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Lipid bilayer polypeptide interactions studied by molecular dynamics simulation

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Abstract. A model membrane with a polypeptide alpha-helix inserted has been simulated by molecular dynamics at a temperature well above the gel/liquid crystalline phase transition temperature. Order parameters of the lipids and other equilibrium and dynamic quantities have been calculated. Three systems, polyglycine constrained into an alpha-helical configuration, glycophorin with similarly conformationally constrained backbone and finally glycophorin free to change its backbone conformation, have been studied. In all cases there was an ordering of the chains close to the helix. This effect was, however, much smaller for glycophorin with its rather bulky side chains than for polyglycine. The dynamics of the lipids were affected by the neighbouring helix, not drastically however. Lateral diffusion and reorientational time correlations of lipids close to the helix were slower than for the bulk ones, but not more than two or three times. Thus, we did not find any evidence of bound or frozen boundary lipids.

Key words: Polypeptide, glycophorin, lipid bilayer, molecular dynamics, order parameters

1. Introduction

Biomolecules such as small peptides in solution, proteins in vacuo and in their crystalline water, parts of nucleic acids in vacuo and lipid bilayers have been studied by computer simulations using molecular dynamics (MD). See e.g. Karplus and McCammon (1981, 1983) for reviews of protein simulations. Here, we report a MD-simulation of a lipid bilayer with a polypeptide incorporated.

Biomembrane/protein (polypeptide) interactions have been studied by a number of experimental and theoretical methods, resulting in seemingly contradictory results. The crucial question is: Are there boundary lipids close to the polypeptide with distinctly different properties from those of the bulk lipid; If this is the case, are the boundary ones more or less ordered than the bulk ones and on which time scale does the transition between the two types occur? These questions have not yet received unambigous answers.

To contribute towards the resolution of these controversies, we have simulated a bilayer of about one hundred 16 unit hydrocarbon chains and an incorporated polypeptide. The temperature has been kept at 330 K i.e. well above the transition temperature between the gel and liquid crystalline phases. As the alpha-helical polypeptide we have first chosen one without side chains, polyglycine. The length has been taken to 22 residues which is enough to span the bilayer. Since polyglycine is not stable as a helix, it was constrained into a helical conformation. As a more realistic system we have chosen one of the most studied membrane polypeptides, glycophorin, of which the 23 central hydrophobic residues were included in the simulation

ILE-THR-LEU-ILE-GLY-PHE-GLY-VAL-MET-
ALA-GLY-VAL-ILE-GLY-THR-ILE-LEU-LEU-
ILE-SER-TYR-GLY-ILE. (1)

To separate effects that come from side chains of the helix from those that have to do with deviations from helical structure we have performed two simulations with glycophorin. In the first one the backbone was kept in an alpha-helical conformation by constraining the positions of the C-alpha atoms. In the second one the backbone was allowed to undergo conformational transitions.

2. Methods

To perform the *MD*-simulation of the bilayer we used the methods developed by van der Ploeg and

Berendsen (1982, 1983) for decanoate bilayers. That is, we did not include water, counter ions and their interactions with the head groups of the lipids. The head groups were left uncharged. Instead, the bilayer was stabilized by a harmonic force that tries to keep each head group in a plane defined by the average position of all the head groups. Thus, the bilayer thickness adjusts automatically to a prescribed surface density.

The bond lengths were kept fixed, while bond angles and dihedrals were allowed to change subject to a force given by a potential. For the dihedral angles in the hydrocarbon chains we used a potential tested for butane by Ryckaert and Bellemans (1975). For the rest of the system potential parameters from van Gunsteren and Karplus (1982) were used. Periodic boundary conditions were imposed upon the system in the two lateral dimensions.

The classical equations of motion were integrated with a time step of $5 \cdot 10^{-15}$ s using a simple Verlet algorithm. For the initial configuration 2×64 all trans chains were generated. Next, a number of them were removed to create space for the helix. After some temperature and density adjustment and 25 ps equilibration, production runs of 75 ps were performed. During the simulation we kept track of temperature, pressure, fraction of gauches and a few other averages. Coordinates were saved each 0.2 ps for further analysis.

3. Results

In Table 1 we show some of the parameters for and results from the simulations. The lateral density was chosen to be close to experimental ones for pure lipid bilayers. However, we adjusted the surface density slightly to get approximate agreement with experimental order parameters of pure dipalmitoylphosphatidylcholine (DPPC) for the lipids far away from the helix. As seen from Fig. 1, this has not succeeded completely. The best fit is probably achieved with an area per chain of 0.33 nm^2 instead of 0.32 and 0.34 nm^2. The lateral and normal pressures are also given in the table as calculated during the simulation from the virial. Regrettably, they cannot be used for adjusting to the correct surface density since the interactions between head groups and surrounding water and ions are not properly modeled. Therefore, important contributions to the pressures are missing.

The density of headgroups as a function of the distance from the center of the helix is shown in Fig. 2. In the polyglycine case there are two well pronounced maxima at 0.58 and 1.0 nm. This indicates that the alpha-helix takes up approximately

Table 1. Some parameters of and results from the three simulations, polyglycine, glycophorin 1 (constrained alpha-helical backbone) and glycophorin 2 (free to move the backbone)

Quantity	Polyglycine	Glycophorin 1	Glycophorin 2
Temperature [K]	330	330	330
Lateral pressure [atm]	− 7.5	− 7.4	− 8.6
Normal pressure [atm]	− 9.3	− 8.5	− 9.9
Pot. energy [kJ/mol]	− 1,480	− 1,790	− 2,073
Fraction gauches	0.200	0.226	0.211
No. of chains	120	100	100
No. of atoms in helix	113	192	192
Total no. of atoms	2,033	1,792	1,792
Forces cutoff at [nm]	0.7	0.7	0.7
Area per chain [nm^2]	0.32	0.34	0.34
Membrane thickness [nm]	3.06	2.78	2.60

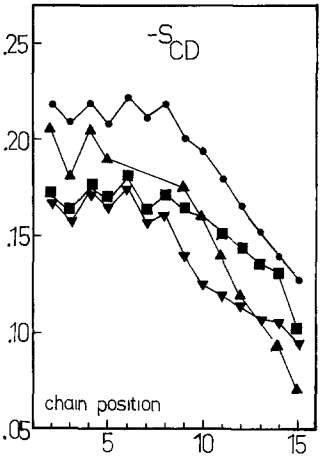

Fig. 1. The order parameter S_{CD} calculated from the three simulations in the outermost region($r > 1.68$ nm), which should correspond to bulk lipid. The four curves represent lipids with a polyglycine helix (●), with constrained glycophorin (▼), with free glycophorin (■) and experimental order parameters for pure dipalmitoylphosphatidylcholine (▲) (Seelig and Seelig 1974)

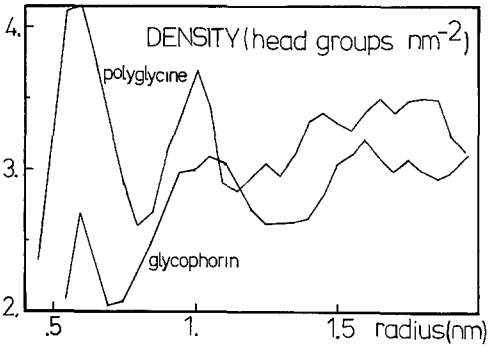

Fig. 2. Density of lipid head groups (number nm^{-2}) as a function of the distance (nm) from the centre of the polyglycine and glycophorin helices

the same area as a single lipid chain. For a pure hexagonally close packed lipid bilayer at the density 0.32 nm^2 per chain the first and second neighbour peaks of the pair correlation function would be at 0.61 and 1.05 nm. In the glycophorin case there is a small first neighbour peak at 0.60 nm and a higher and broader second neighbour peak at 1.05 nm.

A number of order parameters can be defined that characterize the average orientation of the CH_2-groups with respect to the normal of the bilayer plane (an extensive discussion of this is given in Edholm (1982)). We use two Euler angles, α and β, to describe the orientation of the CH_2-group with respect to the bilayer normal. The second one is the angle between the bilayer normal and the normal of the C−H−H-plane. The first one is chosen as the angle one has to rotate around the latter normal to get the direction bisecting the H−C−H angle into the plane spanned by the two normals. Equivalently one can see the two angles as the spherical coordinates that define the orientation of the bilayer normal in a suitable local frame of reference attached to the CH_2-group. The main order parameter is then

$$S_{\text{chain}} = 0.5\,(3\,\langle\cos^2\beta\rangle - 1) = \sqrt{4\pi/5}\; Y_{20}(\beta) \qquad (2)$$

$Y_{1m}(\beta, \alpha)$ are here and in the following spherical harmonics. But of interest is also

$$S_{22} = \sqrt{\pi/5}\,\langle Y_{22}(\beta, \alpha) + Y_{2-2}(\beta, \alpha)\rangle$$
$$= \sqrt{3/8}\,\langle\sin^2\beta\cos 2\alpha\rangle\,. \qquad (3)$$

The latter order parameter turns out to be positive which means that the plane defined by three consecutive CH_2-groups will tend to be perpendicular to the bilayer plane. Now, S_{chain} is experimentally accessible through electron spin resonance (ESR) while deuterium nuclear magnetic resonance (NMR) gives another order parameter which characterizes the orientation of a C−D-bond. The latter order parameter can be given as a linear combination of S_{chain} and S_{22}:

$$S_{CD} = -0.5\,S_{\text{chain}} - \sqrt{1/6}\;S_{22} \qquad (4)$$
$$= -0.25\,(3\,\langle\cos^2\beta\rangle - 1) - 0.25\,\langle\sin^2\beta\cos^2\alpha\rangle\,.$$

In Fig. 3 the order parameter S_{chain} averaged over all the chain positions is shown as a function of the distance from the centre of the helix. In Fig. 4 the average fraction of gauch bonds is plotted as a function of the distance from the centre of the helix. In the polyglycine case, both figures indicate an ordering of the chains close to the helix. The order parameter is 0.48 there compared to 0.32 far away and the fraction gauche is 0.16 and 0.22 respectively. A similar but less pronounced effect can be observed for glycophorin. The fraction of gauches

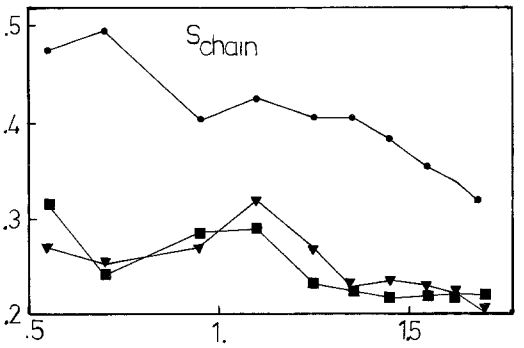

Fig. 3. Average order parameter S_{chain} as a function of head group distance from the centre of the helix. The three curves are for systems with (●) polyglycine, (▼) constrained glycophorin and (■) free glycophorin

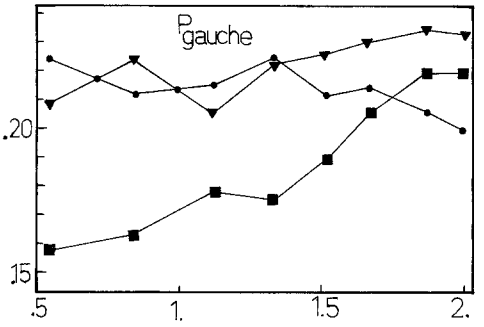

Fig. 4. Average fraction gauche bonds in the chains as a function of the head group distance from the centre of the helix. The three curves are for systems with (■) polyglycine, (▼) constrained glycophorin and (●) free glycophorin. We expect a standard deviation due to statistical errors that is less than 0.015

increases from around 0.21 to 0.23 and the order parameter starts at 0.27 close to the helix, goes through a maximum of 0.32, and drops to just above 0.20 far away from the helix. In Figs. 5 and 6 we show the whole order parameter profile for some distances from the helix. Again we see a clear increase in the order parameters of most of the hydrocarbon groups close to the polyglycine helix. In the glycophorin case there is a pronounced ordering close to the polypeptide of the hydrocarbon groups at the end of the chain (beyond say position 6−7). In the upper parts of the chains the situation is more unclear or even reversed. The order parameter S_{22} is 0.04 to 0.10 and is essential to get the correct value of S_{CD} through Eq. (4) to compare with the experimental deuterium order parameters. If we compare the S_{CD} of different layers we get a similar picture as for S_{chain}, however with somewhat smaller differences in the polyglycine case since there S_{22} is smallest close the helix.

Lateral diffusion constants for the lipids were also calculated from the simulation, by plotting the

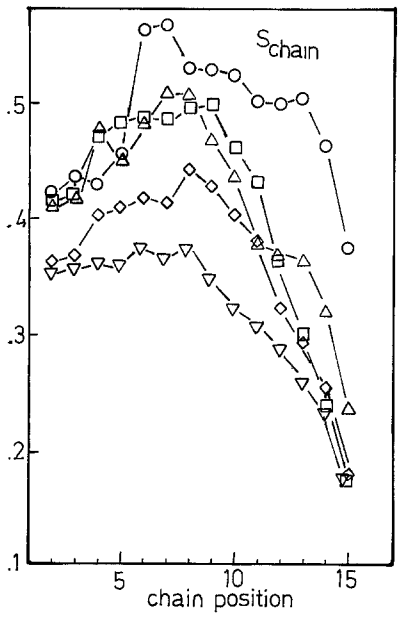

Fig. 5. Variation of the order parameter profile with distance from the centre of the polyglycine helix. The five curves correspond to the following regions ○ $r < 0.85$ nm, △ $0.85 \leqq r < 1.17$ nm, □ $1.17 \leqq r < 1.41$ nm, ◇ $1.41 \leqq r < 1.68$ nm and ▽ $r \geqq 1.68$ nm

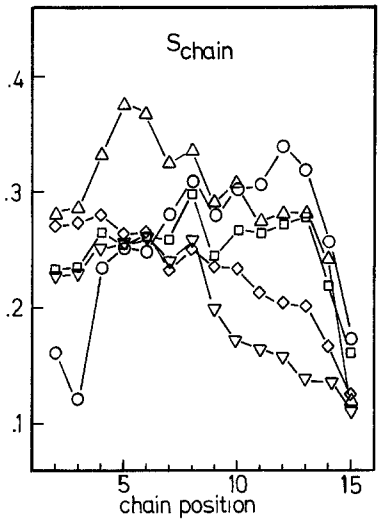

Fig. 6. Variation of the order parameter profile with distance from the centre of the glycophorin helix. The five curves correspond to the following regions ○ $r < 0.85$ nm, △ $0.85 \leqq r < 1.17$ nm, □ $1.7 \leqq r < 1.41$ nm, ◇ $1.41 \leqq r < 1.68$ nm and ▽ $r \geqq 1.68$ nm

square of the lateral displacement of the head groups against time for 10 ps. This gave almost perfect straight lines from the slope of which a diffusion constant of $8 \cdot 10^{-9}$ m^2 s^{-1} was deduced. This is a factor 8 faster than found by van der Ploeg and Berendsen (1983) for pure decanoate at 30 K lower temperature by a similar simulation, which in its turn is a factor 10 faster than experimental ones.

Table 2. Reorientational correlation times τ_1, and parameters B and A calculated from the time correlation functions of spherical harmonics, Y_{20}

Shell	Polyglycine			Glycophorin		
	τ_1 [ps]	B	A	τ_1 [ps]	B	A
1	13.	0.35	0.60	19.	0.18	0.51
2	12.	0.33	0.55	7.	0.15	0.60
3	6.	0.28	0.62	7.	0.18	0.56
4	13.	0.21	0.55	5.	0.10	0.51
5	8.	0.20	0.45	5.	0.14	0.51

Their explanation was that the damping influence from surrounding water which is not included in the model is essential to get the proper rate of diffusion. Thus, although our diffusion constant is too large, it is still interesting to study its variation with the distance from the centre of the helix. We found only a small variation (less than a factor of two). Thus, for the simulated system there are no immobilized lipids close to the helix.

We have also calculated correlation times for the orientational reorientation of the hydrocarbon groups:

$$g_{2m}(t) = \sqrt{4\pi/5}\,\langle Y_{2m}(\theta(t), \varphi(t))\, Y^*_{2m}(\theta(0), \varphi(0))\rangle. \tag{5}$$

We have here chosen θ, φ as the two spherical coordinates that describe the orientation of a C–H bond in the laboratory frame since it is such functions that occur in the formulae for NMR-relaxation times. As seen from Fig. 7, such a function initially decays very fast (time constant τ_2 of the order a ps), is then well described by a single exponential (τ_1, 5–20 ps) to end up at a value, B, that is given by the order parameters. Normalized so that $g(0) = 1$, we have:

$$g_{20}(t) = B + (1 - B)\,(A \exp(-t/\tau_1) + (1 - A) \exp(-t/\tau_2))). \tag{6}$$

The relaxation from deuterium NMR is by, e.g. by Seelig and Seelig (1980)

$$1/T_1 = (3\pi^2/2)\,(e^2 q Q/h)^2 (1 - S^2_{CD})\, A\, \tau_1 \tag{7}$$

if $\tau_2 \ll \tau_1 \ll \omega_L^{-1}$, where ω_L is the Larmor frequency, T_1 is the NMR relaxation time and $e^2 q Q/h$ the static quadrupole coupling constant (170 kHz). As seen from Table 2 we get a decay time that is about 6 ps far away from the helix. This gives NMR relaxation times that are far too slow (500 ms against experimental ones around 35 ms). This is probably to do with the absence of hydrodynamic and electrostatic interactions for the heat group. Thus not only the lateral diffusion but all the dynamics becomes too fast.

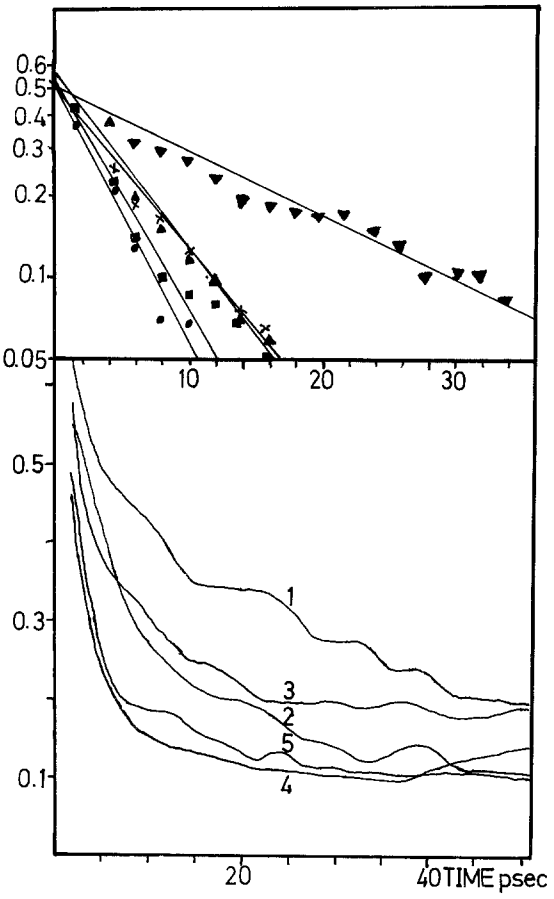

Fig. 7. Time correlation functions $g_{20}(t)$ (upper diagram in logarithmic scale) in different shells around the glycophorin helix. The five curves correspond to the following regions ▼ $r < 0.85$ nm, × $0.85 \leqq r < 1.17$ nm, ▲ $1.17 \leqq r < 1.41$ nm, ● $1.41 \leqq r < 1.68$ nm and ■ $r \geqq 1.68$ nm

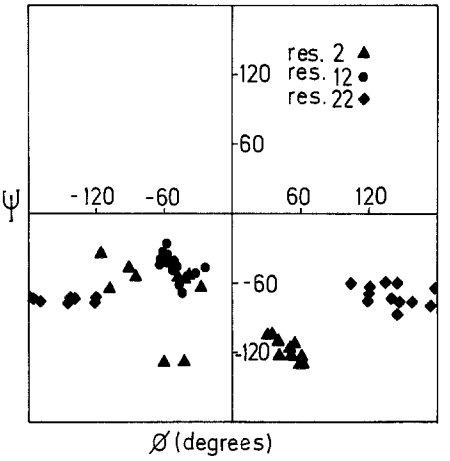

Fig. 8. Ramachandran map of the backbone angles Φ, Ψ of residues 2 (▲), 12 (●) and 22 (◆) averaged over consecutive periods of 2.5 ps

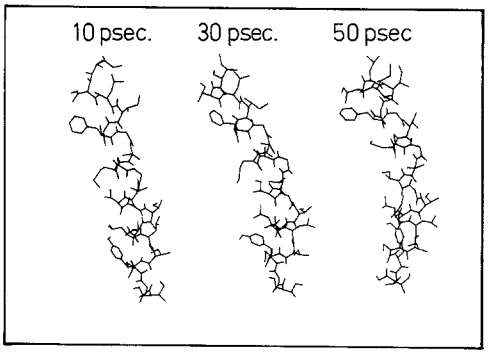

Fig. 9. Glycophorin structure after 10, 30 and 50 ps of simulation with the backbone allowed to move freely. All bonds are shown except those involving hydrogens

There is, however, a slowing down in the rotational dynamics close to the helix, especially in the glycophorin case (a factor of 3). This slowing down occurs only for the functions $g_{20}(t)$ not for $g_{21}(t)$ or $g_{22}(t)$. The main conclusion is, thus, that we find no evidence for a frozen boundary layer of lipids close to the helix, although there is some slowing down of the motions.

Now, we give some comments about what happened to the helix during the third simulation when the backbone was free to change conformation. It turned out that during a 50 ps run the polypeptide remained rather close to its original helical conformation. In Table 3 the average values and standard deviations of the 20 central Φ and Ψ angles, defined according to the IUPAC-IUB convention (1970) averaged over consecutive periods of 5 ps are shown. However, there were clear and increasing deviations from the angles of a perfect helix at both ends of the polypeptide. In Fig. 8 we show a Ramachandran map of the angles of residues number 2, 12 and 22 averaged over 20 consecutive periods of 2.5 ps. This illustrates that the central residues of the polypeptide remain very close to a perfect alpha-helix $(\Phi, \Psi) = (-60°, -50°)$ during the whole 50 ps of the simulation, while there are considerable deviations towards the ends of the chain. As seen from the plots of the polypeptide in Fig. 9, it remains rather close to a helix during the whole simulation, although there are observable differences.

Table 3. The backbone angles Φ and Ψ averaged over the 20 central residues and over consecutive periods of 5 ps together with standard deviations

Time [ps]	2.5	7.5	12.5	17.5	22.5	27.5	32.5	37.5	42.5	47.5
Φ [degrees]	−51	−50	−48	−48	−46	−44	−47	−47	−44	−48
standard dev.	12	13	14	12	14	14	15	14	17	20
Ψ [degrees]	−47	−58	−59	−58	−57	−58	−57	−59	−60	−49
standard dev.	14	12	14	14	15	15	18	16	20	36

However, for several reasons we do not want to draw any conclusions about the structure of glycophorin in a lipid bilayer from this simulation. First, it may take a lot longer time than 50 ps before an equilibrium conformation is reached. Secondly, there may, as for many polypeptides in solution, be no definite equilibrium conformation but a rather rapid passage between a large number of conformations. Thirdly, results regarding the polypeptide structure are probably very sensitive to the choice of model for the hydrogen bond forces. We have just used fractional charges and electrostatic interactions to represent these. Even if one had a more elaborate model with a more realistic directional and distance dependence, there is probably not enough known about the proper parameters of such a model to really be able to judge the stability of such a hydrogen rich structure as an alpha-helix.

4. Discussion

The conclusion is that there certainly is a perturbing effect from the polyglycine alpha-helix upon the neighbouring lipids and also, but to a smaller extent, from the glycophorin helix. This extends several layers out from the helix, but the exchange rate between boundary and bulk lipids is very fast and its order of magnitude is given by the lateral diffusion constants of pure lipid bilayers.

These results may be compared to those obtained by other authors using different theoretical and experimental approaches. For the theoretical articles see e.g. Marčelja (1976), Owicki et al. (1978), Scott and Cherng (1978), Owicki and McConnell (1979), Pink and Chapman (1979), Jähnig (1981a, 1981b), van der Ploeg (1982) and Scott and Coe (1983).

Most of the theoretical articles do not predict the size or sign of the perturbation of the order parameter close to the protein surface but this could be adjusted by varying some parameter in the model. It is then calculated how far out in the lipid this perturbation will extend and what effect it will have on the phase transition. In two cases, those of Scott and Cherng (1978) and van der Ploeg (1982), the effect upon the lipids of the introduction of a rigid cylinder in the bilayer is actually calculated. In the first case a Monte Carlo simulation of a simple chain model gives a clear ordering of the lipids close to the hard protein wall. In the second case a molecular dynamics simulation similar to ours of a decanoate bilayer with a Lennard-Jones interacting cylinder (with somewhat larger radius than our helix) results in lower order parameters close to the cylinder. This result is explained by the fact that the chains close to the cylinder seem to curve around the cylinder resulting in a low order parameter. The different theoretical articles predict different ranges for the perturbation among the lipids. Jähnig (1981b) predicts exponential decay with a decay length around 1.5 nm. This agrees reasonably with our results, while other articles that predict a range of just one or two layers do not.

Experimentally, lipid/protein interactions in the fluid phase have been studied by differential scanning calorimetry (van Zoelen et al. 1978) and spectroscopic techniques such as ESR (Jost et al. 1973; Stier and Sackmann 1973), NMR (Bloom and Smith 1985; Brûlet and McConnell 1976; Dahlquist et al. 1977; Oldfield et al. 1978; Rice et al. 1979; Pauls et al. 1985; Post et al. 1981) or Raman scattering (Taraschi and Mendelsohn 1980; Jähnig et al. 1982). In the experimental literature somewhat different and contradicting conclusions have been reached. Some authors claim that there are boundary lipids close to the protein surface, which are more ordered than the bulk lipids. Other authors get the opposite result while still others cannot see any boundary lipids at all. We shall not go into any detail about these controversies here but just point to a few facts that may be essential when this literature is inspected.

First, the different experimental techniques probe essentially three different things: a shift in the equilibrium order parameters of lipids close to a protein, a change in the dynamics of boundary lipids and finally a shift in the gel/liquid crystalline phase transition temperature. A simplified picture would equalize increased order, slower dynamics and lower phase transition temperature and conversely more disorder, faster dynamics and higher phase transition temperature. This is not necessarily true. We see from our simulation, on the contrary, that polyglycine has a much stronger ordering effect on the lipids than glycophorin while the latter is more effective in arresting the reorientational dynamics.

Secondly, it is important to observe that our simulation indicates that the exchange rate between boundary and bulk lipids is given by the lateral diffusion constant of pure lipid bilayers. If, instead of the too fast lateral diffusion constants obtained from the simulation experimental ones (see e.g. Lindblom and Wennerström 1977) are used, we get typical exchange times (i.e. times for moving a lipid over the nearest neighbour distance, 0.5 nm) that are of the order 10 ns or faster. As noted by Post et al. (1981), this would make it possible to probe the difference between bulk and boundary lipids by ESR but not by NMR due to the different time scales of the methods.

Thirdly, it is conceivable or even likely that different proteins and peptides affect the neighbouring

lipids in different ways. There are electrostatic interactions between the head groups of the lipids and side chains or backbone of the protein. Further, surfaces of realistic proteins are shaped in different ways, which in itself will have large effects upon the structure of neighbouring lipids. Finally, proteins may be their shape, size or hydrophobicity in different regions induce changes in the thickness of the bilayer which will influence the lipid chains (the mattress model of Mouritsen and Bloom (1984)). Factors such as these may result in completely different results what regards order parameters and dynamics of boundary lipids and exchange times between these and the bulk ones.

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