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Thermodynamics of Inter-leaflet Cavitation in Lipid Bilayer Membranes

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Abstract

Inter-leaflet cavitation in lipid bilayer membranes or shortly, intra-membrane cavitation (IMC) is the formation of gas bubbles between the two leaflets of the membrane. The present paper focuses on the thermodynamics of IMC, namely on the minimum work required to form an intra-membrane cavity. The minimum work can be separated into two parts, one that depends on the volume and number of gas molecules in the bubble and the other that depends on the bubble geometry. Minimization of the second part at a fixed bubble volume determines the optimized bubble shape. In homogeneous cavitation this part is proportional to the bubble surface area and, therefore, the bubble is spherical. In contrast, in IMC the second part is no more a simple function of the bubble area and the optimized cavity is not spherical because of the finite elasticity of the membrane. Using a simplified assumption about the cavity shape, the geometry-dependent term is derived and minimized at a fixed cavity volume. It is found that the optimized cavity is almost spherical at large bubble volumes, while at small volumes the cavity has a lens-like shape. The optimized shape is used to analyze the minimum work of IMC.

I. INTRODUCTION

Cavitation is a spontaneous formation of vapor/gas bubbles due to liquid tension (i.e., negative pressure), gas super-saturation, or boiling. The probability of cavitation is exponentially decreasing with the minimum work W required to form the bubble [1]. W is associated with Gibbs or Helmholtz free energy, depending on the constant pressure or constant volume conditions, respectively. Independently of the conditions, W can be separated into two terms. The first one, denoted by $W_1(V_b, N_b)$, is independent of the bubble geometry being a function of the number of gas molecules N_b in the bubble and its volume V_b . The second term, which is referred to here as the separation boundary energy, depends on the shape of the bubble. In the case where cavities are formed in the bulk, the so-called homogeneous cavitation (HC), where the interface layer can be considered infinitesimally thin, and shear forces may be neglected, the separation boundary energy is linearly proportional to the surface area A_b between the two phases

$$W_{HC} = W_1(V_b, N_b) + \sigma_{WG} A_b. \quad (1)$$

Here, σ_{WG} is the interface tension between the water-gas phases. In HC, bubbles are considered to be spherical since the spherical shape minimizes the interfacial energy part

(the second term of Eq.(1)) at any given volume. Therefore, the minimum work is a function of the bubble radius R_b since $V_b=4\pi R_b^3/3$ and $A_b=4\pi R_b^2$.

The present paper focuses on the thermodynamics, namely, the minimum work, of gas bubble formation between lipid bilayer leaflets (schematically shown in Fig. 1), the so-called intra-membrane cavitation (IMC). In IMC, where the monolayers are connected to the rest of the membrane and must be negatively curved at the edge (Fig. 1), the shape of the cavity cannot be spherical. In analyzing the shape of the intra-membrane cavity, both the membrane deformation energy (associated with membrane curvature) U_c and the interfacial tension energy must be taken into account. On one hand, decreasing the surface area of a cavity of a given volume will decrease the interfacial tension energy by forming a spherical cavity. On the other hand, this will increase the bending energy due to the sharp cavity edge. Conversely, smoothing the edge will decrease the bending energy, but increase the interface energy. In the present paper we propose an approximate solution for the optimal shape of the cavity, which minimizes the minimum work at a given volume. The solution shows that the bubble is close to a sphere when its volume is large, and has a lens-like shape when the volume is small.

There is an obvious resemblance between intra-membrane bubbles and a special case of isolated bubbles stabilized by amphiphilic molecules [2] or by other soft layers such as artificial micro-bubble contrast agents used in diagnostic ultrasound [3]. However, in the case of isolated bubbles, even if the elasticity of the stabilizing layer is taken into account, the bubbles are spherical. Another important difference between isolated bubbles and IMC is that the total amount of the material in the stabilizing layer of an isolated bubble is conserved and, therefore, variation of the bubble size is accompanied by the layer stretching/compressing [4]. In contrast, in IMC where the monolayers coating the cavity are connected to the rest of the membrane, the number of lipids may vary so that the area per lipid does not change, and, therefore, variations of the stretching/compressing energy can be neglected.

This study was motivated by recent publications [5–7], in which it was suggested that IMC, rather than HC, is crucial in ultrasound-induced membrane injury. Cavitation is considered to be an important factor in the ultrasound- and shock wave-induced bioeffects [8]. It is induced by a rapid pressure drop, which makes the dissolved gas supersaturated. Therefore, the theory developed in the present paper is of potential importance for medical applications of ultrasound and shock waves, including lithotripsy (destruction of kidney stones by shock wave), drug delivery [7], ultrasound diagnostics, etc. In addition, the thermodynamics of IMC may be of importance for understanding the mechanism of blast-induced traumatic brain injury.

The outline of the paper is as follows. The separation boundary energy and cavity shape of the intra-membrane cavity are considered in section II. The optimized shape is then used to analyze the minimum work of intra-membrane cavity formation in section III. Some concluding remarks are made in the final section IV.

II. THE SHAPE OF INTRA-MEMBRANE CAVITY

The part of the minimum work in IMC that depends on the bubble volume and is independent of the bubble shape is identical to that in HC. Denoting the contribution due to separating boundary (sb) by W_{sb} one can write the minimum work in IMC, W_{IM} , as

$$W_{IM}=W_1(V_b, N_b)+W_{sb}. \quad (2)$$

In this section we derive an approximate expression for W_{sb} . First, we specify the energy W_{sb} and the cavity shape in Sections II A and II B, respectively. Then we find the optimal cavity shape by minimizing the term W_{sb} at a given volume in Section II C. In addition, we analyze the case of large cavities in Section II D

A. Contribution of the separating boundary to the free energy

The term W_{sb} entering into Eq. (2) is a sum of two contributions, the energy difference due to the leaflet separation (ls), U_{ls} , and the contribution due the leaflet curvature (c), U_c ,

$$W_{sb}=U_{ls}+U_c. \quad (3)$$

Not much is known about inter-leaflet interaction. We assume that it can be described as a sum of van der Waals interactions. It was shown that such interactions between two infinite flat layers can be expressed in terms of the interfacial tension energy [9]. As an approximation, we use the same approach, which leads to

$$U_{ls}=\sigma_{HG}A_b, \quad (4)$$

where σ_{HG} is the hydrocarbon-gas interface tension and A_b is the area of the hydrocarbon-gas interface. The expression for the leaflet interaction energy in Eq. (4) is similar to the last term in Eq. (1) in the case of HC. Both the former and the later expressions are based on the approximation that fails at small cavity volume, but works reasonably well for spherical cavities of radii of a few nm [10].

The free energy change due to the leaflet deformation is a sum of stretching and bending energies [11]. The stretching modulus of the membrane monolayer is typically very high (about $\sim 100\text{mJ}/\text{m}^2$) [12]. Therefore, the membrane monolayer/bilayer are practically non-stretchable and non-compressible under normal conditions. In addition, we assume that in IMC the rest of the membrane acts as a lipid reservoir, and the number of lipids covering the intra-membrane cavity may vary to maintain constant area per lipid molecule. For this reason the contribution of stretching/compressing energy is neglected in the further analysis. This approximation is valid as long as the cavity is much smaller than the liposome size. Note that as discussed above this is in contrast to a spherical micro-bubble stabilized by a lipid layer, where the number of lipid molecules is constant, and, therefore, the contribution of stretching/compressing energy is important.

The bending energy of an infinitely thin film can be expressed in terms of its local mean and Gaussian curvatures denoted by H and K , respectively, $H=(C_1 + C_2)/2$ and $K= C_1 C_2$, where C_1 and C_2 are the principal local curvatures. For an interface of a finite thickness there may be another term which couples the stretching/compressing associated with bending. One can choose a neutral (n) surface where surface area is invariant to bending and this cross-term disappears [13]. The neutral surface is assumed to be parallel to the hydrocarbon-gas interface, which we will refer to as inner surface, with the distance between the two surfaces equal to d_n . We found that the qualitative results of our analysis are weakly sensitive to the value of d_n in the parameter range of interest.

As accepted, it is assumed that the bending energy U_c of each monolayer is given by the Helfrich expression [14]

$$U_c=\int dA_b^{(n)}(2\kappa(H-J_0)^2+\bar{\kappa}K) \quad (5)$$

where the integration is performed over the neutral surface, J_0 is the local spontaneous curvature, and κ and $\bar{\kappa}$ are the bending moduli associated with the mean and Gaussian curvatures, respectively. In the case of intra-membrane cavity, the energy (i.e., the work required to form a cavity) is measured relatively to that in the absence of the cavity, and, since the topology of each leaflet is not changed, the energy due to the Gaussian curvature is not changed as well (i.e., Gauss-Bonnet theorem). Furthermore, the term associated with J_0^2 doesn't depend on cavity's curvature and vanishes, so that Eq. (5) reduces to

$$U_c = \int dA_b^{(n)} \left(\frac{1}{2} \kappa (C_1 + C_2)^2 - 2\kappa (C_1 + C_2) J_0 \right). \quad (6)$$

B. Geometry of the intra-membrane cavity

It is assumed that the intra-membrane cavity is formed in a planar membrane, i.e., we assume that the length scales associated with the membrane without a cavity significantly exceed the bubble size. The coordinate system is chosen so that the xy plane is identical to the plane separating the two leaflets of the membrane without the bubble. We also assume that the cavity is symmetric about the xy plane and possesses rotational symmetry about the z -axis that passes through the center of the cavity perpendicular to this plane. Let r be the distance of a given point in the xy plane from the origin located in the cavity center. Denoting the z -coordinate of the cavity inner surface (hydrocarbon-gas interface) above this point by $h(r)$, we can write the bubble volume and inner surface area as

$$V_b = 4\pi \int_0^{r_b} dr r h(r) \quad (7)$$

and

$$A_b = 4\pi \int_0^{r_b} dr r \sqrt{1 + h_r^2}, \quad (8)$$

where $h_r = h/r$. The expression in Eq. (8) gives the hydrocarbon-gas interface area that enters into Eq. (4).

As mentioned earlier, the curvatures determining the bending energy are defined for neutral surface, which is represented by the height $h^{(n)}(r')$ as a function of the transformed radius r' . The relations between r' and $h^{(n)}(r')$, on the one hand, and radius r , height $h(r)$, and the distance d_n , on the other hand, are

$$r' = r - d_n \frac{h_r}{\sqrt{1 + h_r^2}} \quad (9)$$

and

$$h^{(n)}(r') = h(r) + d_n \frac{1}{\sqrt{1 + h_r^2}}. \quad (10)$$

The local principal curvatures of the neutral surface are given by [11]

$$C_1 = \frac{-h_{r'}^{(n)}}{r' \sqrt{1 + (h_{r'}^{(n)})^2}} \quad (11)$$

and

$$C_2 = \frac{-h_{r'r'}^{(n)}}{\left(1 + (h_{r'}^{(n)})^2\right)^{\frac{3}{2}}}, \quad (12)$$

where $h_{r'}^{(n)} \equiv \partial h^{(n)} / \partial r'$ and $h_{r'r'}^{(n)} \equiv \partial^2 h^{(n)} / \partial r'^2$. Note that $h_{r'}^{(n)} \equiv h_r$.

The optimal cavity shape can be found by minimizing the energy W_{sb} , Eq. (3), at a given volume V_b defined in Eq. (7). To achieve this, we first postulate a general shape of the cavity and then optimize it by choosing free parameters and minimizing the energy U_{sb} . Since the cavity is symmetric about the xy plane, we describe only the shape $h(r)$ of its upper part, i.e., for $z \geq 0$. We assume that the central part of the inner surface is spherical (s). It is characterized by radius R_s and the position of the center of the sphere, which is located on the z -axis at distance a below the xy plane. The spherical cap is connected to the flat part of the membrane by a torus of radius R_b that touches the xy plane along the circle $r = r_b$ and forms the boundary between the cavity and the rest of the membrane. This circle is the projection of the center line of the torus onto the xy plane. The torus crosses the sphere forming the central cap along the circle of radius r_1 . It is assumed that the derivative h_r is a continuous function of r at $r = r_1$. In Fig. 2 the three parts, the central spherical cap, the torus, and the rest of planar membrane are illustrated as blue, red, and green lines/surfaces. Detailed cross section is given in Fig. 2(c). The model of the cavity described above is similar to the model introduced in the papers cited in Ref. 15.

It is convenient to choose the cup radius R_s as a unit of length. Below, this scaling is indicated by a wavy line above the letters, for example, $\tilde{r} = r/R_s$, $\tilde{r}_1 = r_1/R_s$, etc. With this notations, the height of the inner cavity is given by

$$\tilde{h}(\tilde{r}) = \begin{cases} \sqrt{1 - \tilde{r}^2} - \tilde{a} & 0 < \tilde{r} < \tilde{r}_1 \\ \tilde{R}_t - \sqrt{\tilde{R}_t^2 - (\tilde{r} - \tilde{r}_b)^2} & \tilde{r}_1 < \tilde{r} < \tilde{r}_b \\ 0 & \tilde{r}_b < \tilde{r} \end{cases} \quad (13)$$

One can find the first and second derivatives of $\tilde{h}(\tilde{r})$ in Appendix A. The continuity of $\tilde{h}$ and $\tilde{h}_{\tilde{r}}$ at the tangential point $\tilde{r} = \tilde{r}_1$ leads to the relations

$$\tilde{a} = \sqrt{1 - \tilde{r}_1^2} (1 + \tilde{R}_t) - \tilde{R}_t \quad (14)$$

and

$$\tilde{r}_b = (1 + \tilde{R}_t) \tilde{r}_1, \quad (15)$$

which allow us to decrease the number of independent parameters determining the cavity from five (R_s , a , R_b , r_1 , and r_b) to three. Note that the scaled variables allow one to easily

distinguish bubbles of different shapes. Indeed, for stretched bubbles we have $\tilde{r}_1 < 1$ and $\tilde{a}$ is close to unity, while for spherical bubbles $\tilde{R}_b \tilde{a} \ll 1$ and $\tilde{r}_1, \tilde{r}_b$ are close to unity. The dependence of the cavity shape on these parameters is illustrated in Figs. 2(d) – 2(f).

The bubble volume and its inner surface area can be obtained by substituting $h(r)$, Eq. (13), into Eqs. (7) and (8) and performing the integration. The results can be written as

$$V_b(R_s, \tilde{r}_1, \tilde{R}_t) = \frac{4\pi}{3} R_s^3 \tilde{V}_b(\tilde{r}_1, \tilde{R}_t), \quad (16)$$

and

$$A_b(R_s, \tilde{r}_1, \tilde{R}_t) = 4\pi R_s^2 \tilde{A}_b(\tilde{r}_1, \tilde{R}_t), \quad (17)$$

where $\tilde{V}_b$ and $\tilde{A}_b$ are dimensionless functions of the parameters $\tilde{r}_1$ and $\tilde{R}_t$, given in Eqs. (A3) and (A4) of Appendix A, respectively.

C. Optimal shape of the inter-leaflet bubble of a given volume

For the sake of simplicity, we first consider the case of zero spontaneous curvature $J_0 = 0$. Without spontaneous curvature the bending energy of a spherical membrane is $2\pi\kappa$ independent on the sphere size. Similarly, the bending energy of intra-membrane cavity is (see Appendix B)

$$U_c = f_c(\tilde{r}_1, \tilde{R}_t, R_s) 2\pi\kappa, \quad (18)$$

where f_c , given in Eq. (B7), is a function that is weakly dependent on the cavity size through $\tilde{d}_n = d_n/R_s$, and for large cavities (i.e., $d_n \ll R_s$) it is only shape-dependent. Nevertheless, as we will show later, the optimized shape is dependent on cavity size and so the bending energy.

Other contributions to the minimum work, Eq. (2), are given in terms of the cavity volume, Eq. (16), and the interface surface area, Eq. (17). Thus, we have the W_{IM} as a function of the three free parameters R_s , r_1 and R_t .

For a fixed cavity volume, we can further reduce the number of free parameters from three to two. Introducing radius R_0 of an equivalent sphere whose volume V_0 is equal to the volume of the cavity, $V_b = V_0 = \frac{4}{3}\pi R_0^3$, we use Eq. (16) to find R_s as a function of two dimensionless radii $\tilde{r}_1$ and $\tilde{R}_t$ at a given R_0 ,

$$R_s(\tilde{r}_1, \tilde{R}_t | R_0) = R_0 \left(\frac{1}{\tilde{V}_b(\tilde{r}_1, \tilde{R}_t)} \right)^{\frac{1}{3}}. \quad (19)$$

Finally, the separation boundary energy takes the form

$$W_{sb} = f_c(\tilde{r}_1, \tilde{R}_t | R_0) 2\pi\kappa + \tilde{A}(\tilde{r}_1, \tilde{R}_t) 4\pi R_s^2 \sigma_{HG}. \quad (20)$$

Minimization of W_{sb} allows one to find the optimal shape of the cavity of a given volume. Because of the complexity of Eq. (20), this step is done numerically.

In Fig. 3 we show the optimized parameters $\tilde{r}_1$, $\tilde{R}_t$ and $\tilde{r}_b$, Eq. (15), as functions of the cavity size for typical values of the monolayer bending rigidity [12] $\kappa = 4 \cdot 10^{-20} J$ and the hydrocarbon-gas interface tension [16] $\sigma_{HG} = 30 mJ/nm^2$. We have found that for large R_0 both $\tilde{r}_1$ and $\tilde{r}_b$ approach unity while $\tilde{R}_t$ approaches zero as $\tilde{R}_t \approx (d_n + \zeta)/R_0$, where ζ is a constant. By fitting the curve shown in Fig. 3, we obtained $\zeta \approx 1.35 nm$. Thus, large cavities have a spherical shape. The radius of the torus connecting the spherical part of the cavity with the rest of the flat membrane is approaching its limiting value $d_n + \zeta$, which is independent of the cavity size. As the cavity volume decreases, $\tilde{R}_t$ increases while the scaled radius $\tilde{r}_1$, which determines the sphere-torus tangent point, decreases. As a result, the cavity becomes more and more stretched and takes the lens-like shape.

The validity of the zero J_0 approximation is discussed in Appendix C. In this Appendix we show that for typical values of the spontaneous curvature of lipid membranes there are no significant changes of the results.

D. Large cavities

It is informative to analyze the limiting case of large spherical cavities. As shown numerically (see Fig. 3), cavities with R_0 above a few nm become almost spherical, which justifies such an approximation. Optimization of Eq. (20) assuming that $R_0 \rightarrow \infty$, $\tilde{r}_1 \rightarrow 1$ and $\tilde{R}_t \ll 1$ shows that the scaled radius of the torus along the neutral surface at the cavity edge is $\tilde{R}_t - \tilde{d}_n \approx \zeta/R_0$, where

$$\zeta \approx \sqrt{\frac{\pi}{(\pi-2)} \frac{\kappa}{2\sigma_{HG}}} + O\left(\frac{1}{R_0}\right). \quad (21)$$

Note that a similar expression for ζ has been used in Refs. 15. Substituting ζ , Eq. (21), into the simplified version of Eq. (20), obtained in the large cavity approximation ($R_0 \rightarrow \infty$, $\tilde{r}_1 \rightarrow 1$ and $\tilde{R}_t \ll 1$), we arrive at

$$W_{sb} \approx (4\pi R_0^2)\sigma_{HG} + (2\pi R_0)\gamma + 2\pi\kappa \left(1 + \frac{\pi}{2}\right), \quad (22)$$

where factor γ is given by

$$\gamma \equiv \left((\pi-2)\sigma_{HG}(d_n + \zeta) + \frac{\pi\kappa}{2\zeta}\right). \quad (23)$$

The expression in Eq. (22) allows a simple interpretation: The first term, which is the product of the surface area and the interface tension, represents the interfacial tension energy, similar to the last term in Eq. (28) in the case of HC. The second term, which is proportional to $2\pi R_0$, represents the edge energy with the line tension γ , defined as the edge energy per unit length. The last term in Eq. (22) is the bending energy of a cavity, which is independent of the cavity size.

III. MINIMUM WORK

Consider a gas-liquid solution that initially was in equilibrium under atmospheric pressure, $P^{(0)}$, which then drops to a lower or even negative value P_l . The term of the minimum work of gas bubble nucleation that depends on V_b and N_b , both for HC and IMC, is given by

$$W_1(V_b, N_b) = P_l V_b - N_b k_B T \left(\ln \left(\frac{P^{(0)} V_b}{N_b k_B T} \right) + 1 \right). \quad (24)$$

Here it is assumed that the process is isothermal, there is only one gas component in the solution, and the effect of vapor is negligible. In addition, Eq. (24) is valid under the assumption that P_l and the concentration of gas dissolved in water are not changed during cavitation. In this section a brief summary of HC barrier for such a system is given in III A. A full analysis of IMC minimum work is given in III B

A. Minimum work in HC

The work W_{HC} , Eq. (1), that depends on two parameters, V_b and N_b , has a saddle point (sp) where the conditions of both chemical equilibrium, $W_{HC}' N_b = 0$, and mechanical equilibrium, $W_{HC}' V_b = 0$, are satisfied. Above this point, the work done by the pressure difference is larger than the interfacial energy penalty and a bubble tends to grow, forming a so-called “stable” bubble. On the other hand, below this point, the surface tension dominates and the bubble tends to disappear. Using Eqs. (1) and (24) one can find that the bubble radius at the saddle point is

$$R^{(sp)} = \frac{2\sigma_{wg}}{\Delta P^{(0)}}, \quad (25)$$

and the minimum work required to create such a bubble is given by

$$W_{HC}^{(sp)} = \frac{16\pi\sigma_{wg}^3}{3(\Delta P^{(0)})^2}. \quad (26)$$

A simplification of the W_{HC} -expression can be achieved by assuming chemical equilibrium (i.e., fast gas diffusion relatively to mechanical response), $N_b = P^{(0)} V_b / (k_B T)$. Under this assumption Eq. (24) reduces to

$$W_1^{(ch)}(V_b) = -\Delta P^{(0)} V_b, \quad (27)$$

where $\Delta P^{(0)} = P^{(0)} - P_l$. In this case the minimum work, Eq. (1), takes the form

$$W_{HC}^{(ch)} = -\Delta P^{(0)} \frac{4}{3} \pi R_b^3 + \sigma 4\pi R_b^2, \quad (28)$$

which is widely used in the nucleation theory.

B. Minimum work in IMC

In IMC, as mentioned earlier, the second term of W_{IMC} , Eq. (2), is not a simple function of the bubble radius as it is in HC. Nevertheless, once the shape parameters of the intra-membrane cavity of a given volume $V_0 = 4\pi R_0^3/3$, $R_s(R_0)$, $r_1(R_0)$, $R_t(R_0)$, $r_b(R_0)$, and $a(R_0)$, are known, the minimum work, Eq. (2), can be written as a function of cavity size R_0 and the number of gas molecules in the cavity N_b as

$$W_{IM}(R_0, N_b) = W_1(V_0, N_b) + \sigma_{HG} A_b(R_0) + U_c(R_0), \quad (29)$$

where $A_b(R_0)$ and $U_c(R_0)$ are given by Eqs. (17) and (18), respectively. Two contour maps of Eq. (29) for the negative and positive P_l are shown in panels (a) and (b) of Fig. 4, respectively.

The surfaces $W_{IM}(R_0, N_b)$ can be analyzed as follow. Minimizing $W_{IM}(R_0, N_b)$ with respect to N_b at fixed R_0 (chemical equilibrium), one can find that the optimal number of gas molecules in the cavity of volume V_0 is given by

$$N_b^{(ch)}(R_0) = \frac{P_g^{(0)} V_0}{k_B T} = \frac{4\pi R_0^3 P_g^{(0)}}{3k_B T}. \quad (30)$$

Minimization of $W_{IM}(R_0, N_b)$ with respect to R_0 at fixed N_b gives a complicated relation. In our further analysis we use the simplified version of W_{sb} given in Eq. (22) which is applicable when the cavity is large enough and its shape is close to the spherical one. As a result $W_{IM}(R_0, N_b)$ in Eq. (29) takes the form

$$W_{IM}(R_0, N_b) = W_1(V_0, N_b) + 4\pi R_0^2 \sigma_{HG} + 2\pi R_0 \gamma + 2\pi \kappa \left(1 + \frac{\pi}{2}\right). \quad (31)$$

Minimizing this function with respect to R_0 at fixed N_b , we arrive at a modified Young-Laplace (YL) equation,

$$\Delta P = \frac{N_b k_B T}{V_0} - P_l = \frac{2\sigma_{HG}}{R_0} + \frac{\gamma}{2R_0^2}. \quad (32)$$

This leads to the following expression for the number of gas molecules in the cavity of volume V_0 , on condition that R_0 satisfies the modified YL equation,

$$N_b^{(YL)}(R_0) = \frac{V_0}{k_B T} \left(P_l + \frac{2\sigma_{HG}}{R_0} + \frac{\gamma}{2R_0^2} \right). \quad (33)$$

Solution to the modified YL equation has qualitatively different behavior depending on the sign of the liquid pressure. When $0 \leq P_l < P_g^{(0)}$, the equation has a unique positive solution that exists at arbitrary N_b . This solution gives the radius of the bubble containing $N_b^{(YL)}$ gas molecules, which is in the so-called Laplace mechanical equilibrium with the surrounding liquid. When $P_l < 0$, the modified YL equation has two positive roots, if $N_b < N_b^*(P_l)$, the only positive root at $N_b = N_b^*(P_l)$, and no positive root, if $N_b > N_b^*(P_l)$, where $N_b^*(P_l) = N_b^{(YL)}(R^*)$ and

$$R^* = \frac{2\sigma_{HG}}{3|P_l|} \left[1 + \sqrt{1 + \frac{3\gamma|P_l|}{8\sigma_{HG}^2}} \right]. \quad (34)$$

The first of the two roots at $N_b < N_b^*(P_l)$ corresponds to a metastable minimum (Laplace mechanical equilibrium), while the second root corresponds to a maximum. If the radius of the bubble containing $N_b^{(YL)}$ gas molecules exceeds the second root, the bubble tends to grow. The YL equation has no positive root when $N_b > N_b^*(P_l)$, since $W_{IM}(R_0, N_b)$ is a monotonically decreasing function of the bubble radius for such N_b .

Dependences $N_b^{(ch)}(R_0)$ and $N_b^{(YL)}(R_0)$ are shown in Fig. 4 by bold dashed black and solid red lines, respectively. $N_b^{(ch)}(R_0)$ represents a system where diffusion of gas molecules is fast and therefore chemical equilibrium is reached instantly. On the other extreme, when diffusion is much slower, mechanical equilibrium is reached and the state of the bubble is described by the line $N_b^{(YL)}(R_0)$.

Assuming chemical equilibrium, $N_b = N_b^{(ch)}(R_0)$, we find that $W_{IM}(R_0, N_b^{(ch)}(R_0))$ in the large bubble approximation, Eq. (22), is given by

$$W_{IM}(R_0, N_b^{(ch)}(R_0)) = -\frac{4}{3}\pi R_0^3 \Delta P^{(0)} + 4\pi R_0^2 \sigma_{HG} + 2\pi R_0 \gamma + 2\pi \kappa \left(1 + \frac{\pi}{2}\right). \quad (35)$$

Minimizing this with respect to R_0 , we find the value of R_0 at the saddle point,

$$R_0^{(sp)} = \frac{\sigma_{HG}}{\Delta P^{(0)}} \left(1 + \sqrt{1 + \frac{\gamma \Delta P^{(0)}}{2\sigma_{HG}^2}}\right). \quad (36)$$

In the large bubble approximation, the second term under the square root is much smaller than unity. Therefore, $R_0^{(sp)}$ can be approximately written as

$$R_0^{(sp)} \approx \frac{2\sigma_{HG}}{\Delta P^{(0)}} \left(1 + \frac{\gamma \Delta P^{(0)}}{8\sigma_{HG}^2}\right). \quad (37)$$

Substituting this into Eq. (35), we find the minimum work corresponding to the saddle point in IMC,

$$W_{IM}^{(sp)} \approx \frac{16\pi\sigma_{HG}^2}{3(\Delta P^{(0)})^2} + \frac{4\pi\gamma\sigma_{HG}}{\Delta P^{(0)}} + 2\pi\kappa \left(1 + \frac{\pi}{2}\right). \quad (38)$$

The last two terms in the right-hand side of Eq. (38) are small compared to the first one. As consequence, the barrier height is proportional to the interface tension cubed like in HC, Eq. (26).

IV. CONCLUDING REMARKS

The thermodynamics of the intra-membrane cavitation discussed in the present paper is more complex than that of the homogeneous one. The reason is that when analyzing IMC one faces the problem of the cavity shape, which has a simple solution in the case of HC where the cavity is spherical. We give an approximate solution to this problem, which involves two steps. First, we postulate a general shape of the cavity and derive an analytical expression for the separation boundary energy required for the cavity formation. Second, by

minimizing the separation boundary energy at a given cavity volume, we find the values of the free parameters, which determine the optimal cavity of the postulated general shape. Finally, substituting the optimal parameter values into the expression for the minimum work, we obtain this quantity as a function of the cavity volume and number of gas molecules in the cavity.

Our analysis shows that the shape of the intra-membrane cavity depends on its volume. It is determined by the competition between the leaflet bending energy and the interfacial tension energy. The later plays a critical role in large cavities, which are of the spherical shape. In contrast, small cavities are found to be stretched and have a lens-like shape. The knowledge of the shape of the cavities is crucial also for the dynamics of such cavities under sound waves (e.g., ultrasound and shock waves). In general, a modified Rayleigh-Plesset equation, where the non-spherical shape is taken in account should be derived.

The surface representing the minimum work as a function of the bubble volume and the number of gas molecules in the bubble has a saddle point, which corresponds to the smallest barrier separating “shrinking” and “growing” bubbles. The saddle point is in the parameter range where the bubbles are large and spherical. Therefore, the minimum work at the saddle point, $W_{IM}^{(sp)}$, Eq. (38), is, roughly speaking, given by the same formula as in the case of HC, Eq. (26), in which $\sigma = \sigma_{HG}$. As a consequence,

$$\frac{W_{HC}^{(sp)}}{W_{IM}^{(sp)}} \approx \left(\frac{\sigma_{WG}}{\sigma_{HG}} \right)^3. \quad (39)$$

Since $\sigma_{WG}/\sigma_{HG} \approx 7/3$, we have $W_{HC}^{(sp)}/W_{IM}^{(sp)} \approx 13$. This shows that the minimum work of the cavity formation in HC significantly exceeds the one in the case of IMC. As the rate of cavitation decreases exponentially with the minimum work $\propto e^{-W/(kBT)}$, one might tentatively conclude that the probability of IMC is higher than that of HC. However, the pre-factors in those two cases are crucial and since, as far as we know, little is known about the pre-factor in IMC, this conclusion may be inaccurate. Calculation of the pre-factor involves analysis of the system dynamics along both N_b and R_0 coordinates (see Fig. 4). In other words, it requires consideration of both diffusive transport of gas molecules to a growing bubble and the dynamics of fluctuations of the bubble volume at fixed N_b . Consideration of these highly nontrivial questions is beyond the scope of the present paper.

It is important to emphasize that in both cases, HC and IMC, the minimum work is huge. However, the minimum work of the intra-membrane bubble formation is very sensitive to the value of the hydrocarbon-gas interface tension. The smaller is the tension, the lower is the energy barrier. In our discussion above we use the value of σ_{HG} given in Ref. [16]. At the same time, an order of magnitude smaller value of the hydrocarbon-gas interface tension has been reported in the literature [17]. Such small interface tension would make the formation of intra-membrane cavities much more probable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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19. The integral, Eq. (B6), has a different solution when $R_t - d_n > r_b$ (i.e., cavity with small and sharp center, and smooth large edges). Nevertheless, in the parameter range of interest the energy of such cavities is always higher.

Appendix A: Useful relationships

The formulas for the derivatives $\tilde{h}_f$ and $\tilde{h}_{\overline{m}}$ respectively, are

$$\tilde{h}_{\tilde{r}}(\tilde{r}) = \begin{cases} \frac{-\tilde{r}}{\sqrt{1-\tilde{r}^2}} & 0 < \tilde{r} < \tilde{r}_1 \\ \frac{\tilde{r}-\tilde{r}_b}{\sqrt{\tilde{R}_t^2-(\tilde{r}-\tilde{r}_b)^2}} & \tilde{r}_1 < \tilde{r} < \tilde{r}_b \\ 0 & \tilde{r}_b < \tilde{r} \end{cases}, \quad (\text{A1})$$

$$\tilde{h}_{\tilde{r}}(\tilde{r}) = \begin{cases} \frac{-1}{(1-\tilde{r}^2)^{3/2}} & 0 < \tilde{r} < \tilde{r}_1 \\ \frac{\tilde{R}_t^2}{(\tilde{R}_t^2-(\tilde{r}-\tilde{r}_b)^2)^{3/2}} & \tilde{r}_1 < \tilde{r} < \tilde{r}_b \\ 0 & \tilde{r}_b < \tilde{r} \end{cases}. \quad (\text{A2})$$

The dimensionless bubble volume $\tilde{V}_b$ and surface area $\tilde{A}_b$ are given by

$$\tilde{V}_b(\tilde{r}_1, \tilde{R}_t) = \left\{ (1+\tilde{R}_t^3) \left(1 - (1-\tilde{r}_1^2)^{\frac{3}{2}} \right) - \frac{3}{2} [(1+\tilde{R}_t^2)(1+\tilde{R}_t)(1-\tilde{r}_1^2)^{\frac{1}{2}} \tilde{r}_1^2 - \tilde{R}_t (1+\tilde{R}_t(2+\tilde{R}_t)) \tilde{r}_1^2 + (1+\tilde{R}_t)\tilde{R}_t^2 \tilde{r}_1 \arcsin(\tilde{r}_1)] \right\}, \quad (\text{A3})$$

and

$$\tilde{A}_b(\tilde{r}_1, \tilde{R}_t) = \left[\left(1 - \sqrt{1-\tilde{r}_1^2} \right) (1-\tilde{R}_t^2) + \tilde{R}_t(1+\tilde{R}_t)\tilde{r}_1 \arcsin(\tilde{r}_1) \right]. \quad (\text{A4})$$

Appendix B: Bending energy

With the help of Eqs. (9), (10), and (13) the height function of the neutral surface is given by

$$\tilde{h}^{(n)}(\tilde{r}') = \begin{cases} \frac{\sqrt{(1+\tilde{d}_n)^2 - \tilde{r}'^2} - \tilde{a}}{\tilde{R}_t - \sqrt{(\tilde{R}_t - \tilde{d}_n)^2 - (\tilde{r}' - \tilde{r}_b)^2}} & 0 < \tilde{r}' < \tilde{r}'_1 \\ \tilde{R}_t - \sqrt{(\tilde{R}_t - \tilde{d}_n)^2 - (\tilde{r}' - \tilde{r}_b)^2} & \tilde{r}'_1 < \tilde{r}' < \tilde{r}_b \\ 0 & \tilde{r}_b < \tilde{r}' \end{cases}, \quad (\text{B1})$$

where $\tilde{r}'_1 = (1+\tilde{d}_n)\tilde{r}_1$, and we have taken advantage of the fact that $\tilde{r}'_b = \tilde{r}_b$. Using the definitions of the principal curvatures, Eqs. (11) and (12), and the fact that $h_A(0) = h_A(r_b) = 0$, one can check that the integral of the product $C_1 C_2$ over the neutral surface is zero,

$$\int dA^{(n)} C_1 C_2 = 0. \quad (\text{B2})$$

Since $C_1 = C_2 = \frac{1}{R_s + d_n}$ in the central part of the bubble, $r' < r'_1$, where the bubble is spherical, the bending energy, Eq. (6), can be simplified and written as

$$U_c = 4\pi\kappa \int_{r'_1}^{r_b} dr' r' \sqrt{1 + (h_{r'}^{(n)})^2} (C_1 - C_2)^2. \quad (\text{B3})$$

Using the explicit expressions for the principal curvatures at this region,

$$C_1 = \frac{(r_b - r')}{r'(R_t - d_n)}, \quad (\text{B4})$$

and

$$C_2 = \frac{-1}{R_t - d_n}, \quad (\text{B5})$$

the bending energy, Eq. (B3), can be presented in the form

$$U_c = \frac{2\pi\kappa\tilde{r}_b^2}{(\tilde{R}_t - \tilde{d}_n)} \int_{\tilde{r}_1'}^{\tilde{r}_b} d\tilde{r} \frac{1}{\tilde{r} \sqrt{(\tilde{R}_t - \tilde{d}_n)^2 - (\tilde{r} - \tilde{r}_b)^2}}. \quad (\text{B6})$$

Note that for $\tilde{r}_1' \leq \tilde{r} \leq \tilde{r}_b$ the integrand is a real, positive function of $\tilde{r}$ since $\tilde{R}_t - \tilde{d}_n > \tilde{r}_b - \tilde{r}_1'$. Performing the integration [18], under the condition that $R_t - d_n < r_b$ [19], we arrive at Eq. (18), in which

$$f_c(\tilde{r}_1, \tilde{R}_t, R_s) = \frac{1}{\left(\frac{\tilde{R}_t - \tilde{d}_n}{\tilde{r}_b}\right) \sqrt{1 - \left(\frac{\tilde{R}_t - \tilde{d}_n}{\tilde{r}_b}\right)^2}} \times \left[\arcsin\left(\frac{\tilde{R}_t - \tilde{d}_n}{\tilde{r}_b}\right) + \arcsin\left(\frac{\tilde{r}_b}{1 + \tilde{d}_n} - \frac{(\tilde{R}_t - \tilde{d}_n)}{\tilde{r}_1(1 + \tilde{d}_n)}\right) \right]. \quad (\text{B7})$$

Appendix C: Nonzero spontaneous curvature

In the case of nonzero spontaneous curvature $J_0 \neq 0$, the term

$$-2\kappa J_0 \int dA^{(n)} (C_1 + C_2) = -8\pi\kappa J_0 R_s (1 + \tilde{R}_t) \left[2(1 - \sqrt{1 - \tilde{r}_1'^2}) + \tilde{r}_1' \arcsin(\tilde{r}_1') \right] \quad (\text{C1})$$

is added to the energy. This term is proportional to the cavity radius $\propto \kappa J_0 R_s$ and may be dominant only for small cavities (i.e., small surface area). In order to estimate the range of applicability of the zero J_0 approximation, the factor κJ_0 should be compared with the term associated with the “line tension” γ in Eqs. (22) and (23). One can see that as long as

$J_0 \ll \gamma/\kappa \approx \sqrt{\sigma_{HG}}/\kappa \approx nm^{-1}$ this approximation is valid. For most of lipids common for cells or liposomes, membranes have small curvature. For example, dioleoylphosphatidyl-choline (DOPC) membrane has $J_0 \approx -1/20 nm^{-1}$. At that value the effect is negligible. Even for higher values of curvature, e.g., dioleoylphosphatidyl-ethanolamine (DOPE) membrane, $J_0 \approx -1/3 nm^{-1}$, there are no qualitative changes, only an insignificant increase in the size where cavity becomes spherical. Much higher curvatures do not exist since $1/J_0$ cannot be much smaller than the monolayer thickness ($\approx 2.5 nm$).

FIG. 1. (color online) Schematic representation of cross sections of two intra-membrane cavities. The upper is mostly spherical with sharp edges but relatively small surface area, and the lower is more stretched with smoother edges but relatively large surface area. One of the goals of this study is to find an optimal cavity shape at a given volume. We will see that the optimal shape depends on the cavity size: Large cavities are almost spherical, whereas small cavities have a lens-like shape.

FIG. 2.

(color online) Cavity geometry (only upper leaflets are shown) is a combination of central spherical cap (blue), torus-like edge (red) and planer membrane (green) (panels (a) and (b)). Panel (c) illustrates the geometric structure details discussed in the text. Panels (d)–(f) are examples of cavities of equal volume but different scaled parameters (d) $\tilde{r}_1 = 0.5$, $\tilde{R}_t = 0.6$, (e) $\tilde{r}_1 = 0.8$, $\tilde{R}_t = 0.2$, and (f) $\tilde{r}_1 = 0.9$, $\tilde{R}_t = 0.05$.

FIG. 3.

(Color online) Optimized dimensionless radii $\tilde{r}_1$ (black squares), $\tilde{R}_t$ (red circles), and $\tilde{r}_b$ (blue triangles) are shown as functions of the radius R_0 . The inset shows these radii in a wider range of R_0 . The dependences are obtained for $\sigma_{HG} = 30 \text{ mJ/m}^2$, $\kappa = 4 \cdot 10^{-20} \text{ J}$, and $T = 310 \text{ K}$. At large volumes $\tilde{r}_1 \rightarrow 1$ and $\tilde{R}_t \rightarrow (d_n + \zeta)/R_0$, so the cavities are almost spherical while at small volumes they have a stretched lens-like shape.

FIG. 4.

(color online) The contour maps of $W_{IM}(R_0, N_b)$, Eq. (29), at $P_g^{(0)} = 1 \text{ atm}$, $\sigma_{HG} = 30 \text{ mJ/m}^2$, and $T = 310 \text{ K}$. Panels (a) and (b) show the maps at $P_l = -2 \text{ atm}$ and $P_l = 0.1 \text{ atm}$, respectively. Bold lines show $N_b^{(ch)}(R_0)$, Eq. (30), (dashed black), and $N_b^{(YL)}(R_0)$, Eq. (33), (solid red). The bold lines cross each other at the saddle points. When $0 \leq P_l < P_g^{(0)}$ the modified YL equation, Eq. 32, has a unique solution for R_0 at arbitrary N_b . Substituting this solution into Eq. (33) we obtain the dependence $N_b^{YL}(R_0)$ shown in panel (b). When $P_l < 0$ Eq. (32) has two positive roots if $N_b < N_b^{(YL)}(R^*)$, the only positive root at $N_b = N_b^{(YL)}(R^*)$, and no positive root if $N_b > N_b^{(YL)}(R^*)$. We use these roots to draw the dependence $N_b^{(YL)}(R_0)$ shown in panel (a).