The formation hat-shaped liposomes on solid support

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Abstract

We introduce a simple dynamical model, which can explain the formation of hat-shaped surface attached liposomes by taking membrane-membrane adhesion into account. The model reveals that hat formation is a general phenomenon, although it is difficult to observe experimentally. We discuss under what conditions hat-shaped vesicles can become observable. One such scenario, which is also consistent with experiments, is that the dynamics is slowed down by the low outflow rate of the internal fluid of the vesicle through the narrow space between the two bilayers of the brim.

Introduction

Lipid bilayers on solid support, often referred to as supported lipid bilayers (SLBs), are frequently used models of biological membranes. These bilayers are most often produced by the spontaneous rupture and fusion of unilamellar vesicles depositing from solution. Due to the high scientific and technological importance of SLBs, their formation has been studied extensively over the past two decades. Early ensemble techniques, such as quartz crystal microbalance (QCM)[1] or surface plasmon resonance (SPR),[2] indicated that SLB formation requires a critical vesicle coverage. Microscopic techniques, such as fluorescence microscopy (FM),[3] atomic force microscopy (AFM),[4] and cryotransmission electron microscopy (cryo-EM),[5] on the other hand, revealed the occurrence of isolated ruptures of individual vesicles. Recent FM studies by Weirich et al.[6] and interferometric scattering microscopy (iSCAT) by Andrecka et al.[7] reconciled the apparent conflict between the existence of isolated ruptures and the required critical vesicle coverage for SLB formation, suggesting that spontaneous ruptures of isolated vesicles provide small bilayer patches, which then act as nucleation sites and grow by inducing the rupture of vesicles at the patch edges. Efficient bilayer growth can thus occur only at sufficiently high vesicle coverage.

In their seminal work, Jass et al.[8] used tapping mode AFM to visualize the sequence of events involved in the transition from attached liposomes to bilayer patches. They observed that on hydrophilic supports the vesicles initially take a spherical cap shape (see Fig. 1(a) without the pore), and at a later stage they start flattening from the vesicle-support

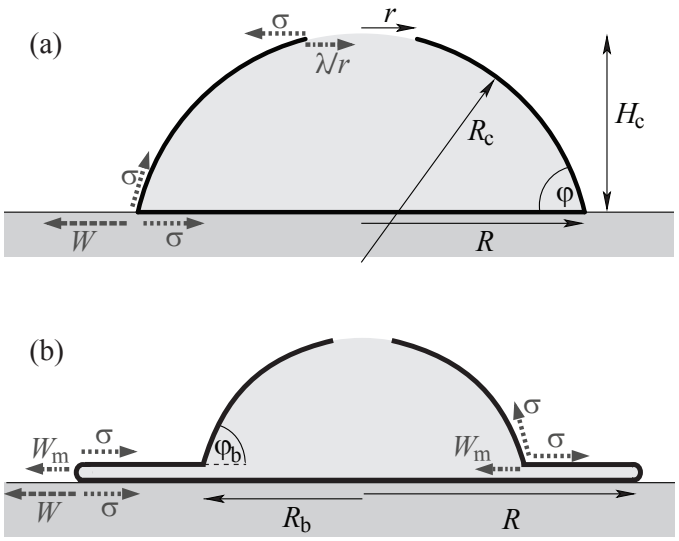

Figure 1: Schematic pictures of the cross sections of surface attached (a) cap-shaped and (b) hat-shaped vesicles in the limit of strong adhesion, with membrane pores at the top. Several parameters and force vectors (per unit length) are also indicated.

contact line toward the center, resembling a cylindrically symmetric hat (see Fig. 1(b) ignoring the pore) with a brim growing inward and a shrinking cap-shaped crown. After the crown disappears, the top bilayer of the resulting flat disk-like vesicle either rolls or slides over the bottom bilayer to form a single bilayer patch. The AFM cross sections of a cap-shaped and a hat-shaped vesicle are demonstrated in Figs. 2(a) and (b), respectively. Jass et al. also notes that hat formation appears to occur when the edge of an already existing bilayer patch gets in contact with the vesicle.

We have recently developed a theoretical model to understand and describe the details of the rupture process of liposomes along solid surfaces.[9] This and other previous models,[10,11] however, cannot account for brim formation, because the interaction of bilayers has not been taken into consideration in any of those models. Our goals here are (i) to extend our model by taking membrane-membrane adhesion into account; and to examine (ii) how frequently brim formation occurs during vesicle rupture if membrane-membrane adhesion is present; and (iii) under what conditions hat-

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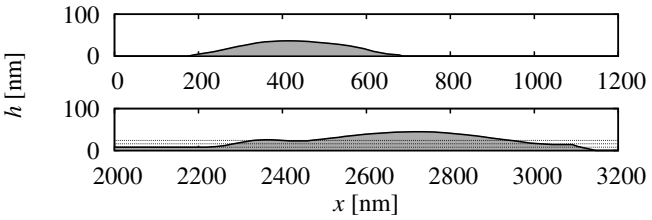

Figure 2: The AFM cross sections of (a) a cap-shaped and (b) a hat-shaped vesicle reproduced from Fig. 3C of Ref. 8. The three dotted lines (separated by the bilayer thickness) indicate that the brim is two bilayers thick, and that the brim on the left lies on top of a single bilayer.

shaped vesicles can last long enough to be observed experimentally.

Model and results

In the presense of membrane-membrane adhesion [12] the stable geometry of a vesicle (at fixed volume and surface area) attached to a solid support is either a spherical cap [13,14] or a hat, as illustrated in Figs. 1(a) and (b), respectively. For simplicity, we assume that the radius of curvature of the membrane at both the vesicle-support and the crown-brim contact lines is small compared to the size of the vesicle, i.e., the system is in the strong adhesion regime. In case of a cap-shaped vesicle the surface tension of the membrane (σ) in thermal equilibrium is given by the Young-Dupre equation, [15] which is simply the condition of force balance at the vesicle-support contact line:

$$\sigma = \frac{W}{1+\cos\varphi}\,, \tag{1}$$

where W is the adhesion energy between the membrane and the solid support per unit area ($W > 0$ for attractive interaction) and φ is the contact angle between the vesicle and the solid support. The contact angle is uniquely determined by the volume V and the projected area $A_\parallel$ (i.e., the area of the shape after averaging out the thermally induced membrane undulations) of the vesicle. This projected area is smaller than the total area of the membrane (A_0) by usually less than a few percent. [15]

For a hat-shaped vesicle the force balance conditions at the vesicle-support and the crown-brim contact lines are

$$\sigma = \frac{W+W_\mathrm{m}}{2} \tag{2}$$

and

$$\sigma = \frac{W_\mathrm{m}}{1-\cos\varphi_\mathrm{b}}\,, \tag{3}$$

respectively, where W_m is the membrane-membrane adhesion energy per unit area and φ_b is the contact angle between the crown and the brim. Note that W_m characterizes the adhesion between a surface bound and a free-standing membrane, and this adhesion might be stronger than between two free standing membranes, because the surface bound membrane is flatter and has already lost a portion of its entropy. After eliminating σ from Eqs. (2) and (3), the value of φ_b can be expressed as

$$\cos\varphi_\mathrm{b} = \frac{1-(W_\mathrm{m}/W)}{1+(W_\mathrm{m}/W)}\,, \tag{4}$$

which is independent of the geometrical properties of the vesicle.

The hat shape is always a stable stationary state, because any perturbation of the position of the crown-brim contact line (e.g., by increasing its radius, R_b, and concomitantly decreasing its contact angle φ_b) results in a net force that points towards the stationary position. Thus, whenever the geometry of the vesicle allows for both cap-shaped and hat-shaped geometries, i.e., when $\varphi < \varphi_\mathrm{b}$, the hat-shaped geometry will be the stable one, because any infinitesimal brim along the cap-shaped geometry will grow until the stationary hat shape will have been reached.

We make two remarks here. One is that we have neglected the curvature energy cost associated with brim formation, which can offset the transition between the cap shape and the hat shape to lower values of φ. For strong adhesion however, the curvature energy of the membrane at the outer edge of the brim [15] (which scales as $RR_\mathrm{curv}W$, where R denotes the vesicle-support contact radius and the local radius of curvature R_curv of the brim edge is only a few tens of nm) is indeed small compared to the total adhesion energy (which scales as R^2W). The other remark is that the crown could in principle be positioned anywhere with respect to the brim (as long it does not touch the brim edge). The central position is, however, preserved (i.e., the cylindrical symmetry remains unbroken) if the hat evolves via an isotropic shrinkage of its crown.

Combining the trigonometric relation $\cos\varphi_\mathrm{b} = (R_\mathrm{c} - H_\mathrm{c})/R_\mathrm{c}$ with the Pythagorean theorem $R_\mathrm{c}^2 = (R_\mathrm{c}-H_\mathrm{c})^2 + R_\mathrm{b}^2$, where R_c and H_c denote the radius and height of the crown, respectively, one can also express the contact angle as

$$\cos\varphi_\mathrm{b} = \frac{1-(H_\mathrm{c}/R_\mathrm{b})^2}{1+(H_\mathrm{c}/R_\mathrm{b})^2}\,. \tag{5}$$

Comparing this expression with Eq. (4) results in

$$\frac{W_\mathrm{m}}{W} = \left(\frac{H_\mathrm{c}}{R_\mathrm{b}}\right)^2\,, \tag{6}$$

which provides a simple way for measuring the membrane-membrane adhesion strength for equilibrium hat-shaped vesicles. In the experiments of Jass et al., [8] where the slowly changing vesicles can be considered close to equilibrium, the ratio $H_\mathrm{c}/R_\mathrm{b}$ is about 0.1, as can be seen in Fig. 2(b), thus the membrane-membrane adhesion is about two orders of magnitude weaker than the adhesion of the membrane to the solid support ($W_\mathrm{m}/W \approx 0.01$).

The evolution of slowly changing (quasi-static) vesicles can phenomenologically be described as follows. When a vesicle gets in contact with a flat hydrophilic surface it takes either a cap or a hat shape, and develops a surface tension σ given by Eq. (1) or Eq. (2), respectively. The surface ten-

sion then induces an excess pressure, the so-called Laplace pressure, $2\sigma/R_c$, inside the vesicle, where R_c is the radius of the spherical cap or crown. If the membrane is leaky (e.g., it contains a pore), then the pressure will drive the internal fluid out of the vesicle and make the vesicle loose its volume. For slow leakage (i.e., under quasi-static conditions, which is the case in the experiments of Jass et al.[8]) the shape of the vesicle remains always close to equilibrium. Even if the initial geometry is a cap, it will transform into a hat, when its contact angle φ decreases to φ_b due to volume loss. As the hat-shaped vesicle keeps loosing volume, its crown shrinks and its brim grows, while the crown-brim contact angle φ_b stays fixed. Eventually the vesicle looses all of its volume and becomes a flat disc.

To provide a more quantitative description, which is valid not only in the quasi-static limit, a detailed dynamical model is required. Firs we summarize our recently introduced model of cap-shaped vesicles with spontaneous pore openings,[9] and we extend it to hat-shaped geometries and include the possibility of edge-induced pore openings. The model assumes that the cap is always spherical (with cap radius R_c, cap height H_c, contact angle φ, and radius of contact area R) and the surface tension is homogeneous along the entire membrane. In fact, it can be shown that the surface tension equilibrates much faster than the shape of the vesicle.[9]

Spontaneous pore opening is an activated process and can occur anywhere along the membrane. It is, however, neglected at the contact area, where the adhesion makes it energetically less favorable. For simplicity, pore opening is also neglected at the contact line. The energy of a pore of radius r can be written as[16–19] $E = 2\pi r\lambda - \pi r^2\sigma$, where the first term is the energy contribution of the free membrane edge with line tension λ, and the second term accounts for the energy gain due to the shrinkage of the membrane under surface tension σ (for illustration see Fig. 1(a)). This energy function provides a parabolic barrier at radius $r^* = \lambda/\sigma$ with an activation energy of $E^* = \pi\lambda^2/\sigma$. The opening of a pore of radius r^* can thus be considered to occur at a rate of

$$k = k_0 \frac{A_c}{a^2} \exp\left(-\frac{\pi\lambda^2/\sigma}{k_B T}\right), \tag{7}$$

where k_B is the Boltzmann constant, $T \approx 300$ K is the absolute temperature, $A_c = A_0 - \pi R^2$ is the non-adhering surface area of the cap-shaped vesicle, a^2 is the surface area of a lipid molecule with linear size $a \approx 0.8$ nm,[14] and k_0 is the local attempt rate of pore nucleation. It is estimated to be of the order of $k_0 \approx 10^8$ 1/s, which is consistent with the ns time scale of molecular diffusion at nm distances, and also with the molecular dynamics simulations of the formation and disappearance of a single file of water across a lipid bilayer.[20] Its exact value is largely irrelevant because of the strong sensitivity of the exponential term on the value of σ. The line tension λ is typically of the order of 10 pN.[21,22]

All the parameters of the rate of pore opening are material properties of the membrane, except for the surface tension σ, which depends on the geometry of the vesicle. If only entropic stretching is considered, the surface tension can be expressed as[23]

$$\sigma = \frac{\pi^2\kappa}{a^2} \exp\left(-\frac{8\pi\kappa}{k_B T}\frac{A_c - A_{c\|}}{A_{c\|}}\right), \tag{8}$$

where $\kappa \approx 10^{-19}$ J is the bending rigidity of the bilayer,[24] and $A_{c\|} = 2\pi R_c H_c - \pi r^2$ is the projected area of the non-adhering part of the vesicle. As pore formation is accompanied by the reduction of the surface tension, formation of a second pore is an unlikely event, therefore, no more than one pore is allowed to be present at the same time.

Since the geometry of a spherical cap is uniquely determined by its volume V and contact radius R, the time evolution of the shape of the vesicle is completely given by three differential equations describing the dynamics of R, V, and r. The contact radius propagates[2,5,25–28] towards the Young-Dupre equilibrium at a rate

$$\dot{R} = \frac{W - (1+\cos\varphi)\sigma}{\eta_0 c_s}, \tag{9}$$

where $\eta_0 \approx 10^{-3}$ Pa s is the viscosity of the aqueous medium, and c_s denotes the surface drag coefficient. This latter quantity has several different components.[9] Hydrodynamic friction makes a contribution of the order of unity. The relative sliding between the two membrane layers (due to the smaller area of the inner layer) provides a more significant contribution of the order of $\pi\eta_m/\eta_0 \approx 10^3$, where $\eta_m \approx 0.2$ Pa s is the viscosity of the membrane.[16] Surface inhomogeneities and impurities can further increase the drag coefficient by several orders of magnitude.

When a pore is present in the membrane (which can be anywhere along the non-adhering part of the cap) the volume of the vesicle V changes as[17,18,29]

$$\dot{V} = -\frac{2}{3}\frac{r^3\sigma}{R_c\eta_0}, \tag{10}$$

due to leakage driven by the internal Laplace pressure $2\sigma/R_c$.

The radius of the pore is governed by[17,18]

$$\dot{r} = \frac{\sigma r - \lambda}{2\eta_m d}, \tag{11}$$

where $d \approx 5$ nm is the thickness of the bilayer.[14] This equation is valid as long as $r \ll R_c$, which usually holds until the final stages of vesicle rupture. Pore closure occurs when the pore radius becomes zero.

Numerical simulations of this model reveal a number of different scenarios for the fate of a surface attached vesicle (including partial flattening or SLB formation via either the formation of a single pore or the opening and closing of several subsequent transient pores) depending on the system parameters and the initial conditions.[9] To be able to recover brim formation, the vesicle dynamics has to be extended to hat geometries. As Fig. 1(b) illustrates, the dynamics of the vesicle-support contact radius R changes to

$$\dot{R} = \frac{W + W_m - 2\sigma}{\eta_0 c_s}, \tag{12}$$

and a fourth independent geometrical variable, the crown-brim contact radius R_b appears, which propagates towards its equilibrium position at a rate

$$\dot{R}_\mathrm{b} = -\frac{W_\mathrm{m} - (1-\cos\varphi)\sigma}{\eta_0 c_\mathrm{b}}\,, \tag{13}$$

where c_b is its drag coefficient. Because c_b is affected only by hydrodynamic and intermonolayer friction, it is expected to be of the order of 10^3. The transition from a cap to a hat shape occurs when the condition $\dot{R} - \dot{R}_\mathrm{b} > 0$ becomes satisfied, and the transition back to a cap shape requires that the width of the brim $R - R_\mathrm{b}$ decreases to zero.

Numerical simulations of this model reveal that after pore opening the surface tension of the membrane usually drops down to such an extent that the condition $\dot{R} - \dot{R}_\mathrm{b} > 0$ gets satisfied, and a brim forms. If, however, the pore closes back again, the brim disappears, unless the equilibrium geometry at the given volume is a hat shape.

The model can also produce long lasting transient brims (an example is shown in Fig. 3) as observed experimentally by Jass et al.,[8] but only in a very narrow range of parameters. A small change in W or c_s either speeds up the dynamics dramatically or slows it down such that the vesicles cannot reach the hat shape during the observation time. This might be the reason, why hat-shaped vesicles have not been reported in other experiments.

Jass et al. noted that hat formation appears to occur when the edge of an already existing bilayer patch gets in contact with the vesicle. Such an edge can induce the formation of a membrane pore at the vesicle-support contact line and fuse with the bottom bilayer of the vesicle, thereby making the pore permanent. As long as the vesicle has a cap shape its volume leaks out rapidly through this permanent pore. When the vesicle's shape changes to a hat, the leakage slows down, because the internal fluid has to flow through the narrow space between the two bilayers of the brim. This can naturally explain the existence of long lasting transient hat-shaped vesicles in case of edge induced pore formation.

The rate of Poisseuille's flow driven by a pressure difference Δp between two parallel plates of length L_x and width L_y separated by distance h is $h^3 \Delta p L_y/(12\eta_0 L_x)$. Although the flow geometry inside the brim is slightly different, the rate of the volume loss of the vesicle can be estimated by Poisseuille's flow rate under the assumptions that the driving pressure is the Laplace pressure $2\sigma/R_\mathrm{c}$ and that the effective length and width of the plates are of the same magnitude (both comparable to width of the brim):

$$\dot{V} \approx -\frac{1}{6}\frac{h^3\sigma}{R_\mathrm{c}\eta_0}\,. \tag{14}$$

Thus, in case of an edge induced permanent membrane pore, Eq. (10) should be replaced by Eq. (14), and Eq. (11) can be omitted. The separation h of the top and bottom bilayers of the brim is a couple of nm.

For strong adhesion ($W \approx 10^{-3}$ N/m, resulting in $\sigma \approx 100.5 \times 10^{-3}$ N/m in the quasi-static limit), assuming $h \approx 2$ nm, and using the crown geometry of Fig. 2(b) ($R \approx 300$ nm, $H_\mathrm{c} \approx 30$ nm, leading to $R_\mathrm{c} = (R^2 + H_\mathrm{c}^2)/(2H_\mathrm{c}) \approx$

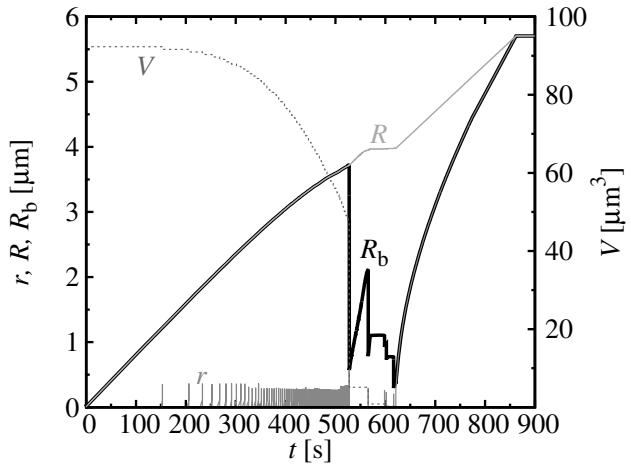

Figure 3: An example of the time evolution of the four main geometrical variables (V, r, R, and R_b) of a hat forming vesicle. The brim appears at about 530 s, and the crown diminishes at about 620 s. The system parameters are $W = 4 \times 10^{-3}$ N/m, $W_\mathrm{m} = 4 \times 10^{-4}$ N/m, $\lambda = 10$ pN, $c_\mathrm{s} = 5 \times 10^7$, $c_\mathrm{b} = 10^3$, $A = 100\ \mu\mathrm{m}^2$.

1500 nm) the volume loss rate is about 4×10^5 nm^3/s. The volume of the same hat-shaped vesicle is about $\pi R^2 H_\mathrm{c}/2 \approx 4 \times 10^6$ nm^3, i.e., it takes about 10 s for the vesicle to completely loose its volume. Although this is a crude estimation (e.g., the real value of W might be considerably smaller and, thus, the volume loss slower), it is consistent with the minute-long flattening times observed by Jass et al., and supports their hypothesis that hat formation is induced by a free membrane edge.

Discussion and Conclusion

In conclusion, we have introduced a simple model of the dynamics of surface attached vesicles, which, for the first time, can account for the formation of hat-shaped vesicles. The model reveals that if membrane-membrane adhesion is present (even if it is several orders of magnitude weaker than the membrane-support adhesion) hat formation is a general phenomenon. First, a brim often appears when the surface tension of the membrane drops down (and $\dot{R} - \dot{R}_\mathrm{b} > 0$ becomes satisfied) due to the formation of a membrane pore. Such a brim can rapidly disappear when the pore recloses and the surface tension goes up again. Second, a brim also appears, when the volume of the vesicle becomes small enough (such that $\varphi < \varphi_\mathrm{b}$). Hat-shaped vesicles are, however, difficult to observe, because if the conditions are suitable for pore opening and volume loss, then vesicle rupture usually proceeds quickly. The are two exceptions. One is when the surface inhomogeneities make the surface drag coefficient c_s large enough (of the order of 10^8) to slow down the dynamics to the appropriate time scale. This however, requires the parameters to be fine-tuned. The other exception is, when pores do not open spontaneously, but they can be induced at the contact lines by the edges of preexisting membrane patches. When the volume of the vesicle becomes

small enough for a brim to appear, the volume loss automatically slows down, due to the low flow rate of the fluid between the two bilayers of the brim. This scenario requires less fine-tuning of the parameters, and is consistent with the experimental observations by Jass et al.[8] The relevance of this type of hat formation is that it not only makes the hat-shaped vesicles observable, but it also slows down the SLB formation significantly.

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