Molecular dynamics simulation of a bilayer membrane

van der Ploeg, P.; Berendsen, H. J. C.

Molecular dynamics simulation of a bilayer membrane

P. van der Ploeg, and H. J. C. Berendsen

Molecular dynamics simulation of a bilayer membrane

P. van der Ploeg and H. J. C. Berendsen[a]

Laboratory of Physical Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

We have applied the computer simulation method of molecular dynamics (MD) to a realistic representation of a lipid bilayer, which serves as a model for a biological membrane. The bilayer consists of 2×16 decanoate molecules and is periodic in two dimensions. Interactions include Lennard-Jones, dihedral, and bond angle potentials while bond lengths are constrained. Head groups are confined near the bilayer surfaces by harmonic forces representing their interaction with the water layer. After equilibration, a simulation extending over 80 ps at 300 K was carried out for a head group surface area of 25 Å^2. Experimental order parameters are perfectly reproduced. A highly interesting cooperative tilt of the molecules, persisting over several tens of picoseconds, is observed. The molecular plane is strongly correlated with the plane of tilt. The popular kink model for the hydrocarbon chain order and dynamics is not supported. In view of the observed extended spatial correlation, a simulation was also carried out for a bilayer consisting of 2×64 decanoate molecules.

I. INTRODUCTION

Lipid bilayer systems have been extensively studied as model systems for biological membranes. One of the most simple models is the decanoate–decanol–water system that forms smectic liquid crystals consisting of multibilayers. This system has been thoroughly investigated by x-ray diffraction and NMR techniques.[1] Above its gel to liquid crystal phase transition at 20 °C the hydrocarbon chains are rapidly reorienting about the bilayer normal and from NMR measurements on specifically deuterated methylene groups detailed information has become available on the average molecular ordering.

The molecular interpretation of such experimental data is a matter of speculation and involves hypotheses that cannot separately be verified. Until now it has not been possible to derive the properties of such bilayer membranes from the knowledge of inter- and intramolecular interactions. This is due to the essential many-body character of the interaction, leading to cooperative effects.

Theoretical treatments thus far have relied on simplifications such as mean field potentials[2] or specific defect structures.[3,15] The recent availability of large computers have given great impetus to the application of computational methods such as Monte Carlo and molecular dynamics (MD) to large multiparticle systems. The MD method[4] is the more powerful of the two since it produces full structural and dynamic details on the basis of simple interactions.

Previously, the MD method has been applied to rough models of monolayers.[5-7] The most detailed simulation[7] is restricted to a monolayer of hexane molecules without dihedral angle potential functions and with hard-core repulsion between methylene groups. The omission of dihedral potential functions may cause serious deviations from realistic behavior.

[a] To whom correspondence should be addressed.

II. METHOD AND MODEL

We have used the algorithm of Verlet[8] using Cartesian coordinates and constraining bond lengths by the SHAKE method.[9] The system consists of two layers of 16 decane molecules each, periodic in two dimensions (x, y). Head groups are confined in the z direction by a harmonic potential; the position of the minimum of this potential is the average z coordinate $\bar{z}$ of the head groups in either layer. Hence, the bilayer thickness is not a parameter but adjusts itself in equilibrium with an external pressure exerted on the head groups. We used a pressure of 1 atm which corresponds to a negligible force. The head group density was taken as 4 nm^{-2}, corresponding to the experimental surface area of 0.25 nm^2 per head group.[1] The box size is 2×2 nm. The interaction model for the chain is based on that of Ryckaert and Bellemans,[10] which has been extensively tested on liquid butane and decane. It consists of a dihedral potential function[10]

$$V(\phi) = \sum_{i=0}^{5} C_i (\cos \phi)^i \; \text{kJ/mol} , \qquad (1)$$

with $C_0 = 9.2789$, $C_1 = 12.1557$, $C_2 = -13.1201$, $C_3 = -3.0597$, $C_4 = 26.2403$, $C_5 = -31.4950$, (*trans–gauche* barrier energy $= 12.3428$ kJ/mol; energy of *gauche* minimum $= 2.9288$ kJ/mol) and a united atom (CH$_2$ and CH$_3$ groups are considered as one center) Lennard-Jones interaction between all intermolecular pairs and those intramolecular pairs (i, j) for which $j > i + 3$

$$V(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right] . \qquad (2)$$

There are three types of atoms: head groups, methylene units, and methyl end groups. For ϵ and σ of methylene the literature values of 0.4301 and 0.374 were taken,[10] for methyl and head groups (considered as COO$^-$ group) ϵ and σ values were derived from polarizabilities and van der Waals radii[11] using standard methods,[12] resulting in 0.6423, respectively, 0.274 for methyl and 0.9203, respectively 0.422 for head groups (units kJ/

mol and nm). Standard combination rules[12] were used for mixed interactions. An interaction cutoff radius of 1 nm (half the box size) was used. Bond angle potentials were taken as harmonic functions

$$V(\alpha) = \tfrac{1}{2}k_b(\alpha - \alpha_0)^2 , \tag{3}$$

where $k_b = 520$ kJ mol^{-1} rad^{-2} was derived from a potential function used by Weber.[13] Interactions of head group units with the water layer are represented by a harmonic potential in the z direction

$$V(z) = \tfrac{1}{2}k_h(z - \bar{z})^2 , \tag{4}$$

which we consider to be more physically realistic than a full constraint. The value of k_h (300 kJ mol^{-1} nm^{-2}) was chosen high enough for the dynamic properties of the dihedral angle transitions to become insensitive to k_h. When k_h is taken too low, the dihedral transitions appear to become very infrequent. In addition, a weak harmonic restoring force is active on all carbon atoms of the chain, when the atom is outside the plane of the head groups. This does not affect the normal dynamics of the chain, but prevents that a molecule occasionally turns its tail outside the bilayer.

After a long equilibration, considerably longer than 100 ps, from an originally random configuration, a MD run was carried out over a time interval of 80 ps at $T = 300$ K. The time step used was 8×10^{-3} ps which was selected to produce sufficient numerical accuracy (fluctuations of the total energy was about 7% of the kinetic energy fluctuation; no significant temperature drift occurred). The 10 000 steps took ~10 h of computer time on the Cyber 74/18 of the Computer Centre of the University of Groningen.

III. RESULTS AND DISCUSSION

A. Order parameters

Experimental deuteron resonance data are available for the order parameter S_{CD} which is a measure for the anisotropy of the CD bond direction with respect to the bilayer normal. The general order parameter tensor[14] S_{ij} is defined as

$$S_{ij} = \tfrac{1}{2}(3\,\overline{\cos\theta_i\cos\theta_j} - \delta_{ij}) ,$$

where θ_i is the angle between the ith molecular axis and the bilayer normal and the bar denotes time averaging. We define molecular axes for the nth CH_2 unit as follows:

x: H–H vector;

y: bisectrix of HC_nH angle;

z: vector from C_{n-1} to C_{n+1} .

S_{zz} is also referred to as a local S_{chain}. Order parameters can vary between $+1$ (fully ordered parallel to bilayer normal) and $-\tfrac{1}{2}$ (fully ordered perpendicular to normal), while isotropic orientation corresponds to a value of zero. For reasons of symmetry, S is diagonal except for S_{yz} which is usually small. The sum of the diagonal elements is zero, which leaves essentially two independent order parameters per CH_2 unit. If the molecular motion is such that isotropic rotation around the molecular z axis occurs $S_{zz} = -2S_{xx} = -2S_{yy}$ and only one order parameter remains.

Figure 1 shows the experimental order parameters S_{CD} for different positions along the chain, as well as S_{CD} derived from the simulation. The latter follows from $S_{CD} = \tfrac{2}{3}S_{xx} + \tfrac{1}{3}S_{yy}$. The agreement is striking and gives considerable confidence in the model and method used. The plateau observed in the order parameters along the chain is well reproduced. This feature has been often discussed in terms of various models; we are now in a position to investigate the origin of this phenomenon in detail.

The possible anisotropy of rotation around the molecular z axis can be investigated by comparing S_{zz} with $-2S_{xx}$ (Fig. 1). It is observed that this rotation is indeed anisotropic, in contrast to most models that have been proposed[16,1] to explain the plateau in the order parameters. Recent experimental evidence from ^{19}F NMR on the C_4 position of myristate[17] as well as from proton and deuteron NMR on the C_1 position of decanoate/ decanol[18,19] and palmitate,[20] supports this lack of axial symmetry around the molecular axis. In all cases
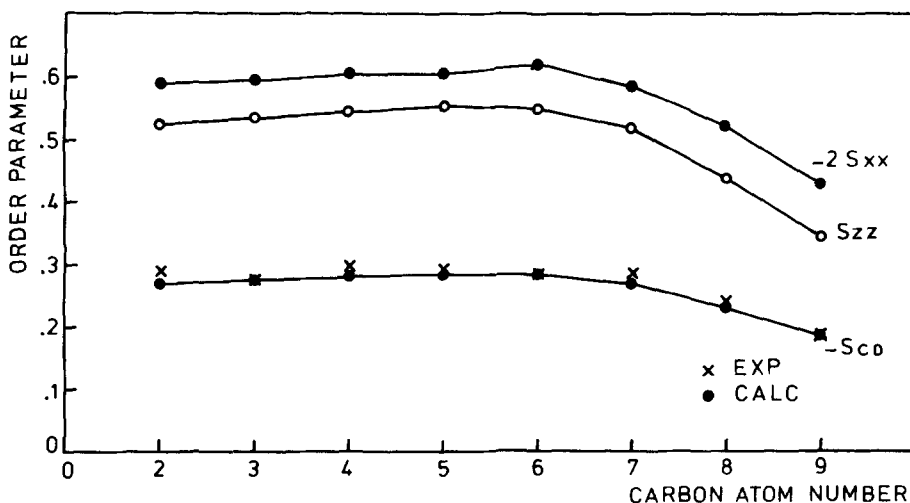

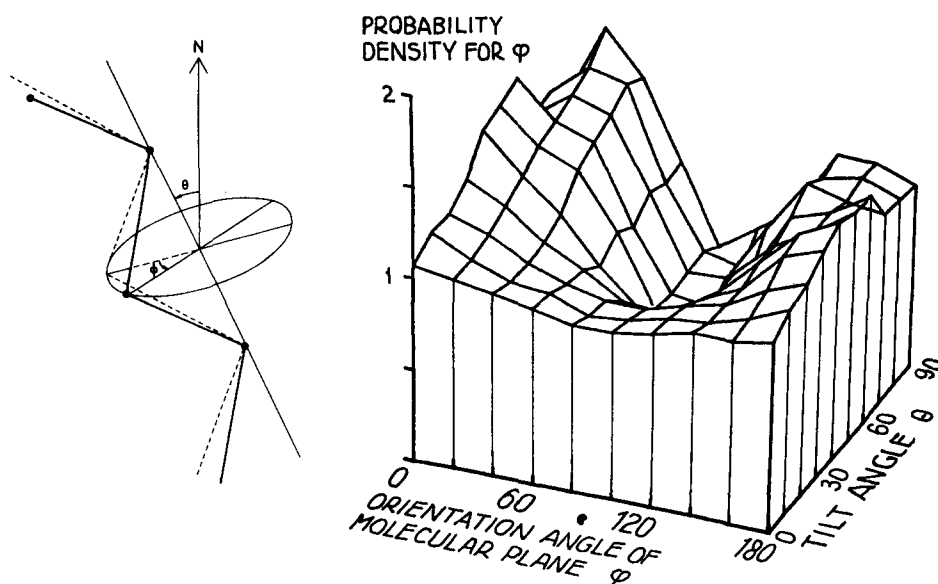FIG. 1. Order parameters as function of carbon atom number (1 = head group). x indicate experimental values of Seelig.[15]

FIG. 2. Probability density for orientation angle ϕ of molecular plane with respect to the plane of tilt, as a function of tilt angle θ.

$|S_{HH}|$ is larger than $|S_{CD}|$, as is observed in the simulation.

In order to obtain insight in the cause of asymmetry we investigated whether the angle ϕ between the molecular yz plane and the plane defined by the molecular z axis is correlated with the angle θ between normal and z axis. Figure 2 shows that a correlation exists, becoming more pronounced at higher local tilt angle θ. Configurations in which the two planes coincide are clearly preferred. Apparently the molecule swings out as a knife blade in the direction in which it is thinnest. Further analysis shows that for the first six C–C bonds odd and even-numbered bonds behave differently: odd-numbered bonds were more closely aligned to the normal than even-numbered bonds.

B. Tilt

The angle θ mentioned above can be considered as a local tilt angle for each methylene group. The tilt of the molecule can be defined by a normalized vector S_i connecting the middle of the first C–C bond with the middle of a bond further along the chain. For the latter we chose the C_6–C_7 bond because the first six carbon atoms seem to behave in a correlated fashion. We now address the question whether the molecular tilt is a collective property.

The correlation between molecular tilts is given by the correlation between the S_i vectors. This is represented by the length of the average tilt vector $T = 1/N \times \sum_{i=1}^{N} S_i$. A large $|T|$ indicates a strong correlation between the directions in which the molecules tilt, 1 representing full alignment. The angle θ_t between T and the bilayer normal gives the angle of average tilt.

Figure 3 shows both $|T|$ and θ_t as a function of time during the full simulation. There is a slowly fluctuating collective tilt; the extent of the molecular alignment is strongly correlated with the angle of average tilt. The
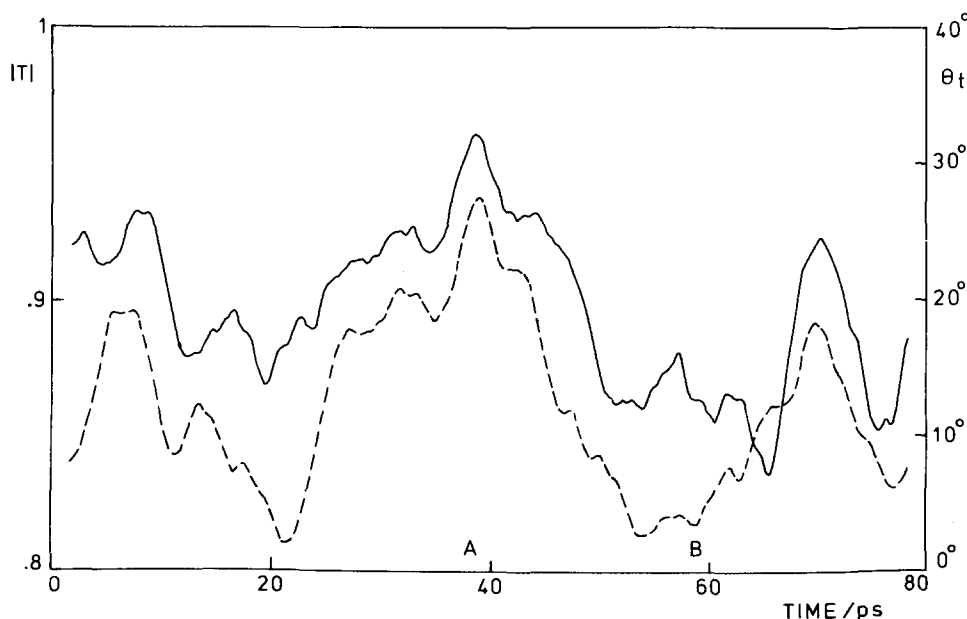

FIG. 3. Angular correlation between molecular vectors S_i, expressed as the length $|T|$ of the total vector $T = 1/N \sum S_i$ (drawn curve, left scale) and the angle θ_t of average tilt (broken line and right scale). Both quantities are plotted against time for the full dynamics run.
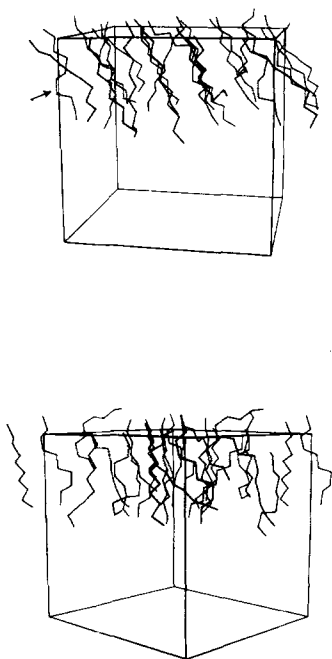
FIG. 4. Two configurations taken from an ordered (A in Fig. 3) and less ordered (B in Fig. 3) state of the bilayer. For clarity only upper layer is shown. Arrow indicates kink.

characteristic time of the fluctuation is 10–20 ps. The limited length of the simulation does not allow a full statistical analysis. Figure 4 shows two configurations; one taken while a collective tilt exists (indicated with A in Fig. 3) and one when the directional correlation is low (B in Fig. 3). For clarity, only one-half of the bilayer is shown. The collective tilt is quite apparent and extends over the whole unit cell.

It is of interest to investigate by what mechanism the collective tilt changes in magnitude and direction. A change in direction of the collective tilt would involve strong boundary effects between domains of aligned molecules. This seems an unlikely mechanism. Alternatively, the change could be effected via intermediate disordered configurations. In our simulation the change in collective tilt indeed follows the latter mechanism. Figure 5 shows simultaneously the time course of the direction of average tilt in a polar diagram and the correlation between molecular vectors. It is clear that different periods in which collective tilt occurs are separated by periods without tilt and with less angular correlation.

The observation of collective tilt extending over the whole unit cell implies that the chosen unit cell dimensions are too small to produce reliable results: the
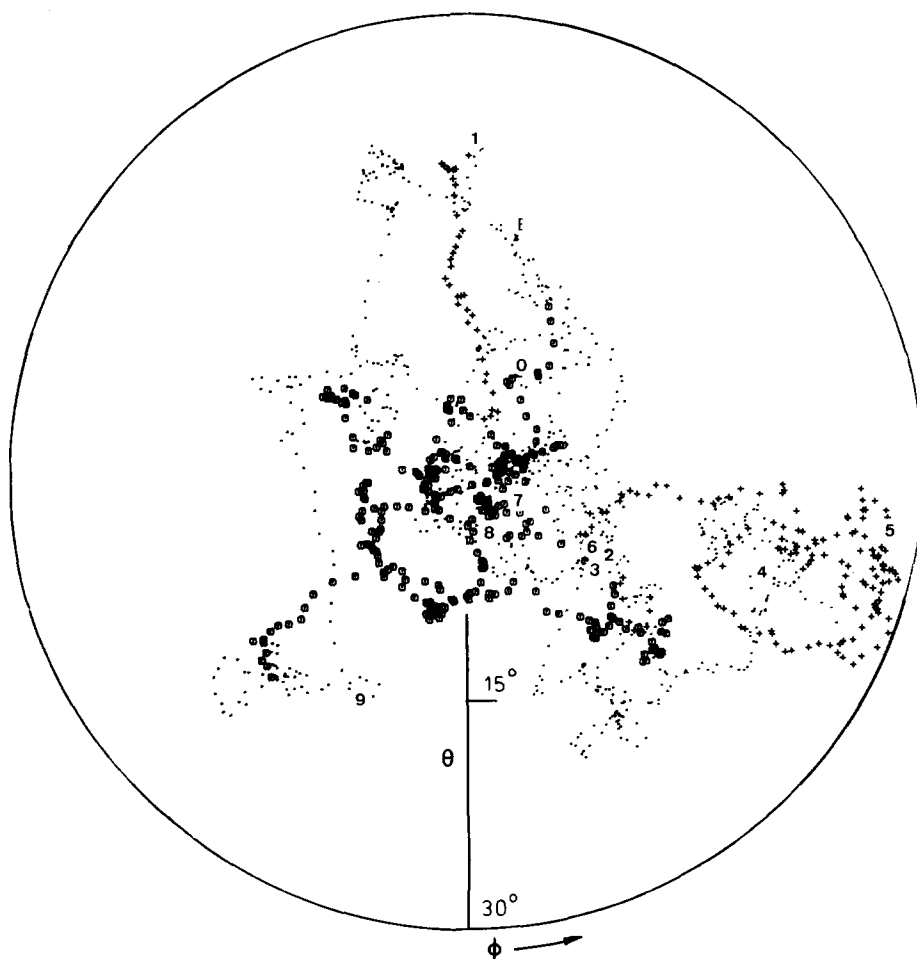

FIG. 5. Polar diagram of orientation of average tilt vector T during the course of the simulation. Numbers indicate time in units of 8 ps elapsed since start of simulation (E indicates end). + indicates angular correlation exceeding an average plus one standard deviation σ; o denotes correlation less than average $-\sigma$; dots give region of average $\pm\sigma$.
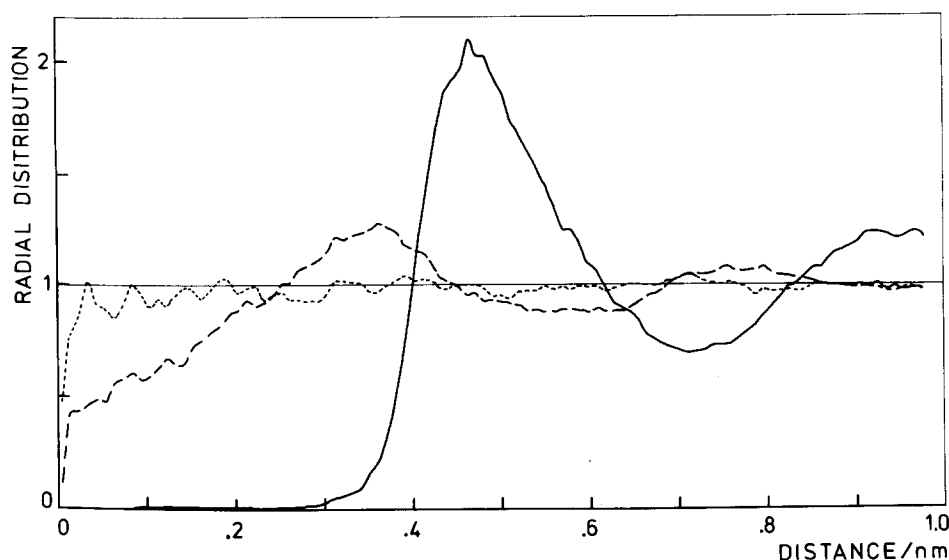
FIG. 6. Two-dimensional radial distribution curves for head groups in the same layer (drawn curve), tail atoms in different layers (broken line), and head groups in different layers (dotted curve).

periodic boundary condition can in principle enhance long range correlation. Therefore, we also performed an MD run on a 4×larger system, consisting of 2×64 decanoate molecules. In that case, the collectivity does not extend over the whole unit cell; for short range properties the results of the smaller simulation as presented here, are qualitatively correct.

In order to explain the plateau in the order parameters along the chain the "kink" model has been often quoted.[3] A kink is a g^+tg^- or g^-tg^+ sequence of dihedral angles where $g^\pm$ and t denote dihedral angles of $\pm 120°$ (gauche) and $0°$ (trans), respectively. A kink does not change the direction of the chain (as a single gauche would), but only produces a local displacement.[15] It is assumed that the kink can move up and down the chain; in this model the order parameters are constant along the chain. In order to explain the observed order parameters, about one kink per chain is required. From our simulation we can unequivocally conclude that the kink model is incorrect. Although kinks do occur (see Fig. 4), their occurrence is in agreement with the probability expected from a random distribution of gauche conformations,[21] while shifts of kinks along the chain are not observed. The reason for the plateau in the order parameters is the occurrence of an average tilt of the chains. Such a tilt is sterically possible because the tilt is to a certain extent a collective property.

Correlation between the positions of molecules in the xy plane can be represented by two-dimensional radial distribution curves $g(r)$. The normalized probability of finding a molecule within an interval $(r, r + dr)$, where r is the distance in the xy plane from a given molecule, is $2\pi r g(r)dr$. In Fig. 6 radial distribution functions are shown for three cases: head groups in the same plane, tail carbon atoms in the upper plane relative to tail atoms in the lower plane, and head groups in the upper plane relative to head groups in the lower plane. The head groups in one plane show a liquid-like radial distribution, but are not correlated with head groups in the other plane. On the other hand, the tail atoms in one layer are correlated with the tail atoms in the other

layer in such a way that simultaneous presence of two tails opposite to each other is less likely.

The head group $g(r)$ is still highly structured at half the box size. This also calls for a simulation of a larger system. Our subsequent simulation of a 2×64 decanoate bilayer, the results of which will be reported elsewhere, shows in the range to 1 nm a $g(r)$ which is quite similar to the one presented here, while an additional third peak is formed at larger distance.

IV. CONCLUSION

The method of molecular dynamics, which was only recently developed for the study of simple liquids, can now be successfully applied to larger and more complicated systems of chemical and biochemical interest. Our study has shown that, for membrane models, reliable results can be obtained with existing interaction potentials. The simulations give detailed insight into the structural and dynamic properties on a molecular scale. Unlike most theories, it is not necessary to introduce simplifications of which the validity cannot easily be tested. The plateau in the order parameters as a function of carbon atom number is caused by fluctuating collective tilt of the aliphatic chains. No support for the role of kinks has been found.

[1]J. Seelig, Q. Rev. Biophys. 10, 353 (1977).
[2]S. Marcelja, Biochem. Biophys. Acta 367, 165 (1974); H. L. Scott, Jr., ibid. 469, 264 (1977).
[3]H. Träuble, J. Membr. Biol. 4, 193 (1971); H. Träuble and D. H. Haynes, Chem. Phys. Lipids 7, 324 (1971).
[4]J. P. Hansen and I. R. McDonald, Theory of Simple Liquids (Academic, London, 1976).
[5]R. M. J. Cotterill, Biochem. Biophys. Acta 433, 264 (1976).
[6]S. J. Toxvaerd, J. Chem. Phys. 67, 2056 (1977).
[7]A. J. Kox, J. P. J. Michels, and F. W. Wiegel, Nature 287, 317 (1980).
[8]L. Verlet, Phys. Rev. 159, 98 (1967).
[9]W. F. v. Gunsteren and H. J. C. Berendsen, Mol. Phys. 34, 1311 (1977); J. P. Ryckaert, G. Ciccotti, and H. J. C. Berendsen, J. Comput. Phys. 23, 327 (1977).

[10]J. P. Ryckaert and A. Bellemans, Faraday Discuss. Chem. Soc. **66**, 95 (1978); Chem. Phys. Lett. **30**, 123 (1975).

[11]K. D. Gibson and H. A. Scheraga, Proc. Natl. Acad. Sci. U.S.A. **58**, 420 (1967).

[12]P. K. Warme and H. A. Scheraga, J. Comput. Phys. **12**, 49 (1973).

[13]T. A. Weber, J. Chem. Phys. **70**, 4277 (1979).

[14]A. Saupe, Z. Naturforsch. Teil A **19**, 161 (1964).

[15]J. Seelig and W. Niederberger, Biochemistry **13**, 1585 (1974).

[16]M. P. McDonald and W. E. Peel, Trans. Faraday Soc. **67**, 890 (1971).

[17]J. F. M. Post, E. James, and H. J. C. Berendsen, J. Magn. Reson. (in press 1982).

[18]P. Diehl and W. Niederberger, J. Magn. Reson. **15**, 391 (1974).

[19]G. Stulen, Ph.D. thesis, University of Groningen, The Netherlands, 1979.

[20]T. P. Higgs and A. L. MacKay, Chem. Phys. Lipids **20**, 105 (1977).

[21]About 25% *gauche* conformations are observed, thus allowing a maximum of about one kink per chain, whereas a random distribution (with g–g excluded) implies 0.16 kinks per chain. We observe 0.20 kinks per chain.