conditions. Middle panels: heterogeneous chain model with $E = -1kT/(R_g)$ (which corresponds to $F = 10 kT/R_c$ driving force acting on the entire chain) at good (b) and bad (e) solvent conditions. Bottom panels: uniform chain model with the driving force magnitude of $0.1 kT/R_c$ per bead at good (c) and bad (f) solvent conditions.](image-url)
segment starts growing, the $R_g$ for the cis segment changes very
little or even shows a slight increase, visible for hydrostatic force
(Figure 7a). Hydrostatic force affects polymers and solvents
alike, creating a flow of solvent, with the velocities of particles at
the narrow opening much faster than in the middle of the cis or
trans compartments. The solvent flow, which is developing as
the polymer is pulled through the opening, apparently makes
the polymer accept a conformation stretched in the lateral
direction. In both compartments, the polymer is expanded
compared to a normal coil, as the lateral $R_g$ achieves a
maximum far exceeding that of a chain composed of two
tethered equilibrium coils. In the final configuration, the
polymer is more extended than in the initial configuration.

Strong nonequilibrium effects and asymmetric chain
gility were also observed with the heterogeneous chain
model. The initial conformations of the chain are more
extended than the normal tethered coil conformations used
with the hydrostatic force, apparently due to electrostatic forces
between the charged monomers. Radii of gyration monotonically
decrease in the cis and increase in the trans compartment
as the polymer proceeds through the opening, showing that
nonmonotonic behavior observed under hydrostatic force these
effects should be attributed to the solvent flow. Still, the
maximum $R_g$ for the heterogeneous model in good solvent
exceeds that of a chain composed of two tethered equilibrium
coils, and the final conformation of the chain is more extended
in the lateral direction than the initial conformation (Figure
7b). Both uneven charge distribution and existence of mobile
countersions might have contributed to the nonequilibrium
effects. First, the middle segment experiences a force opposite
the translocation direction, which causes translocation to slow
down. Second, countersions are much more mobile compared to
the polymer. Therefore, anions create a cocurrent flow and
cations create a counter-flow through the opening. The
separation of cations from the polyelectrolyte contributes to
the expansion of the latter due to uncompensated electrostatic
repulsion between the chain anions. This force vanishes when
the cation counterions are also evident: the power law correlation
$n_{\text{trans}} \sim (N - 1)^{\nu}$ was completely inapplicable in either compartment. The polymer
chain, however, was rather symmetric, with $R_g$ on the trans side
approximately equal to that on the cis side of the same length,
in lateral and normal directions alike (Figure 7c).

In bad solvent, the polymer adopted globular configurations
at the start of translocation and is threaded through the
opening, gradually entering a globule that forms on the other
side. This scenario was observed under hydrostatic driving force
and with the homogeneous chain model (Figure 7d,f). The
configurations of the chain were rather symmetric, with $R_g(N)$
showing similar behavior for the trans and cis segments.
Nevertheless, the scaling relationship $R_g \sim (N - 1)^{\beta}$
inapplicable in cis and trans compartments alike. Because the
heterogeneous chain model in this paper does not exhibit a true
coil–globule transition, translocation in bad solvent was rather
similar to that in good solvent, as was already demonstrated
already by $r$ vs $N$ scaling (Figure 7e).

7. CONCLUSIONS AND DISCUSSION

We present the first three-dimensional DPD simulation study
of the forced translocation, which explicitly takes into account
electrostatic interactions between the charged monomers and
solution countersions. Translocation of a polymer chain through
a membrane nanopore driven by an applied force was
extensively studied in the literature using a variety of experimental and theoretical techniques, and there is a substantial disagreement among the published data. We considered the dependence of the translocation time $\tau$ on a variety of factors, such as the chain length $N$, the driving force magnitude $E$, and the solvent quality characterized by the
solvent–polymer interaction parameter $\eta_{PS}$, which varied in the range from 0 to 45 $k_BT/R_g$ that should be compared with the solvent–polymer interaction parameter $a_{\text{trans}} \approx 25k_BT/R_g$. The simulation results were interpreted in terms of scaling exponents $\beta$ and $\xi$ obtained from linear correlations in double
logarithmic coordinates, assuming scaling relationships $\tau \sim N^\beta$ and $r \sim E^{-\xi}$, respectively. The chain conformation was characterized by the Flory exponent $\nu$ calculated from the
chain length dependence of the radius of gyration, $R_g \sim N^{\nu}$. The evolution of chain conformations in the process of translocation was explored by monitoring the radii of gyration of the cis and trans fragments of the translocating chain in normal and lateral directions.

We considered two types of driving force: the uniform
hydrostatic-type force acting on both solvent and polymer and
the uniform electrostatic-type force acting on the selected or all (charged) chain beads and selected (counter-charged) solvent beads. In the electrostatic case, two types of charge distributions along the chain were assigned: uniform and heterogeneous. In the latter, the charge distribution corresponded to that in $\mu$G. These models were chosen for their simplicity and qualitative difference; in the uniform chain model, the force is proportional to the chain length, while in the protein model the force is independent of the chain length. A realistic consideration of DNA, which bears a large negative charge, is hardly possible without a large solvent bath with $\mu$G added electrolyte, which would make a reliable collection of statistics performed in this work unfeasible. In the case of a heterogeneous model that roughly describes protein translocation, the very consideration of polyelectrolyte conformation under different solvent conditions is actually a major challenge, as it has not been analyzed before.

To set a reference, we explored the coil–globule transition in free chains by varying the solvent quality parameter $\eta_{PS}$. For the system studied, we found a gradual transition from $\nu = 0.55$ to $0.6$ under good solvent conditions ($\eta_{PS} = 25k_BT/R_g$) to $\nu = 0.3$ under bad solvent conditions ($\eta_{PS} = 40k_BT/R_g$) with the $\theta$-point value $\nu = 0.5$ achieved at $\eta_{PS} = 27.25k_BT/R_g$. It is worth noting that, for the limited chain length ($<100$ beads), the $\theta$ transition is pretty gradual with the Flory exponent continuously varied from $0.6$ at $\eta_{PS} \approx 15$ to $0.3$ and $\eta_{PS} \approx 30$ crossing the ideal value of $0.5$ at $\eta_{PS} \approx 27.25$.

The scaling correlations, $r \sim E^{-\xi}$ and $\tau \sim N^\beta$, were established only for coil-like chains, and could not be identified with a reasonable accuracy for globular chains. Regardless of the type of the driving force, we found the driving force exponent $\xi \approx 0.9$. This generally confirms the approximate inverse-proportional correlation between the translocation time and driving force magnitude ($\xi = 1$) reported previously in the majority of published experimental and theoretical studies. This models were chosen for their simplicity and qualitative difference; in the uniform chain model, the force is proportional to the chain length, while in the protein model the force is independent of the chain length. A realistic consideration of DNA, which bears a large negative charge, is hardly possible without a large solvent bath with $\mu$G added electrolyte, which would make a reliable collection of statistics performed in this work unfeasible. In the case of a heterogeneous model that roughly describes protein translocation, the very consideration of polyelectrolyte conformation under different solvent conditions is actually a major challenge, as it has not been analyzed before.

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The obtained correlation between the translocation time $\tau$ and the chain length $N$ with the scaling exponent $\beta \approx 1.44$ for coils in good solvent driven by the hydrostatic force agrees with the $\beta = 1 + \nu$ relationship between the translocation exponent $\beta$ and the Flory exponent $\nu$ suggested in some of the published theoretical works.\textsuperscript{18,21} However, simulations of the systems with different solvent quality showed that the $\beta \neq 1 + \nu$ relationship did not hold for bad solvent conditions. In contrast, we found that, as the solvent quality worsens, $\beta$ increases and the accuracy of linear regression analysis deteriorates. That is, the influence of the translocation time that we adopted.

The chain conformations of the translocating chains analyzed from the variation of the gyration radii of cis and trans fragments showed strong nonequilibrium effects for all systems, especially pronounced under the hydrostatic driving force that creates a solvent flow with very nonuniform particle velocities. In good solvent, the nonequilibrium effects lead to extended and asymmetric conformations of the chain. Translocation of globules occurred faster than translocation of coils of the same length that is somewhat counterintuitive. This effect is related to the definition of the translocation time that we adopted.

Indeed, our clocks started when the chain end penetrated into the pore, so that the time needed for the chain end to reach the pore is not counted. And once the translocation started, the chain threaded out of the globule experienced less hydrodynamic friction than the chain threaded out of the coil. We did not observe the globule opening up during the translocation process. The chain adopted a symmetric globular configuration on the cis and trans sides alike.

The methodological novelty of this work is in the demonstration of the feasibility of the 3D DPD method for modeling the translocation phenomena under different conditions and accounting for the electrostatic interactions with explicit counterions, as well as for the solvent quality, in a computationally efficient manner (compared with hard-potential models). Further studies should involve customization of the coarse-graining procedure to reflect the complex structure of biopolymers of practical interest. This would require introduction of different chain beads, incorporation of side subchains, and multicomponent solvent solutions, including added electrolyte that contributes to screening of the electrostatic interactions between monomers and counterions. Also, the driving force should be considered as spatially distributed; in the electrostatic case, this distribution can be obtained from the simultaneous solution of the Poisson–Boltzmann equation.

### ASSOCIATED CONTENT

- **Supporting Information**

Charge profile of $\beta$-lactoglobuline at normal pH and its mapping on model polymers of different chain lengths used in translocation simulations with the heterogeneous chain model.

This material is available free of charge via the Internet at http://pubs.acs.org.

### ACKNOWLEDGMENTS

This work was supported in part by the PRF-ACS Grant No. 48890-ND6, NSF CBET Grant No. 1064170, and by the National Basic Research Program (973) of China (No. 2007CB815603).

### REFERENCES
