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Molecular dynamics simulations of membrane proteins and their interactions: from nanoscale to mesoscale

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Molecular dynamics simulations provide a computational tool to probe membrane proteins and systems at length scales ranging from nanometers to close to a micrometer, and on microsecond timescales. All atom and coarse-grained simulations may be used to explore in detail the interactions of membrane proteins and specific lipids, yielding predictions of lipid binding sites in good agreement with available structural data. Building on the success of protein–lipid interaction simulations, larger scale simulations reveal crowding and clustering of proteins, resulting in slow and anomalous diffusional dynamics, within realistic models of cell membranes. Current methods allow near atomic resolution simulations of small membrane organelles, and of enveloped viruses to be performed, revealing key aspects of their structure and functionally important dynamics.

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Introduction

Membrane proteins play a key role in the biology of cells. Around 20% of genes encode membrane proteins, and they form a major class of drug targets. There has been considerable progress in the structural biology of membrane proteins resulting in over 2500 structures in the PDB, corresponding to over 700 distinct membrane protein species [1•]. Molecular dynamics (MD) and related molecular simulation approaches provide important tools which allow us to simulate both individual membrane proteins and more complex membrane systems [2]. Thus, MD simulations have become a valuable addition to the range of experimental structural and biophysical techniques for studying membrane proteins and their interactions with lipids [3].

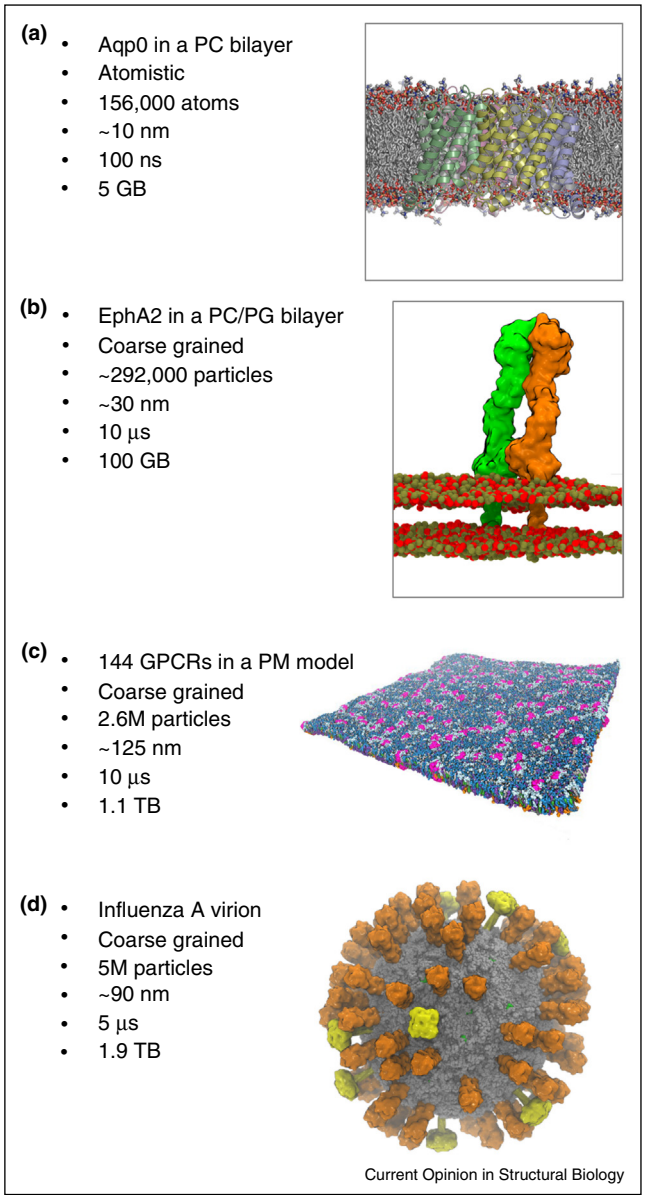
In this article we will review two major and complementary trends in molecular simulations of membrane proteins: (i) to probe protein–lipid interactions of single membrane proteins and (ii) to model more complex membranes containing mixtures of multiple lipid species and multiple copies of membrane proteins (Figure 1). It remains a challenge to develop biologically realistic models of cell membranes, but recent methodological advances enable an integrated approach to the problem, drawing together structural, biophysical and biochemical data into dynamic models which aid interpretation of structural and imaging data on membranes of cells and their organelles. We will survey these advances and a number of recent applications. We will therefore also discuss the development of mesoscale approaches which allow very large scale simulations, exploring membrane behaviour beyond the nanoscale and thus narrowing the gap between simulations and experiment.

Lipid–protein interactions at the nanoscale

MD simulations may be thought of as a computational microscope [4]: one may 'zoom in' to atomic resolution to examine detailed interactions of a membrane protein with water, ions, and lipids, or 'zoom out' to a lower resolution using for example coarse-grained (CG) [5••,6] simulations to address longer length and timescales, albeit with some loss of detail in modelling interatomic interactions. This approach has been successfully used to reveal the dynamic interactions of membrane proteins with lipids at the nanoscale [1•,7,8].

Simulations have been used to predict lipid interaction sites for a number of mammalian integral membrane proteins, providing detailed views of both the lipid annulus, as for aquaporin [9,10] (Figure 1a), and of interactions of specific lipids. A number of recent studies have characterised experimentally observed interactions between cholesterol molecules and G-protein coupled receptors (GPCRs), reviewed in [7], and have explored how such protein–lipid interactions may modulate the dimerization of GPCRs and its possible effects on receptor function (see e.g. [11]). In addition to interactions of membrane proteins with cholesterol, simulations have been used to identify binding sites for phosphatidyl inositol 4,5-bisphosphate (PIP_2) binding sites on ion channels, transporters, and receptor proteins. Thus, PIP_2 binding sites have been characterised for ion channels including Kir2.2

Figure 1



Overview of MD simulations of membranes. For each simulation granularity of the simulation (atomistic versus coarse-grained), the number of atoms/particles (including water, which are omitted for clarity from all of the images) in the simulation system, the approximate linear dimension of the simulation box, the duration of the production run simulation, and the resultant trajectory file size are given. **(a)** A single integral membrane protein (Apq0) in a phospholipid bilayer [10] (figure courtesy of Dr. Phillip J Stansfeld). **(b)** CG simulation of an EphA2 receptor dimer [21], with the lipids in brown (PC) and red (PG). Reprinted with permission from [21]. **(c)** A large plasma membrane (PM) model containing multiple copies of a GPCR. Seven different lipid species are present in an asymmetric bilayer (blues/grey/green/orange), with the GPCRs (S1P1 receptors) in pink. Reprinted with permission from [51•]. Copyright 2015 American Chemical Society. **(d)** The membrane envelope of a complete influenza A virion with the lipids in grey, hemagglutinin in orange, neuraminidase in yellow and the M2 channel protein in green [65••] (figure courtesy of Dr. Tyler Reddy).

[12] and Kv7.1 [13] potassium channels, and PIP_2 regulation of dopamine transporters has been explored [14•]. CG simulations have been used to compare interactions of PIP_2 molecules with the transmembrane and juxtamembrane domains of all 58 human receptor tyrosine kinases [15•], illustrating how high throughput approaches to membrane protein simulations [16,17] enable systematic surveys of families of membrane proteins and their lipid interactions. CG simulations have also been used to explore the free energy landscapes of PIP_2 and of glycolipids with the transmembrane domain of the EGFR [18].

More recent simulation studies of intact receptor tyrosine kinases (i.e. not simply the transmembrane domain) have revealed how lipid mediated interactions between the membrane surface and the ectodomains of the receptor may modulate the overall conformation of these complex multi-domain membrane proteins. Thus ectodomain/bilayer interactions may result in an asymmetric conformation of the EGFR dimer [19•], and these interactions can be influenced by receptor glycosylation [20••]. Ectodomain/bilayer interactions of the related EphA2 receptor are mediated primarily via anionic lipids, and may stabilize different conformations at the membrane of liganded versus unliganded forms of the receptor [21] (Figure 1b).

Simulations have also been used to explore the interactions with proteins of more 'specialized' lipids from mitochondrial and bacterial inner membranes such as cardiolipin (CL). CG-MD simulations have been used to assess binding sites for CL with cytochrome bc_1 [22] or cytochrome c oxidase [23••] and to estimate the free energy landscapes of these interactions [23••]. A comparable approach has been used to examine the interactions of cardiolipin with the ADP/ATP carrier ANT1 (Figure 2a). These studies confirm that such simulations can accurately reproduce lipid binding sites seen in the X-ray structure of this key mitochondrial transport proteins [1•,7].

Simulations have also been applied to bacterial membranes [24] and their proteins. For example, combined structural, biophysical and computational studies have explored the role of lipids in the mechanosensitivity of the *Escherichia coli* ion channel MscS [25]. Selective interactions of CL with UraA, a bacterial inner membrane transporter, have also been explored [26]. Realistic modelling of the more complex outer membranes of Gram negative bacteria has required development of models for lipopolysaccharide (LPS), the major constituent of the outer leaflet of these membranes [27,28]. Recent progress in both atomistic [29•] and coarse-grain [30] simulations of LPS enable studies of the interactions of a number of *E. coli* outer membrane proteins, for example FecA [31••], OmpLA [29•] and OmpF [32], with this complex membrane environment.