Simulating Protein-Mediated Membrane Remodeling at Multiple Scales

Mijo Simunovic and Gregory A. Voth

Abstract The reshaping of the cell membrane is integral in many important cellular pathways, such as division, immune response, infection, trafficking, and communication. This process is generally modeled by considering lipid membranes to be thin elastic sheets that resist bending and stretching deformations. However, biological membranes are much more complex, as the macroscopically observed behavior of the membrane is deeply connected to the underlying atomic-level interactions between proteins and lipids. Computational methods can be developed to tackle this complex and innately multiscale phenomenon, as they can model the behavior at both the molecular and the macroscopic levels. In this chapter, we discuss the general mechanisms of membrane curvature generation and computational tools developed and applied to study this problem. We focus especially on finite-temperature simulation methods that are designed to model the complex behavior of the system. We review recent efforts in multiscale simulation designed to study the large-scale membrane reshaping by proteins.

Keywords BAR proteins · Multiscale simulations · Coarse-grained simulations · Mesoscopic simulations · Membrane curvature · Lipid model · Computational modeling

1 The Multiscale Nature of Lipid Membranes

Structural features of lipid membranes are observable at multiple scales. In other words, to understand how lipids form membranes of various shapes, we need to approach the problem from molecular, mesoscopic, and macroscopic points of view. Let us first consider the molecular perspective. The key ingredients of biological membranes are the phospholipids. Chemically speaking, they are considered to be

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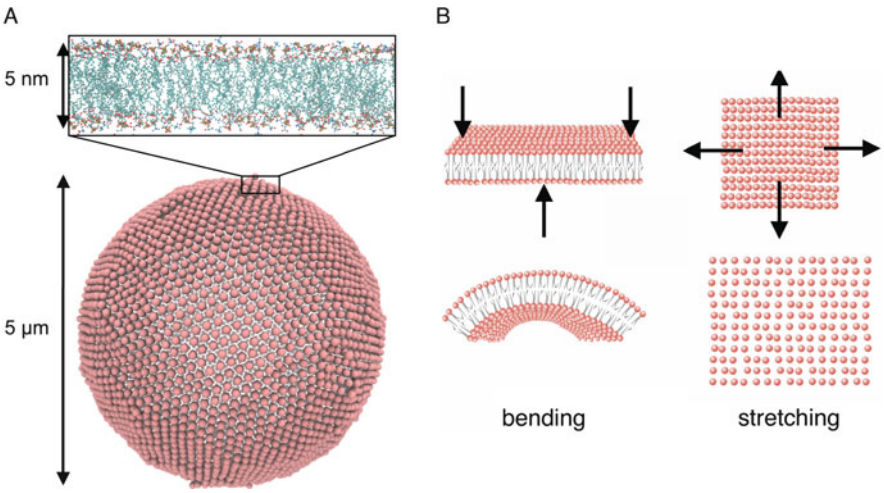

Fig. 1 The multiscale nature of lipid membranes. (**a**) Separation of scales: a bilayer spans microns in length and width where it is governed by macroscopic mechanics, while at the level of its thickness (inset), it only spans two molecules where it is governed by hydrophobic and polar interactions. (**b**) A membrane is modeled as a thin elastic sheet that resists bending and stretching deformations

amphipathic molecules, because their phosphate head group is polar, i.e., it attracts water, whereas their lipid tails are hydrophobic, i.e., they attract apolar molecules [1]. The consequences of such interactions are that when phospholipids are mixed with water, lipid tails stick to one another and the hydrophilic moieties are solvated by water. Various geometries can accommodate such interactions, but the most relevant to biology is a lipid bilayer (Fig. 1) [2].

Although the thickness of the bilayer only spans two molecules, lipids form macroscopic assemblies in lateral dimensions, and understanding their behavior at this level demands a macroscopic point of view (Fig. 1a). At larger scales, the membrane behaves like an elastic sheet, resisting bending and stretching deformations (Fig. 1b). Its long-wavelength dynamics is seemingly unconnected to its molecular nature; however, the two scales actually strongly couple [3]. How is this so? Imagine immersing a bilayer patch in water. The hydrophobic repulsion at the interface of water and lipid tails gives rise to line tension that works to minimize the edge of a bilayer. This molecular interaction has a macroscopic impact as it forces the membrane into a closed surface. The interactions among lipid molecules set the preferred area they occupy, giving rise to surface tension, i.e., the membrane's elastic resistance to stretching. Furthermore, line and surface tension compete with the elastic energy associated with the cost of bending the membrane. Finally, a result of these opposing forces—that operate at different scales—gives biological membranes a wide range of geometries [3].

The elastic description of the cell membrane has been remarkably successful in explaining the physical basis of large-scale membrane behavior, and it has

provided a very useful analytical framework for analyzing and understanding the experimental data. However, biological membranes are far more complex than thin elastic sheets. First, they are fluid, which means that they do not resist shearing—sliding of layers past each other—and they cannot tear or form sharp corners, unlike solid bendable materials. Second, membranes can contain hundreds of different components that are likely not homogenously mixed along the length of the cell membrane. Therefore, predicting its actual phase behavior seems nearly impossible. Lastly, the cell membrane is not at equilibrium, making the thermodynamic treatment all the more difficult.

Accounting for all the complexities and the innate multiscale character of a cell membrane in modeling its behavior is a daunting task. An approach uniting molecular, mesoscopic, and macroscopic scales is essential in accessing a fuller scope of membrane phenomena in biology. In this chapter, we describe computational methodologies used to study lipid membranes, specifically focusing on methods applied to investigate how proteins can change membrane shape.

2 The Reshaping of Biological Membranes

It has been widely accepted that membrane curvature plays significant roles in the cell. On the one hand, cells use curvature on larger scales to form complex intracellular structures or for motility of the whole cell. For example, the high curvature of the inner mitochondrial membrane significantly adds to the total membrane area (compared to a flat membrane enveloping the same volume), which is why the mitochondrion can host an enzymatic power source of the cell. On the other hand, membranes can be temporarily curved—usually on sub-μm scales—enabling dynamic processes, such as communication and trafficking [4].

How is membrane curvature generated in the cell? Thermal fluctuations give rise to membrane curvature, however only transiently, as the energy associated with random fluctuations is an order of magnitude lower than the bending stiffness of biological membranes [5–7]. The most commonly understood mechanism of generating curvature is by imposing an asymmetry into the bilayer, either by lipid composition or by protein binding. Consider enriching one membrane layer with a non-cylindrically shaped lipid, such as sphingomyelin or phosphatidylethanolamine. The bulky head of sphingomyelin will force one layer to expand and hence generate curvature (the first cartoon in the upper left of Fig. 2). Another way lipids may induce curvature is by phase separation. The energy resulting from the formation of edges between domains will tend to minimize, which is achieved either (a) by coalescence of like phases or (b) by squeezing the domain boundary, which results in budding [8]. Numerical calculations have been carried out to understand the morphological consequences of phase-separated vesicles, and they have resulted in a very rich shape diagram of such systems. The ultimate shape of the membrane depends on the size of domains, the elastic properties of the membrane, as well as surface and line tensions [9–17].

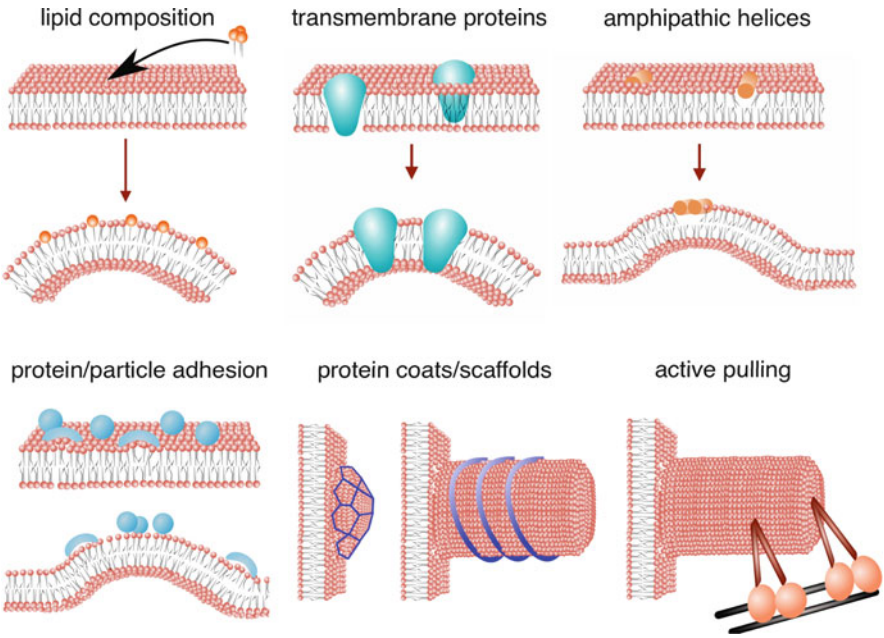

Fig. 2 Mechanisms of generating membrane curvature

Although lipids can affect the shape of membranes, the main role of curvature generators in cells belongs to proteins. It has been shown that conically shaped proteins spontaneously redistribute into membrane tubules, likely because their packing is more efficient in curved membranes [18]. In light of this discovery, the accumulation of conically shaped proteins, such as the nicotinic acetyl receptor [19] and the voltage-gated potassium channel [20], in principle could induce membrane curvature (Fig. 2).

Another way proteins may induce curvature is by inserting their amphipathic domains into the membrane [21]; however, this process is more complicated to understand with simple shape arguments (Fig. 2). Theoretical calculations have demonstrated that the magnitude of spontaneous curvature depends on the insertion depth in a non-monotonous way, which means that a deeper insertion does not lead to more curvature. Instead, there is a maximum, achieved at the insertion depth at approximately one-third of one layer [22, 23]. Many cytosolic and peripherally binding proteins contain amphipathic helices. Apolipoproteins, for example, solubilize lipids, including cholesterol, for their transport through the blood [24, 25]. Many proteins involved in endocytosis contain amphipathic helices, such as epsins and Bin/amphiphysin/Rvs (BAR) proteins, implicated in various forms of membrane remodeling [26, 27].

The peripheral binding or adhesion of proteins and particles can also lead to membrane curvature (Fig. 2). The mechanisms of curvature generation by such

proteins are even more complex and seem to tightly depend on the shape of the proteins, their surface density, and the material and morphological properties of the membrane [27, 28]. Several simplified mechanisms have been proposed: (1) each bound protein or particle alters the underlying lipid organization [29, 30], (2) proteins form a three-dimensional network that imposes a shape as a mold or a scaffold (e.g., clathrin or dynamin; see Fig. 2) [31, 32], and (3) crowding of bound particles forces membrane bending to maximize the distance between particles. An entropy-driven mechanism has also been proposed, based on a computational study showing that polymers grafted on the membrane may induce curvature [33, 34]. In this case, the loss of conformational entropy is compensated by pushing away the underlying surface from the polymers. The calculations were later experimentally demonstrated by tethering DNA and proteins on the membrane [35, 36].

Finally, membrane can be actively reshaped by an external pulling force (Fig. 2), such as with the cytoskeleton machinery and molecular motors [32]. For example, the polymerization of actin filaments gives rise to many curved cellular geometries, such as filopodia, pseudopodia, and axonal growth cones [37]. In vitro reconstitution has demonstrated that molecular motors, such as kinesins and myosins, can attach to the membrane and, walking along cytoskeletal filaments, they can extrude a tubule from a vesicle [38, 39].

Let us briefly focus on the superfamily of BAR domain proteins, key regulators of cell membrane curvature [40]. They have been implicated in many important cellular tasks, from generating membrane curvature and maintaining complex membranous geometries to helping assemble multiprotein machineries in a number of membrane-remodeling phenomena [26]. Numerous experiments have isolated the effects of BAR proteins, e.g., with overexpression in the cell, chemical targeting of BAR proteins to specific organelles, or in vitro reconstitution, all demonstrating that BAR proteins are powerful membrane remodelers [41–45]. Although BAR proteins are structurally quite diverse, they all contain a banana-shaped BAR domain [42]. To make matters even more complicated, the BAR domain itself varies in size, charge, and the magnitude of intrinsic curvature from member to member (Fig. 3). The membrane-binding region of this domain is lined with positively charged residues, so they are highly reliant on negatively charged lipids, such as phosphatidylserine and phosphatidylinositol 4,5-bisphosphate (PIP_2). Most BAR proteins also contain an N-terminal amphipathic helix, thus termed N-BAR proteins, which enhance their curvature-sensing and curvature-generating capabilities (Fig. 3, first structure on the left).

The way N-BAR proteins interact with the membrane is a combination of adhesion of an anisotropic BAR domain, the shallow insertion of amphipathic helices, and under some conditions, the scaffolding by a BAR oligomer [27, 28, 31, 46, 47]. BAR proteins often interact with other proteins, such as with molecular motors in scission of membrane nanotubes [48], making this problem very challenging. Many of these phenomena have been addressed by multiscale computer simulations, and we will outline these results below.

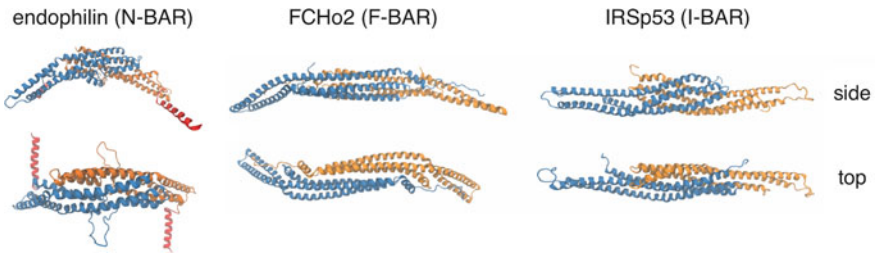

Fig. 3 Ribbon structures of various BAR protein dimers—the functional protein unit—each monomer colored differently. The N-terminal helices in endophilin (colored red) are added by hand, as they were not resolved in X-ray structural imaging. Top views along the bottom line of images represent viewing from above the bilayer surface

3 Computational Simulations of Biomembranes

Theoretical and computational approaches to studying biological phenomena have seen appreciable advancements in the past decade, allowing detailed structural and thermodynamic descriptions of fundamental cellular processes, such as protein folding, lipid vesicle formation, and large-scale structural rearrangements of macromolecules. Computational simulations are particularly attractive as they provide direct visualization of the complex evolution of the system, along with a wealth of thermodynamic and high-resolution structural data. In addition, simulations give insights into the distribution and time-dependent properties of the system and not just their average as in most experimental techniques [49].

The basic steps in computational modeling of a biomolecular system are (1) choosing the resolution of the model and the number of degrees of freedom (the so-called level of theory), (2) calculating the forces between particles (the so-called force field), and (3) simulating the movement of particles (i.e., generating a trajectory).

The choice of level of theory depends on the resolution of the system and the number of degrees of freedom we wish to simulate. For example, if we are interested in the submolecular details of the structure of a protein, we will opt for an atomic-level simulation. On the other hand, if we wish to understand processes that do not rely on specific atomic interactions, such as the large-scale remodeling of lipid membranes, we will prefer mesoscopic models. When considering the level of theory, we also need to be aware that simulating systems with many degrees of freedom is computationally very costly. Most biological problems involve many atoms so we are often forced to compromise resolution for computational feasibility. In this chapter, we will focus on three levels of theory relevant to biological membranes: (1) atomic, (2) coarse-grained (CG), and (3) continuum or mesoscopic. The scheme in Fig. 4 depicts scales associated with these three levels of theory. It also shows the flow of information from atomic to continuum descriptions, and back, in the context of N-BAR-mediated remodeling (The reader should not focus

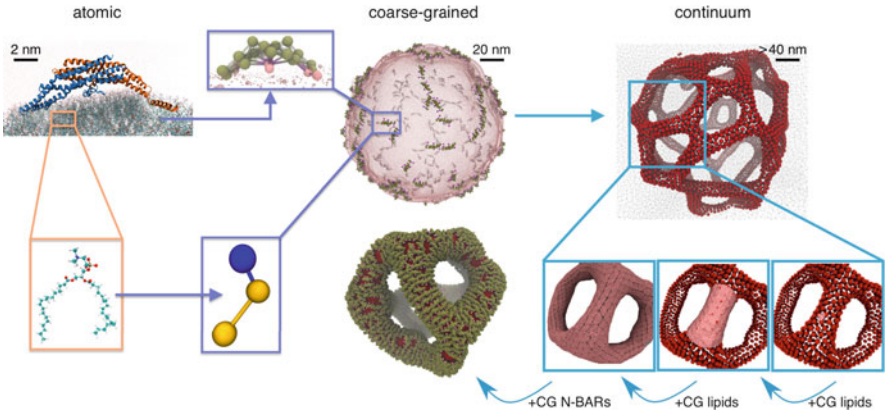

Fig. 4 A scheme of multiscale simulations of membrane remodeling by N-BAR proteins. Arrows pointing to the right represent coarse-graining (from atomic, to CG, to mesoscopic). Arrows pointing to the left depict the reverse approach—fine-graining—in which information at low resolution is used to build a model of higher resolution (see text)

on the meaning of the particular membrane phenomena shown in the figure at this point; we will refer to this scheme later in the chapter).

The dynamics of particles can be simulated in multiple ways. Molecular dynamics (MD) is the most commonly used method in biological simulations. In MD, the movement of particles is simulated by numerically integrating Newton's equations of motion, wherein the force on each atom is calculated based on the interactions defined by the force field. MD is particularly attractive because it is computationally feasible and it gives, in principle, both the static and the time-dependent properties of the system [50]. In Monte Carlo (MC) simulations, new configurations are generated by a random movement of particles, in a way that ensures the Boltzmann distribution. The strength of MC is that it does not require smooth derivatives of the potential and, considering that it permits unphysical random moves, it helps the system sample more space than allowed by MD for the same computational effort. However, it cannot be used to study the time-dependent dynamics of the system [50].

Smoothed particle hydrodynamics (SPH) is a method used for simulating continuum models based on Newtonian hydrodynamics, although originally designed to study astrophysical problems [51, 52]. SPH is particularly attractive because it discretizes continuum equations, which allows simulating complicated morphologies at the mesoscopic scale [53]. A similar method, called dissipative particle dynamics (DPD), supplements Newton's equation of motion with a dissipative and a random force [54, 55]. The combination of forces helps to conserve the momentum and the temperature of the system. Unlike MD and MC methods, SPH and DPD are by nature approximate. They are not necessarily designed to yield correct equilibrium properties; however, they reproduce the hydrodynamic behavior at large scales,

sufficient for understanding the long-wavelength behavior of the membrane [50, 56, 57].

Each modeling method comes with its own advantages and challenges. Combining different levels of theory—in what can be called the multiscale approach—can significantly extend the simulation timescale, while keeping the resolution as high as possible. A notable example is combining the quantum mechanics with the molecular mechanics (QM/MM) applied to modeling chemical reactions in the enzyme's active site [58]. QM/MM modeling elucidates how electron-level processes (i.e., the change in chemical bonding) couple with the atomic-level dynamics of the protein. Another approach in multiscale modeling is using the calculations from atomic-level simulations to estimate forces in lower resolution models, such as in CG or continuum models [59]. This approach is especially appropriate in studying membrane-remodeling phenomena where the interactions at the molecular scale communicate with much larger scales.

The use of multiscale simulations has exploded in the past decade, and it has seen tremendous success in modeling complex systems in biology and materials science. The development of multiscale models has had such an important impact on modern research that Martin Karplus, Michael Levitt, and Arieh Warshel—pioneers in certain early aspects of multiscale simulation development—received the Nobel Prize in Chemistry in 2013 [60–63].

4 Atomic Modeling

In the atomic-level (also called atomistic or all-atom) models, each atom (or in some cases a small united subset of atoms) is represented with a sphere of defined volume, mass, charge, and other physical properties (note the atomic representations of a lipid and a BAR domain in Fig. 4, left). The interactions between atoms are derived from quantum mechanical calculations or empirically fit from experimental measurements. One typically casts these interactions in a simple analytical form and divides them into (a) bonded and (b) nonbonded terms. Bonded interactions maintain the equilibrium bond length, the angle between neighboring bonds, and, often, a dihedral angle between four atoms, all modeled as a harmonic potential. Nonbonded interactions describe electrostatic, polar, and van der Waals interactions, usually modeled respectively with a Coulomb and a Lennard-Jones potential [49].

A major limitation of all-atom MD simulations is that they become computationally very expensive if the system exceeds a million atoms, roughly corresponding to a large protein surrounded by a box of water. With a recent development of high-power computing and efficient parallelization of MD computer codes, it has become possible to access microsecond dynamics of large biomolecular complexes with a computer. Notable examples include simulating entire viruses, namely, the tobacco mosaic virus [64] and the HIV-1 capsid [65]. These simulations have shown to be complements to experimental biology, as they have provided a more detailed insight into the structural properties of viral particles than cryo-electron microscopy, X-ray

crystallography, or NMR. Additionally, atomic-level MD simulations can elucidate the electrostatic environment of proteins and show the short-scale conformational dynamics of its subdomains. However, the range of time and length scales that such simulations sample is very small compared to the relevant scales in the cell and in many in vitro experiments.

Simulating membranes embedded with proteins thus tends to be more challenging. The interactions and the initial configuration in protein-membrane systems can be more complicated to model. Moreover, lipid molecules comprise a higher number of interactions for the same volume than the water-solvated protein, which makes these simulations more costly. For these reasons, simulating membrane-related phenomena at atomic resolution demands significant computational power or clever tricks that artificially enhance the sampling. For example, researchers have developed a computer architecture solely purposed for generating milliseconds-long trajectories of all-atom MD simulations [66]. They have demonstrated conformational dynamics of a transmembrane protein receptor stimulated by ligand binding [67, 68]. In addition, noteworthy efforts have been made to elucidate the way ion channels interact with the membrane and how they respond to chemical, electrical, and mechanical signals [69–73]. Even though these studies typically access much shorter timescales than in experiments, they have proven to be valuable to structural biology, helping to reveal the interactions of transmembrane proteins with the membrane and the mechanism by which they operate at the atomic level, which is in turn a difficult task for experiment alone.

In the aforementioned studies, atomic simulations mostly addressed the dynamics of the protein. The focus of this chapter is discussing the dynamics of the membrane. Several studies have used atomic-level MD simulations to study how BAR proteins deform membranes. Recall that BAR proteins couple with membrane curvature in the course of trafficking events such as endocytosis [27, 40, 47]. Simulations of the representative members of the N-BAR and F-BAR subfamilies have shown that these proteins can bend membranes, generating 20–35 nm in radius of curvature in only 25–100 ns of the simulated time (Fig. 5) [74–76]. According to subsequent simulations, however, crucial for bending the membrane are the ionic interactions between positively charged residues of the protein and the negatively charged lipids in the bilayer, as well as the screening of those interactions by the solvent [77]. In other words, these proteins are reliant on general ionic interactions, as opposed to, for instance, some specific stereochemistry [75, 78].

These works have also demonstrated that amphipathic helices of N-BAR proteins play an important role in membrane remodeling at the atomic scale. If the helices are not partially inserted (or wedged) into the bilayer, the binding of the N-BAR domain is significantly reduced, often leading to its dissociation from the surface. The loss of binding affinity may be compensated by a higher concentration of highly charged PIP_2 lipids, although PIP_2 does not fully recover the membrane-bending power of the N-BAR protein, at least not at a nanosecond timescale. With this result, we are tempted to conclude that helices are key factors for bending the membrane. However, isolated helices could only bend the membrane if their surface density was significantly increased (Fig. 5) [78]. Interestingly, in addition to surface density,

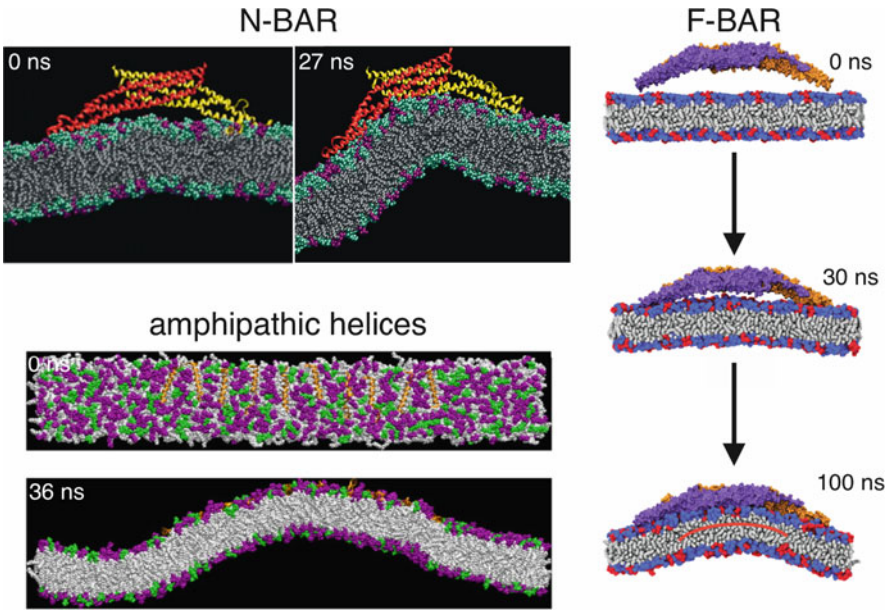

Fig. 5 Membrane remodeling by proteins modeled by all-atom simulations. Shown are initial and final snapshots of all-atom simulations of lipid bilayers embedded with N-BAR, F-BAR domains, or isolated amphipathic helices of an N-BAR domain protein. Approximate lipid-to-protein ratio for systems with N-BAR, F-BAR, and amphipathic helices, respectively: 70, 30, and 150. Note that a higher concentration of proteins is required to remodel a membrane with amphipathic helices (see text). Membrane composition in all: 30% DOPS, 70% DOPC. Figures adapted from (N-BAR) [75] copyright (2006) National Academy of Sciences; (F-BAR) [76] licensed under CC BY; (amphipathic helices) reprinted from [78] with permission from Elsevier

the orientation of the additional small helices at the dimerization interface (termed insert helices) with respect to the axis of the BAR domain also determines the magnitude of curvature [79]. The combined result indicates that both modules in N-BAR proteins—the BAR domain and the helices—are key for efficient remodeling of the membrane.

Despite the growth in computer power and parallel MD algorithms over the past 10 years, simulating large-scale membrane-remodeling phenomena at atomic resolution is still beyond reach. In fact, since the original simulation of membrane curvature induced by an N-BAR protein in 2006 [75], larger-scale all-atom MD simulations of this problem have not been reported. This comes as no surprise as membrane-remodeling phenomena involve many proteins at the mesoscopic scale and they typically comprise billions of atoms [32]. To understand these processes by a computational simulation, we need to significantly decrease the simulated number of degrees of freedom.

5 Coarse-Grained Modeling

The sheer size of membrane-remodeling events makes it too difficult a challenge to simulate at atomic resolution. Even if the system size is computationally tractable, timescales accessible by all-atom MD simulations are often insufficient to provide useful thermodynamic information at the mesoscopic level. More importantly, processes such as endocytosis invoke certain long-wavelength aspects of the membrane whose description does not even require modeling the atomic-level interactions.

Coarse-graining is a process of reducing the number of degrees of freedom by representing many atoms with a single CG particle [80]. Note on the left side in Fig. 4 the depiction of coarse-graining of lipid and N-BAR domain molecules. The first choice in coarse-graining is determining the level of resolution, i.e., how many CG particles to use to describe a molecule, such as a lipid. Figure 6 illustrates a lipid molecule (or a membrane patch) at different levels of resolution, each further discussed below. Clearly, low-resolution models will give access to much larger systems due to their computational efficiency, although deriving their effective

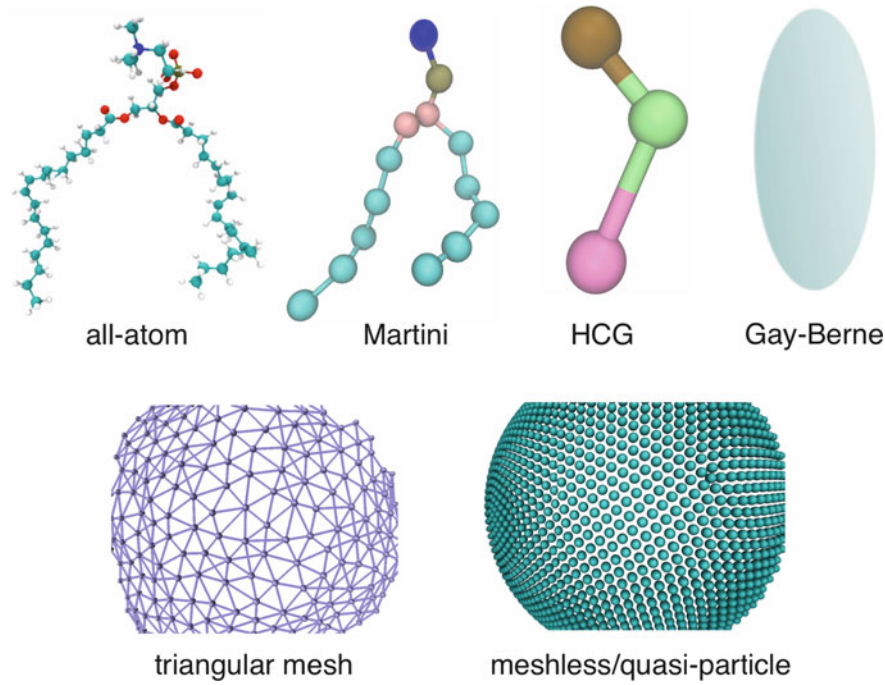

Fig. 6 Various lipid models. Top panel represents one lipid molecule in different degrees of resolution or coarseness (left to right—from finest to coarsest). Bottom panel shows a cutout of a triangular mesh and meshless membrane models (the latter may also represent a quasi-particle continuum model). Each model is described in the text. Image of the triangular mesh courtesy of Andela Saric

potentials in a systematic fashion can be more difficult. Eliminating the water molecules by making their contribution implicit, both in the potential itself and by adding stochastic terms into the dynamics (e.g., Langevin dynamics), can appreciably decrease the computational cost. No matter the approach, a good lipid CG model should as best as possible reproduce the molecular, the mesoscopic, and the macroscopic properties of the membrane, namely, (a) fluidity, (b) phase behavior, (c) structural factors (e.g., radial distribution functions), (d) material properties (e.g., bending stiffness and area compression modulus), and (e) fluctuation spectrum. However, the lateral diffusion rate of lipids is never reproduced in CG modeling, because the averaging of high-frequency motions leads to an artificially accelerated timescale, a drawback of all coarse-graining techniques, unless the effects of the missing degrees of freedom in the CG model are explicitly accounted for in the dynamics [81]. Therefore, it is important to note that most CG MD simulations—albeit providing an apparent time-dependent dynamics of the system—cannot easily be used to predict the actual timescale of molecular processes [82].

5.1 CG Lipid Models

The most difficult task of coarse-graining is accurately mapping the underlying atomic interactions onto their CG representation. There are two contrasting ways of generating a CG force field: (1) a bottom-up approach in which the forces are somehow derived from all-atom simulations and (2) a top-down approach in which the interactions are approximated by matching with experimental measurements [80]. Let us consider some CG lipid models before discussing important computational studies of membrane remodeling. First, we focus on the bottom-up models. Multiscale coarse-graining (MS-CG) methodology is a bottom-up approach that uses a rigorous statistical mechanical framework in designing a CG force field [59]. As it uses a variational calculation, in principle, MS-CG yields the optimum CG force field relative to the exact many-body potential of mean force in the CG variables [83, 84]. Important caveats of the model are that (a) it can be numerically challenging to solve the equations for complex systems, (b) it requires a reasonable sampling of the configurational space by an atomic-level MD simulation, and (c) the resulting interactions may be too complex for seamless transferability to other physical systems because, in fact, the concept of transferability of rigorously derived CG interactions from one system to another is not yet founded on clear physical principles. The MS-CG method has been used, e.g., to develop explicit solvent [85] and solvent-free models [86, 87] of phospholipids and cholesterol, in which the lipids were reduced to ten CG sites. Simulations of a binary mixed bilayer using these models have reproduced the fluidity and the structural parameters of the membrane; however, they have not yet been used to study membrane remodeling (Fig. 6).

Simulating large-scale shape changes requires more aggressively coarse-grained lipid models due to the large length and time scales involved. Bottom-up development of highly coarse models is often compromised by insufficient sampling in atomic-level simulations, especially in the short-range interactions. A way to overcome this problem is by supplementing the MS-CG forces, derived from well-sampled atomic-level simulations, with analytical functions that can be based on some known physical behavior at short range. This hybrid approach has been used to develop a solvent-free single-site lipid model [88] in which a lipid molecule was mapped onto an ellipsoidal particle, whose interactions were modeled using an anisotropic Gay-Berne potential (Fig. 6) [89]. A similar approach has been applied to develop a more flexible and physically accurate three-site hybrid CG lipid model (called HCG) using more traditional spherical CG sites [90]. Both models successfully reproduced the structural properties of bilayers at the molecular level and all of the elastic properties of the membrane at the mesoscopic level. Importantly, both models have been used in studying membrane remodeling (see more below). The HCG model has recently been expanded to model the effects of charged lipids separately from the van der Waals interactions [91]. This improvement will allow for quantitative insights into the electrostatic properties in protein-membrane systems.

A number of bottom-up methods, which are similar in spirit, derive the CG force field not by calculating a multi-body potential of mean force for the CG sites, but instead by relying on one reduced statistical distribution of the system, such as the radial distribution function, the distribution of intramolecular distances, or, say, the stress profile (e.g., [92, 93]). The effective CG potential is computed numerically, using the inverse Boltzmann [94] or inverse MC methods [95]. The inverse MC approach was used to derive CG lipid models, comprising one to ten sites, which reproduced correct structural and phase behavior at the 100-nm length scale [96–98]. However, in making of some of these models, external constraints were applied to reproduce the experimentally measured elastic parameters. By adding an effective cohesion term mimicking the hydrophobic effect, a lipid model was developed that can reproduce both the correct structural and the elastic membrane parameters [99]. The underlying modeling method was the iterative Boltzmann inversion used to match to atomic-level parameters. Its relatively high resolution (16 sites per lipid) makes it less suitable for studying long-wavelength phenomena, but it is useful when the chemical specificity of lipids is essential. Of note, a poor choice of the underlying atomic-level configuration (such as starting from an unphysical or biologically irrelevant phase of a bilayer) can adversely affect the bottom-up CG modeling [100].

The basic philosophy of a top-down coarse-graining approach is to fit the CG interactions so as to reproduce certain experimental observations, usually the self-assembly into a bilayer, and such membrane models date almost three decades [101]. A top-down model that has become popular in recent years is the MARTINI model (Fig. 6) [102]. Here, CG interactions—cast in the form of analytical functions—are fit to some bulk thermodynamic data, namely, the oil/water partitioning free energy. Due to the empirical nature of MARTINI models, they do not have a connection to the real atomistic forces that underlie each CG particle; however, they provide a

flexible framework for qualitative modeling of large-scale biomolecular processes. As the MARTINI model is built upon the amphipathic affinities, it seems suited to studying lipid systems. Indeed, MARTINI lipids have been shown to spontaneously form bilayers [103]. However, the downside of such models are that (a) not all physical interactions can be used in their parameterization and (b) the model could unintentionally bias the experimental observation that it tries to reproduce.

Some CG models use more sophisticated functional forms to describe the interactions among particles [104–106], and, although these CG lipids readily assemble into membranes, their elastic parameters are not necessarily in the experimental range. Driven by this issue, other methods are designed ensuring that the bending stiffness of the membrane is correctly reproduced, usually via tunable parameters [107–109].

Finally, there are CG models wherein each particle represents more than one lipid molecule (see bottom panel in Fig. 6). In one realization of such models, the membrane is described as a thin elastic sheet composed of a mesh of interconnected particles. Triangulating the mesh provides a computationally simple and rapid way of calculating elastic energies associated with bending and stretching deformations [110–114]. Typically, the forces are calculated using a form of a Helfrich–Canham Hamiltonian [6, 115]. Mesh-free models provide a more flexible membrane surface, and they can simulate deformations inaccessible by imposing an unbreakable meshwork (e.g., pore formation). The abovementioned self-assembly model from 1991 is an example of such a model [101], but there are many other more recent examples, which employ a combination of attractive and repulsive potentials [116–120]. These models rarely provide the correct phase behavior of the membrane, and they are devoid of molecular-level information (e.g., lipid diffusion). However, they are suited for simulating the very long-wavelength behavior, owing to their adjustable resolution and the well-reproduced mechanical parameters.

It is difficult to argue whether the bottom-up or the top-down approach is superior in practice, as each comes with its own challenges. What is important is that a CG model needs to be predictive—at least in a semi-quantitative manner—and in order to do so, it would seem to need connections to real physics. Otherwise, CG simulations run the risk of becoming solely an animation, or worse, a visualization tool for biomolecular behavior.

5.2 CG Simulations of Membrane Remodeling

Let us first consider some studies that used CG models to simulate biological membranes. Simulations employing the relatively high-resolution MARTINI or derivatives of the MARTINI model have revealed large-scale dynamics at the level of a single protein molecule, such as the conformational change of proteins and the local membrane deformation. For example, CG MD simulations have shed light on the behavior of voltage- and tension-gating of ionic channels [121–125] and the way in which embedding of small peptides couples with the local membrane

curvature [126, 127]. Furthermore, simulations of large lipid bilayers with a complex composition have revealed a transient formation of lipid nanodomains [128]. Interestingly, according to MARTINI simulations, certain lipids become enriched in regions of higher curvature [129], a phenomenon called lipid sorting [28]. The resolution of the MARTINI model is suitable for addressing questions that require the knowledge of lipid specificity, and for processes that involve a few protein molecules, such as the protein-mediated fusion [127, 130, 131]. They are still too finely grained (i.e., their resolution is too high) to address the many-protein behavior on the membrane leading to large-scale remodeling.

Three-site and lower resolution CG lipid models, on the other hand, are better suited for simulating long-wavelength phenomena while retaining a quasi-molecular level of detail. A simulation employing a tunable CG lipid model demonstrated that membrane curvature can give rise to strong attractions among particles adhered to the membrane—in their case, circular caps and capsids. The consequence of these interactions is the initial clustering of particles, followed by their engulfment and transport through the membrane [132]. This study implies that the attraction of membrane-bound objects, such as viruses and nanoparticles, may be a very general mechanism. The only requirement is that the object strongly curves the membrane locally [133]. The assembly of the capsid itself—albeit partially promoted by membrane curvature—can actually be impeded by diffusion barriers formed by very strong membrane deformations, as revealed by CG simulations [134, 135]. Interestingly, the formation of microdomains assuages these obstacles, helping the capsid fully assemble and generate a membrane bud [135].

Let us now return our focus to BAR proteins. As was discussed in the previous section, atomic-level MD simulations have shed light on the detailed interactions that give rise to the nanometer-scale membrane curvature. Since BAR proteins couple with much larger scales associated with membrane reshaping in the cell, there is high motivation to simulate their behavior with CG simulations. It should be kept in mind that modeling proteins as particles of arbitrary shape may not be adequate to capture the relevant phenomena, not even in low-resolution models. Proteins are more complex than particles: (1) because they are comparable in size to membrane thickness, (2) their shape is not simple, (3) the way they interact with the membrane is typically multimodular, and (4) proteins may undergo conformational changes. BAR proteins are especially challenging to theorists, as they often have both the shallow insertion domain and the adhesive component; therefore, it is difficult to correctly account for all these interactions.

Several studies have employed a three-site bottom-up CG lipid model to study the interaction of N-BAR proteins with the membrane. The internal conformations of the N-BAR domains were described using an elastic-network approach, which approximates the vibrational fluctuations of biomolecules using a network of elastic bonds between CG sites, often based on fluctuations derived from atomic-level simulations [136–138]. This approximation works very well for proteins that mostly exist in one conformation, such as BAR proteins. The simulations started with N-BARs randomly placed on a planar bilayer or on a lipid vesicle of optically resolvable size. The work showed that N-BAR proteins undergo a specific

self-assembly mechanism, marked by a rapid formation of long strings of protein aggregates [139]. Similar to the aforementioned study of capsid aggregation, local membrane curvature was also the primary driving force in the association of N-BAR proteins. However, the protein does not induce as high local curvature as in the capsid model, where it was shown that very high curvature is crucial in inducing effective attractions [133]. Rather, the anisotropic curvature interactions with the membrane give rise to long-range quasi-one-dimensional ordering of proteins on the membrane. This general phenomenon was first predicted with MC simulations using an analytical N-body potential, which also showed linear and circular assemblies of nonspecific anisotropic inclusions [140]. Curiously, MC simulations, using a triangular-mesh membrane model, have shown that spherical particles adhered to the membrane also undergo linear aggregation [141]. This work has implicated particle-membrane binding force—a term typically absent in analytical modeling of membrane inclusions—as the driving force that overcomes the cost of local deformations. Local deformations then mediate the effective inter-particle attractions, although, hypothetically, the anisotropic interactions that form upon the initial particle pairing might also strongly contribute to the formation of lines.

What is striking is that three very different membrane models demonstrated the same association behavior of objects interacting with the membrane (Fig. 7). The important implication for biology is that proteins that form anisotropic curvature interactions—and BAR proteins are an excellent example—may rapidly form long-range anisotropic assemblies on the membrane, even when they are present at low densities. The linear aggregation phenomenon of particles on membranes has been shown by experiments using giant vesicles decorated with nanoparticles [142]. Strikingly, a very recent study employing electron and fluorescence microscopy has confirmed the theoretical prediction that BAR proteins form linear oligomers on the surface of the membrane [143, 144].

In order to generate global membrane curvature, N-BAR proteins need to be bound at sufficiently high densities. According to CG MD simulations, at 20% surface density, proteins form a percolating meshwork on the surface, giving rise to budding instabilities at the center of protein meshes (see Fig. 7, right) [139]. Interestingly, the sign of curvature of emerging buds is positive, i.e., the membrane bends toward the proteins. Such geometry is the same as in endocytosis, where the endocytic vesicle forms on the side where the membrane-remodeling proteins are bound [31]. The association of spherical particles, on the other hand, leads to tubulation in the opposite direction, especially at high binding force (Fig. 8) [145, 146]. According to these observations, even though membrane-bound objects start from the same association geometry, the anisotropy and particle size determine the ultimate membrane shape (i.e., positive versus negative curvature).

The association of bound particles also couples with membrane's mechanical parameters, namely, membrane tension. Increasing surface tension changes the way N-BARs interact with one another: from changing the geometry of dimerization and breaking the meshwork topology to, at highest tension, inhibiting association altogether [147]. Therefore, the anisotropic shape of N-BAR proteins enriches the

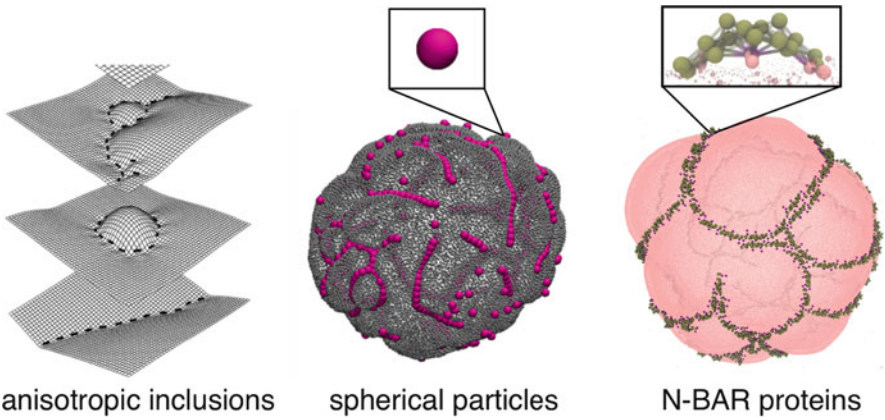

Fig. 7 Linear aggregation of membrane-bound objects [from left to right: (1) analytically modeled inclusions, (2) spherical particles, and (3) N-BAR proteins] simulated by three very different models. Left: reprinted from [140] with permission from Springer; center: courtesy of Andela Saric, based on [141]; right: based on [139]

range of geometries into which they assemble at different conditions. Moreover, these observations and a recent experimental study [148] implicate membrane tension as an important effector of membrane remodeling by proteins. Understanding this mechanism may be key to understanding how BAR proteins assemble in the course of endocytic events that involve actin, an important tension modulator [149].

When overexpressing BAR proteins in the cell, the typical phenotype is a massive tubulation of the membrane [42]. Has such remodeling been captured with CG MD simulations? A recent study using a highly CG meshless model, in which the rigidity and the spontaneous curvature of the membrane are tuned, has shown that curved rods, representing BAR proteins, could generate very long tubules from the membrane (Fig. 8). The study has also shown that the proteins initially go through stages of linear aggregation and meshing, in line with the aforementioned simulation studies, although, interestingly, the meshwork forms only if the spontaneous curvature term is positive in one direction and negative in the other [150]. In fact, the aforementioned CG study of N-BARs aggregating on vesicles, where no assumption on local curvature has been made a priori, has shown that N-BARs imprint this type of curvature on the surface [139]. When local curvature deformations by the protein have equal sign in both directions, bent particles (or in one study nematogenic inclusions) do not form a meshwork, but they still remodel the membrane into tubular and disk-like instabilities, as shown by a meshless and a triangular membrane model [150–152]. Again, subtle changes in the way proteins interact locally with the bilayer have a global impact on the shape of the membrane.

In these three studies, protein-covered membrane tubules grew continuously from the membrane surface. CG MD simulations, using a bottom-up three-site lipid model and an internal elastic network N-BAR model interacting with the membrane,

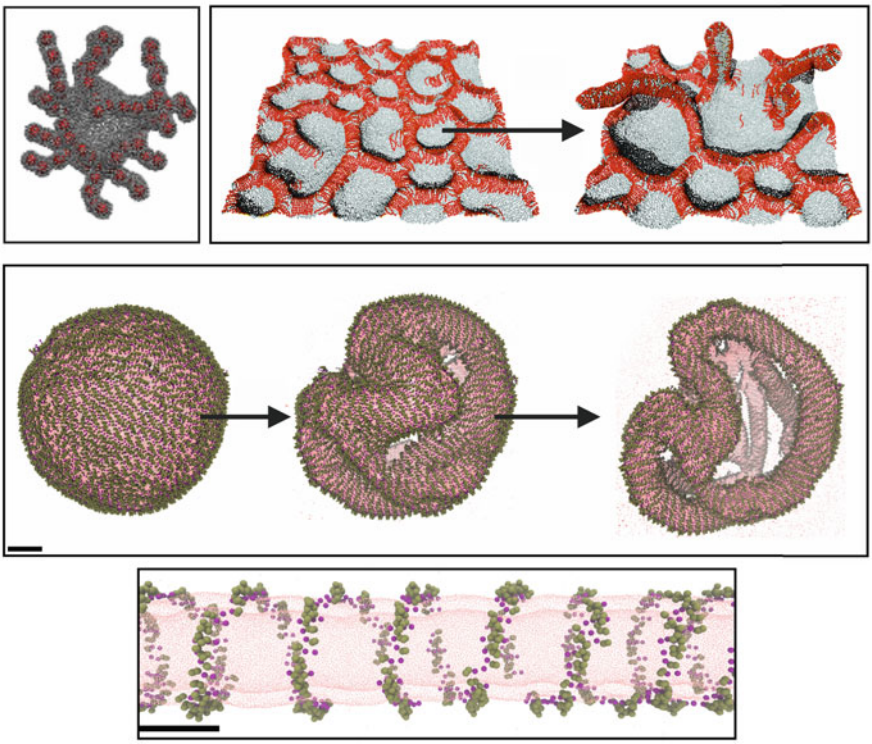

Fig. 8 Top: forming membrane tubules by spherical particles (left) and by bent rods (right). Left, courtesy of Andela Saric and based on work from [146]; right, courtesy of Hiroshi Noguchi and based on work from [150]. Center: Forming reticular membranes by breaking the bilayer topology by N-BAR proteins. Scale bar, 20 nm. Based on the work in [151]. Bottom: CG MD simulation snapshot of a membrane tube coated by an N-BAR domain scaffold. Scale bar, 20 nm. Adapted from [43], copyright (2016) National Academy of Sciences

have revealed another mechanism of forming membrane tubules. Here, the bilayer topology breaks due to high in-plane stresses imposed by many protein molecules. The prerequisites for this pathway are a rapid and a high-density binding of N-BAR proteins that essentially fold the membrane into a tubule. When they bind to a vesicle, this process leads to a transformation into a tubular network (Fig. 8), a structure which has been confirmed by cryo-electron microscopy under the same conditions [153]. According to simulations, the N-BAR proteins spontaneously form a nematic arrangement which dictates an average tubule radius of 10 nm, in remarkable agreement with experimental observations [44, 153]. Apparently, the radius of the folded tubule is also affected by the way individual proteins are arranged in this coat, as shown by MARTINI-like simulations of N-BAR and F-BAR protein lattices on membrane patches with exposed edges [76, 154]. Finally, a different CG MD study, using an internal elastic network N-BAR model

interacting with a Gay-Berne CG potential to model lipids, addressed the influence of amphipathic helices on the protein coat dynamics. They found that the presence of N-terminal helices and their antiparallel orientation (i.e., each helix oriented on the opposite side of the BAR domain) are important in stabilizing the lattice organization of the protein and the tubule rigidity [41, 155].

Less is known at the molecular level on how BAR proteins assemble on already formed tubules, an intermediate step in many endocytic pathways, e.g., in endocytosis driven by an N-BAR protein endophilin [149]. One simulation study has shown that curved rods undergo a phase separation on membrane tubules, modeled with a meshless lipid model. More precisely, the proteins get enriched in one region of the tubule, squeezing it into an hourglass shape [151]. The formation of high-density regions could explain the initial constriction of membrane tubules by BAR proteins, as observed in experiments [156]. A study combining in vitro reconstitution, CG MD simulations, and mathematical modeling shed light on the molecular details and the mechanism by which BAR proteins assemble on membrane nanotubes to form a protein scaffold. Apparently, the strength by which BAR proteins constrict the underlying tube determines where the protein nucleation takes place. Proteins that strongly constrict the membrane, such as endophilin, which creates very thin scaffolds, only 10 nm in diameter, initiate the scaffold at the base of the nanotube. By contrast, weakly constricting BAR proteins, such as β2 centaurin, which creates 40-nm-wide nanotubes, uniformly bind along the tube while making the scaffold [43]. CG MD simulations, employing a three-site lipid model, have revealed that N-BARs polymerize into a highly ordered helical structure on the tube, likely contributing to the very strong mechanical properties of the protein scaffold [43].

Simulating other proteins involved in endocytosis presents even bigger challenges, because of their more complicated structure or because their activity couples with an active, energy-driven process. For instance, clathrin is a protein that drives one of the most prominent pathways to enter cells [157]. The basic unit of clathrin is shaped like a triskelion, which polymerizes into a fullerene-like basket [158, 159]. This basket is believed to mold the membrane into a vesicle, engulfing the cargo bound on the opposite side of the bilayer (recall the coating mechanism of inducing curvature depicted in Fig. 2). Considering that clathrin (a) forms a complex polymeric structure and (b) it interacts with the membrane via adaptor proteins, it will be a great challenge to design a bottom-up CG model. Patchy particles—particles with sticky domains on the surface—have therefore been used to design shape-based models of clathrin, with interactions motivated from structural biology. These studies—albeit semi-quantitative—have fleshed out some key interactions that drive clathrin-like objects to assemble into a basket in the solution [160, 161]. They have also shown how the remodeling of the membrane by a clathrin-like basket depends on membrane's flexibility and stiffness [162]. A more flexible CG model, wherein the interactions have been derived with a parameterization scheme, has been shown to assemble into a basket both in the solution and on the membrane, identifying new intermediates in the budding pathway (Fig. 9) [163].

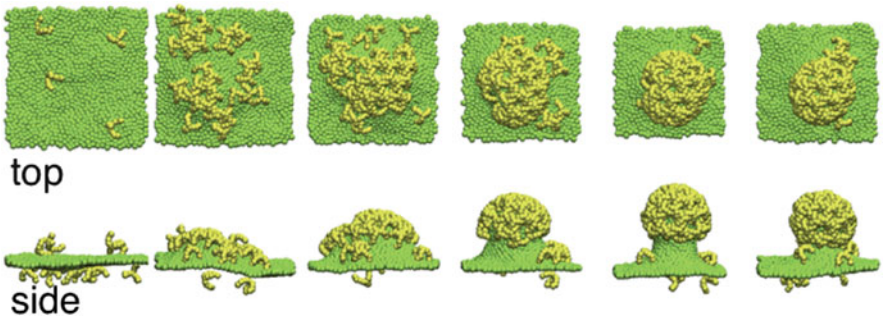

Fig. 9 The assembly of clathrin from triskelia into a basket-like structure and subsequent membrane remodeling into a vesicle. Shown are snapshots taken at regular time intervals in the simulation, viewed from the top of the membrane and from the side. Reproduced from [163] with permission from The Royal Society of Chemistry

In light of the demonstrated power of CG simulations, one may ask, "Do we then need atomic-level simulations to study membrane remodeling?" Returning to our initial discussion on multiscale nature of membranes, we immediately recognize the importance of understanding the molecular organization at the atomic scale. Although the collective action of proteins couples with the long-length scale phenomena, the small-scale interactions of individual proteins with the membrane and, in cases such as clathrin, the specific protein–protein attractions need to be studied in detail. Furthermore, CG models at present cannot account for the conformational changes of proteins that normally alter the way they interact with one another and with the membrane. Finally, the chemical reactions, such as the conversion between certain types of lipids and the hydrolysis of GTP or ATP, play key roles in membrane remodeling and will need to be addressed with atomic-level or mixed-resolution simulation techniques.

6 Continuum Modeling

Continuum modeling tackles the behavior at the mesoscopic level. The term mesoscopic in membrane physics encompasses a fairly wide range of scales, generally much larger than the membrane thickness but much smaller than the cell membrane. Scales of many CG simulations discussed in the previous section can surely be described as mesoscopic, such as the CG simulations of vesicles coated with N-BAR proteins [139]. Continuum models ignore individual molecules and describe them using collective or field variables, whose dynamics then gives only the collective properties of the system [164]. The triangular-mesh and the meshless models described in the previous section are similar to continuum models, as they do not resolve individual molecules; however, the use of discrete particles and MC or MD to integrate their motion makes them more similar to CG methods.

The premise of most continuum models is the assumption that the membrane can be described as a fluid thin elastic sheet, modeled by the Helfrich–Canham Hamiltonian [6, 115]. Minimizing the free energy functional, usually with numerical simulations, provides insight into the shape and the statistical properties of the membrane. Curvature can be modeled in multiple ways, such as by varying the value of preferred curvature [6, 115] or by imposing various constraints, such as on the area difference between the two leaflets upon asymmetric inclusion of particles [165–168]. Historically, these approaches have been used to explain the shapes of the red blood cell or vesicles embedded with inclusions, for example [169–174] and many other studies.

In the present discussion, we are more interested in continuum studies focused on the process of membrane remodeling. For studying membrane reshaping, such an approach would comprise simulating the finite-temperature dynamics, compositional variations, membrane fluctuations, and hydrodynamic effects. The so-called elastic membrane version 2 (EM2) model embodies all of these aspects of the membrane, and it has been used to study the remodeling of large lipid vesicles by BAR proteins. Given the complexity of calculating the radii of curvature for complex surfaces, such as a liposome, the free energy of the continuum membrane is discretized into quasi-particles immersed into a mesoscopic quasi-particle solvent, in the spirit of SPH techniques. The discretization allows for large-scale membrane restructuring, thermal fluctuations, and a more flexible and efficient computational approach that resembles MD simulations [175]. Equivalent to triangular-mesh models, bending and stretching energies are explicitly calculated as a pair-wise potential between two particles. However, an important advance is that each quasi-particle also has superimposed field variables, namely, lipid and protein compositions, cast in the form of a phenomenological Landau free energy functional [176]. The morphological effect on the membrane is modeled by coupling protein and lipid area fractions with the spontaneous curvature of the membrane, bending stiffness, and other parameters [175]. Other terms can be easily incorporated, for instance protein–protein interactions in the form of oligomerization energy. Finally, the composition field variable evolves according to the Landau–Ginzburg equation by using the smooth particle applied mechanics [177], which is similar to SPH.

EM2 simulations of large vesicles under the influence of a protein field variable have given insights into an unexpected molecular mechanism of forming tubules and a range of membrane morphologies. First, rapid protein binding at high surface densities transformed a vesicle into a tubular (reticulated) network, in the same way as in the CG simulations discussed in the previous section (Fig. 10). As expected, increasing the effective spontaneous curvature term in the Hamiltonian increased the propensity of the membrane to change shape. Keeping in mind that in continuum simulations the protein is only represented as a field variable, one therefore does not have knowledge of its molecular scale assembly. However, one can study how the membrane changes shape depending on how the protein couples with curvature. It turns out that the ultimate fate of the membrane depends whether the curvature field of the protein is isotropic or anisotropic [178]. In the case of the anisotropic curvature field, the vesicle transforms into a tubular network (Fig. 10). This result

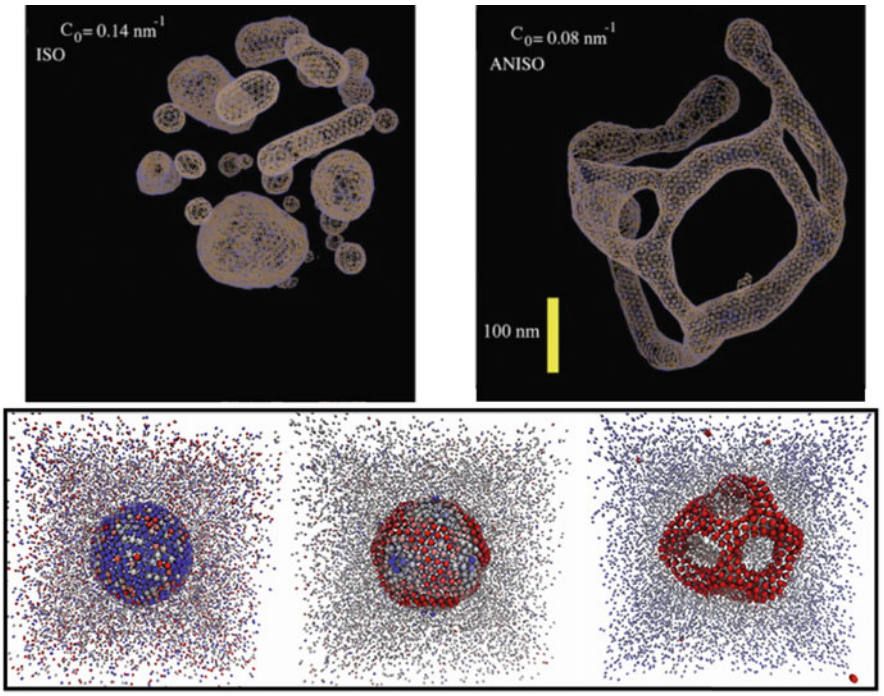

Fig. 10 Formation of tubular networks by N-BAR proteins in continuum mechanics simulations. Top: the influence of the isotropic (left) versus the anisotropic (right) spontaneous curvature. Adapted from [178] with permission from Elsevier. Bottom: time lapse of vesicle transformation, depicting the rapid recruitment of N-BARs from the mesoscopic solvent to the membrane surface. Color coding: protein concentration (red—high; white—intermediate; blue—low). Reprinted from [153] with permission from Elsevier

indicates that the proteins initially assemble on the membrane with a preferred direction, caused by interactions with other proteins. Indeed, recall that N-BAR proteins simulated at the CG level form linear aggregates when bound on a flat membrane surface [139]. In the case of an isotropic curvature field, the vesicle fragments into smaller vesicles [178]. This vesiculation phenomenon has indeed been experimentally reported when incubating curvature-coupling proteins that have amphipathic helices (such as N-BAR proteins) with 200-nm-wide liposomes [179]. It is not clear what process may disrupt the anisotropic alignment of proteins, but we can speculate that the embedding of amphipathic helices, perhaps in a different way on small liposomes than on quasi-flat membranes, introduces an additional radius of curvature. Moreover, it is possible that the high spherical curvature prevents the anisotropic ordering of BAR proteins.

It has also been shown that the formation of tubular networks takes place in a narrow configurational space, favoring membranes with a lower bending stiffness ($<15\ k_BT$) and for a range of spontaneous curvatures characteristic of N-BAR

proteins [153]. In the same simulation, if the applied spontaneous curvature is more characteristic of F-BAR proteins—which typically induce tubules of larger diameter—the EM2 model requires an additional oligomerization term in order to bend the membrane (Fig. 10) [180]. This result indicates that F-BAR proteins require explicit protein–protein interactions to reshape the membrane into a tubule, whereas for stronger curvature generators such as N-BARs, the protein–protein attractions are mostly driven by the underlying membrane.

Another notable continuous model of a fluctuating membrane that integrates the motion over time and carefully treats the hydrodynamic effects is the Fourier space Brownian dynamics [181, 182]. The method received its name because the shape of the membrane is calculated in the Fourier space, although the forces are calculated in the real space. The model is designed such that the membrane can couple with an arbitrary external force and so it can be expanded to study protein-mediated remodeling; however, it has yet not been used to address this biological question. One example using this model is a study of a membrane interacting with the cytoskeleton. The simulations have indicated that thermal fluctuations contribute to the macroscopic diffusion of proteins on the surface of a red blood cell [182].

7 Outlook: Mixed-Resolution Models

From the present discussion, it is evident that membrane remodeling by proteins is a complex process that challenges experimentalists and theorists alike. Let us briefly summarize the advantages and problems of each level of theory applied to simulating membrane reshaping by proteins. Atomic-level simulations are key in revealing the detailed interactions at the interface of the protein and the membrane. For instance, they can show the local orientation of lipids or measure the thermodynamics of binding. However, the atomic model is unable to access the mesoscopic scales of membrane remodeling. Fortunately, studying these long-length and time scale processes does not require knowing the position and the state of each individual atom in the system. CG simulations, on the other hand, access much larger scales and provide information on the collective behavior of proteins on the surface. These models also give the detailed shape of the membrane embedded by proteins, which is crucial in explaining its macroscopic morphological consequences. CG models are still limited by the challenges in obtaining an accurate CG effective force field that will not bias specific protein assembly or membrane geometry and, similar to atomic-level simulations, they can suffer from rising computational cost when simulating very large systems. Finally, continuum methods are crucial in investigating cell-sized membrane phenomena. However, application of continuum method to study protein-mediated membrane reshaping has been sparse, likely as these processes rely on thermal fluctuations, hydrodynamics, bending and stretching mechanics, but also on the lateral distribution of lipids and proteins, which are very difficult to take into account in a single model.

How can we overcome the discrepancy in scales? Let us revisit the idea behind a multiscale approach. One strategy is to connect the information between different scales in separate simulations, which is essentially the philosophy behind bottom-up coarse-graining [183]. Recall that this approach is challenging conceptually and mathematically. We can also choose some averaged properties from one resolution and take those values as a parameter in a different resolution model. In one example applied to membranes, the continuum and the atomistic descriptions were coupled. The approach used material properties of the bilayer obtained in atomic-level simulations as fixed parameters in solving the elastic free energy in the continuum model. In the opposite direction, the lateral stress profile extracted from a mesoscopic undulating surface was applied to the atomic-level simulation [184].

Another strategy is to first use the computationally less expensive simulation to generate a configuration and then to use it to make a higher-resolution model. One example employing this strategy is a study of N-BAR proteins on a reticular membrane. The formation of a reticular membrane was simulated using the mesoscopic continuum EM2 model (see the previous section). Then, the continuum membrane was fine-grained by mapping CG membrane patches atop of a triangulated mesh of EM2 quasi-particles [185]. Subsequent CG MD simulations have revealed important molecular information, such as the strongly hindered lipid mobility underneath a protein scaffold and especially in tubular junctions. This kind of information cannot be obtained from continuum models alone [153]. To visualize this fine-graining procedure, the reader is directed back to Fig. 4, where arrows from the continuum to the CG model illustrate how the mapping was accomplished. A more sophisticated approach for the future would include using field variables to accurately map the protein and lipid distribution in a CG representation.

An alternative strategy—often termed the mixed-resolution approach—consists of modeling different scales in the same simulation system. As mentioned earlier, integrating quantum mechanics with atomic-level force fields has proven very useful in modeling enzymatic reactions [58]. Similar hybrid approaches can be envisioned (1) between atomic and CG levels, (2) between CG and continuum levels, and (3) even between atomic and continuum levels [186].

Although various approaches have been developed to study proteins in solution at mixed resolution, let us focus on membrane models. One way to split a membrane system between two resolutions is by having some particle types (e.g., lipids) at one resolution and the rest (e.g., proteins or solvent) at a different resolution. For instance, one approach treated the membrane using a continuum model while it described the proteins as particles. The very low resolution of the membrane significantly accelerated the dynamics, allowing, at the same time, us to study the diffusion of proteins [187]. An alternative resolution-splitting scheme is to have one region of the space (typically smaller) at high resolution, and the rest of the system at low resolution, in the spirit of QM/MM simulations. A recent model employing a similar strategy combined CG with continuum mechanics in a way to calculate the intramolecular forces using a CG model (MARTINI in that case), whereas the computationally expensive nonbonded interactions are averaged out in the style of the mean field theory [188]. In other words, individual molecules were resolved, but

instead of interacting with many neighbors, they interacted with a field. The model has been used to simulate membrane self-assembly [189] and the insertion of carbon nanotubes into the bilayer [190].

Mixed-resolution models are yet to be used to study membrane remodeling by proteins; however, they may provide a very promising approach that deserves attention in the coming years. Future challenges will involve correctly modeling the collective behavior of proteins on the membrane, so as to permit different protein orientations at the molecular level and, even further, the interactions between different types of proteins to simulate their cooperative assembly in the course of complex membrane-remodeling processes.

References

1. Atkins P, de Paula J (2010) Atkins' physical chemistry. Oxford University Press, Oxford
2. Ashrafuzzaman M, Tuszynski JA (2012) Membrane biophysics. Springer, New York
3. Lipowsky R (1991) The conformation of membranes. Nature 349(6309):475–481. https://doi.org/10.1038/349475a0
4. Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P (2014) Molecular biology of the cell. Taylor & Francis, New York
5. Evans EA (1983) Bending elastic modulus of red blood cell membrane derived from buckling instability in micropipet aspiration tests. Biophys J 43(1):27–30. https://doi.org/10.1016/S0006-3495(83)84319-7
6. Helfrich W (1973) Elastic properties of lipid bilayers: theory and possible experiments. Z Naturforsch C 28(11):693–703
7. Kwok R, Evans E (1981) Thermoelasticity of large lecithin bilayer vesicles. Biophys J 35(3):637–652. https://doi.org/10.1016/S0006-3495(81)84817-5
8. Baumgart T, Hess ST, Webb WW (2003) Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension. Nature 425(6960):821–824. https://doi.org/10.1038/nature02013
9. Funkhouser CM, Solis FJ, Thornton K (2010) Dynamics of two-phase lipid vesicles: effects of mechanical properties on morphology evolution. Soft Matter 6(15):3462–3466
10. Hu JL, Weikl TR, Lipowsky R (2011) Vesicles with multiple membrane domains. Soft Matter 7(13):6092–6102
11. Li J, Zhang H, Qiu F (2013) Budding behavior of multi-component vesicles. J Phys Chem B 117(3):843–849. https://doi.org/10.1021/jp308043y
12. Rim JE, Ursell TS, Phillips R, Klug WS (2011) Morphological phase diagram for lipid membrane domains with entropic tension. Phys Rev Lett 106(5):057801
13. Semrau S, Idema T, Holtzer L, Schmidt T, Storm C (2008) Accurate determination of elastic parameters for multicomponent membranes. Phys Rev Lett 100(8):088101
14. Sens P, Turner MS (2006) Budded membrane microdomains as tension regulators. Phys Rev E 73(3):Artn 031918. https://doi.org/10.1103/Physreve.73.031918
15. Taniguchi T (1996) Shape deformation and phase separation dynamics of two-component vesicles. Phys Rev Lett 76(23):4444–4447
16. Taniguchi T, Yanagisawa M, Imai M (2011) Numerical investigations of the dynamics of two-component vesicles. J Phys Condens Matter 23(28):284103
17. Ursell TS, Klug WS, Phillips R (2009) Morphology and interaction between lipid domains. Proc Natl Acad Sci USA 106(32):13301–13306. https://doi.org/10.1073/Pnas.0903825106
18. Aimon S, Callan-Jones A, Berthaud A, Pinot M, Toombes GE, Bassereau P (2014) Membrane shape modulates transmembrane protein distribution. Dev Cell 28(2):212–218. https://doi.org/10.1016/j.devcel.2013.12.012

19. Unwin N (2005) Refined structure of the nicotinic acetylcholine receptor at 4A resolution. J Mol Biol 346(4):967–989. https://doi.org/10.1016/j.jmb.2004.12.031
20. Mackinnon R (2004) Structural biology. Voltage sensor meets lipid membrane. Science 306(5700):1304–1305. https://doi.org/10.1126/science.1105528
21. Drin G, Antonny B (2010) Amphipathic helices and membrane curvature. FEBS Lett 584:1840–1847
22. Campelo F, McMahon HT, Kozlov MM (2008) The hydrophobic insertion mechanism of membrane curvature generation by proteins. Biophys J 95(5):2325–2339. https://doi.org/10.1529/biophysj.108.133173
23. Zemel A, Ben-Shaul A, May S (2008) Modulation of the spontaneous curvature and bending rigidity of lipid membranes by interfacially adsorbed amphipathic peptides. J Phys Chem B 112(23):6988–6996. https://doi.org/10.1021/jp711107y
24. Walther TC, Farese RV Jr (2009) The life of lipid droplets. Biochim Biophys Acta 1791(6):459–466. https://doi.org/10.1016/j.bbalip.2008.10.009
25. Wilson C, Wardell MR, Weisgraber KH, Mahley RW, Agard DA (1991) Three-dimensional structure of the LDL receptor-binding domain of human apolipoprotein E. Science 252(5014):1817–1822
26. Mim C, Unger VM (2012) Membrane curvature and its generation by BAR proteins. Trends Biochem Sci 37(12):526–533. https://doi.org/10.1016/j.tibs.2012.09.001
27. Simunovic M, Voth GA, Callan-Jones A, Bassereau P (2015) When physics takes over: BAR proteins and membrane curvature. Trends Cell Biol 25(12):780–792. https://doi.org/10.1016/j.tcb.2015.09.005
28. Callan-Jones A, Bassereau P (2013) Curvature-driven membrane lipid and protein distribution. Curr Opin Solid State Mater Sci 17(4):143–150
29. Lipowsky R (2013) Spontaneous tubulation of membranes and vesicles reveals membrane tension generated by spontaneous curvature. Faraday Discuss 161:305–331. https://doi.org/10.1039/C2fd20105d
30. Lipowsky R, Dobereiner HG (1998) Vesicles in contact with nanoparticles and colloids. Europhys Lett 43(2):219–225
31. Johannes L, Wunder C, Bassereau P (2014) Bending "on the rocks"—a cocktail of biophysical modules to build endocytic pathways. Cold Spring Harb Perspect Biol 6(1):a016741. https://doi.org/10.1101/cshperspect.a016741
32. McMahon HT, Gallop JL (2005) Membrane curvature and mechanisms of dynamic cell membrane remodelling. Nature 438(7068):590–596. https://doi.org/10.1038/nature04396
33. Bickel T, Jeppesen C, Marques CM (2001) Local entropic effects of polymers grafted to soft interfaces. Eur Phys J E 4(1):33–43
34. Breidenich M, Netz RR, Lipowsky R (2000) The shape of polymer-decorated membranes. Europhys Lett 49(4):431–437
35. Nikolov V, Lipowsky R, Dimova R (2007) Behavior of giant vesicles with anchored DNA molecules. Biophys J 92(12):4356–4368. https://doi.org/10.1529/biophysj.106.100032
36. Stachowiak JC, Schmid EM, Ryan CJ, Ann HS, Sasaki DY, Sherman MB, Geissler PL, Fletcher DA, Hayden CC (2012) Membrane bending by protein-protein crowding. Nat Cell Biol 14(9):944–949. https://doi.org/10.1038/ncb2561
37. Sheetz MP (2001) Cell control by membrane-cytoskeleton adhesion. Nat Rev Mol Cell Biol 2(5):392–396. https://doi.org/10.1038/35073095
38. Koster G, VanDuijn M, Hofs B, Dogterom M (2003) Membrane tube formation from giant vesicles by dynamic association of motor proteins. Proc Natl Acad Sci USA 100(26):15583–15588. https://doi.org/10.1073/pnas.2531786100
39. Roux A, Cappello G, Cartaud J, Prost J, Goud B, Bassereau P (2002) A minimal system allowing tubulation with molecular motors pulling on giant liposomes. Proc Natl Acad Sci USA 99(8):5394–5399. https://doi.org/10.1073/pnas.082107299
40. Qualmann B, Koch D, Kessels MM (2011) Let's go bananas: revisiting the endocytic BAR code. EMBO J 30(17):3501–3515. https://doi.org/10.1038/emboj.2011.266

41. Mim C, Cui H, Gawronski-Salerno JA, Frost A, Lyman E, Voth GA, Unger VM (2012) Structural basis of membrane bending by the N-BAR protein endophilin. Cell 149(1):137–145. https://doi.org/10.1016/j.cell.2012.01.048
42. Peter BJ, Kent HM, Mills IG, Vallis Y, Butler PJ, Evans PR, McMahon HT (2004) BAR domains as sensors of membrane curvature: the amphiphysin BAR structure. Science 303(5657):495–499. https://doi.org/10.1126/science.1092586
43. Simunovic M, Evergren E, Golushko I, Prevost C, Renard HF, Johannes L, McMahon HT, Lorman V, Voth GA, Bassereau P (2016) How curvature-generating proteins build scaffolds on membrane nanotubes. Proc Natl Acad Sci USA 113(40):11226–11231. https://doi.org/10.1073/pnas.1606943113
44. Sorre B, Callan-Jones A, Manzi J, Goud B, Prost J, Bassereau P, Roux A (2012) Nature of curvature coupling of amphiphysin with membranes depends on its bound density. Proc Natl Acad Sci USA 109(1):173–178. https://doi.org/10.1073/pnas.1103594108
45. Suarez A, Ueno T, Huebner R, McCaffery JM, Inoue T (2014) Bin/Amphiphysin/Rvs (BAR) family members bend membranes in cells. Sci Rep 4:4693. https://doi.org/10.1038/srep04693
46. Ambroso MR, Hegde BG, Langen R (2014) Endophilin A1 induces different membrane shapes using a conformational switch that is regulated by phosphorylation. Proc Natl Acad Sci USA 111(19):6982–6987. https://doi.org/10.1073/pnas.1402233111
47. Simunovic M, Bassereau P (2014) Reshaping biological membranes in endocytosis: crossing the configurational space of membrane-protein interactions. Biol Chem 395(3):275–283. https://doi.org/10.1515/hsz-2013-0242
48. Simunovic M, Manneville JB, Renard HF, Evergren E, Raghunathan K, Bhatia D, Kenworthy AK, Voth GA, Prost J, McMahon HT, Johannes L, Bassereau P, Callan-Jones A (2017) Friction mediates scission of tubular membranes scaffolded by BAR proteins. Cell 170(1):172–184.e11
49. van Gunsteren WF, Bakowies D, Baron R, Chandrasekhar I, Christen M, Daura X, Gee P, Geerke DP, Glattli A, Hunenberger PH, Kastenholz MA, Oostenbrink C, Schenk M, Trzesniak D, van der Vegt NF, Yu HB (2006) Biomolecular modeling: goals, problems, perspectives. Angew Chem 45(25):4064–4092. https://doi.org/10.1002/anie.200502655
50. Frenkel D, Smit B (2001) Understanding molecular simulation: from Algorithms to applications. Elsevier Science, San Diego
51. Gingold RA, Monaghan JJ (1977) Smoothed particle hydrodynamics: theory and application to non-spherical stars. Mon Not R Astron Soc 181(2):375–389
52. Lucy LB (1977) A numerical approach to the testing of the fission hypothesis. Astron J 82:1013–1024
53. Liu MB, Liu GR (2010) Smoothed Particle Hydrodynamics (SPH): an overview and recent developments. Arch Comput Meth Eng 17(1):25–76. https://doi.org/10.1007/S11831-010-9040-7
54. Hoogerbrugge PJ, Koelman JMVA (1992) Simulating microscopic hydrodynamic phenomena with dissipative particle dynamics. Europhys Lett 19(3):155–160. https://doi.org/10.1209/0295-5075/19/3/001
55. Koelman JMVA, Hoogerbrugge PJ (1993) Dynamic simulations of hard-sphere suspensions under steady shear. Europhys Lett 21(3):363–368. https://doi.org/10.1209/0295-5075/21/3/018
56. Shillcock JC, Lipowsky R (2002) Equilibrium structure and lateral stress distribution of amphiphilic bilayers from dissipative particle dynamics simulations. J Chem Phys 117(10):5048–5061. https://doi.org/10.1063/1.1498463
57. Yamamoto S, Maruyama Y, Hyodo S (2002) Dissipative particle dynamics study of spontaneous vesicle formation of amphiphilic molecules (vol 116, pg 5842). J Chem Phys 117(6):2990. https://doi.org/10.1063/1.1494416
58. Warshel A, Levitt M (1976) Theoretical studies of enzymic reactions: dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. J Mol Biol 103(2):227–249

59. Izvekov S, Voth GA (2005) A multiscale coarse-graining method for biomolecular systems. J Phys Chem B 109(7):2469–2473
60. Hodak H (2014) The Nobel Prize in chemistry 2013 for the development of multiscale models of complex chemical systems: a tribute to Martin Karplus, Michael Levitt and Arieh Warshel. J Mol Biol 426(1):1–3. https://doi.org/10.1016/j.jmb.2013.10.037
61. Karplus M (2014) Development of multiscale models for complex chemical systems: from H+H(2) to biomolecules (Nobel Lecture). Angew Chem 53(38):9992–10005. https://doi.org/10.1002/anie.201403924
62. Levitt M (2014) Birth and future of multiscale modeling for macromolecular systems (Nobel Lecture). Angew Chem 53(38):10006–10018. https://doi.org/10.1002/anie.201403691
63. Warshel A (2014) Multiscale modeling of biological functions: from enzymes to molecular machines (Nobel Lecture). Angew Chem 53(38):10020–10031. https://doi.org/10.1002/anie.201403689
64. Freddolino PL, Arkhipov AS, Larson SB, McPherson A, Schulten K (2006) Molecular dynamics simulations of the complete satellite tobacco mosaic virus. Structure 14(3):437–449. https://doi.org/10.1016/j.str.2005.11.014
65. Zhao G, Perilla JR, Yufenyuy EL, Meng X, Chen B, Ning J, Ahn J, Gronenborn AM, Schulten K, Aiken C, Zhang P (2013) Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. Nature 497(7451):643–646. https://doi.org/10.1038/nature12162
66. Shaw DE, Grossman JP, Bank JA, Batson B, Butts JA, Chao JC, Deneroff MM, Dror RO, Even A, Fenton CH (2014) Anton 2: raising the bar for performance and programmability in a special-purpose molecular dynamics supercomputer. In: Proceedings of the international conference for high performance computing, networking, storage and analysis. IEEE Press, Salt Lake City, pp 41–53
67. Arkhipov A, Shan Y, Das R, Endres NF, Eastwood MP, Wemmer DE, Kuriyan J, Shaw DE (2013) Architecture and membrane interactions of the EGF receptor. Cell 152(3):557–569. https://doi.org/10.1016/j.cell.2012.12.030
68. Dror RO, Green HF, Valant C, Borhani DW, Valcourt JR, Pan AC, Arlow DH, Canals M, Lane JR, Rahmani R, Baell JB, Sexton PM, Christopoulos A, Shaw DE (2013) Structural basis for modulation of a G-protein-coupled receptor by allosteric drugs. Nature 503(7475):295–299. https://doi.org/10.1038/nature12595
69. Akitake B, Anishkin A, Liu N, Sukharev S (2007) Straightening and sequential buckling of the pore-lining helices define the gating cycle of MscS. Nat Struct Mol Biol 14(12):1141–1149. https://doi.org/10.1038/nsmb1341
70. Bjelkmar P, Niemela PS, Vattulainen I, Lindahl E (2009) Conformational changes and slow dynamics through microsecond polarized atomistic molecular simulation of an integral Kv1.2 ion channel. PLoS Comput Biol 5(2):e1000289
71. Cuello LG, Jogini V, Cortes DM, Pan AC, Gagnon DG, Dalmas O, Cordero-Morales JF, Chakrapani S, Roux B, Perozo E (2010) Structural basis for the coupling between activation and inactivation gates in K+ channels. Nature 466(7303):272–U154. https://doi.org/10.1038/Nature09136
72. Jeon J, Voth GA (2008) Gating of the mechanosensitive channel protein MscL: the interplay of membrane and protein. Biophys J 94(9):3497–3511. https://doi.org/10.1529/biophysj.107.109850
73. Jogini V, Roux B (2007) Dynamics of the Kv1.2 voltage-gated K+ channel in a membrane environment. Biophys J 93(9):3070–3082. https://doi.org/10.1529/biophysj.107.112540
74. Arkhipov A, Yin Y, Schulten K (2008) Four-scale description of membrane sculpting by BAR domains. Biophys J 95(6):2806–2821. https://doi.org/10.1529/biophysj.108.132563
75. Blood PD, Voth GA (2006) Direct observation of Bin/amphiphysin/Rvs (BAR) domain-induced membrane curvature by means of molecular dynamics simulations. Proc Natl Acad Sci USA 103(41):15068–15072. https://doi.org/10.1073/pnas.0603917103

76. Yu H, Schulten K (2013) Membrane sculpting by F-BAR domains studied by molecular dynamics simulations. PLoS Comput Biol 9(1):e1002892. https://doi.org/10.1371/journal.pcbi.1002892
77. Lyman E, Cui H, Voth GA (2010) Water under the BAR. Biophys J 99(6):1783–1790. https://doi.org/10.1016/j.bpj.2010.06.074
78. Blood PD, Swenson RD, Voth GA (2008) Factors influencing local membrane curvature induction by N-BAR domains as revealed by molecular dynamics simulations. Biophys J 95(4):1866–1876. https://doi.org/10.1529/biophysj.107.121160
79. Cui H, Ayton GS, Voth GA (2009) Membrane binding by the endophilin N-BAR domain. Biophys J 97(10):2746–2753. https://doi.org/10.1016/j.bpj.2009.08.043
80. Saunders MG, Voth GA (2013) Coarse-graining methods for computational biology. Annu Rev Biophys 42:73–93. https://doi.org/10.1146/annurev-biophys-083012-130348
81. Izvekov S, Voth GA (2006) Modeling real dynamics in the coarse-grained representation of condensed phase systems. J Chem Phys 125(15):151101. https://doi.org/10.1063/1.2360580
82. Sundararajan V, Simon SA, Benos DJ, Feller SE (2011) Computational modeling of membrane bilayers. Elsevier Science, San Diego
83. Noid WG, Chu JW, Ayton GS, Krishna V, Izvekov S, Voth GA, Das A, Andersen HC (2008) The multiscale coarse-graining method. I. A rigorous bridge between atomistic and coarse-grained models. J Chem Phys 128(24):244114
84. Noid WG, Liu P, Wang Y, Chu JW, Ayton GS, Izvekov S, Andersen HC, Voth GA (2008) The multiscale coarse-graining method. II. Numerical implementation for coarse-grained molecular models. J Chem Phys 128(24):244115
85. Izvekov S, Voth GA (2006) Multiscale coarse-graining of mixed phospholipid/cholesterol bilayers. J Chem Theory Comput 2(3):637–648
86. Izvekov S, Voth GA (2009) Solvent-free lipid bilayer model using multiscale coarse-graining. J Phys Chem B 113(13):4443–4455
87. Lu LY, Voth GA (2009) Systematic coarse-graining of a multicomponent lipid bilayer. J Phys Chem B 113(5):1501–1510
88. Ayton GS, Voth GA (2009) Hybrid coarse-graining approach for lipid bilayers at large length and time scales. J Phys Chem B 113(13):4413–4424
89. Gay JG, Berne BJ (1981) Modification of the overlap potential to mimic a linear site-site potential. J Chem Phys 74(6):3316–3319
90. Srivastava A, Voth GA (2013) A hybrid approach for highly coarse-grained lipid bilayer models. J Chem Theory Comput 9(1):750–765. https://doi.org/10.1021/ct300751h
91. Srivastava A, Voth GA (2014) Solvent-free, highly coarse-grained models for charged lipid systems. J Chem Theory Comput 10(10):4730–4744. https://doi.org/10.1021/ct500474a
92. Shelley JC, Shelley MY, Reeder RC, Bandyopadhyay S, Klein ML (2001) A coarse grain model for phospholipid simulations. J Phys Chem B 105(19):4464–4470
93. Sodt AJ, Head-Gordon T (2010) An implicit solvent coarse-grained lipid model with correct stress profile. J Chem Phys 132(20):205103. https://doi.org/10.1063/1.3408285
94. Reith D, Putz M, Muller-Plathe F (2003) Deriving effective mesoscale potentials from atomistic simulations. J Comput Chem 24(13):1624–1636. https://doi.org/10.1002/jcc.10307
95. Lyubartsev AP, Laaksonen A (1995) Calculation of effective interaction potentials from radial-distribution functions—a reverse Monte-Carlo approach. Phys Rev E 52(4):3730–3737
96. Lyubartsev AP (2005) Multiscale modeling of lipids and lipid bilayers. Eur Biophys J 35(1):53–61
97. Murtola T, Falck E, Karttunen M, Vattulainen I (2007) Coarse-grained model for phospholipid/cholesterol bilayer employing inverse Monte Carlo with thermodynamic constraints. J Chem Phys 126(7):075101. https://doi.org/10.1063/1.2646614
98. Murtola T, Falck E, Patra M, Karttunen M, Vattulainen I (2004) Coarse-grained model for phospholipid/cholesterol bilayer. J Chem Phys 121(18):9156–9165. https://doi.org/10.1063/1.1803537

99. Wang ZJ, Deserno M (2010) A systematically coarse-grained solvent-free model for quantitative phospholipid bilayer simulations. J Phys Chem B 114(34):11207–11220. https://doi.org/10.1021/jp102543j
100. Mirzoev A, Lyubartsev AP (2014) Systematic implicit solvent coarse graining of dimyristoylphosphatidylcholine lipids. J Comput Chem 35(16):1208–1218. https://doi.org/10.1002/jcc.23610
101. Drouffe JM, Maggs AC, Leibler S (1991) Computer simulations of self-assembled membranes. Science 254(5036):1353–1356
102. Marrink SJ, Risselada HJ, Yefimov S, Tieleman DP, de Vries AH (2007) The MARTINI force field: coarse grained model for biomolecular simulations. J Phys Chem B 111(27):7812–7824
103. Marrink SJ, de Vries AH, Mark AE (2004) Coarse grained model for semiquantitative lipid simulations. J Phys Chem B 108(2):750–760
104. Brannigan G, Brown FL (2004) Solvent-free simulations of fluid membrane bilayers. J Chem Phys 120(2):1059–1071. https://doi.org/10.1063/1.1625913
105. Farago O (2003) "Water-free" computer model for fluid bilayer membranes. J Chem Phys 119(1):596–605
106. Noguchi H, Takasu M (2001) Fusion pathways of vesicles: a Brownian dynamics simulation. J Chem Phys 115(20):9547–9551
107. Cooke IR, Kremer K, Deserno M (2005) Tunable generic model for fluid bilayer membranes. Phys Rev E Stat Nonlin Soft Matter Phys 72(1 Pt 1):011506
108. Noguchi H (2011) Solvent-free coarse-grained lipid model for large-scale simulations. J Chem Phys 134(5):055101
109. Wang ZJ, Frenkel D (2005) Modeling flexible amphiphilic bilayers: a solvent-free off-lattice Monte Carlo study. J Chem Phys 122(23):234711
110. Baumgartner A, Ho JS (1990) Crumpling of fluid vesicles. Phys Rev A 41(10):5747–5750
111. Ho JS, Baumgartner A (1990) Simulations of fluid self-avoiding membranes. Europhys Lett 12(4):295–300
112. Kantor Y, Kardar M, Nelson DR (1986) Statistical mechanics of tethered surfaces. Phys Rev Lett 57(7):791–794
113. Ramakrishnan N, Kumar PBS, Ipsen JH (2010) Monte Carlo simulations of fluid vesicles with in-plane orientational ordering. Phys Rev E Stat Nonlin Soft Matter Phys 81(4):041922
114. Sreeja K, Ipsen JH, Kumar PS (2015) Monte Carlo simulations of fluid vesicles. J Phys Condens Matter 27(27):273104
115. Canham PB (1970) The minimum energy of bending as a possible explanation of the biconcave shape of the human red blood cell. J Theor Biol 26(1):61–81
116. Del Popolo MG, Ballone P (2008) Melting behavior of an idealized membrane model. J Chem Phys 128(2):024705. https://doi.org/10.1063/1.2804423
117. Kohyama T (2009) Simulations of flexible membranes using a coarse-grained particle-based model with spontaneous curvature variables. Physica A 388(17):3334–3344
118. Noguchi H, Gompper G (2006) Meshless membrane model based on the moving least-squares method. Phys Rev E Stat Nonlin Soft Matter Phys 73(2):021903
119. Pasqua A, Maibaum L, Oster G, Fletcher DA, Geissler PL (2010) Large-scale simulations of fluctuating biological membranes. J Chem Phys 132(15):154107. https://doi.org/10.1063/1.3382349
120. Shiba H, Noguchi H (2011) Estimation of the bending rigidity and spontaneous curvature of fluid membranes in simulations. Phys Rev E Stat Nonlin soft Matter Phys 84(3 Pt 1):031926
121. Bond PJ, Sansom MS (2007) Bilayer deformation by the Kv channel voltage sensor domain revealed by self-assembly simulations. Proc Natl Acad Sci USA 104(8):2631–2636. https://doi.org/10.1073/pnas.0606822104
122. Delemotte L, Klein ML, Tarek M (2012) Molecular dynamics simulations of voltage-gated cation channels: insights on voltage-sensor domain function and modulation. Front Pharmacol 3:97. https://doi.org/10.3389/fphar.2012.00097
123. Maffeo C, Bhattacharya S, Yoo J, Wells D, Aksimentiev A (2012) Modeling and simulation of ion channels. Chem Rev 112(12):6250–6284. https://doi.org/10.1021/cr3002609

124. Treptow W, Marrink SJ, Tarek M (2008) Gating motions in voltage-gated potassium channels revealed by coarse-grained molecular dynamics simulations. J Phys Chem B 112(11):3277–3282. https://doi.org/10.1021/jp709675e
125. Yefimov S, van der Giessen E, Onck PR, Marrink SJ (2008) Mechanosensitive membrane channels in action. Biophys J 94(8):2994–3002. https://doi.org/10.1529/biophysj.107.119966
126. Braun AR, Lacy MM, Ducas VC, Rhoades E, Sachs JN (2014) Alpha-synuclein-induced membrane remodeling is driven by binding affinity, partition depth, and interleaflet order asymmetry. J Am Chem Soc 136(28):9962–9972
127. Fuhrmans M, Marrink SJ (2012) Molecular view of the role of fusion peptides in promoting positive membrane curvature. J Am Chem Soc 134(3):1543–1552. https://doi.org/10.1021/ja207290b
128. Ingolfsson HI, Melo MN, van Eerden FJ, Arnarez C, Lopez CA, Wassenaar TA, Periole X, de Vries AH, Tieleman DP, Marrink SJ (2014) Lipid organization of the plasma membrane. J Am Chem Soc 136(41):14554–14559. https://doi.org/10.1021/ja507832e
129. Koldso H, Shorthouse D, Helie J, Sansom MSP (2014) Lipid clustering correlates with membrane curvature as revealed by molecular simulations of complex lipid bilayers. PLoS Comput Biol 10(10):e1003911
130. Lindau M, Hall BA, Chetwynd A, Beckstein O, Sansom MS (2012) Coarse-grain simulations reveal movement of the synaptobrevin C-terminus in response to piconewton forces. Biophys J 103(5):959–969. https://doi.org/10.1016/j.bpj.2012.08.007
131. Risselada HJ, Kutzner C, Grubmuller H (2011) Caught in the act: visualization of SNARE-mediated fusion events in molecular detail. Chembiochem 12(7):1049–1055. https://doi.org/10.1002/cbic.201100020
132. Reynwar BJ, Illya G, Harmandaris VA, Muller MM, Kremer K, Deserno M (2007) Aggregation and vesiculation of membrane proteins by curvature-mediated interactions. Nature 447(7143):461–464. https://doi.org/10.1038/nature05840
133. Reynwar BJ, Deserno M (2011) Membrane-mediated interactions between circular particles in the strongly curved regime. Soft Matter 7(18):8567–8575
134. Matthews R, Likos CN (2013) Dynamics of self-assembly of model viral capsids in the presence of a fluctuating membrane. J Phys Chem B 117(27):8283–8292. https://doi.org/10.1021/jp4037099
135. Ruiz-Herrero T, Hagan MF (2015) Simulations show that virus assembly and budding are facilitated by membrane microdomains. Biophys J 108(3):585–595
136. Lyman E, Pfaendtner J, Voth GA (2008) Systematic multiscale parameterization of heterogeneous elastic network models of proteins. Biophys J 95(9):4183–4192
137. Sinitskiy AV, Voth GA (2013) Coarse-graining of proteins based on elastic network models. Chem Phys 422:165–174
138. Tirion MM (1996) Large amplitude elastic motions in proteins from a single-parameter, atomic analysis. Phys Rev Lett 77(9):1905–1908
139. Simunovic M, Srivastava A, Voth GA (2013) Linear aggregation of proteins on the membrane as a prelude to membrane remodeling. Proc Natl Acad Sci USA 110(51):20396–20401. https://doi.org/10.1073/pnas.1309819110
140. Dommersnes PG, Fournier JB (1999) N-body study of anisotropic membrane inclusions: Membrane mediated interactions and ordered aggregation. Eur Phys J B 12(1):9–12
141. Saric A, Cacciuto A (2012) Fluid membranes can drive linear aggregation of adsorbed spherical nanoparticles. Phys Rev Lett 108(11):118101
142. Koltover I, Radler JO, Safinya CR (1999) Membrane mediated attraction and ordered aggregation of colloidal particles bound to giant phospholipid vesicles. Phys Rev Lett 82(9):1991–1994. https://doi.org/10.1103/Physrevlett.82.1991
143. McDonald NA, Vander Kooi CW, Ohi MD, Gould KL (2015) Oligomerization but not membrane bending underlies the function of certain F-BAR proteins in cell motility and cytokinesis. Dev Cell 35(6):725–736. https://doi.org/10.1016/j.devcel.2015.11.023
144. Traub LM (2015) F-BAR/EFC domain proteins: some assembly required. Dev Cell 35(6):664–666. https://doi.org/10.1016/j.devcel.2015.12.003

145. Bahrami AH, Lipowsky R, Weikl TR (2012) Tubulation and aggregation of spherical nanoparticles adsorbed on vesicles. Phys Rev Lett 109(18):188102
146. Saric A, Cacciuto A (2012) Mechanism of membrane tube formation induced by adhesive nanocomponents. Phys Rev Lett 109(18):188101
147. Simunovic M, Voth GA (2015) Membrane tension controls the assembly of curvature-generating proteins. Nat Commun 6:7219. https://doi.org/10.1038/ncomms8219
148. Shi Z, Baumgart T (2015) Membrane tension and peripheral protein density mediate membrane shape transitions. Nat Commun 6:5974. https://doi.org/10.1038/ncomms6974
149. Renard HF, Simunovic M, Lemiere J, Boucrot E, Garcia-Castillo MD, Arumugam S, Chambon V, Lamaze C, Wunder C, Kenworthy AK, Schmidt AA, McMahon HT, Sykes C, Bassereau P, Johannes L (2015) Endophilin-A2 functions in membrane scission in clathrin-independent endocytosis. Nature 517(7535):493–496. https://doi.org/10.1038/nature14064
150. Noguchi H (2015) Membrane tubule formation by banana-shaped proteins with or without intermediate network structure. Sci Rep 6:20935
151. Noguchi H (2014) Two- or three-step assembly of banana-shaped proteins coupled with shape transformation of lipid membranes. EPL 108(4):48001
152. Ramakrishnan N, Sunil Kumar PB, Ipsen JH (2013) Membrane-mediated aggregation of curvature-inducing nematogens and membrane tubulation. Biophys J 104(5):1018–1028. https://doi.org/10.1016/j.bpj.2012.12.045
153. Simunovic M, Mim C, Marlovits TC, Resch G, Unger VM, Voth GA (2013) Protein-mediated transformation of lipid vesicles into tubular networks. Biophys J 105(3):711–719. https://doi.org/10.1016/j.bpj.2013.06.039
154. Yin Y, Arkhipov A, Schulten K (2009) Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains. Structure 17(6):882–892. https://doi.org/10.1016/j.str.2009.03.016
155. Cui H, Mim C, Vazquez FX, Lyman E, Unger VM, Voth GA (2013) Understanding the role of amphipathic helices in N-BAR domain driven membrane remodeling. Biophys J 104(2):404–411. https://doi.org/10.1016/j.bpj.2012.12.006
156. Prevost C, Zhao H, Manzi J, Lemichez E, Lappalainen P, Callan-Jones A, Bassereau P (2015) IRSp53 senses negative membrane curvature and phase separates along membrane tubules. Nat Commun 6:8529. https://doi.org/10.1038/ncomms9529
157. McMahon HT, Boucrot E (2011) Molecular mechanism and physiological functions of clathrin-mediated endocytosis. Nat Rev Mol Cell Biol 12(8):517–533. https://doi.org/10.1038/nrm3151
158. Fotin A, Cheng Y, Sliz P, Grigorieff N, Harrison SC, Kirchhausen T, Walz T (2004) Molecular model for a complete clathrin lattice from electron cryomicroscopy. Nature 432(7017):573–579. https://doi.org/10.1038/nature03079
159. Kirchhausen T (2000) Clathrin. Annu Rev Biochem 69:699–727. https://doi.org/10.1146/annurev.biochem.69.1.699
160. den Otter WK, Renes MR, Briels WJ (2010) Asymmetry as the key to clathrin cage assembly. Biophys J 99(4):1231–1238. https://doi.org/10.1016/j.bpj.2010.06.011
161. den Otter WK, Renes MR, Briels WJ (2010) Self-assembly of three-legged patchy particles into polyhedral cages. J Phys Condens Matter 22(10):104103
162. Matthews R, Likos CN (2012) Influence of fluctuating membranes on self-assembly of patchy colloids. Phys Rev Lett 109(17):178302
163. Matthews R, Likos CN (2013) Structures and pathways for clathrin self-assembly in the bulk and on membranes. Soft Matter 9(24):5794–5806
164. Ramakrishnan N, Sunil Kumar PB, Radhakrishnan R (2014) Mesoscale computational studies of membrane bilayer remodeling by curvature-inducing proteins. Phys Rep 543(1):1–60. https://doi.org/10.1016/j.physrep.2014.05.001
165. Heinrich V, Svetina S, Zeks B (1993) Nonaxisymmetric vesicle shapes in a generalized bilayer-couple model and the transition between oblate and prolate axisymmetrical shapes. Phys Rev E 48(4):3112–3123. https://doi.org/10.1103/Physreve.48.3112

166. Iglic A, Kralj-Iglic V, Bozic B, Bobrowska-Hagerstrand M, Isomaa B, Hagerstrand H (2000) Torocyte shapes of red blood cell daughter vesicles. Bioelectrochemistry 52(2):203–211
167. Miao L, Seifert U, Wortis M, Dobereiner HG (1994) Budding transitions of fluid-bilayer vesicles: the effect of area-difference elasticity. Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Top 49(6):5389–5407
168. Svetina S, Zeks B (1989) Membrane bending energy and shape determination of phospholipid-vesicles and red blood-cells. Eur Biophys J 17(2):101–111
169. Auth T, Gompper G (2009) Budding and vesiculation induced by conical membrane inclusions. Phys Rev E 80(3):031901
170. Bozic B, Kralj-Iglic V, Svetina S (2006) Coupling between vesicle shape and lateral distribution of mobile membrane inclusions. Phys Rev E 73(4):041915
171. Kabaso D, Bobrovska N, Gozdz W, Gov N, Kralj-Iglic V, Veranic P, Iglic A (2012) On the role of membrane anisotropy and BAR proteins in the stability of tubular membrane structures. J Biomech 45(2):231–238. https://doi.org/10.1016/j.jbiomech.2011.10.039
172. Kralj-Iglic V, Hagerstrand H, Veranic P, Jezernik K, Babnik B, Gauger DR, Iglic A (2005) Amphiphile-induced tubular budding of the bilayer membrane. Eur Biophys J 34(8):1066–1070. https://doi.org/10.1007/s00249-005-0481-0
173. Mukhopadhyay R, Lim HWG, Wortis M (2002) Echinocyte shapes: bending, stretching, and shear determine spicule shape and spacing. Biophys J 82(4):1756–1772
174. Su YC, Chen JZ (2015) A model of vesicle tubulation and pearling induced by adsorbing particles. Soft Matter 11(20):4054–4060. https://doi.org/10.1039/c5sm00565e
175. Ayton GS, McWhirter JL, Voth GA (2006) A second generation mesoscopic lipid bilayer model: connections to field-theory descriptions of membranes and nonlocal hydrodynamics. J Chem Phys 124(6):64906. https://doi.org/10.1063/1.2165194
176. Ayton GS, McWhirter JL, McMurtry P, Voth GA (2005) Coupling field theory with continuum mechanics: a simulation of domain formation in giant unilamellar vesicles. Biophys J 88(6):3855–3869. https://doi.org/10.1529/biophysj.105.059436
177. Hoover WG, Hoover CG (2003) Links between microscopic and macroscopic fluid mechanics. Mol Phys 101(11):1559–1573. https://doi.org/10.1080/0026897021000026647
178. Ayton GS, Blood PD, Voth GA (2007) Membrane remodeling from N-BAR domain interactions: insights from multi-scale simulation. Biophys J 92(10):3595–3602. https://doi.org/10.1529/biophysj.106.101709
179. Boucrot E, Pick A, Camdere G, Liska N, Evergren E, McMahon HT, Kozlov MM (2012) Membrane fission is promoted by insertion of amphipathic helices and is restricted by crescent BAR domains. Cell 149(1):124–136. https://doi.org/10.1016/j.cell.2012.01.047
180. Ayton GS, Lyman E, Krishna V, Swenson RD, Mim C, Unger VM, Voth GA (2009) New insights into BAR domain-induced membrane remodeling. Biophys J 97(6):1616–1625. https://doi.org/10.1016/j.bpj.2009.06.036
181. Lin LC, Brown FL (2004) Brownian dynamics in Fourier space: membrane simulations over long length and time scales. Phys Rev Lett 93(25):256001
182. Lin LCL, Brown FLH (2005) Dynamic simulations of membranes with cytoskeletal interactions. Phys Rev E 72(1):Artn 011910. https://doi.org/10.1103/Physreve.72.011910
183. Ayton GS, Voth GA (2010) Multiscale simulation of protein mediated membrane remodeling. Semin Cell Dev Biol 21(4):357–362. https://doi.org/10.1016/j.semcdb.2009.11.011
184. Chang R, Ayton GS, Voth GA (2005) Multiscale coupling of mesoscopic- and atomistic-level lipid bilayer simulations. J Chem Phys 122(24):244716. https://doi.org/10.1063/1.1931651
185. Lyman E, Cui H, Voth GA (2011) Reconstructing protein remodeled membranes in molecular detail from mesoscopic models. Phys Chem Chem Phys 13(22):10430–10436. https://doi.org/10.1039/c0cp02978e
186. Liu P, Voth GA (2007) Smart resolution replica exchange: an efficient algorithm for exploring complex energy landscapes. J Chem Phys 126(4):045106. https://doi.org/10.1063/1.2408415
187. Sigurdsson JK, Brown FLH, Atzberger PJ (2013) Hybrid continuum-particle method for fluctuating lipid bilayer membranes with diffusing protein inclusions. J Comput Phys 252:65–85

188. De Nicola A, Zhao Y, Kawakatsu T, Roccatano D, Milano G (2011) Hybrid particle-field coarse-grained models for biological phospholipids. J Chem Theory Comput 7(9):2947–2962. https://doi.org/10.1021/Ct200132n
189. De Nicola A, Zhao Y, Kawakatsu T, Roccatano D, Milano G (2012) Validation of a hybrid MD-SCF coarse-grained model for DPPC in non-lamellar phases. Theor Chem Accounts 131(3):Artn 1167. https://doi.org/10.1007/S00214-012-1167-1
190. Sarukhanyan E, De Nicola A, Roccatano D, Kawakatsu T, Milano G (2014) Spontaneous insertion of carbon nanotube bundles inside biomembranes: a hybrid particle-field coarse-grained molecular dynamics study. Chem Phys Lett 595:156–166. https://doi.org/10.1016/J.Cplett.2014.01.057