The Physics of Flexible Membranes

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Summary: Two introductory sections describe different aspects of membranes and give a short history of membrane research. The main part of this paper is concerned with (i) the morphology of vesicles and (ii) the adhesion and interaction of membranes.[1] The morphology of vesicles can be understood in the framework of curvature models. One particularly intriguing class of shape transformations are budding or invagination phenomena. Adhesion of membranes leads to additional shape transformation and to unbinding transitions driven by thermally-excited shape fluctuations. For two interacting surfaces, one has a whole line of nontrivial transitions. Recent theoretical work indicates that such a line also governs the unbinding for bunches of more than two membranes.

1 Introduction

The structure of matter is determined by the interplay of *energy* and *entropy* which usually favors order and disorder, respectively.[1] At low temperatures, energy dominates and the forces between the molecules lead to highly ordered crystalline states. At high temperatures, entropy dominates and the molecules form a disordered gas.

However, the world around us (and within us!) is full of *soft matter* or *complex fluids* which are governed by a real competition between energy and entropy. Examples for complex fluids are liquid crystals, polymer systems, gels, adhesives, colloids, soaps, microemulsions etc. In addition, all biological systems belong to this category.

The membranes considered here represent important structural elements for many complex fluids. In addition, these membranes separate the different compartments of biological systems and, thus, are responsible for the complex architecture of these systems. An example for this architecture is shown in Fig. 1.

In view of the ubiquity of membranes, it is not surprising that a large number of scientists from different disciplines is involved in their study. Even within the relatively small group of physicists, there are several communities which focus on different aspects of membranes. These aspects will be briefly summarized in the next section.

[1] The entropy of one subsystem can induce order in another subsystem as discussed below for the hydrophobic effect.

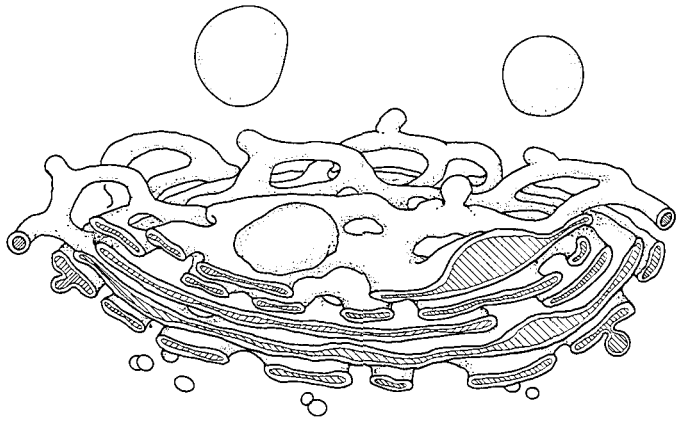

Fig. 1 In spite of its complex topology, the membrane bounding the Golgi–apparatus forms a closed surface without edges.

2 Different aspects of membranes

2.1 From micelles to bilayers

When viewed with the eyes of the chemical physicist, the membranes considered here are assemblies or aggregates of molecules which have the form of very thin sheets. In the following, I will focus on membranes composed of amphiphilic molecules such as lipids or surfactants.

In aqueous solution, amphiphilic molecules can form a large variety of different thermodynamic phases. The driving force behind the assembly of these different structures is the so–called *hydrophobic effect.*[2] A lipid molecule, for example, has a polar head group which is hydrophilic and two nonpolar hydrocarbon chains which are are hydrophobic. Water prefers to be in contact with the head group but tries to avoid any contact with the hydrocarbon chains. Therefore, the amphiphilic molecules arrange themselves in such a way that the heads shield the chains from the surrounding water.

It is now generally believed that the hydrophobic effect is mainly of entropic origin. A nonpolar hydrocarbon chain in contact with water acts to constrain the network of hydrogen bonds and to lower the configurational entropy of the surrounding water molecules. Thus, the aggregation of the amphiphilic molecular into ordered structures is primarily driven by the associated increase in the entropy of water.

Because of the hydrophobic effect, a disordered 'gas' of amphiphilic monomers is only possible at very low concentrations. As soon as the concentration of the amphiphile exceeds a certain critical concentration, these monomers start to assemble spontaneously. Above this critical concentration, surfactant molecules with one nonpolar tail usually form spherical or cylindrical micelles. For lipids,

the critical concentration is typically very low and of the order of 1 molecule per μm^3.[3] In the latter case, the molecules assemble into bilayers which are covered, on both sides, by the head groups of the lipids. The low value of the critical concentration implies that the exchange of molecules between the membrane and the surrounding solution is very slow and may be ignored in many situations.

2.2 From bilayer crystals to vesicles

At relatively high concentrations, lipid molecules form bilayers which are stacked on top of one another into lamellar phases. Within these phases, the bilayers are separated by thin layers of water. Thus, the lamellar phase can be diluted or swollen by adding water. Within each bilayer, the lipid molecules can exhibit a *fluid phase* at high temperatures and/or relatively large dilution, in which the nonpolar chains of the lipids are disordered, and one or several *gel–like phases* at low temperatures and/or relatively small dilution, in which the chains are rigid and form a lattice. For fluid bilayers, the lamellar phase represents a smectic liquid crystal. For gel–like bilayers, the lamellar phase could represent a three–dimensional crystal.[2]

In principle, the separation of the bilayers can reach a maximal value or can increase indefinitely depending on the interactions between the bilayers. In practise, the interface between the lamellar phase and the aqueous solution often undergoes complex changes. For example, the swelling process can lead to the formation of tubular structures, so–called myelin figures, in which the bilayers form concentric cylinders.[3]

Similar swelling procedures are also used in order to produce *liposomes* or *vesicles*. Liposomes are onion–like structures in which the bilayers form concentric spheres. Unilamellar vesicles, on the other hand, are closed bags bounded by a single bilayer. Nowadays, several preparation methods are available by which one can obtain giant unilamellar vesicles with a linear size of the order of 10 μm.

If the bilayer of the vesicle is in the fluid state, it is rather flexible and can easily change its shape. The vesicle can then undergo shape transformations such as the invagination process shown in Fig. 2.[4-6]

2.3 Biomembranes as complex interfaces

In the biophysics community, lipid bilayers represent the simplest model systems for biomembranes.[7] Indeed, all biomembranes contain a bilayer composed of lipids and proteins.[8]

[2]The experimental literature seems to be ambiguous on this point. The registry between the bilayers is strongly perturbed if the headgroup and the hydrocarbon chains favor different two–dimensional lattice structures.

[3]Such structures were first observed in 1853 by Virchow for the swelling of various tissues.

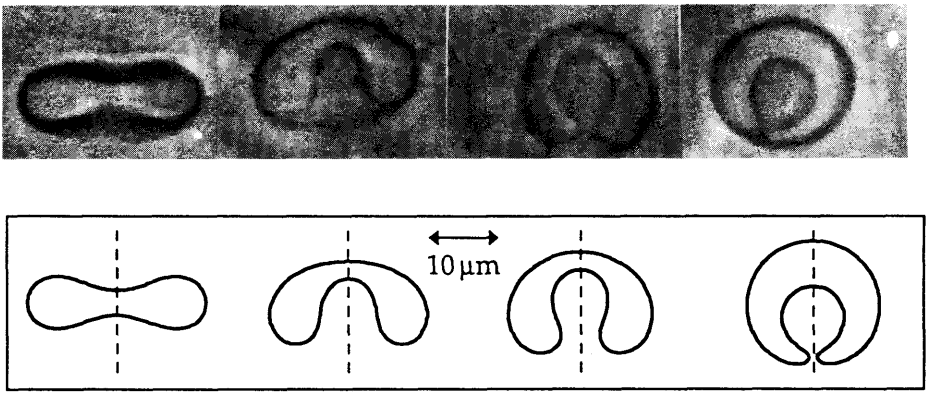

Fig. 2 Shape transformation of a single lipid vesicle induced by a change in temperature. The shapes are axisymmetric with respect to the broken lines. The vesicle has initially the discocyte shape of red blood cells (left) and finally consists of a sphere which contains a smaller spherical bud (right).

The main function of these bilayer membranes is to partition space into separate compartments. The membranes form closed surfaces without edges which represent highly selective filters maintaining the essential differences between the inside and the outside of the various compartments, compare Fig. 1. The proteins embedded or 'dissolved' in the bilayer mediate a variety of specific functions: they form channels used for the transport of small molecules across the membrane; they act as enzymes which catalyze membrane-associated reactions which are rather effective as a result of the two-dimensional geometry; they serve as receptors for chemical signals; they provide anchors for polymer networks such as the cytoskeleton or the extracellular matrix.

2.4 Engineering of membranes

Bilayer membranes are also studied as building blocks for a new nano- or micro-technology based on soft matter. There are two major areas: (i) vesicles and liposomes as *delivery systems* and (ii) immobilized membranes as part of *biosensors.*

Vesicles and liposomes are currently used as delivery systems in pharmaceutics, cosmetics, and genetic engineering. They are especially useful in order to transport all kinds of chemicals into the skin. Thus, they seem to have a large potential to improve the treatment of skin diseases.

Another more general goal is specific targeting of diseased cells. If these cells are macrophages, this goal is easy to achieve since the macrophages treat most vesicles just like parasites and rapidly ingest them. In general, this response of

the immune system creates a major problem, however, since the vesicles are eaten up before they can reach their target. Very recently, it has been found that one can solve this problem, at least to a certain extent, if the vesicles are covered by a coat of polymers.

As mentioned, biomembranes contain many receptor proteins. These receptors bind to specific ligands with high affinity. The binding between receptor and ligand produces a signal which can be an ionic current across the membrane, the activation of another membrane–bound protein, or, for catalytic receptors, the release of another molecule.

Various attempts are currently made to use receptor proteins as sensing elements for biosensors. In general, biosensors are devices which transform chemical signals into electric ones. In order to detect a certain biologically active molecule, one would like to cover the surface of the detector by the corresponding receptor molecule. One obvious way to achieve this is to dissolve the receptors in a lipid bilayer membrane which is immobilized on the solid surface.

4.3 Roughening of fluid and polymerized membranes

When viewed under the microscope, the membranes of vesicles exhibit thermally–excited shape fluctuations. Quite generally, low–dimensional objects such as interfaces, membranes or polymers undergo such fluctuations in order to increase their configurational *entropy*. A membrane is usually more flexible than an interface but less flexible than a polymer. It is important to realize, however, that the character of its shape fluctuations depends on the *internal state* of the membrane. In addition to the fluid bilayer of lipids and proteins, biomembranes often contain 2–dimensional networks. One example is the network of clathrin molecules as shown in Fig.7. Other examples are (i) the cell wall of bacterial cells which contains a peptidoclycan network and (ii) the cytoskeleton in some eucaryotic cells such as the spectrin network of red blood cells. These networks provide examples for polymerized or solid–like membranes.
On length scales which are large compared to the meshsize of the network, a polymerized membrane can be regarded as a thin elastic sheet. The shape fluctuations of such a sheet consist both of bending and of stretching modes. In contrast, fluid membranes are governed by bending modes alone.
The shape fluctuations lead to a certain membrane *roughness*, which is characterized by anisotropic humps: a membrane segment of linear size L makes transverse excursions of size[23]

$$L_\perp \sim \mathcal{A} L^\zeta \tag{6}$$

which defines the roughness exponent ζ, see Fig. 8. For fluid membranes with bending rigidity κ, one has $\zeta = 1$ and $\mathcal{A} = (T/\kappa)^{1/2}$ at temperature $T > 0$.[24] In general, one may define an effective scale–independent rigidity K via $\mathcal{A} = (T/K)^{1/2}$ or

$$K \equiv T/\mathcal{A}^2 \ . \tag{7}$$

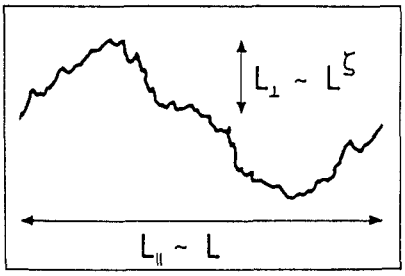

Fig. 8 Rough membrane consisting of anisotropic humps governed by the roughness exponent ζ.

For polymerized membranes, the value of ζ is still a matter of some controversy. Several simulations of tethered networks with free boundaries gave the estimate $\zeta = 0.65 \pm 0.05$.

In contrast, we have simulated continuum models in which the membrane is treated as a solid–like elastic sheet.[25] From these simulations, we concluded that the exponent ζ is presumably equal to $\zeta = 1/2$. This conclusion was based (i) on the assumption that the amplitude $\mathcal{A}$ should not depend on the small–scale cutoff of the model and (ii) on the empirical observation that the behavior of the shape fluctuations does not change significantly for the continuum model in the limit of zero (bare) bending rigidity, $\kappa = 0$. The assumption (i) is consistent with the diagrammatic perturbation series of the continuum model. Furthermore, a smooth limit for zero κ was found for various variants of the continuum model. Very recently, Abraham studied tethered nets with periodic boundary conditions and found $\zeta \simeq 0.53$.[26] This is much closer to our value than to previous estimates for tethered networks with free boundaries.
One should note that these results apply to polymerized membranes which are *planar* in the undeformed reference state (e.g. at zero temperature). If the reference state has non–zero (spontaneous) curvature, the shape fluctuations have a different character. Indeed, for a polymerized vesicle, stretching and bending modes are already coupled at the Gaussian or harmonic level which tends to suppress the fluctuations.[27]

4.4 Coarsening and relaxation of membrane undulations

Consider a membrane at temperature T which is initially in a flat state away from thermal equilibrium. At a later time t, the membrane has a certain roughness, $L_\perp(t)$, which grows continously with t. This represents a coarsening process of the membrane fluctuations: the largest humps which are excited at time t have a wavelength of order $L(t) \sim [L_\perp(t)/\mathcal{A}]^{1/\zeta}$ as follows from (6).
In order to determine the growth law for $L_\perp(t)$, it is useful to consider a slightly different situation in which the roughness of the membrane is confined by a planar wall interacting with the membrane.[5] All shape fluctuations of the free membrane that exceed a certain wavelength L_{max} are inaccessible to the confined membrane. The membrane then suffers a loss of entropy. The corresponding difference, $\Delta S = S_b - S_f$, between the entropies of the bound and of the free state can be estimated by the difference in the number of accessible modes. If the membrane has a linear size R, the difference in the number of modes scales as $-(R/L_{max}^2)$ in the limit of large R. The excess free energy per unit area arising from the confinement is then given by [23]

$$V_{fl} = -T\Delta S/R^2 \sim T/L_{max}^2 \sim T(\mathcal{A}/L_\perp)^{2/\zeta} \; . \tag{8}$$

This repulsive fluctuation–induced interaction leads to the disjoining pressure

$$P_{fl} = \partial V_{fl}/\partial L_\perp \sim -1/L_\perp^{1+2/\zeta} \tag{9}$$

[5]This is, in fact, the adhesion geometry discussed in Sect. 5 below.

between the membrane and the wall.
The relaxational dynamics of Monte Carlo simulations is equivalent to [28,23]

$$\partial L_\perp / \partial t \propto -P_{fl} \ . \tag{10}$$

Inserting the expression (9) for P_{fl}, one obtains the power law behavior [23,29]

$$L_\perp(t) \sim t^{\theta_\perp} \qquad \text{with} \quad \theta_\perp = \zeta/(2+2\zeta) \tag{11}$$

and

$$L(t) \sim t^{\theta_\parallel} \qquad \text{with} \quad \theta_\parallel = 1/(2+2\zeta) \tag{12}$$

for the coarsening of the membrane humps. This implies that the equilibration or relaxation time, t_{R1}, for humps of wavelength L or wavelength $q \sim 1/L$ is given by [30,25]

$$t_{R1} \sim 1/q^{2+2\zeta} \ . \tag{13}$$

In real systems, the fluctuating membrane may be coupled to overdamped surface waves in the aqueous medium which decay as $\exp(-qz)$ with the distance z from the membrane. These surface waves have a different relaxation time, t_{R2}, which can be estimated from dimensional analysis.
On large scales, the elastic response of the membrane is governed by the effective (scale-independent) rigidity $K = T/\mathcal{A}^2$ as given by (7). It follows from this relation and $L_\perp \sim \mathcal{A} L^\zeta$ that K is an energy/length$^{2-2\zeta}$. The energy dissipated in the surface waves within the aqueous medium is governed by the dynamic viscosity η which is an (energy $\times$ time)/ length^3. The only time scale which can be obtained from q, K, and η is the relaxation time

$$t_{R2} \sim \eta / K q^{1+2\zeta}. \tag{14}$$

Thus, the viscous damping by the fluid decreases the relaxation time on large scales. For fluid membranes with $K = \kappa$ and $\zeta = 1$, one has $t_{R2} \sim \eta/\kappa q^3$ as has been previously obtained by Brochard and Lennon.[24] More recently, the dynamics of polymerized membranes has been studied by Frey and Nelson [31] using a set of coupled Langevin equations. For free draining membranes, they recover the relaxation time t_{R1} as given by (13) (which they call Rouse dynamics). In addition, they also derive the relaxation time t_{R2} as in (14) (which they call Zimm dynamics).
Finally, consider again a membrane which is initially flat but is now coupled to overdamped surface waves as it develops larger and larger humps. The roughness now grows as

$$L_\perp \sim t^{\theta_\perp} \qquad \text{with} \quad \theta_\perp = \zeta/(1+2\zeta) \tag{15}$$

with time t as follows from (14) and $L_\perp \sim L^\zeta \sim 1/q^\zeta$. Thus, the coupling to the hydrodynamic flow acts to *enhance* the coarsening process: in the absence of such a coupling, the growth exponent $\theta_\perp$ is $\theta_\perp = \zeta/(2+2\zeta)$ as in (11) which is smaller than the value $\theta_\perp = \zeta/(1+2\zeta)$ as in (15).

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