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Biochimica et Biophysica Acta 1768 (2007) 2393–2399

Biochimica et Biophysica Acta BBA

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Lipid tail chain asymmetry and the strength of membrane-induced interactions between membrane proteins

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Received 20 February 2007; received in revised form 9 April 2007; accepted 1 May 2007
Available online 22 May 2007

Abstract

Many lipids are composed of asymmetric tail chains that differ by their molecular weight (MW) and/or degree of saturation. Previous studies found that membrane moduli vary with the degree of lipid tail asymmetry. However, to date little is known regarding the effect (if any) of tail asymmetry on the membrane-induced interactions between embedded proteins. In this paper we use a self-consistent field model to examine the effect of lipid tail asymmetry on membrane proteins. We first examine the case where the overall tail length (sum of both chains) is held constant, which implies that the membrane thickness remains constant as well, independent of tail asymmetry. We find that, in these systems, the membrane area stretch and bending moduli decrease with increasing chain asymmetry, thereby reducing the magnitude of the membrane-induced barrier to protein aggregation. Since in symmetric lipid bilayers the energy barrier is typically of order ~1–2 times the thermal energy kT, the asymmetry-induced reduction in barrier height may increase the probability of protein aggregation significantly. In systems where one tail chain is held constant, increasing asymmetry involves changes in the bilayer thickness which are found to dominate any effect arising from the asymmetry.

Keywords: Transmembrane protein; Bending modulus; Area modulus

1. Introduction

A large number of membrane lipids are asymmetric, containing tail chains that differ by their degree of saturation, molecular weight (MW), or both [1]. Recent studies have shown that the properties of monolayers and bilayers [2–7] composed of asymmetric lipids differ from those of equivalent, symmetric ones: For example, Ali et al. [3] found that the area stretch modulus of an asymmetric PC was lower than that of the equivalent, symmetric lipid, a trend captured in the particle dynamic simulations of Illya et al. [4]. Rawicz et al. [7] find that the bending modulus of an asymmetric PC lipid with two unsaturated bonds on one chain is nearly half that of the equivalent, symmetric lipid (i.e., with one unsaturated bond on each chain).

The inclusion of membrane proteins disturbs the local structure of bilayers, giving rise to a perturbation profile whose magnitude depends on the induced deformation and the bilayer moduli [8–22]. The membrane perturbation profile was predicted to decay as an oscillatory exponential [9–11], with a periodicity that depends on the ratio between the membrane area and bending moduli. The predictions of this model for the membrane perturbation profile have been confirmed in simulations [see, for example, [17–19]].

The perturbation of bilayer structure by embedded membrane proteins gives rise to an energetic penalty that plays a role is several protein properties: First, the membrane deformation penalty may reduce the equilibrium concentration of proteins in the bilayer [10]. The pressure exerted by the deformed membrane on the protein may also change protein configuration, and thus functions [12,14]. Last but not least, the sensitivity of the membrane deformation penalty to the protein spacing causes a membrane-induced force between proteins that can play a role in their spatial distribution [8].

The membrane perturbation profile due to embedded proteins, and the coupled effect of the membrane on protein structure and protein–protein interactions, depend on the membrane's area and bending moduli [8–21]. These parameters have been shown to vary with lipid tail asymmetry [2–

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doi:10.1016/j.bbamem.2007.05.003

7]. However, to date little is known regarding the effect of lipid tail asymmetry on the membrane-induced forces acting on embedded proteins.

In this paper we derive a model for membrane perturbation by embedded proteins, and the resulting membrane-induced forces between proteins, as a function of the lipid tail asymmetry. We find that for a given head group and fixed overall tail length (sum of both chains), the bending and area stretch moduli decrease with increasing chain asymmetry: bilayer composed of symmetric-tailed lipids are stiffer to both area perturbations and bending perturbations when compared to those of asymmetric amphiphiles, even though the bilayer thickness is the same.

The reduction in membrane stiffness with increasing tail asymmetry translates to a reduction in both the magnitude and range of membrane deformation by embedded proteins. For a reasonably asymmetric lipid (where one chain is about ~2/3 that of the other, e.g. a C14 and a C18) the reduction in the height of the energy barrier when compared to the equivalent symmetric lipid (diC 16) may be of order 20–30%. Since, as will shown below, the height of the energy barrier in the symmetrical case is of order 1–2 the thermal energy kT, the decrease due to asymmetry may enhance the probability of protein aggregation. The protein–protein separation at which the energy barrier is located is less sensitive to the tail asymmetry, found to be of order 2 nm.

What is the biological significance of membrane-induced interactions between proteins, and, specifically, of lipid tail asymmetry? As mentioned earlier, many biological lipids are composed of asymmetric tail chains, where the chains differ by their number of carbons, degree of saturation, or both [1–7]. Thus, it is of interest to determine whether the degree of asymmetry of the tails affects the organization of membrane proteins. It may be argued that due to their short range (1–2 membrane thickness) and relative weakness (1–2 kT) [9–11,17–19], membrane-induced interactions between proteins are negligible in biological membranes. However, it must be recalled that the density of proteins in cell membranes is very high: Jacobson et al. [22] recently estimated an average ratio of 50 lipids per protein, which translates to a separation of order 6 nm (for area per lipid ~0.7 nm^2 [22]). The characteristic scale of membrane nanodomains and clusters is up to 10 nm [22]. Thus, the short range of the membrane-induced forces between proteins is of the same order of magnitude as the relevant biological length scales. The membrane-induced interactions are stronger than either electrostatic forces over the same distances in physiological conditions, or thermal energy, and may therefore affect the probability of aggregation.

2. Model

We first briefly review the derivation of the protein-induced membrane perturbation energy [9–11]: an unperturbed bilayer is locally flat and is composed of two identical monolayers characterized by a (dimensionless) thickness l_m which is coupled to a surface density of $\sum_0$ (dimensionless area per molecule) through an equation of state. Here we take this equation of state to be lipid tail incompressibility, so that $l_m\sum_0$ is equal to the volume of the lipid tail (namely, both chains). Incorporation of an embedded protein leads to a local deformation [9–11] which may be expressed by $\Delta(z)=l(z)/l_m-1$, where $l(z)$ is the thickness of the bilayer at distance z from the protein boundary (where z is within the plane of the membrane). The membrane perturbation gives rise to a penalty associated with the change in the membrane area and a penalty associated with local bending [9–11]:

$$F_M = \int_0^D l_m\left(B\Delta^2 + Kl_m^2\left[\frac{d^2\Delta}{dz^2}\right]^2\right)dz \tag{1}$$

where B is the area stretch modulus and K the bending modulus (Note that K/B has units of length squared). D is the distance, along the z axis (in the plane of the membrane), between two adjacent proteins. All energies in Eq. (1) are given in units of kT, where k is the Boltzmann coefficient and T the temperature.

The equilibrium perturbation profile is calculated by minimization of F_M with respect to the perturbation profile $\Delta(z)$ [9–11], subject to the protein-imposed boundary condition at $z=0$ and the protein spacing D. For an isolated membrane protein where $D\to\infty$ and a thickness mismatch $\Delta(0)=\Delta_0$ [9–11]

$$\Delta(z) = \frac{\Delta_0}{2}\left[e^{i^{3/2}\left(\frac{B}{Kl_m^2}\right)^{1/4}z} + e^{-i^{1/2}\left(\frac{B}{Kl_m^2}\right)^{1/4}z}\right] \tag{2}$$

Somewhat unexpectedly, the bilayer thickness profile does not decay as a simple exponential with z, but is an exponentially decaying *oscillating* function, with a characteristic length scale of $(Kl_m^2/B)^{1/4}$. This oscillating profile (modified to account for a two dimensional array [11]) has been observed in simulations [17,19,20]. Substituting the deformation profile into Eq. (1) yields the protein-induced membrane perturbation energy, as a function of the protein spacing D:

$$F_M = \Delta_0^2 B^{3/4}K^{1/4}l_m^{1/2} \times \frac{e^{\sqrt{2}(2+i)\left(\frac{B}{Kl_m^2}\right)^{1/4}D} - ie^{\sqrt{2}(1+2i)\left(\frac{B}{Kl_m^2}\right)^{1/4}D} + ie^{\sqrt{2}\left(\frac{B}{Kl_m^2}\right)^{1/4}D} - e^{i\sqrt{2}\left(\frac{B}{Kl_m^2}\right)^{1/4}D}}{\sqrt{2}\left(1+e^{\sqrt{2}(1+i)\left(\frac{B}{Kl_m^2}\right)^{1/4}D}\right)\left(e^{\sqrt{2}\left(\frac{B}{Kl_m^2}\right)^{1/4}D} + e^{i\sqrt{2}\left(\frac{B}{Kl_m^2}\right)^{1/4}D}\right)} \tag{3}$$

To calculate the effect of lipid tail asymmetry on the membrane-induced interactions between transmembrane proteins requires correlating the tail asymmetry to three parameters; The membrane thickness l_m (which defines the value of the thickness perturbation at the protein boundary, Δ_0), the membrane area stretch modulus B and the bending modulus K.

Examining the effect of lipid tail asymmetry on membrane parameters may be done in two ways: In the first, the overall MW of the lipid tail (namely, sum of both chains) is held constant. Thus, lengthening one chain is linked to a shortening of the other. The second scenario is where one chain is held at a

fixed length, while the second chain is varied. Milner and Witten [23] derived the moduli of mixed layers of end-attached chains as a function of the chain MW and degree of asymmetry: Adaptation of their [23] results to the first scenario yields for the area (B) and bending (K) moduli

$$B = \frac{\pi^2 N_t[1+6y]}{24\Sigma_0^2} = \frac{\pi^2 l_m[1+6y]}{24\Sigma_0} \tag{4.a}$$

$$K = \frac{\pi^2 N_t^3}{128\Sigma_0^4\{1-y\}^5}\left(4+16y-44y^2+24y^3+9\ln[3]y^3 \times (1-2y)\{4+\ln[3]\}\right)$$

$$= \frac{\pi^2 l_m^3}{128\Sigma_0\{1-y\}^5}\left(4+16y-44y^2+24y^3+9\ln[3]y^3 \times (1-2y)\{4+\ln[3]\}\right) \tag{4.b}$$

A symmetric lipid with equal chains is defined, in this case, by $y=1/2$. In the second scenario, where one tail chain is held constant, and the other varied:

$$B = \frac{\pi^2 N_1[8+\mathrm{d}N]}{24\Sigma_0^2} \tag{5.a}$$

$$K = \frac{\pi^2 N_1^3}{2048\Sigma_0^4\{1+\mathrm{d}N\}^2}\left(4\{8+\mathrm{d}N\}\{2+3dN+\mathrm{d}N^2\}^2 +9\ln[3]\mathrm{d}N\{8+4\mathrm{d}N+\ln[3](2\mathrm{d}N+1)\}\right) \tag{5.b}$$

where N_1 is the length of one chain (namely, yN_t), and dN is the difference in MW between the two tail chains. For symmetric lipids where the two tails are identical ($y=1/2$ or d$N=0$) the moduli become

$$B = \frac{\pi^2 N_t}{6\Sigma_0^2} = \frac{\pi^2 l_m}{6\Sigma_0} \tag{6.a}$$

$$K = \frac{\pi^2 N_t^3}{\Sigma_0^4} = \frac{\pi^2 l_m^3}{\Sigma_0} \tag{6.b}$$

3. Results

In Fig. 1 we plot the membrane perturbation energy F_M and the membrane-mediated force between proteins, $f=-\partial F_m/\partial D$ as a function of the protein spacing. The membrane perturbation energy is minimal when the two proteins are in contact, since this minimizes the area of membrane subject to deformation. For isolated non-interacting proteins where $D\to\infty$, the protein-induced membrane perturbation energy is

$$F_M^{\infty} = \sqrt{\frac{l_m}{2}\Delta_0^2 B^{3/4}K^{1/4}} \tag{7}$$

F_M^{∞} defines the energetic penalty associated with the inclusion of one isolated protein in the membrane, namely, the membrane component of the protein adsorption energy. The membrane-mediated interaction between proteins is attractive until D exceeds a critical value

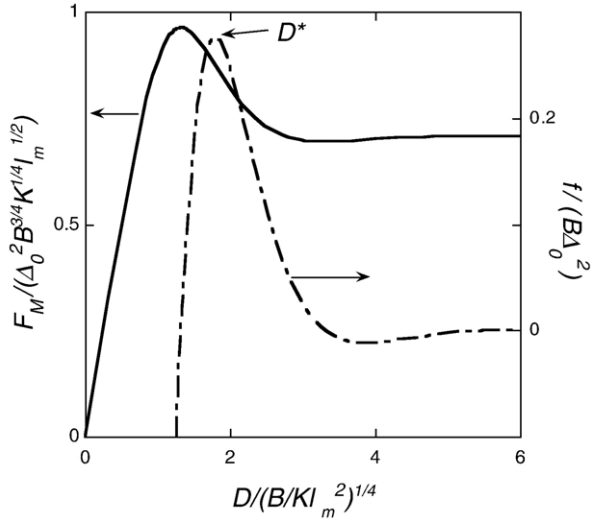

Fig. 1. Membrane perturbation energy due to embedded proteins, as a function of protein spacing D. The perturbation free energy F_M (solid line) is calculated by Eq. (3), and the membrane-induced force f (dashed line) is equal to $-\partial F_M/\partial D$. The protein–protein spacing D is normalized by the characteristic membrane perturbation length, $(B/Kl_m^2)^{1/4}$. Δ_0 defines the normalized membrane thickness perturbation at the protein boundary, B is the membrane area stretch modulus, K the bending modulus, and l_m the thickness. We see that at large distances the proteins do not significantly interact: F_M and f are close to zero. As the separation between proteins decreases, the membrane-induced force becomes weakly attractive, turning to a sharply repulsive force when D decreases below a critical value. At short distances the membrane-induced interaction between proteins becomes purely attractive, favoring aggregation.

$$D^* = 1.8\sqrt{l_m}\left(\frac{K}{B}\right)^{1/4} \tag{8}$$

Above D^* the interactions between neighboring proteins are repulsive, until reaching a shallow, secondary minimum. The free energy continues to oscillate as a function of D, but the magnitude of these oscillations is small. The height of the energy barrier, which we define as the difference in free energy between the secondary minimum and the barrier maximum, is given by

$$\mathrm{d}F_M = \sqrt{\frac{2l_m}{25}\Delta_0^2 B^{3/4}K^{1/4}} \tag{9}$$

The results displayed in Fig. 1 are general and expected to apply to any membrane/protein system. Indeed, the simulations of Sintes and Baumgarten [22] find such a profile (although with more significant oscillations). However, their use requires a model that correlates lipid properties to bilayer moduli. Here we propose to use the Milner and Witten [23] moduli, assuming that

(1) the surface area, per lipid, is insensitive to lipid chain length and asymmetry. This is in agreement with several studies: For example, Niemela et al. [6] find that the

surface area is constant for lipids where one chain is fixed and the other contained a varying number of carbons. Similarly, Illya et al. [4] find that the area per chain in symmetric lipids is quite insensitive, in the range studied, to either head group or tail size [24].

(2) the bilayer thickness, l_m, is equal to the tail volume divided by the area per molecule, $\sum_0$. Combined with assumption (1), this means that the bilayer thickness should increase linearly with the tail MW, as indeed observed by Illya et al. [4] and Niemela et al. [6]. For lipids with the same overall tail MW (sum of both tails), the bilayer thickness is taken to be insensitive to the degree of asymmetry [24]. This is in agreement with the results of Illya et al. [4].

These assumptions, applied to the Milner and Witten [23] model, suggest that the area stretch modulus of a bilayer composed of a symmetrical lipid (Eqs. (6.a) and (6.b)) will increase linearly with the bilayer thickness l_m and the bending modulus with l_m^3 (since $\sum_0$ is fixed). In Fig. 2 we plot the parameters of phosphatidylcholine (PC) bilayers composed of symmetrical lipids measured by Rawicz et al. [7]. We see that the ratio of the moduli, K/B, scales roughly as l_m^2, as expected. Also, K and B increase approximately as l_m^3 and l_m, respectively. Illya et al. [4] also find that the area stretch modulus increases linearly with the chain length. Applying this scaling to the membrane induced interactions between proteins (Eq. (9)) suggests that the membrane-induced energy barrier to protein aggregation, dF_M, should scale with l_m^2 and the protein–protein separation at which the barrier is located scale as l_m.

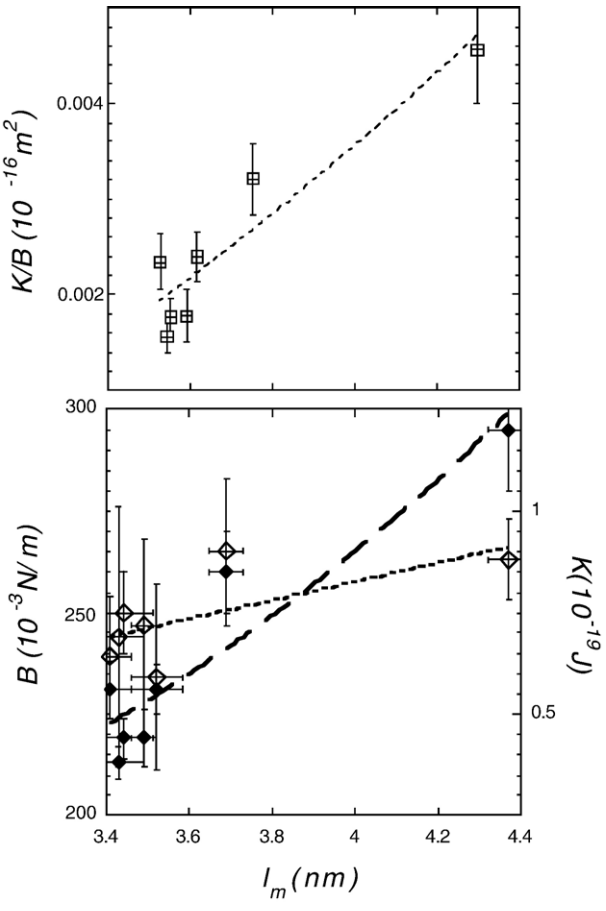

Fig. 2. Membrane moduli of PC bilayers composed of symmetric lipids, measured by Rawicz et al. [7], as a function of the bilayer thickness. The layer thickness is in nm, B (open diamonds) is in mN/m and K (full diamonds) is in 10^{-19} J. The dotted lines denote the scaling dependence of the moduli on l_m predicted by Eqs. (6a) and (6b): $B \sim l_m$, $K \sim l_m^3$, and $K/B \sim l_m^2$. We see that the predictions of Eqs. (6a) and (6b) are consistent, in a scaling manner, with the data of Rawicz et al. [7].

However, membrane moduli have been found to be sensitive to lipid tail asymmetry, even if the bilayer thickness is the same. For example, Illya et al. [4] find that the area stretch modulus of an asymmetric lipid is about 2/3 that of the corresponding symmetric chain lipid, although the associated change in the bilayer thickness was ~1.5%. Thus, we use the Milner and Witten [23] model to estimate the effect of chain asymmetry on membrane moduli, and apply that to calculate the membrane-induced interactions between proteins. Below we examine two cases: In the first, the overall tail MW (sum of both chains) is held constant, but the degree of asymmetry is varied. In this case the membrane thickness is taken to be fixed (see our assumptions above), independent of the tail asymmetry. In the second case, the MW of one tail is taken to be constant, while the MW of the other chain is varied. In this case, the layer thickness should increase linearly with the MW of the second chain.

3.1. Tail asymmetry in lipids with fixed overall tail MW

Here we examine lipids where the overall MW of the tail is fixed. The fraction of the tail MW of one chain is given by y, so that symmetric lipids are defined by $y=1/2$. Increasing chain asymmetry is associated with a decreasing value of y. As shown in Fig. 3A, the membrane-induced barrier to protein aggregation (dF_M, as given in Eq. (9)) and the protein separation at which the barrier is maximal (D^*, Eq. (8)) decrease with increasing degree of asymmetry, namely, with decreasing y value.

For lipids where both chains are saturated, y may be estimated by taking the ratio between the number of carbons in one chain and the sum of both chains: For example, if the symmetric lipid contains 13 carbons on each chain (diC13:0), an asymmetric lipid containing C10 and C16 chains will have y ≈10/26=0.38. As can be seen in Fig. 3A, for a lipid with y ≈0.4 the value of D^*, the location of the membrane-induced energy barrier to aggregation is lower than that of the symmetric one by ~25%, and the height of the barrier dF_M is reduced by ~20%.

Symmetric lipids may also be composed of unsaturated chains—as long as both chains have the same number of carbons and the same degree of saturation. Asymmetry, then, can be obtained either by changing the number of carbons on the chains (keeping the sum constant), and/or by changing the degree of saturation (keeping the sum constant): For example, Rawicz et al. [7] compared the moduli of the symmetric diC18:1 (each chain having 18 carbons and one unsaturated bond) to C18:0/2 (each chain having 18 carbons, one saturated and the other with two unsaturated bonds). However, unlike changing

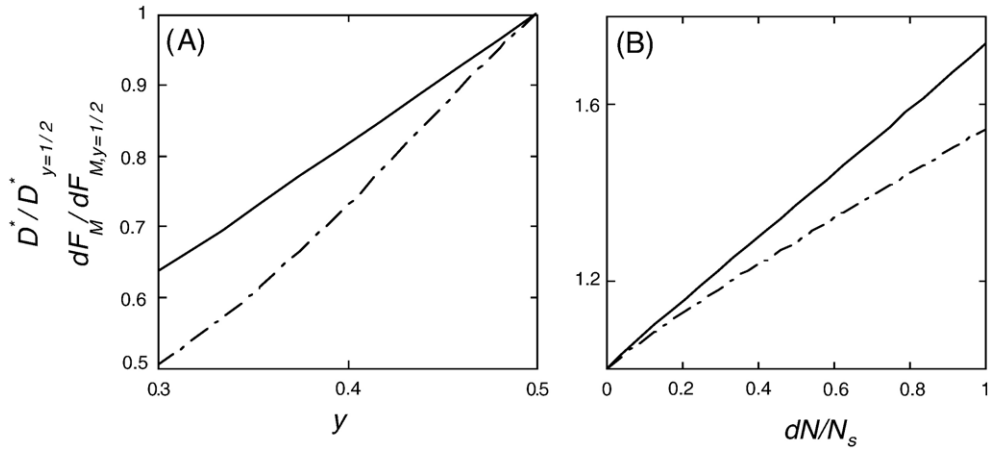

Fig. 3. Effect of lipid tail asymmetry on the height of the membrane-induced energy barrier to protein aggregation, dF_M (solid line) and the protein spacing D^* (dashed line) at which the barrier is located. (A) Systems where the overall tail length (sum of both chains), and therefore the bilayer thickness, is fixed: $y=1/2$ denotes a symmetrical lipid where both chains are identical. Both dF_M, and D^* are normalized by the values of the symmetrical lipid. We see that increasing the degree of chain asymmetry, namely decreasing y, leads to a reduction in the barrier height and spacing. For reasonably asymmetric proteins where $y \approx 0.4$ this reduction may be of order 20–30%. (B) Systems where one tail is fixed, and the other varied. dN denotes the difference in length between the two chains, and N_s is the length of the fixed, shorter chain. Therefore, a symmetrical lipid is given by d$N=0$ (same as $y=1/2$), while a typical asymmetric one will have a dN of up to $\sim 0.4N_s$ (e.g. a lipid with C12 and C16 chains will have $dN/N_s=1/3$). Note that $dN/N_s=1$ is equivalent to $y=1/3$ (namely, where one chain is twice the length of the other chain). Since the shorter chain is held constant, increasing dN increases the overall tail MW, and thus the bilayer thickness. In this case, both D^* and dF_M increase as well.

the number of carbons, it is unclear how to directly link saturation asymmetry to our y parameter, especially since the location of the unsaturated bond was also shown to affect membrane properties [7].

3.2. Tail asymmetry in lipids with one fixed tail chain

Here we examine lipids where the MW of one tail chain is fixed, while the other one varies. In this case, the bilayer thickness is not constant, but increases with increasing length of the longer chain (if the shorter one is held constant). The degree of asymmetry in this case is given by dN, the difference in MW between the two tail chains.

As shown in Fig. 3B, increasing the degree of asymmetry in this case increases both D^* and dF_M. However, we need to clarify whether this increase is dominated by the associated increase in bilayer thickness. Consider, for example, a comparison between a lipid with diC18 (d$N=0$) chains and one with C18 and C24 chains where dN is 1/3. The bilayer thickness should increase by ~12% according to our model (Niemela et al. [6] find an increase of approximately 15% in such a case). As discussed above, the energy barrier height should scale, in cases where asymmetry is not an important factor, with l_m^2, leading thereby to an expected increase of ~25% due to the thickness. Examining Fig. 3B, we find that for d$N=1/3$ the barrier height of the asymmetric chain is approximately 25% higher than that of the symmetric, d$N=0$ one, thereby indicating that the contribution of asymmetry in such cases is minor.

4. Discussion and conclusions

The perturbation of membranes by embedded proteins is unfavorable. As a result, membrane energy is minimized when the proteins are aggregated. However, previous studies have shown that the membrane perturbation energy gives rise to a membrane-induced energy barrier to protein aggregation [9–11,17–21]. The location of this barrier and the height are set by the membrane thickness, area stretch modulus and bending modulus [9–11,17–21]. In this paper we examine the effect of lipid tail asymmetry on the membrane-induced interactions between proteins, and specifically the location and magnitude of the energy barrier.

Lipid tail asymmetry may be due to differences in the number of carbons in each chain, differences in the degree of chain saturation, or a combination of both. If both chains are saturated, the degree of asymmetry may be defined by the ratio of the number of carbons in each chain. y, the fraction of the number of carbons in one chain can typically vary between 0.5 for the symmetrical lipids to ~0.3 (such as, for example, in an 18:0–8:0 PC [3]).

In systems where the overall MW of the lipid tail (sum of both chains) is fixed, the thickness of the bilayer is independent of the chain asymmetry [see, for example, [4]]. Our model suggests that the area stretch modulus and the bending modulus decrease in these systems with increasing chain asymmetry, resulting (Fig. 3A) in a decrease in both the height of the membrane-induced energy barrier to protein aggregation, and the interaction distance, namely, the protein separation at which the barrier is located.

As shown in Fig. 3A, reasonable chain asymmetries of order $y \sim 0.4$ can reduce the height of the energy barrier by about 20%, and the interaction distance by about 25–30%. However, to see whether such a reduction can have a real impact on the interactions between proteins, we must estimate the magnitude of these quantities.

Using the data of Rawicz et al. [7] for symmetric, saturated PC lipids with 13 or 14 carbons yields for D^* a value of ~2.3 nm. This distance is smaller than the average separation

between proteins in biological membranes, which is of order 5–6 nm [22], but is of a similar order of magnitude. Thus, reducing this distance by ~30% to ~1.6 nm may enhance the probability of protein aggregation in membrane nanodomains.

The height of the energy barrier, calculated by applying the values measured by Rawicz et al. [7] for K, B and l_m to Eq. (9) is of order $2\times10^{10}\ \Delta_0^2\ kT$/m, where the relevant length scale is the circumference of the protein. For a protein with a diameter of ~1.5 nm and a thickness mismatch Δ_0 of order 0.1 the energy barrier dF_M is of the same magnitude as the thermal energy kT. Thus, a reduction of this height by 20% can significantly increase the probability of crossing this barrier (as given by $e^{-dF_M/kT}$). The membrane-induced barrier is larger for longer PC chains: Using data for a symmetric, unsaturated PC diC18:1 [7] yields a barrier height, for this hypothetical protein, of ~1.3 times the thermal energy, and for diC22:1 a barrier height of 1.6 kT.

In lipids where the length of one of the chains is fixed and the other varied, the thickness of the bilayer increases with increasing length of the longer chain (or decreases with decreasing length of the shorter chain, depending on which one is held fixed). In these systems, the membrane-induced energy barrier height and location are largely set by the changes in the membrane thickness: Increasing the thickness increases the barrier height, and vice versa (see Fig. 3B).

Unfortunately, we are not aware of any experiments that measure the effect of lipid asymmetry on protein–protein interactions. However, the importance of chain asymmetry can be estimated by examining its effect on membrane moduli: If both chains are saturated (or unsaturated to the same degree), y, the degree of asymmetry, can be estimated by dividing the number of carbons in one chain by the overall sum of both chains. Illya et al. [4] found, using dissipative particle dynamics, that the area stretch modulus of a lipid with $y=0.42$ is lower by about 30% when compared to that of the symmetric lipid with the same overall tail length, although the bilayer thickness changed by less than *2%*. Ali et al. [3] measure the area stretch modulus of PC lipids, finding that the modulus of an asymmetric lipid in the fluid phase with $y=0.36$ is approximately 80% that of the equivalent symmetric lipid.

Chain asymmetry can also be obtained by introducing (or removing) unsaturated bonds, although in this case it is difficult to explicitly assign a y value. Rawicz et al. [7] find that although the area stretch modulus of a symmetric, diC18:1 PC (two 18 long chains with one unsaturated bond) is similar to that of the asymmetric C18:0/2 (one chain saturated and the other with two unsaturated chains), the bending modulus of the asymmetric lipid was approximately 50% that of the symmetric lipid. These studies clearly demonstrate that lipid tail asymmetry can have a significant effect on membrane moduli even if the bilayer thickness does not vary, therefore confirming our prediction that the degree of asymmetry can affect the membrane-induced interactions between proteins.

In the case of lipids where one chain is held fixed while the other one varies, the bilayer thickness does not remain constant. As shown by, for example, Niemela et al. [6] and Petrache et al. [18], bilayer thickness increases linearly with increasing length of the varying chain. It is well established that bilayer moduli, and in particular the bending modulus, increase with membrane thickness. Thus it is difficult to determine whether in such lipids the membrane-induced interactions between proteins would be dominated by the changes in bilayer thickness, or by chain asymmetry. Our model suggests (see Fig. 3) that the membrane thickness effect are more significant, but further studies are needed.

In conclusion, we examine the effect of lipid tail asymmetry on the membrane-induced interactions between proteins, focusing on the height of the energy barrier to aggregation, and the location of this barrier (namely, the protein separation at which the barrier is located). We find that reasonable chain asymmetries found in common lipids (e.g. [4–6]) should lead to a ~30% reduction in the height of the energy barrier and its' location. As a result, proteins are more likely to aggregate in bilayers composed of asymmetric lipids when compared to their symmetric counterparts.

Acknowledgements

The support of the Louis and Bessie Stein Foundation is gratefully acknowledged.

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[24] Note that changing the degree of chain saturation (for a fixed number of carbons) is known to affect the surface area per lipid (see, for example, Illya [4] and Niemela [6]). In our model, the thickness of a bilayer composed of saturated 16:16 or 14:18 lipids should be the same, in agreement with previous work [e.g. 4]. However, since introducing an unsaturated bond changes the surface area, the thickness may change as well. As a result, the thickness of a bilayer composed of two saturated 16:16 lipid chains would differ from that of a 16:16 lipid with an unsaturated bond, as shown, for example, by Rawicz et al. [7].