PHYSICAL REVIEW E VOLUME 57, NUMBER 1 JANUARY 1998

Polymer release out of a spherical vesicle through a pore

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(Received 16 June 1997)

Translocation of a polymer out of a curved surface or membrane is studied via the mean first passage time approach. Membrane curvature gives rise to a constraint on polymer conformation, which effectively drives the polymer to the outside of confinement, where the available volume of the polymer conformational fluctuation is larger. Considering a polymer release out of a spherical vesicle, the polymer translocation time τ is changed to the scaling behavior $\tau \sim L^2$ for $R < R_G$, from $\tau \sim L^3$ for $R \gg R_G$, where L is the polymer contour length, and R and R_G are the vesicle radius and polymer radius of gyration, respectively. Also, the polymer capture into a spherical bud is studied, and a possible apparatus for easy capture is suggested. [S1063-651X(97)08012-4]

PACS number(s): 36.20.Ey, 83.10.Nn, 05.40.+j

I. INTRODUCTION

Membrane and polymer flexibility is the major intrinsic physical property of biological organisms. A typical value of the biomembrane bending rigidity κ is of the order of $1 \sim 100 k_B T$, which determines membrane persistence length $\xi \simeq a \exp(4\pi\kappa/3k_B T)$, where a is the molecular length scale. Below the length scale ξ, which is usually much larger than molecular scales, the membrane can be regarded as flat, although there exist small-scale thermal undulations.

Consider a polymer interacting with a curved surface or membrane with a fixed radius of curvature R. The effective interaction between the polymer and membrane is significantly modified due to the curvature. For instance, the adsorption-desorption transition of a polymer on a curved surface is known to occur at a lower transition temperature [1]. This is because the entropy of a polymer increases near a convex surface, compared with that near a planar surface. In this case, the criteria that determines the importance of membrane curvature are given by $R \lesssim R_G$, where R_G is the radius of gyration of the polymer.

In this paper we examine the dynamics of polymer translocation out of a spherical vesicle, as shown in Fig. 1 within the context of ideal chain theory. To highlight the curvature effect, we neglect the effect of the small-scale fluctuation of the membrane. We take into account only the steric interaction between the polymer and membrane, from which we derive the entropic free-energy barrier of polymer translocation through a curved membrane. For the translocation dynamics, we use our previous model [2] in terms of the Fokker-Planck equation, where a mean first passage time is obtained as a measure of polymer translocation time. As results of our study, we present the effects of the chain length and membrane geometry on translocation time. Two specific examples of different membrane geometries are considered to exemplify the curvature effect on translocation dynamics. The first one is a release of a polymer out of a spherical vesicle, and the second one is a polymer translocation crossing two joined vesicles through a small bottleneck. The main results of this paper are the following: (1) Membrane curvature drives the polymer out of a spherical vesicle due to polymer entropy effect. (2) Polymer capture into a small bud takes very long time proportional to exp(L), which can be reduced to L^3 and further to L^2 (L is the polymer contour length) if there is segmentwise energetic bias larger than critical values. The problem we consider here has some relevance to drug delivery as well as biological processes such as endocytosis or extocytosis by which a vesicle containing certain macromolecular entities is incorporated to the inside or outside cell [3].

In Sec. II, the equilibrium conformation and entropic free energy of a translocating polymer are determined as a function of membrane curvature. The dynamics of a polymer translocation is examined, and the mean first passage time is calculated in Sec. III. In Sec. IV, a summary and conclusion are given.

II. FREE ENERGY FUNCTION OF POLYMER RELEASE OUT OF A SPHERE

Suppose there is a polymer located either inside or outside of a sphere. The polymer inside is confined in a sphere of radius R, and the outside one is excluded by the same sphere. We consider an ideal flexible polymer, which is composed of n segments with Kuhn length b either inside or outside a sphere, whose one end position is fixed at $\mathbf{r}_0 = (r_0, \theta_0, \phi_0)$ in spherical coordinates. Then the Green's function of this

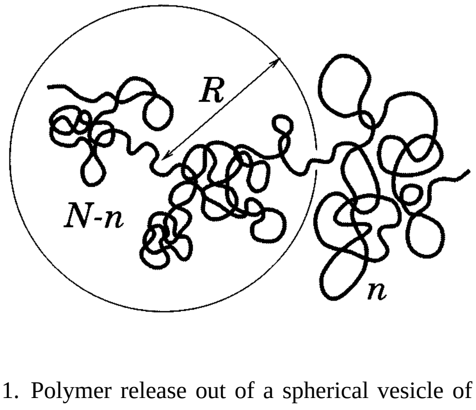

FIG. 1. Polymer release out of a spherical vesicle of radius R. The translocating polymer can be identified with two end anchored polymers composed of n and $N-n$ segments outside and inside of the vesicle, respectively.

polymer satisfies Edwards' equation [4]

$$\left[\frac{\partial}{\partial n}-\frac{b^2}{6}\nabla^2\right]G^{\pm}(\mathbf{r}|\mathbf{r}_0;n)=\delta^{(3)}(\mathbf{r}-\mathbf{r}_0)\,\delta(n), \tag{1}$$

where $\mathbf{r}=(r,\theta,\phi)$, and $G^{\pm}(\mathbf{r}|\mathbf{r}_0;n)$ denotes the Green's function for the polymer inside and outside the sphere, respectively. The impenetrability condition due to the sphere can be represented by the boundary conditions

$$G^{\pm}(\mathbf{r}|\mathbf{r}_0;n)=0 \quad \text{at } r=R. \tag{2}$$

Then the partition functions of polymers of n segments located at the inner and outer space of a sphere are given by

$$Z_n^{\pm}(\mathbf{r}_0)=\int_{\Omega_\pm}dr\int_0^{\pi}d\theta\,\sin\theta\int_0^{2\pi}d\phi\;r^2G^{\pm}(\mathbf{r},\mathbf{r}_0;n), \tag{3}$$

where $\Omega_\pm$ represents the radial integration range given by $(0,R)$ and (R,∞) for $Z_n^{\pm}$, respectively. Now that the physics should be invariant under rotation of the coordinate around the origin, $Z_n^{\pm}$ is independent of θ_0 and ϕ_0, and should be a function only of r_0.

Integrating Eq. (1) over θ and ϕ yields the radial equation

$$\left[\frac{\partial}{\partial n}-\frac{b^2}{6}\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}\right]Z_n^{\pm}(r,r_0)=\frac{1}{r^2}\,\delta(r-r_0)\,\delta(n), \tag{4}$$

where $Z_n^{\pm}(r,r_0)$ are the radial Green's functions defined by

$$Z_n^{\pm}(r,r_0)\equiv\int_0^{\pi}d\theta\,\sin\theta\int_0^{2\pi}d\phi\;G^{\pm}(\mathbf{r},\mathbf{r}_0;n). \tag{5}$$

The solution of this radial equation with the boundary conditions in Eq. (2) is then given by [5]

$$Z_n^{+}(r,r_0)=\frac{2}{rr_0R}\sum_{k=1}^{\infty}\exp\left(-\frac{\pi^2b^2n}{6R^2}k^2\right)\times\sin\left(\frac{k\pi r}{R}\right)\sin\left(\frac{k\pi r_0}{R}\right) \tag{6}$$

$$Z_n^{-}(r,r_0)=\frac{1}{rr_0}\left[\frac{3}{2\pi nb^2}\right]^{1/2}\times\left[\exp\left(-\frac{3(r-r_0)^2}{2nb^2}\right)-\exp\left(-\frac{3(r+r_0-2R)^2}{2nb^2}\right)\right]. \tag{7}$$

Using these results, we can finally arrive at the partition function of a polymer whose one end is fixed at radial position r_0 as

$$Z_n^{\pm}(r_0)=\int_{\Omega_\pm}dr\;Z_n^{\pm}(r,r_0). \tag{8}$$

Let us now consider the partition function of a polymer whose one end is anchored on a spherical surface. Introducing a sufficiently small anchorage size ϵ, which is used to define the anchored end position of the polymer as $r_0=R\mp\epsilon$ inside and outside, respectively. Substituting this into the partition function, we have the following explicit expressions for partition functions of end anchored polymers:

$$Z_n^{+}=\left[\frac{2\epsilon}{R}\right]\sum_{k=1}^{\infty}\exp\left(-\frac{\pi^2nb^2}{6R^2}k^2\right), \tag{9}$$

$$Z_n^{-}=\left[\frac{\epsilon}{R}\right]\left[1+2\left(\frac{3R^2}{2\pi nb^2}\right)^{1/2}\right], \tag{10}$$

up to leading order in ϵ. Note that Eqs. (9) and (10) are the statistical weights of polymers anchored on a curved surface relative to that in free space. The relative statistical weight, due only to the curvature effect, can be obtained as follows:

$$\frac{Z_n^{+}(R)}{Z_n^{+}(R/R_G\to\infty)}=1-\left(\frac{\pi}{2}\right)^{1/2}\left(\frac{R_G}{R}\right)+O\left(\frac{R_G}{R}\right)^2, \tag{11}$$

$$\frac{Z_n^{-}(R)}{Z_n^{-}(R/R_G\to\infty)}=1+\left(\frac{\pi}{2}\right)^{1/2}\left(\frac{R_G}{R}\right)+O\left(\frac{R_G}{R}\right)^2, \tag{12}$$

which is identical to the result of Hiergeist and Lipowsky [6] valid in the small curvature limit. Using Eqs. (9) and (10), the free energy of the polymer whose one end anchored on a surface can be obtained as

$$F^{\pm}(n;R)=-k_BT\,\ln Z_n^{\pm} \tag{13}$$

$$=\begin{cases}-k_BT\,\ln\sum_{k=1}^{\infty}\exp\left(-\frac{\pi^2b^2n}{6R^2}k^2\right) & \text{(inside)}\\ -k_BT\,\ln\left[1+\left\{\frac{6R^2}{\pi nb^2}\right\}^{1/2}\right] & \text{(outside)}\end{cases} \tag{14}$$

apart from additive constants. Note that these free energy expressions are valid for all curvature values. In the limit of $R\gg R_G\equiv N^{1/2}b/3$, both inside and outside free energy expressions converge to

$$F^{\pm}(n;R)\approx\frac{k_BT}{2}\ln n+\text{ const}, \tag{15}$$

which is the conformational free energy of a polymer whose one end is anchored on a planar membrane [2].

For the transmembrane chain of N segments with $N-n$ segments inside and with n segments outside (Fig. 1), the free energy function is given by

$$\mathcal{F}(n)=F^{-}(n;R)+F^{+}(N-n;R) \tag{16}$$

$$=-k_BT\ln\left[1+\left(\frac{6R^2}{\pi nb^2}\right)^{1/2}\right]-k_BT\ln\sum_{k=1}^{\infty}\exp\left(-\frac{\pi^2b^2(N-n)}{6R^2}k^2\right). \tag{17}$$

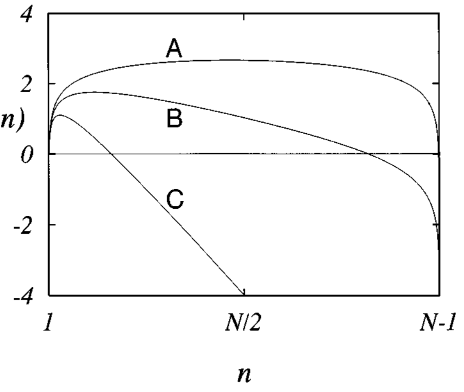

FIG. 2. Free energy function $\mathcal{F}(n)$, in units of k_BT, of polymer release out of a sphere as a function of translocation coordinate n. [$N=1000$; (A) $R=10R_G$, (B) $R=R_G$, and (C) $R=0.5R_G$.]

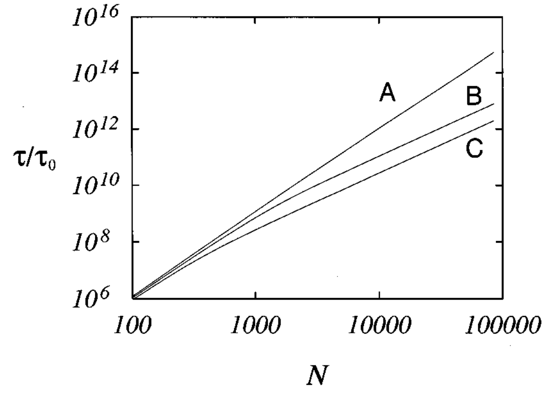

FIG. 3. Time τ for polymer release (translocation) out of a sphere, in units of $\tau_0 \equiv b^2/(2D_0)$, with $D_0 = k_BT/\gamma$, vs chain length N. (A) $R=300b$. (B) $R=30b$. (C) $R=15b$. Crossover from $\tau \sim L^3$ to $\tau \sim L^2$ occurs near the N corresponding to $R=R_G$.

As depicted in Fig. 2 for different values of R, $\mathcal{F}(n)$ exhibits a nearly symmetric barrier like that of the translocation across the planar membrane for $R \gg R_G$. If R becomes comparable to or less than R_G, $\mathcal{F}(n)$ becomes slanted down to the right, which indicate that the polymer release is favorable for $R \lesssim R_G$.

III. DYNAMICS OF POLYMER TRANSLOCATION

As shown in Ref. [2], the translocation of a polymer can be thought of as a one-dimensional diffusion process of translocation coordinate n, defined by the number of polymer segments on the target side, under the effective potential field $\mathcal{F}(n)$. The probability density of $n(t)$, given the initial value n_0, is described by the Fokker-Planck equation

$$\frac{\partial}{\partial t} P(n,t|n_0) = \mathcal{L}_{\mathrm{FP}}(n) P(n,t|n_0), \tag{18}$$

where $\mathcal{L}_{\mathrm{FP}}(n)$ is the Fokker-Planck operator given by

$$\mathcal{L}_{\mathrm{FP}}(n) \equiv \frac{1}{b^2} \frac{\partial}{\partial n} D(n) \exp[-\beta \mathcal{F}(n)] \frac{\partial}{\partial n} \exp[\beta \mathcal{F}(n)], \tag{19}$$

with $D(n)$ defined as the diffusion coefficient of the whole chain. The translocation time of a polymer can be defined in terms of the mean first passage time $\tau(n;n_0)$, time taken for diffusion from n_0 to n, which satisfies [7]

$$\mathcal{L}^{\dagger}_{\mathrm{FP}}(n_0) \tau(n;n_0) = -1, \tag{20}$$

where $\mathcal{L}^{\dagger}_{\mathrm{FP}}(n_0)$ is the backward Fokker-Planck operator defined by

$$\mathcal{L}^{\dagger}_{\mathrm{FP}}(n_0) \equiv \frac{1}{b^2} \exp[\beta \mathcal{F}(n_0)] \frac{\partial}{\partial n_0} D(n_0) \exp[-\beta \mathcal{F}(n_0)] \frac{\partial}{\partial n_0}. \tag{21}$$

Using the boundary conditions

$$\frac{\partial}{\partial n_0} \tau(n;n_0=1) = 0, \tag{22}$$

$$\tau(n;n_0=N-1) = 0, \tag{23}$$

the solution of the above backward equation [Eq. (21)] can be formally obtained as

$$\tau \equiv \tau(N-1,1) = \frac{b^2}{D} \int_1^{N-1} dn\, e^{\beta \mathcal{F}(n)} \int_1^n dn' e^{-\beta \mathcal{F}(n')}. \tag{24}$$

Here, using the Rouse model, we set the diffusion coefficient $D(n) = D = k_BT/(N\gamma) \sim N^{-1}$, where γ is hydrodynamic friction coefficient for a single segment. Equation (24) measures the diffusion time of the polymer starting from the front segment located on the target side, and ending up with only the last segment remaining on the incipient side. The reflecting boundary condition at $n=1$ means the front segment cannot cross the pore via backward diffusion, and hence it is allowed to be located only on the target side.

As a first example with a curved membrane, let us consider polymer release out of a spherical vesicle, as shown in Fig. 1. The translocation time [Eq. (24)], using the free energy function Eq. (17), is calculated for the case $R \gg R_G$:

$$\tau = \left[\frac{L^2}{2D}\right] \left[\frac{\pi^2}{8} + A\alpha + \mathcal{O}(\alpha^2)\right], \tag{25}$$

where $A = (8\pi/15 - 448/225) \simeq -0.3156$, $L = Nb$, and $\alpha \equiv (\pi/2)^{1/2}(R_G/R)$ with $R_G = Nb^2/3$. The $\alpha = 0$ limit, $\tau \simeq (\pi^2/8)L^2/(2D) \sim L^3$, is just the planar membrane translocation time [Fig. 3(A)], which is the same as in Ref. [2]. As R decreases, τ decreases, because the confinement free energy of inside polymer drives the translocation outwards. This effect becomes more prominent when $R \lesssim R_G$. In the limit of $\alpha \to \infty$, i.e., $R \ll R_G$, the translocation time is given by

$$\tau = \left[\frac{L^2}{2D}\right] \left[\frac{2}{\pi \alpha^2} + \mathcal{O}(\alpha^{-4})\right]. \tag{26}$$

Note that the leading term scales as $\tau \sim L^2$, since $\alpha \sim L^{1/2}$ and $D \sim L^{-1}$. This reflects the fact that confined polymer is

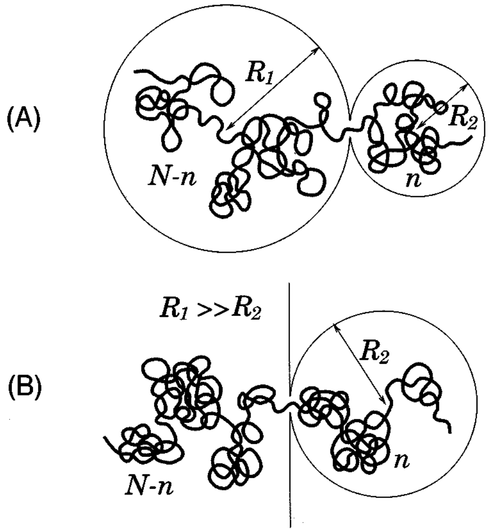

FIG. 4. Polymer transfer between two joining vesicles with different radii R_1 and R_2. Translocation is considered from the R_1 vesicle to the R_2 vesicle. (A) R_1 is larger than R_2. (B) $R_1 \gg R_2$.

squeezed out to the outside, because confinement costs more free energy than outward release.

The chain length dependence of translocation time is shown in Fig. 3 for different values of R. It is remarkable that the translocation time exhibits a crossover from $\tau \sim L^3$ to $\tau \sim L^2$ near $R = R_G$ [Fig. 3(B) and 3(C)]. Also interesting is the fact that this crossover of length scaling behavior is the same as that by chemical potential bias studied by us previously [2]. In both cases, crossovers are consequences of membrane asymmetry, which adds a linear term to the free energy function.

In fact, as the polymer segmental concentration is high enough when $R \ll R_G$, the excluded volume effect(EVE) becomes non-negligible, and affects the translocation dynamics significantly. A simple scaling argument gives the confinement free energy expression with EVE [8],

$$F_{\mathrm{in}}(N) \simeq k_B T \left[\frac{R_G}{R} \right]^{1/\nu} \sim N, \tag{27}$$

where $\nu \simeq 3/5$ is the swelling exponent of a self-avoiding polymer in three dimension. Now that this free energy is larger than that without EVE, it would definitely enhance the outward translocation. Since the free energy $F_{\mathrm{in}}(N)$ is proportional to N just like the ideal polymer free energy expression for the $R \ll R_G$ limit, however, the scaling behavior of the translocation time discussed above will not be changed due to EVE. Only the prefactor is modified to reduce the translocation time.

As a second example, we consider two joined vesicles of different radii R_1 and R_2 between which a small bottleneck is opened, as shown in Fig. 4(A). In the limiting situation in which both R_1 and R_2 are much larger than R_G, the problem is reduced to that of the planar membrane. The free energy function of the polymer translocation for arbitrary R_1 and R_2 is given by

$$\mathcal{F}(n) = F^{+}(n;R_2) + F^{+}(N-n;R_1), \tag{28}$$

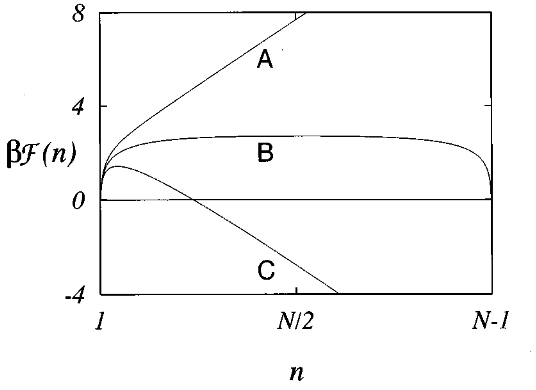

FIG. 5. Free energy $\mathcal{F}(n)$, in units of $k_B T$, of a polymer translocating two spheres as a function of translocation coordinate n. [$N = 1000$; (A) $\alpha_1 = 0.5$ and $\alpha_2 = 2$, (B) $\alpha_1 = \alpha_2 = 1$, and (C) $\alpha_1 = 2$ and $\alpha_2 = 0.5$.]

which is depicted in Fig. 5 for various values of R_1 and R_2. For $R_1 \gg R_2$, as shown in Fig. 4(B), the problem is reduced to polymer capture (delivery) dynamics into a finite size bud from the planar membrane side. As the capture proceeds, the polymer free energy increases, which prohibits the capture process, and translocation will take longer time than other cases. On the other hand, in the opposite limit of $R_1 \ll R_2$, the problem becomes polymer release to the planar membrane side out of spherical confinement. This is qualitatively similar to the previous example, where the main driving mechanism is confinement free energy due to the vesicle.

The translocation time as a function of arbitrary R_1 and R_2 has the following form:

$$\tau = \left[\frac{L^2}{D} \right] \int_0^1 dx \int_0^x dy \times \frac{\sum_{k=1}^{\infty} \exp(-\pi \alpha_1^2 (1-y) k^2) \sum_{k=1}^{\infty} \exp(-\pi \alpha_2^2 y k^2)}{\sum_{k=1}^{\infty} \exp(-\pi \alpha_1^2 (1-x) k^2) \sum_{k=1}^{\infty} \exp(-\pi \alpha_2^2 x k^2)}, \tag{29}$$

where $\alpha_1 = (\pi/2)^{1/2} (R_G/R_1)$ and $\alpha_2 = (\pi/2)^{1/2} (R_G/R_2)$, with $R_G = Nb^2/3$. In Fig. 6, the translocation time is shown for various values of α_1 and α_2. For polymers of short length such as $R_G \ll R_1, R_2$, the translocating chain does not "feel" the membrane curvature. In this case, the translocation time is given by $\tau \sim L^3$, the result of the planar membrane translocation. If $\alpha_1 \simeq \alpha_2$ for a long chain, the effective potential exhibits a symmetric barrier and the translocation time becomes $\tau \sim L^3$ [Fig. 6(B)] again. No dramatic driving mechanism can be seen in this case, because there is no asymmetry across the bottleneck.

For $\alpha_1 \gg \alpha_2$, the translocation time is changed to $\tau \sim L^2$, provided that $R_G \gtrsim R_1$ [Fig. 6(C)]. The confinement of the R_1 radius vesicle squeezes out the polymer in this regime. On the other hand, for $\alpha_1 \ll \alpha_2$, the translocation time rapidly increases if $R_G \gtrsim R_2$. This signifies that spontaneous capture by a small bud ($R_2 \lesssim R_G$) rarely occurs because the free en-

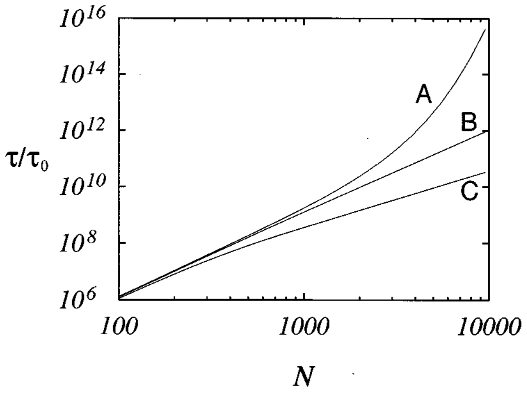

FIG. 6. Translocation time τ, in units of $\tau_0 \equiv b^2/(2D_0)$, with $D_0 = k_B T/\gamma$, between two spheres vs chain length N. [$R_2 = 30b$; (A) $R_1 = 60b$, (B) $R_1 = 30b$, and (C) $R_1 = 15b$.]

ergy barrier height increases linearly as the chain length increases [Fig. 5(A)], which finally results in an exponential increase of the translocation time as the chain length increases [Fig. 6(A)]. To overcome this difficulty of the capture process, segmental energetic bias [2] or its fluctuation [9] can be used as an apparatus to make the capture accelerate. Let us consider here the segmental chemical potential difference $\Delta\mu$ between the two sides, which will add a new contribution to the free energy function in Eq. (28) of

$$\Delta\mathcal{F}(n) = n\Delta\mu, \tag{30}$$

which is identical to that introduced in Ref. [2]. For $\Delta\mu < 0$, the capture process will be accelerated and this effect can be dominant over the oppositely directed entropic bias due to membrane curvature, provided that

$$|\beta\Delta\mu| \gtrsim |\beta\Delta\mu_c| \equiv \frac{\pi^2 b^2}{6R_2^2}, \tag{31}$$

where $|\beta\Delta\mu_c| \ll 1$. If Eq. (31) is fulfilled, the chemical potential bias reduces the entropic free energy barrier due to the confinement, and the translocation time scales as $\tau \sim L^3$. Further, the chemical potential becomes dominant over the barrier to yield $\tau \sim L^2$, if $|\beta\Delta\mu| \gtrsim |\beta\Delta\mu_c| + 1/N$, which is also much smaller than unity. In addition, as is shown in Ref. [9] for translocation across a planar membrane, the chemical potential fluctuation can also enhance the translocation dramatically. These signify that a minute segmental chemical potential bias or its fluctuation can be used to make the capture occur easily.

IV. SUMMARY AND CONCLUSION

The membrane curvature effect on polymer translocation is explored within our stochastic barrier crossing model. The geometrical constraint determines the entropic free energy barrier to a translocating polymer, and the asymmetries given by the membrane curvature are found to be a possible driving mechanism of polymer translocation. There occurs a crossover in the chain length dependence of the translocation time depending upon the membrane curvature. Further, the excluded volume effect is found to be irrelevant to the chain length scaling behavior of the translocation time, although it affects the polymer conformation and translocation dynamics significantly. Finally, entropically prohibited polymer capture into a bud can be accomplished if a minute chemical potential bias larger than a critical value is introduced.

ACKNOWLEDGMENTS

We acknowledge financial support from POSTECH BSRI of the Korea Science Foundation (K96 004), and the BSRI program (N96 093) of the Ministry of Education.

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