Mobility and Elasticity of Self-Assembled Membranes

Rüdiger Goetz, Gerhard Gompper, and Reinhard Lipowsky*

Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Kantstrasse 55, 14513 Teltow, Germany
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Molecular dynamics simulations are used in order to study the self-assembly process and the physical properties of flexible membranes composed of amphiphilic molecules. On molecular scales, these membranes are observed to be rather mobile and to have rough surfaces arising from molecular protrusions, i.e., from the relative displacements of individual molecules. On length scales that are only somewhat larger than the membrane thickness, on the other hand, the membranes are found to undergo smooth bending undulations. In this way, our study provides the first explicit connection between computer simulations with molecular resolution and elastic membrane models based on differential geometry. [S0031-9007(98)08125-3]

Flexible membranes and lipid bilayers have fascinating physical properties which have been studied for a long time both experimentally and theoretically. During the last decades, two theoretical approaches have reached a certain level of maturity. On the one hand, we have a successful theoretical description based on differential geometry by which we can understand the morphology of closed membranes or vesicles on the micrometer scale; see, e.g., [1]. On the other hand, molecular models of lipid bilayers on the nanometer scale with (almost) atomic resolution have been intensely studied by computer simulations; see, e.g., [2,3].

However, these two approaches have remained rather distinct and unrelated. In the computer simulations, the self-assembled bilayers are found to be rather mobile structures. In particular, the two interfaces bounding these bilayers are roughened by relative displacements or protrusions of individual molecules [4,5]. Such protrusions have also been deduced from scattering data of real bilayers [6–8], and they are believed to make an important contribution to the short-ranged repulsion between bilayers [9,10].

On the micrometer scale, on the other hand, the behavior of membranes is well understood in terms of smooth surfaces as described by differential geometry and curvature energies. In this latter description, the most important phenomenological parameter is the bending rigidity κ which describes the resistance of the membrane against bending. So far, this elastic parameter has not been addressed in any of the numerous simulations of membrane models with molecular resolution. Below, we show, for the first time, that one can indeed extract a value for the bending rigidity from molecular dynamics (MD) simulations of such models.

In order to investigate the concept of bending elasticity via computer simulations of molecular models, we used a two-step strategy. First, we systematically studied the effect of boundary conditions on the membrane behavior and determined the lateral tension induced in the membrane by these boundary conditions. In this way,

we have been able to identify those parameter values which correspond to *tensionless* states. This aspect of our work which is rather technical has been described elsewhere [11]. Second, we have performed a detailed analysis of the shape fluctuations of the membranes in their tensionless state. The results of the latter analysis are reported below. Note that we used molecular dynamics rather than Monte Carlo simulations, which implies that our model systems exhibit a realistic dynamics.

We also find that our data are in fair agreement with a relatively simple relation in which the bending rigidity is expressed in terms of the area compressibility and the membrane thickness. This relation provides a shortcut for future simulations since it is much easier and less time-consuming to determine the area compressibility from such simulations.

A variety of theoretical approaches has been used previously in order to provide a microscopic basis for bending elasticity: (i) calculations based on the stress profile across the bilayer membrane [12,13], (ii) self-consistent calculations in which the amphiphilic molecules are treated as short polymers confined to the curved membrane [14,15], and (iii) theories based on local density functionals and gradient expansions starting from nonlocal density functionals [16].

In all of these approaches, the interfaces bounding the membrane were treated as smooth surfaces and molecular protrusions were not taken into account. Therefore, none of these previous approaches can give us information about the transition regime from protrusions to bending deformations. In particular, these approaches cannot tell us how far we have to go above the molecular level in order to treat the membrane as a quasielastic sheet. In the work reported here, we obtain a definite prediction for this latter length scale. In fact, our data give strong evidence that the concept of bending elasticity is already meaningful on rather microscopic length scales which are only somewhat larger than the bilayer thickness.

Bilayer membranes are formed by the self-assembly of lipids, surfactants, and other amphiphilic molecules;

see, e.g., [17]. This process can be studied in the context of binary model systems consisting of solvent and amphiphilic particles. The model for which we present our data is a binary Lennard-Jones fluid in which each amphiphile consists of one lyophilic headgroup particle connected to a chain of four lyophobic particles [11]. The basic energy and length scales are provided by the depth ϵ and the range λ of the Lennard-Jones potential, respectively. The basic time scale is given by $t_{\rm sc} = \lambda\sqrt{m/\epsilon}$, where m denotes the mass of the particles. Similar models have been previously studied for ternary mixtures of oil, water, and surfactant [18].

In the context of such a model, one may first observe the self-assembly of the amphiphilic molecules into bilayers; see Fig. 1. Furthermore, direct observation of the motion of the amphiphiles within the self-assembled bilayer shows that these particles undergo rapid lateral diffusion which implies that the bilayer is in a fluid state. The observed diffusion coefficient was of the order of $10^{-5}\lambda^2/t_{\rm sc}$ [11].

The MD simulations were performed using the leap-frog algorithm at constant temperature $k_B T = 1.35\epsilon$. The time increment per MD step was taken to be $\Delta t = t_{\rm sc}/2000$. As discussed in [11], one has some freedom in the assignment of numerical values to the basic parameters ϵ, λ, and m. A reasonable choice for this assignment is given by $\lambda = 1/3$ nm, $\epsilon N_A = 2$ kJ, and $m N_A = 0.036$ kg, where N_A denotes Avogadro's number. This leads to the basic time scale $t_{\rm sc} = 1.4$ ps and to the time increment $\Delta t = 0.7$ fm per MD step. The lateral diffusion coefficient then has a value of the order of 10^{-8} cm^2/s as observed experimentally.

A real bilayer membrane which is not subject to external constraints adopts an essentially *tensionless* state. It takes a certain computational effort to obtain such states in simulations. Indeed, the bilayer segments which can be studied via simulations are usually constrained by the finite size of the simulation box which induces substantial lateral tensions in the membrane. Therefore, one must first determine the membrane tension as a function of the size of the simulation box for fixed surfactant number [11]. As shown in Fig. 2, one then finds that the tension changes its sign at a certain box size and, thus, at a certain
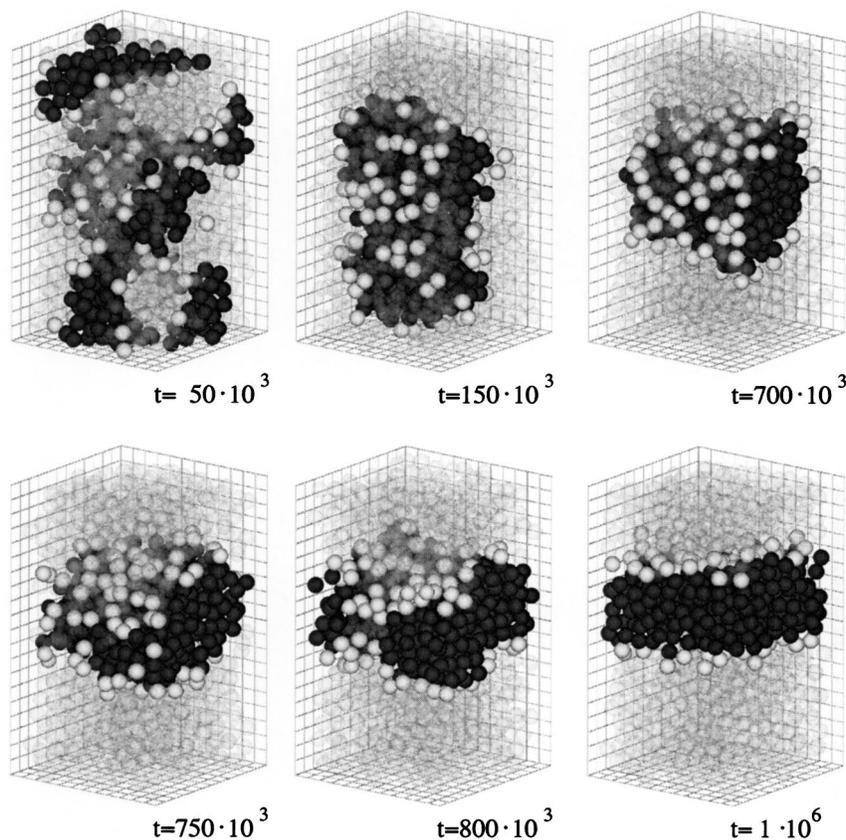

FIG. 1. Self-assembly of bilayer membrane in a mixture of amphiphiles and solvent particles. Each amphiphile consists of four black chain particles connected to one white headgroup particle. The solvent particles are transparent. The initial configuration, which is not shown, consists of a random mixture of 100 amphiphiles and 840 solvent particles. The six configurations are snapshots which illustrate the time evolution of the structure; the time t is given in units of molecular dynamics steps. The time increment per MD step corresponds to about 1 fs. After about 1.5×10^5 MD steps, the amphiphiles form a cylindrical micelle which spans the simulation box horizontally. This state is stable up to about 7×10^5 MD steps. After this time, the micelle undergoes a transformation, which takes about 10^5 MD steps towards a bilayer state. The resulting bilayer is found to be stable for at least 3×10^6 MD steps.
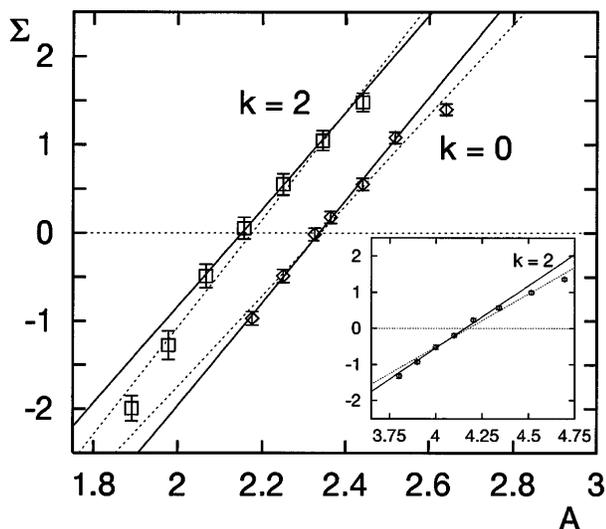
FIG. 2. Lateral tension Σ within the bilayer as a function of projected area A per amphiphile. The two different sets of data correspond to amphiphiles which differ in their chain stiffness k. For comparison, the inset shows analogous data for amphiphiles with two chains, each of which consists of four lyophobic particles. All quantities have been made dimensionless using the range λ and the depth ϵ of the Lennard-Jones potential.

projected area per molecule, A_0. For molecular areas A close to A_0, one finds a Hookian behavior and the tension Σ behaves as

$$\Sigma \approx K_A(A - A_0)/A_0, \qquad (1)$$

which defines the area compressibility modulus K_A.

The projected molecular area A_0 depends, to some extent, on the details of the molecular model. This is illustrated in Fig. 2. The latter figure contains data for two different lyophobic chains which are distinguished by their chain stiffness k. For comparison, we have also included data for amphiphiles with two chains, each of which consists of four lyophobic particles. However, in all three cases, we obtain roughly the same value for the area compressibility modulus K_A. In the following, we will focus on amphiphiles with a single chain and chain stiffness $k = 2\epsilon$. In this case, the area compressibility modulus is found to be $K_A \simeq 12\epsilon/\lambda^2$.

A snapshot of a tensionless membrane state is displayed in Fig. 3. In this example, the membrane consists of 1152 amphiphilic molecules and the ambient temperature is $k_BT = 1.35\epsilon$. Inspection of this figure shows (i) that the two interfaces bounding the bilayer are not smooth on small scales but roughened by protrusions of the amphiphilic molecules and (ii) that the overall shape of the bilayer resembles an elastic sheet which is curved in a smooth way.

A quantitative measure for the shape fluctuations of the bilayer membrane is given by the fluctuation spectrum as shown in Fig. 4. The shape of the membrane is described by the height variable $h(r)$ which gives the position of the midsurface between the two interfaces
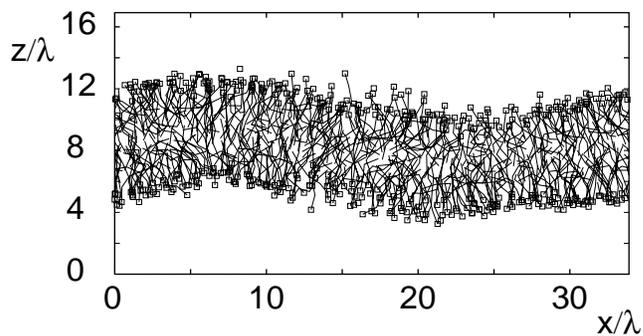

FIG. 3. Typical configuration of a bilayer membrane composed of 1152 amphiphiles. At small scales, one sees individual molecules which protrude from the bilayer membrane. At large scales, the bilayer looks like an elastic sheet which is curved in a smooth way. The basic length scale λ represents the range of the Lennard-Jones potential. The thickness of the membrane is $\ell_{\mathrm{me}} \simeq 6\lambda$.

bounding the bilayer. The corresponding deformation mode $\tilde{h}(q)$ with wave number q is the Fourier transform of $h(r)$. The fluctuation spectrum or static structure factor $S(q) \equiv \langle|\tilde{h}(q)|^2\rangle$, which is directly accessible to scattering experiments, represents the excitation strength of these deformation modes. The computational effort to determine $S(q)$ via simulations is quite substantial: It took about 18 months of CPU time on a silicon graphics workstation (R4400, 150 Mhz) in order to collect the data on which our fluctuation analysis is based.

We find that the data of the fluctuation spectrum $S(q)$ as displayed in Fig. 4 are well fitted by the functional form

$$S(q) \sim \frac{k_BT}{\kappa q^4} + \frac{k_BT}{\sigma_{\mathrm{pr}} q^2}. \qquad (2)$$
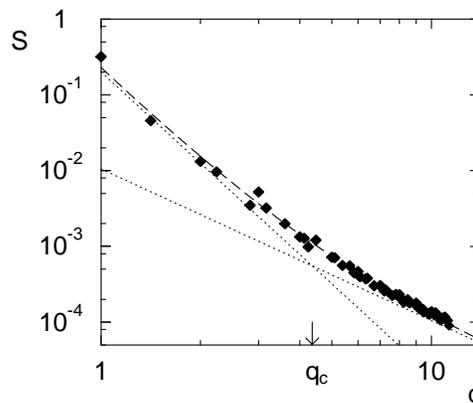

FIG. 4. Fluctuation spectrum S of thermally excited membrane deformations as a function of the dimensionless wave number q. The largest wavelength is provided by the box size and corresponds to $q = 1$. The symbols represent the molecular dynamics data, the full curve the superposition of protrusions and bending modes as explained in the text. The two dotted lines show the separate contributions of protrusions at large q and bending modes at small q. These two contributions intersect at the characteristic wave number q_c which corresponds to the wavelength $\simeq 7.7\lambda$.

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This q dependence of the fluctuation spectrum corresponds to a superposition of (i) bending deformations which behave as $\sim 1/q^4$ [19] and (ii) protrusion modes $\sim 1/q^2$ [10]. The fit of the data as shown in Fig. 4 leads to the bending rigidity $\kappa \simeq 10\epsilon$ and to the protrusion tension $\sigma_{\mathrm{pr}} \simeq 6.5\epsilon/\lambda^2$.

The two contributions to the fluctuation spectrum arising from protrusions and from bending modes have the same strength at the characteristic wave number $q_c \equiv (\sigma_{\mathrm{pr}}/\kappa)^{1/2}$. The corresponding length scale is $2\pi/q_c \simeq 7.7\lambda$. This must be compared with those length scales which characterize the bilayer on the molecular level. There are two such length scales: the lateral size of the amphiphile and the bilayer thickness ℓ_{me}. For the tensionless bilayers discussed here, the lateral size of the amphiphile is $\simeq 1.4\lambda$ and the bilayer thickness $\ell_{\mathrm{me}} \simeq 6\lambda$. Therefore, the shape fluctuations of the bilayer represent bending modes as soon as the wavelength is somewhat larger than the bilayer thickness.

Somewhat surprisingly, the value of the bending rigidity which we have deduced from the analysis of the shape fluctuations of the bilayer can be understood in a rather simple way. For thin *solidlike* films, classical elasticity theory leads to a free energy which depends on two Lame coefficients, $\lambda_{\parallel}$ and $\mu_{\parallel}$, and the area compressibility and the bending rigidity of such films are given by $K_1 = \lambda_{\parallel} + \mu_{\parallel}$ and $\kappa_1 = (\lambda_{\parallel} + 2\mu_{\parallel})\ell^2/12$, respectively, where ℓ denotes the film thickness [20]. If one treats each monolayer of the bilayer as a thin structureless film with vanishing two-dimensional shear modulus $\mu_{\parallel} = 0$, and if one further assumes that the two monolayers can slide freely against each other, the bending rigidity of the bilayer is then found to be given by the simple relation

$$\kappa = K_A \ell_{\mathrm{me}}^2/48, \qquad (3)$$

where K_A and ℓ_{me} are, respectively, the area compressibility modulus and the bilayer thickness as before. Using the values for K_A and ℓ_{me} as determined independently from the simulations, one obtains the estimate $\kappa \simeq 9\epsilon$, a value which is in fair agreement with the value $\kappa \simeq 10\epsilon$ as obtained directly from the spectral analysis of the shape fluctuations.

In summary, we have shown that membranes exhibit both protrusions on molecular scales and bending undulations on larger scales. The latter fluctuations are already present as soon as the wavelength is only somewhat larger than the membrane thickness. The bending rigidity extracted from the fluctuation analysis is in fair agreement with a simple model for two adjacent monolayers with vanishing shear modulus. In this way, we have provided, for the first time, an explicit connection between the motion of individual molecules on the nanometer scale and elastic surface behavior as observed on the micrometer scale.

In the present work, we have used simplified models for the solvent and for the amphiphiles. It is obvious, however, that our approach can also be used for refined models with (almost) atomic resolution. It will then be possible to study how the elastic properties of the membranes depend on the molecular architecture of the amphiphiles and how these properties are affected by variations in the composition of multicomponent membranes. One important example is provided by two-component bilayers consisting of phospholipid and cholesterol, for which the bending rigidity has been measured experimentally and was found to increase rather strongly with the cholesterol concentration. We expect that the simple relation between area compressibility, membrane thickness, and bending rigidity as found here will also apply to such more complex membranes, but this remains to be studied.

*Author to whom correspondence should be addressed.

[1] *Structure and Dynamics of Membranes,* Handbook of Biological Physics Vol. 1, edited by R. Lipowsky and E. Sackmann (Elsevier, Amsterdam, 1995).

[2] R. W. Pastor, Curr. Opin. Struct. Biol. **4**, 486 (1994).

[3] D. J. Tobias, K. Tu, and M. L. Klein, Curr. Opin. Coll. Interface Sci. **2**, 15 (1997).

[4] E. Egberts and H. Berendsen, J. Chem. Phys. **89**, 3718 (1988).

[5] S. Marrink, M. Berkowitz, and H. Berendsen, Langmuir **9**, 3122 (1993).

[6] S. König, W. Pfeiffer, T. Bayerl, D. Richter, and E. Sackmann, J. Phys. II (France) **2**, 1589 (1992).

[7] M. Wiener and S. White, Biophys. J. **61**, 434 (1992).

[8] T. McIntosh and S. Simon, Biochemistry **32**, 8374 (1993).

[9] J. Israelachvili and H. Wennerström, J. Phys. Chem. **96**, 520 (1992).

[10] R. Lipowsky and S. Grotehans, Europhys. Lett. **23**, 599 (1993).

[11] R. Goetz and R. Lipowsky, J. Chem. Phys. **108**, 7397 (1998); R. Goetz, Ph.D. thesis, University of Potsdam, Germany, 1997.

[12] W. Helfrich, Z. Naturforsch. **C29**, 510 (1974); in *Physics of Defects,* edited by R. Balian *et al.* (North-Holland, Amsterdam, 1981).

[13] A. G. Petrov and I. Bivas, Prog. Surf. Sci. **16**, 389 (1984).

[14] R. Cantor, Macromolecules **14**, 1186 (1981).

[15] A. Ben-Shaul, in Ref. [1].

[16] G. Gompper and M. Schick, in *Self-Assembling Amphiphilic Systems,* Phase Transition and Critical Phenomena Vol. 16, edited by C. Domb and J. Lebowitz (Academic, London, 1994).

[17] C. Tanford, *The Hydrophobic Effect: Formation of Micelles and Biological Membranes* (Krieger, Malabar, FL, 1991), 2nd ed.

[18] B. Smit, P. Hilbers, K. Esselink, L. Rupert, N. van Os, and A. Schlijper, J. Chem. Phys. **95**, 6361 (1991).

[19] F. Brochard and J. Lennon, J. Phys. (Paris) **36**, 1035 (1975).

[20] L. Landau and E. Lifshitz, *Elastizitätstheorie* (Akademie-Verlag, Berlin, 1989).