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Phase transitions of a polymer threading a membrane coupled to coil-globule transitions

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We theoretically study phase transitions of a polymer threading through a pore imbedded in a membrane. We focus on the coupling between a partition of the polymer segments through the membrane and a coil-globule transition of the single polymer chain. Based on the Flory model for collapse transitions of a polymer chain, we calculate the fraction of polymer segments and the expansion factor of a polymer coil on each side of the membrane. We predict a first-order phase transition of a polymer threading a membrane; polymer segments in one side are discontinuously translocated into the other side, depending on solvent conditions and molecular weight of the polymer. We also discuss the equilibrium conformation of the polymer chain on each side of the membrane. © *2004 American Institute of Physics.* [DOI: 10.1063/1.1758939]

I. INTRODUCTION

Translocation processes of polymer molecules [deoxyribose nucleic acid (DNA), ribonucleic acid (RNA), proteins, and biopolymers] threading through a pore imbedded in a membrane play an important role for many biological processes[1] and for biological applications. Examples include the translocation of RNA through nuclear pores[2] and the incorporation of proteins into membranes in nearly all cells.[3] *In vitro* experiments show that single-strand DNA polymers can be driven through a single α-hemolysin pore (inside diameter ~ 2 nm) by an external field.[4,5]

The problems of a polymer threading a membrane have both kinetics and equilibrium aspects. Recent theoretical studies[6–13] have described the polymer translocations as a diffusion processes through a pore imbedded in a flat membrane. DiMarzio *et al.*[14,15] have considered the equilibrium properties of a polymer molecule whose two ends reside on opposite sides of a membrane or partition separating two solutions in the limit of no self-excluded volume. They have pointed out that the polymer threading a membrane transition is coupled to the other phase transitions of a single polymer chain, such as a helix-random coil transition, collapse transitions, and adsorption onto a surface, and showed many possible translocation pair couplings.[14]

The insertion of a single polymer chain into a pore occurs in most biological cells which can transport polymers across membrane to function. The number of conformations of a polymer can produce an entropy force tending to pull the chain out of the pore. It is well known that, in polymer physics, the conformation of a polymer chain depends on solvent conditions, temperature, and ionic strength.[16–19] In a good solvent condition, a polymer is in a coiled state, while in a poor solvent region a polymer has a globular conformation. The change in temperature and solvent conditions can undergo a coil-globule transition of a single polymer chain in

a solution.[16,17] Then it is important to study the coupling between a polymer threading a membrane and a coil-globule transition.

In this paper we study the equilibrium properties of a polymer threading a membrane, taking into account interactions between polymer and solvent molecules, based on the Flory model for coil-globule transitions of a single polymer chain.[18,19] The polymer segments on one side (region 1) of the membrane can translocate to the other side (region 2) by going through a pore in the flat membrane, depending on the interaction between polymer and solvent molecules. The interaction between polymer and solvent molecules in region 1 (2) can be described in terms of the Flory–Huggins interaction parameter χ_1 (χ_2). In a thermal equilibrium state, the polymer segments are partitioned into the two regions, where the conformation of the polymer are determined by the balance between the elastic free energy and the interaction energy. We calculate the fraction of polymer segments and the expansion factors of a polymer coil on each side of the membrane and predict a first-order phase transition of a polymer threading a membrane, depending on the solvent conditions and the molecular weight of the polymer.

II. FREE ENERGY OF A POLYMER THREADING A MEMBRANE

Consider a polymer threading through a pore imbedded in a membrane. The segments of the polymer on one side (side 1) of the membrane can translocate to the other side (side 2) only by going through this pore whose diameter is comparable to the size of the chemical repeat units on the polymer. In a thermal equilibrium state, the monomer segments are divided among side 1 and side 2 as shown in Fig. 1. To derive the equilibrium conformation of the polymer and the fraction of polymer segments on each side of the membrane, we consider the thermodynamics of the system based on the Flory–Huggins theory for polymer solutions.[19]

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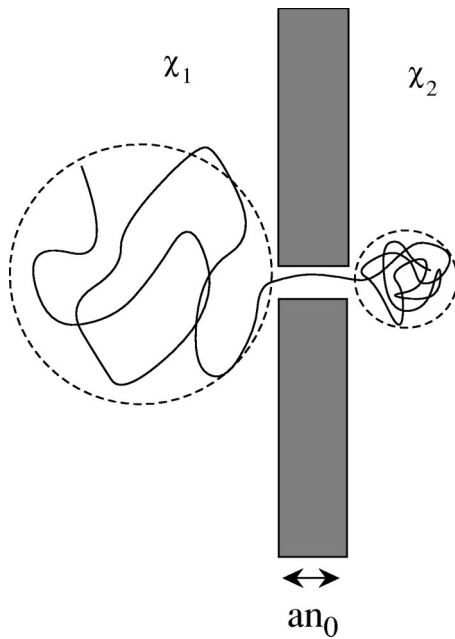Phase transitions of a polymer threading a membrane   605

FIG. 1. A polymer molecule consisting of n monomers is threaded through a pore in a flat membrane. The hole is sufficiently small that double threading does not occur.

Let n be the number of segments (each of size a) on a polymer and n_1 and n_2 are the numbers of segments on sides 1 and 2, respectively. The polymer chain can translocate through a membrane with finite thickness corresponding to an_0. Then we have $n=n_0+n_1+n_2$. The free energy of the polymer chain is given by

$$F=F_1+F_2+F_0, \tag{1}$$

where F_1 (F_2) shows the free energy of the polymer on side 1 (side 2) and F_0 is the free energy of the segments in the pore.

Let R_1 (R_2) be the mean radius of the occupied region of the monomer segments on side 1 (2). Then the volume fraction of the segments in the sphere R_i is given by

$$\phi_i=\tfrac{4}{3}\pi a^3 n_i/(\tfrac{4}{3}\pi R_i^3)=a^3 n_i/R_i^3, \tag{2}$$

where $(4/3)\pi a^3$ corresponds to the volume of an unit segment on the polymer. Hereafter the suffix i shows side 1 or 2 ($i=1,2$). We here define the expansion factor α_i of the polymer chain in region i as

$$\alpha_i=R_i/R_{0,i}, \tag{3}$$

where $R_{0,i}=a\sqrt{n_i}$ is the radius of gyration of the ideal chain with n_i segments. The volume fraction, Eq. (2), of the monomer segments in the sphere i is then given by

$$\phi_i=\frac{1}{\alpha_i^3\sqrt{n_i}}. \tag{4}$$

The presence of the surface (membrane) may change the polymer conformation. The chain is stretched by a factor $\sqrt{2}$ in the perpendicular direction.[20] In our model, we neglect the stretching of the chain near the wall.

The free energy F_i on side $i(=1,2)$ is given by

$$F_i=F_{i,\text{el}}+F_{i,\text{mix}}, \tag{5}$$

where $F_{i,\text{el}}$ shows the elastic free energy due to the deformation of the segment distribution from the ideal state. This free energy is given by Flory[19]

$$\beta F_{i,\text{el}}=3[\tfrac{1}{2}(\alpha_i^2-1)-\ln\alpha_i], \tag{6}$$

where $\beta\equiv 1/k_B T$, T is the absolute temperature, and k_B is the Boltzmann constant. The second term in Eq. (5) shows the free energy for a mixing of a polymer chain with solvent molecules on side i and is given by the Flory–Huggins theory[19]

$$\beta F_{i,\text{mix}}=\frac{R_i^3}{a^3}[(1-\phi_i)\ln(1-\phi_i)+\chi_i\phi_i(1-\phi_i)], \tag{7}$$

where χ_i shows the Flory–Huggins interaction parameter between a polymer segment and a solvent molecule on side (i). The translational entropy term $(\phi_i/n)\ln\phi_i$ of the polymer chain can be neglected since the center of gravity of the polymer chain is fixed near a membrane in a thermal equilibrium state. The prefactor R_i^3/a^3 is the total number of unit cells in the sphere of the radius R_i.

The free energy F_0 of the segments in the pore is simply given by

$$\beta F_0=\beta\epsilon_0 n_0, \tag{8}$$

where ϵ_0 is the interaction energy between a polymer segment and a pore. We assume here that the diameter of the pore is of the order of the segment on the polymer. Then we can choose the value of n_0 as one numerical parameter characterizing the thickness of the membrane. In this assumption, the free energy Eq. (8) becomes a constant, but it is an important factor for the dynamics.[12]

When the interaction energy between a polymer segment and a pore is weak, the polymer can escape completely from the vicinity of the membrane (or either side) because of the conformational entropy of the chain. In our model, however, the chain is tethered to the membrane. This would occur for a polymer chain which has a large end group on the both ends.

In a thermal equilibrium state, the expansion factors α_i of the polymer in side $i(=1,2)$ are determined by minimizing the free energy (1) with respect to α_i:

$$(\partial F/\partial\alpha_1)_{\alpha_2,n_1}=0, \tag{9}$$

$$(\partial F/\partial\alpha_2)_{\alpha_1,n_1}=0. \tag{10}$$

These lead to

$$\alpha_1^2-1+n_1\left[\frac{1}{\phi_1}\ln(1-\phi_1)+1+\chi_1\phi_1\right]=0, \tag{11}$$

$$\alpha_2^2-1+n_2\left[\frac{1}{\phi_2}\ln(1-\phi_2)+1+\chi_2\phi_2\right]=0. \tag{12}$$

The number n_1 of the segments in side 1 is determined by

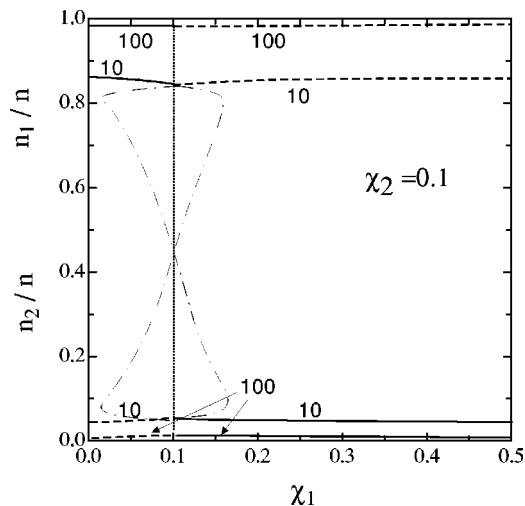$$(\partial F/\partial n_1)_{\alpha_2 1,\alpha_2,}=0, \tag{13}$$

FIG. 2. Fraction of polymer segments on each side of the membrane plotted against the Flory–Huggins parameter χ_1 with $\chi_2 = 0.1$. The number n of the segments on the polymer is varied. The solid curve shows the fraction n_1/n and the dotted curve corresponds to n_2/n.

FIG. 3. Expansion factors plotted against χ_1 with $\chi_2 = 0.1$ for various values of n. The solid curve shows the expansion factor α_1 and the dotted curve corresponds to α_2.

where we have used $n_2 = n - n_0 - n_1$ before the differentiation. We then obtain

$$\alpha_1^3 \sqrt{n_1}[(\tfrac{3}{2} - \phi_1)\ln(1 - \phi_1) + \tfrac{1}{2}\phi_1 + \chi_1\phi_1(1 - \tfrac{1}{2}\phi_1)]$$
$$= \alpha_2^3 \sqrt{n_2}[(\tfrac{3}{2} - \phi_2)\ln(1 - \phi_2) + \tfrac{1}{2}\phi_2 + \chi_2\phi_2(1 - \tfrac{1}{2}\phi_2)],$$
(14)

where the volume fractions are given by

$$\phi_1 = \frac{1}{\alpha_1^3 \sqrt{n_1}}, \tag{15}$$

$$\phi_2 = \frac{1}{\alpha_2^3 \sqrt{n - n_0 - n_1}}. \tag{16}$$

The equilibrium values of α_1, α_2, and n_1 are determined from the three coupled Eqs. (11), (12), and (13).

III. RESULTS AND DISCUSSION

In this section we show some results of our theory. Here we put $n_0 = 1$ and assume that the value of the parameter χ_2 in region 2 remains a constant when the parameter χ_1 in region 1 is changed. The Flory–Huggins parameter χ can be changed by pH, ionic strength, solvent conditions, and temperature.[19]

Figure 2 shows the fraction of polymer segments on each side of the membrane plotted against the Flory–Huggins parameter χ_1 with $\chi_2 = 0.1$, which means the solution of region 2 corresponds to a good solvent condition for the polymer. The total number n of polymer segments is varied. The solid curve shows the fraction n_1/n and the dotted curve corresponds to n_2/n. The dash-dotted line shows the unstable region for $n = 10$. When $\chi_1 < \chi_2$, most polymer segments is in region 1. At $\chi_1 = \chi_2$ we find that the polymer segments in region 1 can be translocated into region 2 by changing the solvent condition χ_1 in region 1. A first-order phase transition of the polymer threading a membrane occurs
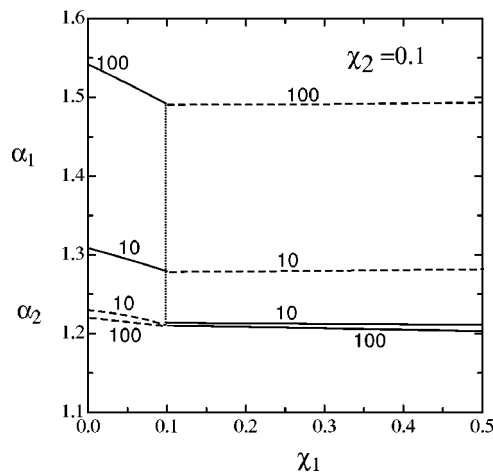
at $\chi_1 = \chi_2$. On increasing the molecular weight of the polymer, the width of the jump becomes larger. Figure 3 shows the expansion factor of the polymer chain on each side of the membrane plotted against χ_1 with $\chi_2 = 0.1$ for various values of n. The solid curve shows the expansion factor α_1 and the dotted curve corresponds to α_2. When $\chi_1 = 0$, the value of the expansion factor α_1 in region 1 is large and the polymer is in a coiled state. On increasing χ_1, the value of the expansion factor α_1 is decreased and jumps at $\chi_1 = \chi_2 = 0.1$. For $\chi_1 > \chi_2 = 0.1$, the polymer in region 2 is in a coiled state with a expanded conformation because $\chi_2 = 0.1$.

Figure 4(a) shows the fraction of polymer segments on each side of the membrane plotted against χ_1 with $\chi_2 = 0.5$. The number n of the segments on the polymer is changed. The solid curve shows the fraction n_1/n and the dotted curve corresponds to n_2/n. For $n = 10$, the fraction of polymer segments in region 1 is continuously decreased with increasing χ_1 and the polymer segments in region 1 are translocated into region 2 through a hole in the membrane. For larger values of n, we find the first-order phase transition of the polymer threading a membrane. When the solvent condition becomes poorer, the polymer segments of a short polymer chain are continuously translocated into region 2. Figure 4(b) shows the expansion factors of the polymer chain on each side of the membrane plotted against χ_1 with $\chi_2 = 0.5$ for $n = 10,100$. The solid curve shows the expansion factor α_1 and the dotted curve corresponds to α_2. On increasing χ_1, the value of the expansion factor α_1 is decreased and slightly jumps at $\chi_1 = \chi_2 = 0.5$. As shown in Fig. 4(a), the value of the fraction n_1 is almost constant when $\chi_1 < 0.5$ and drastically changed near $\chi_1 = \chi_2 = 0.5$. The polymer chain in region 1 is condensed with increasing χ_1 and most polymer segments remain in region 1 for $\chi_1 < \chi_2$. At $\chi_1 = \chi_2 = 0.5$, the polymer segments in region 1 are translocated into region 2.

Figure 5(a) shows the fraction of polymer segments on each side of the membrane plotted against χ_1 with $\chi_2 = 0.7$ for various values of n. The solid curve show the fraction n_1/n and the dotted curve corresponds to n_2/n. When n
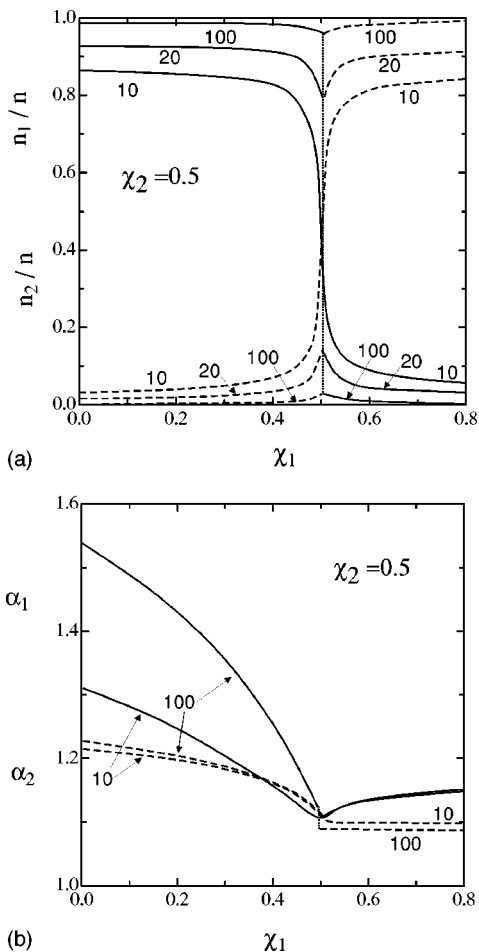
FIG. 4. (a) The solid curve shows the fraction n_1/n and the dotted curve corresponds to n_2/n plotted against χ_1 with $\chi_2 = 0.5$ for various values of n. (b) The expansion factor plotted against χ_1 with $\chi_2 = 0.5$ for $n = 10, 100$. The solid curve shows the expansion factor α_1 and the dotted curve corresponds to α_2.

FIG. 5. (a) The solid curve shows the fraction n_1/n and the dotted curve corresponds to n_2/n plotted against χ_1 with $\chi_2 = 0.7$. The number n of the segments on the polymer is varied. (b) The expansion factor plotted against χ_1 with $\chi_2 = 0.7$ for various values of n. The solid curve shows the expansion factor α_1 and the dotted curve corresponds to α_2.

$= 10$, the fraction n_1/n of the polymer segments in region 1 is continuously decreased with increasing χ_1. For larger values of n, we find the first-order phase transition of the polymer threading a membrane at $\chi_1 = \chi_2 = 0.7$. As increasing the number of segments on a polymer, the width of the jump becomes larger. Figure 5(b) shows the corresponding expansion factors plotted against χ_1 with $\chi_2 = 0.7$ for $10, 100, 1000$. For $n = 100$ and 1000, the expansion factor α_1 is sharply decreased near $\chi_1 = 0.5$ and the conformation of a polymer chain in region 1 is changed from a coiled state to a globular one. At $\chi_1 = \chi_2 = 0.7$, the radius of the polymer chain on each side of the membrane is discontinuously changed.

From Eq. (3), the gyration radius R_i of the polymer chain in region $i(=1,2)$ is given by

$$R_i/a = \alpha_i \sqrt{n_i}. \tag{17}$$

Figure 6 shows the radius R_i plotted against χ_1 with $n = 100$ for $\chi_2 = 0.1, 0.5,$ and 0.7. The solid curve shows the radius R_1/a and the dotted curve corresponds to R_2/a. When $\chi_1 < \chi_2$, the radius of the polymer coil in region 1 is larger than that in region 2. At $\chi_1 = \chi_2$, it is switched the radius of the polymer coil in region 1 and that in region 2. The radius of the polymer coil in region 1 becomes smaller
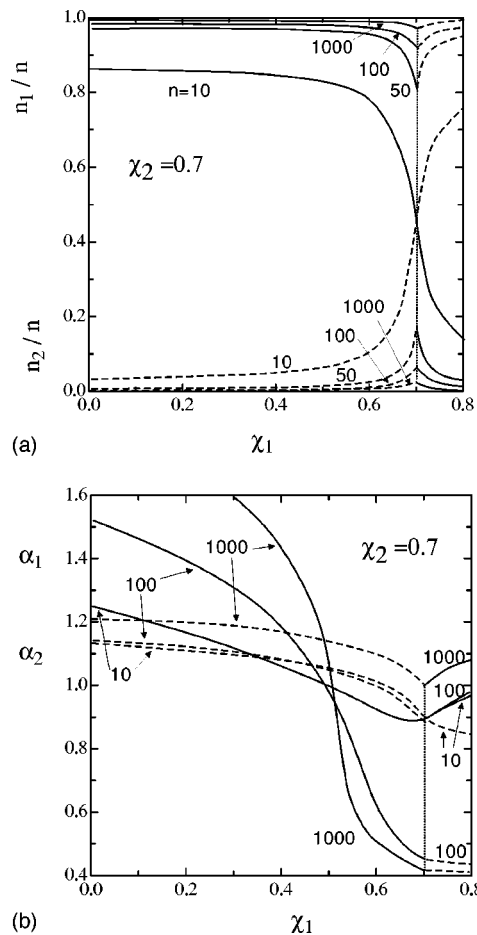
than that in region 2 for $\chi_1 > \chi_2$. We find that the radius of the polymer chain on each side of the membrane is discontinuously changed when the first-order phase transition of a polymer threading a membrane takes place.
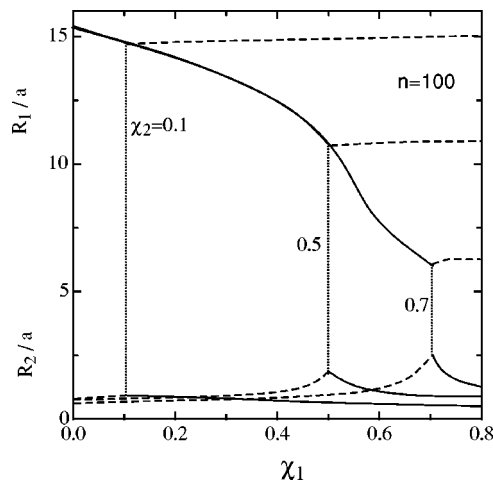

FIG. 6. Radius R_i plotted against χ_1 with $n = 100$ for $\chi_2 = 0.1, 0.5,$ and 0.7. The solid curve shows the radius R_1/a and the dotted curve corresponds to R_2/a.
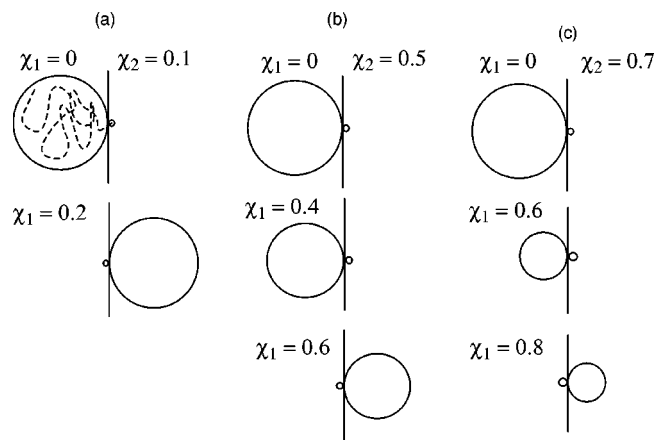
FIG. 7. Schematically shown the conformation of the polymer occupied in regions 1 and 2 in a thermal equilibrium state. The equilibrium values of the radius for each sphere are given in Fig. 6. Circles show the occupied region of polymer segments and the vertical line shows the flat membrane.

In Fig. 7, we schematically show the conformation of the polymer chain ($n=100$) occupied in regions 1 and 2 in a thermal equilibrium state. The equilibrium value of the radius for each sphere is given in Fig. 6. Circles show the occupied region of polymer segments and the vertical line shows the flat membrane. When $\chi_1 < \chi_2$, the radius of the polymer in region 1 is larger than that in region 1. On increasing $\chi_1 (<\chi_2)$, the polymer chain is condensed. Note that most polymer segments remain in region 1 for $\chi_1 < \chi_2$. At $\chi_1 = \chi_2$, the conformation of the polymer chain on each side of the membrane is drastically changed.

IV. CONCLUSION

We have theoretically studied phase transitions of a polymer threading through a pore imbedded in a membrane. The theory takes into account the coupling between a partition of the polymer segments through the membrane and a coil-globule transition of a single polymer chain. Based on the Flory model for the collapse transition of a polymer chain, we have calculated the fraction of polymer segments and the expansion factor of a polymer chain on each side of the membrane.

It was found that the change in a solvent condition and molecular weight of a polymer is an important role for phase transitions of a polymer threading a membrane. When χ_1 $< \chi_2$, most polymer segments is in region 1. At $\chi_1 = \chi_2$ we find that the segments on the polymer in one side can be translocated into the other side by changing the solvent condition. A first-order phase transition of the polymer threading a membrane occurs at $\chi_1 = \chi_2$. We also have found that the radius of the polymer coil on each side of the membrane is discontinuously changed when the first-order phase transition of a polymer threading a membrane takes place. When the solution of region 2 is in a poor solvent condition ($\chi_2 > 0.5$), a continuous phase transition of a polymer threading a membrane can occur for short polymer chains. In this paper we have focused on the dependence of the phase transition on molecular weight and solvent conditions. On increasing the value of n_0 (thicker membranes) the first-order phase transition becomes the continuous one.

Our results may offer insights into a invasion of RNA viruses into cells, incorporation of membrane proteins into a lipid bilayer, and drug delivery systems.

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