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# Functional consequences of lipid packing stress

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**Abstract**

When two monolayers of a non-lamellar lipid are brought together to form a planar bilayer membrane, the resulting structure is under elastic stress. This stress changes the membrane's physical properties and manifests itself in at least two biologically relevant functional aspects. First, by modifying the energetics of hydrophobic inclusions, it influences protein–lipid interactions. The immediate consequences are seen in several effects that include changes in conformational equilibrium between different functional forms of integral proteins and peptides, membrane-induced interactions between proteins, and partitioning of proteins between different membranes and between the bulk and the membrane. Secondly, by changing the energetics of spontaneous formation of non-lamellar local structures, lipid packing stress influences membrane stability and fusion. © Published by 2000 Elsevier Science Ltd.

*Keywords:* Integral proteins; Intra-membrane pressure; Non-lamellar lipids

## 1. Introduction

Membrane lipids are no longer regarded as a kind of filler or passive solvent for the membrane protein machinery. It is now well established that lipids play an important role at several levels of cell regulation. This functional involvement naturally explains why cells exquisitely control the lipid composition of their membranes. Still, the mechanisms of membrane–protein interaction and the constraints upon the lipid composition of organelles and cell membranes are poorly understood.

The ways by which lipids fulfill their regulatory role are complex and diverse, but they can be conditionally divided into *specific* and *non-specific*. Probably the best known example of a *specific* mechanism is the inositol phospholipid signaling pathway. Here, lipid-derived second messengers serve as ligands for highly specific biochemical reactions. Although a role for phosphoinositides in signal transduction was first suggested about half a century ago, recent reviews [1,2] have demonstrated new exciting developments in this growing field. Another example of specific regulation is the highly selective interaction of cytochrome *c* oxidase with cardiolipin [3]. Cardiolipin is unique to the mitochondrial membrane of mammalian cells and is found to be a very efficient activator of this enzyme. High specificity is also reported in lipid-assisted protein folding where lipids may play a role of molecular chaperones [4].

*Non-specific* regulation does not involve any biochemical reactions or high selectivity with respect to fine chemical details [5]. Instead, it is realized through the changes in membrane physical parameters, such as membrane hydrocarbon thickness, surface charge density, polar layer potential, lipid headgroup hydration, etc. This paper discusses only one aspect: non-specific regulation from the elastic stress

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of packing of non-lamellar lipid molecules into planar bilayer structures.

Almost 40 years ago it was observed [6] that many phospholipids found in plasma membrane bilayers, when purified, do not form lamellar phases. Instead of forming a 'stacked bilayer phase', they favor packing into inverted hexagonal bulk phases. This observation led researchers to suggest that that these 'non-bilayer' lipids have a special functional role in biological regulation [7–9]; however, the range of functional consequences and underlying physical mechanisms are still energetically discussed [10,11].

When a planar membrane is formed by two monolayers of non-lamellar lipids, these monolayers undergo elastic deformation. Their spontaneous state with a finite equilibrium curvature is disturbed by flattening, which is necessary to form a planar structure. The resulting elastic stress can be seen as a lateral pressure that varies with depth in the membrane [12–15]. Diagrams in Fig. 1 illustrate the idea and also provide an example of possible pressure distributions. The pressure profiles are comprised of repulsion between headgroups and between the hydrocarbon chains of adjacent lipid molecules, which is compensated by attractive interfacial tension. In the case of exact compensation, the membrane tension is zero. The higher the lipid spontaneous curvature, the higher the repulsion between hydrocarbon chains.

Several physical properties of a membrane are modified by lipid packing stress. The direction of the change, however, depends on the particular way the stress is introduced. Even if all manipulations lead to an increasing negative curvature strain (lipid monolayers that tend to form inverted hexagonal or cubic phase but held in a planar configuration), the outcome depends on whether the repulsion between headgroups is reduced or the repulsion between hydrocarbon chains is increased. NMR experiments [16] show, for example, that going from phosphatidylcholine (PC) to smaller phosphatidylethanolamine (PE) reduces repulsive forces between headgroups and reduces the area per lipid molecule by a few square Å. It also increases chain order and hydrophobic membrane thickness. On the other hand, an increase in the negative curvature strain obtained by an increase in hydrocarbon chain length or in degree of unsaturation increases the area per molecule and lowers the chain order. From osmotic stress/X-ray diffraction experiments, it is also known that going from PC to PE changes the hydration properties of lamellar phases. In the case of PE bilayers, an additional short-range attractive interac-

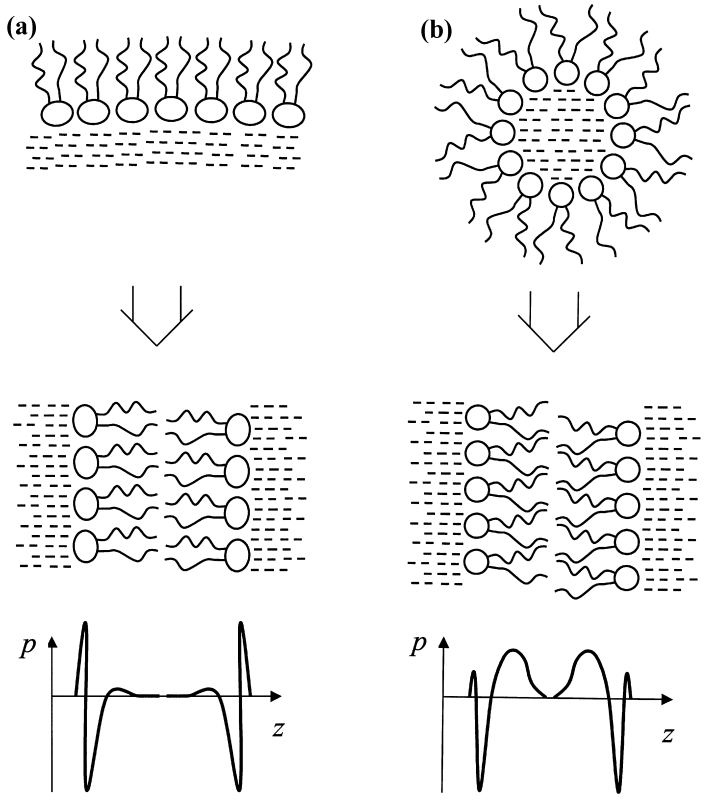


Fig. 1. Lateral pressure $p$ in a planar bilayer membrane changes along the membrane depth $z$ and depends on the lipid nature. (a) When a membrane is assembled from spontaneously lamellar lipids or lipids with a small spontaneous curvature, the corresponding pressure profile in the hydrocarbon tail area is shallow. (b) Lipids of higher negative spontaneous curvatures introduce higher pressures in the chain area.

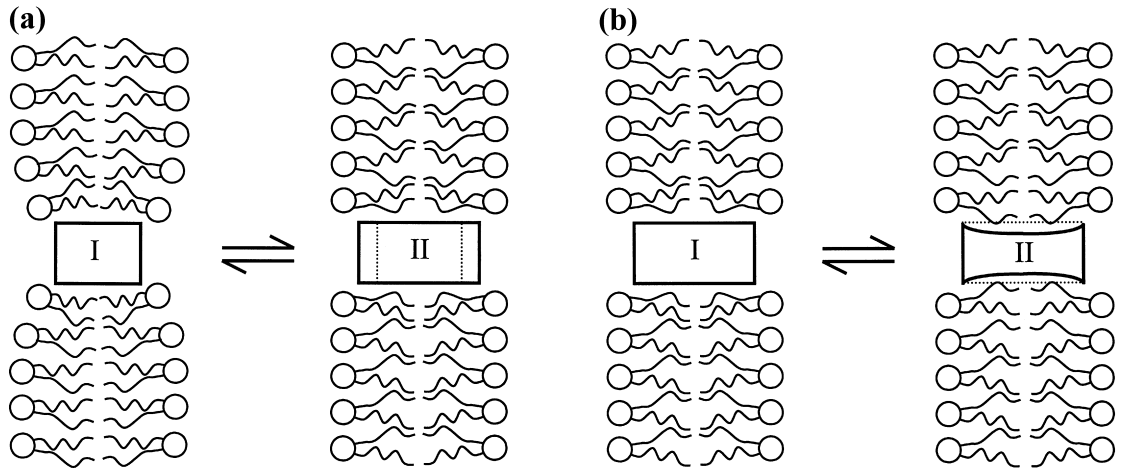


Fig. 2. Two models showing sensitivity of hydrophobic inclusions to the lipid packing stress. (a) Changes in hydrophobic mismatches upon conformational transition modify lipid packing around the inclusion. For a negative curvature stress, conformation II is energetically preferred. (b) Conformation transition resulting in a changing shape may also change lipid packing around the inclusion. Conformation II relieves elastic stress and is energetically favorable.

tion was found. However, this interaction is possibly due to a hydrogen-bonded water interaction that is specific for PE headgroups of the opposing bilayers [17].

## 2. Hydrophobic inclusions under lipid packing stress

Non-lamellar lipids affect the activity of membrane proteins and peptides. Though the physics of this phenomenon remains largely unclear, the number of phenomenological examples is impressive [10]. Among recent findings are the modulation of volume-regulated anion currents in bovine endothelial cells [18], where the authors attributed cholesterol-induced effects to the membrane deformation energy associated with channel opening, and the results on the elastic-stress-modified activity of bacteriorhodopsin in a novel refolding system [19].

The physical mechanisms by which membrane proteins respond to the elastic stress of lipid packing are attracting significant interest [20–29•]. Obviously, to be sensitive to mechanical stress, protein conformational transitions have to be coupled to some mechanical displacements that change the elastic stress of nearby lipids. Two main ideas are illustrated in Fig. 2. The first model (Fig. 2a) is based on the concept of hydrophobic mismatch [30,31,25]. Mechanical coupling between the protein's hydrophobic exterior surface and the membrane hydrocarbon area is due to the fact that the exposure of the hydrophobic regions of either the lipid or protein to a water phase is energetically unfavorable. Indeed, hydrophobic coupling can be used in models of protein–membrane interactions as long as the hydrophobic energy of a system exceeds its elastic deformation energy [28•]. In the case of strong coupling and short inclusions, lipids with negative curvature stress will favor conformational transitions that increase the hydrophobic length of inclusions to a larger degree than lamellar lipids. Length-increasing transitions not only decrease the elastic stress of compression caused by hydrophobic mismatches, but also reduce the positive curvature of the surrounding lipid [20].

In the second model (Fig. 2b), lipid packing stress is relieved by the cylinder-hourglass transition [22•,23••,27••]. Sensitivity to non-lamellar lipid components comes from a redistribution of lateral pressures. Higher lateral pressures in the hydrocarbon chain region are expected for lipids with higher negative spontaneous curvatures (Fig. 1) and, therefore, these lipids promote the hourglass conformation.

According to statistical calculations by several groups [12,13,15], the average lateral pressure in the hydrocarbon chain region can be as high as several hundred atm, and, at certain points along the membrane depth, can even peak to above 1000 atm [12]. These results are in reasonable agreement with a simple estimate based on the work of Rand et al. [32,33], which showed that the change in the lateral pressure upon the reentrant hexagonal–lamellar transition in dioleoylphosphatidylethanolamine must be approximately 100 atm. Indeed, an estimate for the elastic energy per one lipid molecule was approximately 0.5 kT [33], while the characteristic area at the chain terminals changed approximately from 120 to 60 $Å^2$ [32]. Here taking 15 Å for the chain length and using a simple elastic cone model, we arrive at pressures of approximately $10^7$ $N/m^2$.

Direct measurements of lateral pressures in the hydrocarbon chain area are difficult to perform. One of the promising attempts used a homologous series of dipyrenyl PC probes that could sense lateral pressure variation in the hydrocarbon chain region [14•]. Pyrene moieties were attached to the ends of symmetrical chains of varying length in a PC molecule. Measuring the relative intensity of the intra-molecular excimer to monomer signal, it was possible to detect non-homogeneity in the lateral pressure distribution along the membrane depth.

Recently, it was shown [26] that lipid packing stress significantly modified peptide partitioning between the membrane and the aqueous bulk by decreasing the peptide–membrane binding constant by a factor of four when non-lamellar dioleoylPE was admixed to lamellar dioleoylPC in a concentration of 60 mol.%. Obviously, in the case of membrane proteins, the increase in lipid chain pressure can also obstruct protein insertion. In experiments with bacteriorhodopsin refolding [19], it was found that the regeneration yield decreased as the lateral pressure in hydrocarbon chain region increased. However, it was impossible to discriminate between the hindered insertion of the protein and the slowing down of a folding step.

## 3. Alamethicin and gramicidin channels

The uncertainty between changes in partitioning or activity can be excluded in single-channel experiments that allow the observation of single molecules or single molecular aggregates embedded in a membrane. Such measurements were performed with two model channels: alamethicin and gramicidin. Two strategies were used to introduce elastic stress. First, alamethicin [34] or gramicidin [35] channels were reconstituted into bilayer lipid membranes of changing lipid composition to vary the elastic stress of lipid packing. Second, bilayers were formed from one lipid species only, phosphatidylserine (PS), and, while monitoring single gramicidin [20] or alamethicin [36] channels, the elastic stress was varied by changing the pH of the bathing solution.

The qualitative findings are illustrated by Fig. 3. It shows that an increase in elastic stress in the hydrocarbon tail region decreased the gramicidin channel lifetime and increased the duration of the alamethicin single-channel 'burst'. Thus, manipulations that suppressed gramicidin channels promoted alamethicin channels by favoring larger alamethicin aggregates. The mechanism of gramicidin channel suppression by negative curvature stress is pretty well understood [20,24•,28•,35]. However, there is no consensus on

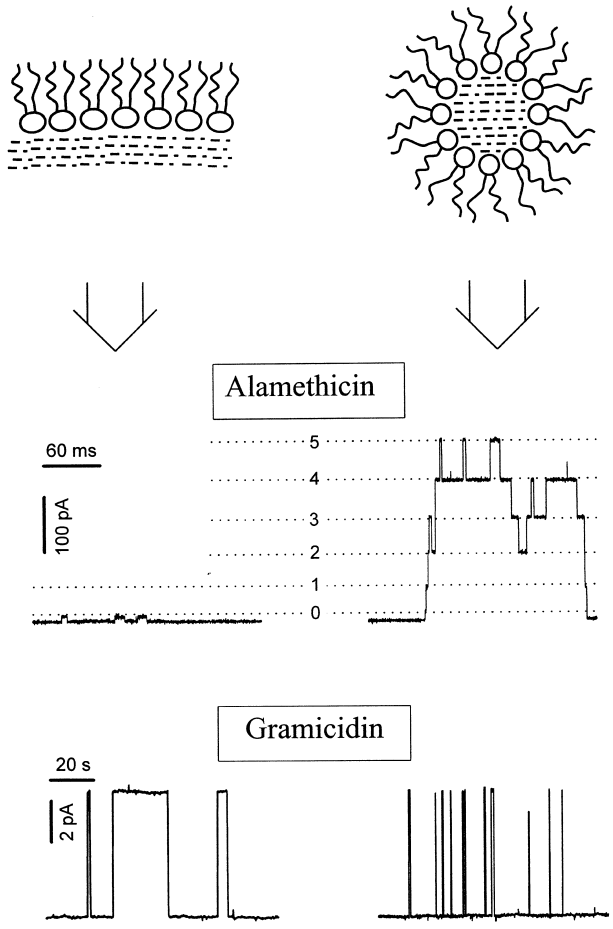


Fig. 3. Influence of non-lamellar lipids on two model channels — gramicidin A and alamethicin. It can be seen that lipid packing stress promotes higher conductance states of alamethicin channels [34,36] (data from [36]) but decreases gramicidin A channel lifetime [20,35] (data from L. Kullman and S.M. Bezrukov, unpublished results; PS, 0.1 M KCl, left panel = pH 7.0, right panel = pH 2.2).

the mechanisms involved in the stress sensitivity of alamethicin conductance.

At least two theoretical models claim to describe alamethicin channel behavior at the varying lipid packing stresses. In the first model [23••], different states of the alamethicin channel are represented by a rigid hourglass (right panel in Fig. 2b) of varying diameter and a height that exactly matches the hydrophobic bilayer thickness. Contact angles with the membrane monolayers were assumed to be the same for all channel states, so that the only difference between them was area. Assuming also that both contact angles were small, and calculating the system energy by methods previously described by Dan et al. [37], the authors were able to describe alamethicin channel behavior both qualitatively and even quantitatively. Among other experimental findings [34], the model explained the exponential dependence of the ratio of times spent by the channel in different conductance states on the spontaneous curvature.

The second model [29•] is a modification of the 'mattress model' [31] for hydrophobic mismatches. It is based on the structural data suggesting that the central hydrophobic region of alamethicin molecule is shorter than the width of the hydrocarbon region of the lipid bilayer (left panel in Fig. 2a). As a consequence, the transmembrane insertion of the peptide brings about membrane elastic deformation, resulting in a free energy penalty. The aggregation of alamethicin molecules into a conducting cluster reduces the peptide–lipid interactions. The larger the cluster, the weaker the peptide–lipid interaction. This explains the experimentally-found stabilization of the larger-cluster higher-conductance states [34,36] by the non-lamellar lipids that increased the free energy penalty.

Both models predict qualitatively similar behavior. The hydrophobic mismatch model [29•] uses reliable structural data, while the 'contact angle' model [23••] only assumes the hourglass shape for the channel. However, numerical simulations of alamethicin channels seem to support this assumption. Alamethicin helices are linked into the conducting cluster by the glycine–*X*–*X*–proline motif, so that the cluster is somewhat 'hourglass shaped' [38]. The change in shape from roughly cylindrical alamethicin monomers to the hourglass channel may account for its elastic stress sensitivity. Indeed, a simple estimate shows that, if upon every transition to a higher conductance state the channel 'economizes' (in comparison with a cylindrical configuration) approximately 100 $Å^3$ in volume in the hydrocarbon chain region, then the work of the 500-atm pressure is approximately 1 kT. This estimate gives the right order of magnitude for the change in the states' free energy found experimentally [34,36]. Importantly, the 100-$Å^3$ volume change would amount only to approximately 3% of the single alamethicin molecule volume.

Alamethicin has also been found to promote the formation of a non-lamellar phase at a surprisingly low concentration of this peptide [39]. This is a strong argument in favor of the direct interaction of the alamethicin channel with the elastic stress of lipid packing. The peptide, whose aggregation properties are sensitive to the spontaneous curvature of lipids used for bilayer formation, is expected to modulate the spontaneous curvature of lipid monolayers [40].

The stress of lipid packing [8], and more generally, the 'material properties' [28•] of the membrane are emerging as the dominant factors in protein–membrane interactions that significantly influence protein conformational equilibria and folding [41•]. They seem to be much more important than membrane tension per se. A careful recent study of the effect of membrane tension on the kinetics of the gramicidin channel [42••] shows that 'tension transduction' actually works through membrane thinning, i.e. the applied tension reduces hydrophobic mismatch in thickness between the gramicidin dimer and membrane and thus increases the channel lifetime. This important finding may be crucial to the general interpretation of mechano-sensitivity of ion channels and other membrane proteins [11,43,44].

## 4. Lipid packing stress and membrane fusion

Though under appropriate experimental conditions it is possible to force pure lipid bilayers to fuse, membranes do not usually fuse spontaneously. The repulsive energy between two approaching bilayers is very high at atomic distances [45]. Besides, there is an additional energetic cost of forming the structural intermediates, fusion stalks and fusion pores [46•,47–49]. To overcome these problems, evolution created specialized fusogenic proteins that change their conformation upon interaction with specific triggers and facilitate biological membrane fusion [50].

Lipids of high spontaneous curvature facilitate the formation of non-bilayer fusion intermediates to promote membrane fusion. The formation of a stalk is helped by negative curvature stress because this structural intermediate has a net negative curvature [46•]. Any lipid or protein that promotes negative curvature strain will generally facilitate this stage in membrane fusion. The regulating role of membrane lipid composition is widely recognized [50,51•], although in specific cases the phenomenology can be different. For example [52], short-chain alcohols, known to promote positive spontaneous curvature, support rather than suppress hemifusion. The authors explained their observation by surface binding of alcohol, which breaks the continuity of each of the contacting monolayers.

A recent study of the fusion activity of the influenza virus and Golgi membranes shows that, as expected from the lipid packing stress considerations, lysolipids inhibit fusion when they are present in the target membrane [53•]. To understand the mechanism better, the authors employed a special membrane-anchored peptide system and came to a conclusion that unifies the two seemingly separate themes of this short review — protein–membrane and membrane–membrane interactions. They explained their findings by a structural switch at the level of the fusion peptide whose state is sensitive to the target membrane lipids.

## 5. Conclusions

Researchers have taken the first crucial steps in appreciating the role of non-lamellar lipids in pro-

tein–membrane and membrane–membrane interactions. However, to fully realize the consequences of the membrane elastic stress, further approaches will have to include more detailed structural knowledge encompassing the important issues of lipid molecular separation [54], demixing [55], lipid domains [56,57], and 'rafts' [58]. A better understanding of biological membrane architecture and thermodynamics is necessary for an adequate description of membrane functional regulation by the stress of lipid packing.

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