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Review

Computer modelling studies of the bilayer/water interface☆

Marta Pasenkiewicz-Gierula *, Krzysztof Baczynski, Michal Markiewicz, Krzysztof Murzyn

Department of Computational Biophysics and Bioinformatics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland

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ABSTRACT

This review summarises high resolution studies on the interface of lamellar lipid bilayers composed of the most typical lipid molecules which constitute the lipid matrix of biomembranes. The presented results were obtained predominantly by computer modelling methods. Whenever possible, the results were compared with experimental results obtained for similar systems.

The first and main section of the review is concerned with the bilayer–water interface and is divided into four subsections. The first describes the simplest case, where the interface consists only of lipid head groups and water molecules and focuses on interactions between the lipid heads and water molecules; the second describes the interface containing also mono- and divalent ions and concentrates on lipid-ion interactions; the third describes direct inter-lipid interactions. These three subsections are followed by a discussion on the network of direct and indirect inter-lipid interactions at the bilayer interface. The second section summarises recent computer simulation studies on the interactions of antibacterial membrane active compounds with various models of the bacterial outer membrane. This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

Contents

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* Corresponding author at: Department of Computational Biophysics and Bioinformatics, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University, ul. Gronostajowa 7, 30-387 Krakow, Poland.
E-mail address: marta.pasenkiewicz-gierula@uj.edu.pl (M. Pasenkiewicz-Gierula).

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1. Introduction

Cells and sub-cellular organelles are surrounded by membranes. These membranes play a vital role in living cells. They act as selective barriers separating and protecting the enclosed structure from the environment and at the same time enabling communication and transport between them. Moreover, membranes possess high mechanical strength and a high degree of flexibility. These biomembrane features and roles are possible thanks to their particular molecular composition and structural characteristics. The key molecules constituting the membrane are lipids, proteins, and water. The lipids form a fundamental structural element of each biomembrane, which is commonly known as the lipid matrix. In most cases, the lipid matrix is a lipid bilayer whose molecular composition varies among cell types within the same organism and depends on the cell function [1]. The matrix determines bulk membrane properties and provides a proper dynamic and active surrounding for membrane proteins which allows them to perform their biological functions. Among the main biological functions of membrane proteins are inter-compartmental communication and the controlled transport of various types of molecules. Water plays a basic role in the structure, stability, and physical properties of the lipid matrix and enables the biomembrane to function.

Biological membranes are complex, multicomponent, dynamic systems, making them extremely difficult to study by biophysical and other methods. For this reason, most biophysical studies of biomembranes are carried out on models that are hydrated bilayers comprising either one or a simple mixture of lipid species. As biomembranes are lamellar structures, models of them are generally single bilayers or multi-lamellar systems.

The physicochemical properties and structure of lipid bilayers follow directly from the chemical structures of the lipid constituents and of the water molecule. A lipid is an amphipathic molecule and water is a polar molecule so that, under dispersion in water, lipids spontaneously self-organise into bilayers or other ordered aggregates, although non-lamellar lipid aggregates are not discussed in this review. In the absence of water, a bilayer cannot form and in most cases, complete dehydration of a bilayer, often not possible or very difficult [2,3], leads to its damage, e.g. [4,5]. Thus water is an essential and integral part of the bilayer.

In a bilayer, lipid molecules are in a back-to-back arrangement with their polar head groups exposed to the water phase, with acyl chains forming the nonpolar bilayer core. This spatial organisation of molecules creates distinct horizontal regions within the bilayer [6] with contrasting properties. These regions are the bulk water phase, the bilayer/water interface, and the hydrophobic core (Fig. 1). The bulk water phase and the bilayer core contain mainly one type of molecule (water) or chemical group (CH_2, CH_3). In contrast, the bilayer/water interface is a complex region consisting of water molecules, the number of which decreases with the bilayer depth (Fig. 1), and various, mainly polar, chemical groups of lipid heads that form transient interactions with one another, e.g. [7–11]. The interface separates the isotropic bulk water from the anisotropic nonpolar bilayer core.

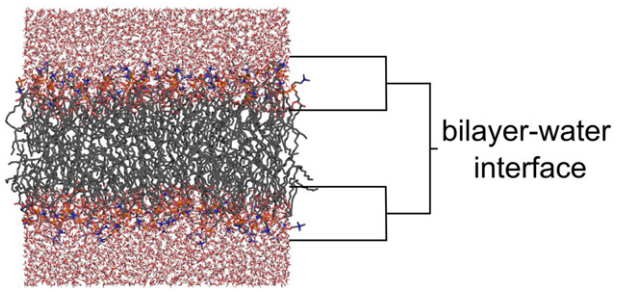

Fig. 1. Distinct regions of a liquid-crystalline lipid bilayer: the bulk water phase, the bilayer/water interface (marked), and the hydrophobic core. The lipid molecules are in the united atom representation and the atoms are represented in standard colours (carbon atoms are dark grey).

Many important cellular processes take place near or at the biomembrane interface and its properties have a great impact on these processes, e.g. [12]. Thus, elucidation of the properties of the membrane interface is a matter of great importance. These properties have been studied on lipid bilayers using a variety of methods. Until the early 90s, lipid bilayers were studied predominantly by experimental methods. These methods revealed several bulk bilayer properties summarised in e.g., Refs [13,14]. They also provided limited information about the bilayer/water interface. From the authors' perspective, the most notable concerned water molecules strongly bound to a PC head group e.g. [15]; strong interaction between the phosphate group and the methyl groups of the choline moiety of different PC molecules e.g. [16]; and putative water mediated PC–PC interactions e.g. [17,18]. However, it was not possible to obtain other detailed information about the bilayer/water interface due to the limited spatial and temporal resolutions of the methods and because a lipid bilayer, being only a simplified model of the biomembrane, is still difficult to investigate due to its complexity.

Since the beginning of the 90s, hydrated phospholipid bilayers have also been investigated using computer modelling methods (more details are given in Section 2.1.1). In contrast to experimental methods that provide structural and dynamic information about molecules that are averaged over a large number of molecules, and within the time window of the experimental method, computational methods, particularly molecular dynamics (MD) simulation, may have atomic resolution and span the observation time (on the time scale of 10^{-6} s or longer) by femtosecond steps. Such concurrent resolutions are indispensable to obtain significant insights into the basic mechanisms of membrane functioning. In terms of simultaneous space and time resolutions, molecular modelling methods are certainly superior to experimental ones.

Now, MD simulation is an established research method to study the dynamic structure of lipid bilayers and the interatomic and intermolecular interactions which take place in the bilayer on a μs or longer time scale. However, even though MD simulation may be regarded as an independent method it still needs validation. The validation process requires access to relevant experimental data that can be compared with the results obtained with MD simulation. Most often sets of experimental and MD simulation results overlap only to a certain extent. Nevertheless, if the overlapping data are similar or display similar trends, one can assume that the computer model is positively validated and that the remaining results of the MD simulation are accurate. Without validation, a computer model of the bilayer, as any other computer model, is meaningless.

The decisive factor in the correctness and reliability of the computer model is the parameterisation of the atoms which constitute the model and their interactions. It is these parameters and the energy function (force field) which ensure that the model accurately simulates a real