REVIEW

Morphology Control of Self-Assembled Amphiphilic Surfactants - A Survey of Simulation Methods

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One of the grand challenges of amphiphilic self-assembly is the design of ordered structures whose morphology or shape can be explicitly and dynamically controlled by adjusting the properties of the amphiphiles or their surroundings. Such a capacity would enable researchers to create synthetic systems with functionality that meets or exceeds biological cells, and provide a robust platform for a broad range of engineering applications such as artificial tissues, drug delivery, and separation membranes. Despite significant progress, important fundamental questions remain unanswered, due in part to the limited resolution andthe restricted parameter spaces that are readily accessible in experiments. Computational studies thus provide an important complement to experiments, enabling in-depth insight into underlying mechanisms and an exploration of the parameter spaces for behavior that has not yet been achieved in experiments. In this review, we briefly introduce fundamental concepts and pertinent experiments related to dynamic shape modulation in self-assembled amphiphiles. Then, in the bulk of the review, we survey the most influential simulation studies that investigate and identify approaches to control the self-assembled shape of amphiphiles, with an emphasis on kinetic and mechanical effects. Finally, we conclude with a perspective on prospective research directions in this exciting field.

KEYWORDS
amphiphile, self-assembly, morphology control, computer simulation, computational methods

1 | INTRODUCTION

Observing and studying how organisms behave have enabled human beings to develop new technologies or optimize existing ones. One particularly noticeable phenomenon in living systems is the self-assembly of amphiphilic molecules into organized structures to create separate aqueous compartments. Examples include cell membranes that protect the interior of all cells from the outside environment [1, 2], and exosomes that transfer molecules between different parts of the organisms via membrane vesicle trafficking [3, 4]. Amphiphiles are comprised of both solvophobic and solvophilic segments, and when dissolved in aqueous solutions at a concentration above the critical micelle concentration (CMC) [5, 6], they self-assemble into structures of various sizes and shapes, including micelles, tubular structures, fibers, unilamellar vesicles, and multilamellar vesicular compounds. In more concentrated systems they further organize into a multitude of ordered patterns [7, 8].

Self-assembly of both naturally occurring and synthetic amphiphiles have been widely used to achieve biomimetic behaviors [9, 10, 11] and to guide bottom-up nanotechnology for the purpose of engineering new materials with novel functions [12, 13]. Since the early 2000s, there has been explosive growth in the number of scientific reports regarding amphiphile self-assembly. Most of the existing studies have focused on understanding equilibrium or near-equilibrium self-assembly. Researchers have identified a number of molecular properties (e.g., chemical identity [14, 15], segment length ratio [16, 17, 18, 19, 20, 21, 15]) as well as environmental variables (e.g., solvent quality [22, 23, 24, 25, 26]) that give rise to the plethora of self-assembled structures described above. This work has significantly improved our understanding of the fundamental chemistry and physics of amphiphilic self-assembly, and provides invaluable guidance for creating tailor-made structures for desired applications.

Interest in out-of-equilibrium and dynamic self-assembly has increased in recent years enabling exciting new fields such as “morphogenic engineering” and intelligent “self-architecturing” systems [27, 28, 29]. We use the term “out-of-equilibrium assembly” or “dynamic self-assembly” to mean a system that is subject to local or external sources of energy that drive the system away from equilibrium (and possibly keep it away from equilibrium) to form different or more complex (and hopefully more desirable) structures than is possible at equilibrium. Dynamically self-assembled structures depend not only on the physical properties and chemical interactions between different molecular segments, but also on dynamic variables, such as time-varying changes to the environment, chemical reaction rates, and more. Non-equilibrium processes provide a pathway for forming structures with constant energy input and dissipation, thus giving rise to more complex biomimetic behaviors.

While exciting progress has been made in both equilibrium and non-equilibrium assembly [30, 31, 32, 33], current technology remains considerably limited compared to biological systems. In the latter, cells can intelligently communicate through signaling, they can harness external mass, energy and information to move through rugged energy landscapes, and they can execute a series of autonomous behaviors including formation of ordered structures, division, and reproduction. By contrast, control of assembly processes in synthetic systems relies on either bottom-up assembly driven by simple, static interactions, or top-down manipulation with limited degrees of freedom. In cases that are out-of-equilibrium, such control is even harder due to the constant input and dissipation of energy, and knowledge regarding such dynamic processes is still limited. Consequently, control of self-assembled amphiphilic systems remains largely empirical, and there remain significant open questions about the methods and fundamental principles that will permit emulation of the behaviors listed above.

In this review, *we will focus on studies related to the non-equilibrium control of either the global or local shape of an individual amphiphilic aggregate*. By “control” we mean the design of particle interactions, molecular chemistry and conformations, solvent environment to form a desired structure and reliably manipulate the morphological changes. The control strategies in the context of our discussion are summarized in Fig. 1, including (a) *in situ* modification of environmental variables to cause *global* morphological transition (i.e., change of the morphology of the entire assembly), (b) inserting external surfactants

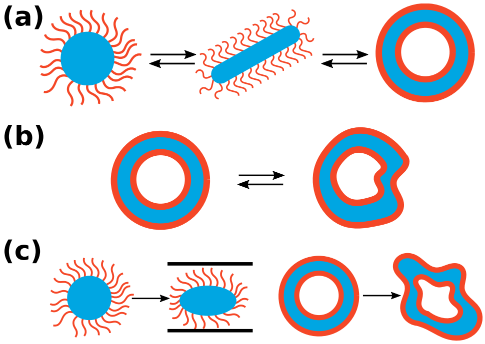

FIGURE 1 Schematic illustration of global and local morphology change. (a) Global transition of the morphology of the entire assembly; (b) Local structural change of self-assembled amphiphiles; (c) Mechanical stress-induced morphology change in amphiphilic assemblies;

or using enzymatic reactions to modify the *local* structures of a self-assembled amphiphile (i.e., change the shape of part of an assembly), and c) exerting mechanical stress that generates shape changes such as distortion, rupture, protrusion and so on.

It is of fundamental interest to obtain mechanistic insights into morphological control of amphiphilic aggregates for several reasons. First, self-assembled amphiphiles with controllable shapes may be the key to applications such as drug delivery with a high drug loading, spatially separated nanoscale reactions, and synthetic morphogenesis. Second, understanding the physical principles behind synthetic systems may shed light on the principles governing cellular morphing behavior in biological systems. Finally, understanding fundamental mechanisms will increase our capacity to synthesize or reverse engineer biomimetic cellular materials with precise hierarchical microstructures, potentially leading to materials that are healable, growable, or otherwise possess novel properties.

In addition to a focus on the manipulation of the global or local shape of an aggregate, we will restrict our attention to simulation studies. With increasing computer power, computer simulations have gained increasing importance in understanding amphiphilic self-assembly in recent years. They complement experiments by providing rational models for investigating the structure and dynamics of self-assembly at a molecular level and beyond. Computer simulations are especially important for understanding shape control of amphiphilic assemblies for at least two reasons. First, simulations lead to a greater understanding of fundamental mechanisms. That is, they provide a way to both generate and test hypotheses that can be used to explain existing experimental observations. This will be especially important for non-equilibrium assembly, where molecular-scale dynamics that are hard to measure play a critical role. Second, simulations provide a relatively easy and cheap way to explore different parameters via so-called *in silico* experiments. This feature of simulations will enable one to guide experiments by predicting potentially viable structures that have not yet been synthesized, thereby significantly reducing the time and cost it takes to discover novel materials.

The rest of the review is organized as follows. We first discuss some fundamental concepts of curvature, and briefly introduce some practical ways to create either a global or a local morphological change to the amphiphilic assemblies in Sec. 2, which are crucial for the purpose of our discussion and might point to new directions of theoretical studies. We then provide an overview of the different types of simulation techniques that have been used to study amphiphilic self-assembly processes in Sec. 3. We will then discuss recent simulation results organized into two distinct types of mechanisms for controlling morphology. In Sec. 4, we discuss the first: simulations where kinetic effects result in either a global or a local morphological transition. These kinetic effects include environmental variables such as temperature, solvent condition, and solute species, insertion of external surfactants, and reaction-induced modification of either the amphiphiles or their surroundings. In Sec. 5, we discuss the second: simulations where mechanical effects including spatial confinement, external flow, and internally generated active stress lead to a distortion of the shape or even an instability of the self-assembled structure. Finally, we conclude by providing some synthesis of the current direction of the field, and we propose some prospective research directions for the future in Sec. 6.

2 | THEORIES AND EXPERIMENTS OF SHAPE-CHANGING BEHAVIORS OF SELF-ASSEMBLED AMPHIPHILES

Before addressing the question of how to simulate the shape change of self-assembled structures, we first elaborate on fundamental concepts regarding the morphologies of self-assembled amphiphiles and briefly review some pertinent experimental observations to date.

2.1 | Principles of shape control

The self-assembly behavior of amphiphilic surfactants is a balance of a series of factors such as the relative hydrophobicity of molecular segments and conformational entropy. In the literature, there are two ways generally used to describe the shape of amphiphilic assemblies, either from a molecular perspective, or describing the tendency of bending at a larger length scale.

The simplest way to explain self-assembly behavior is to use the molecular packing parameter [34]. The packing parameter of an amphiphile, shown in Fig. 2, is calculated as

$$p = \frac{v_0}{a l_0} \tag{1}$$

where v_0 and l_0 are the volume and the length of the amphiphile tail, respectively, and a is the equilibrium area per amphiphilic molecule at the head-tail interface [34, 35]. The packing parameter p is a measure of preferred geometry adopted by amphiphiles, and empirically correlates with simple self-assembled shapes with $p < 1/3$ corresponding to spheres, $1/3 < p < 1/2$ corresponding to cylinders, and $1/2 < p < 1$ corresponding to bilayers or vesicles.

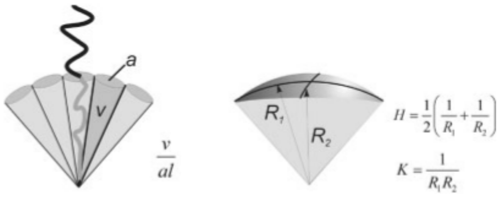

FIGURE 2 Left: drawing of amphiphiles showing the packing parameter. Right: schematic demonstration of interfacial mean curvature (H) and Gaussian curvature (K). Reprinted with permission from Ref. 35. Copyright 2003 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

While the packing parameter relates the self-assembled amphiphiles to molecular information and gives a qualitatively accurate prediction of morphologies, it does not provide quantitative information such as size and extent of bending. However, the packing parameter can also be connected to larger scale properties such as membrane curvature parameters [35, 36],

$$p = 1 + H l_0 + \frac{K l_0^2}{3} \tag{2}$$

where H and K are the mean and Gaussian curvature, respectively. The mean and Gaussian curvature are given by

$$H = \frac{1}{2}\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \tag{3}$$

$$K = \frac{1}{R_1 R_2} \tag{4}$$

where R_1 and R_2 are the radii of curvature at a specific point on the surface along the two principal directions, both of which are perpendicular to one another and perpendicular to the tangential plane at the point. H and K (or R_1 and R_2) offer a geometric characterization of a self-assembled structure and provide a quantitative description of the surface profile. By convention, the curvature is negative when the surface bulges towards the interior of the self-assembled structure, and positive when it bends towards the exterior compartment [37].

The *spontaneous curvature* of an amphiphile is an alternate way to conceptualize the shape of an amphiphilic assembly without relying on the assumptions of the packing parameter model. Spontaneous curvature describes the intrinsic tendency of an amphiphile to

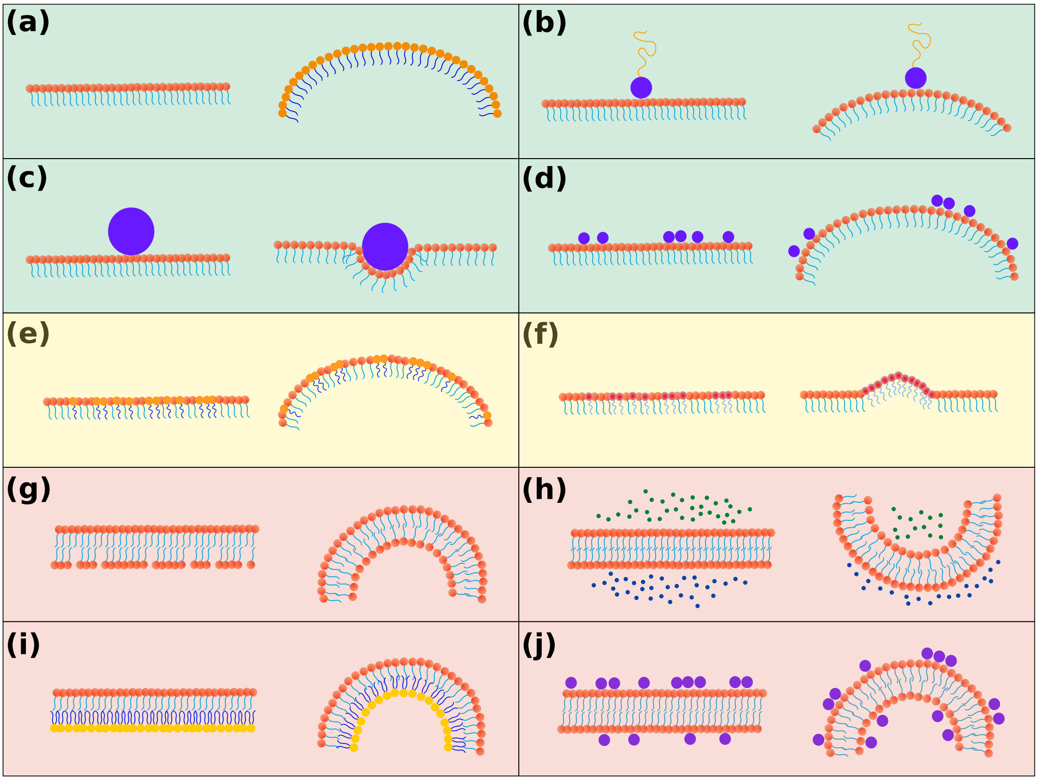

FIGURE 3 Summary of molecular mechanisms for inducing curvature change in homogeneous monolayer (a-d), hybrid monolayer (e-f), and bilayer (g-j) amphiphilic assemblies: (a) Packing parameter change; (b) Anchored molecules; (c) Large particle adhesion; (d) Small particle adhesion; (e) Miscible case; (f) Phase separated case; (g) Asymmetric amphiphile density; (h) Asymmetric solvent condition; (i) Asymmetric composition; (j) Asymmetric adsorption density.

form curved structures with the lowest bending energy *subject to no bending resistance or constraints* [38, 37, 39]. Like the packing parameter, the spontaneous curvature depends on molecular properties such as composition, exposure to aqueous environments, the relative size of the head and tail, etc., but it is conceptually tied to the structural length scale rather than the molecular [38]. As such, the spontaneous curvature does not have a simple relationship to molecular properties and is often calculated in simulation studies and used to understand the assembly behavior in unperturbed systems [37, 39]. Consequently, the difference between the *actual* and spontaneous curvature is key to interpreting how the system will evolve.

We identify ten molecular mechanisms for modifying the curvature of homogeneous monolayers, hybrid monolayers, and bilayer assemblies, and each is summarized with a cartoon in Fig. 3. For homogeneous assemblies, the most intuitive way, as demonstrated in Fig. 3 (a), is to modify the chemistry of the amphiphile and change the packing parameter [40, 41]. As illustrated in Fig. 3 (b), curvature is also modified when molecules or surfactants are tethered to the surface of the assembly. Such an anchored molecule will create a curvature change by increasing the configurational entropy [42, 43, 44]. Particles that adhere to the surface can also alter curvature, but the mechanism differs with particle size. This is important because particles that interact with amphiphilic assemblies span several orders of magnitude, ranging from sub-nanometer-sized ions to micron-sized objects. If the adhesive particle is large enough (i.e. the radius is larger than the thickness of the assembled structure), the particles can impose their curvature onto the surface, as demonstrated in Fig. 3 (c) [45]. Alternatively, when small solute particles are decorated to the surface as shown in Fig. 3 (d), the curvature depends on the size and concentration of adhesive particles. The induced curvature is a result of balancing the enthalpy and entropy between the particles and the amphiphiles. There are also established theories for predicting this adsorption-induced curvature change [46, 47].

Assemblies composed of molecules with more than one packing parameter (hybrid assemblies) can also induce curvature changes. As demonstrated in Fig. 3 (e), when the two types of molecules are miscible with each other, curvature occurs to accommodate all the molecules in the same aggregation [48]. When the two molecules are immiscible and tend to phase separate, one might observe domain-dependent behaviors as drawn in Fig. 3 (f). The emergent curvature can be controlled by the intrinsic repulsion between the two components, the composition ratios of the two molecules, as well as other environmental conditions that affect the interaction between the molecules and the solvent [49, 50, 51].

Specifically for the bilayer structures, curvature can be driven by asymmetric properties in the two leaflets [39, 37]. In fact, a perfectly symmetric bilayer is extremely exceptional, and often only serves as a minimal model for understanding basic physics. Leaflet asymmetry can be caused by a variety of reasons. For instance, as shown in Fig. 3 (g), the density of the amphiphiles within the two leaflets can be different, and this difference causes the bilayer to bend towards the high-density leaflet [37]. Even when densities are similar, when exposed to different solvent environments, curvature could still emerge due to distinct interactions between the amphiphile and different solvents [52, 53], as shown in Fig. 3 (h). In cases where the membrane is composed of two or more amphiphiles with different conformations and spontaneous curvatures, Fig. 3 (i), or when the two layers are exposed to different solvent environments, the bilayers have a tendency to demonstrate a stress-induced curvature [54]. Alternatively, as described by Fig. 3 (j), when particles get adsorbed by the solvophilic head groups, the difference in adsorption density can give rise to a change in curvature. Here a higher adsorption density imposes a higher pressure onto the head groups, thus driving the bilayer to bulge towards the leaflet with higher adsorption density [37].

With even more fine control of local packing parameter, we could also anticipate a shape-control rationale based on choosing the molecules of a specific packing parameter at each point along the surface of the self-assembled structures can give rise to a spontaneous curvature distribution that maps the desired morphologies [55]. Such modifications can possibly happen at different length scales, depending on the variations of desired structures [56, 57, 58, 59].

2.2 | Experimental observations of morphology control

Despite the large list of theoretical mechanisms listed above, there are still a significant amount of experimental observations that remain unexplained. One of the major reasons for this is process complexity; there are often multiple mechanisms that can influence aggregate shape occurring simultaneously in a given system. In addition, theories on dynamic morphological control of amphiphiles are still incomplete, leaving lots of open questions regarding non-equilibrium self-assembly. Accordingly, we categorize some noteworthy experimental work here, with the hope of providing future direction and inspiration for researchers in the theory and simulation community.

In biological systems, many self-assembled structures exhibit a unique combination of properties. They generally form closed surfaces to separate different aqueous compartments, and possess the robustness and stability to sustain the separation, while keeping some level of mass exchange between the different compartments. Aside from robustness, these biological amphiphilic assemblies are also highly flexible and exist in a fluid state, which means that they can migrate with relatively fast lateral diffusivity and easily adapt to the fluctuations in the environment, thereby enabling remodeling of composition and topology [60, 61]. Such fascinating remodeling processes have also been found in synthetic amphiphilic assemblies or in *in vitro* experiments.

In synthetic systems, amphiphilic chemistry and composition and the environment surrounding the amphiphiles affect the global equilibrium morphology of the assembly. Small molecules such as lipids and lysosomotropic surfactants tend to form aggregates with thinner layers of ordered structures and good permeability, whereas amphiphilic copolymers typically have molecular weights ranging from 1000 to 15,000 g/mol and form structures with thicker assembled layers and poor permeability [62]. Hybrid amphiphilic copolymer/lipid assemblies are also emerging that combine the functionality of lipids with the robustness of copolymer chains and form morphologies with desired properties [63]. Systematic studies have also shown that changing amphiphile molecular weight also significantly affects morphology. For instance, poly(butadiene)-b-poly(ethylene oxide) (PB-b-PEO) was observed to form different morphologies at different hydrophilic PEO block lengths [64]. With increased PEO block length, morphologies switch from vesicles to cylinders to spheres due to an increased contribution to the spontaneous interfacial curvature [64]. Similar changes occur when solvent quality is adjusted. Shen et al. reported a ternary phase diagram of polystyrene-block-poly(acrylic acid) (PS-b-PAA) copolymer in dioxane/water mixtures [65]. They observed a sequence of morphologies from pure spheres to spheres/rods, pure rods, rods/vesicles, and pure vesicles as water content increased due to an increasing interfacial tension between the core and the corona [65].

In addition to these more well-defined equilibrium structures, amphiphilic assemblies can also undergo significant transitions in morphology subject to *dynamic* in-situ adjustment of external conditions including pH, temperature, ionic strength, and so on [22, 66]. In situ modifications to the amphiphiles, such as changes to the chemistry of the molecules or side chain lengths, can also render similar shape transitions [67, 19]. Some of the more intricate manipulations can be achieved using non-equilibrium techniques. For example, solvent vapor annealing can be used to control the ordering and orientation of nanodomains [68], and dual/hybrid responsive amphiphilic assemblies have been shown to exhibit stepwise conformational changes in response to a combination of various external stimuli [69].

Besides techniques for changing the global morphology, several approaches have been proposed to induce a *local* shape change of self-assembled amphiphiles. Local shape change requires some kind of spatial heterogeneity on length scales at or below the size of the assembly. The most intuitive technique for doing so is through microinjection of a solution in the external environment near the assembled structure [70, 71, 72, 40, 41]. Creating a difference between the fluids inside and outside of a vesicle (i.e., an enclosed basic solution and external acid solution) is an alternative way of observing independent shape-changing behaviors of the two monolayers [52]. The spontaneous curvature changes in the above cases are mainly attributed to the chemical modification and the subsequent rearrangement of amphiphiles. One can also observe local shape change by introducing tethered molecules (e.g., proteins) to create stress-induced spontaneous curvature changes, thus forming membrane necks in a controlled manner by adjusting the concentration of the bounded molecules [73, 74].

More advanced approaches to realize *local* shape controls are also possible within hybrid amphiphile assemblies or using enzyme-induced catalytic reactions. In the first scenario, the hybrid system is composed of both stimulus-inert and stimulus-responsive amphiphiles, for example a pH-inert block copolymer and a pH-responsive cationic switchable lipid. External stimulus will only result in property changes to the stimulus-responsive species, thus triggering a series of local structural variations including protrusions, shape fluctuations, and fission [75]. Such shape change behavior can also be fine-tuned by controlling the ratio of the inert to responsive components [75]. In the second scenario, Miele et al. reported a similar case to Ref. 52, with a different pH environment inside and outside the vesicles [53]. Instead of manually changing the outside pH, they enclosed urea/urease inside the lumen of a vesicle, and the urease-catalyzed hydrolysis reaction can change the interior pH, leading to vesicle fission [53].

In addition to all the kinetic effects discussed above, mechanical stresses also significantly affect the shape and stability of amphiphile assemblies. For instance, microfluidic techniques have been applied to assembly of amphiphiles with uniformly distributed sizes and morphologies [76]. Unlike assembly in bulk solutions, the laminar flow in microfluidic channels could provide accurate and consistent control over the motion of amphiphilic molecules [77]. Meanwhile, spatial confinement could reliably manage the size of microstructures, and the interfacial tension between the channel and the molecules could serve as a template of alignment [78, 79]. Another example would be amphiphilic assemblies in shear flow. The elastic response of the molecules to shear often results in elongated shapes, or in case of very strong shear, leads to complete rupture of the structure [80].

Finally, dynamic morphology control of the self-assembled amphiphiles has a wide array of potential applications, as far-from-equilibrium dynamic behavior possesses many similarities to autonomous biological behaviors that involve chemical signaling and communication pathways. Such smart responsive materials have attracted considerable attention in a wide variety of research areas including drug delivery, coatings, water purification, sensor materials, artificial tissues, and so on [81, 82, 83, 84].

3 | OVERVIEW OF SIMULATION TECHNIQUES OF MODELING AMPHIPHILE SELF-ASSEMBLY

The rapid development of computing systems has facilitated theoretical studies of physical processes such as amphiphile self-assembly. One major advantage of computer simulations is that they allow access to time and length scales that are very hard or impossible to study in laboratory settings. The literature on the physics of amphiphile self-assembly is vast, ranging from atomistic-level approaches [85, 86] to statistical field theories [87, 88]. Fig. 4 shows the most common classes of simulation methods including all-atomistic models, coarse-grained models, and continuum phase field models, arranged by accessible time and length scales.

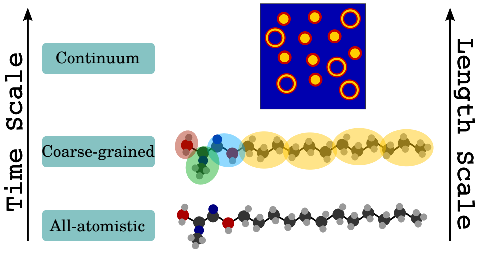

FIGURE 4 Illustration of different types of simulation methods. The accessible length scale and time scale increase from all-atomistic models at small scales, coarse-grained models at intermediate scales, and continuum models at the largest scales.

Atomistic-level simulations are carried out at relatively small length scales, and can explore chemically-specific interactions. Consequently, such results usually reveal the in-depth mechanism of amphiphilic behavior within the accuracy limits imposed by methodological limits (e.g., the force field) [89]. However, the timescale of atomistic level simulation is on the order of picoseconds to several nanoseconds, which severely limits its application to assembly processes with long relaxation times [89].

Field theory models stand in stark contrast to atomistic-level simulations and can reach much larger length and time scales, but sacrifice small length-scale accuracy. For example, phase field models are widely used in science and engineering to model a variety of moving interface phenomena, suitable for studying fluid mechanics on a mesoscopic scale [90, 91]. Self-consistent field theory (SCFT) is a frequently used field theory method for simulating polymer systems, appropriate for investigating equilibrium morphologies and phase diagrams of inhomogeneous systems [92, 93, 94]. However, special techniques are required to use field theory techniques for amphiphile solutions because the mean-field assumption breaks down when there are structures such as micelles and vesicles in the solution [95].

Coarse-grained (CG) molecular models serve as a balanced trade-off between efficiency and accuracy, and have been extensively applied to studying the equilibrium behavior of amphiphile self-assembly in the past two decades. Simpler (more “coarse-grained”) CG models provide a generalized understanding of the qualitative behaviors of amphiphilic systems [96, 97, 98, 99], while more detailed (“fine-grained”) CG models have parameters that are mapped to specific chemistries to better compare to experimental observations [100, 101, 102]. There are also many studies focused on the equilibrium (or metastable) morphologies of block polymer micelles and vesicles. Much of this literature focuses on connecting molecular properties (e.g., block length, solvent/polymer interaction parameter) to the final self-assembled structure [103, 104, 105, 106, 98, 107, 108, 109, 110, 111].

The above models are solved using either particle-based or field-based simulation methods. The most frequently used methods for particle-based models include molecular dynamics (MD) [112], Brownian dynamics (BD) [113], dissipative particle dynamics (DPD) [114], and Monte Carlo (MC) methods [115]. In MD, one solves Newton’s equations of motion between atoms or coarse-grained “beads”, with pairwise potentials between the beads determined by the particle chemistry. MD is typically the method of choice for all-atom simulations. BD is a type of Langevin dynamics (usually an overdamped Langevin equation) that models the motion of particles when there is a disparity in length/time scales between particles of interest and some background solvent. The random force describes the thermally driven motion and kinetics, but does not intrinsically include hydrodynamics, which must be accounted for separately. DPD is a more coarse-grained method with a softer pairwise potential, which means that the particles can overlap and easily move past each other. It also accounts for the thermal fluctuation through a random force, but unlike BD, it includes hydrodynamic interactions with an additional dissipative force. MC uses advanced random sampling techniques to obtain ensemble averages of energy and entropy. A big advantage of MC is that judicious choices of random move sets can potentially avoid commonly encountered kinetic frustrations and long relaxation time scales in MD-type methods, making it appropriate for studying the equilibrium states of systems. Finally, there are a variety of methods for solving field-based simulations such as phase-field models and SCFT. These typically rely on well-established techniques for solving partial differential equations [116], but there must be special considerations for complex-valued models and thermally fluctuating fields [95].

The above techniques encompass the broad categories of models and methods available for simulating the formation of self-assembled structures, and we have only provided a brief introduction to them here. In the next two sections, we will discuss how these methods have been modified, extended, and applied to provide meaningful insight into the manipulation of the global and local morphology of amphiphilic assemblies.

4 | SIMULATION OF MORPHOLOGY CONTROL DUE TO KINETIC EFFECTS

As discussed in previous sections, the conventional rationale for designing self-assembled amphiphiles generally relies on thermodynamic-based reasoning. In reality, assembled structures are often trapped at some random metastable state—a state at a local free energy minimum—and the equilibrium structure might not be reached within a reasonable time scale [117, 118]. Moreover, kinetically trapped structures that form more complicated morphologies could possibly even contribute to making new materials [119, 120].

In this section, we review recent simulation work regarding self-assembled amphiphiles whose morphology is controlled via kinetic effects. This is not to be confused with equilibrium or near-equilibrium self-assembly under various conditions where a system is carefully perturbed about an equilibrium state. Kinetic effects result from an abrupt change, due to either top-down inputs or bottom-up signals that are applied to a system to drive it away from its current state, thus resulting in structures that might not exist in the equilibrium regime. In such a system, the free energy profile may not give useful insight into how the system self-organizes due to the potential for path-dependency of self-assembly.

Here, we consider three different cases where kinetics can affect the morphologies of self-assembled structures. We first focus on applying top-down changes to global properties of the system, such as titration of pH, annealing to different temperatures and so on, to adjust the interactions between the amphiphilic components or between the surfactants and the solvent environment. This usually results in an overall transition of the morphology, e.g., micelle to vesicle to multivesicular, or disorder to order transitions. Second, we discuss the effect of inserting extra surfactants or molecules to the system and how this can result in morphological changes. Finally, it is also possible to simulate a localized change in the amphiphile systems, thus modifying the local curvature of the equilibrium structure, say from flat to concave or convex, which is often seen in behaviors such as endocytosis.

4.1 | Applying global changes to induce shape transition

There are a large number of metastable states on a “rough” free energy landscape that can be accessed through rapid quenching or annealing via changes in pH, temperature, pressure, or other system properties [121, 122, 123, 124, 125]. Quenching and annealing techniques can create structures that are otherwise inaccessible because there are kinetic processes in self-assembled amphiphile systems with very different timescales. Generally, quenching takes milliseconds to seconds, while the self-assembly processes of amphiphilic molecules can be on the order of seconds or even hours [121, 122]. We survey here cases where global conditions, specifically temperature, solute concentration, and solvent quality, are used to trigger a shape transition. The intent here is not to survey exhaustively all the global variables that can be controlled. Rather, we want to highlight some examples to demonstrate the methodology and analysis that can be useful to study the process-directed/path-dependent phenomena in non-equilibrium shape transition. We also want to draw some general conclusions from these results regarding how simulations can assist in understanding the fundamentals of shape control, and what can potentially be improved for more accurate and advanced outcomes.

4.1.1 | Temperature-induced shape change

Thermoresponsive amphiphiles are one of the most studied systems that give rise to interesting morphology transitions, since they exhibit drastic transitions in solubility at either an upper critical solution temperature (UCST) or a lower critical solution temperature (LCST) [126, 127, 128, 129, 123, 130]. Molecules that demonstrate UCST behaviors dissolve in solution when the temperature is above the UCST, whereas molecules with LCST tend to mix with solvent when the temperature is below the LCST. The main advantage of using temperature is the ease of control, and therefore it is relatively easy to perform cycling changes compared to some of the other global variables. Computational simulation techniques have been used to provide details of these dynamic processes, thereby assisting the *in silico* design of thermoresponsive amphiphiles for specific applications.

One of the pioneering simulation works of controlled conformational modification was done by Rodríguez-Hidalgo et al. where they used DPD to study the thermoresponsive behavior of poly(2-(N-morpholino)ethylmethacrylate)–b-poly(sulfobetaine methacrylate) (PMEMA–b-PSBMA) copolymer [128]. PMEMA–b-PSBMA copolymers form micelles in water

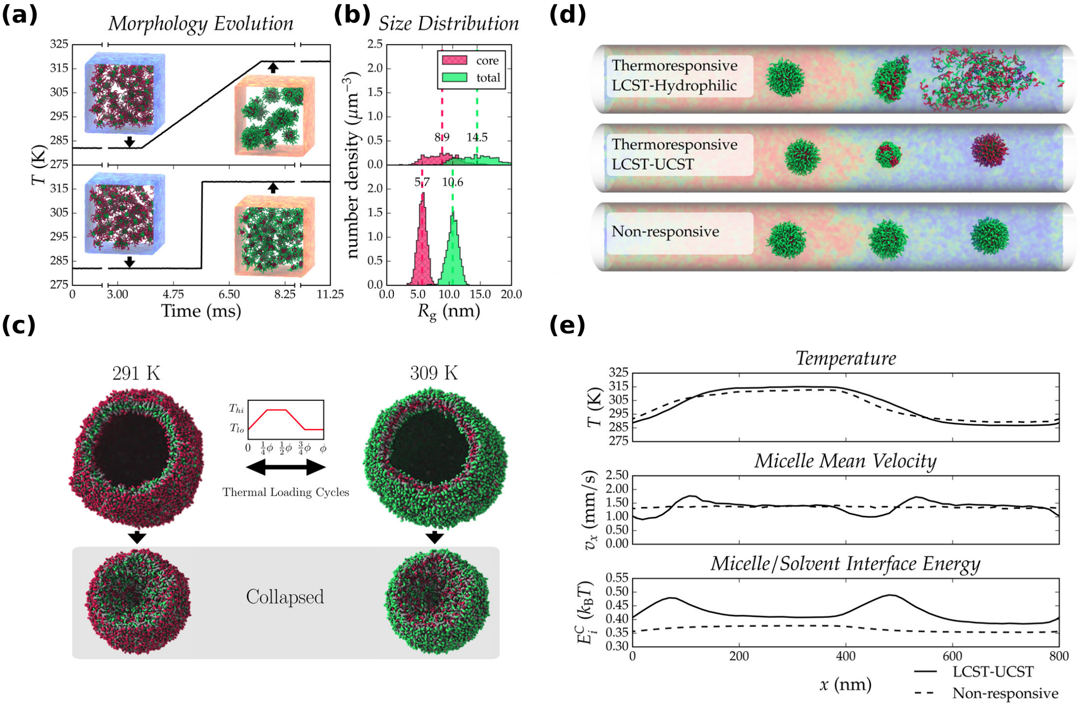

FIGURE 5 eDPD simulations of double thermoresponsive diblock copolymers. (a) Morphology evolution of micelles undergoing thermal annealing at different heating rates. (b) Size distribution of the final micellar structures at different heating rates. (c) Demonstration of the heating-cooling cycle of double thermoresponsive vesicles. (d) Micelle flowing through a thermally variant channel. (e) Corresponding temperature, velocity and energy profiles along the flow direction. Reprinted with permission from Ref. 123. Copyright 2016 American Chemical Society.

with PSBMA-cores at low temperature, and PMEMA-cores at high temperature. Rodríguez-Hidalgo et al. explored self-assembly behavior using two different temperature profiles. In the first, they performed simulations with a continuous thermal input, where they changed the interaction parameters between the polymer and solvent to gradually increase the temperature from 276 K to 333 K with an increment of $\Delta T = 1$ K. They observed three phases during the transition, i.e. micelle dissociation, free chain stabilization, and formation of inverse micelles, which agrees qualitatively with the experimental observations [128]. In the second, they investigated a one-step annealing to heat the system directly to 333 K from an equilibrated system at 276 K. The latter simulation results revealed a two-step inversion, including the contraction of PMEMA blocks, and the extension of PSBMA blocks with simultaneous formation of PMEMA cores [128]. Rodríguez-Hidalgo et al. concluded that the transitory states are controlled by the combination of the critical solution temperatures of each block and the rate of temperature increase. They also postulated that by adjusting the LCST and UCST of the different blocks, one can possibly manipulate and predict the local micellar structure by controlling the heating rate [128].

The Karniadakis's group used a different simulation method called energy-preserving DPD (eDPD) method to investigate temperature-dependent processes [131, 129, 123]. The eDPD formulation treats internal energy as a degree of freedom, thus enabling the simulation of transient and local behaviors of thermoresponsive block copolymers under dynamic conditions such as heating rates and inhomogeneous temperature of the environment [131, 129]. Tang et al. used the eDPD method to study the non-equilibrium micellization process of double-thermoresponsive diblock copolymers with one UCST block and one LCST block (LCST-b-UCST) [123]. They investigated the dynamic processes under a couple of different scenarios. Similar to the previous authors, they first examined an inverse micellization process at different heating rates by comparing the final structure of a continuous heating procedure to that of an abrupt temperature change. As shown in Fig. 5 (a) and (b), the continuous heating process produces larger aggregates with a wider distribution of size due to fusion of smaller ones, whereas the abrupt temperature change generates a population of smaller micelles with a narrower distribution of size. These results clearly demonstrate the non-equilibrium nature of micelle inversion, and provide a potential approach to tune the size and distribution of thermoresponsive micelles [123].

Tang et al. also studied the thermoresponsive behavior of unilamellar vesicles when subject to repeated heating–cooling cycling, as shown in Fig. 5(c). They tested heating-cooling rates ranging between 5 μs/cycle and 1.25 ms/cycle and observed collapsing vesicles at both very low and very high thermal loading frequencies. Testing at intermediate frequencies resulted in a vesicle survival rate of around 50–70%. The collapse of vesicles at low frequencies can be reasonably ascribed to the relatively persistent condition where both blocks interact similarly with the solvent [123].

To emulate the process of drug delivery cargo traveling in a circulatory system, they also simulated amphiphilic assemblies flowing through vessels with an uneven distribution of temperatures [123]. They compared aggregates of three different components, including LCST-b-hydrophilic, LCST-b-UCST, and non-responsive diblocks. Simulated transitions of micelles are shown in Fig. 5 (d). The LCST-b-hydrophilic micelle undergoes disassociation after passing through the vessel, the LCST-b-UCST micelle is inverted when reaching the lower temperature end, and the non-responsive micelle has no apparent changes throughout the process [123]. The corresponding temperature, velocity and energy profiles for the non-responsive and LCST-b-UCST micelles are shown in Fig. 5 (e). There is clearly a major difference in the interfacial energy between the two cases when the micelles experience similar temperature transitions [123]. These results validated the applicability of eDPD to studying dynamic thermal processes, and provided valuable evidence for potential applications of thermoresponsive amphiphiles in controlled loading/release of drug delivery systems.

4.1.2 | Solvent-induced shape change

Owing to the natural solvent selectivity of different segments of amphiphiles, morphological change can also be triggered by a change in solvent conditions to form a rich diversity of micellar morphologies [133, 134, 135, 125, 136, 137]. The formation of various structures could be a consequence of different mechanisms. For a given type of amphiphile, the packing parameter could be significantly different when solvated in polar or non-polar solvents, thus forming different structures [135]. In addition, in systems with more than one solvent, the solvent ratio can be adjusted to tune the final assembled structures [137, 132]. Finally, amphiphiles with more complex molecular structures or higher molecular weights tend to form more complicated morphologies when quenched between different solvent conditions [136]. The reason is two-fold: complex molecules (a) intrinsically contain more degrees of freedom for forming more complex assemblies [138], and (b) have longer relaxation times and larger energy barriers, thus creating more long-lived metastable structures. In this section, we summarize simulation results for the above mechanisms, with the intention to expand our perception of how complex metastable structures can form using solvent annealing approaches.

CG particle simulations have been regularly used for simulating solvent-induced shape change, where (similar to temperature changes) quenches can be modeled by altering the interaction between solvent and amphiphilic components. For example, Fu et al. examined the role of solvent on the self-assembly of peptide amphiphiles (PA) using CG molecular dynamics

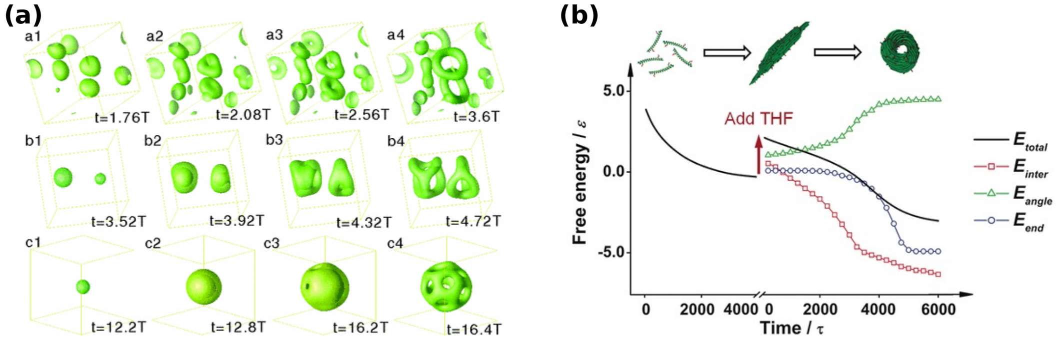

FIGURE 6 Solvent-induced kinetic control of self-assembled amphiphiles. (a) Morphology transition from spherical micelles to kinetic controlled morphologies after peptide cleavage. Reprinted figure with permission from Ref. 125. Copyright 2008 by the American Physical Society (b) The snapshots show the closure of rod-like micelles upon adding THF solvent. The change in total energy, as well as the three components, i.e. interfacial energy, end-cap energy and bending energy, are plotted to show the contribution of each component. Adapted with permission from Ref. 132. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(CGMD) simulations [139]. Instead of the commonly used Lennard-Jones (LJ) potential, they adopted discontinuous potentials (i.e., hard-sphere and square-well potentials) to model the collision dynamics. Hydrogen bonding, which plays a vital role in microstructure formation, was modeled with a direction-dependent square-well potential. The solvent effect was modeled using an implicit approach that allows for a larger scale calculation [139]. The simulated systems started from random initial conditions that were quickly quenched to three different types of aqueous media, in which the tails displayed different levels of solvophobicity and packing parameters. At the lowest solvophobicity, PA molecules form small aligned β sheets due to the hydrogen bonding between the peptides. The small sheets then gradually aggregate together to form an open network without obvious segregation of the solvophobic cores. At intermediate solvophobicity, PA molecules first assemble into spherical micelles. The micelles then bump into each other to form a cylindrical nanofiber with vertically aligned β sheets. At the highest solvophobicity, PA molecules also form spherical micelles. Instead of a cylinder with secondary structures, the micelles eventually merge into worm-like micelles without any secondary structures [139].

We can draw several conclusions from the above results. The formation of stable solvophobic domains is largely due to solvophobic interactions, whereas the organization of secondary microstructures and directional alignment are ascribed to hydrogen bonding. The final assembled structure is a consequence of the interplay between the solvophobic interaction and hydrogen bonding. Moreover, based on the micellization pathway at intermediate solvophobicity, solvophobic interactions have a dominant effect on the early-stage behavior of PA assembly, and hydrogen bonding contributes more to the subsequent alignment and the formation of elongated structures. This yields a qualitative understanding of how solvent conditions affect the self-assembly of PA molecules, and provides meaningful guidance for experimental design to produce desired structures.

CG models have also been used to investigate shape change behavior in mixtures of different solvents, where both slow solvent addition and fast solvent addition have been studied. Campos-Villalobos et al. performed CGMD simulations to understand the self-assembly behavior of poly(ethylene oxide)-b-poly(butylmethacrylate) (PEO-b-PBMA) in a THF/water mixture [137]. They modeled PEO-b-PBMA in mixtures of different ratios of THF to water, mimicking the process of slowly adding water, and discovered a variety of structures including random clusters, kinetically-trapped spheres, spherical and cylindrical vesicles, dispersed bilayer structures, and lamellar phases [137]. Gumus et al. performed a series of DPD simulations to investigate the impact of fast solvent quenching on the self-assembly behavior of bottlebrush copolymers, denoted as $(\mathrm{C}\text{-}g\text{-}\mathrm{A}_k/\mathrm{B}_m)n$), with A as solvophobic beads, B as solvophilic beads, and C as slightly solvophobic backbone beads [136]. The fully relaxed homogeneous polymer solutions were immediately quenched into a bad solvent condition for the A blocks. A number of non-equilibrium nanostructures were revealed under different conditions of miscibility between solvophilic and solvophobic blocks, molecular weight, and solvent quality [136]. Both results suggest that solvent quenching could give rise to non-equilibrium structures due to the relatively slow relaxation of amphiphilic molecules between different solvent conditions. However, in order to obtain a more quantitative understanding of solvent kinetic trapping, characterization of different time scales is still needed.

More complex structures, such as vesicular and toroidal structures, can also be formed by quenching into different solvent conditions. Though these structures are energetically less favorable due to a large bending energy, they can still form spontaneously due to entropic or kinetic driving forces. He et al. used a phase field model to simulate the formation pathway of complex micellar structures at different solvent conditions by adjusting the Flory-Huggins parameter between the solvophilic segment and the solvent [125]. They simulated solvent quenches directly from a homogeneous state to the target conditions, and typical time series that led to the formation of toroidal structures are shown in Fig. 6 (a). From these and similar calculations, they constructed a state diagram of the metastable morphologies and determined that the morphology transitions from vesicles to spheres and rods to toroidal structures with increasing solvophilicity. In addition, they found that there were two distinct pathways of forming complex micelles. One is the coalescence of multiple small micelles, the other is the growth of individual micelles. The pathway the system takes is largely dependent on the polymer concentration [125]. Both mechanisms corroborate the importance of the presence of initial nuclei, since they serve as a template for growing further structures. Thus adjusting the number of initial nuclei is a potential way of controlling the formation of complex structures. Starting with initial seeds of different shapes is another promising approach to guide structure formation.

Yang et al. also studied toroidal structure formation in water/THF mixture with BD simulations [132]. They proposed an alternative mechanism of forming toroids by end-to-end closure of rodlike micelles. They started with a self-assembled rod-like micelle in water, and then gradually decreased the compatibility between the micelle core and shell in a step-wise fashion, mimicking the process of gradually adding tetrahydrofuran (THF) solvent to the system. The simulations, shown in Fig. 6 (b), reveal an increased bending of the rod-like micelle with the addition of THF [132]. Eventually the ends of the rod-like micelle enclose to form a toroidal structure. The simulation results have very good qualitative agreement with their reported experimental results, and they yield a possible explanation for biological processes such as DNA molecules forming toroidal bundles [132].

To further understand the driving forces for morphology change during solvent quenching, Yang et al. calculated the contributions of three different components to the total free energy, namely the interfacial energy (E_{int}), the end-cap energy (E_{e}) and the bending energy (E_{b}). As shown in Fig. 6 (b), adding THF solvent results in a higher total free energy due to the increase in the first two components (interfacial and end-cap energy), and the rod-like micelles tend to bend themselves and close the end to reduce the unfavorable exposure of solvophobic components. Therefore, the formation of closed toroidal structure is a consequence of balancing the end-cap energy and bending energy [132].

4.1.3 | Solute-induced shape change

Solute stimuli are also often used to control the morphologies of self-assembled amphiphiles, especially ionic surfactants [140, 141, 142, 143, 124, 144, 145]. Unlike the solvent-induced shape changes where the interfacial energy change is driven by different solvent environments, solute-induced change often involves modifying the chemistry of the amphiphilic molecules. Dynamic rearrangement is generally due to a chemical change of a specific ionic functional group (e.g., a carboxyl group or an amino group) in response to a change in pH or ionic strength [146]. In this section, we discuss simulations of solute-induced shape changes caused by selective salt and pH changes in the system. Note that these simulations use models at a variety of length scales, thus providing information at different levels of resolution enabling mechanistic insights from different perspectives.

At the atomistic scale, Zhang et al. performed all-atom MD (AAMD) simulations to study the effects of salt on the conformation and mobility of a salt-responsive copolymer poly(OEGMA-co-TFEA) [147]. They compared the conformations of a single chain in pure water and in a NaCl solution. Looking at the simulation snapshots, they saw that the polymer chain takes on a more extended conformation in pure water, whereas with in presence of NaCl the chain folds into a globular shape [147]. By comparing the pair-wise radial distribution function, they concluded that the change in conformation is due to the affinity of sodium ions with the ether oxygen atoms of OEGMA segments, resulting in partial dehydration of the polymer chains [147]. Importantly, these atomistic-level simulations not only provide a visualization of how conformations of single molecules change in the presence of salt, but they also provide detailed information such as interatomic distances and energies that are inaccessible in mesoscopic models where coarse-graining has “smeared out” such information.

At the mesoscopic scale, simulations can provide information about dynamics, due to larger accessible length and time scales. Along these lines, a DPD simulation was reported by Rodríguez-Hidalgo et al. studying the formation of PMEMA-b-PSVBP inverse micelles in water with the addition of different inorganic salts [148]. In pure water, PMEMA-b-PSVBP copolymers form spherical micelles with PSVBP-core and PMEMA corona. Using stabilized micelles as the initial condition, they investigated three different salt-addition protocols: (i) adding NaBr first followed by $NaSO_4$, (ii) adding $NaSO_4$ first followed by NaBr, and (iii) the simultaneous addition of NaBr and $NaSO_4$. The simulation results demonstrated three distinct kinetic pathways for micelle inversion, which matched qualitatively with experimental observations [148]. In case (i), they observed a direct disassociation of the micelle upon adding NaBr, followed by the formation of inverted micelles after adding $NaSO_4$. In case (ii), micelle fusion occurred with the addition of $NaSO_4$, and the subsequent inversion happened with simultaneous ascent and immersion of two blocks. Finally, in case (iii), an intermicellar fusion mechanism dominated the inversion process under the combined effects of both inorganic salts [148].

This latter study provides a useful example of both the power and the challenges of mesoscopic simulations for understanding and predicting the dynamic pathways of micelle shape change. As discussed above, the DPD simulations by Rodríguez-Hidalgo and co-workers qualitatively match experimental observations of pathway-dependent behavior of micelle inversion kinetics. However, their model makes some drastic physical approximations that make this result somewhat puzzling. For example, electrostatics were included only through adjustments to the soft DPD repulsive potentials, and the salts NaBr and $NaSO_4$ were modeled as single non-dissociated coarse-grained beads. As is sometimes the case with mesoscale models, one is left to speculate whether the physical principles that were omitted (in this case charge physics and dissociating ionic species) are insignificant for modeling the micelle inversion process in salt solutions or whether these specific results are serendipitous. Either way, additional investigation with mesoscale models that specifically include these phenomena or a more rigorous mapping between atomic and mesoscale models for this or similar problems would go a long way to helping to solve such puzzles.

Simulations that model pH-responsive amphiphilic systems are also important, because pH is one of the more effective shape modulators in both *in vivo* and *in vitro* settings [144, 145]. Yu et al. studied the pH-dependent self-assembly of carboxy-terminated polyester dendrimers [144]. They first performed AAMD simulations for each pair of components to map the Flory-Huggins parameters between a coarse-grained representation of the molecule. They then performed DPD simulations to simulate pH-dependent behavior, with electrostatic interactions modeled using a smeared charge approach with exponential decay [149, 144]. In the DPD simulations, a change in pH is modeled by changing the degree of ionization, i.e. the number of charged carboxyl groups. They proceeded to examine the effect of pH on morphology by simulating dendrimer assembly as a function of pH by applying a step-change in pH to random initial conditions. In the simulation results, they observed a transition from spherical micelles to wormlike micelles to bilayer sheets to vesicles as pH increased [144]. Although the authors only modeled a process of a rapid one-step change in pH, the method should be easily extended to more gradual pH changes between different states by using different initial conditions.

Luo et al. used a similar procedure to study pH-sensitive drug loading and releasing processes from assemblies of the amphiphilic block copolymer poly(amino ester)-b-poly(ethylene glycol) (PAE-b-PEG) [145]. Similar to the previous study, Luo et al. also mapped binary Flory-Huggins parameters from MD simulations in order to obtain a more coarse-grained DPD model that could reach longer time-scales. In PAE-b-PEG, the PAE block can convert from hydrophobic to hydrophilic upon protonation with the breakage of hydrogen bonds between the drug and the PAE beads. Luo et al. observed that after protonation of PAE, the PAE blocks of the assembled structures are rapidly swollen with solvent and the hydrophobic cores start to collapse. Eventually, the micelle structures are destabilized into soluble diblock copolymer chains and the drug is simultaneously released. The morphology and the pathway of pH-dependent loading/releasing from simulations are qualitatively comparable to the experimental observations [145].

The results by Luo et al. provide invaluable insights into pH-responsive behaviors of amphiphiles, and more questions could also be addressed with their model. For example, one could test the hypothesis that pH-dependent micelle stability scales with the PAE block length, since the degree of segregation is known to scale with χN. Additionally, there are interesting questions that could be addressed about the interactions between the properties of molecular load (i.e., a drug) and shape-changing behavior. Modeling different rates of pH change may also assist the exploration of drug delivery within different circulatory paths due to the distinct physiological pH conditions in different organs and tissues. We anticipate that exploring a wider parameter space with the current model would grant us a more systematic understanding of such pH-responsive systems.

4.2 | Local modification of self-assembled amphiphiles

Until now, we have been focused on global changes to the entire morphology of an amphiphilic assembly. Zooming in and focusing on the local shape of a self-assembled structure, one can often observe regions where amphiphiles behave differently due to either a difference in membrane composition or a difference in the environment. An example of the former is a vesicle whose membrane can phase separate into compartments of different amphiphiles with a lateral extension [150, 151]. An example of the latter case is a vesicle whose membrane is exposed to heterogeneous solvent conditions, e.g. different enclosed and external solvents [53]. A common fascinating connection between these local morphological changes is the phenomenon of symmetry-breaking, which is an essential process in biology to increase complexity and functional specialization [152]. The emergence of asymmetry in synthetic structures is also appealing due to the enriched chemical and mechanical properties that can be applied to dif-

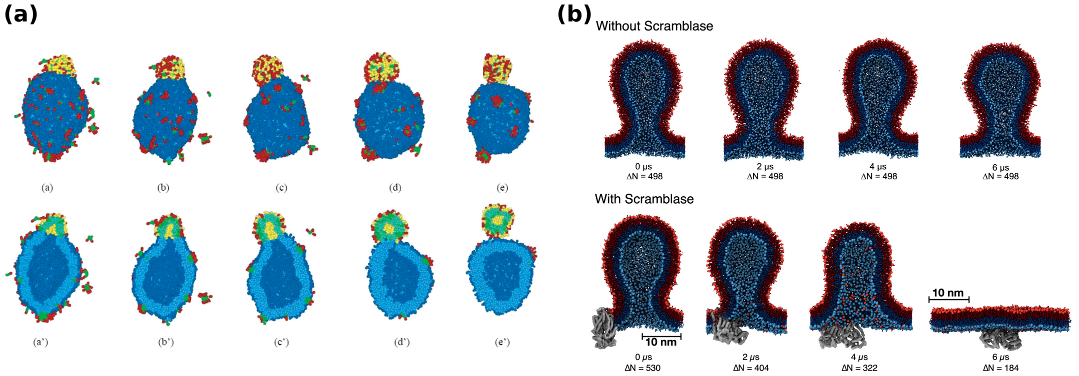

FIGURE 7 Insertion-induced shape change. (a) Fission process of a hybrid vesicle induced by inserting external surfactants. Amphiphile A is represented by dark blue/light blue. Amphiphile B is colored in yellow/light green. The inserted molecules are in red/green. The images are taken at 6000, 20000, 86000, 106000, and 118000 simulation steps, with the top panel showing the whole structure, and the bottom showing a cross-sectional view. Reprinted with permission from Ref. 153. Copyright 2009 American Chemical Society. (b) Membrane shape changes with and without lipid scramblase. Top: a cross-sectional view of simulation without lipid scramblase. Bottom: a cross-sectional view of simulation with scramblase, indicated as the aggregated gray rods. Corresponding time stamps and number differences of lipids between the two monolayers are described in the text below each snapshot. Reprinted from Ref. 154 under the terms of Creative Commons Attribution 4.0 licence.

ferent research areas.

We will organize our discussion around two distinct paradigms that researchers use to achieve local shape control of amphiphilic assemblies. One is through the insertion of external molecules to rearrange the distribution of amphiphiles and remodel the shape of assembled structures. The other is to create bottom-up manipulation through catalytic reactions. Chemical reactions can alter shape by several mechanisms including modification of the length of amphiphilic segments, cleavage of side chains or end groups from the amphiphile, alteration of the chemical identity (and properties) of amphiphiles, or changes to the local solvent environment.

4.2.1 | Effect of inserting external molecules

Interacting with external surfactants can effectively alter the composition of self-assembled structures, hence tuning the phase behavior and structural properties [155, 156, 56, 157, 154]. Yang et al. reported a facile approach of inducing budding/fission of hybrid vesicles with the addition of extra surfactants [153]. The initially assembled vesicle was composed of two different amphiphiles A and B, and each formed a separate domain in the vesicle. A third amphiphilic surfactant C, with a similar chemistry to amphiphile B, was then introduced and got drawn into the vesicle. As shown in Fig. 7 (a), most of the C surfactants accumulate within the B domain in the outer corona of the vesicle due to the higher miscibility between B and C, meanwhile forming a budding region. As time progressed, the budding region gradually elongates and eventually detaches from the parent vesicle to form a smaller hybrid vesicle of B and C. It is noteworthy that the insertion of C only happened in the outer corona, causing an asymmetry between the outer and inner layers of the vesicle. The outer layer tends to bulge outwards to accommodate the rearrangement of all the surfactants, and once the adsorption is above a critical point, the domain completely separates from the original vesicle due to the strong area difference effect [158]. The authors also discussed a list of factors that can affect the insertion-induced shape change, including the concentration, the tail length and bending rigidity of the C surfactant [153].

Insertion and adsorption of nanoparticles can have a similar effect on self-assembled structures. Siggel et al. demonstrated that nanoparticles can affect structure by modifying amphiphile chain kinetics [154]. They showed that protein nanoparticles (lipid scramblase) embedded in a bilayer membrane can serve as a shuttle to facilitate the translocation of amphiphiles between the two monolayers, hence relaxing the assembled structure to reorganize into different shapes. Siggel et al. simulated the effect of adding scramblase nanoparticles to an asymmetric bilayer membrane that initially contained a stable bud shape [154]. Upon the insertion of the scramblase nanoparticle, flip-flop events started to occur. During the process, there is an obvious acceleration of lipid flipping compared to the case without scramblase nanoparticles, shown in Fig. 7 (b). Once the system overcame the energy barrier between budding and flat membrane, the budding region relaxed to a metastable flat bilayer, even if there was still a significant difference between the number of lipids in the two monolayers [154]. The oriented migration of lipids regulated by the scramblase nanoparticles opens up a novel pathway for inducing controlled morphological changes in bilayer membranes.

The discussed bilayer shape changes are caused by the change in property symmetries between the two monolayers. In the first scenario, asymmetry is created due to the direct insertion of a foreign molecule to the outer layer. In the second scenario, the bound nanoparticle assists the amphiphile transport between the two layers, thus diminishing the asymmetry in amphiphile density between the two monolayers and creating a flatter surface. The simulations not only provide a detailed visualization of the occurrence of asymmetry or symmetry, but also explains how such changes happen. To the best of our knowledge, similar approaches to the first scenario have recently been applied in lipid membranes, where fission or necking could be induced by bounded protein molecules at different concentrations [74]. More quantitative controls remain to be explored, including the size and stiffness of the bounded proteins. The second technique has not yet been reported in any synthetic systems. As such, these simulations serve as a useful prediction tool for finding novel methods of controlling bilayer shape.

4.2.2 | Catalytic reaction-induced modification

Chemical reactions, especially enzyme-catalyzed reactions, are considered as one of the most efficacious ways to realize dynamic self-assembly. Compared to both physical and chemical stimuli discussed in the previous sections, shape manipulation with enzymatic reaction exhibits a number of advantages. Some enzymatic activities are built-in functions in living organisms, therefore displaying better biocompatibility when applied to *in vivo* research and applications. Enzymatic reactions also have excellent specificity with few side reactions and high yield, meaning that they can exert more precise control over the system. In addition, the kinetics can be fine-tuned by the concentration and spatial distribution of the catalyst, providing better viability for forming different structures. We discuss here several examples of reaction-driven local modifications in more detail, hoping to demonstrate the potential of the catalytic reaction paradigm to direct dynamic self-assembly, as well as promote some of the more advanced modeling techniques that can help further the development of this line of research.

We first discuss an example given by Wright et al, where they simulated a catalytic reaction of functional group cleavage [102]. They presented DPD simulation results, along with experimental data, to understand the kinetic control of the self-assembly of peptide–polymer amphiphiles (PPA), and investigated the effect of catalytic reaction under different solvophobicity of the polymer segment. They performed and compared two sets of simulations. In the first, they investigate the equilibrium morphologies of the already truncated PPA. In the second, they mimic the kinetically driven shape transition due to peptide cleavage. In the former, PPAs with different solvophobic polymer segments assemble

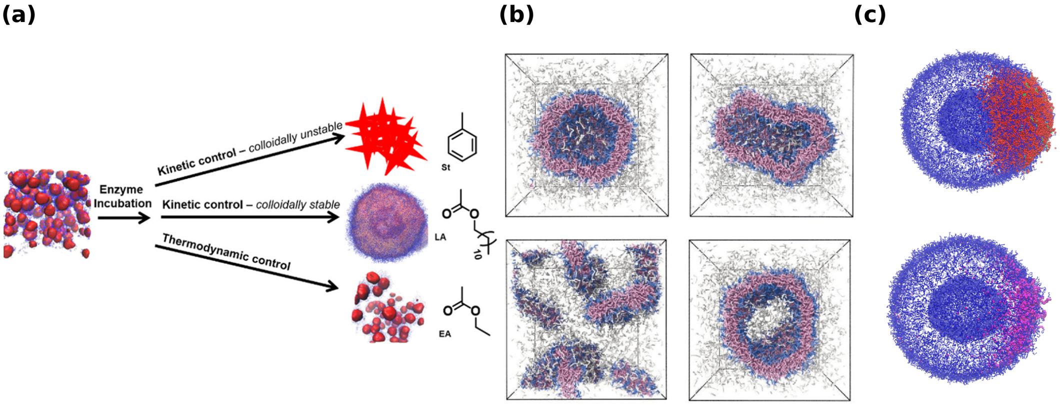

FIGURE 8 Catalytic reaction-induced kinetic control of self-assembled amphiphiles. (a) Morphology transition from spherical micelles to kinetic controlled morphologies after peptide cleavage. Reprinted with permission from Ref. 102. Copyright 2019 American Chemical Society. (b) Chain-growth reaction-induced metastable morphologies at steady states. Pink and blue represents the solvophobic and solvophilic components, respectively. The gray rods represent the free homopolymer chains. The structures remain vesicles when the driving force is low to induce shape change (the top panels), and convert to worm-like micelles or perforated vesicles when the driving force is high (the bottom panels). Adapted with permission from Ref. 159. Copyright Science China Press and Springer-Verlag GmbH Germany, part of Springer Nature 2019. (c) Enzyme-embedded membrane undergoing catalytic reaction. Top: altering the local solvent condition. The converted solvent particles are shown in red.; Bottom: modifying the chemistry of solvophobic block. The converted solvophobic beads are colored in mauve. Adapted from Ref. 160 with permission from the Royal Society of Chemistry.

into spherical micelles. In the latter, as shown in Fig. 8 (a), spherical micelles remain unchanged after peptide cleavage at low solvophobicity of the polymer segment, whereas at relatively high solvophobicity the reactions result in a large vesicular structure through the fusion of smaller micelles.

Most of the *in silico* results match qualitatively with the experimental observations [102]. However, there are also some limitations of the models. As the authors themselves pointed out, the soft repulsive potentials are not appropriate to model polymer segments (i.e., the polystyrene segment) with a high glass transition temperature. Additionally, they modeled the enzymatic reaction by instant deletion of side chain beads after equilibration, which only approximately represents the limiting case of ultra-fast reaction and does not account for the stochasticity and spatial inhomogeneity of the catalytic reaction. Nevertheless, the simulation results demonstrate that enzymatic reaction can give rise to nonequilibrium transitions of self-assembled structures, and that the resulting structures can be highly pathway-dependent [102].

Another emerging trend that can benefit from the catalytic reaction is the *in situ* modification of the amphiphilic segment lengths [159, 161, 162]. Designing amphiphilic molecules that have different lengths and molecular weights can significantly alter the final assembled structures. Approaches such as polymerization induced self-assembly that enables dynamic growth of different blocks can possibly render complex hierarchical self-assembled morphologies [161]. Along these lines, Xu et al. reported simulations using a DPD model to account for the motion of particles, and a stochastic reaction model to simulate the bonding reaction between a homopolymer (A_4) and an amphiphilic diblock (A_2B_6) [159]. The simulation of this dynamic process reveals the formation of irregular morphologies such as perforated vesicles, as shown in Fig. 8(b). Such exotic structures can only be observed at a relatively fast reaction rate with suitable reversible reactions. The author concluded that the fast reaction significantly alters the local composition of the system, hence causing an increase in the local surface tension that induces the formation of pores at the vesicle surface [159].

Alternatively, given an already-assembled aggregate, one can incorporate enzymes, either docking to the surface or embedded within the aggregate, to adjust the local environment or chemistry of partial amphiphiles that gives rise to local structural changes. Our group recently published simulations combining DPD [114] with Split Reactive Brownian Dynamics (SRBD) [163] to simulate a diblock copolymer vesicle with embedded enzymes that undergoes stochastic chemical reactions [160]. We hypothesized two different enzymatic reaction mechanisms that will lead to a change in local morphology, i.e. catalyze the conversion of local solvent from good solvent to bad solvent for solvophilic block, and modifying the solvophobic beads in the outer corona into solvophilic ones. As shown in Fig. 8 (c), the two mechanisms resulted in similar swelling at the reaction site, but the long-time behavior showed a more persistent local shape change in the second scenario. We attributed this to the relatively slower lateral diffusion of the bonded polymer chains relative to the non-bonded solvent beads. We also demonstrated a controlled manipulation of a local morphology by adjusting the chemistry of the converted solvophobic beads, which might be a useful guide for future experimental design [160]. These reactive DPD models can explicitly solve the equation of motion, and can also account for the dynamic changes due to stochastic reactions at a reaction rate that depends on the local concentration of the reactant. We expect to apply the algorithm in other model systems to study more complex behaviors such as inter-micellar interaction and communication via chemical signals.

As suggested by the above studies, the framework of reaction-diffusion in dynamic amphiphile self-assembly yields a rich source of pathways to forming complex structures. These models could possibly be adapted to study other systems with more extensive local deformations such as protrusion and necking/fission. Meanwhile, there is still room for improvement in the current reaction-diffusion models. All of the models mentioned above adopt the classical DPD model, which is most commonly implemented in the canonical ensemble (i.e., holding the number of particles, volume and temperature constant). But often times when studying the reaction-diffusion process, one must consider mass transfer and energy exchange with the environment to account for the continuous input and dissipation process. Therefore, it may be valuable to adapt these methods to other ensembles, thus enabling more sophisticated reaction types that involve decomposition and size changes of simulation particles.

5 | SIMULATION OF MORPHOLOGY CONTROL DUE TO MECHANICAL EFFECT

Since self-assembled amphiphiles are deformable materials embedded within a fluid, there are also considerable mechanical effects that can cause deformation or even an instability of the structure. This is commonly seen in biological systems, for example, red blood cells adapt their shapes dynamically when passing through blood vessels of different sizes at different flow rates, as well as in synthetic systems where micellar structures are extruded through micron-sized filters to get more uniformly distributed sizes. Subject to external mechanical forces, amphiphilic molecules exhibit a series of dynamic variations such as migration, rearrangement/reorientation, and exchange between different aggregates, thereby causing fluctuations in shape.

In this section, we summarize the literature of modeling mechanical effects on self-assembled structures, with emphasis on spatial confinement, external flows, and internal active stress. In reality, these mechanical effects often function cooperatively to affect the shape. For instance, different geometries and sizes of the microfluid channel result in distinct fluid dynamics, and the internal stress exerted on the surface of an assembly will also influence the surrounding fluid and alter the hydrodynamic interactions between the assembly and its environment. Regardless, we want to identify the dominant factor in each of the examples, and introduce some of the computational approaches that are appropriate for studying the corresponding dynamic processes.

5.1 | Spatial confinement-induced shape change

Spatial confinement can significantly affect the structures, thermodynamics, and mobility of amphiphilic molecules, thus resulting in different shape-forming behaviors compared to those under unconstrained equilibrium conditions. [164, 165, 166, 167] When the size of confinement is comparable to that of the self-assembled aggregates, the shape-changing behavior of a confined aggregate can be complex, and the morphology can be quite different from an aggregate with identical components in the bulk. In such cases, the interfacial energy and entropy become the dominant factors that affect the morphology of self-assemblies [168]. The capability to predict and control the morphologies of amphiphile assemblies in confined space opens new possibilities for designing soft materials with desired physical behaviors and mechanical properties for drug delivery, sensor technology, and nanoreactors, among other useful applications.

Confinement-induced changes are often susceptible to the properties of the self-assembled structure, as suggested by a combined simulation and experimental work in Ref. 166. In this work, Mukherjee et al. investigated the effect of nucleus stiffness on the deformation of a nucleus when passing through confined porous structures. A plane strain finite element (FE) model system was set up to mimic the process of a cell entering pores within a tissue, and the evolution of cell nucleus deformation was tracked during the confined migration at various levels of nucleus stiffness and tissue stiffness. The nucleus was modeled as an elastoplastic element with deformation behavior described by a strain-hardening power law [169]. The model predicted that plastic deformation can happen in two different cases: (1) a stiff nucleus passing through an even stiffer pore, and (2) a very stiff nucleus going through a softer tissue matrix. A dramatic drop in nucleus circularity was observed in both cases, while kinking of the nuclear membrane only occurred in the first case. For a soft cell nucleus, the nucleus membranes only went through an elastic deformation during the confined migration. These predictions were corroborated by experimental results [166]. This FE model suggests a possible protective mechanism of cells by softening the nucleus while migrating through confined channels since the plastic deformation of nucleus can result in irreversible DNA damage. It may also inspire the synthesis of artificial materials with better stability in confined spaces.

Another factor that can affect shape-changing behavior is the geometry of confinement. Kahraman et al. reported a numerical study of the shape transition of vesicle membranes within rigid spherical and elliptical confinement geometries [164]. They imposed this confinement on a simplified model of bilayer membranes by setting constraints on the total surface area and enclosed volume, while ignoring any other changes in topology. Then, they numerically solved a set of differential equations that describes axisymmetric invaginations. In spherical confinement, when the surface area of the vesicles increased, they observed a transition from axisymmetric invaginations to ellipsoidal invaginations to stomatocyte shapes with a slit-like biconcave area in the center. The same transition was also observed in elliptical confinement except for minor differences in local arrangements. They also found that the length scale of invaginations can be tuned by the spontaneous curvature of the membrane, e.g., by introducing compositional asymmetry in the bilayers. Despite the simplicity, the model successfully reproduces the basic invaginations that are fundamental to membrane folding under external confinement, and contributes to the understanding of mechanical effects on complex folding behaviors of the membranes [164].

Some of the more complex confinement geometries were studied by Ye et al. using a hybrid numerical method that combines the smoothed dissipative particle dynamics (SDPD) and immersed boundary method (IBM), denoted as SDPD-IBM [165]. They first proved

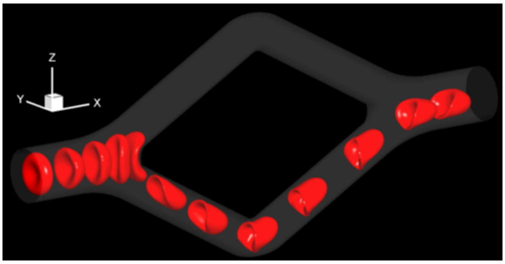

FIGURE 9 Shape evolution of a red blood cell in a bifurcated channel. From left to right, the snapshots are taken at t=0, 5, 10, 15, 30, 60, 75, 90, 105, 120, 130, and 135, respectively. Reprinted figure with permission from Ref. 165. Copyright 2017 by the American Physical Society.

the accuracy of their models by (a) comparing the simulation results to the analytical solution for a Newtonian fluid flow in a rectangular channel, and (b) comparing the simulation and experimental results of the morphological change of vesicle in a rectangular tube. Both validation approaches suggest good agreement between simulation, theory, and experiments. With proof of credibility, they also demonstrated the capability of the model by simulating the dynamic shape change of red blood cells in a variety of geometries. We show in Fig. 9 an example of their SDPD-IBM simulations time series of a red blood cell flowing in a bifurcate tube [165]. The SDPD-IBM model is a powerful tool for predicting the behavior of self-assembled amphiphiles in complex spatial confinement, which are otherwise hard to solve using analytical approaches. However, such numerical approaches would benefit from increased attention to a more general explanation of how confinement geometries regulate the shape-changing dynamics,

5.2 | External flow-induced shape change

Understanding the dynamics of self-assembled amphiphiles in external flow is tough because their shapes are actively fluctuating and are highly dependent on the mechanical properties as well as the dynamic evolution of hydrodynamic interactions and interfacial stresses [173, 174]. It is also of vital importance since fluid flow effects contribute to biological characteristics of living organisms such as cell division, and can also be applied to synthetic systems to create similar behaviors [175]. In this section, we are particularly interested in simulation studies of how vesicular structures deform in external flow. Multiple modes of motion, including tank-treading, tumbling, and trembling are observed to be a function of the shear rate as well as the viscosity contrast between the vesicle, the encapsulated fluid, and the surrounding fluid [173, 174, 176, 177, 178, 179, 180]. These different modes of motion can further generate structural and viscoelastic property variations in the amphiphiles, hence producing a variety of morphoregulation pathways.

It is insightful to first examine how flat bilayers respond to external shear flow as a basis for understanding deformation mechanisms and shape stability of vesicles. At the individual molecule level, DPD simulations by Chen et al. suggest that different values of the external flow rate can have a significant impact on the radius of gyration of individual amphiphiles, thus changing the local spontaneous curvature of bilayer structures [181]. Aggregate bilayer assembly behavior in shear flow parallel to the bilayer was more systematically investigated using CGMD by Hanasaki et al. [182]. With an increasing shear rate, the microscopic structures shift from slight tilting in the shear direction, to buckling, to a Kelvin-Helmholtz-like instability with swirling patterns, eventually leading to the collapse of the bilayer structure. The instability is due to a significant shear flow velocity gradient across the normal direction of the bilayer that pulls apart the individual amphiphiles. When the undulation is insufficient to maintain the dynamic molecular reorganization, the membrane starts to fall apart and rupture. The critical shear rate and other physical parameters are highly dependent on the domain size of the bilayer [182].

The effects of flow rate and amphiphile properties on vesicle shape have been extensively studied using DPD simulations [183, 170, 171]. For example, Liu et al. studied diblock copolymer vesicles in cylindrical flow fields [183]. They found that increasing the shear rate

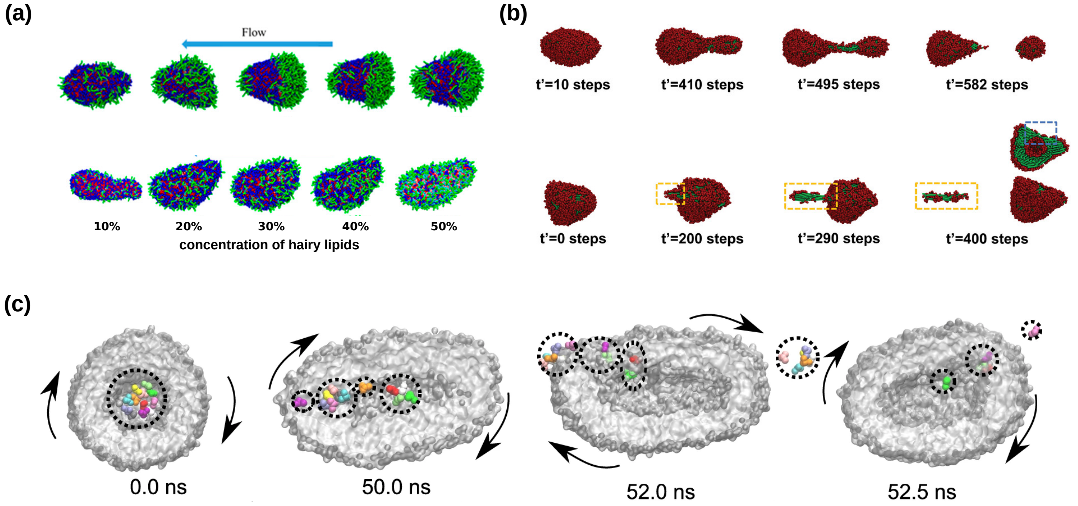

FIGURE 10 Flow induced morphological change in vesicles. (a) Stable structures of vesicles with hairy lipids in Poiseuille flow at Re = 38 and different lipid concentrations. The top panel shows hairy lipids with longer tethered segments, and the bottom shows shorter tethered segments. Adapted with permission from Ref. 170. Copyright 2017 American Chemical Society. (b) Time series of block copolymer vesicles in external flow fields. The top panel demonstrates the division of coil-coil vesicles, whereas the bottom panel shows the detachment of a group of rod-coil chains and the subsequent formation of a tail-like micelle. Adapted with permission from Ref. 171. Copyright 2022 Wiley-VCH GmbH. (c) Simulation snapshots of vesicles with loaded small molecules (colored particles) in shear flow. The vesicle displays an elongated shape, and the loaded molecules are released without vesicle rupture. Adapted with permission from Ref. 172 under the terms of the Creative Commons CC BY license.

causes the elongation and subsequent shape transition of the vesicle. A series of morphologies were spotted at different shear rates in their simulations, including bullet-like vesicles, leaking vesicles, spherical micelles, hamburger-like micelles, and bilayers. They also found that the shape-changing effect is more pronounced under stronger confinement. Additionally, they discovered that the rupture time displays a non-linear decreasing trend as a function of increased shear rate [183].

Chu et al. explored a bacteria-mimicking hybrid vesicle with normal lipids and hairy lipids (i.e., lipids with tethered hydrophilic heads) under Poiseuille flow conditions [170]. Fig. 10 (a) summarizes the results at a relatively high Reynolds number (Re = 38) and different concentrations of hairy lipids, with the top panel showing longer tethered segments and the bottom demonstrating shorter tethered segments. Their results suggest that the vesicles become more resistant to deformation with the increase in length and concentration of tethered segments, since they tend to create a larger excluded volume and shield the vesicles from the mechanical impact of solvent beads [170].

Finally, Wu et al. examined the effect of stiffness of the block copolymer on the mechanical stability of vesicles under flow fields [171]. Their simulations demonstrate that rod-coil block copolymer (RC) vesicles (where the block copolymer has one semiflexible block) have a less distorted shape compared to coil-coil block copolymer (CC) vesicles under the same conditions. The rupture behaviors are also different between the two different kinds of assemblies, as shown in Fig. 10 (b). For the CC vesicles, rupture occurs via a division-like pathway where necking occurs and the vesicles break into two separate parts. Whereas for the RC vesicles, the structures largely maintain the original organization, with a couple of chains pulled out to form an elongated tail-like micelle due to the stretch in flow [171].

Changes in structural properties can also be implied from the simulation results. Brandner et al. presented a Lattice Boltzmann Molecular Dynamics (LBMD) simulation of vesicles in external shear flow [172]. As expected, they observed a transition from a spherical to a prolate shape when the vesicle is subject to external shear flow. Meanwhile, they also investigated the shear-induced release of small molecules encapsulated in the vesicle. As shown in Fig. 10 (c), their results show that shear also induces a small amount of release of material from the vesicle interior, followed by a collective evacuation due to the constant mechanical stress from the external fluid. It is noteworthy that the release occurs without any breakage or disruption of the closed vesicle structure, which implies that the release is a consequence of an increase in the permeability of the vesicle [172]. Hypothetically this is due to the local reorientation of the amphiphiles and the associated decrease in the energy barrier of membrane transport. More parameters can be systematically explored to achieve the controlled adjustment of the effective permeability of the vesicle membrane using fluid flow.

5.3 | Internal active stress-induced shape change

Besides exterior mechanical effects, morphological changes can also emerge from the internal stresses caused by active self-propelled components encapsulated within the closed surfaces. The self-propelled components can push against the flexible surface, exerting forces pointing outwards and causing deformations such as protrusion or elongation. In addition, spherical active particles under confinement have the tendency to get trapped in regions with a high concave curvature, which is not a property that has been discovered in passive Brownian particles [184, 186]. In the case of active filaments, the alignment of the rods also has a similar effect to that of the spherical ones [185].

Vutukuri et al. presented a combined experimental and simulation study that demonstrates an exciting case of a giant unilamellar vesicle with encapsulated spherical Janus particles [184]. They performed coarse-grained Langevin dynamics simulations to understand the dynamic membrane changes observed in experiments. As shown in Fig. 11 (a), they constructed a simulated state diagram as a function of the Péclet number (Pe) and volume fraction of the Janus particles (ϕ). Exotic structures including tether-like protrusions and dendritic structures were observed at low or medium ϕ and relatively high Pe regimes. At low ϕ and low Pe, the vesicles only demonstrate slight fluctuation and maintain a quasi-sphericle shape. At high ϕ, the vesicles go through a more global shape change with more extended shapes at relatively higher Pe, and the Janus particles tend to accumulate on one side of the structure [184].

Another similar model system, but with anisotropic active filaments, was reported by Peterson et al. [185] They also constructed a series of morphology diagrams. We show in Fig. 11 (b) one of the representative diagrams, where the abscissa is the volume fraction of the active filament (ϕ) and the ordinate is the aspect ratio (α) of the filament. More state diagrams in other dimensions such as filament rigidity and Péclet can be found in Ref. 185. In addition to exerting mechanical forces on the surface, the filaments themselves can also organize into a diversity of structures, including highly aligned rings and caps with controllable sizes and symmetry. The simulation results suggest a positive feedback loop of the vesicle shape change, where the active stress from active motion causes the deformation of the surface, and the lateral stress from deformation in return affects the organization of the active filaments. The authors also presented a scaling analysis with regard to how the feedback can lead to the final emergent structures [185]. They compared two different time scales: the pairwise collision of filaments (τ_{coll}) and the filament-vesicle alignment due to rotation (τ_{rot}). They concluded that the deformation is more pronounced when $\tau_{\text{coll}} < \tau_{\text{rot}}$, that is, when the deformation response of the membrane is faster than the self-organization of the active filaments [185].

Studies of internal active stress-induced morphology

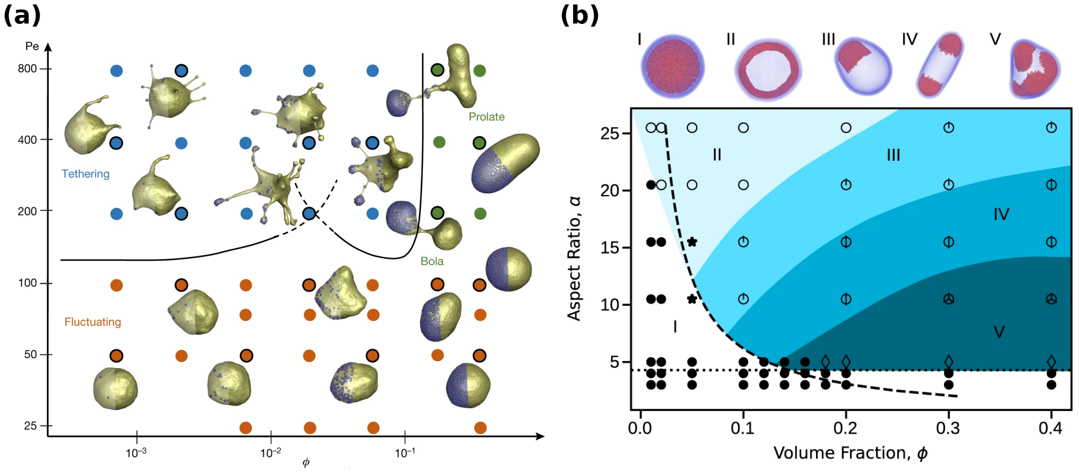

FIGURE 11 Internal active stress induced shape change. (a) Simulated state diagram of vesicles with enclosed spherical Janus Particles. The x-axis is the volume fraction of the Janus particle (ϕ), and the y-axis is the Péclet numbers (Pe). Adapted with permission from Ref. 184 under exclusive license to Springer Nature Limited. (b) An example morphology diagram of vesicles with encapsulated active filaments. The x-axis is the volume fraction of the Janus particle (ϕ), and the y-axis is the aspect ratio of the filament (α). Reprinted from Ref. 185 under the terms of the Creative Commons CC BY license.

changes have just started to emerge in synthetic systems. The above simulation results provide a deeper understanding of the underlying mechanisms of forming these unique morphologies and could have a profound impact on future experimental designs for materials of self-assembled structures with enclosed active components. The simulated state diagrams can be used to guide the engineering of amphiphilic assemblies with desirable shapes and dynamics, or even more exciting biomimetic behaviors. In addition, as suggested by the authors, the emergence of novel morphologies involves two major processes. One is the deformation of the membrane due to internal stress imposed by the active components. The other is the reorganization of the active filaments or the accumulation of the active spheres in response to the generated surface curvature. The combined process has the potential to serve as an intricate feedback loop to enable dynamic control of self-assembled structures. We envision that further development in this area can inspire the synthesis of novel functional materials.

6 | CONCLUSIONS AND OUTLOOK

While the self-assembly of amphiphilic molecules has been an active research topic for decades, ongoing work continues to be a fruitful area of research in modern nanotechnology, and the knowledge generated in this field contributes to the development of current and future technologies in drug delivery, bioremediation, sensor materials, nano-reactors and so on. In this review, we summarize some of the recent simulation studies related to non-equilibrium morphological control over self-assembled amphiphiles using a variety of different types of models and methods. We have focused on two primary categories of morphological controls: those arising from kinetic effects and those from mechanical effects. The literature surveyed here provides especially pertinent insights into actively controlling the shape of a self-assembled aggregate and using path-dependency to realize complex metastable structures. Despite the recent progress, there are a number of open problems related to non-equilibrium mophological control. Because general theories of non-equilibrium assembly are not widely available, simulations will continue to be important, and improved simulation models and methodologies will play a key role. Looking forward, we provide some thoughts about prospective research directions and open questions that may be important in the years to come.

Despite years of investigation, there still remain open questions about equilibrium physical properties that are important for morphological control. For instance, the bending rigidity and elasticity of self-assembled structures play an important role in controlling the shape, because they describe the sensitivity of structures subject to environmental fluctuation. The bending stiffness of membranes has been actively researched for decades, and important fundamental work has been published relating the effect of parameters including composition, membrane thickness, surface charge and beyond to continuum membrane properties [187, 188, 189]. However, to the best of our knowledge, the literature is still sparse regarding the quantitative relationships and the possible cooperative effects of these features on the bending modulus. A better understanding of these physical properties will allow for more precise manipulation of the assembled structures.

Though we primarily focus on coarse-grained models in this review, there are also important open questions at the atomistic level in order that one must address to fully understand the mechanisms of non-equilibrium morphological control. Atomistic models are suitable for studying detailed dynamics of small systems with very few surfactants or a single aggregate, but such calculations are costly for problems involving interactions of multi-colloidal systems. The limitations imposed by high computational costs can potentially be solved by developing better parallelization algorithms and utilizing ever-increasing computational ability, or by developing force fields that implicitly account for solvation effects (the majority of the simulation beads are solvent species since the micellar systems are essentially dilute solutions of amphiphilic surfactants). Most implicit models are built on some simple assumptions, for example, that non-polar groups occupy the non-polar media, whereas polar and charged groups possess an extended and relaxed conformation in water. It is important to properly account for the relative contributions from different groups of atoms, and a more careful selection of mapping metrics (e.g., contour length, excluded volume) is needed for optimizing the force field parameters instead of the relatively simple free energy matching. Note that these same principles also apply to CG mapping for coarse-grained models. Additionally, more work is needed on solvent species other than water.

Machine learning is currently revolutionizing other areas of simulation, and it provides another promising direction in terms of studying the shape control of self-assembled amphiphiles. As a matter of fact, some state-of-art approaches have already emerged to use machine learning algorithms to predict amphiphile structures, protein aggregation, conformation switching, among others [190, 191, 192, 193]. Generally speaking, predictions using machine learning methods work well for systems with relatively few input degrees of freedom. However, it is not easy to identify which degrees of freedom are predictive of non-equilibrium self-assembly processes, and the rugged energy landscapes present in these systems lead to degeneracy that further complicates predictions. Additionally, accurate predictions require a gigantic amount of data points as the training set, which can be extremely expensive to obtain, and the reliability of the learning algorithm is highly susceptible to errors. Consequently, successfully applying machine learning predictions to non-equilibrium self-assembly will likely require some combination of more accurate and less expensive models to provide reliable training sets, and dimensionality reduction to identify the dominant factors that affect dynamic assembly processes,

Finally, computational studies are needed to address more complex systems including those with multiple species and more intricate (e.g., highly-branched or dendritic) amphiphile architectures. Multi-component systems tend to produce structures with balanced mechanical stability and biocompatibility, and complex hierarchical assemblies might facilitate the design of multi-stage programmable responses, both of which could contribute to material systems with biomimetic or other useful properties or behaviors. Simulations of these systems might also accelerate the discovery of dual or even multiple stimuli-responsive amphiphiles that are applicable under various conditions.

In conclusion, there is much progress to be made in this exciting field and simulations will be a critical component to our understanding of controlling the non-equilibrium morphology of amphiphilic assemblies. We anticipate that the future development of computer-aided approaches in these areas will both deepen our understanding of fundamental biological processes and will lead to the design and implementation of smart synthetic systems in current and future technologies.

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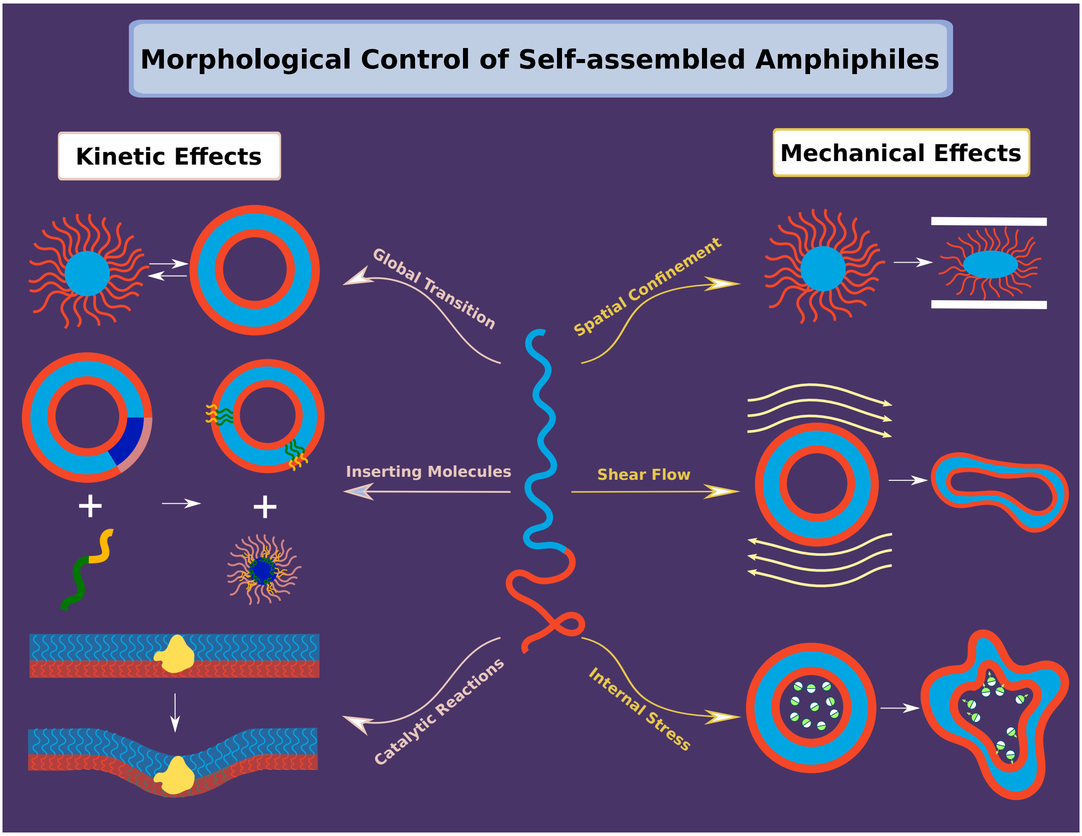

FIGURE 12 Graphical Abstract