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Multiscale simulations of protein-facilitated membrane remodeling

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ABSTRACT

Protein-facilitated shape and topology changes of cell membranes are crucial for many biological processes, such as cell division, protein trafficking, and cell signaling. However, the inherently multiscale nature of membrane remodeling presents a considerable challenge for understanding the mechanisms and physics that drive this process. To address this problem, a multiscale approach that makes use of a diverse set of computational and experimental techniques is required. The atomistic simulations provide high-resolution information on protein-membrane interactions. Experimental techniques, like electron microscopy, on the other hand, resolve high-order organization of proteins on the membrane. Coarse-grained (CG) and mesoscale computational techniques provide the intermediate link between the two scales and can give new insights into the underlying mechanisms. In this Review, we present the recent advances in multiscale computational approaches established in our group. We discuss various CG and mesoscale approaches in studying the protein-mediated large-scale membrane remodeling.

1. Introduction

Biological membranes are multicomponent, self-assembled molecular sheets that surround the cells and its organelles. Besides separating the cell from the environment, compartmentalizing its components, and providing a mechanical protection, membranes play a crucial role in many biological processes that are vital for cell's survival and function. Examples of such processes are cell adhesion, cell signaling, and the selective transport of ions and organic molecules in and out of the cell (Conner and Schmid, 2003; McMahon and Gallop, 2005). In order to perform such a diverse set of functions, membranes possess inherently multiscale material properties. While exhibiting fluid properties at molecular scales, membranes behave like elastic sheets at length scales that are large compared to their thickness (Helfrich, 1973). As a result, membranes can exhibit a remarkable variety of shapes and morphologies (Lipowsky, 1991) dictated by their composition and the surrounding environment (Johannes et al., 2014; Lipowsky and Sackmann, 1995).

Membrane remodeling is facilitated by the action of proteins that bind peripherally to the membrane, partially insert their domains, or are fully included into the bilayer (McMahon and Gallop, 2005). These proteins induce a local asymmetry between the layers of the membrane, which generates spontaneous curvature. It is believed that a cooperative behavior of multiple proteins gives rise to large-scale membrane remodeling (Gallop et al., 2006; Jao et al., 2010; Saarikangas et al., 2009; Zimmerberg and Kozlov, 2006). Perhaps the most studied membrane remodelers are Bin/Amphiphysin/Rvs (BAR) domain proteins. They play a crucial role in many cellular processes, including clathrin-mediated and clathrin-independent endocytosis (Boucrot et al., 2015; Doherty and McMahon, 2009; Renard et al., 2015; Slepnev and De Camilli, 2000), T-tubule morphogenesis (Lee et al., 2002; Peachey and Eisenberg, 1978), cytokinesis (Arasada and Pollard, 2015), and many others. BAR domain is a crescent-shaped dimer with positively charged residues on its membrane-interacting surface (Frost et al., 2007; Gallop and McMahon, 2005). It is believed to generate curvature by a combination of (1) adhesive interactions with the membrane surface, (2) insertion of amphipathic helices, and (3) by forming three-dimensional ordered structures that mold membrane tubules (Simunovic et al., 2015).

The inherently multiscale nature of membrane remodeling makes it quite challenging to study the mechanisms behind these phenomena. Due to a strong coupling between microscopic properties of the membrane (e.g., diffusion rate and packing defects) and its macroscopic characteristics (e.g., bending modulus and bulk compressibility), membrane remodeling cannot be studied using a single computational technique; rather, it requires a hierarchical approach. Atomistic simulations can provide invaluable insights into direct protein-membrane interactions, see, e.g., (Blood and Voth, 2006; Blood et al., 2008; Cui et al., 2009; Lyman et al., 2010). However, the high computational cost limits their applicability beyond single protein simulations. Coarse-grained

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(CG) simulations, on the other hand, can reach biologically relevant time and length scales, owing to a reduction in the number of degrees of freedom achieved by grouping lipid and protein atoms into CG sites and, often, by an implicit treatment of the bulk solvent. The effective interactions between CG sites can be derived, at least mostly, from atomistic simulations (the so-called bottom-up approach) (Ayton and Voth, 2009b; Ayton et al., 2010; Izvekov and Voth, 2009; Srivastava and Voth, 2012, 2014). The resulting CG models can be very valuable for studying complex behavior of protein cooperation during membrane remodeling.

In recent years, a number of mesoscopic membrane models have also been developed. Those models are beyond the resolution of individual molecules, but rather employ quasi-particle description of the membrane, often complimented with the use of vector as well as other continuum or semi-continuum fields that can represent the inhomogeneity of membrane composition or protein concentration on the membrane (Ayton et al., 2007, 2009; Shiba and Noguchi, 2011; Sreeja et al., 2015).

This Review will survey the multiscale computational methods developed in our group for studying membrane-protein interactions and membrane remodeling (Ayton and Voth, 2009a, 2010b). The remainder of this article is organized as follows: Section 2 shortly presents different CG models of lipids and proteins and discusses the main results of the CG approach. Section 3 is dedicated to mesoscopic modeling. We present the Elastic Membrane Version 2 (EM2) model and recapitulate the key results that this model predicts. We also draw a brief comparison with mesoscopic models that have been developed by other groups. Section 4 contains the concluding remarks.

2. CG simulations of membrane remodeling by BAR proteins

Large-scale atomistic simulations have provided valuable insights into mechanisms of protein-membrane interactions and curvature coupling, especially by BAR proteins such as endophilin (Blood and Voth, 2006; Blood et al., 2008; Cui et al., 2009; Lyman et al., 2010). However, at present it is too challenging to expand those simulations to treat many proteins bound to the membrane. To reach the sub-cellular length and time scales (~μm and ~ms, respectively) that can be examined experimentally, various CG approaches have been developed in our group in recent years to model lipids (Ayton and Voth, 2009b; Izvekov and Voth, 2009; Lu and Voth, 2009; Srivastava and Voth, 2012, 2014) and proteins (Ayton and Voth, 2010a; Ayton et al., 2010; Srivastava and Voth, 2014). Those models rely on effective interactions between CG sites that represent the average interactions between the underlying atoms and the effect of the solvent. Moreover, the CG interactions are derived from the corresponding atomistic forces in a systematic way that ensures the consistency between CG and more detailed atomistic models.

While earlier CG lipid models were of relatively high resolution (10–15 CG sites per lipid (Izvekov and Voth, 2009; Lu and Voth, 2009)), lower-resolution models, namely, the hybrid analytic-systematic (HAS) model (Ayton and Voth, 2009b), the hybrid coarse-grained (HCG) model (Srivastava and Voth, 2012), and the charged hybrid coarse-grained (cHCG) model (Srivastava and Voth, 2014), were more successful in overcoming the barrier between simulations and experiments.

In the HAS approach each lipid is modeled as a single ellipsoid of revolution (see Fig. 1a), whose CG interactions with the surrounding lipids consist of an analytical and a systematic component. The systematic part gives the in-plane interaction potential that is derived using the multiscale coarse-graining (MS-CG) method (Izvekov and Voth, 2005; Noid et al., 2008a,b). MS-CG provides a rigorous framework for constructing CG models from data acquired in atomistic simulations using a variational principle. The analytical part models the lipid-lipid interactions for distances closer than 0.5 nm and for out-of-plane interactions, where the all-atom simulations do not provide a sufficient sampling. This part is given by a liquid-crystal Gay-Berne potential with a 3:1 ratio (Gay and Berne, 1981). Its parameters are determined empirically in order to obtain the desired elastic properties of the membrane (e.g., bending modulus and area compressibility), while the MS-CG potential captures the correct local properties (e.g., lateral diffusion and radial distribution function) (Ayton and Voth, 2009b). When combined with CG protein models (see below), an extra CG site is added, representing the lipid head group (see Fig. 1a), which only interacts with the protein (Ayton et al., 2010; Cui et al., 2013).

In the case of the HCG and cHCG methods, each lipid is represented by either three or four spherical CG sites (Fig. 2a). The general idea behind the parameterization of these models is similar to the HAS approach. At short distances, poorly sampled by all-atom simulations, an analytical Lennard-Jones potential is used. At longer distances, where the atomistic simulations provide good sampling, the MS-CG method is used to find the interactions between the CG sites. The cHCG method explicitly represents screened electrostatic interactions between the CG sites. The electrostatic potential is derived using the MS-CG method, by dividing the non-bonded interactions into electrostatic and van der Waals (vdW) contributions. Also, a more general Lennard-Jones-like function is used for the analytical potential in the case of the cHCG method. HCG and cHCG models of single or multicomponent lipid membranes successfully capture both the short-range properties, namely, the radial distribution function and the z-density, and the long-range properties, such as area compressibility, bending modulus, and the lateral stress profile (Srivastava and Voth, 2012, 2014).

Area compressibility and bending modulus are key indicators of the quality of a membrane model. For HCG model described above, the area compressibility modulus of pure DLPC and DOPC lipid systems have values of 310 ± 6 dyn/cm and 254 ± 9 dyn/cm, respectively. The DLPC value is consistent with 461 ± 6 dyn/cm value obtained from all-atom simulations that are known to overestimate the area compressibility modulus (Poger and Mark, 2009), and the DOPC result is within 188—265 dyn/cm experimental range (Rawicz et al., 2000; Tristram-Nagle et al., 1998). While the pure DLPC and DOPC values are nearly comparable, much smaller value is obtained for mixed DLPC/DOPC lipid system 165 ± 12 dyn/cm, consistent with recent experiments (Rodowicz et al., 2010). This reduction of area compressibility modulus for mixed systems is also consistent with values of 97 dyn/cm and 121 dyn/cm obtained for 1:1 and 3:1 DOPC/DOPS systems, respectively, from the cHCG model. The bending modulus for pure DLPC, pure DOPC, and mixed DLPC/ DOPC systems are estimated to be approximately 15 k_BT, 18—19 k_BT, and 7 k_BT, respectively, from HCG system. For the mixed DOPC/DOPS system values of 15.5 k_BT and 15.9 k_BT are obtained for 1:1 and 3:1 compositions. Those values are generally consistent with expected range from a few k_BT to tens of k_BT for lipid bilayer (Marsh, 2007). Moreover, the individual values are typically within 1—2 k_BT of known experimental measurements, as detailed in correspond HCG and cHCG papers (Srivastava and Voth, 2012, 2014).

The lipid models described above can be used to carry out long time scale simulations of membrane sheets or liposomes that can contain even millions of lipids. Here, we will highlight the application of these models in studying membrane remodeling induced by BAR proteins. Similar approaches can be used to study the mechanism of other membrane-curving proteins.

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