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# Microscopic view of lipids and their diverse biological functions

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Biological membranes and their diverse lipid constituents play key roles in a broad spectrum of cellular and physiological processes. Characterization of membrane-associated phenomena at a microscopic level is therefore essential to our fundamental understanding of such processes. Due to the semi-fluid and dynamic nature of lipid bilayers, and their complex compositions, detailed characterization of biological membranes at an atomic scale has been refractory to experimental approaches. Computational modeling and simulation offer a highly complementary toolset with sufficient spatial and temporal resolutions to fill this gap. Here, we review recent molecular dynamics studies focusing on the diversity of lipid composition of biological membranes, or aiming at the characterization of lipid–protein interaction, with the overall goal of dissecting how lipids impact biological roles of the cellular membranes.

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## Introduction

Biological membranes define the physical boundaries of living cells and their internal compartments. Composed of a myriad of diverse molecular constituents, ranging from phospholipids and other small amphiphilic/hydrophobic molecules, to peptides and proteins, many components of biological membranes have been shown to directly participate in a multitude of cellular processes, for example, signaling, transport, cell–cell communication, and chemical catalysis. Moreover, a considerable fraction of cellular processes take place at the membrane or its proximity, where the membrane serves as a platform for signaling partners to convene, assemble and function.

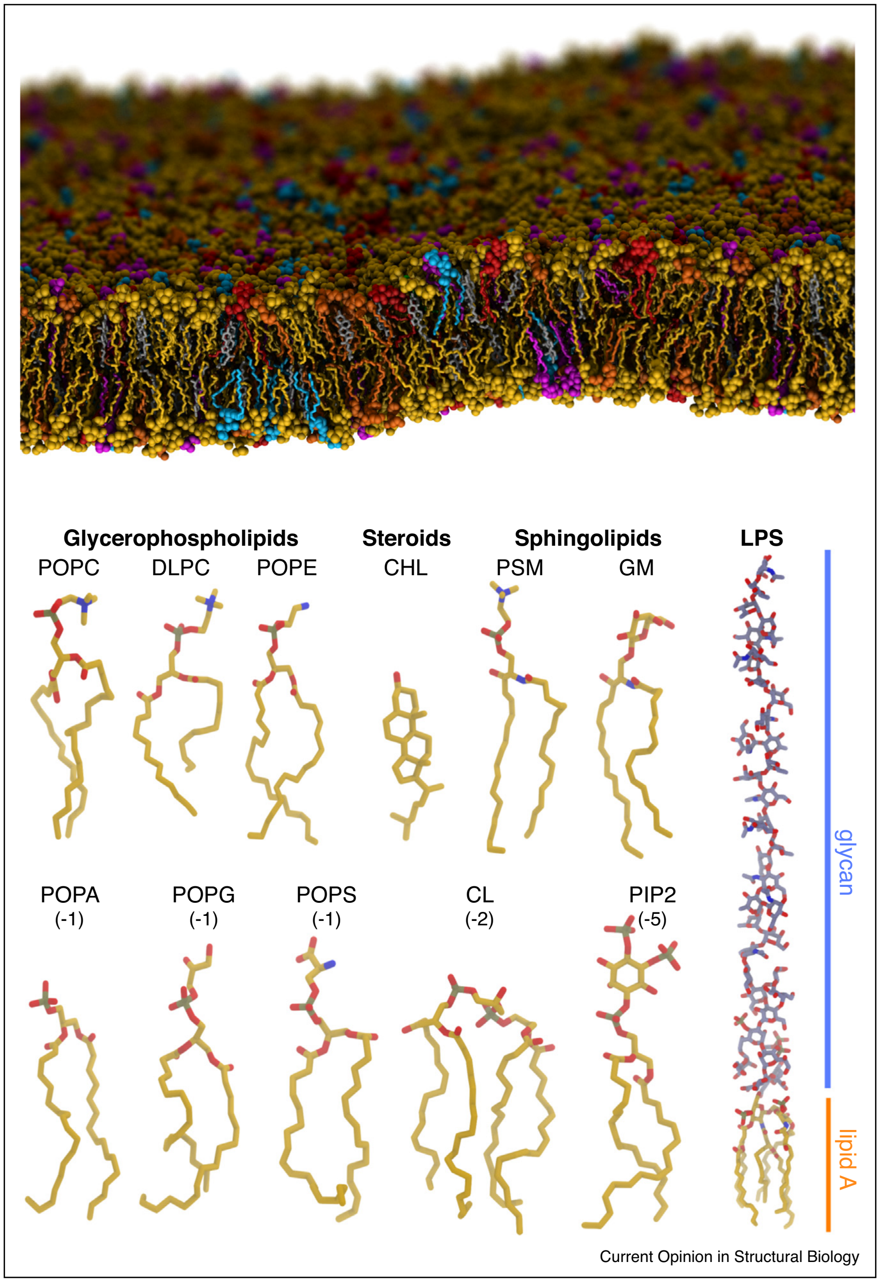
At least 1/3 of human genes encode membrane or secretory proteins, and approximately 1/2 of drug targets are membrane proteins. The function of these proteins not only depends on their localization in the membrane but also is often regulated by specific interactions with certain lipid molecules. As a result, investigating lipids and characterizing their functional roles are now integral parts of modern structural and functional studies of membrane proteins. However, even with the significant progress made over the last decade in structural biology of membrane proteins, lipids and membranes continue to pose a major challenge to detailed experimental structural studies. This is mostly due to the highly dynamic nature of lipid bilayers, compounded by the diversity of the molecular constituents commonly found in biological membranes. Computational modeling methods, in particular molecular dynamics (MD) simulations, have served as a powerful complementary approach to experiments in this regard and have been used quite effectively to fill the gap in our structural description of biological membranes.

In this article, we review recent molecular simulation studies of biological membranes, where the focus has been on the characterization of functional roles of diverse membrane lipid constituents, most importantly in the context of structure, dynamics, and function of membrane-associated proteins.

## Heterogeneous lipid composition of biological membranes

The majority of MD simulations of biological membranes and membrane proteins have been limited to homogeneous bilayers of a single lipid type, particularly glycerophospholipids such as phosphatidylcholine (PC, most representative of eukaryotic cells), and phosphatidylethanolamine (PE, for bacterial membranes). These bilayers, however, do not emulate realistic biological membranes, as other membrane components including sphingolipids, sterols, glycolipids (Figure 1), play essential roles in not

**Figure 1**




Heterogeneous lipid composition of biological membranes. (Top) An atomistic MD simulation system of a membrane with a complex, heterogeneous lipid composition. Seven different lipids, including cholesterol, cardiolipin, and a variety of phospholipids, are shown in different colors. Spontaneous curvature of the membrane arising from thermal fluctuations in the simulation can be observed. (Bottom) Structures of some exemplary lipids highlighting a variety of important features (e.g. head group charge and size, tail length and saturation, etc.) associated with lipids. Phospholipids and cholesterol are major constituents of cellular membranes. Sphingolipids are common signaling lipids, cardiolipins are essential mitochondrial lipids, and lipopolysaccharides are vital bacterial lipids of the outer membrane.

only maintaining membrane integrity and properties but also in its function. Several membrane building tools, for example, CHARMM-GUI [1•], LipidBuilder [2], insane [3•], and MemProtMD [4•]), paired with continuously improved contemporary lipid force fields [5], have now enabled the construction and simulation of heterogeneous membrane systems of diverse lipid compositions.

Cholesterol (CHL), a sterol, and sphingomyelin (SM), a sphingolipid, are major lipids, besides glycerophospholipids,