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Computer simulation of the temperature- and hydration-dependent lateral diffusion of phosphatidylcholine in lipid bilayers

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Abstract

A lattice model of a lipid bilayer near the so-called main phase transition between the liquid crystalline (L_α) and the gel (L_β) phase is presented. It is based on a two-state model. Jump dynamics are defined for the lattice molecules to simulate lateral diffusion. The temperature and hydration dependence of the lateral diffusion coefficients of the model are calculated for the L_α phase using Monte Carlo simulation techniques. The results obtained allow the estimation of the hydration dependent part of the lateral diffusion activation energy by thermodynamical quantities. We compare these results with measured activation energies of dipalmitoylphosphatidylcholine (DPPC) and propose a model to describe the total lateral diffusion activation energy of such systems.

Keywords: Bilayer model; Lateral diffusion coefficients; Lateral diffusion activation energy

1. Introduction

A rigorous study of transport phenomena in biological membranes is necessary to understand the connection between the composition and function of such systems. A basic step on this way is the investigation of the lateral self-diffusion of the membrane-forming molecules. In this field a few measurements were performed on lipid bilayers near the so-called main phase transition between the liquid crystalline (L_α) and the gel (L_β) phase using several techniques [1–7].

The dependence of the lateral diffusion coefficients of the lipids on temperature is well known from these measurements for a number of pure and mixed systems [1–4]. In contrast the dependence on hydration had received little attention [5–7] regardless of the fact that many processes in biological membranes depend on lipid dehydration [8,9]. The results obtained can be explained using a free volume theory or an excess area theory [4,8–11]. Nevertheless, there is no standard way to describe both the temperature and the hydration dependence of the lateral diffusion coefficients near the main phase transition.

For a theoretical treatment of this problem several lattice models of lipid bilayers are available, which give a good qualitative and quantitative molecular picture in particular of the main phase transition [12–17]. Furthermore, there are a couple of studies dealing with the problems to model the self-diffusion of molecules on a lattice using MC techniques [18–24].

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In this study, we propose first a lattice model of a pure lipid bilayer. Second, we define dynamics for the lattice molecules to derive the temperature and hydration dependence of their lateral diffusion coefficients using MC techniques. From the results obtained for the temperature and hydration dependence we propose a simple model for activating lateral diffusion.

2. Model

The model describes a lipid bilayer near the so-called main phase transition. It is based on a two-state model [12,13].

Lattice points on a two-dimensional square lattice define the position of model molecules of a layer. The molecules consist of a phophatidylcholine (PC)-like head-group and a saturated hydrocarbon chain with N methylene groups. They are described in terms of two states of the hydrocarbon chains; a non-degenerate ground state G (*all-trans* state) and a highly degenerate excited state E (thermal average over all rotationally isomeric states). Each state m (m = E,G) is characterised by its state energy $E(m)$, cross-sectional area $A(m)$ and degeneracy $D(m)$.

We assume, that only two lipid–lipid interactions are relevant for this bilayer model. At first, an attractive Van der Waals interaction of the hydrocarbon chains is considered using a potential of long, cylindrical molecules [13,14,25]. The corresponding Hamiltonian of the model can be written as:

$$H_a = -\frac{J_{GG}}{2} \sum_{\langle i,j \rangle} \sum_{(n,m)} I_m^a I_n^a L_{m,i} L_{n,j} \qquad (2.1a)$$

with

$$I_m^a = \left[\frac{r(G)}{r(m)} \right]^{5/2} S_m^{chain} \qquad (2.1b)$$

where $\langle i,j \rangle$ denotes a sum over nearest neighbors and (n,m) a sum over the chain states. J_{GG} is the energy of the G–G interaction and $L_{m,i}$ describes the projection operator for state m at occupied site i. Furthermore, S_m^{chain} denotes the chain order parameter and $r(m)$ the radius corresponding to the cross-sectional area of a molecule in state m [26].

Second, a repulsive interaction between the polar head-groups is considered using a dipole potential. For this, the Hamiltonian can be written as:

$$H_r = +\frac{K_{GG}}{2} \sum_{\langle i,j \rangle} \sum_{(n,m)} I_{m,n}^r I_{n,m}^r L_{m,i} L_{n,j} \qquad (2.2a)$$

with

$$I_{m,n}^r = \left[\frac{r(G)}{\sqrt{r^2(m) + r_p^2}} \right]^{3/2} S_{m,n}^{head} \qquad (2.2b)$$

where K_{GG} is the G–G interaction energy and $S_{m,n}^{head}$ denotes the head-group order parameter of a molecule at chain state m where its neighbor chain state is n (Appendix A). The parameter r_p is described in the text below.

Steric hindrance of the molecules is considered by allowing only single-site occupation and by introducing a lateral pressure Π, as described in [14–16]. Furthermore, the hydration of the bilayer, i.e. lipid–water interaction, is modelled by coupling this lateral pressure to the hydration pressure P as known from [27]:

$$\Pi = P * d_w/2 \qquad (2.3)$$

where d_w describes the water layer thickness between two adjacent layers.

A layer roughness is stated following the concept of an intrinsic surface [28,29]. It is realized by a mean relative shift $2r_p$ between the molecules perpendicular to the surface. The shift varies between 0 and $2r_{p,max}$ self-consistent with the mean total interaction energy per molecule (Appendix B). Note, that this allows for an approximately constant temperature T_f of the main phase transition of the system for all higher hydrated states, as known from measurements [30].

Summarized, the total Hamiltonian of the system can be written as:

$$H_t = H_a + H_r + \sum_{\langle i \rangle} \sum_{(n)} (E_n + \Pi A_n) L_{n,i} \qquad (2.4)$$

where $\langle i \rangle$ denotes a sum over the lattice.

The two-state model is now treated in terms of the spin variables of a two-dimensional site-diluted spin-1/2 Ising model. The Ising variables σ are associated with the different chain states of a molecule ($\sigma = 1$ corresponds to G and $\sigma = -1$ to E). So, one

can derive a mean order parameter of the chains, $\langle \sigma \rangle = s$, from the thermal average taken over all molecules with respect to all configurations for a fixed occupation number x of the lattice. One then obtains the self-consistent mean-field equation:

$$s = s(T, \Pi, \boldsymbol{C}, \xi, s) \tag{2.5}$$

where $\boldsymbol{C}$ is the parameter set of the model.

In the model, a free lattice site indicates a disturbed lipid–lipid as well as a disturbed lipid–water interaction of the neighboring molecules. Therefore, the energy to build up a free lattice site includes the energy to reduce the effective number of interacting molecules of the neighboring molecules by one and the energy necessary for a molecule to overcome steric hindrance. The thermal occupation probability ξ of the lattice is controlled by these energies. By taking the thermal average over local occupation variables v ($v = 1$ occupied, $v = 0$ not occupied) over all lattice points one gets for $\langle v \rangle = \xi$:

$$\xi = \xi(T, \Pi, \boldsymbol{C}, \xi, s) \tag{2.6}$$

If $x = \xi$ and for suitable parameter sets $\boldsymbol{C}$, the self-consistent equation system {2.5–2.6} has solutions which model the phase behavior of real lipid bilayers (see Section 4).

We have dealt in detail with a model of a dipalmitoylphosphatidylcholine (DPPC) bilayer, i.e. $N = 16$. For the special parameter set $\boldsymbol{C}^*$, see Appendix C.

3. Monte Carlo (MC) method

To get a numerical solution of the behavior of the system based on the Hamiltonian we have used a conventional Metropolis MC-sampling scheme supplemented with a continuum-time method [17,31,32]. For modelling the dynamics we define two transition types for the molecules; first, a Glauber-type single-site conversion, i.e. a transition between the different chain states; second, a Kawasaki-type hopping of the molecules to non-occupied nearest neighbor lattice sites (jump diffusion). Both transitions are characterized by typical time scales, τ_s and τ_d, respectively.

While the Glauber-transition probabilities are derived exactly for all different nearest neighbor configurations of the molecules (30 transition classes), averages are taken for the probabilities of the Kawasaki transitions. Here, we have assumed transitions to the mean energetical state and derived the transition probabilities for all nearest neighbor configurations with a constant number of vacancies. This is done separately for each chain state of the hopping molecule (10 transition classes). Therefore, the simulation generates the correct distribution of the lattice energy only in the limit of a complete occupied lattice [23].

We have used the standard interpretation of a MC simulation via master equation formulation [33]. Generally, the associated time scales are not physical time scales, because the true equations of motion are not invoked. However, we assume that the MC-time series have some relevance for the equilibrium dynamics of both the chain isomerization as well as the diffusional process.

The different time scales of the defined transitions constitute their own problem in interpreting the simulated dynamics, because the processes may be coupled. For simplification we have decoupled them. First, for fixed occupation numbers x taken from the mean-field solution (random distributed free lattice sites), the systems were allowed to come to thermal equilibrium via Glauber transitions. Second, to model the lateral diffusion, only Kawasaki transitions were allowed. This is a well-known technique used in several jump diffusion studies [18–20,23], which allows, under the assumptions made, to associate a typical physical time with each MC step per site (MCS/S).

Apart from these simulations, we have studied lateral diffusion for coupled processes too, i.e. Kawasaki as well as Glauber transitions were allowed at both steps described. The simulation were performed for several time-scale ratios τ_d/τ_s. No significant differences could be derived for the behavior of the diffusion coefficients changing temperature T and lateral pressure Π in comparison to the decoupled simulations, indicating that all results for the diffusion behavior presented below are nearly independent of the time-scale ratio τ_d/τ_s for the technique used.

The MC simulations were carried out on a finite lattice subject to periodic boundary conditions. A variety of lattice sizes have been studied, ranging

from 40×40 to 120×120 sites, to control finite size effects.

4. Results

4.1. Phase behavior

By the numerical evaluation of the self-consistent equation system {2.8–2.9} one gets for the parameter set C^* (Appendix C) a phase behavior of the system which agrees quite well with the behavior of DPPC (see e.g. [34,35]). For example Fig. 1a and b show the mean-chain-order parameter s of the system for several isobars and isotherms from which quantities like the mean cross-section area of a molecule or the lateral compressibility and the specific heat of the system can be derived [16,17].

The high hydration states ($\Pi < 5$ dyn/cm) are not well described. Here, one has to deal with sensitive equilibrium states where small energy contributions become important; e.g. by morphological changes of the system [36].

4.2. Lateral diffusion

The diffusion coefficients $D(T,\Pi)$ were determined using the Einstein equation for two-dimensional Brownian diffusion

$$\langle R^2 \rangle = 4Dt \qquad (4.1)$$

where t is the observation time and $\langle R^2 \rangle$ the mean square displacement per molecule realized during t via the described 'jump process'. The observation time has been measured in MC steps per site (MCS/S). The calculated values of $D(T,\Pi)$ were obtained using a linear regression procedure. An equilibration time of 10^3 MCS/S and a measuring time of about 10^4 MCS/S were used. Note, that the diffusion could only be studied for occupation numbers $x < 0.999$ because of the limited system size. Therefore, we had to restrict our study to the range $s < 0$ (L_α-phase).

Above but near the main phase transition the calculated diffusion coefficients show a strong temperature and lateral pressure (hydration) dependence. Increasing the temperature they increase monotonously, dependent on the lateral pressure Π.

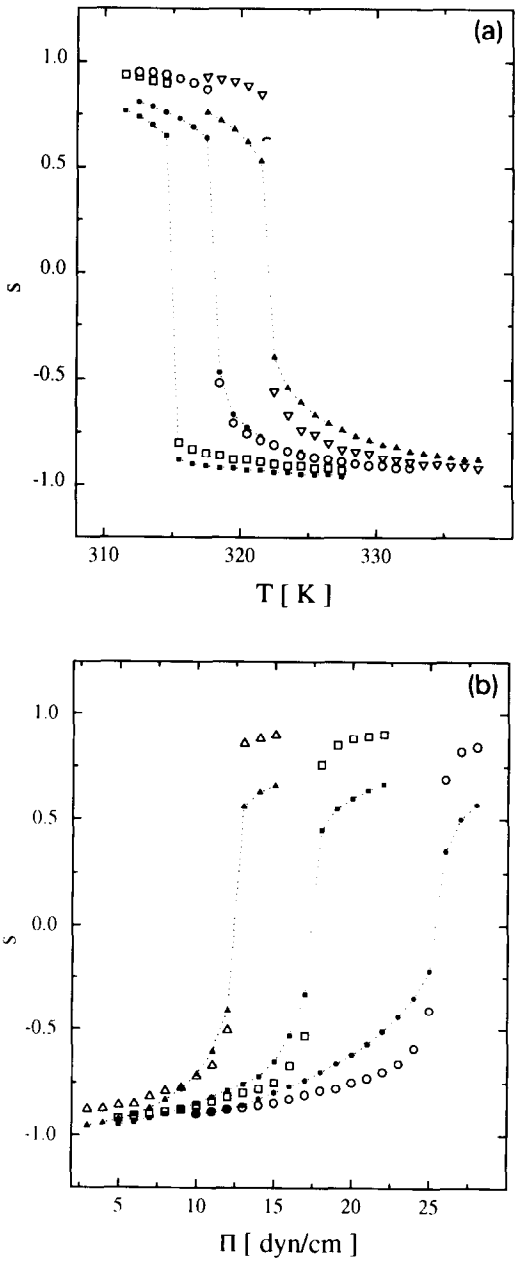

Fig. 1. Mean chain-order parameter s of the system as obtained from mean field solutions (small solid symbols) and MC calculations (large open symbols). (a) Isobars; (□) 5 dyn/cm, (○) 10 dyn/cm, (▽) 15 dyn/cm. (b) Isotherms; (△) 320 K, (□) 325 K, (○) 330 K.

This is in agreement with measurements of the lateral diffusion coefficients of lipids [5,6]. A double-logarithmical plot for the values of different isobars

versus the reduced temperature $(T - T_f)/T_f$ (Fig. 2a) shows straight lines which are fitted by:

$$D(T, \Pi = \text{const.}) = D_\pi \left(\frac{T - T_f}{T_f} \right)^{y_\pi} \quad (4.2)$$

where $0 < (T - T_f)/T_f \ll 1$.

A nonlinear curve fitting procedure with lateral pressure-dependent parameters D_π and y_π was applied to the data using PEAKFIT (Jandel Sci.). The values of T_f were derived from the MC results for the mean chain order parameter s of the system. Fig. 2b shows $D(T, \Pi = 10$ dyn/cm) versus T.

While the parameter D_π was found to be nearly lateral pressure independent ($D_\pi \approx 2 \times 10^{-20}$ $m^2/(MCS/S)$), for the lateral pressure dependence of y_π a linear behavior was found. This is shown in Fig. 3. From this we make a first approximation for the exponent:

$$y_\pi \simeq \frac{\Pi A_{eff}}{2 k_b T_f} \quad (4.3)$$

where A_{eff} denotes an effective required excess area for a molecule to diffuse at the temperature T_f ($A_{eff}/T_f \approx$ const.). We have found $A_{eff} \geq 28$ Å^2 for the lattice molecules.

Using the Eqs. (4.2) and (4.3) and the obtained values of D_π and A_{eff} one can estimate the lateral diffusion coefficients as a function of Π. This requires again the values of $T_f(\Pi)$. Here, they can be derived with sufficient accuracy from the mean-field results for the mean chain order parameter s of the system. In Fig. 4 the values obtained in this manner are compared with that from the MC calculations at constant temperature $T = 320$ K. Note, that the deviations for small lateral pressures are mainly due to the problems with the transition probabilities described in Section 3.

5. Activation energies

In the literature, e.g. [2,6] the lateral diffusion activation energy is usually presented as a constant value, extracted using Arrhenius plots. But it contains contributions from different processes, e.g. the activation energy for head-group rotation, chain isomerization etc. It is known from recent NMR measurements [37], that some of these contributions are not hydration dependent themselves. In contrast, there is no doubt that the lateral diffusion activation energy is hydration dependent [5–7].

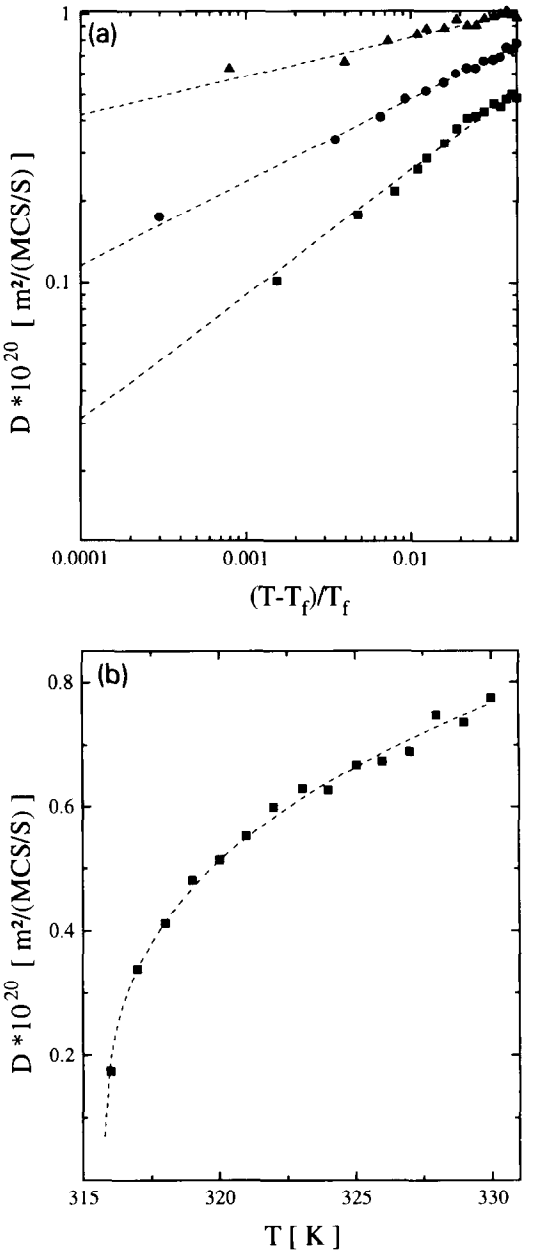

Fig. 2. Lateral diffusion coefficients D as obtained from MC calculations. Symbols denote the calculated values and the dashed lines the fits according to Eq. (4.2). (a) Double-logarithmic plot of D vs. the reduced temperature for different isobars; (▲) 5 dyn/cm, (●) 10 dyn/cm, (■) 15 dyn/cm. (b) D vs. T for the isobar $\Pi = 10$ dyn/cm.

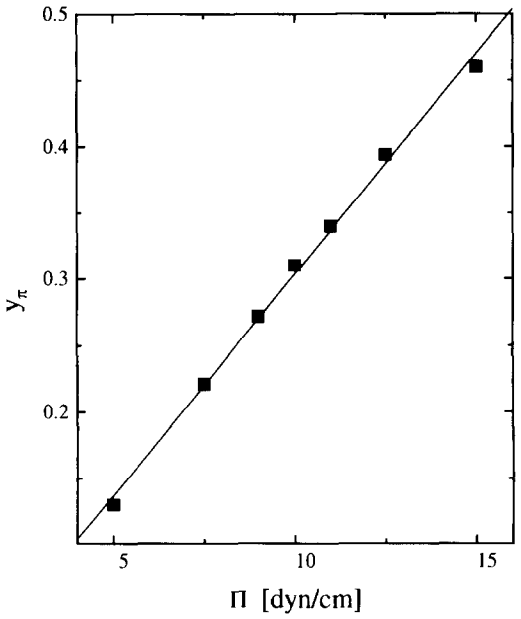

Fig. 3. Lateral pressure dependence of the parameter y_π in Eq. (4.2). The symbols denote the obtained values and the line a linear fit to the data. $A_{eff} \approx 28.5$ Å^2.

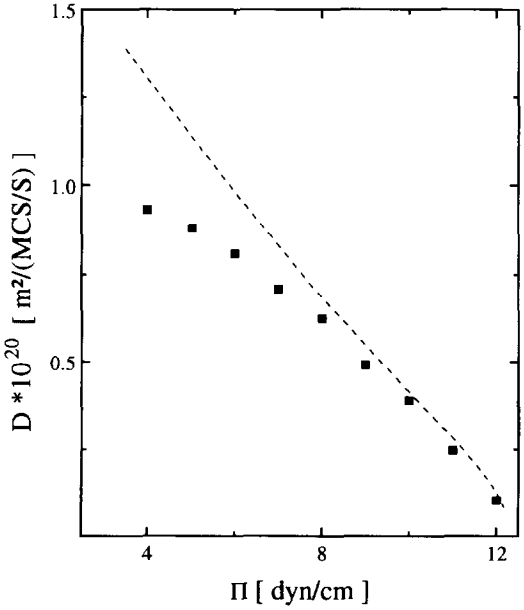

Fig. 4. Lateral diffusion coefficients D vs. Π for the isotherm $T = 320$ K. Symbols denote the values obtained from MC calculations and the dotted line the result of the estimation described in the text.

In the following we propose a simple model to understand the measured lateral diffusion activation energies. Proceeding from a discrete jump model of the diffusion process (free volume theory) we assume, that a diffusion jump of a single molecule is possible only if it is in a highly excited isomerization state, correlated with adequate head-group rotation. Because of the different time scales of the isomerization ($\tau_{iso} = 0.1$ ns), head-group rotation ($\tau_{rot} = 1.0$ ns) and lateral diffusion ($\tau_{diff} = 10$ ns) [34,38], this is a good approximation. The activation energy E_0 for such a state can be estimated e.g. from that for molecule rotation for full hydrated systems and it depends on the structure of the molecule. It is about 50 kJ/mol or more for DPPC [34].

Apart from this we assume, that in order to realize a diffusion jump a molecule needs a further excitation E_π to reduce the neighbor interactions and to overcome steric hindrance. E_π is assumed to be the hydration dependent part of the total lateral diffusion activation energy.

In the model described above these assumptions are approximately satisfied and for the modelled lateral diffusion a thermodynamical description of E_π can be derived from the results for the diffusion coefficients. Following the usual analysis of the diffusion coefficients in terms of the Arrhenius expression:

$$D = D_0 \exp\left(\frac{-E_a}{k_b T}\right) \tag{5.1}$$

where D_0 denotes the lateral diffusion coefficient at infinite temperature, one gets a total activation energy for the lateral diffusion:

$$E_a = E_0 + E_\pi \tag{5.2a}$$

with

$$E_\pi \simeq -\frac{\Pi A_{eff}}{2} \ln\left(\frac{T - T_f}{T_f}\right) \tag{5.2b}$$

where $0 < (T - T_f)/T_f \ll 1$.

For low lateral pressure (high hydration) as well as for temperatures far above T_f the term E_π is small in comparison with E_0. If the system is close to the transition temperature or in the case of high lateral pressure (low hydration) the contribution of E_π becomes important.

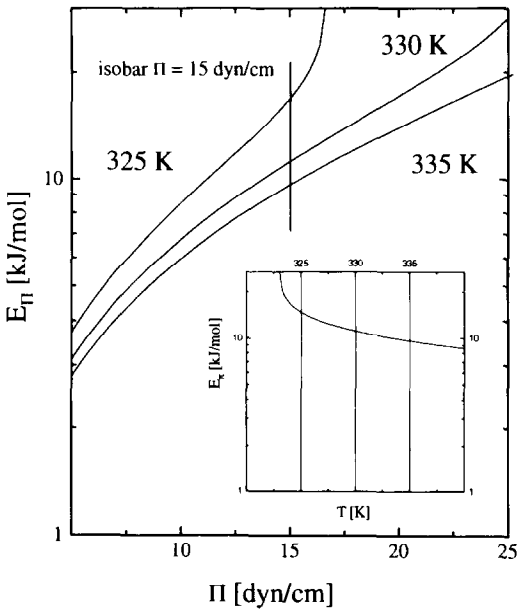

Fig. 5. The lateral pressure dependent part E_π of the activation energy vs. Π as obtained from Eq. (5.2b) using $A_{eff} = 50$ Å^2 for several isotherms. The values of $T_f(\Pi)$ were derived from the mean field solutions for s. The insert shows E_π vs. T for the isobar $\Pi = 15$ dyn/cm. Note the strong temperature dependence near above $T_f \approx 323$ K.

The effective required excess area A_{eff} for lateral diffusion of a DPPC molecule was estimated fitting the measured data of the activation energies from [6] using Eqs. (5.2a/b) with A_{eff} as free parameter. One gets a value $A_{eff} \geq 50$ Å^2, which is correlated with the total area of a double chain molecule. Fig. 5 shows E_π versus Π for the model described using this excess area. Note, that there should arise an error, when extracting the activation energies assuming temperature independent values as is usually done. This is demonstrated by the insert showing the strong temperature dependence of E_π near above $T_f(\Pi)$.

6. Conclusion

Lateral diffusion of molecules on a lattice was simulated by introducing dynamics into the model of the lipid bilayer described. A behavior for the modelled diffusion coefficients above but near the main phase transition was derived which agrees qualitatively with that in real lipid bilayer systems obtained by several techniques. Their temperature and lateral pressure dependence was fitted by exponential functions of the reduced temperature. In a first approximation the exponents were described using thermodynamical quantities as the lateral pressure and the main phase transition temperature.

Furthermore, the lateral pressure dependence of measured activation energies of the lateral diffusion in lipid bilayers was qualitatively explained based on a simple model of activating a diffusion jump of a single molecule. This dependence was quantified for the bilayer model described and an estimation of it for DPPC bilayers was made. Because the hydration dependent part of the activation energy should also be temperature dependent, as shown by the model calculations, we suggest to improve the analysis of measured data using Eqs. (5.2a/b). This requires hydration dependent measurements of the temperature of the main phase transition which are reported for several lipids in the literature (e.g. [35]).

Even though all results presented here are related to DPPC, the model would have the same structure for other saturated phosphatidylcholine and therefore should lead to qualitatively comparable solutions. However, a direct quantitative comparison would be very difficult because of the different hydration behavior of the different lipid species, especially in the high hydration range [27]. This range, although biological the most interesting, is very complicated to treat and described only roughly by the model.

Nevertheless, the model can be extended to more complex systems, like lipid/tensid systems, without any extra effort.

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Appendix

Appendix A: Model of dipole–dipole interaction

Based on the structure of a PC head-group we use an effective dipole (one-sided fixed at the molecule

chain), which rotates in a space sector between the plane of the layer and a maximum angle $(\Pi/2 - \alpha)$. Each orientation of the dipole is related to a steric energy dependent on the chain state of the molecule and its neighbors. By taking the average over all orientations for a fixed chain state n and neighbor chain state m the mean normal component $q_{n,m}$ of the dipole can be written as:

$$q_{n,m} = q_0(\cos(\alpha)/2)\left[1 + F_L\left(\frac{\cos(\alpha)W_{n,m}}{2k_bT}\right)\right] \tag{7.1}$$

where F_L denotes the Langevin function, q_0 is the dipole moment and $W_{n,m}$ describes the energy of the steric hindrance of a dipole parallel to the bilayer plane. One gets for the interaction energy of two neighboring head-groups:

$$K^w_{n,m} = K_0\left(\frac{\cos(\alpha)}{2}\right)^2\left[1 + F_L\left(\frac{\cos(\alpha)W_{n,m}}{2k_bT}\right)\right] \times\left[1 + F_L\left(\frac{\cos(\alpha)W_{m,n}}{2k_bT}\right)\right]R \tag{7.2a}$$

$$R = \left[\frac{r_G^2}{\sqrt{r^2(m) + r_p^2}\sqrt{r^2(n) + r_p^2}}\right]^{3/2} \tag{7.2b}$$

where K_0 is the interaction of parallel dipoles.

The parameters used are defined by:

$$K_{GG} = K_0(\cos(\alpha))^2 \tag{7.3}$$

$$S^{head}_{n,m} = \left[1 + F_L\left(\frac{\cos(\alpha)W_{n,m}}{2k_bT}\right)\right]/2 \tag{7.4}$$

Appendix B: Roughness parameter r_p

The energy of a molecule protruding r from the equilibrium state is assumed to be proportional to r^2 (Hooke's law). For a self-consistent variation of the mean relative shift r_p with the mean total interaction energy per molecule W_G — which depends on r_p via Eqs. (2.1a/b) — we have assumed for each equilibrium state:

$$\left(\frac{r_{p,max} - r_p}{r_{p,max}}\right)^2 = \frac{W_G}{W_{G,max}}$$

where $|W_{G,max}|$ denotes the maximum of $|W_G|$.

Table 1

Chain state G	Chain state E	Comment
$E_G = 0$ Nm	$E_E = 2.7\times10^{-20}$ Nm	Measured [14]
$A_G = 20$ Å^2	$A_E = 34$ Å^2	Measured [35]
$D_G = 1$	$D_E = 3^{15}$	Set [13]
$J_{GG} = 4.5\ 10^{-20}$ Nm		Calculated [25]
$S^{chain}_G = 1.0$	$S^{chain}_E = 0.6$	Measured [34]
$K_{GG} = 2.0\times10^{-20}$ Nm		Fitted
$S^{head}_{GG} = 1.0$	$S^{head}_{EE} = 0.5$	Set (Appendix A)
$S^{head}_{EG} = S^{head}_{GE} = 0.8$		Fitted
$r_{p,max} = 2.5$ Å		Set [39]

Therefore, the equilibrium state conditions of the system depend on the value of $2r_{p,max}$ denoting the equilibrium shift at disappearing interactions.

Appendix C: Parameter set C^* for DPPC

Table 1 shows the parameter set C for DPPC.

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