Homo-polymers with balanced hydrophobicity translocate through lipid bilayers and enhance local solvent permeability

Marco Werner,*ab Jens-Uwe Sommerab and Vladimir A. Baulincd

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Recent experimental studies indicate that polymeric structures with a well-adjusted balance of amphiphilic parts may translocate through self-assembled phospholipid bilayers and enhance the passive trans-membrane transport of smaller molecules. Using a coarse grained lattice Monte Carlo model with explicit solvent we investigate self-assembled lipid bilayers interacting with a linear polymer chain under variation of the hydrophobicity of the chain. Here, we focus on the relationship between the chain’s hydrophobicity and its translocation behavior through the membrane as well as induced membrane perturbations. We show, that there is an adsorption transition of the polymer at the bilayer interface, where effectively the solvent phase and the tail phase of the bilayer are equally repulsive for the polymer. Close to this adsorption threshold of the polymer both the translocation probability of the polymer as well as the permeability of the membrane with respect to solvent are enhanced significantly. The frequency of polymer translocation events can be understood quantitatively assuming a simple diffusion along a one-dimensional free energy profile, which is controlled by the effective lipophilicity of the chain and the tail-packing in the bilayer’s core.

1 Introduction

Passive transport of molecules through phospholipid bilayer membranes plays an essential role for the metabolism and signaling processes of living cells. While one objective of modern medicine is to make use of such APT-independent diffusion processes to specifically target active components into the cell interior, some potentially helpful underlying physical mechanisms are poorly understood. In particular, recent experiments have shown that random amphiphilic copolymers as well as polymeric surfactants may translocate non-endocytically through biomembranes of living mammalian cells and model bilayer membranes without membrane disruption.

On the other hand, amphiphilic polymer structures such as block copolymers with hydrophilic/hydrophobic blocks as well as polymers with random distribution of amphiphilic sites such as polyelectrolytes and polyacrylates may destabilize bilayer membranes and enhance passive transport of other molecules such as DNA strands, oligonucleotides or salt. Destabilization effects can be observed as leakage of vesicles, hemolysis of red blood cells and increased rates of lipid flip-flops. In particular, experiments on red blood cells indicate that amphiphilic pseudo-peptides with hydrophobic side groups increase their membrane permeability for trehalose (small sugars), when the density of side groups is carefully adjusted.

Computer simulation studies on passive transport through lipid membranes concentrated on the translocation of smaller molecules and various macromolecules: a first quasi-full atom molecular dynamics (MD) simulation regarding amphiphilic and hydrophobic polypeptides indicated that unexpectedly they do not enter into the hydrophobic bilayer core. Maddox and Longo discovered translocation and bridging states of peptides such as Magainin and M2 through lipid bilayers, which were represented as a one-dimensional force-field along the bilayer normal. Lee and Larson have also found bridging states of polyamidoamine dendrimers between bilayer surfaces and investigated the membrane activity of charged polymers as compared to dendrimers using MD simulations. Recently, the influence of neutral and partially charged nano-particles on the fluid–gel transition of DPPC bilayers as well as the adsorption and inclusion of hydrophobic and semi-hydrophobic nano-particles have been studied using coarse grained MD simulations.

Many of the simulation studies on macromolecules as described above concentrate on a detailed description of force fields for chemically specific permeants and membrane lipids. Facing the variety of interactions taken into account, it is often challenging to distinguish physical principles behind the obtained effects.

Suggested mechanisms of interaction between polymers and lipid membranes include adsorption on the surface of the...
membrane, insertion and anchoring of amphiphilic polymers into the hydrophobic core, clustering and pore formation. Most of these mechanisms imply the formation of static or transient well-ordered structures resulting from particular block-copolymer composition. However, a defined sequence composition of the polymer chain may not be required to induce perturbations to lipid bilayers structure and permeability to low molecular solutes. In this study we show how a homo-polymer can translocate through the membrane and enhance the permeability for solvent by inducing a transient rearrangement of lipids.

We investigate the interaction of single polymer chains with self-assembled lipid bilayers using an efficient lattice Monte Carlo method. Here, we focus on the role of the mean compatibility of the polymer with the bilayer core phase as compared to the solvent phase to mimic effects of tuned hydrophobicity/lipophilicity. In Section 2 we describe the explicit solvent method which we introduced to model self-assembled amphiphilic bilayers as well as freely diffusing polymers in a collapsed globule phase on a lattice. In Section 3, we investigate the adsorption transition of the polymer at the bilayer by varying the degree of hydrophobicity of the chain. We show that critical adsorption controls the translocation behavior of the chain through the membrane. In Section 4 we study the polymer-induced perturbations in the lipid organization of the bilayer and show that the membrane permeability is significantly increased close to the adsorption threshold of the polymer chain. Our conclusions are presented in Section 5.

2 Self-assembled bilayer membranes using the bond fluctuation model with explicit solvent

We use the bond fluctuation method (BFM) with explicit solvent to model self-assembled lipid bilayers on a coarse grained level. The driving force for the self-organization of lipid bilayers is the hydrophobic effect: an effective short-range repulsive interaction between polar and apolar molecules in the order of $k_B T$. In coarse grained molecular models with implicit solvent such as the "classic" BFM, one may map short-range repulsive interactions between segments of the molecule itself. However, in a simplified model head- and solvent monomers are represented as connected unit cubes on a simple cubic lattice. The distance between bonded monomers is constraint to a bond vector set of 108 bond vectors given by $\{2, 0, 0\}, \{2, 1, 0\}, \{2, 1, 1\}, \{3, 0, 0\}, \{2, 2, 1\}, \{3, 1, 0\}\}$ and all possible permutations in order and sign of their vector components. To model excluded volume effects, the eight corners of a monomer cube occupy eight neighboring lattice sites and each lattice site is allowed to be occupied by one monomer only. We use short-range thermal interactions between monomers of arbitrary species A and B associated with the interaction constants $\epsilon_{A,B}$ in units of $k_B T$. The corresponding discretized interaction potential for a monomer cube of species A at position $\mathbf{r}$ is given by

$$U_A(\mathbf{r}) = \sum_{\mathbf{r}'} \epsilon_{A,B}(\mathbf{r}) \delta(\mathbf{r} - \mathbf{r}')$$

where $\epsilon_{A,B}(\mathbf{r})$ is the number of occupations by monomers of species B at the 24 next nearest lattice sites of the monomer cube of species A at position $\mathbf{r}$. The athermal and thermal interactions of the monomers are taken into account during simulation in terms of elementary Metropolis steps. An elementary step consists of the random selection of one monomer of species A at position $\mathbf{r}$ in the simulation box and one of the six possible next nearest neighbor positions on the lattice, $\mathbf{r}'$, where the monomer is attempted to move. If at the new position $\mathbf{r}'$ the athermal bond and excluded volume constraints are fulfilled, we calculate the potential energy difference $\Delta U_A = U_A(\mathbf{r}') - U_A(\mathbf{r})$ and accept the move for $\Delta U_A \leq 0$ or with the probability $\exp(-\Delta U_A/k_B T)$ otherwise. The time unit Monte Carlo Step (MCS) is defined as the average number of attempted moves per monomer.

In our model, lipids consist of three head-group monomers (h) and two tails (t) of five monomers each as shown in Fig. 1(a). To mediate the hydrophobic interaction we use an explicit solvent (s) in the form of unconnected monomers, which are free of any bond-constraint. Apart from lipids and other molecules, the simulation box is filled by explicit solvent up to a mean lattice occupation of 0.5 corresponding to a dense state in terms of the BFM. The hydrophobic effect is modeled as a short-range repulsive interaction between hydrophobic and hydrophilic components:

$$\epsilon_0 = \epsilon_t = \epsilon_h; \epsilon_s = 0.$$ (2)

In our simplified model head- and solvent monomers are considered as identical in terms of hydrophobic interactions. Throughout this work we used a cubic simulation box of the size 64 lattice units and periodic boundary conditions in all directions. In the following we fix the repulsive energy constant

![Fig. 1](image-url) (a) and (b) Scheme of the simulation model used: (a) coarse grained representation of lipids, explicit solvent and polymer chains as used in our BFM simulations, (b) repulsive interactions between the four components as defined in (a) and their associated energy constants $\epsilon_0$ and $\epsilon_t$. In (c) we define the orientation vector $\mathbf{b}$ of a single lipid using the normalized difference vector between the head group and the mean position of the end monomers of the tails. The arrow indicates the direction of $\mathbf{b}$ only.
to $\epsilon_0 = 0.8k_BT$, where we have obtained stable self-assembled bilayers for various numbers of lipids, $N_{\text{lip}}$, in the box. A typical self-assembling process starting with a random configuration of molecules is shown in Fig. 2(a) for $N_{\text{lip}} = 300$. Fig. 2(b) shows the corresponding time series of internal energy per lipid,

$$ U_{\text{lip}} = \frac{1}{2N_{\text{lip}}} \sum_k U_{S_k}(\vec{r}_k) = \frac{\epsilon_0}{N_{\text{lip}}} (m_{t,h} + m_{s,B}), $$

(3)

where $U_{S_k}(\vec{r}_k)$ denotes the internal energy of the monomer $k$ (running over all monomers in the box) according to eqn (1) and (2) and its species $S_k$ and $m_{A,B}$ denotes the total number of contacts between monomers of species A and B (hydrophobic and hydrophilic). Fig. 2(b) indicates a direct equilibration into a stable bilayer state without trapping in intermediate meta-stable states.

Our model lipid bilayers are in a fluid state, since we did not introduce any explicit bending stiffness within the lipid tails. The density profiles (see Fig. 5(a)) contain all essential features of typical bilayer models using Lennard-Jones-type interactions.\(^\text{11}\) The aim of this study was to obtain a better understanding of possible permeability mechanisms using the most simple parameter space in a first step.

To find a tensionless state for our model membrane, we use several indicators as described in the following. First, Fig. 3(a) shows the time average, $\langle U_{\text{lip}} \rangle$, of the internal energy per lipid as defined in eqn (3). There is a local minimum of $\langle U_{\text{lip}} \rangle = 2.8k_BT$ per lipid for $N_{\text{lip}} = 320$ ($\rho_A \approx 0.078$ lipids per projected area unit) that indicates the energetically favored area per lipid. Generally, the conformational degrees of freedom of the lipids will also depend on the area per lipid and the minimum in free energy per lipid will be shifted to slightly different values of $\rho_A$ as compared to the minimum in internal energy. Second, we characterize the orientational order of lipids by calculating the order parameter of tensorial orientation defined as the largest eigenvalue, $Q$, of the tensor-order parameter,

$$ Q_{ab} = \left\langle \frac{1}{N_{\text{lip}}} \sum_{i=1}^{N_{\text{lip}}} (3b_{ab}b_{\beta} - \delta_{ab}) \right\rangle, $$

(4)

where $b_{ab}$ denotes the $a$-component of the normalized orientation vector $b$ of the $i^{th}$ lipid as given in Fig. 1(c) and $Q_{ab}$ have been calculated as the average over the relevant simulation time and all lipids in the box. Results for the orientational order parameter $q$ as a function of the number of lipids in the box are presented in Fig. 3(b). If the bilayer is stretched, i.e. there are too few lipids per area, we expect the lipids to show larger deviations from the director (approximately $z$-axis), packing is reduced and the fluctuations of tail orientation are increased. On the other hand, in the case of a higher number of lipids per area, there appear larger out-of-plane undulations where the embedded lipids lose their alignment with the average director. The maximum in the orientational order at $N_{\text{lip}} \approx 280$ ($\rho_A \approx 0.068$) indicates the state with the most stable lipid orientation. Third, we calculate the flip-flop rate of single lipids to characterize the stability of the bilayer composition on both sides: We averaged the orientation vector of individual lipids within intervals of $10^6$ MCS and counted events, where the $z$-component of the pre-averaged orientation vector jumped between two time intervals. As can be seen in Fig. 3(b),

![Fig. 2](image-url)  
(a) Simulation snapshots of a self-assembling model bilayer in the BFM from a random start configuration at various simulation times $t$ with interaction constant $\epsilon_0 = 0.8k_BT$ (see eqn (2)). The solvent is not shown. The starting configuration at $t = 0$ is the result of a relaxation run at $\epsilon_0 = 0$ for $10^6$ MCS. (b) Time series of the internal energy per lipid during the self-assembling process as shown in (a).

![Fig. 3](image-url)  
(a) Mean internal energy per lipid (see eqn (3)) in self-assembled lipid bilayers according to the lipid model in Fig. 1 and eqn (2). (b) Orientational order parameter, $q$, defined as the largest eigenvalue of the tensor order parameter $Q$, see eqn (4); flip-flop rate: the number of changes of sign of the $z$-component of individual lipid orientations (see text) according to Fig. 1(c) per lipid and $10^7$ MCS.
the flip-flop rate per lipid has a minimum close to \( N_{lip} \approx 310 \) \((\rho_A = 0.076)\). In the following we decided to fix the number of lipids for this study to \( N_{lip} = 300 \) \((\rho_A = 0.073)\). We found that our simulation results for \( N_{lip} = 300 \) as shown in the following sections are qualitatively equivalent for a wide range of lipid density \( \rho_A \) of about \( \pm 7\% \) and in this range a positive or negative tension on the membrane plays only a minor role in the found local permeability mechanism.

In order to count permeation events of solvent molecules or of polymer chains, we use the trajectories of the molecule’s center of mass with a time resolution of 100 MCS. In order to decide about a permeation event of a molecule of species A, the boundaries of the bilayer, \( z_A^{(t)} \), have to be defined. Since the chains’ extensions are much larger as compared to the solvent molecules also the effective boundary for their centers of mass must be chosen differently. For solvent-molecules \((s)\) and for polymer chains \((c)\) we have defined the boundaries as follows:

\[
\begin{align*}
    z_s^{(0)} &= \bar{z} \pm 2\sigma_z, \\
    z_c^{(0)} &= \bar{z} \pm 23. \\
\end{align*}
\]

(5)

Here, \( \bar{z} \) denotes the center of mass of all tail monomers in \( z \)-direction (center plane of the bilayer) and \( \sigma_z \) is the corresponding standard deviation. Typical values for \( \sigma_z \) are \( \sigma_z = 4.3 \) lattice units for a bilayer without polymer chain. The thresholds \( z_A^{(t)} \) for the polymer chain are chosen such that the largest chain, \( L_c = 128 \), can be considered as separated from the bilayer for \( H > 0.5 \), which is (as will be shown by our results in the next Section) the only relevant range for polymer translocations. The effective boundaries are updated every \( 10^4 \) MCS. In the case, that a molecule entered the bilayer at one boundary \( z_+ \) or \( z_- \) and left the bilayer at the opposite boundary, we counted one translocation event. Let us define a permeability, \( P_A \), of the bilayer with respect to molecules of species \( A \) as

\[
P_A = \frac{n_A}{\Delta t \cdot A},
\]

(6)

where \( n_A \) is the number of translocation events of molecules of species \( A \) through the bilayer during the simulation time \( \Delta t \) and \( A \) is the projected area of the considered membrane patch.

3 Polymer adsorption and -translocation

To investigate the interaction of our model lipid bilayer with a linear polymer chain, we introduce homopolymers of monomer species \( (c) \) and various chain lengths, \( L_c \). Additionally to the interaction model in eqn (2) a short-range repulsive interaction with the interaction constant, \( \epsilon_t \), is defined to model an effective hydrophobicity of the statistical chain segments. The overall interaction model now reads

\[
\begin{align*}
    \epsilon_0 &= \epsilon_{h,k} = \epsilon_{l,t} \\
    \epsilon_t &= \epsilon_{b,k} = \epsilon_{l,k} = \epsilon_0 - \epsilon_{l,c} \\
    \epsilon_{b,h} &= 0.
\end{align*}
\]

(7)

and is sketched schematically in Fig. 1(b). Let us define a relative hydrophobicity, \( H \), of the polymer given by

\[
H = \epsilon_t / \epsilon_0.
\]

(8)

Here, \( H = 0 \) corresponds to hydrophilic monomers and \( H = 1 \) represents hydrophobic monomers. Monte Carlo simulations have been performed with chain lengths \( L_c \in \{16, 32, 64, 128\} \) and various relative hydrophobicities \( 0 \leq H \leq 1 \). The start configurations have been arranged such that after equilibration a stable planar lipid bilayer spans between periodic boundaries in \( x \)- and \( y \)-direction, as has been discussed in the previous section. The systems have been relaxed for \( 10^7 \) MCS before we started the sampling. The total simulation time for each pair of parameters \((L_c, H)\) was at least \( 3 \times 10^8 \) MCS and up to \( 9 \times 10^8 \) MCS for values of \( 0 < H < 1 \) and chain lengths \( L_c > 16 \). Typical simulation snapshots for characteristic values of \( H \) and chain length \( L_c = 64 \) are shown in Fig. 4. The snapshots can be compared to Fig. 5 showing density profiles of all components in the system for characteristic values of \( H \) and chain length \( L_c = 64 \) as a function of the distance, \( z \), from the bilayer center. Hydrophilic polymer chains, \( H = 0 \), as shown in Fig. 4(a) and 5(b) form random coils in the solvent phase and are rejected from the bilayer, which is acting as a potential barrier. On the other hand, hydrophobic chains form a dense globule in the solvent phase and get absorbed (see Fig. 4(c) and 5(f)) by the hydrophobic core of the bilayer as soon as the polymer gets in contact with the tail phase. For \( H = 1 \) the chain monomers are indistinguishable from tail monomers with respect to the interaction model, eqn (7). Here, the bilayer’s core acts as a potential trap, where the polymer is confined in a quasi-two-dimensional solvent of tails. This is reflected by the splitting of the lateral and perpendicular components of the root mean squared radii of gyration of the polymer for \( H = 1 \) as shown in Fig. 6.

In between the limiting cases of \( H = 0 \) and \( H = 1 \) there has to be a transition between the free polymer in the solvent phase and the trapped polymer in the bilayer’s core. In the simulation snapshots for a partially hydrophobic polymer chain in Fig. 4(b) \((H = 0.68)\) one can already observe some effects associated with this transition: the polymer approaches from below the membrane and first adsorbs at the lower surface of bilayer. Eventually, it translocates to the opposite side of the bilayer and
detaches from the membrane again. As long as the polymer is in contact with the self-assembled membrane, the local ordering of the bilayer is perturbed and individual lipids are displaced by the fluctuating polymer. During the whole process, the polymer forms a dense globule, because both environments act as poor solvents (compare Fig. 6). If translocation events as indicated in Fig. 4(b) are typical on the time scale for polymer relaxations for $H = 0.68$, the effective free energy barrier for the polymer in the core of the bilayer will be in the order of $k_BT$. Indeed, in Fig. 5(d) the transparency of the membrane with respect to the polymer chain becomes visible by significant contributions of the polymer density for all distances $z$.

To characterize the transition of the polymer between $H = 0$ and $H = 1$, we consider the fluctuations, of the total contact energy between chain- and tail monomers, $U_{tc}$ given by

$$\langle \Delta U_{tc} \rangle^2 = \langle U_{tc}^2 \rangle - \langle U_{tc} \rangle^2.$$  

(9)

Note that the mean squared fluctuations of the energy correspond to the heat capacity related with adsorption. As can be seen in Fig. 7(a), there is a peak in the energy fluctuations in a range of $0.65 \leq H \leq 0.7$, which indicates a critical adsorption scenario for $L_c \to \infty$. To estimate an upper bound for the statistical error of $\langle \Delta U_{tc} \rangle^2$ as shown in Fig. 7(a) we divided the total simulation time for the longest chain, $L_c = 128$, at the point of peak fluctuations, $H = 0.68$, into intervals of the longest relevant time scale, $\sim 5 \times 10^7$ MCS, where we observe translocation events of the chain through the membrane (the translocation rate is $2.0 \pm 0.5$ per $10^8$ MCS with $\approx 70\%$ confidence, as presented further below). This gives an estimation for the energy fluctuations close to the critical point, $\langle \Delta U_{tc} \rangle^2 = (66.1 \pm 5.1)(k_BT)^2$ with $95\%$ confidence, if we fix the translocation rate to $2.0$ per $10^8$ MCS. Note that the sampling of the full simulation time (without interval pre-averaging) leads to a slightly different result, $\langle \Delta U_{tc} \rangle^2 = 69.1(k_BT)^2$, for $L_c = 128$, $H = 0.68$ as shown in Fig. 7(a) and is in agreement with the given error. Taking into account the statistical error for $\langle \Delta U_{tc} \rangle^2$ of $\approx8\%$ close to the critical point, we expect that our simulation results determine the peak position of $\langle \Delta U_{tc} \rangle^2$ for $L_c = 128$ as shown in Fig. 7(a) within an interval of $H = 0.68 \pm 0.02$.

Close to the peak position of contact energy fluctuations we obtain also a transition point for the empiric probability of the chain, to be located inside the tail phase as shown in Fig. 8. At the same time, there is a localization of chain monomers at the surfaces of the bilayer as shown in Fig. 5(d). As the bilayer itself is a penetrable interface for the polymer (see for instance the translocation event as shown in Fig. 4(b) and the discussion further below), we might compare the adsorption transition with those of an ideal polymer chain at a penetrable potential well, where one would expect an effective adsorption threshold, $H_{A,L_c}$ for finite chain lengths according to

$$H_{A,L_c} - H_{A,crit}/H_{A,crit} \sim L_c^{-\phi}.$$  

(10)

Here, $\phi = 1 - \nu$ is a cross-over exponent for potential wells, where $\nu$ denotes the Flory exponent relating the radius of gyration, $R_g \propto L_c^\nu$, of a polymer chain to its linear size, $L_c$. From the
adsorption transition. Using phases as well as the tail phase act as a poor solvent close to the solvent-permeability, the maxima levels of the simulation result. (c) Simulation results for the lipid bilayer and monomers of a linear chain of length corresponding to nearest neighbor-contacts between tail-monomers in a H component of the center of mass of the chain, z_h, has to be closer to the lipid bilayer center, z, than twice the standard-deviation, σ, of the tail distribution. The transition point according to Fig. 7(a), \( H_A = 0.68 \), is marked by the dashed line.

Fig. 7 (a) Fluctuation of the internal energy, \( \langle \Delta U_{\text{int}} \rangle^2 = \langle U_{\text{int}} \rangle^2 - \langle U_{\text{int}} \rangle^2 \), corresponding to nearest neighbor-contacts between tail-monomers in a lipid bilayer and monomers of a linear chain of length \( L_c \) as a function of the relative hydrophobicity, \( H \). The extrapolated adsorption transition, \( H_{\text{crit}} = 0.667 \pm 0.005 \), is indicated by the vertical dotted line. The vertical dashed line corresponds to the adsorption transition for \( L_c = 64 \) at \( H_A = 0.68 \). (b) Simulation results (closed symbols) for the frequency of translocations, \( T_c \), of a polymer chain of length \( L_c \) through a lipid bilayer as a function of \( H \). Open symbols show the inverse mean first escape time, \( 1/t_{\text{fe}} \), according to the free energy profile for the chain center of mass, see eqn (11). The \( 1/t_{\text{fe}} \)-curves have been stretched along the \( T_c \)-axis to meet the maxima levels of the simulation result. (c) Simulation results for the solvent-permeability, \( P_s(\text{patch}) \) of a circular patch of the membrane (projected radius \( R = 20 \), see text) around the projected center of mass of the polymer chain as a function of \( H \). The results are normalized with respect to the permeability for a membrane not interacting with polymer chains, \( P_{\text{0}} \).

simulation results for \( R_s \) as shown in Fig. 6 we obtain an empirical exponent \( \nu_{\text{ads}} \approx 0.29 \) for values of \( H \) close to the adsorption transition. This is close to the \( \nu \)-exponent of a compact globule, \( \nu = 1/3 \), and indicates, that the solvent/head phases as well as the tail phase act as a poor solvent close to the adsorption transition. Using \( \nu = 1/3 \) we graphically extrapolated the critical adsorption threshold of \( H_{\text{crit}} = 0.667 \pm 0.005 \) according to eqn (10). Note that the propagation of polymer-induced local density changes in the membrane as well as polymer-induced changes in the spectrum of capillary waves are restricted by our box size. Hence, the exact transition point might slightly deviate for an infinite membrane. In the following we will mainly concentrate on the results for chain length \( L_c = 64 \) as the longest chain with high statistical stability also for more sensitive observables as discussed later. In view of the uncertainty of the extrapolation we define the adsorption threshold as \( H_A = H_{\text{crit}} = 0.68 \), labeling the peak fluctuations in Fig. 7(a) for \( L_c = 64 \).

We note that for an ideal, penetrable interface we would expect a threshold of \( H_A = 0.5 \). The self-organized bilayer structure, however, leads to ordering and packing of lipid tails in the bilayer core, and the total density in the membrane center is increased (see Fig. 5(a)). Thus, at \( H = 0.5 \) there is an additional free energy penalty \( \mu_{\text{ins}} \) for a chain monomer to be inserted into the bilayer’s core (compare Fig. 5(c)) and a higher degree of hydrophobicity is necessary to compensate for this barrier as sketched in Fig. 9(a). As a consequence the adsorption transition is shifted towards higher values of \( H \).

In Fig. 9(b) we display the free energy \( F(|z|) \) of a polymer chain of chain length \( L_c = 64 \) as a function of the distance, \(|z|\), of its center of mass coordinate with respect to the center of the membrane. The free energy profile as shown in Fig. 9 has been obtained using the probability distribution, \( p(z) \approx \exp(-F(z) / k_BT) \), of the center-of-mass position of the chain and represents its potential of mean force.86 Essential features as discussed above such as the residual free insertion barrier at \( H = 0.5 \), the localization effects at the bilayer surface as well as the potential trap for larger values of \( H \), can be recognized in the free energy profiles of Fig. 9(b). Note that at the point of adsorption, \( H_{\text{A}} \), (compensation between insertion potential and excess hydrophobicity of the chain, \( H_A - 1/2 \), inside the bilayer) the surface
of the bilayer becomes attractive. This is indicated in the simplified potential model of the membrane, Fig. 9(a), and is also displayed in the free energy profile, Fig. 9(b). It is interesting to compare the free energy profiles as shown Fig. 9(b) with those obtained using Molecular Dynamics simulations for fullerenes as a function of their density of polar/apolar surface groups, which might be controlled by a similar interplay between the attractive bilayer surface and the insertion barrier.  

Using the free energy profile as shown in Fig. 9(b) we can estimate, the inverse mean first escape time $\tau_{fe}$ of the polymer from an interval $[\xi^0, \xi^t]$, where we define $\xi^0$ as the reflecting boundary and $\xi^t$ as the absorbing boundary and the polymer starts to diffuse from $\xi^0$:

$$\tau_{fe} \propto \int_{\xi^0}^{\xi^t} dz \left( e^{F(z)/k_B T} \right) dz = \int_{\xi^0}^{\xi^t} dz e^{-F(z)/k_B T}.$$

(11)

Here, we implicitly assume that the chain diffusion constant is independent of $z$ and the diffusion time through the rest of the box is negligible as compared to the translocation time. In Fig. 7(b) we compare our simulation results for the translocation rate of the polymer chain with the inverse mean first escape time calculated according to eqn (11). Excellent agreement between the data indicates that translocation events of the chain through the membrane can be well understood as passage events through a free energy barrier (trap). The data in Fig. 7(b) show pronounced peaks of maximum permeability with respect to the polymer close to the adsorption threshold. The adsorption threshold corresponds to the nearly flat free energy barrier in Fig. 9.

### 4 Bilayer perturbations and solvent permeability

In this section we analyze the local solvent permeability of the membrane and relate the results to local static and dynamic perturbations of the bilayer configuration. For each translocating solvent molecule, we recorded the projected distance between the center of mass of the chain and the solvent position, $d = (d_x, d_y)$, in the moment of entering the bilayer at one of the two boundaries $x^0$, see eqn (5). Fig. 7(c) shows the solvent permeability, $P_{S_{patch}}/P_{S_{00}}$, for a membrane patch with $|d| < 20$ compared to the average permeability, $P_{S_{00}}$, without polymer. The condition $|d| < 20$ defines the membrane patch as a “shadow” of the polymer chain on the bilayer projected area. As can be seen in Fig. 7(c), for all chain lengths, $L_c$, there is a significant peak in solvent permeability close to the adsorption transition of the polymer. Furthermore, the peak positions in Fig. 7(c) show a direct correspondence to the chain-length dependent adsorption thresholds, see Fig. 7(a). For values of $H$ beyond the adsorption transition, $H \rightarrow 1$, there is a significant reduction of local permeability close to the polymer chain, which might be associated with the steric hindrance of the polymer chain and also a slight local thickening of the membrane (see Fig. 5(f) as compared to (a)), where the polymer is confined in the hydrophobic core.

A more detailed insight into the influence of the polymer on local solvent permeability is given in Fig. 10, where the relative local change in $P_s$ as compared to the unperturbed membrane as a function of $d$ is shown for chain length $L_c = 64$. Fig. 10 shows no significant change in local permeability for $H \leq 0.5$ (see also Fig. 7(c)), whereas close to the adsorption transition ($H_A = 0.68$) there is a pronounced peak in the vicinity of the polymer chain. Note that the solvent permeability histograms as shown in Fig. 10 for $H > 0.5$ have a local minimum at the projected chain center of mass, $|d| = 0$, reflecting a partial screening of translocation events by the polymer itself. Highest solvent permeation
a polymer-induced perturbation of the membrane integrity leads to an increased solvent permeability. However, the correlation of the peak reduction in \( q \) and the permeability increase (Fig. 10) is not as direct as for the increase of flip-flop rates (Fig. 11). For hydrophobic polymers (\( H = 1 \)) the orientational order almost recovers values of an unperturbed bilayer, although no stabilization effects can be observed in Fig. 12.

5 Conclusions

We introduced the bond fluctuation model with explicit solvent, which can be used to simulate polymer structures under poor solvent conditions without freezing effects on a lattice. Using this model, self-assembled bilayer membranes on a coarse grained level have been simulated and their interaction with flexible homopolymers as a function of the relative degree of hydrophobicity of the polymer, \( H \), has been analyzed. For the hydrophilic polymer, \( H = 0 \), the membrane acts as a potential barrier for the polymer, which forms a random coil in the solvent phase. On the other hand, the fully hydrophobic polymer, \( H = 1 \), gets trapped in the bilayer’s core. Our simulation results indicate an adsorption transition of the polymer at the surface of the model bilayer with a transition point close to \( H_A \approx 0.68 \). The transition takes place, where an effective attractive interaction between polymer segments and tail environment compensates for the insertion barrier of the polymer chain in the bilayer’s core due to the self-organized packing of tails. Close to the transition point, the membrane becomes energetically transparent for the polymer and we observe an increased rate of polymer translocation in agreement with mean first passage time calculations. This represents a new mechanism for chain translocations through lipid membranes based on physical principles only. Close to the adsorption transition of the polymer, the permeability of the membrane for solvent molecules increases significantly as a consequence of the induced static and dynamic perturbations of the self-organized lipid ordering.

At the transition point, the effective repulsions of the chain from the solvent phase as well as from the tail phase are balanced. This implies that a proper hydrophobic matching of the polymer chain close to its adsorption transition enhances the passive transport for the molecule itself as well for small solutes through a phospholipid bilayer. We expect, that one key feature for the effective use of cell penetrating peptides and -polymers will be a precise hydrophobic matching of the permeant between the bilayer core and solvent.

Since our simulations are focused on the liquid state of the bilayer, experimentally, model lipid bilayers in liquid state such as giant vesicles of DPhPC at room temperature would be most suitable for performing experimental tests. An ideal experimental system to test the suggested mechanism is by using polymers with tunable hydrophobicity of the monomers, such as used by Lynch et al.10 where poly (L-lysine iso-phthalamide) was grafted with hydrophobic groups. On the other hand, copolymers made of hydrophilic and hydrophobic units seem to be a practical alternative. We also note here the potential model as discussed in this work will lead to similar predictions for the optimal hydrophobic balance for translocation. If the heterogeneity of monomer composition is restricted to small scales such as the Kuhn segment (for instance using alternating copolymers), our results can be directly applied. If the chemical heterogeneity persists on

**Fig. 11** Rate of sign-changes of the averaged z-component of the lipid orientation vector (see Fig. 1(c)) over time intervals of \( 10^5 \) MCS (flip-flops). The lipid flip-flop rate is given for various intervals of the projected lipid-chain-distance, \( d \), and as a function of the relative chain hydrophobicity, \( H \).

**Fig. 12** Orientational order parameter according to eqn (4) for various intervals of \( d \) as a function of mean chain-hydrophobicity (see eqn (8)).

is achieved in a ring around the chain’s center of mass close to the adsorption transition.

The enhanced solvent permeability has to be related with static and dynamic perturbations of the bilayer due to chain adsorption. In Fig. 11 and 12 we display the flip-flop rate and orientational order of lipids for chain length \( L = 64 \) as functions of the polymer hydrophobicity, \( H \), and of the projected distance, \( \tilde{d} \), from the center of mass of the polymer chain to characterize polymer-induced perturbations of the bilayer locally. The local flip-flop rates of lipids are displayed in Fig. 11. The flip-flop rates show a direct correspondence to the permeability increase close to the adsorption transition, \( H_A \approx 0.68 \). Also these rates are reduced for hydrophobic chains indicating that here the chain stabilizes the bilayer. In Fig. 12 we show the orientational order parameter, \( q \), as a function of the projected distance \( |\tilde{d}| \) to the center of mass of the chain, where the tensor-order parameter, \( Q_{\alpha\beta} \), has been averaged with respect to separate bins in \( |\tilde{d}| \) according to eqn (4). In an interval of \( |\tilde{d}| \) with the largest enhancement of solvent permeability, \( 2 \leq |\tilde{d}| \leq 10 \) (see Fig. 10), we obtain a corresponding minimum in the orientational order close to the adsorption transition, \( H_A \approx 0.68 \), indicating that here a polymer-induced perturbation of the membrane integrity leads...
larger scales such as for random copolymers, polarization of monomer sequences around the interfaces will cause an additional localization effect at the membrane interfaces as we have shown in the recent work on idealized interfaces.40 This interface localization effect can in turn reduce the translocation of the copolymer chain, but also sustain the induced permeability. Therefore, copolymers with balanced hydrophobicity can mimic “pore-forming” proteins by sticking on the membrane for a longer time. Further studies are necessary to understand the interplay between the effect of hydrophobic balance and a copolymer-induced interface localization in more detail.

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