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Modeling membrane reshaping driven by dynamic protein assemblies

Yiben Fu and Margaret E. Johnson

Abstract

Remodeling of membranes in living systems is almost universally coupled to self-assembly of soluble proteins. Proteins assemble into semi-rigid shells that reshape attached membranes, and into filaments that protrude membranes. These assemblies are temporary, building from reversible protein and membrane interactions that must nucleate in the proper location. The interactions are strongly influenced by the nonequilibrium environment of the cell, such as gradients of components or active modifications by kinases. From a modeling perspective, understanding mechanisms and control thus requires 1. time-dependent approaches that ideally incorporate 2. macromolecular structure, 3. out-of-equilibrium processes, and 4. deformable membranes over microns and seconds. Realistically, tradeoffs must be made with these last three features. However, we see recent developments from the highly coarsened molecule-based scale, the continuum reaction-diffusion scale, and hybrid approaches as stimulating efforts in diverse applications. We discuss here methodological advances and progress towards simulating these processes as they occur physiologically.

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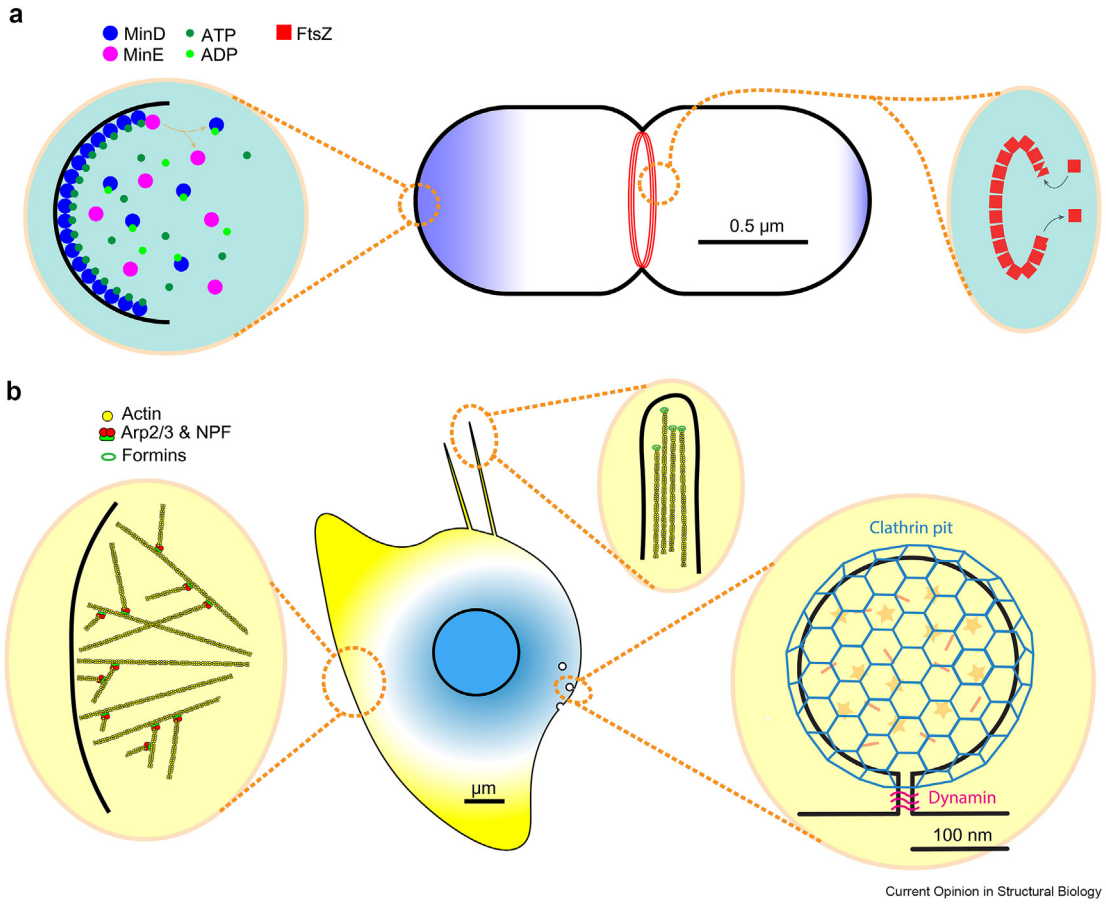
Introduction

Membrane remodeling is essential for cells to divide [1], crawl [2], and transport diverse nutrients and proteins into the cell during endocytosis [3] (Figure 1). While cell division and endocytosis, for example, operate at very different scales and serve markedly different functions for the cell state, they share common physical principles. For these and other remodeling processes, the physical reshaping of the membrane requires cytoplasmic proteins such as clathrin, actin, dynamin, or septin (to name a few) that peripherally and transiently link to membranes [4,5]. This arrival of proteins at the membrane provides a spatio-temporal cue to initiate remodeling. Membrane remodeling is influenced by multiple modes of curvature induction [6–8], but structured protein assemblies play a special role in sculpting the shape of membrane [9]. These semi-rigid structures provide mechanical work to bend the softer membrane into specific geometries like spheres [9], narrow or broad protrusions [2,10], and narrowed necks [11–13]. Molecular structure thus clearly impacts their remodeling function [6,13,14], but the assembled structures need not represent singular free energy minima. For example, a variety of accessory proteins can help stimulate macromolecular assembly without integrating into functional structures during endocytosis [15,16], and ATP hydrolysis and phosphatases can actively modify the stability of contacts during assembly [3,17]. We discuss in this work the efforts to incorporate these shared principles into increasingly realistic models and simulations of membrane remodeling driven by protein assemblies, while contrasting key differences in model assumptions that impact current capabilities and directions for growth.

We see modeling and simulation of these membrane remodeling processes as increasingly indispensable for establishing biological mechanisms from ever-growing volumes of quantitative data. Quantitative models can act as a bridge between *in vitro* measurements, whether of macromolecular structure, biochemical rates, or membrane energies [7,18], and the emergent collective dynamics seen *in vitro* [4,10] and *in vivo* [19,20]. The underlying physics of self-assembly, membrane bending, and enzyme reactions does not change outside the test-tube; integrating these disparate sources of information into one model, although short of the complexity within cells, gives modelers combinatorial control to directly test whether a mechanism we hypothesize is sufficient to explain what we observe. Computer simulations can thus impose a sense of order on complex experimental measurements, eliminating physically impossible justifications [10,21], establishing bounds on force, rate, or concentrations [4,22], and predicting responses to novel stimuli [23,24].

Figure 1



Self-assembled proteins drive membrane remodeling across the cell at nanometer and micron length scales, with similar variations in timescales. **(a)** Physical control of cell division in *E.coli*. For cells to physically divide, proteins must locate the center of the cell and perform mechanical work to constrict the cell membrane. Identification of the cell division plane in the center is dependent on the Min protein system, which involves cytoplasmic proteins localizing, polymerizing, and detaching from the membrane. These dynamics are dependent on ATP binding and hydrolysis, setting up oscillations of ~60s period that promote recruitment of the tubulin homolog FtsZ to the cell center. While until recently modeled purely as a pattern forming system, evidence suggests Min proteins are sensitive to membrane mechanics as well [30]. The assembly of FtsZ filaments on the membrane is also actively dependent on GTP and is central to forming a ring-like structure that constricts over several minutes [12], pulling the membrane with it. Primary questions remain on how FtsZ assembly and treadmilling can produce constricting forces. **(b)** Cell motility in animal cells. Cell motility is generated by dynamic protrusive structures at the membrane edge, such as lamellipodia and filopodia, which are controlled by actin assembly filaments. Branched actin networks actively assemble with the aid of proteins like the ARP2/3 complex to push the membrane into thin, sheet-like protrusions or lamellipodia, allowing cells to crawl forward. Actin is anchored to the membrane in diverse ways, via peripheral membrane proteins like N-WASP or ERM proteins that bind transmembrane proteins [5]. Bundled actin filaments can also induce thin needle-like structures called filopodia during motility that help cells sense their environment, with these structures forming over several minutes [2]. The diversity of structures, forces, and molecular connections formed by actin filaments makes predicting cell fate a major challenge [20]. **(c)** Clathrin-mediated endocytosis in eukaryotes. Transport of many nutrients and receptors into the cell requires the plasma membrane to reshape into vesicles of ~100–200 nm in diameter [9]. These more localized events happen persistently, with downstream trafficking events ultimately recycling membrane and receptors back to the plasma membrane in a form of homeostasis. Here again, cytoplasmic proteins like clathrin localize to and assemble at the membrane, reshape a spherical membrane bud that is fissioned off via a constricting assembly of the GTPase dynamin. The process only takes ~1 min [3]. Fundamental questions persist about how the diverse cargo receptors control proper vesicle formation and budding.

A persistent challenge for simulations is that to reach beyond static or equilibrium structures, we must numerically integrate equations of motion tracking populations of distinct species over seconds to minutes of real time and hundreds of nanometers. During each time-resolved and calibrated step, we aspire to include macromolecular structure, mechanics, and nonequilibrium driving forces such as enzymatic reactions or spatial gradients (Figure 2). Currently, this cannot be achieved in a single model spanning initiation to completion of membrane remodeling. Towards this goal, however, we see increasing development and

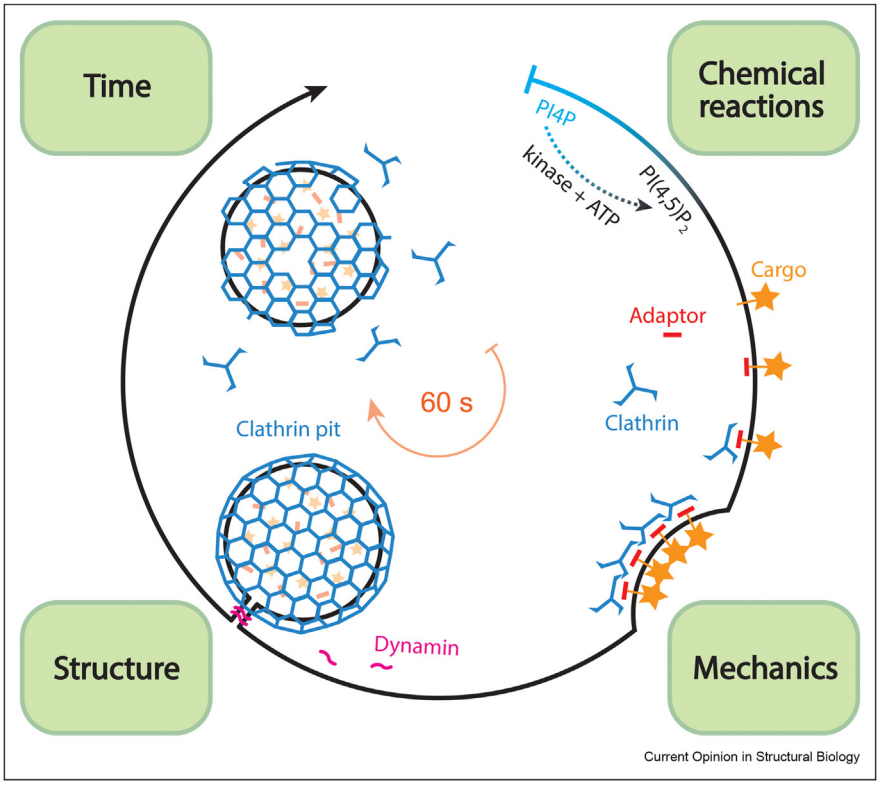
overlap from the two largely separate fields of highly coarsened molecular-scale modeling [22,25,26] and cell-scale modeling [27]. From the coarse molecular scale, one naturally captures structure and mechanics, but with limited access to experimental time-scales and nonequilibrium events. From the rate-based reaction-diffusion scale, the advantages and limits are swapped; slow, nonequilibrium dynamics is natural, while incorporating structure and mechanics is challenging. Bridging these levels of biological realism requires expanding the underlying mathematical models by, for example, building in coarse structural features in reaction-diffusion models [28] or adding in rate-based reactions to coarse molecular models [29]. With a more wide-spread embrace of open-source code release and model repositories, we are hopeful that more united efforts in method development will produce needed advancements in the underlying theory and numerical implementations.

Across diverse models and simulations, essential physical features and principles are shared

Before discussing specific computational methods, we identify here the elements we consider most essential for biologically realistic models of protein-driven membrane reshaping. The examples cited here model the single or sub-cellular level, excluding multi-cellular processes due to the additional length-scales involved. We also exclude membrane fusion, as the proteins involved are not mechanically reshaping the membrane.

Cytoplasmic components recruit to and depart from the membrane. Part of the directionality of these pathways simply involves a build-up of proteins from the 3D solution to the 2D membrane surface [4,31]. The speed and strength of peripheral protein-membrane interactions are thus a key factor of assembly, as is the membrane composition that controls specificity of proteins for membranes [22].

Figure 2



Four key features we aspire to include within each model during assembly driven remodeling. Currently, models and simulations trade-off whether to include these four key features: time-resolution, macromolecular structure, mechanics, or chemical reactions (or other nonequilibrium events). As illustrated by the example of clathrin-mediated endocytosis (CME), however, they all play essential roles throughout a successful vesicle budding cycle. We illustrate a chemical reaction via phosphorylation of the essential membrane lipid PI(4,5)P_2 which influences membrane recruitment. The structure of the clathrin cage forces the membrane into a spherical vesicle, overcoming the membrane mechanical energy which prefers to be flat. After ~1 min, the vesicle buds off via the GTP hydrolyzing dynamin assembly. Coarse molecular-scale models naturally include structure and mechanics, whereas cell-scale models naturally include experimentally relevant timescales and chemical reactions.

Volume to surface area affects assembly The relative size of the cytoplasm to the membrane area is a critical control variable [31], as the effective concentration of proteins restricted to the membrane surface is dramatically increased by this dimensional reduction for essentially all cell membranes [32]. Assembly timescales can be accelerated dependent on this lengthscale [33], with spatial gradients established by the disparate times to reach or remain at the membrane [31]. Cell shape and confinement can further restrict the geometry or arrangement of protein assemblies, as in the cytoskeleton [34].

A network of protein interactions influences these complex processes As with most of cell biology, remodeling processes are combinatorially complex, involving participation of many distinct components in a large biochemical network [35]. The full biochemical complexity is too much to include in any one model due to the number of parameters required and inevitable unknowns. However, distinct protein classes are important in regulating assembly without playing both structural and mechanical roles. For example, some adaptor proteins like AP-2 establish physical links to the membrane without reshaping the membrane (Fig 1), while others like FCHo1/2 help nucleate assemblies but are excluded from completed assemblies [15,16].

Mechanisms of membrane remodeling require high protein density Membrane bilayers have a preferred curvature that depends on the difference in lipid composition across both leaflets; a bilayer with a symmetric composition prefers to be flat and thus resists bending. There are multiple mechanisms for proteins to induce membrane bending and curvature [6–8,24,36], and even individual proteins can induce curvature through helix insertion on one leaflet of the bilayer [18,37]. Protein assemblies, however, can sculpt the softer membrane into large deformations to match their specific shapes, like spherical vesicles [21]. Constriction of the membrane in cell division or vesicle scission involves ring-like assemblies that attach to the membrane and shrink in radius via ATP/GTP hydrolysis [23,29]. Filamentous assemblies can act like beams to protrude the membrane, or provide pulling and pushing force to tubulate the membrane [38,39]. Even disordered protein assemblies that lack specific rigid shapes can generate stress to induce membrane bending [7].

Active out-of-equilibrium events influence timing or localization The assembly dynamics of actin and other cytoskeletal components are well-known to be strongly influenced by their binding and hydrolysis of ATP [40]. Enzymatic turnover of lipids in the membrane can dynamically alter the mechanical properties of the membrane by creating asymmetry in lipid composition across both leaflets, for example [17,41], but also the adhesiveness, helping to trigger disassembly [28]. Spatial gradients of proteins can emerge due to production and degradation, with gradients playing a clear role in assembly dependent pattern formation [31].

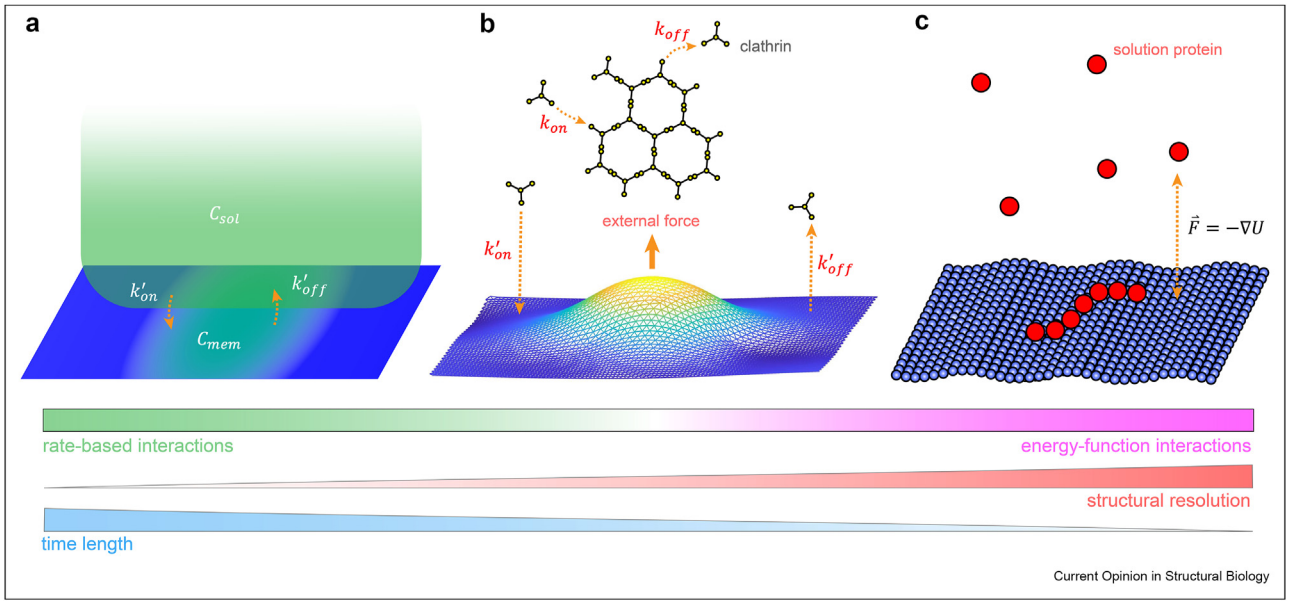
Computational models and methods tradeoff resolution, speed, and parameterization requirements

We compare here a spectrum of computational models from the continuum to coarse structural representations that are too complex to be solved analytically. In the dynamical methods we describe below, the usual tradeoff between resolution and computational cost is accompanied by major differences in the types of parameters required (Figure 3). The models do not simply represent a sliding scale of systematic coarse-graining, but a change in the mathematical model of reactions and interactions, and how they give rise to mechanical resistance of the membrane. We narrow our focus to methods that can capture at least two of the central features we depicted in Figure 2, and exclude models solved using systems of ordinary differential equations (ODE) because they lack any spatial resolution. We exclude atomistic or near-atomistic molecular modeling approaches, as although they encode intermolecular forces and dynamics that support time, structure, and mechanics [42], they are far short of reaching timescales occurring biologically. While not a comprehensive review of research applying computer simulations to remodeling processes of Figure 1, we highlight representative recent examples.

Background on mesoscale membrane models Numerical methods for modeling membrane dynamics and mechanics that approach cellular scales follow continuum surface approaches or highly coarsened particle-based approaches, with hybrids that contain elements of both. Because the theoretical and numerical development of these methods is critical to the attainment of more realistic biological models, we briefly summarize these methods here.

For continuum surface methods, the physical model commonly invoked to describe the energy and mechanics is the Helfrich Hamiltonian from the 1970s [43]. The Helfrich Hamiltonian depends on a small number of emergent material parameters of the membrane that are experimentally measurable, and control bending, tension, and compressibility, for example [44–46]. The membrane surface is a continuum and thus individual lipids are not represented, although we note continuum approaches have also been applied to study lipid domain formation in membranes out-of-equilibrium [47]. For large-scale deformations, the surface is spatially described by the points of a triangular mesh [48]. The advantage of mesh representations is that they do not require an assumption of small-amplitude fluctuations [49] or axial symmetry, and can

Figure 3



Methods for simulating protein assembly coupled with membrane remodeling can vary significantly in resolution and in the parameters required for the underlying models. Moving from fully continuum models (A) to fully particle-based models (C) is not just a sliding scale with higher spatial resolution because of the significant changes in parameters required. The protein interactions shift from being parameterized by macroscopic rates in (A) to distance-dependent energy functions in (C). Parameterizations for interactions with the membrane are more variable, as ultimately forces or energy functions are necessary to describe mechanics. For continuum membrane surfaces, material parameters such as bending modulus control the membrane energy. The deformed triangulated mesh surface illustrated in (B) has an energetic cost due to being forced from its preferred flat geometry. For particle-based membranes, pairwise energies can fully control the interactions, such that the material parameters (like bending modulus) must emerge. (**a**) The continuum methods are solved via partial-differential equations (PDE) following the reaction-diffusion model as a standard. They can reach very large spatial and temporal scales, and concentrations (C_{sol}, C_{mem}) and rates (k'_{on}, k'_{off}) can be defined directly from experimental measurements. Example applications are propagating proteins waves on membranes [35]. (**b**) Hybrid method shown here captures structure-resolved proteins with continuum membranes. Explicit assembly shapes are resolved with multi-site clathrin proteins interacting with one another according to rates (k_{on}, k_{off}), and to the membrane (k'_{on}, k'_{off}) following the reaction-diffusion model [4]. Other methods use energy functions to control interactions [38]. Coupling to a continuum membrane allows membrane reshaping and energies to be computed, with membrane dynamics only rarely included [38]. (**c**) Highly coarsened molecular-scale models where both proteins (red) and membranes (blue) are represented by particles or beads that interact according to a model-specific energy function. The most expensive, these models are thus more limited in the spatial and temporal scales reached, but the particle-scale forces allow for dynamic reshaping of membranes into diverse morphologies, including membrane scission [29].

describe more realistic surfaces of arbitrary topology in 3D space [36,38,50–52]. Variations in these continuum models arise in elaborations to the energy functions, e.g. adding in surface viscosity [53], and in numerical implementations of the mesh to control smoothness, for example [48]. The dynamics of the surface can be integrated using fully deterministic models [35] or stochastic models.

Highly coarsened molecular-scale membrane models can be separated into two approaches, which we will denote as fully particle-based or quasi particle-based. The fully particle-based models are the most 'molecular-scale' and thus the most similar to atomistic models. These methods rely on energy functions that define pairwise interactions between particles as a function of distance and/or orientation [54,55], with each 'particle' capable of representing a range from individual lipids [25,55] to large patches of lipids [56]. Membranes update dynamically following Langevin [57] or Brownian dynamics [22]. They are significantly more computationally expensive than continuum methods, which limits their attainable time and lengthscales. Unlike the Helfrich model, parameters do not describe measurable material properties; material properties instead emerge because of the effective molecular-scale interactions like repulsion and attraction between particles [56]. These models have the advantages of observing dynamic morphological motion of the surface [57,58], localized defects in lipid organization [25], explicit variations in lipid or protein distribution across the membrane [56,59], and events like membrane scission [22,29]. In the quasi particle-based membranes, particles similarly represent lipids or patches with a mass and a size controlled by repulsive potentials. However, particle pairs are bonded or tethered together such that the bending energy can be computed using the Helfrich Hamiltonian, just as in the continuum

surface methods [60—63]. These hybrid methods thus reach longer scales than fully particle-based membrane surfaces.

Fully continuum models of proteins and membranes Continuum PDE-based approaches with continuum surfaces reach the largest spatial and temporal regimes, readily incorporate nonequilibrium dynamics, and are relatively inexpensive [64]. However, they have no structural resolution of proteins, and membrane mechanics and dynamics are not standard features of PDE-based software. A common trade-off is to exclude membrane mechanics entirely, which has been successfully used in reaction-diffusion models of membrane-mediated assembly and pattern formation [31], or to exclude protein and membrane dynamics entirely, which facilitates measurements of shape changes in response to variations in membrane properties [39,45,65]. Yet integrated models are attainable by coupling protein density at the surface to membrane shape, via a local material property like spontaneous curvature that energetically favors a new membrane shape following the Helfrich Hamiltonian [35,66]. When formulated in problem-specific models, dynamic simulations have captured shape changes driven by assembly of BAR proteins [21]. With more generalized, user-friendly dynamical membrane models actively developed [21,50], we anticipate more transferrable application of these methods across disparate remodeling pathways.

Hybrid methods combine particle and continuum proteins and membrane By giving proteins an explicit volume, valency, and structure, the semi-rigid assemblies they dynamically assemble can then shape the membrane into specific geometries like spheres vs finger-like protrusions. While computationally more expensive than fully continuum models, these methods capture how assemblies like viral capsids or clathrin cages have structured limits to their growth and occupancy [4,28], or how cytoskeletal filaments influence orientations or directionality of their growth [40]. Software implementations of these stochastic and dynamic models use forces to control interactions focused on cytoskeletal components [38,67] or the rate-based reaction-diffusion model to study dynamics of arbitrary structures assembling out-of-equilibrium [28]. Because these methods have protein structure, the assembly shapes can be directly coupled to membrane shape changes in vesicle formation [5], with corresponding energetic costs measured [4]. However, a *dynamic* membrane coupled to the assembly adds theoretical and numerical challenges, and is only currently a feature of the cytoskeletal tool MEDYAN, which allows the membrane to move in response to forces from filaments [38].

An alternative hybrid approach combines a quasi-particle-based membrane [68] with continuum protein density [69] or coarse-grained proteins [70]. Such an approach captures membrane dynamics and membrane shape changes over relatively large spatial and temporal scales [71], with capacity to capture local membrane heterogeneity [68]. The advantage is that the resolution of the membrane is much higher; local defects in membrane order are visible and models can predict when scission of the membrane ultimately occurs [69], a feature that is not possible with continuum surfaces.

Fully particle-based proteins and membranes At the highly coarsened molecular-scale, we have particle-based representations of the membrane and the proteins components, obtaining the highest resolution. Interactions between proteins and from proteins to membrane generally all follow pairwise energy functions [29,72], which is more physically accurate but makes chemical reactions a challenge, as it would require a dynamic modification to the strength of energy functions. Membrane reshaping emerges quite naturally from the corresponding forces. Model implementations that introduce proteins to particle-based membranes are formulated in a problem-specific manner, which allows the user to optimize interaction types [23,29,73], but at the cost of transferability. To make simulations tractable, proteins are initialized on the surface, bypassing diffusion and recruitment to the membrane [23,24,29]. These models are successful in resolving a variety of morphological changes driven by protein assemblies, and structures can be directly compared to experiment [24,29]. Hagan and colleagues were able to fully resolve viral capsid formation, from the recruitment and assembly of proteins to the membrane to the subsequent budding and scission, observing how interaction strength tuned the success of both coupled processes [22]. Despite their expense, these models achieve the highest resolution and can propagate membrane dynamics straightforwardly just as they do the proteins, thus requiring fewer assumptions or new theory. Developing software that is generalized and combines proteins with the actively developed membrane models will help expand the more limited applications at this scale.

Conclusions and outlook

Although current simulation tools cannot have it all regarding resolving the full dynamics of membrane remodeling coupled to structural assembly (Figure 2), it is not hard to imagine what we can learn once that time arrives. In clathrin-mediated endocytosis, simulations could uniquely resolve whether the surprisingly stochastic transition from a nascent clathrin-coat to a successful budded vesicle requires capturing specific cargo. For cell motility, we could predict how changing the relative abundances of actin-binding proteins controlled the fate of membrane reshaping. We have focused above on the development of model frameworks and computer

simulations to achieve this, but we acknowledge that another significant challenge in designing realistic models is parameter estimation. The complexity of these biological pathways means that components, interacting partners, or interaction strengths are unknown. For reaction-diffusion models, large parameter-spaces must be traversed for a given model to identify optimal biochemical rates. For coarse-molecular scale models, with each new component, a new multi-parameter energy function must be derived, and these models as a result usually have less diversity in components. The calibration of the coarse time-step is also not trivial and can make dynamics more difficult to compare with experiment. However, parameter estimation is increasingly accelerated by tools from AI and machine learning, with recent applications in reaction-diffusion and molecular dynamics simulations [74,75]. We see software development or open-source projects rather than one-off models as central for reproducibility, improved validation, and transferability from one system to another. Shared standards help resolve whether conflicting conclusions arise because of fundamental differences in models or due to numerical implementations. Lastly, increased communication across the coarse molecular-scale and continuum modeling fields will stimulate better understanding of how molecular-scale parameters map to rates or material parameters, and vice-versa. Ultimately, we expect the same principles to emerge regardless of the specific model being used, and explicitly showing this will bolster applications of modeling at this cellular resolution.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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