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Adhesion-induced vesicle propulsion

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We study theoretically vesicle locomotion. We show how adhesion may lead to vesicle propulsion. The problem is fully solved numerically and an analytical solution is obtained in a perturbative scheme. The analytical result reproduces the numerical one. We provide an expression for the drift velocity as a function of relevant parameters. We discuss how a vesicle or a cell could establish itself this motion from physicochemical concepts, while its environment could be initially homogeneous. We suggest experimental protocols. [S1063-651X(97)51209-8]

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Phospholipid membranes are widely studied both experimentally and theoretically. The reasons are at least twofold: (i) they constitute the major and vital compartments of cells in the realm of biology, (ii) they provide canonical systems that lend themselves to a relatively simple modeling. The famous Helfrich [1] model based only on curvature energy has constituted an important starting point for the modeling of vesicle shapes. Some of these shapes are surprisingly close to those encountered for real biological cells, such as erythrocytes. This has stimulated a myriad of studies and drawn attention to the fact that simple physical concepts may, to some extent, be relevant for describing several features (e.g., the shape) of apparently complex entities [2].

Theoretical studies [3] on equilibrium shapes of a pure phospholipidic vesicle have been successfully conducted in predicting the shape conformations that are expected in a given range of parameter space. Experiments have played an important role [4] in the development of this field, and have even led to the discovery of many surprising forms with nontrivial topologies [5] (such as n-genus torus) predicted by the model [6].

In the realm of biology, many features are of a nonequilibrium dissipative nature. Perhaps one of the most noticeable and puzzling nonequilibrium features of a cell is its ability to move. The understanding of the mechanisms by which crawling, rolling, etc. operate is still quite premature. Several recent attracting experimental works attempt to understand cell locomotion [7,8]. There is also considerable precedent for gradient of substratum bound, insoluble molecules, in playing an important role in orienting the locomotion of cells [9]. That is to say, adhesion gradients selectively guide the movement.

We report on how a phospholipidic vesicle on a substrate can move in the presence of inhomogeneous adhesion. We provide an expression for the velocity as a function of relevant parameters. We shall comment in the conclusion on concepts related to how a cell or a vesicle could establish this motion spontaneously.

Our study is inspired by a recent impressive experiment on reactive liquid droplets [10]. These are droplets of n-alkanes containing chlorosilane. The silane reacts with the OH group of the glass substrate, and makes it hydrophobic. Once a motion has been initiated the droplet escapes the reacted regions; it thus spontaneously moves, and attains a permanent regime. Brochard-Wyart and De Gennes [11] have recently given an interpretation of this phenomenon.

Let us start with a simple case. Suppose that a phospholipid vesicle is deposited on top of two contiguous substrata ''A'' and ''B'' with adhesion energies W_1 and W_2. The initial stage is that the vesicle is straddling the two substrates. If $W_2 > W_1$, one expects the vesicle to move spontaneously from A to B. This is what happens in our simulations. We can then imagine different protocols where the vesicle could permanently experience different adhesion energies backward and forward. Our expectation is that it should acquire a permanent motion. This is the outcome of our study.

Similar to studies on vesicle shapes, we shall keep our description as simple as possible. Since we are interested in dynamics, we shall develop a time-dependent theory that should serve to study any dynamical phenomenon associated with shape conformation and/or global motion. For ease of presentation in this paper, we restrict ourselves to a two-dimensional vesicle. Any fluctuation is associated with a dissipation in some degrees of freedom. The slowest modes are of hydrodynamics type. We shall rather assume an overall constant mobility η. This does not alter the qualitative features. Inclusion of full hydrodynamics will constitute the subject of a forthcoming work. The model below is sufficient in presenting the general concept. The simplest description of vesicle dynamics is based here on a model where the vesicle position $\mathbf{r}$ obeys

$$\eta \frac{\partial \mathbf{r}}{\partial t} = -\frac{1}{\sqrt{g}} \frac{\delta F}{\delta \mathbf{r}} + \theta \hat{\mathbf{t}}, \tag{1}$$

where F is the total free energy including the adhesion part and will be given below, g is the induced metric, and θ ($\hat{\mathbf{t}}$ is the unit tangent vector) is a quantity which ensures a gauge field invariant formulation under any surface reparametrization. As it will appear soon, θ is a quantity which is fixed only by the curve parametrization. We consider that $\mathbf{r}(\alpha,t)$ is

parametrized by α, which is taken at liberty to belong to the interval [0,1]. The simplest Helfrich free energy (including adhesion) takes the form

$$F=\kappa\int_0^L ds\left(\frac{1}{2}c^2-\frac{1}{2}(P/\kappa)\mathbf{r}\times\hat{\mathbf{t}}+(\zeta/\kappa)\right)+W_1x_1-W_2x_2\,. \tag{2}$$

c is the curvature, κ the rigidity, L the total length, x_1 and x_2 the x positions of the two contact points, P and ζ are time-dependent Lagrange multipliers enforcing a constant enclosed area (or volume in 3D) and a total length (or surface in 3D).

Setting $\partial\mathbf{r}/\partial t=\mathbf{v}$ we immediately obtain (except at the end points x_1 and x_2, as we shall see later) from Eqs. (1) and (2),

$$\mathbf{v}=\frac{\kappa}{\eta}\left(\frac{d^2c}{ds^2}+\frac{1}{2}c^3-P/\kappa-\zeta c/\kappa\right)\hat{\mathbf{n}}+\frac{\theta}{\eta}\hat{\mathbf{t}}. \tag{3}$$

The quantity θ is simply the tangential velocity, while the physics is contained in the normal part v_n. The introduction of θ offers the freedom for the choice of any convenient parametrization of the vesicle. Once the parametrization is fixed, the tangential velocity is determined, without altering the physics. Note that the normal part is similar to that found by Goldstein and Langer [12] in the context of dynamics of stiff polymers. We find it convenient to use a parametrisation in a such way that the relative distance between two points s/L on the vesicle remains constant as time proceeds. This fixes θ [13].

We are now in a position to tackle nonequilibrium features. For the adhesion problem one needs to specify the boundary conditions. Let ψ be the angle between the normal and the vertical axis. The first boundary condition is

$$\psi(x=x_1)=\pi,\quad \psi(x=x_2)=-\pi\,, \tag{4}$$

because any other value would imply an infinite curvature at the contact points. The second condition follows from analyzing consequences of virtual displacements of the contact points x_1 and x_2, a classical variational problem with *à priori* nonfixed boundaries [14]. In the present context, Seifert [15] has treated this problem for static vesicles, and provided a boundary condition on the curvature at the contact point. There is *a priori* no reason that the same condition holds in the dynamical case. Any virtual displacement of the contact point by an amount δx leads to an energy change at that point given by $\delta F=\delta x(\kappa c^2-2W)$. Any fluctuation is associated to a dissipation. One of the most serious points to be emphasized [16] is the relation between fluctuations and dissipations. For example, a liquid contact line can dissipate the energy in the hydrodynamic flow in the wedge, or via the microscopic jump of molecules at the tip. Another important question concerns the type of motion at the contact point. We can think of bond breaking on one side of the contact and bond restoring at the other side. In this work we shall postulate a dissipation law where the contact points obey the following dynamical equations:

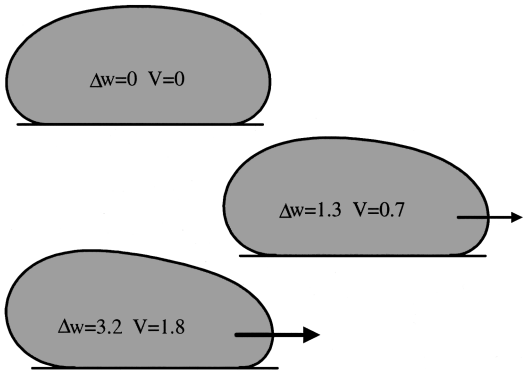

FIG. 1. Typical solution moving at constant speed sideways for different values of parameters. Here p is fixed while the area adapts itself. V is measured in units of 100 μm and W in units of 10^{-4} mJ/m^2.

$$\frac{\partial x_1}{\partial t}=\Gamma^{-1}(\kappa c^2-2W_1),\quad \frac{\partial x_2}{\partial t}=-\Gamma^{-1}(\kappa c^2-2W_2)\,, \tag{5}$$

where Γ is a phenomenological dissipation coefficient. It is an important task for future investigations to determine this coefficient from microscopic considerations. The time scale involved in the dissipation coefficient Γ might be (but not necessarily) fixed by hydrodynamics. Which dissipation dominates in the general case, should clearly depend on specific situations. We hope to address these crucial questions in the future. The signs in Eq. (5) are fixed by the condition that there is either adhesion (energy gain) or detachment (energy loss).

The first result is that the vesicle spontaneously moves towards the B part. If W_1 and W_2 are constant on both sides, the vesicle acquires a constant velocity, a situation on which we now direct our attention. The full transient problem will be presented elsewhere. We set $v_n=\mathcal{V}\sin(\psi)$, where $\mathcal{V}$ is the (constant) drift velocity. Equation (3) can be converted into three differential equations of first order. We then require three conditions. Moreover, $\mathcal{V}$ and ζ are unknown quantities (here we fix p which implies a freedom on the area). There is a hidden unknown, the contact area x_2-x_1. We need six conditions in total. Four conditions are provided by Eqs. (4) and (5), whereas the remaining two conditions stem from the geometric constraints, namely, $\oint\sin(\psi)=0$ (which imposes to the height on both sides to be identical), and $\oint\cos(\psi)ds=x_2-x_1$ (which ensures that the ''landing'' point in a shooting method is precisely x_2, if x_1 is the shooting origin).

Figure 1 shows a typical vesicle for three values of the driving force. Note that the motion direction corresponds to the one where the vesicle has developed a ''foot.'' Figure 2 shows how the velocity behaves as a function of the adhesion difference. Due to various parameters that enter into the problem, it is highly desirable to have analytical results at our disposal. Our starting point is to notice that the velocity is a global quantity, and there should be no need to go into local details to determine it. For that purpose, we start from the third order differential equation for ψ as it follows from Eq. (3). Multiplying on both sides by dc/ds and integrating over the vesicle from x_1 to x_2 yields

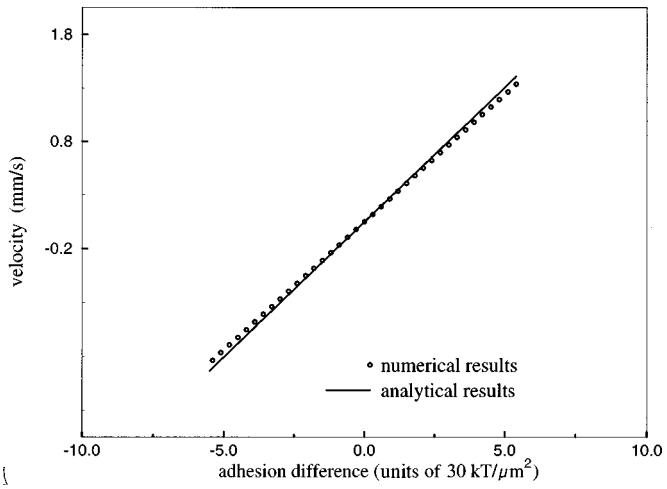

FIG. 2. $\mathcal{V}$ as a function of W_2-W_1. $p=60$ mPa (the area adapts itself), $\eta=10^2$ Kgm^{-2} s^{-1} (note that it has a dimension of a viscosity per unit length), $\kappa=25k_BT$, $L=7$ μm, $\Gamma=110$ Kgm^{-1} s^{-1} (dimension of a viscosity).

$$\mathcal{V}=\frac{\kappa/2\Delta(\ddot{\psi}^2)+\kappa^{-1}\Delta(a^2)-p\sqrt{2/\kappa}\Delta(\sqrt{a})-\zeta/\kappa\Delta(a)}{\eta\int\ddot{\psi}\sin(\psi)ds}, \tag{6}$$

where use has been made of Eqs. (5), and Δ stands for the difference between x_2 and x_1 of the quantity under consideration. Here $a_2=W_2-V\Gamma/2$, and $a_1=W_1+V\Gamma/2$. For example, $\Delta a=W_2-W_1-V\Gamma$. In order to get more insight towards a full analytical expression, we confine ourselves to a relatively small osmotic pressure. In that case ψ is a slowly varying function around a circle geometry [in particular, we can show that for $p\kappa/R^3$ not too large in comparison to unity (this is our meaning of a small osmotic pressure) the free vesicle is circular]. Therefore, $\ddot{\psi}$ can legitimately be disregarded. Within this approximation the numerator in Eq. (6) is completely evaluated as a function of κ and the adhesion difference on both sides. To evaluate the denominator we find it convenient to set $\psi=2\pi s/L-\pi+\phi$ (where L is the length of the vesicle which is not in contact with the substratum). In a perturbative scheme (that is neglecting ϕ^2 as well as $\dot{\phi}^2$), the denominator reads $-(2\pi/L)^2L_{adh}+4\pi/L\int ds\dot{\phi}\cos(2\pi s/L+\phi)$. This integral is related exactly to L_{adh}, the adhering length of the vesicle which is directly accessible to experiments (and which turns to be a weak function of all other parameters), so that the denominator takes the form $(2\pi/L)^2L_{adh}$. This amounts to

$$\mathcal{V}\simeq\frac{A\Delta W}{\eta+A\Gamma},\quad A\equiv\frac{W}{\kappa}(R^2/L_{adh})[1-pR_0/W-\zeta/W], \tag{7}$$

where $R\equiv L/2\pi$ and $R_0\equiv\sqrt{(\kappa/2W)}$. Recall that the dissipation powers are proportional to $1/\eta$ and $1/\Gamma$ for the free part and the contact point, respectively. W is the average adhesion energy. The above expression shows that the two dissipation mechanisms can be viewed as two resistances which are mounted in parallel in an electrical analogy (V would be the current and ΔW the potential difference). The largest

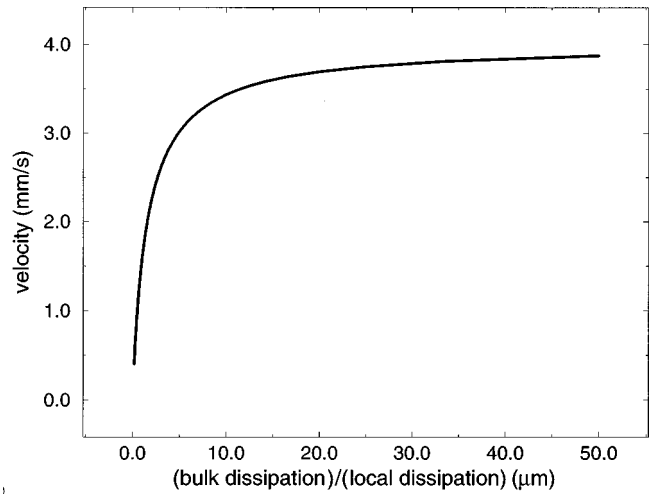

FIG. 3. $\mathcal{V}$ as a function of the bulk to contact dissipation ratio.

resistance dominates the limitation of the vesicle motion. Here we have made an expansion of the numerator in Eq. (6) for small enough ΔW. This corresponds to a linear response limit. However, it is clear from Eq. (6) that the full expression of the velocity is a nonlinear function of the velocity. However, we did not find a very pronounced deviation from a relatively linear behavior (Fig. 2), although ΔW varies by an order of magnitude. In contrast V as a function of the dissipation ratio (Γ/η) shows a nonlinear behavior as displayed in Fig. 3. Suppose Γ is fixed. At small Γ/η (this means large η), most of the energy is dissipated in the free part. The slope of V is very large. On increasing this ratio, a crossover to a regime where contact dissipation dominates. In that case it is easy to check from Eq. (6) that $V\simeq(W_2-W_1)/\Gamma$, which is independent of η. The order of magnitude of the velocity for typical values [$\kappa\sim(10-20)k_BT$, $W\sim10^{-4}$ mJ/m^2 (weak adhesion) a typical size $R\sim10$ μm, $\delta W/W\sim0.1-0.5$, an osmotic pressure of the order of 10^{-4} bar, and $\eta\sim0.1$ g cm^{-2} s^{-1}; this value corresponds to a real dissipation value associated with hydrodynamics transport) is $\mathcal{V}\sim100-1000$ μm/s. This velocity lies in the range of real cells velocities. For example, granulocytes move in the range $10-50$ μm/s in vivo, and can reach 500 μm/s in vitro [7].

The most obvious suggestion is to prepare a vesicle straddling on two substrata with different adhesion energies. The vesicle should spontaneously move sideways. The next step is to use a progressive coating of the substrate in order to establish an adhesion gradient. The vesicle should move towards the strong adhering regions.

Hitherto vesicle locomotion required an inhomogeneous environment from outside. Perhaps the most spectacular situation would be that a vesicle establish the motion itself in an initially homogeneous medium, in a similar manner as with droplets [10]. The vesicle would deposit through channels a substance reducing its adhesion. We believe that, though more complex, this should be feasible with vesicles.

On the general ground cell movement is essential to body survival: the immune system fight infections trough cell locomotion. At the same time cell emigration may also contribute in reinforcing diseases. For example, cancer cells crawl and spread out throughout the organism [17]. It is well

documented that crawling occurs via the bottom of the cell which attaches to the underlying substrate primarily through the action of the membrane-adhesion proteins [17]. Understanding how and by which mechanisms cells move in response to tissue injury is a major branch of research in biological and medical science. It goes without saying, that real cells are much too complex to lend themselves to simple modeling (for example, cytosqueleton should play a decisive role). Selecting few ingredients is thus necessary in order to identify the primary physico-chemical prototypes, which otherwise may express themselves in a quite disguised form in real cells. We thus believe that experiments on *artificial* vesicles with protein channels allowing permeability are good candidates on which to perform experiments. This should constitute a decisive step towards elucidation of elementary physico-chemical concepts, before dealing with more complex entities.

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