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Role of charged lipids in membrane structures — Insight given by simulations☆

Sanja Pöyry [a], Ilpo Vattulainen [a,b,c,*]

[a] Department of Physics, Tampere University of Technology, POB 692, FI-33101 Tampere, Finland
[b] MEMPHYS — Center for Biomembrane Physics, University of Southern Denmark, Odense, Denmark
[c] Department of Physics, University of Helsinki, POB 64, FI-00014 Helsinki, Finland

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ABSTRACT

Lipids and proteins are the main components of cell membranes. It is becoming increasingly clear that lipids, in addition to providing an environment for proteins to work in, are in many cases also able to modulate the structure and function of those proteins. Particularly charged lipids such as phosphatidylinositols and phosphatidylserines are involved in several examples of such effects. Molecular dynamics simulations have proved an invaluable tool in exploring these aspects. This so-called computational microscope can provide both complementing explanations for the experimental results and guide experiments to fruitful directions. In this paper, we review studies that have utilized molecular dynamics simulations to unravel the roles of charged lipids in membrane structures. We focus on lipids as active constituents of the membranes, affecting both general membrane properties as well as non-lipid membrane components, mainly proteins. This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

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1. Introduction

Cell membranes are essentially composed of proteins and lipids. Their roles in membranes are largely quite distinct: membrane proteins carry out the functions, while lipids make sure that the environment felt by the proteins is appropriate to activate and maintain the function. Recent studies have also shown that lipids have a regulatory role highlighted by lipids' ability to modulate proteins either through specific lipid–protein interactions or via membrane-mediated interactions [1], thereby stressing the importance of lipids in cell function.

In cells, there are thousands of different lipid types. It is likely that they all have a role to play in cells, yet their functions are not well understood. The understanding of lipid properties is currently at its best when one considers the most abundant lipid classes in mammalian cell membranes such as those comprised of phosphatidylcholine (PC), sphingolipid, and sterol molecules. Quite substantial work has also been carried out to clarify the roles of lipid classes that are usually in the minority in cells, such as phosphatidic acid (PA), phosphatidylserine (PS), and phosphatidylinositol (PI). While this knowledge is highly valuable, it is still just the tip of the iceberg. Each of the lipid classes have their own subclasses and subspecies that differ in a number of seemingly minor but important ways, such as the degree of unsaturation, the length of hydrocarbon chains, the chemical details of the polar head group, the structural modifications due to e.g. oxidative stress, and charge. It is truly exciting that the information to figure out the amplitude and the gravity of lipid structural details is now emerging thanks to new lipidomics tools combined with cell biology and molecular simulations [2,3].

As a matter of fact, simulations [4,5] are in many cases the method of choice to get to the bottom of the importance of atomistic details. Considering cholesterol as an example, atomistic simulations have enlightened the importance of individual functional groups and double bonds in cholesterol structure, and they have also made successful predictions as to what would happen if cholesterol structure were modified synthetically [6]. The value of molecular simulations in providing accurate predictions is a significant asset given that it is often more cost-effective to

Abbreviations: MD, molecular dynamics; PC, phosphatidylcholine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; CL, cardiolipin; SM, sphingomyelin; DPPC, dipalmitoylphosphatidylcholine; DOPC, dioleoylphosphatidylcholine; DSPC, distearoylphosphatidylcholine; DPPI, dipalmitoylphosphatidylinositol; POPI, palmitoyloleoylphosphatidylinositol; TMCL, tetramyristoylcardiolipin; DMPC, tetramyristoylphosphatidylcholine; DPPS, dipalmitoylphosphatidylserine; POPS, palmitoyloleoylphosphatidylserine; DOPS, dioleoylphosphatidylserine; DSPS, distearoylphosphatidylserine; CHOL, cholesterol; SOPS, stearoyloleoylphosphatidylserine; POPE, palmitoyloleoylphosphatidylethanolamine; DOPA, dioleoylphosphatidicacid; TM, transmembrane; JM, juxtamembrane; SAPC, stearoylarachidonylphosphatidylcholine; GPI, glycosylphosphatidylinositol.

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* Corresponding author at: Department of Physics, Tampere University of Technology, POB 692, FI-33101, Tampere, Finland.
E-mail addresses: ilpo.vattulainen@tut.fi, ilpo.vattulainen@helsinki.fi (I. Vattulainen).

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carry out extensive simulations compared to carrying out an arsenal of more expensive experiments, and as a fringe benefit one is also given atom-scale insight that is hard to obtain through experiments, if possible at all.

In this work, we discuss the knowledge generated by computer simulations about the properties of charged lipids, whose role is exceptionally important in a variety of different processes. PS is one of the key players in programmed cell death [7]. PI is often involved in the modulation of membrane receptors and their signaling processes [8]. Phosphatidylglycerol (PG) is quite abundant in pulmonary surfactant where it functions together with pulmonary surfactant proteins [9], and cardiolipin (CL) binds in a specific manner to mitochondrial membrane proteins associated with ATP production [10]. While these examples are just a few of the many biologically relevant processes where charged lipids are in the spotlight, they do highlight the importance of understanding the function of charged lipids in cells.

Our goal in this review is to discuss recent findings that describe charged lipids as active players in membrane systems, paying particular attention to PS and PI due to their considerable role in many biological processes. We discuss how charged lipids affect membrane properties, how their charged nature comes into play in lipid–protein interactions, and also how the interactions of nanosized molecules/particles with membranes are influenced by lipid charge. We focus on the recent simulation work done in the field and couple the observations to experiments when that is appropriate. In many sections we summarize the views shared by the related simulation studies, or, if that is not possible due to lack of consensus, we highlight the importance to focus more attention to explore the topic in question more systematically. Due to space limitations, we largely exclude papers dealing with pure 1-component model membranes and instead focus on more complex systems that have more biological relevance. To consider simulation studies of 1-component membranes, the readers are referred to other articles providing discussions on e.g. PG lipids [11–15], CL [16–20], PS [13,21–24], PI [21,25], dioctadecyl-ammonium bromide (DODAB) multilayers [26], and ionization dependent behavior of oleic acid bilayers [27].

Despite the fact that our discussion in this work is not fully comprehensive, we will readily see that charged lipids have an important role to play in a number of phenomena including lipid–protein binding, membrane potential, and membrane permeation, and the discussion reveals convincingly that atomistic/molecular simulations can indeed provide one with a detailed picture of the importance and properties of charged lipids.

2. Effects of charged lipids on membrane properties

2.1. Order and elasticity

Since several different charged lipid species constitute a notable fraction of biological membranes, the role of charged lipids in the structural and mechanical properties of model lipid bilayers mimicking such membranes are of great biological interest. In this light, studies examining the properties of mixed protein-free lipid bilayers containing charged lipids are surprisingly few. Partly, this may be due to difficulties in studying such mixtures, e.g. mixtures of PC and PS molecules may be non-ideal or unstable [28,29]. As for PI lipids, their interplay with neighboring lipids has been examined computationally [30]. PIP2 was observed to induce local perturbations in the bilayer, changing the orientation of the surrounding PC head groups. Along the same lines, the presence of CL molecules has also been observed to affect the head group orientations of PCs in an NMR study [31]. CL has also been experimentally observed to decrease water permeability [32] and act to maintain membrane fluidity [33]. Let us here discuss some studies more carefully by focusing on one lipid type at a time.

Data presented by Stanishneva-Konovalova et al. [34] indicate that the ordering of PCs is promoted by the increase of the amount of PI lipids. In this study, the interactions between PI(4,5)P2 and PC were studied by united-atom and coarse-grained MD simulations of mixed model membranes comprising DPPC and DPPI. Data on the area per lipid, bilayer thickness, and deuterium order parameters for the lipid tails all support the increase of the order of DPPC lipids upon the increase in the DPPI content.

The results presented by Cascales et al. [35] suggest that PS lipids may have a strong effect on the mechanical properties of mixed PS/PC bilayers. An increase in the PS content seems to increase the interfacial tension and stiffen the bilayer. Intriguingly, however, the effect was only apparent in the absence of salt. Indeed, when salt (NaCl) was added, the interfacial tension became independent of lipid composition (in the range of 15–70 mol% PS). Furthermore, the effect of PS on the surface tension may have a link to pore formation, as suggested by Levine et al. [36]. Here, adding PS into a PC bilayer slightly increased the pore formation time at lower external electric fields, and greatly decreased the pore annihilation time (for electropores created at all external electric fields). Pore formation time was found to be inversely proportional to the internal electric field of the bilayer. Perhaps surprisingly, the data presented by Wu et al. [37] indicate little difference between the properties of mixed model membranes with and without PS. Since properties such as area per lipid, hydrophobic thickness, heavy atom density profile, and acyl chain order parameters were similar for both kinds of systems, the authors suggested the bilayer properties to be dominated by acyl chain composition instead of lipid head groups. The model systems also included PIPs, whose inositol ring orientations were analyzed. Notably, a larger proportion of the rings stay closer to the surface of PS-rich membranes as compared to PC-enriched ones. This may be explained by hydrogen bonding between the rings and PS head groups.

The results by Boscia et al. [38] suggest that the presence of CL increases the ordering of PC chains and bilayer thickness in mixed bilayers. Moreover, the bilayers were observed to stiffen with increasing CL content, as indicated by the increased bending modulus. For another study of both pure and mixed CL bilayers, please refer to Aguayo et al. [18].

Along the same lines, DOPA was suggested to have an ordering and condensing effect on a mixed PA/PC bilayer at low concentrations [39]. This conclusion was supported both by MD simulations and experiments. The underlying causes for this effect, in the case of DOPA monoanions, seemed to be electrostatic interactions between PA and PC head groups and conformational changes of the tails, leading to tighter packing. For the DOPA dianions, clustering mediated by cations was observed.

In contrast to the influence of the four anionic lipids presented above, the increase of oleate (deprotonated anion of oleic acid) content seemed to increase the area per lipid in oleic acid/oleate bilayers [40]. The atomistic MD simulations also indicated a large difference between the locations of oleate and oleic acid carboxyl groups. The carboxyl groups of oleate were located further away from the bilayer center.

Based on this set of recent computational studies, clear conclusions about the effect of charged lipids on the order and elasticity are hard to draw. In some of the presented cases, anionic lipids seemed to increase the ordering of PC chains and also stiffen the bilayers, in agreement with previous observations of e.g. CL's ability to decrease water permeation [32]. One study reported practically no difference between the ordering of PC chains when PS was present or when it was not, however plausibly these kinds of effects may depend on other constituents of the mixed membranes. We come back to this matter in the end of our article.

2.2. Ion binding and ion-mediated interactions

Ion-mediated interactions, especially clustering of charged lipids as a result of interactions with cations, have been of great interest during recent years, as the following reviewed computational studies indicate.

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