Translocation of closed polymers through a nanopore under an applied external field*

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The dynamic behaviours of the translocations of closed circular polymers and closed knotted polymers through a nanopore, under the driving of an applied field, are studied by three-dimensional Langevin dynamics simulations. The power-law scaling of the translocation time τ with the chain length N and the distribution of translocation time are investigated separately. For closed circular polymers, a crossover scaling of translocation time with chain length is found to be $\tau \sim N^{\alpha}$, with the exponent α varying from $\alpha = 0.71$ for relatively short chains to $\alpha = 1.29$ for longer chains under driving force $F = 5$. The scaling behaviour for longer chains is in good agreement with experimental results, in which the exponent $\alpha = 1.27$ for the translocation of double-strand DNA. The distribution of translocation time $D(\tau)$ is close to a Gaussian function for duration time $\tau < \tau_{\rm p}$ and follows a falling exponential function for duration time $\tau > \tau_{\rm p}$. For closed knotted polymers, the scaling exponent α is 1.27 for small field force ($F = 5$) and 1.38 for large field force ($F = 10$). The distribution of translocation time $D(\tau)$ remarkably features two peaks appearing in the case of large driving force. The interesting result of multiple peaks can conduce to the understanding of the influence of the number of strands of polymers in the pore at the same time on translocation dynamic process and scaling property.

Keywords: Langevin dynamics, closed polymer, scaling behaviour, distribution of translocation time
PACC: 8120S, 8200

1. Introduction

The translocation of polymer molecules across nanopores is an important process in biology, such as DNA and RNA translocation across nuclear pores, protein transport through membrane channels, and virus injection into cells. Theoretical and experimental studies of this process have attracted considerable attention. Among most fundamental quantities associated with translocation,[1] the average translocation time τ as a function of the chain length N is an important measure of the underlying dynamics. For driven translocation, Luo *et al.*[2] found crossover scaling laws $\tau \sim N^{2\nu}$ for relatively short chains and $\tau \sim N^{1+\nu}$ for longer chains, where ν is the Flory exponent and $\nu = 0.588$ in the three-dimensional (3D) case and $\nu = 0.75$ in the two-dimensional (2D) case. Kasianowicz *et al.*[3] demonstrated that an electric field could drive single-stranded DNA and RNA molecules through the water-filled α-hemolysin channel. Because the diameter of the α-hemolysin channel is too narrow to allow double-stranded DNA and other closed circular polymers to pass through, only single-stranded DNA and RNA molecules can go through these protein channels. Recently, solid-state nanopores have been used in similar experiments.[4−6] Artificial solid-state nanopores present a number of potential advantages over protein pores,[7] such as controlled pore size and stability for wide ranges of voltages, temperatures, pH, and concentrations of different chemical compounds.

More recently, due to the tremendous advantages of artificial solid-state nanopores, a number of experimental[5,6] and theoretical[1,7−9] studies were devoted to the translocation of ds-DNA or folded DNA. Storm *et al.* carried out a set of experiments on translocations of circular DNA,[8] and double-stranded DNA,[6] and they found a striking power-law scaling of $\tau \sim N^{1.27}$ for double-strand DNA. Circular molecules are expected to look identical to molecules folded exactly halfway. These circular molecules can pass only the pore in a folded state, where passage starts not at one of the ends of the molecule but somewhere in between.[5] It should be noted that λ-DNA has single-strand 'sticky ends' at both ends and that these ends can bind to form circular DNA.[5]

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In the present paper, we investigate the translocations of closed circular polymers and their knotted polymers by using Langevin dynamics. For closed circular polymers, the scaling behaviour is different from that of linear polymers. A knot in a closed polymer is any closed circular path embedded in 3D space.[10] There will be two strands of polymer in the pore at the same time after any leading passage of polymer has entered a nanopore for a closed circular DNA and two or four strands for a closed knotted polymer.

2. Simulation model

In our numerical simulations, the polymer chains are modelled as bead-spring chains of Lennard–Jones (LJ) particles with a finite extension nonlinear elastic (FENE) potential. A short range repulsive LJ potential exists between all beads, leading to the exclusion of volume interaction and van der Waals interactions, and it is given as

$$U_{\rm LJ}(r) = \begin{cases} 4\varepsilon[(\sigma/r)^{12} - (\sigma/r)^6] + \varepsilon, & r \le 2^{1/6}\sigma, \\ 0, & r > 2^{1/6}\sigma, \end{cases} \quad (1)$$

where r is the distance between the two beads, σ is the diameter of a bead, and ε is the depth of the potential. Neighbouring beads are connected by the finite extension nonlinear elastic (FENE) potential

$$U_{\rm FENE}(r) = -\frac{1}{2}kR_0^2 \ln(1 - (r/R_0)^2), \quad (2)$$

where r is the distance between consecutive monomers, k is the spring constant, and R_0 is the maximum allowed separation between connected monomers. Both ends of open polymer can be connected by the FENE potential, and then these ends can be bound to form a closed circular polymer or its knotted configuration.

As shown in Fig. 1, the wall is rigid and impermeable from which dynamic polymer beads are excluded, extending infinitely in the x and the y directions and ending at coordinate $z = 0$.[11] A cylindrical pore of length L and width D in the centre of the wall connects the cis and the trans sides, and a voltage is applied across the pore to drive the negatively charged DNA through the pore.[12] Between all bead-wall particle pairs, there exists the same short range repulsive LJ interaction as described above. The inner wall of the pore is lined with stationary beads with the distance σ. The pore–monomer interaction is modelled by the LJ potential with a cutoff of 25σ.[12]

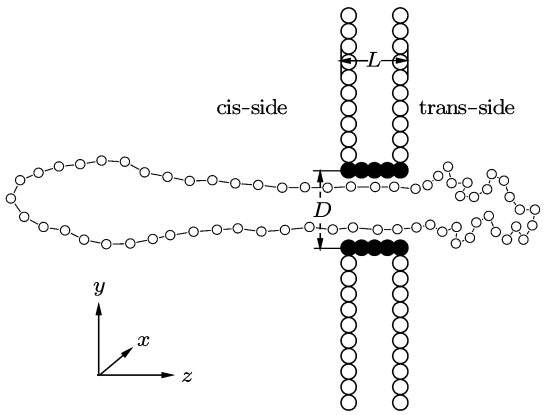


Fig. 1. Schematic representation of closed polymer moving through a cylindrical nanopore in three dimensions. Here the cylindrical nanopore length $L = 5$.

In the Langevin dynamics method, each bead is subjected to conservative, frictional, and random forces, and the equation of motion is[13]

$$m\ddot{\boldsymbol{r}}_{\rm i} = -\nabla(U_{\rm LJ}+U_{\rm FENE}) + \boldsymbol{F}_{\rm ext} - \xi\boldsymbol{v}_{\rm i} + \boldsymbol{F}_{\rm i}^{\rm R}, \quad (3)$$

where m is the bead mass, ξ is the friction coefficient, $\boldsymbol{v}_{\rm i}$ is the bead velocity, and $\boldsymbol{F}_{\rm i}^{\rm R}$ is the random force which satisfies the fluctuation-dissipation theorem,[13]

$$\langle F_i(t) \cdot F_j(t')\rangle = 6k_{\rm B}T\delta_{ij}\delta(t - t'). \quad (4)$$

The collision between particles is considered, and the effect of collision is described by $\boldsymbol{F}_{\rm i}^{\rm R}$. The external force due to the applied voltage is represented by $\boldsymbol{F}_{\rm ext} = F\hat{\boldsymbol{z}}$.

In the present work, we assume that all the particles have identical mass m, diameter σ, and LJ interaction strength ε, which fix the mass, length, and system energy units, respectively, thereby obtaining the corresponding time scale $t_{\rm LJ} = (m\sigma^2/\varepsilon)^{1/2}$ and force scale ε/σ.[12] We set $\sigma \sim 1.5$ mm, average mass $m \approx 936$ amu $=1.55426\times10^{-24}$ kg and $k_{\rm B}T = 1.2\varepsilon$, which means the interaction strength ε is 3.39×10^{-21} J at actual temperature 295 K.[12] This leads to a time scale of 32.1 ps and a force scale of 2.3 pN. Based on the aforementioned reduced unit, the parameters in the model are then chosen to be $R_0 = 2$, $k = 7$, $\xi = 0.7$ and $L = 5$.

3. Results and discussion

In the simulations, one of the closed circular polymer monomers is placed in the vicinity of the pore

entrance, while the remaining monomers are under thermal collisions described by the Langevin thermostat to obtain an equilibrium configuration.[12] Once the polymer reaches its equilibrium state, the fixed monomer at the entrance of the pore is released. The translocation time τ is defined as the time duration between the first monomer entering the pore and all monomers leaving the pore over all successful runs.

3.1. Translocation time and scaling behaviour

As shown in Fig.2(a), the average translocation time τ is plotted as a function of the chain length N for closed circular polymers $\tau \sim N^{\alpha}$, and a scaling behaviour is observed at different values of field force F. One of the main features is that a crossover scaling behaviour is observed for both cases. For a small field force ($F = 5$), $\alpha = 0.71 \pm 0.04$ is found for short chains and it crosses over to $\alpha = 1.29 \pm 0.02$ for longer chains. For a larger field force ($F = 10$), $\alpha = 0.76 \pm 0.04$ is found for short chains and it crosses over to $\alpha = 1.36 \pm 0.02$ for longer chains. The scaling exponents of relatively long chains are consistent with the solid-state nanopore experimental result presented by Storm *et al.*[6] who found an exponent of 1.27.

In many biological processes, a voltage across two sides of membrane, specifically, negative on the cis-side of the membrane and positive on the trans-side,[14] produces an electrical field in the nanopore. In the present work, an electrical field is applied only to the nanopore, and therefore only the monomer of the polymer inside the nanopore experiences the driving force.[6] Those monomers of the polymer reaching trans-side are still subjected to the frictional force, but they are out of the range of the electrical force. The velocities of those monomers decrease, then the number of monomers near the exit of the pore increases, resulting in a large effective conformational entropic barrier.[15,16] At the late stages of translocation, the high density of monomers near the exit of the pore slows down the translocation velocity. The density of monomers near the exit of the pore for a long chain is much higher than for a short chain. With N increasing, the density of monomers near the exit of the pore turns high due to slow relaxation of the polymer.[2] The translocation time for long chains increases faster than for short chains with the increase of chain length N, leading to a crossover scaling behaviour.

In order to compare the results between closed circular polymers and linear polymers, we also perform Langevin dynamics simulations on linear polymers. As shown in Fig. 2(b), a remarkable crossover of scaling behaviour is also found. For a small field force ($F = 10$), α is found to be 1.17±0.05, i.e. $\alpha = 1.17 \pm 0.05$, for short chains and it crosses over to $\alpha = 1.46 \pm 0.01$ for longer chains. For a larger field force ($F = 20$), α is found to be 1.16±0.03, i.e. $\alpha = 1.16 \pm 0.03$, for short chains and it crosses over to $\alpha = 1.54 \pm 0.01$ for longer chains. The results are consistent with theoretical scaling predictions,[2,17,18] i.e. $\tau \sim N^{2\nu}$ for short chains and $\tau \sim N^{1+\nu}$ for long chains in the presence of an applied external field, where the Flory exponent $\nu = 0.588$ in three dimensions.

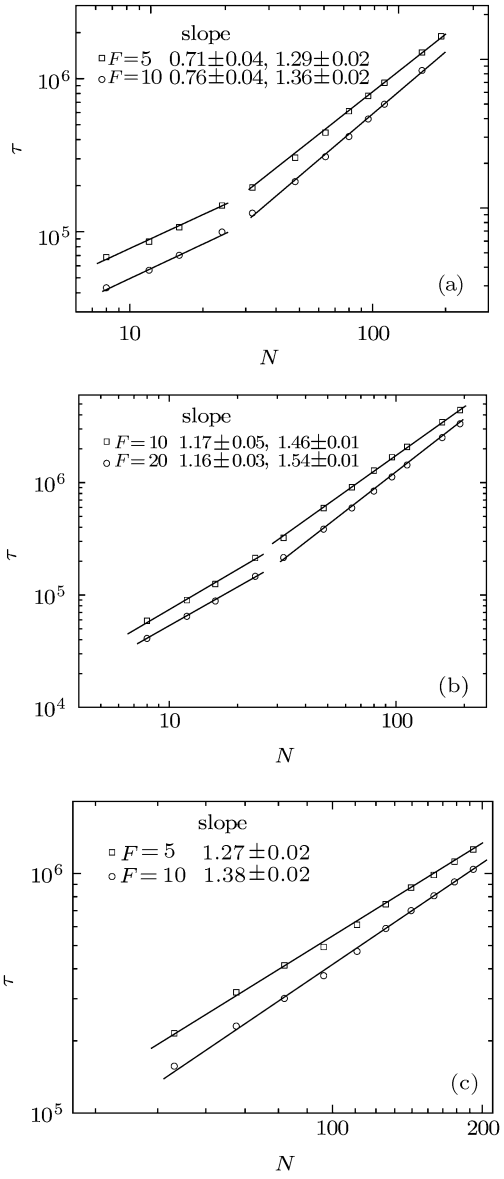


Fig. 2. Average translocation time τ as a function of the chain length N for closed circular polymers (a); linear polymers (b); and closed knotted polymers (c). Here the values of pore width D are 4 (a), 4 (b), and 6 (c).

For closed circular polymers, the scaling exponent is lower than that of linear polymers. Two strands of polymers are in the pore at the same time during the translocation, so the number of monomers in the pore at the same time may be twice as many as that of linear polymers. If the chain length N increases by the same number, the increase in translocation time for closed circular polymers will be smaller than for linear polymers. That is to say, with the increase of length N, the translocation time for closed circular polymers increases more slowly than for linear polymers, leading to a lower scaling exponent.

As mentioned above, for relatively short chains of closed circular polymers, the scaling exponent is 0.71±0.04 under the small field force ($F = 5$), and 0.76±0.04 under the larger field force ($F = 10$), which are much smaller than those of linear polymers. At the late stages of translocation, the density of monomers near the exit of the pore for closed circular polymers is lower than for linear polymers. So the scaling exponent for closed circular polymers is much lower than for linear polymers when polymer chain length is relatively short.

In addition, the translocations of closed knotted polymers are also involved. As shown in Fig. 2(c), there is no clear evidence of a crossover, because the crossovers in the scaling behaviour for closed circular polymers and linear polymers appear at the chain length about $N = 32$, and the length of the shortest closed knotted polymer is 48 in this work. The scaling exponent α is 1.27±0.01 for small field force ($F = 5$) and 1.38±0.01 for large field force ($F = 10$). Thus, we can reasonably conclude that the scaling behaviour depends weakly on a knot for relatively long chains. A knot plays a crucial role in increasing translocation time for a closed polymer translocation through a small pore. The knot in a closed polymer cannot be untied. When the knot is squeezed in a small pore, many available configurations of the polymer will lost due to the geometric constriction. The loss of available configurations of the polymer will result in a large effective entropic barrier.

3.2. Translocation time distribution

The translocation behaviour is characterized by the distribution of translocation time $D(\tau)$. Curves for $D(\tau)$ are plotted in Fig. 3 for closed circular polymers under the values of driving force $F = 3$, 5, and 10, respectively. $D(\tau)$ exhibits only one peak, defined as $\tau_{\rm p}$,[18] which decreases fast with the increase of the driving force. $D(\tau)$ is close to a Gaussian function for duration time shorter than $\tau_{\rm p}$ and follows a falling exponential function for duration time longer than $\tau_{\rm p}$. David *et al.* theoretically deduced the expression of translocation time distribution.[19] The theoretical result indicates that this distribution deviates to some extent from a Gaussian distribution and may be considerably skewed.[20] This distribution is close to a Gaussian function and increases faster than the Gaussian for duration time shorter than $\tau_{\rm p}$, and it changes into a falling exponential function with a long tail for duration time longer than $\tau_{\rm p}$. Experimental[3,21–23] and numerical[18] studies show similar results. The stronger the driving force is, the narrower the distribution of translocation time will be. With the increase of the driving force, the length of the tail becomes shorter and shorter. As shown in Fig. 4, the shape of $D(\tau)$ for closed circular polymer is similar to that

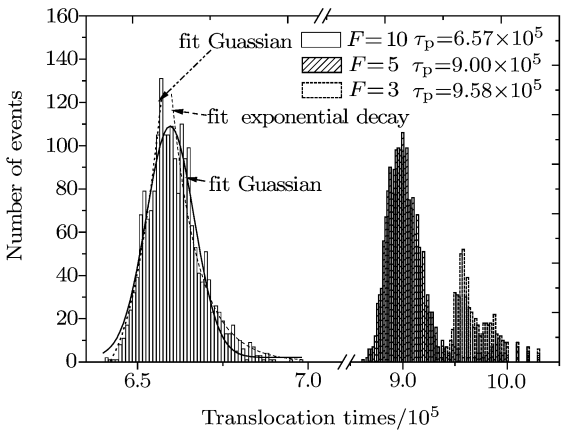


Fig. 3. Translocation time distribution for closed circular polymer with different driving forces. Here $N = 112$ and $D = 5$.

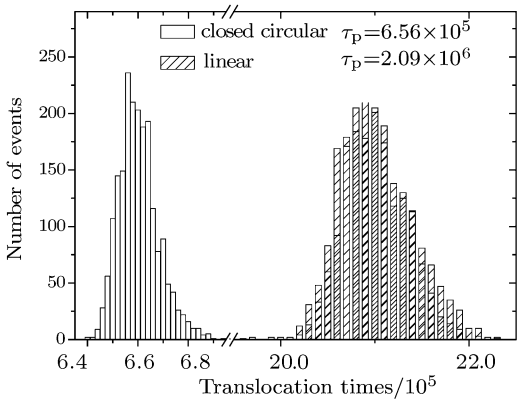


Fig. 4. Translocation time distributions for closed circular polymer and linear polymer with the driving force $F = 10$. Here $N = 112$, and the pore width $D = 3$ for linear polymers and $D = 5$ for closed circular polymers.

of linear polymer. Each monomer of a closed circular polymer plays an equal role in translocation time distribution; so does that of a linear polymer.

As shown in Fig. 5, the distribution of translocation time of closed knotted polymers has a qualitatively different shape compared with that of closed circular polymers. One of the main features is that the double-peak begins to appear. With the driving force F increasing from 5 to 20, see Fig. 5, the sub-peak, appearing with a duration time shorter than main $\tau_{\rm p}$, first increases and reaches a maximum, and then decreases until disappearance. For a weak driving force, the translocation velocity is low, and then the knot is relaxed under the translocation process. For a strong driving force, the knot is compacted, and then the number of monomers in the knot decreases. So the sub-peak is not obvious when the driving force is too weak or too strong.

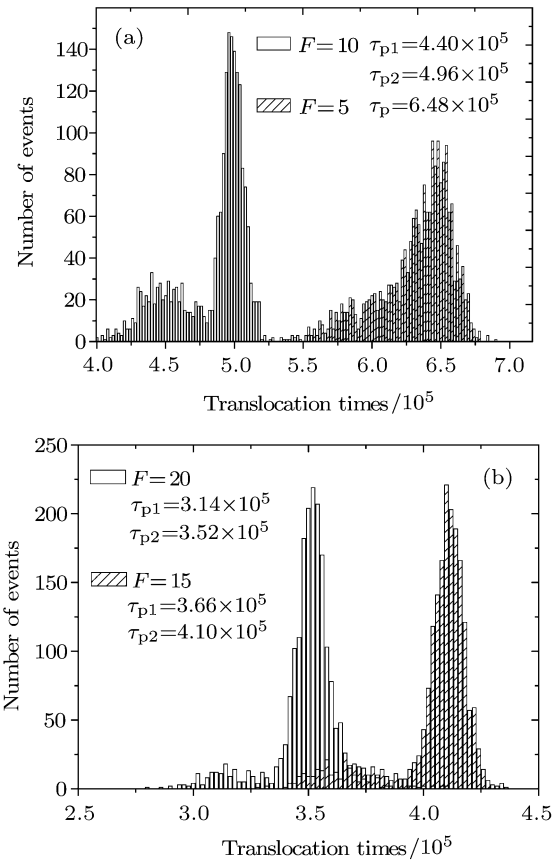


Fig. 5. Translocation time distributions for closed knotted polymer with different values of driving force F = 5, 10 (a), and F = 15, 20 (b), respectively. Here N = 112, L = 5, and D = 5.

The appearance of a double-peak is attributed to the fact that one peak in the translocation time distribution corresponds to the behaviour of four strands of polymer in the pore at the same time and the other corresponds to the behaviour of two strands of polymer in the pore at the same time. To test this idea, we perform the simulations on single polymer translocation through a nanopore with folded configurations. To describe the part of the polymer in the folded state, we introduce a parameter f ($0 \leq f \leq 0.5$) that determines the folded rate, and then the number of monomers in the folded state is $2fN$.[7] When $f = 0$, the linear unfolded polymer moves across the pore (corresponding to linear polymer in this work), while for $f = 0.5$, the whole polymer is in the folded state (folding in the middle of the polymer, and corresponding to closed circular polymer in this work). For folded polymers, $D(\tau)$ is

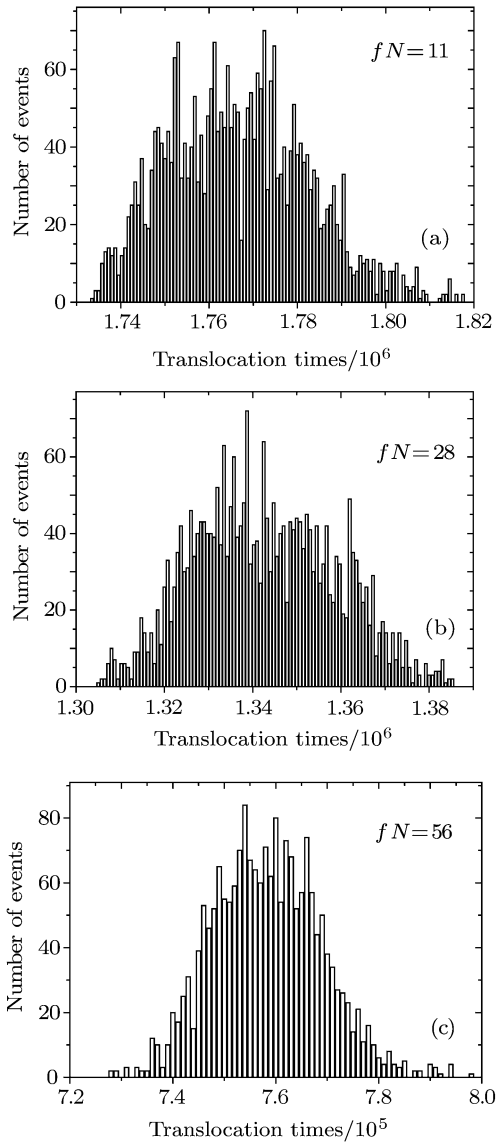


Fig. 6. Translocation time distributions for linear folded polymer under driving force F = 10 for fN = 11 (a), 28 (b), and 56 (c). Here N = 112, L = 5, and D = 5.

plotted in Fig. 6. A strong non-Gaussian character can be seen in Figs. 6(a) and 6(b), corresponding to $fN = 11$ and 28, respectively. A very important feature of $D(\tau)$ for $fN = 56$ is that its shape is close to the translocation time distribution for closed circular polymer, shown in Fig. 6(c). There is clear evidence of one-peak for $fN = 56$ and multiple-peak for other cases. A non-single peak distribution of translocation time can distinguish a dissymmetrical-folded polymer from a linear polymer or a symmetrical-folded polymer in DNA-mixture translocation experiments, such as the experiment performed by Storm *et al.*[8]

The folded configuration on polymer contributes to one or two strands of polymer in the pore at the same time. The translocation velocities of the monomers in the folded state differ from the monomers in the linear state because of different numbers of monomers under the driving force and different interactions between the polymer monomers and the pore.[7] For a folded polymer, if the distribution of translocation time for the folded segment translocation through the pore alone deviates from that for the linear segment translocation through the pore alone, the distribution of total translocation time for the whole folded polymer may present non-single peak behaviour.

A knot in a closed polymer leads to more than two strands of polymer under the driving force in the pore at the same time. The translocation velocities of the monomers in knot differ from other monomers beyond the knot because of different numbers of monomers under the driving force and different interactions between the polymer monomers and the pore. For the same reason as for the folded polymer, the distribution of total translocation time for the whole closed knotted polymer may present non-single peak behaviour, which can be regarded as the general effect of the behaviour for the knotted segments and that for the non-knotted segments.

4. Conclusions

In the present paper, we perform a three-dimensional Langevin dynamics simulation to investigate the translocations of closed circular polymers, linear polymers and closed knotted polymers under an external driving force. There appear clear crossovers on translocation time scaling for closed circular polymers and linear polymers, respectively. For closed circular polymers, the scaling exponent is lower than that of linear polymers, and the scaling exponent for relatively long chains is in good agreement with recent experimental results. For linear polymers, the scaling behaviour accords well with the theoretical prediction of a crossover scaling, i.e. $\tau \sim N^{2\nu}$ for relatively short chains and $\tau \sim N^{1+\nu}$ for longer chains. The scaling exponent α of closed knotted polymers is close to that of closed circular polymers. The knot has only a marginal effect on the scaling law for relatively long closed polymers.

For both closed circular polymers and linear polymers, the distributions of translocation time $D(\tau)$ are close to a Gaussian function for duration time shorter than $\tau_{\rm p}$ and follow a falling exponential function for duration time longer than $\tau_{\rm p}$, which is in good agreement with theoretical,[19] experimental[3,21−23] and numerical[18] results. An interesting phenomenon of double peaks is found in the translocation time distribution for closed knotted polymers, which results from different numbers of strands of polymer in the pore at the same time throughout the translocation process. That is to say, the different important roles of monomers played in a closed knotted polymer or a folded polymer lead to the appearance of a non-single peak in the translocation time distribution. These results can give an understanding of the complex transport processes of non-linear polymers.

References

[1] Luo K F, Ollila S T T, Huopaniemi I, Nissila T A, Pomorski P, Karttunen M, Ying S C and Bhattacharya A 2008 *Phys. Rev.* E **78** 050901

[2] Luo K F, Huopaniemi I, Nissila T A and Ying S C 2006 *J. Chem. Phys.* **124** 114704

[3] Kasianowicz J J, Brandin E, Branton D and Deamer D W 1996 *Proc. Natl. Acad. Sci. USA* **93** 13770

[4] Li J L, Stein D, McMullan C, Branton D, Aziz M J and Golovchenko J A 2001 *Nature* (London) **412** 166

[5] Li J L, Gershow M, Stein D, Brandin E and Golovchenko J A 2003 *Nat. Mater.* **2** 611

[6] Storm A J, Storm C, Chen J, Zandbergen H, Joanny J F and Dekker C 2005 *Nano. Lett.* **5** 1193

[7] Kotsev S and Kolomeiskya A B 2007 *J. Chem. Phys.* **127** 185103

[8] Storm A J, Chen J H, Zandbergen H W and Dekker C 2005 *Phys. Rev.* E **71** 051903

[9] Izmitli A, Schwartz D C, Graham M D and de Pablo J J 2008 *J. Chem. Phys.* **128** 085102
[10] Mansfield M L 2007 *J. Chem. Phys.* **127** 244901
[11] Forrey C and Muthukumar M 2007 *J. Chem. Phys.* **127** 015102
[12] Luo K F, Nissila T A, Ying S C and Bhattacharya A 2008 *Phys. Rev. Lett.* **100** 058101
[13] Allen M P and Tildesley D J 1989 *Computer Simulation of Liquids* (New York: Oxford University Press) p259
[14] Meller A 2003 *J. Phys.: Condens. Matter* **15** R581
[15] Xie Y J, Shi Q W, Wang X P, Zhu P P, Yang H Y and Zhang X Y 2004 *Acta Phys. Sin.* **53** 2796 (in Chinese)
[16] Ding K J, Cai D Q, Zhan F R, Wu L J, Wu Y J and Yu Z L 2006 *Chin. Phys.* **15** 940
[17] Luo K F, Nissila T A, Ying S C and Bhattacharya A 2007 *Phys. Rev. Lett.* **99** 148102
[18] Kong C Y and Muthukumar M 2002 *Electrophoresis* **23** 2697
[19] David K L and David R N 1999 *Biophys. J.* **77** 1824
[20] Cacciuto A and Luijten E 2006 *Phys. Rev. Lett.* **96** 238104
[21] Meller A, Nivon L, Brandin E, Golovchenko J A and Branton D 2000 *Proc. Natl. Acad. Sci.* USA **97** 1079
[22] Meller A, Nivon L and Branton D 2001 *Phys. Rev. Lett.* **86** 3435
[23] Chen P, Gu J J, Brandin E, Kim Y R, Wang Q and Branton D 2004 *Nano. Lett.* **4** 2293