Hydrodynamic Lift on Bound Vesicles

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Bound vesicles subject to lateral forces such as arising from shear flow are investigated theoretically by combining a lubrication analysis of the bound part with a scaling approach to the global motion. A minor inclination of the bound part leads to significant lift due to the additive effects of lateral and tank-treading motions. With increasing shear rate, the vesicle unbinds from the substrate at a critical value. Estimates are in agreement with recent experimental data.

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The *equilibrium* aspects of the interactions between membranes or vesicles and substrates have been explored intensely over the last decade [1]. Quantitative experimental data for both the mean shape and the fluctuations of the bound part of a vesicle have been obtained by using phase contrast microscopy and reflection interference contrast microscopy (RICM) [2]. A qualitative new step concerns the study of bound membranes under controlled *nonequilibrium* conditions such as the behavior of bound vesicles under shear flow. Apart from its fundamental significance, this system can serve as a model for the biologically ubiquitous situation of adhesion of membranes under flow. A prominent example occurs for leucocyte or platelet adhesion in capillary flow. Clearly, for biological systems, the nontrivial kinetics of *specific* adhesion molecule pairs under a ramped force contributes essentially to the dynamic unbinding of these cells (see, e.g., [3–5], and references therein). Still, a thorough understanding of the model case of a bound vesicle with its interplay between *unspecific* interactions and flow will be a prerequisite for gaining a comprehensive picture of these important dynamic interactions.

A significant experimental step in this direction has been achieved recently by combining RICM with a flow chamber [6]. With this setup one can study the configurations of bound vesicles under shear flow. It was observed that these vesicles unbind from the substrate at a critical shear rate. However, the effective lift force was found to be about 2 orders of magnitude larger than what was predicted in previous theoretical work [4].

The purpose of this Letter is to analyze theoretically the dynamically induced interaction between a substrate and a bound vesicle under a lateral force such as arising from shear flow. This problem is challenging since it involves two vastly different length scales. Typically, the vesicle size is of the order of 10 μm, whereas the distance between substrate and vesicle is of order 10 nm. A brute force approach trying to solve numerically the equations of motion of such a configuration as it has been done for free vesicles in shear flow [7] is bound to require a very fine discretization and, consequently, to face high computational costs. A first step in this direction has been achieved recently for the computationally less expensive two-dimensional case [8,9].

For the experimentally relevant three-dimensional case, a two step approach will be followed here. First, the bound part of the vesicle will be treated quantitatively within the lubrication approximation which holds if the lateral extension of the bound part is significantly larger than the distance from the substrate. As a result, we will find that whenever this bound part is tilted a significant hydrodynamic lift arises even for small tilt due to the additive effects of translation and relative membrane motion, i.e., tank treading. In a second step, we couple this lubrication analysis into a scaling approach of the overall vesicle motion. As a result, we predict a critical lateral force beyond which vesicles will detach from the bound state and, thus, undergo a dynamically induced unbinding transition. This transition must be distinguished from an equilibrium unbinding transition due either to fluctuations [10,11] or a competition between adhesion energy and curvature energy [12].

Geometry.—In equilibrium, a vesicle bound to a substrate by a potential $V(h)$ acquires a spherical caplike shape if the depth W of the potential is sufficiently deep; see Fig. 1. The shape can then be characterized by two parameters, the radius R of the spherical cap and the radius $R_a \leq R$ of the adhesion disc. The distance h_0 of

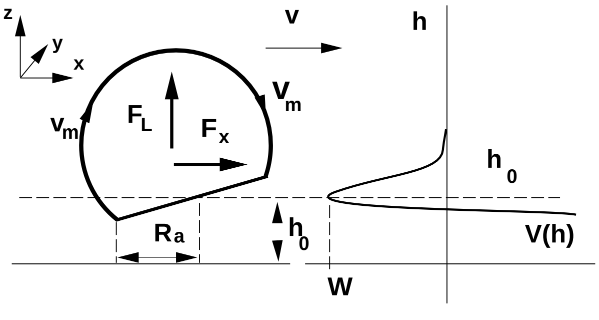

FIG. 1. A bound vesicle under a lateral force F_x (left) in a potential well $V(h)$ with minimum at h_0 and depth W (right). The radius of the adhesion disc is R_a, its tilt angle is α. The vesicle translates at velocity v and tank treads at velocity v_m. This motion generates a lift F_l.

the adhesion disc from the substrate is determined by the location of the minimum of the adhesion potential. In equilibrium, the adhesion disc is parallel to the substrate but we will here allow a small tilt angle α.

We now apply a force F_x parallel to the substrate. The physical origin of this force can either be a linear shear field with shear rate $\dot{\gamma}$ or a gradient in adhesion energy ∇W [8,9]. The force then scales as $F_x \sim \dot{\gamma}\eta R^2$, or $F_x \sim \nabla W R_a^2$, respectively. As a result the vesicle moves with a velocity v into the same direction. Since the membrane is fluid, we have to allow for tank-treading motion which we assume for the spherical part to be a uniform rotation in the x, z plane at an angular speed $\bar{v}_m/R$. This membrane flow on the spherical part enters (or leaves) the rim of the adhesion disc with a y dependent velocity

$$v_m(y) = \bar{v}_m(1 - y^2/R^2)^{1/2}, \tag{1}$$

where $|y| \leq R_a$. The velocities v and $\bar{v}_m$ will later be determined from force balances but for the moment they are assumed to be given. We show first that such a motion generates a significant hydrodynamic lift on the vesicle.

Lubrication theory.—For future reference, the lubrication approximation will be set up not just for a tilted adhesion disc but for a general membrane configuration parametrized by $h(\mathbf{r})$ in a Monge representation above a substrate at $z = 0$ with $\mathbf{r} = (x, y)$. The velocity field is written as $\mathbf{v}(\mathbf{r}, z) = \mathbf{u}(\mathbf{r}, z) + w(\mathbf{r}, z)\mathbf{e}_z$ where $\mathbf{u}(\mathbf{r}, z)$ is the component parallel to the substrate. At the membrane, we specify the velocity as $\mathbf{v}[\mathbf{r}, h(\mathbf{r})] = \mathbf{u}^h(\mathbf{r}) + w^h(\mathbf{r})\mathbf{e}_z$. At the substrate, no-slip boundary conditions imply $\mathbf{v}(\mathbf{r}, 0) = \mathbf{0}$.

The Stokes equations for the incompressible fluid between substrate and membrane read

$$\eta(\partial_z^2 + \nabla^2)\mathbf{u} = \nabla p\,, \tag{2}$$

and

$$\eta(\partial_z^2 + \nabla^2)w = \partial_z p\,. \tag{3}$$

Here ∇ is the gradient operator in the plane, i.e., $\nabla = (\partial_x, \partial_y)$ in Cartesian coordinates. From the continuity equation $\partial_z w + \nabla \mathbf{u} = 0$, it follows that $w/|\mathbf{u}| \sim O(h_0/R_a)$ for small h_0/R_a. This scaling implies via (2) and (3) that the pressure is a function of $\mathbf{r}$ but independent of z to leading order in h_0/R_a. Likewise the ∇^2 term can be ignored in (2). The latter equation can hence be integrated as $\mathbf{u}(\mathbf{r}, z) = \nabla p(\mathbf{r}) z(z - h)/2\eta + \mathbf{u}^h(\mathbf{r}) z/h$, which satisfies the boundary conditions at $z = 0$ and $z = h$. Applying the ∇ operator to this equation, inserting the resulting expression into the equation of continuity, and integrating the latter over z from 0 to h yields a Reynolds-type equation

$$\nabla^2 p + 3\nabla p \nabla h/h = 12\eta w^h/h^3 + 6\eta\nabla(\mathbf{u}^h/h)/h\,. \tag{4}$$

This equation for the pressure holds for any membrane configuration in the lubrication approximation. We now specialize to the circular adhesion disc of radius R_a tilted at a small angle α, i.e., $h(\mathbf{r}) = h_0 + \alpha x$; see Fig. 1. No slip boundary conditions between membrane and fluid imply for the translational and tank-treading motion introduced above the boundary values $w^h(\mathbf{r}) = -\alpha v_m(y)$ and $\mathbf{u}^h(\mathbf{r}) = [v - v_m(y)]\mathbf{e}_x$ for small α. With $\nabla h = \alpha \mathbf{e}_x$, Eq. (4) becomes

$$\nabla^2 p(\mathbf{r}) \approx -6\alpha\eta[v_m(y) + v]/h_0^3 \tag{5}$$

to lowest order in α. First, assume that there was no tank-treading motion, $\bar{v}_m = 0$, and, hence, no $\mathbf{r}$ dependence of the inhomogeneity in this Poisson equation. The solution then is

$$p(\mathbf{r}) = 3\alpha\eta v(R_a^2 - r^2)/2h_0^3 + p(R_a)(r/R_a)\cos\phi\,, \tag{6}$$

where $p(R_a)\cos\phi$ is the ambient pressure along the rim of the adhesion disc parametrized by the azimuthal angle ϕ. Integrating the excess pressure over the entire adhesion disc yields the total lift force on the membrane disc as

$$F_l = 3\pi\alpha\eta v R_a^4/4h_0^3\,. \tag{7}$$

For $\bar{v}_m \neq 0$, the solution of the Poisson equation (5) is slightly more involved because of the y dependence of the right-hand side (rhs). We are interested only in the total lift, which involves averaging over the whole adhesion disc. Given the form (1), it is then clear that (7) still holds with v replaced by $\bar{v}_m$ up to a dimensionless function $f(R_a/R)$ of order unity. The important point is that both translational motion and tank-treading motion contribute similarly to the hydrodynamic lift (7). This lift increases strongly with decreasing distance h_0 of the membrane from the substrate. Note that the reversibility of the Stokes equations implies that there is no hydrodynamic lift for a nontilted configuration with $\alpha = 0$.

Scaling analysis of global motion.—We now have to link this lubrication analysis of the adhesion disc to the overall vesicle dynamics. We apply the force F_x parallel to the substrate and assume first the rotational degree of freedom being locked at $\alpha = 0$. Then, there are two conditions which fix the two velocity parameters v and $\bar{v}_m$ uniquely. Ignoring numerical prefactors these conditions read: (i) Force balance in the x direction:

$$F_x \sim \eta\Delta v R_a^2/h_0 + \eta v R\,, \tag{8}$$

where $\Delta v \equiv v - \bar{v}_m$ is the velocity of the bound part of the vesicle relative to the substrate. The first term on the rhs is the lateral force exerted by the lubrication layer, the second term is the hydrodynamic drag of the exterior fluid outside of the lubrication layer. (ii) Dissipation balance:

$$F_x v \sim \eta(\Delta v)^2 R_a^2/h_0 + \eta v^2 R + \eta\bar{v}_m^2 R\,. \tag{9}$$

The left-hand side represents the power applied by the external force onthe system. The first term on the rhs is the dissipation in the lubrication layer. The second one is dissipation in the exterior fluid outside of the lubrication layer. The third term is the dissipation within the vesicle due to tank treading. We now divide the first equation by ηR, the second one by $\eta v R$, and introduce with $v_S \equiv F_x/6\pi\eta R$ the Stokes velocity of a spherical vesicle in infinite space.

The two equations (8) and (9) then read $v_S \sim \beta\Delta v + v$ and $v_S \sim \beta(\Delta v)^2/v + v + \bar{v}_m^2/v$, where $\beta \equiv R_a^2/h_0 R$ is a dimensionless variable measuring the relevance of the substrate. For the scaling analysis, we have to distinguish three cases.

(i) For $\beta \ll 1$, the vesicle is too far away from the substrate to be affected significantly in its motion. We will not consider this case further.

(ii) For $\beta \sim 1$, we have $\Delta v \sim v \sim \bar{v}_m \sim v_S$. In this case, both translational and tank-treading velocity are of the order of the Stokes velocity.

(iii) For $\beta \gg 1$, we find $\Delta v \sim v/\beta$ and, consequently, $\bar{v}_m \approx v \sim v_S$. In this limit, tank treading and translational velocity become equal and both are of the order of the Stokes velocity [9]. Tank treading thus restores (up to factors of order unity) the free mobility which would be impossible for a rigid object with finite R_a so close to a substrate. In summary, we can write in each of the two interesting cases

$$\bar{v}_m \sim v \sim v_S \sim F_x/\eta R \quad \text{and} \quad \Delta v/v \sim h_0 R/R_a^2 . \tag{10}$$

Hydrodynamic lift.—Using these results, which will hold within perturbation theory also for small nonzero tilt angle α, the lift (7) can be written as

$$F_l \sim \alpha\eta v R_a^4/h_0^3 \sim \alpha F_x (R_a/R)(R_a/h_0)^3 . \tag{11}$$

This expression still depends on the unknown tilt angle α which must be determined next.

In general, the transversal motion considered so far for the rotationally locked shape at $\alpha = 0$ generates a torque M acting in the x, z plane. The origins of this torque are the lateral force and hydrodynamic interactions. Their sum will scale as $M \sim \eta v R^2 \sim F_x R$. Counteracting to such a torque is a torque arising from the confining adhesion potential which favors $\alpha = 0$. The energy $E(\alpha)$ of a tilted adhesion disc compared to a nontilted one is given by $E(\alpha) \approx (\pi/4)\alpha^2 V'' R_a^4$ where $V'' \equiv V''(h_0)$ is the curvature of the adhesion potential at the minimum h_0. Balancing the torque $\partial_\alpha E$ derived herefrom with the hydrodynamic one leads to $\eta v R^2 \sim \alpha V'' R_a^4$ or

$$\alpha \sim \eta v R^2/V'' R_a^4 \sim F_x R/V'' R_a^4 . \tag{12}$$

We have written these relations as if α were positive. For shear flow, evidence for this assumption arises from the following facts. Free ellipsoidal vesicles become tilted with a positive angle [7]. This result can be understood by splitting up shear flow into a rotational and a strain component. In the spherical limit, the former causes only tank treading while the latter leads to a 45° tilt. Since such a decomposition holds true in the presence of a wall, an ellipsoidal shape would also exhibit a positive tilt. This has been confirmed explicitly within perturbation theory for small R/h_0 [13]. Even though only a full hydrodynamic calculation could prove that spherical caps show the same sign of the tilt as ellipsoids do, we will continue with $\alpha > 0$ [14]. Using (12), we can now calculate the lift force from (7) as

$$F_l \sim \eta^2 v^2 R^2/h_0^3 V'' \sim F_x^2/h_0^3 V'' . \tag{13}$$

For further evaluation, we need the specific form of the adhesion potential $V(h)$. A fairly universal relation can be derived if we assume that this potential can be characterized by two scales only, the location h_0 of its minimum and its depth $W \equiv |V(h_0)|$; see Fig. 1. Then, one has $V'' \sim W/h_0^2$, which implies $F_l \sim F_x^2/W h_0$.

For a comparison with experimental quantities, it is convenient to express the adhesion energy W in terms of an effective tension $\Sigma \sim W R^2/R_a^2$ using a Young Dupre equation [11]. For vesicles in shear flow, we can thus write for the lift

$$F_l \sim F_x^2/W h_0 \sim (\eta^2 \dot{\gamma}^2 R^3/\Sigma)(R_a^2/h_0 R) . \tag{14}$$

This result is a factor of order $R_a^2/h_0 R \simeq 10\text{–}10^3$ larger than a previous theoretical estimate [4]. On the basis of the latter, it was argued in Ref. [6] that the experimentally observed lift was 2 to 3 orders of magnitude larger than theoretically expected. In light of the present theory, this apparent discrepancy is most likely due to the factor $R_a^2/h_0 R$ missed in Ref. [4].

Dynamical unbinding.—The lift, if small enough, will displace the vesicle slightly from the static equilibrium at h_0. The new dynamical equilibrium position can now be found by balancing the lift with the restoring force, $F_z \approx -\pi R_a^2 (h - h_0) V''$, arising from an expansion of the potential around its minimum. The relative shift thus becomes

$$(h - h_0)/h_0 \sim F_x^2/h_0^4 V''^2 R_a^2 \sim F_x^2/W^2 R_a^2 . \tag{15}$$

Typically, if $[(h - h_0)/h_0] \sim 1$, the lift will be too strong to be compensated by the attractive potential. Then, the vesicle will unbind from the substrate under the action of a lateral force. Using this criterion, we can determine the critical lateral force F_x^c as $F_x^c \sim h_0^2 V'' R_a \sim W R_a$. If the lateral force arises from a shear field, the critical shear rate is $\dot{\gamma}^c \sim W R_a/\eta R^2$.

Depending on the specific conditions, measurements for the adhesion energy W have obtained a vast range of values from 10^{-1} to 10^{-6} erg/cm^2 [2,15,16]. Consequently, the critical shear rate will also depend strongly on the conditions. Likewise, for a typical shear rate $\dot{\gamma} = 1/\text{s}$, one can estimate a critical adhesion energy W^c at which the dynamical unbinding should occur. For a vesicle with $R = 10\ \mu\text{m}$, $R_a/R = 0.1$, and $\eta = 10^{-2}$ erg s/cm^3, we find a critical adhesion energy of $W^c \sim 10^{-4}$ erg/cm^2 which is well within the above range.

The tilt angle α^c at the critical value is

$$\alpha^c \sim F_x^c R/V'' R_a^4 \sim F_x^c R h_0^2/W R_a^4 \sim h_0^2 R/R_a^3 . \tag{16}$$

Within this simple assumption about the adhesion potential, the scaling of the critical tilt is thus predicted to be determined exclusively by geometrical quantities. Note that since $h_0 \ll R_a \lesssim R$, the critical tilt angle can be very small, e.g., $\alpha_c \simeq 10^{-3}$ for $h_0 = 10$ nm and R, R_a as above.

Role of shape deformation.—So far, we have assumed that the shape remains a spherical cap. However, the flow field could also lead to a deformation of the unbound part of the vesicle. This deformation would break the fore-aft symmetry and, thus, would also be a source of lift. Since such a deformation necessarily implies a smaller area of contact, it will set in significantly when the hydrodynamic stress ($\sim \dot{\gamma}\eta R$) becomes comparable to the adhesion-induced stress ($\sim W R^2/R_a^2$). This happens for $\dot{\gamma} \sim \dot{\gamma}^c (R/R_a)^3 \gtrsim \dot{\gamma}^c$. The shear rate at which deformation becomes relevant is in the worst case comparable to (and in the spherical limit $R_a \ll R$ much larger than) the critical shear rate based on tilt. Thus, for the present scaling analysis, it was safe to consider tilt as the only relevant variable even though deformation may play an additional role modifying numerical prefactors.

Beyond unbinding.—What happens with the vesicle for larger lateral forces $F_x > F_x^c$? If the adhesion potential decays to 0 for large h, one can expect that the vesicle will continously drift away from the substrate presumably in a combination of tank treading and tumbling motion. If, however, as often in experiments, the vesicle is filled with a slightly denser fluid than the surroundings, gravity will keep it close to the substrate. Such a state where after detachment the vesicle still keeps its spherical cap like configuration and translates at about 100 nm above the substrate has been reported experimentally [6]. We close with a somewhat speculative theoretical analysis of this state. The jump in separation from the substrate of about 100 nm could indicate that a short range adhesion potential is no longer responsible to the energetics after detachment. Neither can the potential then exert a restoring torque. Therefore, the total hydrodynamic torque must vanish. At which angle α this happens (if at all) can only be determined by a full hydrodynamic theory. The present scaling approach, however, allows to relate this tilt angle α to the separation h by balancing the lift force (11) with the gravitational force $F_g = g \Delta\rho V$, where $g \simeq 1000$ cm/s^2 and $\Delta\rho$ is the density difference. Such a balance leads to $\alpha \sim (h_0/R_a)^3 (F_g/F_x)(R/R_a)$. Using typical experimental values $F_g \simeq 10^{-7}$ erg/cm, $F_x \simeq 10^{-8}$ erg/cm, $h_0/R_a \simeq 0.1$, and $R/R_a \simeq 10$, one finds with $\alpha \simeq 0.1$ that a quite small tilt angle could generate enough lift to sustain such a stationary state.

Summarizing perspective.—We have analyzed the hydrodynamics of a bound vesicle under a lateral force allowing for tank-treading motion. A positive tilt of the bound part will generate lift. By combining a lubrication analysis with scaling arguments, a dynamically induced unbinding transition is predicted when the lateral force exceeds a critical value. More quantitative theoretical calculations will be needed to fill in numerical prefactors necessarily missing in such a scaling analysis. Such full scale calculations will also reveal the role of transients and assess whether the theoretically somewhat speculative stationary translating state after unbinding exists.

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