Deformation of the equilibrium shape of a vesicle induced by enclosed flexible polymers

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received 15 November 2010; accepted in final form 5 May 2011
published online 8 June 2011

PACS 87.16.D– Membranes, bilayers, and vesicles
PACS 82.35.Lr – Physical properties of polymers
PACS 82.70.Uv – Surfactants, micellar solutions, vesicles, lamellae, amphiphilic systems
(hydrophilic and hydrophobic interactions)

Abstract – Using a field-theoretic approach, we study the equilibrium shape deformation of a vesicle induced by the presence of enclosed flexible polymers. Such a structure can commonly be found in drug delivery systems, endocytosis and polymer/surfactant solutions. To evaluate the total free energy of this system, we combine phase field theory for the membrane and self-consistent field theory for the polymers, and this combination allows us to calculate the bending elastic energy of the membrane, the conformation entropy of the polymers and their interactions simultaneously. Simulations on this coupled model system for axisymmetric shapes show a shape deformation of the vesicle induced by introducing polymers into it. We examined the dependence of the stability of the vesicle shape on the chain length of the polymers and the reduced volume of the vesicle. We present a simple model calculation that shows the relative stability of the prolate shape compared to the oblate shape.

Micelles and vesicles are closed forms of membranes that are composed of amphiphilic molecules, such as surfactants or lipid molecules. These molecules are not only elementary components of biological cells [1] but also important materials in industrial sciences, for example, surface coating, oil recovery, cosmetics and so on [2]. Shape deformation, fusion and fission of membranes in the presence of polymers are interesting targets of membrane physics. For example, a structure of a closed membrane (a vesicle) that contains flexible polymers is a frequently observed structure in various phenomena, such as drug delivery systems (DDS) [3], the endocytosis in biological cells [1], and micelle formation in polymer/surfactant mixtures. To understand these complex phenomena, it is important to start from a simple model system of a closed liquid membrane that contains flexible polymers.

Experimental study on such phenomena was done by Nakaya et al., who performed a small-angle neutron scattering experiment on an inverted micellar phase of a surfactant solution where hydrophilic polymers are enclosed [4]. They reported that micelles show anisotropic deformation upon the inclusion of polymers inside them. In this process, there are several candidates for the reason of the transition, i.e. the configuration entropy of the centers of mass of the enclosed polymers and the solvent and the conformation entropy of the polymers.

In the present paper, we introduce a new theoretical model of a closed-form membrane (a vesicle) that contains polymers, and clarify the mechanism of its shape deformation. A standard technique to study such phenomena is a molecular simulation where the polymers are modeled by bead-spring chains and the membrane is modeled either by a set of short bead-spring chains composed of hydrophilic and hydrophobic beads [5,6] or by a set of vertex points of a triangular mesh on the membrane surface (so-called surface element method) [7,8]. One of the difficulties of these techniques is that an evaluation of the free energy of the system is not easy for such molecular simulations [9]. To overcome this difficulty, we combine the self-consistent field (SCF) theory for polymers [10,11] and the phase field (PF) theory for membranes [12,13]. In the SCF theory, the probability distribution of the conformation of polymer chains is evaluated in terms of the path integral Q(0, r0; N, rN), which corresponds to the statistical weight of a polymer chain composed of N + 1 segments whose two end segments (denoted by the indices 0 and N) are at r0 and rN, respectively [10]. On the other hand, in the
PF theory, the membrane is described with a scalar field \( \psi(r) \), where \( \psi(r) = 0 \), \( \psi(r) > 0 \) and \( \psi(r) < 0 \) correspond to the membrane surface, inside and outside regions of the membrane, respectively. It should be noted that in the PF theory the membrane is treated as a curved surface with a finite thickness. This treatment is different from that of the usual Helfrich’s bending elastic model where the thickness of the membrane is assumed to be negligible [14,15].

Let us describe the detail of our model vesicle that contains polymers. The target system is a three-component mixture composed of amphiphilic molecules (membrane of the vesicle), polymers, and the solvent. For simplicity, we assume that the amphiphilic molecule, the solvent molecule and the polymer segment have the same volume, which is used as the unit of volume in the non-dimensionalization of the model equations. This simple choice of the molecular volumes is not a serious limitation on our model because our molecules are actually coarse-grained objects that in general contain several real molecules. In our model, all of these three components are described in terms of their local density distributions denoted as \( \varphi_M(r) \), \( \varphi_P(r) \) and \( \varphi_S(r) \), respectively. We require an incompressibility condition on these three components:

\[
\varphi_M(r) + \varphi_P(r) + \varphi_S(r) = 1, \tag{1}
\]

where \( \varphi_M(r) \) is related to the phase field \( \psi(r) \). This incompressibility condition produces the coupling between the PF and the SCF.

Using these field variables, the total free energy \( F_{\text{total}} \) of the combined system of the membrane, polymers and the solvent multiplied by \( \beta = 1/k_B T \) is given in the following form:

\[
\beta F_{\text{total}} = \beta F_{\text{PF}}[\psi] + \sigma \left( A_{\text{total}} - A_{\text{total}}^{(0)} \right) + \mu \left( V_{\text{in}} - V_{\text{in}}^{(0)} \right) + \beta F_{\text{SCF}}[\psi, \{ \varphi_K \}], \tag{2}
\]

The first term on the right-hand side of eq. (2) is the free energy of the membrane obtained with the PF theory, which was proposed in ref. [12]. In a non-dimensional form, it is given as [16]

\[
\beta F_{\text{PF}} = \frac{3\kappa}{4\sqrt{2}} \int dr \left[ -\psi(r) + \psi(r)^3 - \nabla^2 \psi(r) \right]^2, \tag{3}
\]

where \( \kappa \) is the bending elastic modulus and the unit of length is chosen as the membrane thickness when this PF model is decoupled with the other components, i.e. the polymers and the solvent. In eq. (3), we neglected the effects of the spontaneous curvature and the Gaussian curvature for simplicity.

The surface area element of the membrane is given by [12,16]

\[
A[\psi(r)] = \frac{3\sqrt{2}}{4} \left[ \frac{\epsilon}{2} \left| \nabla \psi(r) \right|^2 + \frac{1}{4\epsilon} (\psi(r)^2 - 1)^2 \right], \tag{4}
\]

where \( \epsilon \) is the equilibrium membrane thickness. We found that this membrane thickness \( \epsilon \) is 1.4 times larger than that for the original PF model [12] defined by eq. (3) because of the presence of the solvent and the polymer in our model.

Since each amphiphilic molecule occupies a certain constant area on the membrane surface, the local surface area of the membrane is proportional to the local number density of the amphiphilic molecules, \( \varphi_M(r) \). Therefore, the following relation holds:

\[
\varphi_M(r) = CA[\psi(r)], \tag{5}
\]

where \( C \) is a normalization constant that should be determined so that \( \varphi_M(r) \) takes its maximum value 1 on the central surface of the membrane. In general, this normalization constant \( C \) changes depending on the local polymer concentration \( \varphi_P(r) \) because the membrane thickness depends on \( \varphi_P(r) \). However, this effect is small when the polymer density is low. Therefore, we neglect such a dependence and assumed that \( C \) is a constant.

The total area of the membrane surface \( A_{\text{total}} \) and the total enclosed volume by the membrane \( V_{\text{in}} \) are given by

\[
A_{\text{total}}[\psi(r)] = \int A[\psi(r)] dr, \tag{6}
\]

\[
V_{\text{in}}[\psi(r)] = \int_{\psi(r) < 0} (1 - \varphi_M(r)) dr,
\]

respectively. Here, we used the fact that the solubility of the amphiphilic molecules to the solvent is so small that almost all of them are used to form the membrane and there are very few in the solvent.

In the simulations, we fix these quantities \( A_{\text{total}} \) and \( V_{\text{in}} \) to given values \( A_{\text{total}}^{(0)} \) and \( V_{\text{in}}^{(0)} \) by using Lagrange multipliers \( \sigma \) and \( \mu \) in the second and third terms on the right-hand side of eq. (2). These constraints mean that both of the exchange of amphiphilic molecules between the membrane and the environment and the permeation of solvent across the membrane are very slow compared to the equilibration time scales of the membrane shape and the polymer conformations.

Here, we should note that the constraint on \( A_{\text{total}} \) is just a redundant condition because it is already maintained by the local conservation of the membrane density \( \varphi_M(r) \) in eq. (1). However, we keep this term just for the symmetry in the treatments on the total membrane area \( A_{\text{total}} \) and the inside volume \( V_{\text{in}} \). After the equilibrium distribution of the phase field \( \psi(r) \) is obtained, the Lagrange multiplier \( \sigma \) is vanishing, and this constraint term does not affect the results in any ways. Here, we should also point out that the conservation of the membrane area maintained by this Lagrange multiplier \( \sigma \) is not a local conservation meant by eq. (1) but a global conservation. If the membrane thickness is almost uniform, these two conditions are equivalent as long as we are dealing with the equilibrium shapes of the membrane. However, if the membrane thickness is modified by the presence of the polymers, this assumption is no longer valid. In such a case, a detailed

\footnote{In the actual PF simulation, the discontinuous condition \( \int_{\psi(r) > 0} dr \) is replaced by a smoothed function \( \int dr(1/2)(1 + \tanh \alpha \psi(r)) \) with a sufficiently large constant \( \alpha \).}
treatment of local conservation of the membrane area proposed in refs. [17,18] should be used.

The last term on the right-hand side of eq. (2) is the free energy of the polymers and the solvent calculated with the SCF theory. In the SCF calculation, we describe the polymer chains using the path integral $Q(0,r_0;N,r_N)$, while the solvent molecules are assumed to be point particles which possess only translational degrees of freedom.

The mean-field potential used in the SCF calculation is assumed to have the form

$$V_K = \sum_{K'} \chi_{KK'} \varphi_{K'}(r) + \gamma(r),$$  

(7)

where the indices $K$ and $K'$ represent either the polymer (P) or the solvent (S), and $\chi_{KK'}$ is the Flory interaction parameter between the segments of $K$ and $K'$ types, and $\gamma(r)$ is the Lagrange multiplier for the incompressible condition eq. (1), which produces a coupling between the polymer chains and the membrane.

For simplicity, we assume that all the interaction parameters $\chi_{KK'}$ vanish except for $\chi_{PS} \equiv \chi$. We also assume that all polymer chains are confined in the vesicle while the solvent fills both the inside and outside regions of the vesicle. (Due to the constraint of the fixed enclosed volume $V_{in}$, there is essentially no exchange of solvent across the membrane.) To realize this condition, we set the path integral for polymers to be zero outside the vesicle ($Q(0,r_0;i,r) = 0$ for $\psi(r) < 0$), while we impose no restrictions on the region of the distribution of the solvent. As a result of this SCF calculation, we obtain the following contributions from the SCF part to the total free energy [10]:

$$\beta F_{SCF}[\psi, \{\varphi_K\}] = \beta (F_P + F_S + F_{int} + F_{incomp}),$$  

(8)

where $F_P$, $F_S$, $F_{int}$ and $F_{incomp}$ are contributions from polymers, solvent, segment interactions, and incompressibility, respectively. These components are defined as follows:

$$\beta F_P = -M_P \ln \int dr_0 \int dr_N Q(0,r_0;N,r_N) - \int dr \psi_P(r) \varphi_P(r) + M_P \ln M_P - M_P,$$

$$\beta F_S = \int dr [\varphi_S(r) \ln \varphi_S(r) - \varphi_S(r)],$$

(9)

$$\beta F_{int} = \frac{1}{2} \sum_{K,K'} \chi_{KK'} \int dr \varphi_K(r) \varphi_{K'}(r),$$

$$\beta F_{incomp} = \int \gamma(r) \{ \varphi_P(r) + \varphi_S(r) + \varphi_M(r) - 1 \} dr,$$

where $M_P$ is the total number of polymers in the system.

There are three important non-dimensional parameters that specify the state of the system. These are the reduced volume of the vesicle $v$, the volume fraction of polymers inside the vesicle $\phi$, and the chain length of the polymer $N$. The reduced volume $v$ is defined as the ratio between the actual enclosed volume $V_{in}^{(0)}$ and that of the spherical vesicle with the same surface area $A_{total}^{(0)}$ [12,15]:

$$v = (V_{in}^{(0)} + V_M) / \left(\frac{4\pi}{3} \left(A_{total}^{(0)} / 4\pi\right)^{3/2}\right),$$

(10)

where $V_M$ is the total volume occupied by the amphiphilic molecules. This correction term containing $V_M$ is introduced to cancel the effect of the finite thickness of the membrane in our model so that our reduced volume can be directly compared with those in Helmhlich’s model [14,15].

The volume fraction of polymers inside the vesicle $\phi$ is defined by the ratio between the volume occupied by the polymers inside the vesicle and the total enclosed volume defined by eq. (6), i.e.

$$\phi = \int_{\psi(r) > 0} \varphi_P(r) dr / V_{in}.$$  

(11)

where the segment volume is used as the unit of volume.

By changing the parameters $v$, $\phi$, and $N$, we examined the stable shape of the vesicle. In the present study, we simulated over the range $0.69 < v < 0.80$, where the prolate shape is always the most stable shape if the membrane does not contain polymers [15].

Assuming axisymmetric shapes, we minimized the free energy eq. (2) with respect to $\{\varphi_K(r)\}$ and $\psi(r)$ by an iteration method. We used a cylindrical coordinate system with $256 \times 80$ mesh points in the axial and radial directions, respectively, with mesh width $\Delta x = 0.5$. Figures 1(a) and (b) show two typical shapes of the membrane, i.e., the prolate and the oblate shapes, respectively, obtained for the case with $v = 0.69$, $\phi = 0.1$, $\chi = 0.0$, and $N = 100$. The left edge of the figure is the axis of revolution.

In fig. 2, we show the dependences of the components of the free energy on the chain length $N$ for the athermal case with $v = 0.69$, $\phi = 0.1$ and $\chi = 0.0$ (i.e. $F_{int} = 0$). Shown are $\beta F_{PP}$, $\beta(F_P + F_{incomp})$, $\beta F_S$, and the total free energy $\beta F_{total}$ defined by eq. (2), respectively. These quantities are the difference between the values for the prolate vesicle and that for the oblate vesicle. Thus, a negative value
means that the prolate shape has lower free energy than the oblate case. In this figure, the constraint terms that include $\sigma$ and $\mu$ are included in $F_{PF}$ although they give only negligible contributions.

Figure 2(a) indicates that both the conformation entropy of polymers and the bending elastic energy of the membrane tend to prefer the prolate shape when the chain length is increased. On the other hand, the contribution from the translational entropy of the solvents shows a more complex behavior. In the short-chain-length region, this contribution first decreases and then it turns to increase when the chain length becomes longer. As a sum of these components, the total free-energy difference decreases monotonically as the polymer chain length is increased, leading to the equilibrium prolate shape in the long-chain region.

The complex behavior of the translational entropy of the solvent is understood considering the effect of the depletion layer of the polymers near the membrane. When the polymer chain length becomes comparable to the membrane thickness (around $N \sim 3$), the width of the depletion layer is negligibly thin, and the solvent distributes almost uniformly inside the vesicle, which maximizes the translational entropy of the solvent. As the chain length is increased, a depletion layer is formed which induces an inhomogeneous solvent distribution inside the vesicle. Such an inhomogeneous solvent distribution causes a decrease of the translational entropy of the solvent molecules (i.e., an increase in the free energy).

The opposite behavior of this translational entropy of the solvent in the very short-chain-length region ($N < 3$) is an artifact of the present phase field modeling of the membrane which has a finite thickness that is the same order as the gyration radius of the polymer with $N \sim 5$. Due to the smooth density profile and the finite thickness of the membrane distribution $\varphi_M(r)$, either the polymer segments or the solvent molecules must come into the membrane region to fill the vacancy. Such invading molecules are strongly repelled by the membrane and cause an increase in the free energy. As the rate of this increase is different for the prolate and the oblate shapes, it leads to the steep increase of $\beta F_S$ for $N < 3$. Here, it should be noted that the SCF calculation is valid even for $N \sim 1$ because of the self-similar nature of the Gaussian chains assumed in the SCF theory [10].

To understand why the conformation entropy of polymers $\beta F_P$ prefers prolate shape, we give a simple interpretation considering extreme situations. Let us approximate an oblate or a prolate shape with a cylinder with diameter $x$ and height $y$. These two values are determined when the total surface area and the enclosed volume are given. These conditions lead to $x^2 y = C_1$ and $x^2 + 2xy = C_2$, where $C_1$ and $C_2$ are constants that correspond to the total enclosed volume multiplied by $4/\pi$ and the total surface area multiplied by $2/\pi$, respectively. Solving this set of equations for given $C_1$ and $C_2$ gives 3 solutions $(x_i, y_i)$ ($i = 1, 2, 3$) where $x_3 < 0 < x_2 < x_1$. Obviously, the solution $x_3 < 0$ is unphysical. The other two solutions correspond to the oblate $(x_1, y_1)$ and prolate $(x_2, y_2)$, respectively. If $x_2$ is small, we obtain up to the first order in $x_2$ that $x_2 = 2C_1/C_2 \equiv L_{pr}$ (prolate) and $y_1 = C_1/(2C_2) \equiv L_{ob}$ (oblate). Thus, the ratio between the linear dimensions of the confined region for the prolate and oblate cases is $L_{pr} = 4L_{ob}$. Now, we estimate the increase in the conformational free energy due to such confinement. We consider an ideal chain confined in a region of size $L_C$. As the number of segments in a blob of size $L_C$ is proportional to $L_C^3$, a chain made of $N$ segments can be regarded as a linear chain of $N/L_C^2$ blobs. Therefore, the increase in the conformational free energy per chain due
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Fig. 3: (Colour on-line) Distributions of the membrane and the polymers are shown for the case $N = 100$, $v = 0.69$ and $\phi = 0.1$. The interaction parameter $\chi$ is (a) 0.6 (b) 0.65 and (c) 0.7, respectively.

to the confinement is given by

$$\Delta F(L_C) = k_B T \ln 2^{N/L^2} = \frac{N k_B T}{L_C} \ln 2. \quad (12)$$

Using the fact that the number of chains is inversely proportional to the chain length $N$ because of the constant volume fraction $\phi$ inside the vesicle, and the fact that there are two directions of the confinement in the prolate case, we can estimate the difference in the total conformational free energy (i.e. $\Delta F \times$ (number of chains)) between the prolate and the oblate cases as

$$\frac{1}{N} \left[ 2\Delta F(L_{pr}) - \Delta F(L_{ob}) \right] = -\frac{7 k_B T \ln 2}{8 L_{ob}^2} < 0. \quad (13)$$

Equation (13) means that the conformational free energy prefers the prolate shape, which is consistent with the results in the long-chain region in fig. 2(a).

In fig. 2(b), we show similar data as those in fig. 2(a) but for the dependence on reduced volume $v$. As $v$ becomes smaller, the polymers are more strongly confined. The above simple consideration suggests that the prolate shape will be more and more stable than the oblate one when the constraint becomes stronger. Actually, we can confirm this tendency in the behavior of the conformation entropy of polymers and total free energy shown in fig. 2(b).

Finally, we consider the case where there is a repulsive interaction between the polymer segment and the solvent molecule ($\chi > 0$). In fig. 3, we show distributions of the membrane and the polymers for the case with $N = 100$, $v = 0.69$ and $\phi = 0.1$. The interaction parameter between the polymer segment and the solvent $\chi$ is (a) $\chi = 0.6$, (b) $\chi = 0.65$ and (c) $\chi = 0.7$, respectively. Compared to the athermal case ($\chi = 0$) in fig. 1, the polymers distribute inhomogeneously forming depletion layers near the membrane. These depletion layers are a result of the phase separation between the polymer-rich domains and the solvent-rich domains. Because of its large degrees of freedom of the translation compared to the polymer segments, the solvent molecules excluded from the polymer-rich domains are accumulated in the vicinity of the membrane. While the vesicle shows a symmetric shape for a smaller value of the $\chi$-parameter (figs. 3(a) and (b)), the membrane shape becomes asymmetric for a larger value of $\chi$ ($\chi = 0.7$ in fig. 3(c)) in order to reduce the total interface area between the polymer-rich domains and the solvent-rich domains.

In summary, we introduced a new field-theoretic model for a vesicle that encloses polymers. With this model, we succeeded in calculating the equilibrium shape deformation of the vesicle induced by the polymers. This technique has a wide variety of extensions and applications such as the fusion and fission of the membrane by introducing the Gaussian curvature into the model.

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The authors thank Q. Du and I. Takagi for fruitful discussions. The present study is inspired by a collaboration of one of the authors (TK) with K. N. Yaegashi, M. Imai, S. Komura and N. Urakami. The present study is supported by Grant-in-Aid for Scientific Research on Priority Area “Soft Matter Physics” from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and Global COE Program at Tohoku University.

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