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Translocation and insertion of an amphiphilic polymer

Satoshi Tsuchiya and Akihiko Matsuyama*
Department of Bioscience and Bioinformatics, Faculty of Computer Science and System Engineering,
Kyushu Institute of Technology, Kawazu 680-4, Iizuka, Fukuoka 820-8502, Japan

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Translocation of amphiphilic polymers (random and block copolymers), consisting of hydrophilic and hydrophobic monomers, threading a pore is studied by using a three-dimensional dynamic Monte Carlo simulation. We find that there is a "translocation-insertion" threshold in the fraction of hydrophobic monomers on an amphiphilic polymer. The translocation time is given by simple scaling laws and increases with increasing the fraction of hydrophobic monomers.

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I. INTRODUCTION

Translocation of a polymer through narrow channels and pores in a membrane plays an important role for many biological processes [1] and for biotechnologies such as drug delivery and gene therapy. Examples include the translocation of RNA through nuclear pores [2] and the incorporation of membrane proteins into a lipid bilayer [3].

Although the actual system is complicated by many biological factors, a simple model in which a linear polymer chain translocates through a pore embedded in an impenetrable wall provides useful insights for understanding basic physics of a polymer threading membrane [4]. Translocations of "homopolymers" have been received great attention in analytical theories [5–15] and simulations [16–21]. These studies have relevance to the experiments on translocations of single-stranded DNA and RNA through a narrow channel (or pore) by applying an electric field [22,23]. On the other hand, translocations of "amphiphilic polymers," consisting of hydrophobic and hydrophilic groups, are important for insertion transition of proteins into a lipid membrane [24–27]. In reality, many biological proteins and DNA/RNA have such amphiphilic groups and are translocated through pores in a membrane or incorporated into a membrane [28,29]. Some biomembrane phenomena are related to the hydrophobic matching [30] between the bilayer hydrophobic thickness and the protein hydrophobic length. It is therefore of interest to study translocation in terms of the hydrophobic nature of polymer segments and the chemical architecture of a chain.

In this paper we study translocation phenomena of amphiphilic polymers, consisting hydrophobic and hydrophilic groups, threading a pore by using a three-dimensional dynamic Monte Carlo simulation. We examine two types of the polymer chain: one is the hydrophobic and hydrophilic groups are randomly distributed on a chain (random copolymer), which may be a coarse-grained DNA model, and the other is an AB block copolymer. Based on a bead-spring model for polymer translocations, developed by Milchev, Binder, and Bhattacharya (MBB model) [20], we apply it to our amphiphilic polymer chains. We find that insertion or translocation of an amphiphilic polymer depends on the number of hydrophobic groups on the chain and the chemical structure of the polymer chain.

II. MODEL OF SIMULATION

We consider an amphiphilic polymer chain consisting of N monomers. Let N_A and N_B be the number of hydrophilic (A) and hydrophobic (B) monomers on the chain, respectively: $N=N_A+N_B$. We here define the fraction $f_B \equiv N_B/N$ of the hydrophobic monomers. Two effective monomers along the chain are connected by an anharmonic spring, described by the finitely extensible nonlinear elastic potential:

$$U_F = -\frac{K}{2} l^2 \ln\left[1 - \frac{l_i - l_0}{R^2}\right], \tag{1}$$

where l_i is the length of the ith bond varying between $l_{min} < l_i < l_{max}$ and $l = l_{max} - l_0 = l_0 - l_{min}$ and l_0 is the equilibrium value where the potential takes its minimum. We here take $l_{max}=1$, $l_{min}=0.4$, and $l_0=0.7$ for a typical example. The spring constant K is taken as $K/k_BT=40$. The nonbonded interactions between the effective monomers are described by the Morse potential

$$U_M = \epsilon_{ij}\{\exp[-2\alpha(r-r_{min})] - 2\exp[-\alpha(r-r_{min})]\}, \tag{2}$$

where r is the distance between two monomers and ϵ_{ij} shows the strength of the nonbonded attractive interaction between A-A monomers (ϵ_{AA}), A-B monomers (ϵ_{AB}), and B-B monomers (ϵ_{BB}). We take $\epsilon_{AA}/k_BT=\epsilon_{AB}/k_BT=1$, $\epsilon_{BB}/k_BT=5$, $\alpha=24$, and $r_{min}=0.8$. If we take $\epsilon_{ij}/k_BT=1$, all these choices of parameters are identical to the MBB model. In this simulation, we take $T=300$ K to ensure a good solvent condition for A monomers and a poor solvent for B monomers, where the B monomers can aggregate in the solution due to the attractive interaction between B monomers. This model corresponds to the coarse-grained hydrophobic interaction of an amphiphilic polymer in water solvents.

The membrane containing a pore is chosen perfectly flat and structureless. Let L be the thickness of the membrane and D the diameter of a cylindrical pore in the membrane. In the present paper, we chose $D/l_0=1.43$ and $L/l_0=7.14$ which is the order of a thickness of a typical membrane. The trans-

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*matuyama@bio.kyutech.ac.jp

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location processes of an amphiphilic polymer can be given by an asymmetric membrane: one (*cis*) side of which is repulsive, while the other (*trans*) side is attractive for the polymer. Our system consists of an impenetrable wall with the cylindrical pore in it. A potential difference between the *cis* and *trans* sides of the membrane is applied linearly across the wall including the embedded pore along the x axis and is given by

$$U(x,y,z) = \begin{cases} -kx, & \text{if } -L/2 \leqslant x \leqslant L/2 \text{ and } y^2+z^2 \leqslant (D/2)^2, \\ -kL/2, & \text{if } x > L/2, \\ kL/2, & \text{if } x < -L/2, \\ \infty & \text{otherwise}, \end{cases} \tag{3}$$

where k is the strength of the applied force, which determines the tendency of the monomers to move from the *cis* to *trans* side through the pore. For all simulations in this paper, we employ $k=10k_BT$.

The dynamics of the polymer translocation through the pore can be simulated by a dynamic Monte Carlo method. For the present model, an elementary attempted Monte Carlo move is performed by picking an effective monomer at random and trying to displace it from its position (x,y,z) to a new position (x',y',z'), with increments $\Delta x = x'-x$, $\Delta y = y'-y$, and $\Delta z = z'-z$, chosen randomly from the intervals $-0.5 \leqslant \Delta x, \Delta y, \Delta z \leqslant 0.5$. These trial moves are accepted as new configurations if they pass the standard Metropolis acceptance test [31].

For the initial condition of a random copolymer, we put that one monomer of the chain end is on the pore, while all the other monomers are on the *cis* side [Fig. 1(a)]. For the case of block copolymers, we have examined two types of initial conditions. One is the case of that one A (hydrophilic) monomer is on the pore, while all the other monomers are on the *cis* side, where the A monomer becomes the top and moves to *trans* side [Fig. 2(a)]. We refer this as the AB block copolymer. The other is that the end of the B (hydrophobic) monomer is on the pore, while all the other monomers are on the *cis* side. In this case, the B monomer becomes the top and moves [Fig. 3(a)]. We refer this as the BA block copolymer.

We show some snapshots of translocation of the random (Fig. 1), AB (Fig. 2), and BA (Fig. 3) block copolymers with $f_B=0.4$ and $N=50$ at the early (a) and late (b) stages of translocation runs. The left- (right-) hand side of the pore corresponds to the *cis* (*trans*) region. The small circles show the A (hydrophilic) monomers, and the large circles correspond to the B (hydrophobic) monomers. With time, a polymer moves from the *cis* side to the *trans* through the pore. However, there are runs where a polymer is trapped into the pore for larger values of f_B, because the B monomers aggregate on the pore or *cis* side and block the pore. In Fig. 1(b), the B monomers are distributed in both *trans* and *cis* regions. In Figs. 2(b) and 3(b), some of the B monomers are incorporated into the pore and the A block has an expanded conformation in the solution. The entropic force arising from chain connectivity is reduced due to the attractive interaction between B monomers. This entropy reduction can lead to the "insertion" of a polymer into a membrane, which can be controlled by the number of hydrophobic monomers and the chemical structure of a polymer as shown in Fig. 4. We examine the fractions of polymer segments on the *cis*, *trans*, and pore regions as a function of time. The simulation data presented in this paper reflect a statistical average over $M=1000$ repetitions of the translocation with 10^5 Monte Carlo steps.

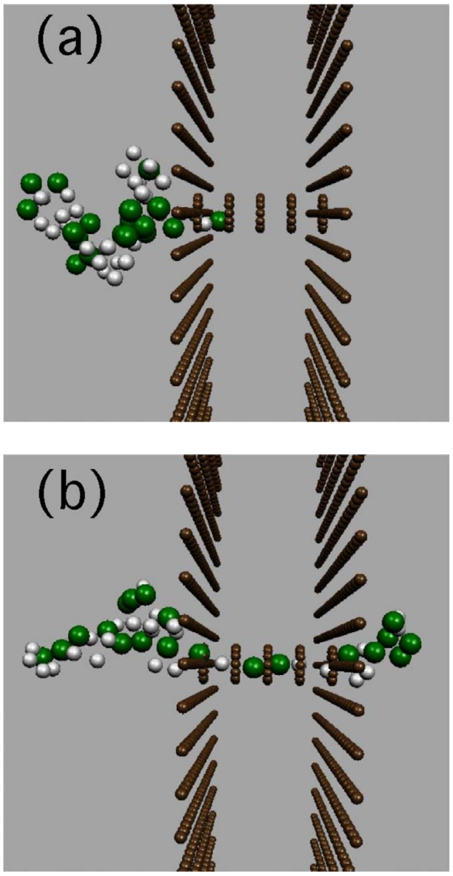

FIG. 1. (Color online) Snapshots of the random copolymer with $N=50$ and $f_B=0.4$ at the early (a) and late (b) stages of a translocation run.

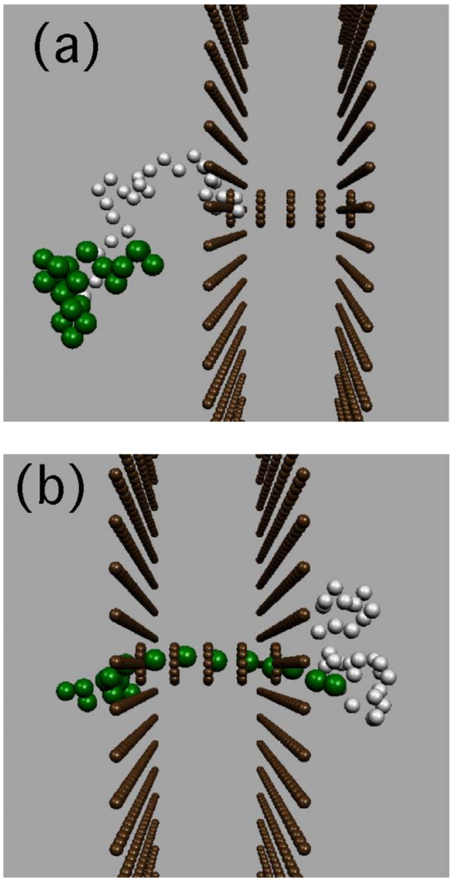

FIG. 2. (Color online) Snapshots of the *AB* block copolymer with $N=50$ and $f_B=0.4$ at the early (a) and late (b) stages of a translocation run. The *A* monomer is the top and moves to the *trans* side.

III. SIMULATION RESULTS

In order to examine the translocation of amphiphilic polymers, we show some results of our simulations.

Figure 4 shows the fraction of monomers on the *cis* (f_{cis}: triangles), *trans* (f_{trans}: solid circles), and pore (f_{pore}: open circles) regions plotted against the monomer fraction f_B for the random copolymer (a), *AB* (b), and *BA* (c) block copolymers with $N=50$. When $f_B=0$, corresponding to that all the monomers consist of hydrophilic monomers, the chain translocates from the *cis* to *trans* region and we then have $f_{trans}=1$. On increasing f_B, we find "translocation to insertion" threshold f_B^* during our simulations. The value of f_B^* is about 0.4 for the random and 0.12 for the *AB* and *BA* block copolymers. When $f_B>f_B^*$, the fraction f_{trans} (f_{cis}) decreases (increases) with increasing f_B due to the aggregation of *B* monomers. At large f_B, many monomers remain on the *cis* and pore regions. When $f_B=1$, corresponding to the case that all the monomers consist of hydrophobic monomers, the polymer is incorporated into the pore with $f_{trans}\simeq 0.12$, $f_{cis}\simeq 0.64$, and $f_{pore}\simeq 0.24$. As shown in Figs. 4(b) and 4(c), the value f_{trans} of the *AB* block copolymer is larger than that of the *BA*. In the case of *BA*, many monomers remain on the *cis* and pore regions [see Fig. 3(b)] because the *B* chain is collapsed due to the attractive interaction between *B* monomers and blocks the pore [32].

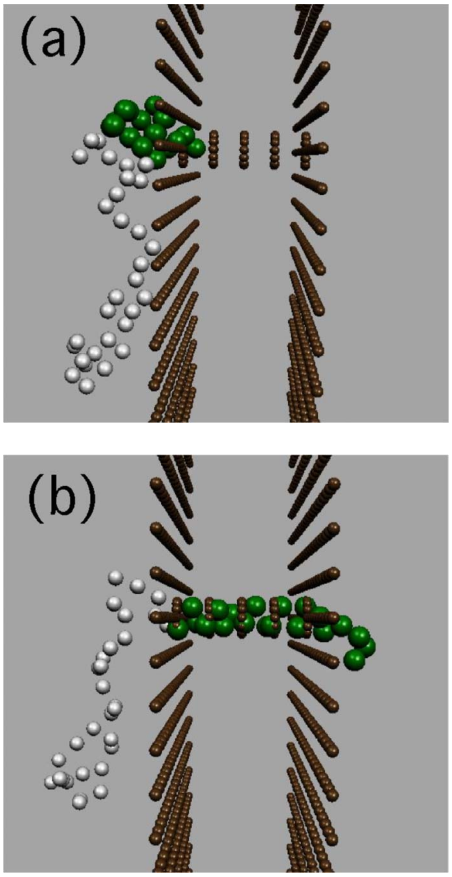

FIG. 3. (Color online) Snapshots of the *BA* block copolymer with $N=50$ and $f_B=0.4$ at the early (a) and late (b) stages of a translocation run. The *B* monomer is the top and moves to the *trans* side.

Figure 5 shows the fraction C_{trans} of the polymers, which are translocated to the *trans* side among $M=1000$ sampling polymers, as a function of f_B for the random (a), *AB* (b), and *BA* (c) copolymers. The number N is changed from 10 to 200. When $f_B<f_B^*$, we have $C_{trans}=1$, which means that all the sampling polymers translocate to the *trans* side. On increasing f_B, the value of C_{trans} decreases above f_B^*. As shown

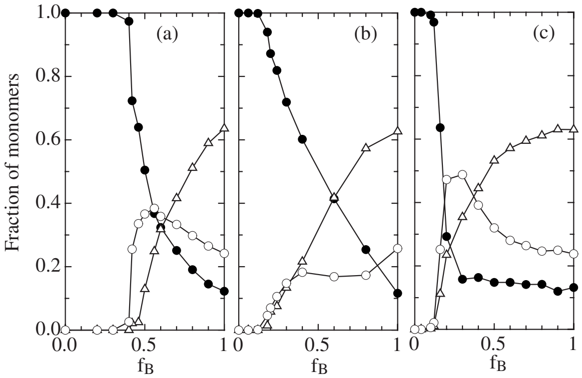

FIG. 4. Fraction of monomers on the *cis* (f_{cis}: triangles), *trans* (f_{trans}: solid circles), and pore regions (f_{pore}: open circles) as a function of the monomer fraction f_B for the random (a), *AB* (b), and *BA* (c) block copolymers with $N=50$.

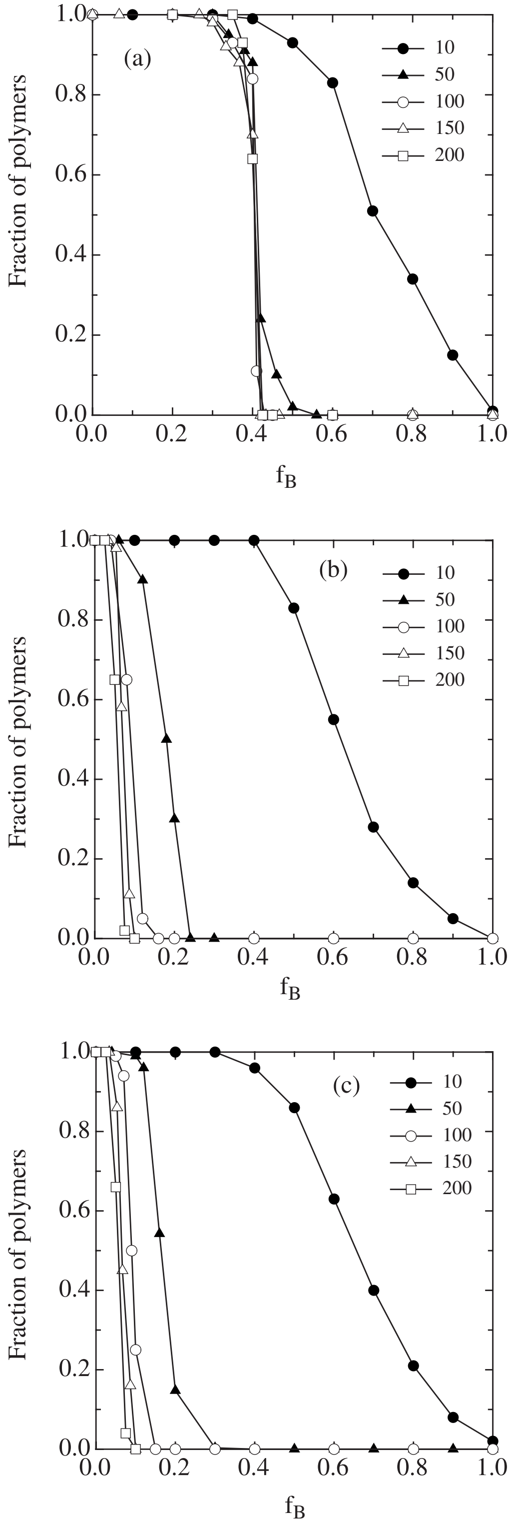

FIG. 5. Fraction C_{trans} of the polymers, translocated to the *trans* side among $M=1000$ sampling polymers, as a function of f_B for the random (a), *AB* (b), and *BA* (c) copolymers. The number *N* is changed from 10 to 200.

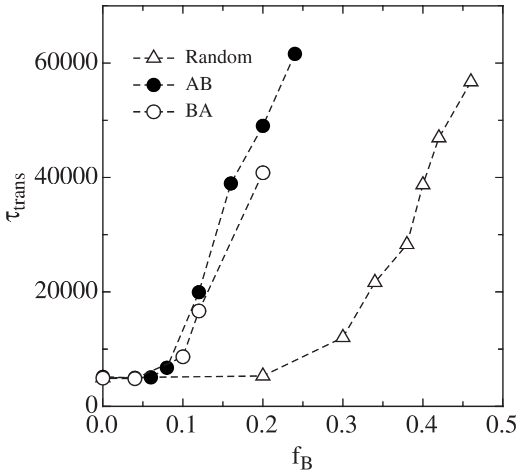

FIG. 6. Translocation time (τ_{trans}) of the random (triangles), *AB* (solid circles), and *BA* (open circles) block copolymers plotted against f_B with $N=50$.

in Fig. 5(a), for long random copolymers, the value of f_B^* does not depend on *N* because it needs *B* monomers, proportional to *N*, to create a globular polymer and block the pore. When $f_B \gtrsim 0.58$, all the random copolymers of large *N* are incorporated into the membrane during our Monte Carlo steps. On the other hand, for block copolymers, the value of f_B^* decreases with increasing *N*. There is the "translocation to insertion" threshold N_B^* in the "number" of hydrophobic monomers on a block copolymer. It is about $N_B^* \simeq 7$ for $\epsilon_{BB}/k_BT=5$. This critical number of hydrophobic monomers almost does not depend on the number *N* because if seven *B* monomers create a globule of the *B* block, the aggregate blocks the pore. The number N_B^* of the hydrophobic monomers is also important to understand the translocation of block copolymers.

Figure 6 shows the translocation time (τ_{trans}) from the *cis* to *trans* side for the random (triangles), *AB* (solid circles), and *BA* (open circles) block copolymers with $N=50$. We have discarded the chains, which do not pass the pore, from the sampling. For smaller values of f_B, the translocation time is independent of f_B and of the chemical architecture of the chain. On increasing f_B, the translocation time exponentially increases. The random copolymers escape faster to the *trans* side than the block copolymers at a fixed f_B because the aggregate of *B* monomers on the random copolymer can be broken easier than that on the block copolymer. The translocation time of the *AB* block copolymer is slower than that of *BA*. We then find $\tau_{trans,random} < \tau_{trans,BA} < \tau_{trans,AB}$. The ratio of two translocation times is given by $r \equiv \tau_{trans,AB}/\tau_{trans,BA} = 1.2$ at $f_B=0.2$. This can be understood by the following: in the case of the *AB*, if the *A* block moves to the *trans* side, the *B* block caps the pore [see Fig. 2(b)]. Then it takes a time to break the aggregate of *B* monomers. On the other hand, in the case of *BA*, if the *B* block moves to the *trans* side, the *A* block can go through without energetically unfavorable situations. As a result we have $r>1$. Similar behaviors have been recently analyzed by Kotsev and Kolomeisky [28], where they study the translocation of polymers consisting of double-stranded and single-stranded blocks. Since only the single-stranded chain can go through a nanopore, the double-stranded segment has to unzip before the translocation. If the first translocated block is the single-stranded one, there is a lot of backward motion which is energetically favored.

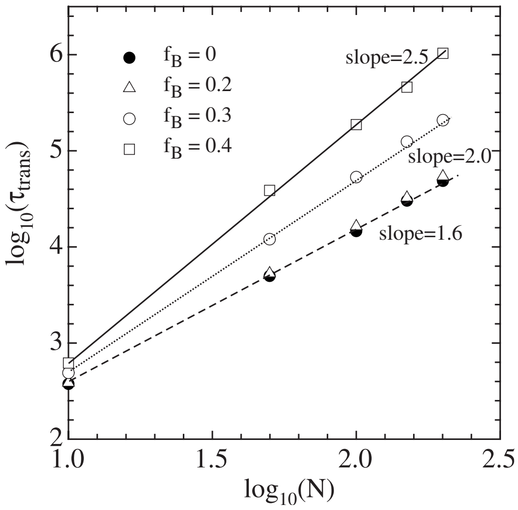

FIG. 7. Translocation time plotted against the number N of monomers for random copolymers. The value of f_B is changed. See the text for the details.

Figure 7 shows the translocation time plotted against the number N of monomers for random copolymers (note the $\log_{10}$-$\log_{10}$ plot). The fraction f_B of the hydrophobic monomers on the chain is changed in $f_B < f_B^*$. The dashed line corresponds to a slope 1.6, the dotted line shows a slope 2, and the solid line shows a slope 2.5. We find that the translocation time can be scaled as $\tau_{trans} \propto N^\alpha$ and the power law α increases with increasing f_B. It is given by $\alpha = 1.6$ for small f_B (=0,0.2), $\alpha = 2$ for f_B (=0.3), and $\alpha = 2.5$ for large f_B (=0.4) [33]. When the fraction of the hydrophobic monomers is small ($f_B \ll f_B^*$), the polymer behaves as a homopolymer in a solvent condition [13,14,21,34]. The aggregation of the hydrophobic monomers on the *cis* and pore regions strongly affects the translocation processes. Although the results of block copolymers do not show in this figure, we have the same scaling law in the translocation region $f_B < f_B^*$ for the *AB* and *BA* block copolymers.

Finally we discuss the dependence of the translocation on the applied force k in Eq. (3). Figure 8 shows the translocation time of a homopolymer with $f_B = 0$ plotted against the applied force k. The value of the vertical axis is divided by a constant. The number N of monomers is changed from 20 to 200. On increasing k, the translocation time decreases in the weak force region and becomes almost a constant in the strong force region of $k > 10 k_B T$. In this paper we have fixed $k = 10 k_B T$. It means that the results of our simulation correspond to a limit of a strong applied force. Then the dependence of the power law α and the threshold f_B^* on the applied force k will be weak in this strong-force region. In the weak-force region, however, it may depend on k. In order to have more precise descriptions between the two regions, we hope to report on the dependence of the translocation phenomena on k, the thickness D, and the diameter L of a pore in the future. The dependence of the translocation on temperature is also important, where the coil-globule collapse of the hydrophobic part of the chain can be controlled by the temperature.

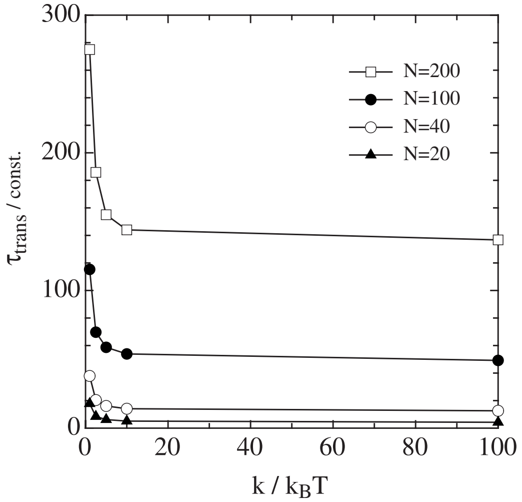

FIG. 8. Translocation time of a homopolymer with $f_B = 0$ plotted against the applied force k in Eq. (3). The number N of monomers is changed from 20 to 200.

IV. SUMMARY

We have studied translocation of amphiphilic polymers, consisting of hydrophilic and hydrophobic monomers, threading a pore by using a three-dimensional dynamic Monte Carlo simulation. We have considered translocation of random, *AB*, and *BA* block copolymers and found that there is a "translocation-insertion" threshold f_B^* in the fraction of hydrophobic monomers on an amphiphilic polymer. The amphiphilic polymers with $f_B > f_B^*$ are incorporated into a pore. The value of f_B^* for random copolymers is larger than that for block copolymers. In the translocation region of $f_B < f_B^*$, the translocation time can be scaled as $\tau_{trans} \propto N^\alpha$ and the value of α increases with increasing f_B. We hope that these results encourage further experimental and analytical studies of polymer translocation. Our coarse-grained amphiphilic polymer model can be applied to modeling of membrane proteins, hydrophobic matching of *ABA* copolymers, and specific interactions between an amphiphilic polymer and a pore, etc.

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