

THE UNIVERSITY OF CHICAGO

DEMONSTRATION OF SINGLE-POLYMER MICELLE SHAPE CONTROL USING
NON-UNIFORM SPONTANEOUS SURFACE CURVATURE AND ASSESSMENT OF
RATIONAL SHAPE DESIGN FEASIBILITY

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ABSTRACT

It is known that micelles formed by simple amphiphiles exhibit only a limited range of shapes in equilibrium. However, practical applications may benefit from increased tunability of micelle shape. In this thesis, we consider an approach to micelle shape control where the many amphiphiles of a conventional micelle are replaced by a single, linear, multiblock copolymer. Guided by an intuitive shape-design rationale, we propose to alter the block lengths of this multiblock to control the curvature of the micelle surface. Using two-dimensional bead-spring simulations, we demonstrate that a long-lived micelle with a nonstandard, dimpled shape can be produced by this strategy. To assess the ease with which shape features may be precisely controlled by the block lengths, we study the effect of changing select aspects of the multiblock composition. We find that the response of the shape is somewhat smooth, but sufficiently irregular that a simple linear model is insufficient to describe the response, so a more sophisticated approach is needed for precise shape design.

PREFACE

This thesis is an examination of a rational shape design scheme for polymeric micelles. The thesis reproduces two papers [1, 2] prepared for *Physical Review E*. These papers have been reformatted for inclusion in the thesis, but are otherwise unchanged. Chapter 1, based on [1], introduces and motivates the question of micelle shapability, presents the proposed mechanism to control micelle shape, defines the scope of the work presented in this thesis, describes the simulation method used to study micelle shapability, develops a mathematical formalism for analyzing micelle shape, validates these statistical analyses, presents proof-of-concept results showing that micelle shape control is possible, and discusses limitations of the work. The source paper, authored by myself and Thomas Witten, has been published in *Physical Review E*. My contribution to this paper was to choose a polymer model and tune the parameters of this model to accurately represent physical polymers, perform simulations of suitable micelles, develop and validate the shape-analysis formalism, and create the figures and most of the text of the paper. Thomas Witten's contribution was the original idea of controlling micelle shape using non-uniform spontaneous surface curvature, the suggestion of several ideas for validating the polymer model and statistical analysis of micelle shape, and to revise and suggest some text for the body of the paper.

Chapter 2, based on [2], provides a more in-depth study of the micelle shape response to changes in its composition. The motivation for this study is to determine how much the proposed rational design scheme facilitates the engineering of shape-designed micelles. The source paper [2] was authored solely by me and has been submitted to *Physical Review E*. Thomas Witten commented on a manuscript of the paper, suggesting ways to improve clarity. Since the source material for Chap. 2 was meant to be a self-contained paper, much of the introductory material from this chapter is redundant with Chap. 1.

CHAPTER 1

DEMONSTRATION OF MICELLE SHAPE CONTROL USING NON-UNIFORM SPONTANEOUS SURFACE CURVATURE

1.1 Introduction

Amphiphilic molecules have self-organizing behavior, which makes them useful for a variety of applications. One application that has received much attention is drug delivery using micelle carriers [3–5]. Among other things, it is found that the shape of the micelles affects their drug delivery performance, for example by altering how much drug can be loaded into the micelle, where in the body the drug accumulates, or how long the drug remains in the body [6, 7]. More generally, shape can be used to facilitate or inhibit interactions, as in the well-known “lock and key” mechanism [8], shown in Fig. 1.1. In fact, the lock and key mechanism has already been used with dimpled sphere-shaped colloids to create self-assembled structures [10], and it would seem straightforward to apply this same concept to micelles. This paper presents a strategy for influencing the natural shape of a micelle by controlling the way it is constructed. Specifically, we demonstrate, through simulation, the ability to design the shape of a micelle constructed from a linear multiblock copolymer by choosing the lengths of its constituent blocks. Our strategy is motivated by recent advances in polymer synthesis allowing for realization of linear multiblock copolymers with individually controlled block lengths¹.

Much work has been done to study the factors influencing micelle shape. One line of investigation is to assume a continuum energy model for the micelle surface, and study the resulting ground states and fluctuations [15–18]. To make contact between the continuum parameters of these models and the physics of the micelle on the scale of a single am-

1. While synthesizing such a multiblock copolymer is by no means trivial, recent experiments [11–14] have demonstrated synthesis of block copolymers of up to twenty blocks having dispersities of 1.2 or less, indicating that the state of the art is rapidly advancing toward, if it has not already achieved, the precision necessary to reliably create these multiblock copolymers.

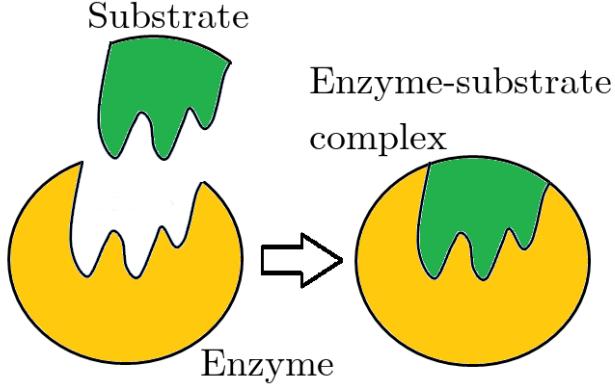


Figure 1.1: Illustration of lock and key mechanism, adapted from [9]. The enzyme, in yellow, is meant to interact specifically with a substrate, shown in green. To avoid unwanted interactions, the enzyme has a specific shape to which only a substrate of complementary shape may bind. More generally, the term “lock and key mechanism” may refer to any interaction controlled by shape.

phiphile, simulations of suitable structures (bilayers, tethers, etc.) made out of the micelle’s constituent amphiphiles may be conducted to determine the continuum parameters inherent to the amphiphiles (such as the amphiphile surface density, bending modulus, etc) [19–28]. Instead of investigating the continuum properties of the micelle shape to infer geometrical features, micelles of interest may be directly simulated with a particle-based model (with either atomic or coarse-grained resolution) [29–34]. Additionally, micelle shape can be studied experimentally [35–38]. In the context of the approaches described in the previous paragraph, our work falls into the category of directly simulating the micelle using a particle-based model. We choose this approach over a continuum representation for two reasons. First, we are interested in micelles whose size is on the order of the amphiphile length, where the scale of surface fluctuations can be roughly ten percent of the micelle size [39]. Second, we attempt to resolve average positions of individual amphiphile junction points. However, unlike the micelle simulations of [29–34], which study only the topology or rough shape features such as size or aspect ratio, this work seeks to obtain precise control of the micelle shape. Fine shape control is desirable both because it is a requirement of the lock and key interactions referenced in [10], and because it can be used to alter a micelle’s drug delivery properties. We revisit these applications in Sec. 1.5.5, discussing how the results of this work may be

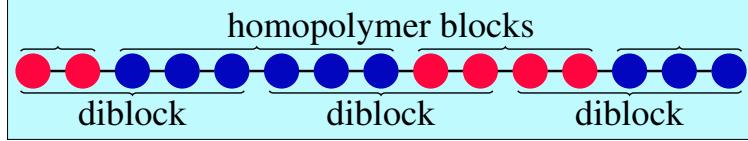


Figure 1.2: Two views of a model multiblock copolymer. The multiblock contains two species of monomer beads, shown in red (light gray) and blue (dark gray), connected by bonds shown in black. One view of the multiblock is as a collection of homopolymer blocks. The other view represents the multiblock as a collection of diblocks joined end to end.

relevant.

1.1.1 *Shape-design rationale*

To obtain this fine shape control we construct the micelle from one linear multiblock copolymer containing two species of monomer, a solvophobic species that is immiscible with the solvent and a solvophilic species that dissolves well in the solvent, arranged into segments of judiciously chosen length made purely of one species or the other. To better explain how the choice of segment length affects the micelle shape, we view the multiblock copolymer not as a sequence of chemically pure homopolymer segments joined together, but rather as a sequence of diblocks joined end to end so that the chemically similar ends of sequential diblocks are joined. In this view, the ends of each homopolymer segment correspond to diblock junction points, and a bond joining sequential diblocks occurs in the middle of a homopolymer segment. Figure 1.2 illustrates the two ways of viewing the polymer chain.

There are two reasons it is advantageous to view the micelle as a collection of diblocks. The first is that the applicability to drug delivery applications cited above, in which the drug carriers are micelles formed from (disconnected) diblock copolymers, becomes more apparent. The second reason is that viewing the micelle as a collection of diblocks having adjustable block lengths provides a straightforward, theoretically informed strategy for choosing the multiblock's segment lengths. The relationship between the diblocks' block lengths and the micelle's shape is determined by the requirement that diblocks pack efficiently on the micelle surface. There are two factors that affect surface packing: the first is the energetic

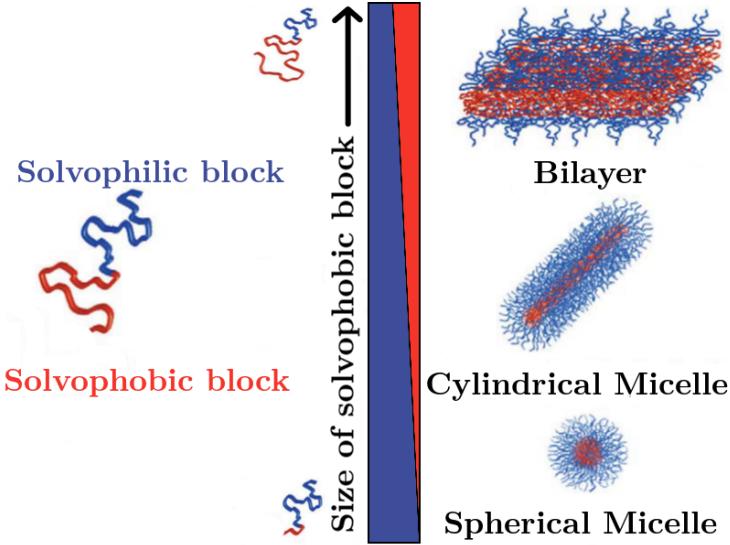


Figure 1.3: Illustration of micelle shape dependence on diblock composition. Diblocks with a very small solvophobic block tend to form highly curved spherical micelles. Diblocks with a more symmetric composition form flat bilayers. The case of cylindrical micelles is intermediate to these two. Figure adapted from [42].

interactions between the monomers, and the second is the diblock chain stretching entropy. Intuition may be gained by considering the limit of long blocks, where scaling arguments yield analytic results, as reported in [40]. For example, one particularly relevant result of [40] is an analytical expression for the dependence of the preferred mean curvature of an interface containing a monolayer of diblocks on the block lengths. Even though a continuous range of preferred mean curvature can be achieved by adjusting the relative block lengths of a diblock, it is known that only three shapes can be achieved by micelles composed of a single species of diblock: spherical, cylindrical, and bilayer [41] (see Fig. 1.3).

By contrast, we expect micelles containing several species of diblock (or, in the alternate view, multiblocks containing homopolymer segments of varying lengths) to exhibit a much larger variety of shapes. The design method for achieving a desired shape presented in this paper is to choose the block lengths of the constituent diblocks so that their associated preferred curvatures match the curvature of the desired shape. In practice, it is not sufficient to simply choose a set of block lengths; additionally, the diblock positions must be controlled

so that the desired curvature is imprinted at the desired location on the surface. It is exactly for this reason that the diblocks are joined together into one linear multiblock copolymer—the added bonds between the diblocks hinder unwanted movement across the micelle surface. An illustration of this shape-design mechanism is given in Fig. 1.4.

1.1.2 Motivation

The micelle shape-design method described above is one means of creating self-assembled globular objects of controlled, macromolecular size. It is useful to contrast this method with other means of making globules of regulated form. The first of these is perhaps the most familiar: crystal growth. Like the micelles we propose in the this paper, crystals have well-defined geometrical characteristics (e.g., lattice planes) that emerge from the local interactions between their constituents. Another similarity with micelles is that crystals result from nonspecific interactions resulting from only a few chemical species. Due to the nonspecificity of the interactions, a crystal may deform (e.g., by dislocation glide), without losing its natural geometric characteristics, as each atom or molecule is left in an identical environment after the deformation. However, there are many differences between micelles and crystals. The most important difference for our purposes is that crystals do not naturally form well-defined finite shapes; instead, the size of the self-assembled structure is determined only by the amount of constituents present. Additionally, the shapes formed by crystals can be categorized into only a few classes, further limiting the shape control that can be achieved through selecting the constituents. Another important difference is that crystals are solid, and therefore do not have fluctuations.

The second naturally occurring system, perhaps more similar to our micelles, is a globular protein. It could be said that globular proteins are more similar to our micelles because they both have a well-defined shape and size determined by their composition. However, unlike the micelles we propose, the shape of a globular protein is determined by specific, high-energy, localized interactions between its constituent amino acids. This leads to the “protein

folding problem”: the folded shape of the protein is difficult to predict from the sequence of amino acids. If the amino acid sequence is even slightly altered, the shape is often completely destroyed. Also owing to the specific nature of the interactions, if a protein’s shape is significantly deformed, many atoms’ environments become completely different, so that the shape is irreversibly lost. By contrast, the nonspecific interactions responsible for amphiphile aggregation allow for a smooth dependence of energy on the micelle configuration, so a perturbed micelle returns to its equilibrium shape. Also, the simplicity of the nonspecific interaction allows for the straightforward design strategy described in Sec. 1.1.1; there should be no analogy to the “protein folding problem” for the micelles we consider. Additionally, the tight nature of the bonds in proteins gives a solid-like character leading to low shape fluctuations, while micelles may have large fluctuations, which may be used, e.g., to regulate drug delivery or reduce the shape specificity of lock-and-key interactions.

1.1.3 Scope of this paper

In Sec. 1.1.1, we described our shape-design strategy as judiciously selecting block lengths for diblock copolymers to achieve a desired preferred curvature profile, and then joining these diblocks into one multiblock copolymer to constrain their positions on the micelle surface. To organize the following discussion, we distinguish two challenges associated with this shape-design mechanism. The first challenge is to determine which block lengths should be selected for each diblock on the micelle surface in order for the micelle to spontaneously adopt the desired shape in thermal equilibrium. We call this the shapability challenge. The second challenge is to constrain the diblocks so they keep their intended positioning on the micelle surface, which we attempt to do by joining the diblocks together. We call this the stability challenge.

Were the diblocks not joined together, there would be a number of ways the stability challenge could fail to be met. For example, the diblocks might diffuse on the surface of the micelle, washing out the intended curvature profile and leaving only a uniform spontaneous

curvature profile in its place. A more extreme example is for the micelle to divide into two disconnected pieces. Alternatively, two micelles could merge into an aggregate containing both constituent multiblock copolymers. Since we wish to avoid these situations, we call a micelle “malformed” if it contains more than one copolymer chain or a single chain’s constituent diblocks do not have their intended relative positioning. Conversely, we call a micelle “well formed” if it is composed of a single copolymer chain with the diblocks in their intended positions.

This work is a first study of the proposed shape-design mechanism and we would like to assess its promise, and so we choose to focus on the shapability challenge. Accordingly, we avoid the stability challenge for the time being. Still, to perform the study of micelle shape needed to address the first challenge, we must somehow produce an ensemble of well-formed micelles. Some progress can be made by joining the diblocks end to end, as described in Sec. 1.1.1, to form a linear multiblock copolymer. Indeed, we find that this scheme causes most simulated micelles to be well formed. Unfortunately, we find that well-formed micelles are only metastable, so that over time the micelle becomes malformed. Nevertheless, well-formed micelles do constitute a statistical ensemble (to be explicitly defined in Sec. 1.3.3), and we can analyze the statistics of the thermodynamic ensemble of well-formed micelle shapes. To determine the appropriate statistical weight of the well-formed micelles in the presence of malformed micelles, we take a rejection-sampling approach: we simply discard any simulation runs containing malformed micelles. However, without a clear path to ensuring the micelles are well formed, one may question the usefulness of this analysis on the grounds that well-formed micelles are unstable, ultimately becoming malformed, so that the well-formed shapes are ultimately irrelevant. To address this concern, we comment on what measures may be taken to stabilize well-formed micelles in Sec. 1.5.3.

The purpose of the paper, then, is to address the shapability challenge: to show that the equilibrium micelle shape features can be controlled by selecting the species of constituent diblocks at each point on the micelle surface. For simplicity, we consider a two-dimensional

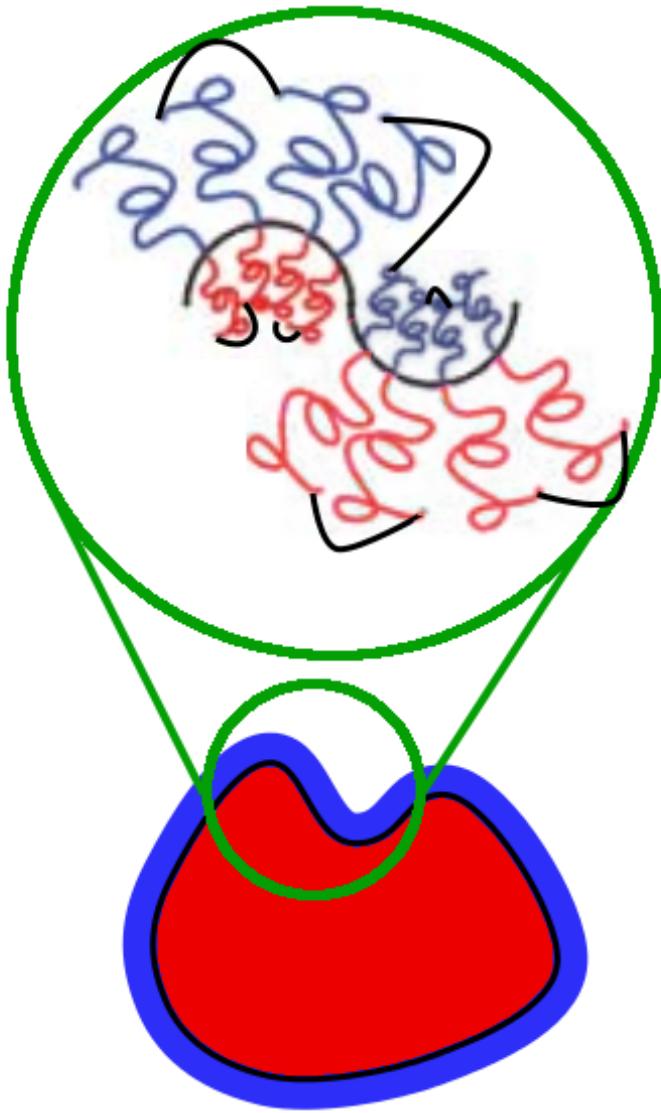


Figure 1.4: Schematic of proposed mechanism for making micelles of designed shape. A shape-designed micelle, shown in two dimensions for simplicity, has a solvophobic interior (shown in red). At the surface, there are diblocks containing both solvophobic and solvophilic (shown in blue) blocks. The interface between the solvophobic and solvophilic regions is shown in black, and it has a concave dimple. The inset shows how our shape-design mechanism gives rise to the designed shape: regions of the micelle surface where a convex curvature is desired are populated with diblocks having a larger solvophilic block and consequently preferring a convex curvature, while regions to be made concave are populated with diblocks containing larger solvophobic blocks, thereby preferring more concave curvature. Bonds, indicated in black, connect the diblocks end to end forming a multiblock copolymer in order to fix diblocks in their intended positions.

system, and we restrict our attention to a case study of a shape with a single concave dimple similar to the one in Fig. 1.4. We choose this shape because it is a minimal example requiring our shape-design mechanism: while it is simple, it does not arise as an equilibrium shape of a micelle composed of diblocks of a single species. While a two-dimensional model is not directly applicable to any realizable polymer system, such a model can nevertheless accurately represent many aspects of the polymer’s behavior. Benefits and limitations of using a two-dimensional model in the context of this work are discussed in Sec. 1.5.4.

In order to show that the shapability challenge can be met, it is necessary to develop a formalism for determining a micelle’s equilibrium shape features. One must make a quantitative measure of the micelle shape, and determine a method of averaging in the presence of large thermal fluctuations. One must also determine the uncertainty in the average in order to assess the significance of the observed dependence of the micelle shape on the species of diblocks on the micelle surface. Additionally, statistical tests must be performed to determine if the results accurately represent thermal equilibrium. The work described in this paragraph requires considerable effort and accordingly a significant fraction of this paper is devoted to addressing these issues.

The remainder of this paper is organized as follows: In Sec. 1.2, we describe our polymer model and how this model is simulated, including the system of units used and how the polymeric micelles are represented and initialized in the simulation. In Sec. 1.3, we describe how micelle shape properties are extracted from the simulation results, how the uncertainties in these properties are estimated, how we test that the results truly represent thermal equilibrium, and which specific shape features we study. In Sec. 1.4, we apply the analysis methods of Sec. 1.3 to micelle simulations, showing that these methods give self-consistent results and demonstrating the extent to which our shape-design mechanism affects features of the micelle shape. In Sec. 1.5, we discuss future work suggested by this research and the implications our results have for the applications mentioned above.

1.2 Method

In this section, we describe how our micelles are simulated. A simulation requires an underlying physical model specifying, for example, the degrees of freedom used to represent the system and the interactions governing the system. To describe these interactions, and to describe the behavior of the micelle model more generally, we choose a system of units for the purposes of nondimensionalization. With the system of units and model specified, it is necessary to choose a method to simulate the model system. Because the applications we consider in Sec. 1.1 concern micelles in thermodynamic equilibrium at some finite temperature, the goal of the simulation is to produce a Boltzmann-distributed ensemble of micelle configurations. Lastly, we describe how shape-designed micelles are represented in the simulation and what initial configuration we give them.

1.2.1 *Model and simulation method*

Since we expect our shape-design mechanism ought to apply very generally without regard to the specific features of a particular chemical structure, we choose a simple model having the minimum content necessary to exhibit our shape-designed mechanism. Specifically, we use a coarse-grained two-dimensional bead-spring model with implicit solvent, similar to the models used in [43–46]. In our model, a polymer is represented as a sequence of beads, each described by only a position and a common diameter. By “coarse-grained”, we mean a simulation bead does not represent just a single atom or even a single monomer, but rather several chemical repeat units. Any sequential pair of beads in the polymer is connected by a bond represented by a harmonic pair potential. In addition to these bond potentials, the beads also interact through a short-range pair potential. Since the solvent is treated implicitly, the nature of the short-range interaction between two beads depends not only on the material composing the two beads, but also on the solvent. For example, beads representing the same nonpolar hydrocarbon would have a more attractive pair potential

when immersed in a polar solvent than they would when immersed in a nonpolar solvent. To represent diblocks, our model has two species of bead: one solvophobic and one solvophilic. The solvophilic-solvophilic and solvophilic-solvophobic pair potentials are purely repulsive, while the solvophobic-solvophobic pair potential has an additional attractive term. The interaction potentials were chosen with an eye to ease of computation and minimal steric constraint, while giving a concentrated, strongly immiscible solvophobic phase. No special effort was made to optimize this potential once a suitable one was found. Details are given in Appendix A.

To meaningfully talk about dimensioned quantities of our model system, we must establish a system of units. Due to the abstract, two-dimensional nature of our model, we do not find it useful to describe our system in terms of real units (e.g., angstroms, nanoseconds, etc.). Instead, we pick a set of constants fundamental to the model itself against which all other quantities will be nondimensionalized. Since we are ultimately interested in finding the thermal equilibrium properties of the micelles, a natural unit of energy is the thermal energy $k_B T$, where k_B is Boltzmann's constant and T is the temperature of the system being simulated, which, as shown in Appendix C, is like room temperature for our model polymer. As we are simulating polymers, we choose the unit of length to be the root-mean-square thermal length L_{therm} of the harmonic spring connecting two adjacent beads (ignoring the close-range pair potential). In two dimensions, the system has two internal degrees of freedom, so we find by the equipartition theorem that the unit of length L_{therm} is given by

$$k_B T = \frac{1}{2} k L_{\text{therm}}^2, \quad (1.1)$$

where k is the spring constant of the harmonic potential. To complete our system of units, we may take our unit of mass to be the bead mass. For the remainder of this paper, we nondimensionalize all physical quantities using this system of units.

To determine the average micelle shape resulting from this model, we perform a constant temperature molecular dynamics simulation using LAMMPS [47]. Details of the simulation

parameters are discussed in Appendix B. Having described the model and the simulation method, it is necessary to show that our choices of parameters for both the model (e.g., parameters governing the bead pair potentials) and simulation method result in the simulated polymer behaving similar to typical real, physical polymers at room temperature; this is the purpose of Appendix C.

1.2.2 *Micelle design*

We now describe how our model is applied to demonstrate our shape-design mechanism. Specifically, we discuss how the shape-designed micelle is represented in the simulation. Recall that the goal of this paper is to create a micelle with a concave dimple by constructing it from multiple diblock species. In Sec. 1.1.3, we identified two challenges in achieving this goal: the shapability challenge of selecting diblock species to produce the desired shape, and the stability challenge of ensuring the diblocks have their intended positioning over the micelle surface.

First, we describe how the shapability challenge is addressed in our model. For simplicity, we construct the micelle using just two diblock compositions. A diblock composition is characterized by the number of its solvophilic and solvophobic beads, denoted n_{ext} and n_{int} , respectively. As explained earlier, we expect a diblock containing relatively more solvophilic beads to prefer a more convex curvature, and a diblock containing relatively more solvophobic beads to prefer a more concave curvature. For a pragmatic measure of the relative prevalence of either species of bead in a diblock, we introduce the “asymmetry ratio” r of a diblock, given by

$$r = \frac{n_{\text{ext}} - n_{\text{int}}}{n_{\text{ext}} + n_{\text{int}}}. \quad (1.2)$$

The asymmetry ratio is zero for diblocks having an equal number of solvophobic and solvophilic beads, and it is 1 or -1 for polymers made purely out of solvophilic or solvophobic beads respectively. We expect a positive correlation between the asymmetry ratio of a

diblock and its preferred curvature. Therefore to implement our shape-design mechanism, we should position higher asymmetry ratio diblocks (we call these diblocks “solvophilic rich”) along most of the surface of the micelle, and lower asymmetry ratio diblocks (we call these diblocks “solvophobic rich”) where the dimple is intended to be.

In addition to the diblocks, we add one more ingredient to the micelle: a solvophobic homopolymer chain, which we call a “core segment”. The number of beads in the core segment gives an additional degree of control over the size of the micelle, which, as will be shown in Sec. 1.4.2, affects other properties of interest. In our simulations, we chose specific block lengths for the core segment and the diblocks; these are given in Sec. 1.4.

Next, we describe how the stability challenge is addressed. We constrain the diblock positions by introducing additional bonds joining all the diblocks and the core segment together into a single linear multiblock copolymer, with the diblocks joined end to end. It remains to specify the order of the core segment and the two species of diblocks within the multiblock copolymer. The core segment appears on one end of the multiblock, followed first by all the solvophobic-rich diblocks and then by the solvophilic-rich diblocks as illustrated schematically in Fig. 1.5. An example of a micelle formed by a multiblock copolymer so constructed is shown in Fig. 1.6.

1.2.3 *Simulation initialization*

To begin a molecular dynamics simulation of a micelle, an initial configuration is required. If the simulation is to address the central question of this paper as outlined in Sec. 1.1.3, there are two requirements the initial configuration must satisfy. First, because we are interested in studying only well-formed micelles, which are only metastable, the initial configuration must be well formed. Indeed, if our multiblock copolymer is initialized in a less favorable configuration (say, a random walk or linear configuration), we find that it does not self-assemble into a well-formed configuration during the course of a simulation, consistent with the results of [48]. Second, because we are interested in showing that a dimpled shape occurs

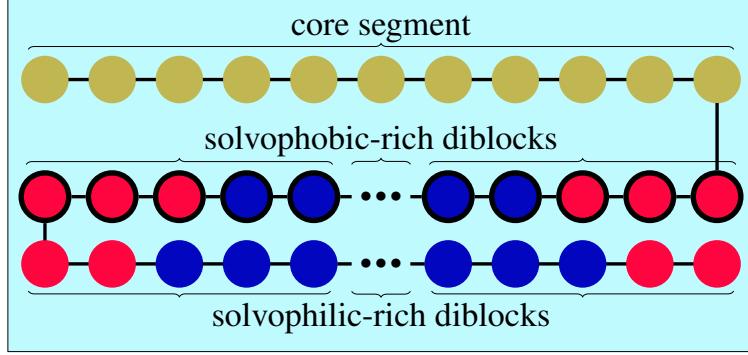


Figure 1.5: Schematic of multiblock bond architecture. The disks in the top row and the red (light gray) disks from the bottom rows represent solvophobic beads, while blue (dark gray) disks represent solvophilic beads. Black segments represent bonds between beads. The multiblock begins with a core segment composed of solvophobic beads shown in tan (top of schematic). To this segment solvophobic-rich diblocks, outlined in black as in Fig. 1.6, are successively attached end to end. Lastly solvophilic-rich diblocks are attached end to end. The “•••” symbols represent further diblocks not shown.

spontaneously in thermal equilibrium, the initial configuration should not be biased toward creating a dimple.

To satisfy these two requirements, we initialize the micelle in a well-formed circular configuration, shown in Fig. 1.7. We now describe the process of generating this configuration in more detail. We begin by initializing the core segment as a random walk starting at the origin with step length similar to the average bond length. Next, each diblock is initialized in a straight line pointing away from the origin. The solvophobic ends of each diblock are evenly spaced on a circle centered at the origin, whose area is equal to the area occupied by the core segment as calculated from the equilibrium homopolymer density. After this configuration is constructed, a conjugate gradient minimization of the micelle energy is performed to relax any extreme forces that may arise due to unnaturally large bond stretching or bead overlaps. The relaxed configuration produced by the energy minimization determines the initial bead positions for the molecular dynamics simulation. Since we perform molecular dynamics, the initial velocities must be specified in addition to the initial positions. These initial velocities are drawn from a Boltzmann distribution having the same temperature as the simulation thermostat. In this initialization scheme, there are two sources of random-

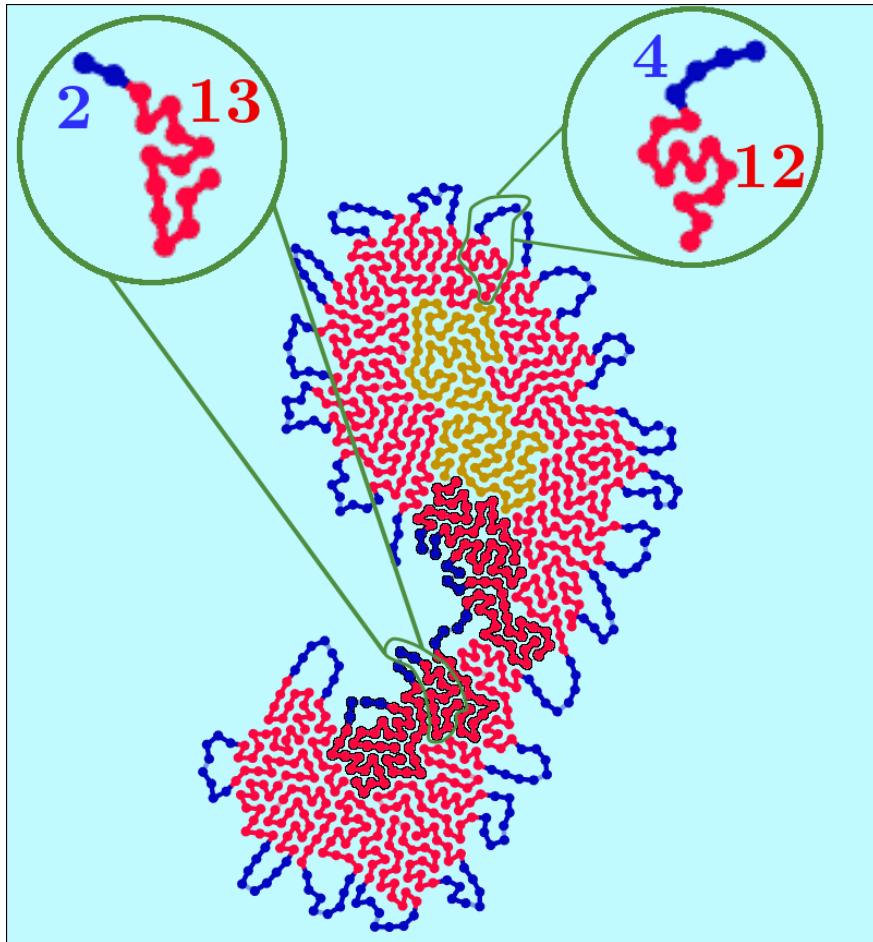


Figure 1.6: Illustration of how a micelle designed to have a dimple is constructed in our model. The micelle contains both species of beads present in our model: solvophobic, shown in red (light gray) or tan (darker gray beads in the micelle interior), and solvophilic, shown in blue (dark gray beads along the micelle surface). The micelle consists of a long “core segment” of solvophobic beads shown in tan (darker gray beads in the micelle interior), and a collection of diblocks. There are two species of diblocks: a “solvophobic-rich” species with two solvophilic beads and thirteen solvophobic beads (outlined with black), and a “solvophilic-rich” species with four solvophilic beads and twelve solvophobic beads. These diblocks are joined end to end. The dimple is intended to appear in the region occupied by the solvophobic-rich diblocks, as shown (indeed, the above configuration was taken from a simulation).

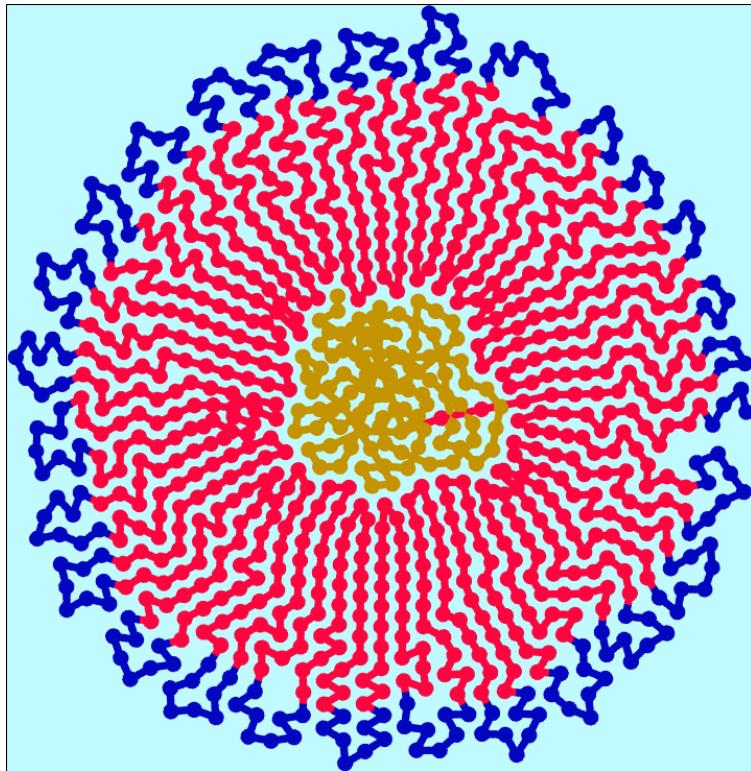


Figure 1.7: Initial relaxed configuration of simulated model shape-designed micelle, as described in the text. Color coding is as in Fig. 1.6. The resulting micelle configuration has the intended topology and surface diblock ordering, but is not biased toward its intended dimpled shape.

ness which ultimately lead to variable results from the otherwise deterministic simulation procedure: the first is the random initial velocities just discussed; the second is the random initial configuration of the core segment.

1.3 Analysis

In this section we discuss how the information from a molecular dynamics simulation is analyzed. Since the goal of this work is to create single-polymer micelles of a designed shape, one goal of the analysis is to determine the average micelle shape from the simulation output. In Sec. 1.3.1, we devote significant effort toward just defining what we mean by shape and how to determine the average of an ensemble of strongly fluctuating shapes. Besides the average shape, another quantity of interest is the shape fluctuations. In Sec. 1.3.2, we describe how we estimate these fluctuations, and how we use this estimate to determine the uncertainty in the mean shape.

The material in Secs. 1.3.1 and 1.3.2 deals with the analysis of a single simulation’s output, but in practice the output of many simulations are combined. Since well-formed micelles are only metastable, simulation results are often discarded as mentioned in Sec. 1.1.3. In Sec. 1.3.3, we specify the exact criteria used to discard a simulation’s results. Section 1.3.4 describes how the remaining results are combined to obtain a best estimate of the quantities of interest. In Sec. 1.3.5, we describe how the results of these independent simulations can be cross-checked against each other to validate the statistical analysis mentioned above. Finally, in Sec. 1.3.6, we define two scalar properties—one characterizing the average shape and one, the shape fluctuation—in order to distill the geometric features we are most interested in.

1.3.1 *Average shape from simulation run*

In this section, we introduce a quantitative representation of micelle shape, and we define, after giving some motivation, a formula for finding the average of a set of micelle shapes. As

a simulation runs, it records information about the micelle configuration at regular intervals of simulation time. Since we are only interested in the shape of the micelle, we do not record the position of every bead. Instead, we record only the location of the junction points: the midpoint of two beads that are adjacent along the polymer backbone but have opposite solvophobicity. A micelle has only as many junction points as diblocks it was constructed from. For the remainder of this paper, we define the term “micelle shape” to mean the ordered sequence of junction points. As such, a micelle shape \mathbf{r} has the mathematical form

$$\mathbf{r} = (\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n, \dots, \mathbf{r}_{N_j}), \quad (1.3)$$

where N_j is the number of junction points in the micelle, and each \mathbf{r}_n is itself a two-dimensional spatial vector representing the n th junction point’s position:

$$\mathbf{r}_n = (r_{n1}, r_{n2}). \quad (1.4)$$

Since we are interested only in the relative positions of the junction points, and not overall translations of the shape, we assume without loss of generality that each shape \mathbf{r} is geometrically centered at the origin so that

$$\sum_{n=1}^{N_j} \mathbf{r}_n = \mathbf{0}. \quad (1.5)$$

A micelle simulation outputs a time series of micelle shapes; however, the statistical information of interest can be summarized by just the average micelle shape and the fluctuations about this average. The process of obtaining this average contains some subtlety. For example, a simple arithmetic average will not suffice because the arithmetic average of a micelle shape and the same shape rotated by 180° is a micelle shape with every junction point at the origin. Instead, since the shapes are merely different by rotations, these two shapes should be considered the same, so that the average would somehow give the same

shape back again.

We define an appropriate average in two steps: first we introduce a metric giving the true difference between two shapes, then we define the average of a set of shapes to be the shape that minimizes the sum of these differences. To define the metric, we first define an “extrinsic” difference metric $\Delta_{\text{ext}}(\mathbf{a}, \mathbf{b})$ between two shapes \mathbf{a} and \mathbf{b} as the sum of square differences of corresponding position components. Introducing some notation, this difference may be written as

$$\Delta_{\text{ext}}(\mathbf{a}, \mathbf{b}) = (\mathbf{a} - \mathbf{b})^2, \quad (1.6)$$

where the square \mathbf{r}^2 of a shape \mathbf{r} is given by the dot product $\mathbf{r} \cdot \mathbf{r}$ of the shape with itself, and the dot product of two shapes is defined as the sum of dot products of corresponding junction points:

$$\mathbf{a} \cdot \mathbf{b} = \sum_{n=1}^{N_j} \mathbf{a}_n \cdot \mathbf{b}_n. \quad (1.7)$$

An illustration of this distance metric is given in Fig. 1.8(a).

The difference metric Δ_{ext} has a shortcoming: it has a nonzero value when evaluated on two shapes differing only by a rotation. Since there is no natural frame in which the shapes are defined, we desire a metric which is insensitive to rotation of either of its arguments. To this end, we define an “intrinsic” difference metric Δ_{int} defined as the minimum of Δ_{ext} with respect to rotations of one of its arguments. The action of a spatial rotation

$$\mathbf{R}_\theta = \begin{pmatrix} \cos \theta & -\sin \theta \\ \sin \theta & \cos \theta \end{pmatrix} \quad (1.8)$$

on a shape \mathbf{r} is defined junction point by junction point:

$$(\mathbf{R}_\theta \mathbf{r})_n = \mathbf{R}_\theta (\mathbf{r}_n). \quad (1.9)$$

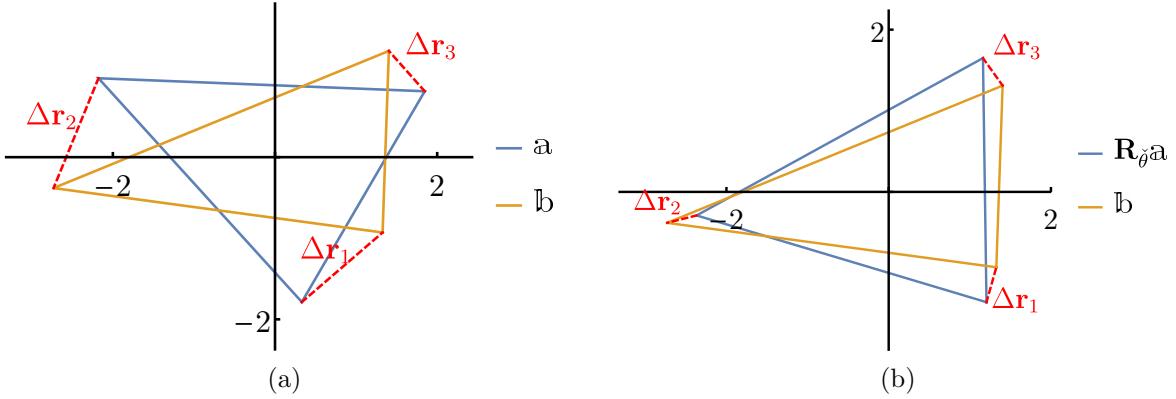


Figure 1.8: Illustration of the difference metrics Δ_{ext} , defined in Eq. (1.6), and Δ_{int} , defined in Eq. (1.10). In (a), two shapes, \mathbf{a} and \mathbf{b} , are shown, together with the displacement vectors $\Delta\mathbf{r}_1$, $\Delta\mathbf{r}_2$, and $\Delta\mathbf{r}_3$ connecting corresponding vertices of the two shapes. As specified by Eq. (1.5), both shapes are geometrically centered on the origin. The difference Δ_{ext} is given by the sum of square lengths of these vectors: $\Delta_{\text{ext}}(\mathbf{a}, \mathbf{b}) = \sum_{i=1}^3 \Delta\mathbf{r}_i^2$. In (b) the same two shapes are shown, except \mathbf{a} is rotated about the origin by the angle $\check{\theta}$ that minimizes Δ_{ext} . Consequently, the displacement vectors $\Delta\mathbf{r}_i$ are clearly smaller here than in (a). The intrinsic difference Δ_{int} is defined as this minimum value of Δ_{ext} .

Then the intrinsic difference Δ_{int} has been defined by

$$\Delta_{\text{int}}(\mathbf{a}, \mathbf{b}) = \min_{\theta} \Delta_{\text{ext}}(\mathbf{R}_{\theta}\mathbf{a}, \mathbf{b}). \quad (1.10)$$

An illustration of the intrinsic difference Δ_{int} is given in Fig. 1.8(b).

It can be shown² that the angle $\check{\theta}$ minimizing Eq. (1.10) is the signed angle that the two-dimensional vector

$$(\mathbf{a} \cdot \mathbf{b}, \mathbf{a} \wedge \mathbf{b}) \quad (1.11)$$

makes with the vector $(1, 0)$, where the wedge product of two shapes is defined by

$$\mathbf{a} \wedge \mathbf{b} = (\wedge \mathbf{a}) \cdot \mathbf{b}, \quad (1.12)$$

2. The proof is simple. Δ_{ext} in Eq. (1.10) is minimized when $(\mathbf{R}_{\theta}\mathbf{a}) \cdot \mathbf{b}$ is maximized. Now, $\mathbf{R}_{\theta}\mathbf{a}$ may be written as $\mathbf{a} \cos \theta + \wedge \mathbf{a} \sin \theta$. Using this representation, the product $(\mathbf{R}_{\theta}\mathbf{a}) \cdot \mathbf{b}$ can be transformed into a two-dimensional dot product $(\cos \theta, \sin \theta) \cdot (\mathbf{a} \cdot \mathbf{b}, \mathbf{a} \wedge \mathbf{b})$. This product is maximized when the unit vector $(\cos \theta, \sin \theta)$ points in the direction of $(\mathbf{a} \cdot \mathbf{b}, \mathbf{a} \wedge \mathbf{b})$, hence Eq. (1.11). With no more effort, we see that the maximum value of the dot product is the length of the same vector, leading to Eq. (1.14).

and where the wedge $\wedge a$ of a shape a is simply the result of rotating it by $\pi/2$:

$$\wedge a = \mathbf{R}_{\pi/2} a. \quad (1.13)$$

Thus e.g., if $b = a$, then $a \cdot b$ is positive and $a \wedge b = 0$, so that $\check{\theta} = 0$. Indeed if a and b are any two aligned shapes, so that $\check{\theta} = 0$, then $a \cdot b$ must be positive and $a \wedge b$ must be zero. If instead $b = \wedge a$, then $a \cdot b = 0$ and $a \wedge b$ is positive, so that $\check{\theta} = +\pi/2$. It can be shown that the intrinsic difference between two shapes can be calculated explicitly as

$$\Delta_{\text{int}}(a, b) = a^2 + b^2 - 2\sqrt{(a \cdot b)^2 + (a \wedge b)^2}. \quad (1.14)$$

If the shape a is then rotated by the minimizing angle $\check{\theta}$, then we say a has been aligned with b . (In general we will use a “ \sim ” to indicate that a quantity has been somehow aligned.) We note that, somewhat counterintuitively, the relationship of being aligned is not transitive: if a is aligned with b , and b is aligned with some third shape c , a is typically not aligned with c .

Having defined the appropriate notion of shape difference, we now define the average. Owing to the nontransitivity of alignment, the definition is more involved than might be expected: it is not possible to simply align all the shapes with each other and then do a simple average, because, as stated above, it is typically impossible for even three shapes to be pairwise aligned with each other. Instead, given a time series of N_s simulated shape samples r_α , $\alpha = 1, 2, \dots, N_s$, we define their average \bar{r} as the shape that minimizes the sum of Δ_{int} with the samples:³

$$\bar{r} = \arg \min_a \sum_{\alpha=1}^{N_s} \Delta_{\text{int}}(a, r_\alpha). \quad (1.15)$$

3. We use $\arg \min$ to represent the operation of finding the argument which minimizes a function. That is, if $x^* = \arg \min_x f(x)$, then $f(x^*)$ is the minimum value of f .

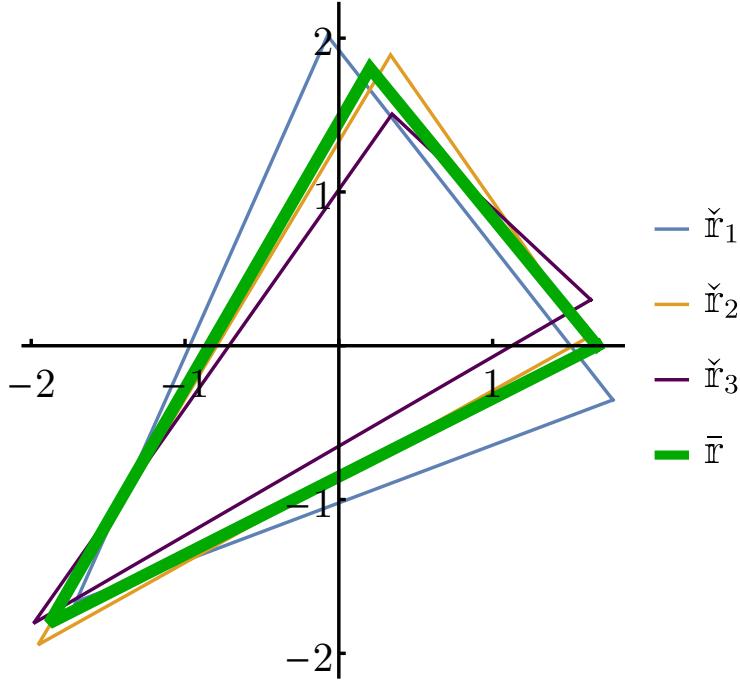


Figure 1.9: Illustration of the average \bar{r} of three shapes r_1 , r_2 , and r_3 . The original r_i are not shown; instead, the result \check{r}_i of aligning r_i with \bar{r} is shown. For definiteness, we have fixed the otherwise arbitrary orientation of \bar{r} by positioning its first junction point on the x axis.

Because Δ_{int} is defined only up to rotations, this definition of \bar{r} is defined only up to rotation. The rotational degree of freedom can be fixed, e.g., by making the first junction point \bar{r}_1 lie on the positive x axis. Once a choice of orientation of \bar{r} has been made, the orientation of each sample r_α can be fixed by aligning it with \bar{r} ; we denote this aligned shape sample \check{r}_α . This method of averaging is illustrated in Fig. 1.9. To justify our choice of this method of averaging, we show in Appendix D that it is equivalent to another natural method of averaging.

1.3.2 Shape variance from simulation run

In addition to the average micelle shape, we have stated that the shape fluctuations can be used to control the micelle's interactions. The fluctuations are characterized by a $2N_j \times 2N_j$

variance matrix Σ , defined by

$$\Sigma = \frac{1}{N_s - 1} \sum_{\alpha=1}^{N_s} (\check{r}_\alpha - \bar{r}) \otimes (\check{r}_\alpha - \bar{r}), \quad (1.16)$$

where the tensor product $a \otimes b$ gives the $2N_j \times 2N_j$ second rank tensor that acts on a shape c according to the rule $(a \otimes b) \cdot c = a(b \cdot c)$.

These shape fluctuations limit the precision to which the mean shape \bar{r} is determined. Naturally, one wants to be able to quantify this precision. Indeed, to convincingly show that the micelle's shape depends on its composition, as we indeed set out to do, we must show that the variability in the mean shapes cannot be explained only by the uncertainty caused by the limited precision of the simulation technique. Consequently, it is necessary to estimate this uncertainty in the mean shape. A naive estimate for the variance matrix $\bar{\Sigma}$ representing the degree of uncertainty in \bar{r} is Σ/N_s . However, this would underestimate the uncertainty since the shape samples are correlated. If the system was described by a single correlation time of τ sampling intervals, then the correlations could be accounted for by using the estimate $\Sigma\tau/N_s$. However, to make matters more complicated, there is no single correlation time describing the correlations in the sample. Typically we find large scale cooperative fluctuations have longer correlation times than high wavenumber fluctuations.

To address this complication, we find the autocorrelation time of each fluctuation mode independently, as we now describe in more detail. A mode m_ℓ is an eigenvector of the variance matrix Σ . This eigenvector has a corresponding eigenvalue Σ_ℓ , so that

$$\Sigma = \sum_{\ell=1}^{2N_j} \Sigma_\ell m_\ell \otimes m_\ell. \quad (1.17)$$

(To fix the ordering of the m_ℓ with respect to ℓ , we arrange them in decreasing order of Σ_ℓ .)

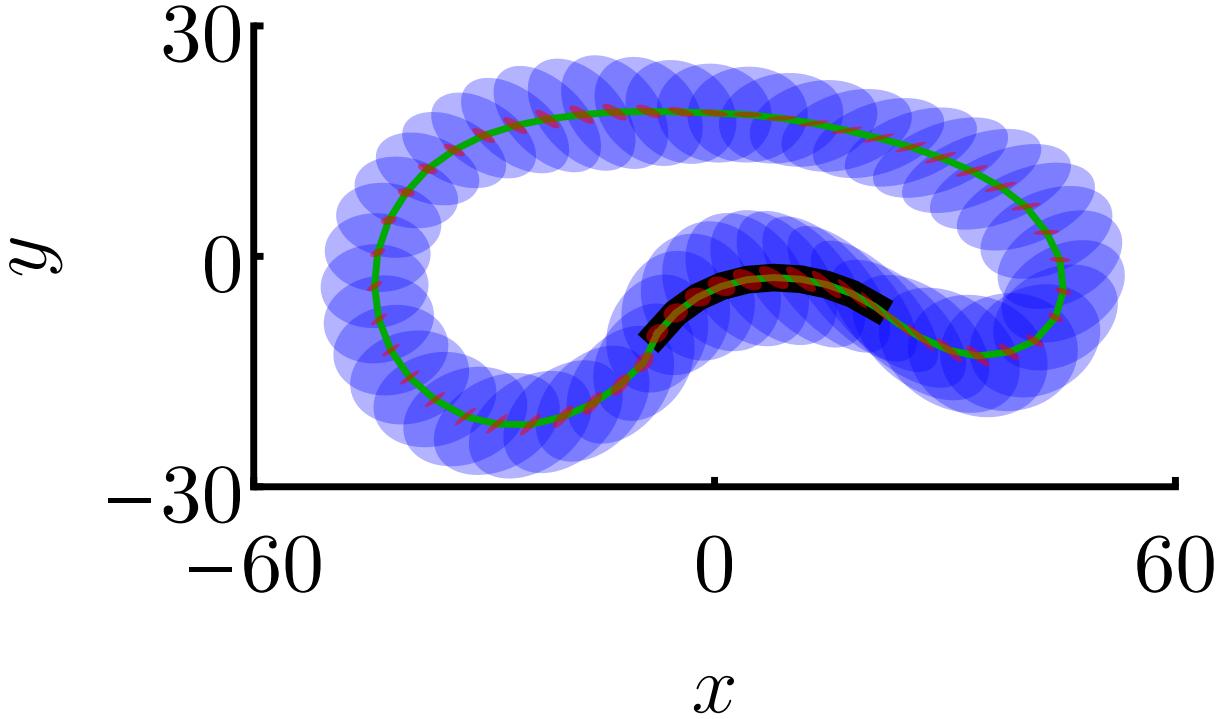


Figure 1.10: Graphical representation of an average micelle shape and its fluctuations and uncertainty. The central green curve linearly interpolates the average position of each diblock junction point. The region of the surface occupied by solvophobic-rich diblocks is outlined in black. For each junction point, a large blue ellipse and a smaller red ellipse is drawn. A blue ellipse represents the 40% confidence region, corresponding to one standard deviation from the mean, for a junction point assuming a Gaussian distribution with variance given by the shape variance Σ of Eq. (1.16). In the same way, a red ellipse represents the variance in the mean shape $\bar{\Sigma}$ of Eq. (1.19).

For each ℓ , we define time series of mode amplitudes $A_{\ell\alpha}$ given by

$$A_{\ell\alpha} = (\bar{\mathbf{r}}_\alpha - \bar{\mathbf{r}}) \cdot \mathbf{m}_\ell. \quad (1.18)$$

Under sufficient simplifying assumptions, the mode amplitudes $A_{\ell\alpha}$ may be used to estimate the uncertainty in $\bar{\mathbf{r}}$, following canonical methods [49]. Specifically, this estimate of uncertainty assumes that the mode amplitudes $A_{\ell\alpha}$ are sufficiently small that shape fluctuates as a harmonic system in thermal equilibrium and consequently the normal mode amplitudes fluctuate independently. In such a harmonic system each mode \mathbf{m}_ℓ has a char-

acteristic autocorrelation time τ_ℓ (in units of the sampling interval), which we estimate using the initial convex sequence estimator of [50]. Samples of the amplitude separated by times longer than τ_ℓ sampling intervals may be viewed as statistically independent, so that the number of independent samples of the ℓ th mode amplitude is N_s/τ_ℓ . Accordingly, the squared uncertainty in the mean along the \mathbf{m}_ℓ direction is estimated to be the variance Σ_ℓ of the shape distribution along this direction divided by the number of independent samples N_s/τ_ℓ . We therefore estimate the variance matrix $\bar{\Sigma}$ given the uncertainty in the mean by

$$\bar{\Sigma} = \sum_{\ell=1}^{2N_j} \frac{\Sigma_\ell}{N_s/\tau_\ell} \mathbf{m}_\ell \otimes \mathbf{m}_\ell. \quad (1.19)$$

A graphical representation of an average micelle shape together with its variance and variance in mean is shown in Fig. 1.10.

Since this uncertainty estimation ignores uncertainties in the mode eigenvectors \mathbf{m}_ℓ , and moreover our system's fluctuations may be too large to permit a harmonic approximation, the estimate of Eq. (1.19) may be inaccurate. However in Sec. 1.3.5, we will describe a way of validating Eq. (1.19) by checking whether the expected uncertainty in $\bar{\mathbf{r}}$ within a simulation run is consistent with the repeatability of $\bar{\mathbf{r}}$ over several simulation runs. Then in Sec. 1.4.1, we will use this validation to show that our results are largely consistent with this harmonic scheme.

1.3.3 Rejecting malformed micelles

In the case shown in Fig. 1.10, the diblock junction points make a smooth curve along the surface of the micelle, indicating that the bonds joining the diblocks were sufficient to make the micelle well formed. However, this is not the case with every simulation. Fig. 1.11(a) shows a case where multiple diblock junction points crossed from one side of the micelle to the other. In addition to this example, we have observed cases where the solvophobic region of the micelle splits into two or more disconnected pieces, as shown in Fig. 1.11(b). Since

this work is concerned only with the behavior of well-formed micelles, we simply discard any such results where the average micelle shape is malformed.

If data are to be discarded in a consistent manner, a precise definition of “well formed” is needed. We considered a shape to be well formed if it satisfies two criteria: an ordering criterion and a smoothness criterion. The ordering criterion is satisfied if the shortest closed path visiting each junction exactly once visits the junction points in the intended order. This criterion detects whether diblocks cross from one side of the micelle surface to another, and it also detects smaller defects such as a transposition of two diblocks. The smoothness criterion is satisfied if the maximum distance between any two sequential junction points exceeds the median distance by less than forty percent. The smoothness criterion detects whether diblocks have broken off from the main surface either to form a small aggregate of diblocks outside the micelle, or to form a cluster of solvophilic beads in the interior of the micelle. We found that about half of the average micelle shapes resulting from our simulations satisfied both criteria for being well formed.

1.3.4 Combining simulation runs

So far, we have discussed how to determine an average micelle shape and its fluctuation from a single simulation run. However, we performed multiple simulation runs of each micelle with different random initial velocities (see Sec. 1.2.3) to both generate more statistical data, and more crucially to confirm that the uncertainties in each simulation run’s mean shape are well estimated. Therefore, for each micelle composition there is not one, but N_a average shapes, denoted \bar{r}_ξ , $\xi = 1, 2, \dots, N_a$, and each of these has a corresponding variance Σ_ξ and variance in mean $\bar{\Sigma}_\xi$. In this section, we describe how these quantities are combined to produce a best estimate of the shape, its fluctuations, and its error. To represent these best estimates, we will use the corresponding symbols, but without the ξ subscript. More explicitly, \bar{r} denotes the combined average; Σ , the combined variance; and $\bar{\Sigma}$, the error in the combined mean.

It would be possible to combine the means \bar{r}_ξ via the simple minimization given in

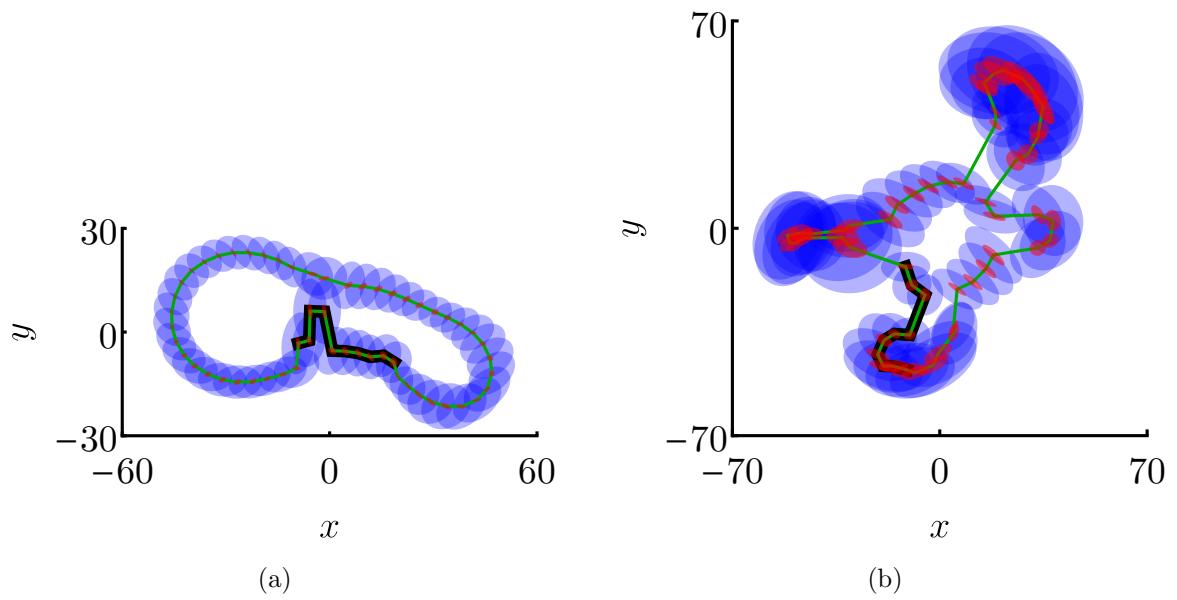


Figure 1.11: Two different types of malformed micelles. The curves and ellipses have the same meaning as in Fig. 1.10. In (a), the average micelle shape contains two junction points in the concave region which approach the opposite surface of the micelle. This occurs because the junction points crossed to the other side during the simulations. In (b), the micelle is broken up into multiple disconnected regions outlined by the junction points. Such malformed micelles are not expected to take the designed shape, and so they are excluded from our analysis.

Eq. (1.15). However, this formula would ignore the uncertainties $\bar{\Sigma}_\xi$ in the means. These uncertainties ought to be taken into account, because mean shapes with lower uncertainty should be given more weight in determining the combined mean. Indeed, as might be predicted from the outliers of Fig. C.3(b), we do find that there is a significant variability in simulation runs' uncertainties in the mean. To account for the uncertainties, we may define the combined mean using a maximum likelihood estimate [49]. Under the canonical assumptions of a harmonic system in thermal equilibrium, we expect the probability distribution of \bar{r}_ξ to be Gaussian, so the log-likelihood $L(\bar{r}, \bar{r}_\xi, \bar{\Sigma}_\xi)$ of a true average shape \bar{r} given an estimated average \bar{r}_ξ and its error $\bar{\Sigma}_\xi$ is (up to an unimportant constant offset) proportional to the following quadratic form:

$$L(\bar{r}, \bar{r}_\xi, \bar{\Sigma}_\xi) = -(\check{\bar{r}} - \bar{r}_\xi) \cdot \bar{\Sigma}_\xi^{-1} \cdot (\check{\bar{r}} - \bar{r}_\xi), \quad (1.20)$$

where $\check{\bar{r}}$ is the result of aligning \bar{r} with \bar{r}_ξ . Since this log-likelihood depends only on $\check{\bar{r}}$, it is independent of rotations of \bar{r} , as desired. The product in Eq. (1.20) involving a matrix inversion is indeed well defined since $\bar{\Sigma}_\xi$ does have full rank when viewed as an operator on the space of shapes aligned with \bar{r}_ξ , and the shapes $\check{\bar{r}} - \bar{r}_\xi$ indeed lie in this space.

Having defined the log-likelihood of a mean given a single simulation, we may now define the same for multiple simulation runs. This is facilitated by the fact that the runs are statistically independent from one another, so that the joint probability of measuring each \bar{r}_ξ with the uncertainty $\bar{\Sigma}_\xi$ given the true mean shape \bar{r} is the product of the individual probabilities, and therefore the log-likelihood of the true mean shape \bar{r} given the \bar{r}_ξ and $\bar{\Sigma}_\xi$ is simply the sum of the individual log-likelihoods. Therefore the maximum likelihood estimate for the true mean shape \bar{r} is given by maximizing the sum of log-likelihoods:

$$\bar{r} = \arg \max_{\mathbf{a}} \sum_{\xi=1}^{N_a} L(\mathbf{a}, \bar{r}_\xi, \bar{\Sigma}_\xi). \quad (1.21)$$

As with Eq. (1.15), this arg max is defined only up to a rotation, so, as with Eq. (1.15), a convention is needed to fix the rotational degree of freedom so that \bar{r} is uniquely defined.

Once the average \bar{r} is found, one can ask what is the best estimate for the fluctuations that can be made from each run's mean \bar{r}_ξ and variance Σ_ξ . We make this best estimate by finding the variance matrix which best represents the fluctuations aggregated over all simulation runs. The variance Σ_ξ represents a set of samples $r_{\xi\alpha}$ aligned with \bar{r}_ξ . The first step in estimating the variance from the shape samples via Eq. (1.16) is to align the samples with the mean (in the present case, \bar{r}). Then an estimate of the variance of the aligned samples can be made using this alignment transformation and the variance Σ_ξ of the unaligned samples.

The alignment transformation can be decomposed into two steps. First we apply to each sample the rotation \mathbf{R}_ξ which aligns \bar{r}_ξ with \bar{r} , producing the aligned mean shape \check{r}_ξ given by $\mathbf{R}_\xi \bar{r}_\xi$ and the rotated samples $\check{r}_{\xi\alpha}$, given by $\mathbf{R}_\xi r_{\xi\alpha}$. However, the alignment of the sample $r_{\xi\alpha}$ with the combined mean \bar{r} is not yet complete: although $\check{r}_{\xi\alpha}$ is aligned with \check{r}_ξ , and \check{r}_ξ is aligned with \bar{r} , nontransitivity implies that $\check{r}_{\xi\alpha}$ is typically not aligned with \bar{r} . Therefore, a second rotation $\mathbf{R}_{\xi\alpha}$ specific to each sample is necessary to complete the alignment. Thus the transformation that rotates the sample $r_{\xi\alpha}$ into alignment with \bar{r} is $\mathbf{R}_{\xi\alpha} \mathbf{R}_\xi$.

We must now make an estimate of the variance in the aligned shape samples from the transformation $\mathbf{R}_{\xi\alpha} \mathbf{R}_\xi$. Since the rotation matrix $\mathbf{R}_{\xi\alpha}$ depends on $r_{\xi\alpha}$, the aligned shapes $\mathbf{R}_{\xi\alpha} \mathbf{R}_\xi r_{\xi\alpha}$ depend nonlinearly on $r_{\xi\alpha}$. Because of this nonlinearity, the variance of the aligned shape distribution may depend on higher order moments of the distribution of shapes $r_{\xi\alpha}$. Since we do not record these higher moments, and we wish to avoid reprocessing all the shape samples, an approximation is needed to obtain the aligned shape distribution's variance. We make the approximation that the distribution of $r_{\xi\alpha}$ is tightly centered on \bar{r}_ξ , from which it follows both that $r_{\xi\alpha} \approx \bar{r}_\xi$ (and therefore the same is true when rotated by \mathbf{R}_ξ : $\check{r}_{\xi\alpha} \approx \check{r}_\xi$) and that the angle $\theta_{\xi\alpha}$ of the rotation $\mathbf{R}_{\xi\alpha}$ is small (after all, if $\check{r}_{\xi\alpha} = \check{r}_\xi$, then the $\check{r}_{\xi\alpha}$ are already aligned with \bar{r} so that $\theta_{\xi\alpha} = 0$). This approximation allows for

linearization of the alignment transformation. The rotated $\mathbf{R}_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha}$ can be approximated as

$$\begin{aligned}\mathbf{R}_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha} &= \cos\theta_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha} + \sin\theta_{\xi\alpha}(\wedge\check{\mathbf{r}}_{\xi\alpha}) \\ &\approx \check{\mathbf{r}}_{\xi\alpha} + \theta_{\xi\alpha}(\wedge\check{\mathbf{r}}_{\xi\alpha}) \\ &\approx \check{\mathbf{r}}_{\xi\alpha} + \theta_{\xi\alpha}(\wedge\check{\mathbf{r}}_{\xi}),\end{aligned}\tag{1.22}$$

where $\wedge\check{\mathbf{r}}_{\xi\alpha}$ is defined in Eq. (1.13) as a 90° counter-clockwise rotation of $\check{\mathbf{r}}_{\xi\alpha}$. In Eq. (1.22), the second line follows because $\theta_{\xi\alpha}$ is small, and the third line follows because $\check{\mathbf{r}}_{\xi\alpha} \approx \check{\mathbf{r}}_{\xi}$. It remains to determine the linear dependence of $\theta_{\xi\alpha}$ on $\check{\mathbf{r}}_{\xi\alpha}$.

The angle $\theta_{\xi\alpha}$ of the rotation $\mathbf{R}_{\xi\alpha}$ is determined by the condition that $\mathbf{R}_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha}$ be aligned with $\bar{\mathbf{r}}$. By the reasoning found below Eq. (1.13), this alignment requires that $\wedge\bar{\mathbf{r}} \cdot \mathbf{R}_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha} = 0$. Inserting the approximation of Eq. (1.22) into this condition for alignment, we obtain

$$\wedge\bar{\mathbf{r}} \cdot (\check{\mathbf{r}}_{\xi\alpha} + \theta_{\xi\alpha}(\wedge\check{\mathbf{r}}_{\xi})) = 0,\tag{1.23}$$

so that $\theta_{\xi\alpha} = -\frac{(\wedge\bar{\mathbf{r}}) \cdot \check{\mathbf{r}}_{\xi\alpha}}{\bar{\mathbf{r}} \cdot \check{\mathbf{r}}_{\xi}}$. Inserting this $\theta_{\xi\alpha}$ back into Eq. (1.22), we find the action of the second rotation on a sample to be

$$\mathbf{R}_{\xi\alpha}\check{\mathbf{r}}_{\xi\alpha} \approx \left(\mathbb{1} - \frac{\wedge\check{\mathbf{r}}_{\xi} \otimes \wedge\bar{\mathbf{r}}}{\check{\mathbf{r}}_{\xi} \cdot \bar{\mathbf{r}}}\right)\check{\mathbf{r}}_{\xi\alpha} \equiv \mathbb{P}_{\xi}\check{\mathbf{r}}_{\xi\alpha},\tag{1.24}$$

where we have defined the projection operator \mathbb{P}_{ξ} to be the tensor in parentheses above. We see that the combined effect of the two rotations on a shape sample is approximately given by the linear operator $\mathbb{P}_{\xi}\mathbf{R}_{\xi}$. Consequently, the variance matrix for the aligned samples is approximated by $\mathbb{P}_{\xi}\mathbf{R}_{\xi}\Sigma_{\xi}\mathbf{R}_{\xi}^T\mathbb{P}_{\xi}^T$, which we denote by $\check{\Sigma}_{\xi}$.

If the aligned fluctuations from each simulation run were aggregated, the resulting variance matrix would be the weighted average of the individual $\check{\Sigma}_{\xi}$ of each run, weighted by the number of samples. However, since each run had approximately the same length, they generate approximately the same number of samples, and so we make the approximation

that the best estimate for the combined variance is a simple average of the $\check{\Sigma}_\xi$:

$$\Sigma = \frac{1}{N_a} \sum_{\xi=1}^{N_a} \check{\Sigma}_\xi. \quad (1.25)$$

To estimate the variance in the mean $\bar{\Sigma}$ giving the uncertainty in \bar{r} , we also perform an average. Just as in Eq. (1.25), we must revise the original $\bar{\Sigma}_\xi$ to account for the fact that the best estimate of the mean is now \bar{r} , and to align $\bar{\Sigma}_\xi$ with this \bar{r} . Accordingly we perform the same alignment transformation on each $\bar{\Sigma}_\xi$ that was done for the sample variances Σ_ξ above. The result is denoted $\check{\Sigma}_\xi$. We then average these $\check{\Sigma}_\xi$ values as in Eq. (1.25). This average doesn't change systematically as N_a increases. However the overall variance in the mean of N_a independent samples is $1/N_a$ times this average. Thus

$$\bar{\Sigma} = \frac{1}{N_a^2} \sum_{\xi=1}^{N_a} \check{\Sigma}_\xi. \quad (1.26)$$

1.3.5 Testing consistency between simulation runs

In Sec. 1.1.3, we explained that we wish to determine the thermal equilibrium statistics of the well-formed micelles. Thus far, we have described a procedure for analyzing the statistics of micelle shapes from a single simulation and for combining the results of multiple simulations, but we have not discussed a way of testing whether the results of an individual simulation accurately reflects thermal equilibrium. In this section, we describe how we verify that individual simulation runs are thermally equilibrated. We do this by comparing, on the one hand, the difference of individual run means \bar{r}_ξ from the combined mean \bar{r} to, on the other hand, $\bar{\Sigma}_\xi$, which represents the error in the estimate of \bar{r}_ξ . If a simulation had not fully equilibrated, the micelle would explore only a small subset of the thermodynamically allowed configurations within a single simulation run, leading to an underestimate of the shape variance, and therefore the variance in the mean shape \bar{r}_ξ . In this case, the observed differences between the \bar{r}_ξ and \bar{r} would be significantly larger than $\bar{\Sigma}_\xi$ would suggest.

We use $L(\bar{r}, \bar{r}_\xi, \bar{\Sigma}_\xi)$ defined in Eq. (1.20) to quantitatively measure the differences between the individual run averages \bar{r}_ξ and the combined mean \bar{r} relative to the variance $\bar{\Sigma}_\xi$ in the individual run averages. Since $L(\bar{r}, \bar{r}_\xi, \bar{\Sigma}_\xi)$ is the negative of the chi-squared statistic and each mean has $2N_j$ degrees of freedom, we expect that this L should be of order $-2N_j$. We may therefore define the reduced chi-squared χ_ν^2 of a combined average \bar{r} by

$$\chi_\nu^2 = \frac{-1}{2N_j N_a} \sum_{\xi=1}^{N_a} L(\bar{r}, \bar{r}_\xi, \bar{\Sigma}_\xi). \quad (1.27)$$

We expect this χ_ν^2 to be near unity; however, if the simulation runs were too short so that the full range of thermal shapes is not explored in a single simulation, then the difference in the means \bar{r}_ξ would be larger than the errors in the means $\bar{\Sigma}_\xi$ would suggest, and χ_ν^2 would be much larger than unity. Thus χ_ν^2 is a statistic that tests not just whether the system is equilibrated, but more generally how well estimated are the uncertainties $\bar{\Sigma}_\xi$ of each mean shape \bar{r}_ξ , so that χ_ν^2 tests also for the issues arising from unvalidated assumptions underpinning Eq. (1.19). Since the $\bar{\Sigma}_\xi$ are defined using Σ_ξ (see Eq. (1.19)), the χ_ν^2 also provide an indirect test of the Σ_ξ as well.

In fact, it is possible to validate the uncertainties $\bar{\Sigma}_\xi$ in more detail. From Eq. (1.19), we expect that the uncertainty of the mean $\bar{\Sigma}_\xi$ in the direction of its ℓ th mode $\mathbf{m}_{\xi\ell}$ is given by $\frac{\Sigma_{\xi\ell}\tau_{\xi\ell}}{N_{s,\xi}}$. To verify this expectation, we can define the chi-squared of the ℓ th mode by

$$\chi_{\xi\ell}^2 = \frac{(\mathbf{m}_{\xi\ell} \cdot (\bar{r}_\xi - \bar{r}))^2}{\Sigma_{\xi\ell}\tau_{\xi\ell}/N_{s,\xi}}. \quad (1.28)$$

For each ℓ , we expect that $\chi_{\xi\ell}^2$ should be near unity. Testing this expectation gives a more thorough validation of Eq. (1.19), and in particular that finding the correlation time $\tau_{\xi\ell}$ of each mode is sufficient to characterize the full correlations of the shape fluctuations. The reduced chi-squared χ_ν^2 for each micelle composition and a representative set of chi-squareds $\chi_{\xi\ell}^2$ for the modes of one simulation run are presented in Sec. 1.4.1.

In addition to testing the formulas for the simulation run averages \bar{r}_ξ and their uncertainties $\bar{\Sigma}_\xi$ defined in Secs. 1.3.1 and 1.3.2, we would like to validate the combined average \bar{r} and its uncertainty $\bar{\Sigma}$. One method of validation is to verify that the result of combining the \bar{r}_ξ and the $\bar{\Sigma}_\xi$ is consistent with the result of first concatenating the list of samples $r_{\xi\alpha}$, and then finding a mean from these samples, using Eq. (1.15) as if the samples were generated from a single simulation. We chose to compare with the average of the combined samples, denoted by \tilde{r} , since the procedure for averaging a time series of shapes can itself be validated using χ_ν^2 and $\chi_{\xi\ell}^2$. Once the average of the combined samples has been found, a χ_ℓ^2 statistic similar to the one in Eq. (1.28) can be computed. More precisely, we define χ_ℓ^2 by

$$\chi_\ell^2 = \frac{(\mathbf{m}_\ell \cdot (\tilde{r} - \bar{r}))^2}{\bar{\Sigma}_\ell} \quad (1.29)$$

where \mathbf{m}_ℓ is the ℓ th eigenmode of $\bar{\Sigma}$ and $\bar{\Sigma}_\ell$ is the associated eigenvalue. An example calculation of this statistic will be presented in Sec. 1.4.1.

1.3.6 Shape features

We have now given a complete description about how to extract micelle shape information from the simulation. However, in this paper we will pay special attention to two features of the micelle shape: the “curvature ratio” and the “normalized fluctuation”. The curvature ratio c_-/c_+ is defined as the ratio of the average signed curvature of the micelle surface region occupied by the solvophobic-rich diblocks to that of the solvophilic-rich diblocks as illustrated in Fig. 1.12. We are interested in this quantity because our intent is to use our shape-design mechanism to produce a micelle of unusual shape, specifically one with a dimple. The curvature ratio quantifies the strength of this dimple, and therefore can help detect the conditions under which our shape-design mechanism works best.

In addition to the average shape, we are interested in the shape fluctuations, as noted previously. We have introduced the variance matrix Σ to characterize the shape fluctuations.

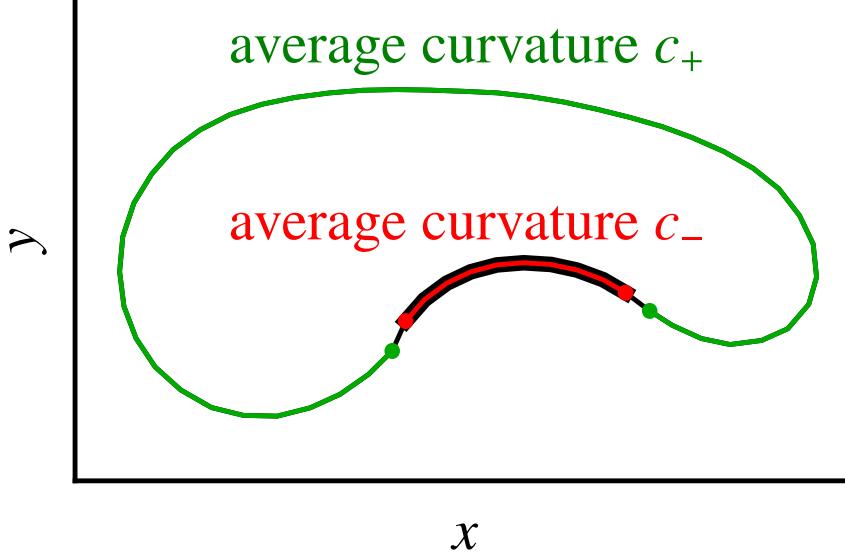


Figure 1.12: Illustration of the curvature ratio definition. The curvature ratio is defined as the ratio of the average curvature c_- in the region occupied by the solvophobic-rich diblocks to the average curvature c_+ in the region occupied by the solvophilic blocks. The curvature ratio is one for a circle, and is negative for a shape with a dimple such as the one shown in the figure, becoming more negative as the dimple grows more pronounced.

We summarize the size of the fluctuations represented by this $2N_j \times 2N_j$ matrix with a single scalar, the normalized fluctuation δ , to measure the amount of fluctuation in the micelle shape, normalized so as not to scale with the number of junction points or the size of the micelle. The normalized fluctuation is defined by

$$\delta = \sqrt{\frac{\text{Tr } \Sigma}{\bar{r}^2}}. \quad (1.30)$$

It is enlightening to notice a connection between the normalized fluctuation δ and the distance metric Δ_{int} : if \bar{r} and Σ are the mean and variance of a single simulation run, then by Eq. (1.16) and Eq. (1.10), the δ for this simulation run is given by

$$\sqrt{\frac{\frac{1}{N_s-1} \sum_{\alpha=1}^{N_s} \Delta_{\text{int}}(\bar{r}, \mathbf{r}_\alpha)}{\bar{r}^2}}. \quad (1.31)$$

Still another, more pictorial interpretation of the normalized fluctuation can be framed in

terms of the error ellipses representing Σ (the larger blue ellipses of, e.g., Fig. 1.9): the normalized fluctuation is roughly the typical linear size of these ellipses relative to the linear size of the micelle.

Since we will be analyzing these two features of micelle shape, we must make an estimate of their uncertainty. The uncertainty of the curvature ratio can be straightforwardly derived from the full variance matrix $\bar{\Sigma}$ giving the variance in the mean.

Estimating the uncertainty in the fluctuation δ is more subtle because δ is defined in terms of the variance Σ , and so the error in delta represents the error in the fluctuations of a quantity rather than the error in the quantity itself. Consequently, we attempt only a rough estimate of the error in δ . The dominant source of uncertainty in δ comes from $\text{Tr } \Sigma$. We find the uncertainty in $\text{Tr } \Sigma$ by recognizing that the trace is the sum of eigenvalues:

$$\text{Tr } \Sigma = \sum_{\ell} \Sigma_{\ell}. \quad (1.32)$$

Evidently, it is sufficient to estimate the uncertainty in each variance. To perform this estimate, we resort to assuming that each Σ_{ℓ} represents the variance of a Gaussian distribution. Given n samples of a univariate Gaussian random variable with variance Σ , a formula for the uncertainty σ_{Σ} of the estimate of the distribution's variance is given by (see [51])

$$\sigma_{\Sigma} = \Sigma \sqrt{\frac{2}{n-1}}. \quad (1.33)$$

To use this formula to estimate the uncertainty in Σ_{ℓ} , we must choose a value for the number of independent samples n_{ℓ} contributing to the estimation of Σ_{ℓ} . We estimate this number of samples for each mode \mathbf{m}_{ℓ} of Σ by taking the ratio of the fluctuation in the mode amplitude Σ_{ℓ} with the uncertainty in the mean along the \mathbf{m}_{ℓ} direction:

$$n_{\ell} = \frac{\mathbf{m}_{\ell}^T \Sigma \mathbf{m}_{\ell}}{\mathbf{m}_{\ell}^T \bar{\Sigma} \mathbf{m}_{\ell}}. \quad (1.34)$$

As this estimate of the normalized fluctuation uncertainty requires approximation in the form of Eqs. (1.33) and (1.34), some degree of validation is in order. To this end, we calculate the normalized fluctuation from each simulation run (i.e., substitute \bar{r}_ξ and Σ_ξ in Eq. (1.30)), and compute the standard error in the resulting normalized fluctuations. While this second method may seem reasonable, we prefer the uncertainty estimate described in the preceding paragraphs for two reasons: first, the second estimate cannot be used if there is only one simulation run producing a well-formed micelle; and second, the first estimate is less likely to underestimate the uncertainty, because it takes into account all modes while the second estimate can result in an underestimate if the normalized fluctuations from individual simulation runs happen to be similar. The results of using these two methods is compared in Fig. 1.15.

1.4 Results

In this section, we present micelle simulation results. The ultimate goal of running the simulations was to determine if the micelle shape features may be controlled by appropriately changing the micelle composition. In Sec. 1.3, we developed a set of tools to determine the equilibrium shape properties of a simulated micelle, but these tools depended on a number of untested assumptions, and so before presenting the results of applying these tools, we first perform in Sec. 1.4.1 the validations discussed in Secs. 1.3.5 and 1.3.6.

With this done, we present the results of simulating micelles of several compositions. The range of micelle compositions was not chosen to be exhaustive but only to demonstrate a significant degree of control over the micelle shape. To this end, we varied two aspects of the micelle composition: the length of the core segment and the composition of the solvophobic-rich diblocks. The length of the core segment ranged from 600 beads to 1000 beads. Two solvophobic-rich diblock compositions were studied, the first being 30 solvophobic beads and 2 solvophilic beads and the second being 27 solvophobic beads and 4 solvophilic beads. Since the first composition has a larger asymmetry, and therefore the micelles containing these

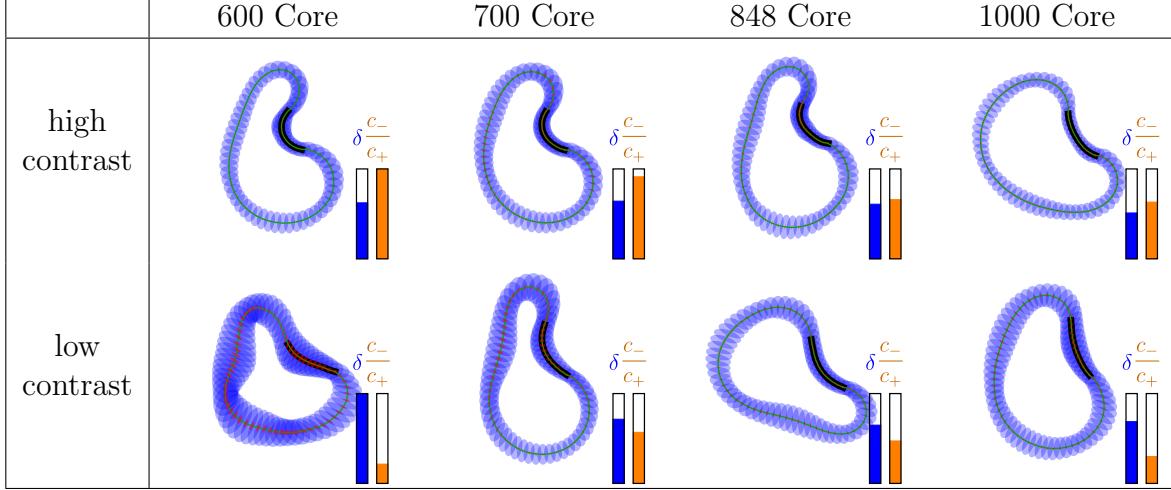


Table 1.1: Average shapes of micelles of various compositions, plotted in the manner of Fig. 1.10. The micelle compositions are described in the first paragraph of Sec. 1.4. The relative magnitudes of the normalized fluctuation δ (blue) and curvature ratio c_-/c_+ (orange) of each shape are indicated by bars next to the shape.

diblocks have a larger asymmetry contrast between their solvophobic-rich and solvophilic-rich diblocks, we refer to these micelles as “high contrast”. Conversely, we refer to the other micelles, whose solvophobic-rich diblocks contain 27 solvophobic beads and 4 solvophilic beads, as “low contrast”. Other aspects of the micelle composition were held constant: each micelle had 12 solvophobic-rich diblocks and 55 solvophilic-rich diblocks, and the solvophilic-rich diblocks each had 24 solvophobic beads and 7 solvophilic beads. To obtain sufficient statistics, each simulation was run in parallel on nine cores for 70 hours, during which time LAMMPS completed about one billion timesteps. The mean shapes, fluctuations, and uncertainties resulting from these simulations are plotted in Table 1.1. In Sec. 1.4.2, we plot the shape features introduced in Sec. 1.3.6 as a function of the size of the core and the asymmetry ratio of the solvophobic-rich diblocks.

1.4.1 Validation of analysis

In Sec. 1.3.5, we introduced two statistics χ_ν^2 and $\chi_{\xi\ell}^2$, defined in Eqs. (1.27) and (1.28), for validating that the variation in the means $\bar{\xi}_\ell$ was consistent with the error $\bar{\Sigma}_\xi$ in these

	600 Core	700 Core	848 Core	1000 Core
high contrast	5.5	0.69	1.8	—
low contrast	59	1.2	2.3	3.2

Table 1.2: Reduced chi-squared χ_ν^2 (defined in Eq. (1.27)) for each of the averages shown in Table 1.1. One of the entries is blank since there was only one well-formed result for that micelle composition, in which case the reduced chi-squared statistic is meaningless. Only one of the simulations runs of the high-contrast micelle having 1000 core beads gave a well-formed average shape, so that all of the other runs were rejected. The reduced chi-squared statistic is meaningless in this case, so it is omitted.

means. We stated that a correctly estimated error leads to the statistics being nearly one, while underestimated error lead to large values and overestimated errors lead to small values. One cause of concern motivating this test is that the simulations may not have been run long enough for the full range of thermal shapes to explore, leading to the estimated mean of a simulation run being strongly biased by the initialization. This would lead to the means being more different than mere thermal fluctuations would predict, and therefore lead to large χ_ν^2 and $\chi_{\xi\ell}^2$. Another cause for concern is that the assumption underpinning Eq. (1.19), namely that the fluctuation mode amplitudes fluctuate independently and are each described by a separate correlation time may be strongly violated to the point that Eq. (1.19) gives an unsatisfactory estimate of the uncertainty in the mean. A shortcoming of the estimate Eq. (1.19) would likely cause a systematic dependence of $\chi_{\xi\ell}^2$ on the mode number ℓ , since we expect the applicability our assumptions to depend on the amplitude or correlation of the mode, both of which vary systematically with ℓ .

Results for χ_ν^2 are given in Table 1.2. The simulations of low-contrast micelles having 600 core beads had a large χ_ν^2 . This happened because two of the four simulations fluctuated only modestly about significantly different but well-defined mean shapes. The other two of the four simulation runs showed large fluctuations. This suggests that, for this micelle composition, there are multiple metastable shapes between which the micelle can fluctuate.

This example demonstrates the benefit of doing multiple independent simulation runs and shows the limitations of representing a shape with a single mean and a variance about the mean.

On the other hand, besides the two aforementioned cases, all the χ_ν^2 are near unity, indicating that the simulations are well equilibrated and the uncertainty in the mean shape from each run is well-estimated.

Next we consider the $\chi_{\xi\ell}^2$ of Sec. 1.3.5. A more detailed diagnostic than the χ_ν^2 , the $\chi_{\xi\ell}^2$ indicate how well the shape error of the ξ th simulation run in the direction of the ℓ th mode is estimated. To illustrate that the low- ℓ modes are markedly different from the high- ℓ modes, and thereby motivate the mode-by-mode validation offered by the $\chi_{\xi\ell}^2$ statistic, we first show representative plots of the mode amplitude variances $\Sigma_{\xi\ell}$ vs ℓ , the correlation times $\tau_{\xi\ell}$ vs ℓ , and a few modes $m_{\xi\ell}$ in Fig. 1.13. We find that the mode amplitude variance $\Sigma_{\xi\ell}$ varies by three orders of magnitude. With this in mind, we plot in Fig. 1.14 $\chi_{\xi\ell}^2$ for a representative simulation run of a low-contrast micelle with 848 core beads. Although the mode variances $\Sigma_{\xi\ell}$ and correlation times $\tau_{\xi\ell}$ vary by several orders of magnitude, the $\chi_{\xi\ell}^2$ remain mostly

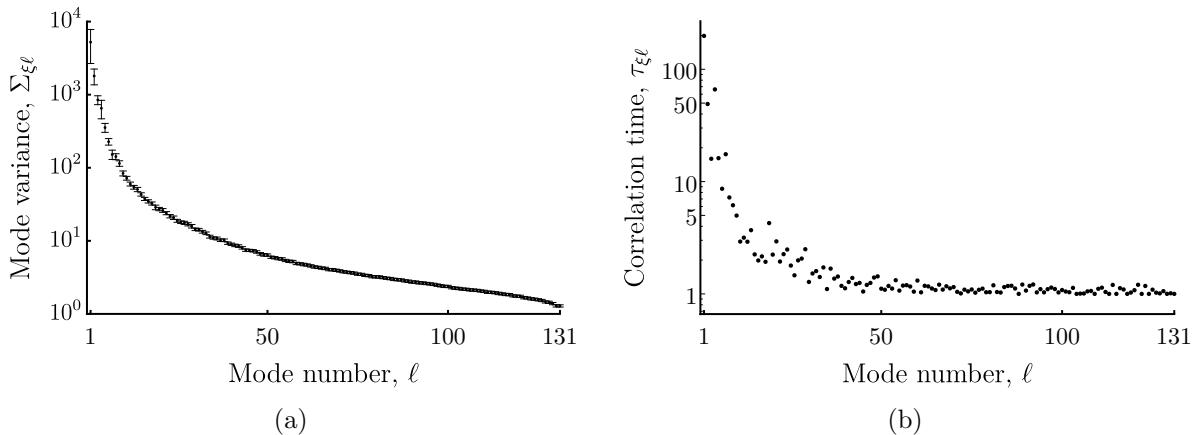


Figure 1.13: (a) Plot of the mode amplitude variance $\Sigma_{\xi\ell}$ vs mode number ℓ and (b) the correlation time $\tau_{\xi\ell}$ (in units of the sampling interval) from a single simulation run (i.e., single value of ξ) for a low-contrast micelle containing 848 core beads. The three modes corresponding to rigid motions are omitted because their amplitude variance is zero. The variances range over three orders of magnitude.

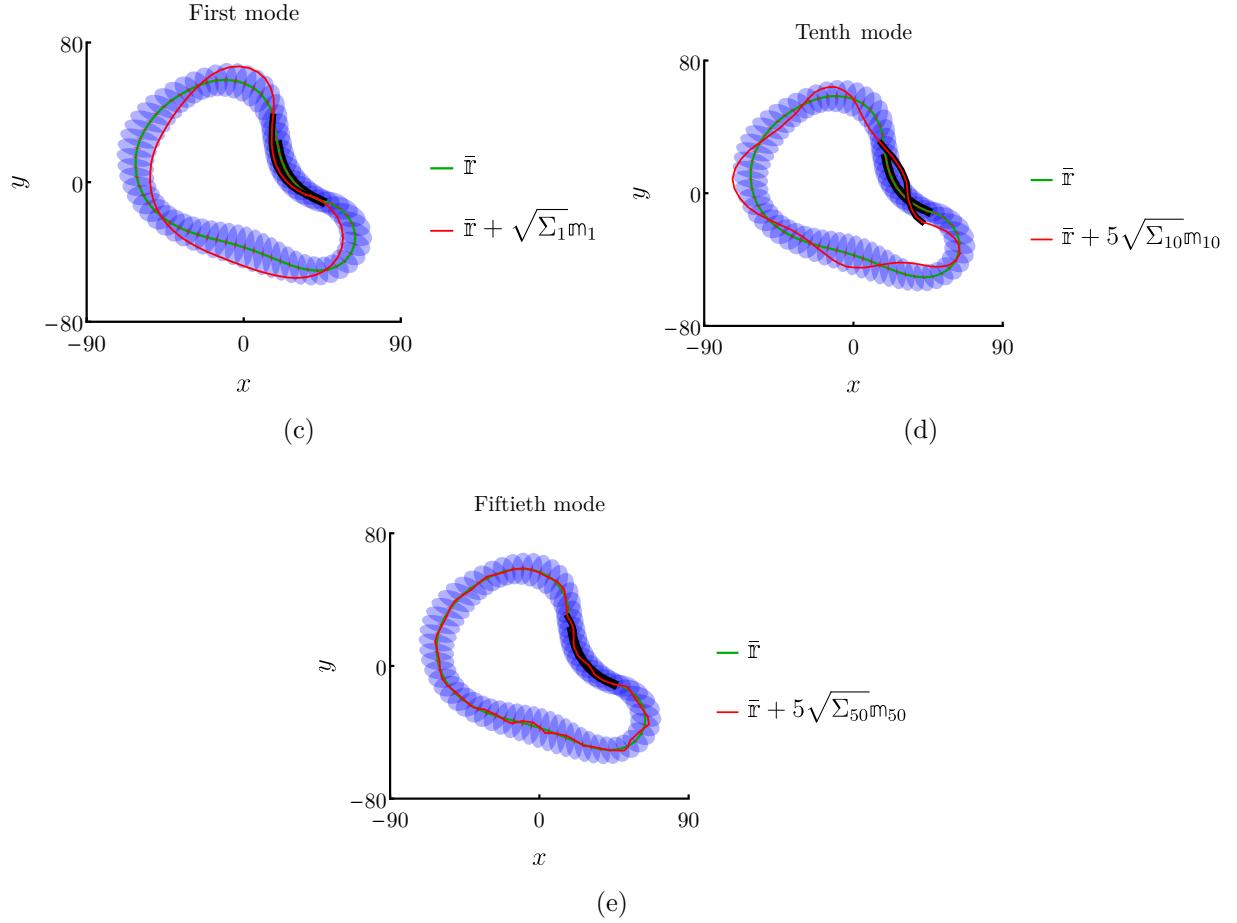


Figure 1.13: (c), (d), and (e) Plots of the $\ell = 1$, $\ell = 10$, and $\ell = 50$ modes. The average shapes are plotted as well as a deformation of the shape in the direction of the mode m_{ℓ} . In (c), the size of this deformation is $\sqrt{\Sigma_{\ell}}$, which represents one standard deviation of sampled shape distribution in the direction of m_{ℓ} . In (d) and (e), the size of the deformation is increased to five standard deviations for clarity.

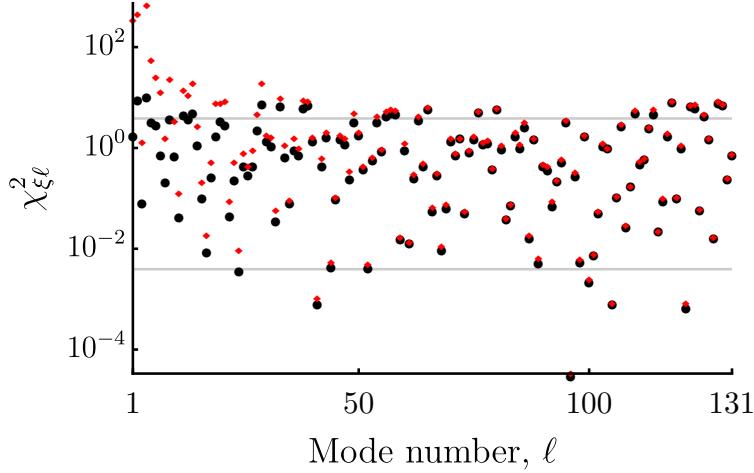


Figure 1.14: Plot of $\chi_{\xi\ell}^2$ (defined in Eq. (1.28), black circles) vs ℓ for the representative simulation run of Fig. 1.13 of a low-contrast micelle with 848 core beads. As in Fig. 1.13, the modes are ordered by their amplitude, so that the first mode ($\ell = 1$) is the mode with highest amplitude. The horizontal lines bracket the 90% confidence interval for the $\chi_{\xi\ell}^2$ statistic, assuming the mean shape distribution is Gaussian. Most of the $\chi_{\xi\ell}^2$ fall in this range, with no apparent systematic dependence on ℓ . For contrast, we present $\chi_{\xi\ell}^2$ with correlations ignored (by substituting $\tau_{\xi\ell} \rightarrow 1$ in Eq. (1.19), red diamonds). In this case, the $\chi_{\xi\ell}^2$ show a clear dependence on ℓ , in that $\chi_{\xi\ell}^2$ is much larger than unity for small ℓ .

within their 90% confidence interval with no apparent systematic dependence on ℓ , giving a positive validation of the assumptions used to calculate $\bar{\Sigma}_\xi$. In particular, this validation gives credence to the form of Eq. (1.19) used to calculate the error in the mean of a single run, where each mode is assumed to have an independent correlation time estimated by the time series of that mode's amplitude.

If the correlation times were estimated incorrectly, then the $\chi_{\xi\ell}^2$ for small ℓ would be significantly different than the $\chi_{\xi\ell}^2$ for large ℓ . As an extreme example of an incorrect correlation time estimation, consider the effect of ignoring correlation times completely (i.e., inserting $\tau_{\xi\ell} = 1$ into Eq. (1.19) as done in Fig. 1.14): the error in the mean along the high-amplitude modes is underestimated and so the corresponding $\chi_{\xi\ell}^2$ are much larger than unity. This analysis was done for a single run using one of our more stable compositions. Naturally, less well-behaved micelle compositions and runs, such as the low-contrast composition with 600-bead core, are not expected to fare as well under the same analysis.

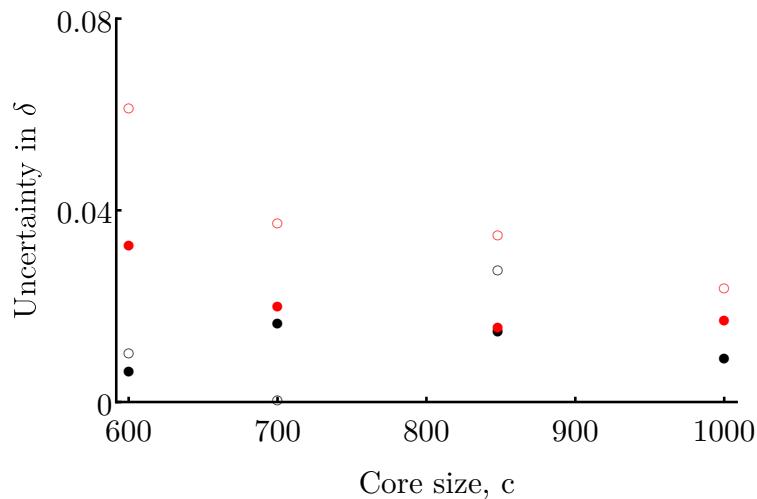


Figure 1.15: Plot of two estimates of the uncertainty in the normalized fluctuation δ for the different micelle compositions of Table 1.1. Black (red) symbols represent high (low) contrast micelles. Closed symbols represent the first estimate defined using Eqs. (1.32) to (1.34); open symbols represent the second estimate described below Eq. (1.34). Since simulations of the high-contrast micelle with 1000 core beads only resulted in one well-formed shape, the second estimate of its normalized fluctuation uncertainty cannot be made. Besides this case, and the case of the high-contrast micelle with 700 core beads, where the two simulation runs giving well-formed micelles had very similar normalized fluctuations, the estimates agree to within a factor of two.

Next, in Sec. 1.3.6, we described a way to estimate the uncertainty in the normalized fluctuation δ by individually estimating the uncertainty in each mode variance Σ_ℓ . The estimate of this uncertainty is crucial to understanding the significance of our quoted values for the shapes' normalized fluctuations, but this estimate relied on two as yet unvalidated approximations represented by Eqs. (1.33) and (1.34). Therefore it is necessary to validate this estimate, which we proposed to do by performing a comparison to the standard error of the normalized fluctuations individually calculated from each simulation run. The comparison is shown Fig. 1.15. We expect only rough agreement because the estimate being validated assumed the shape data are drawn from a Gaussian distribution. In fact the size of the errors are only consistent to about a factor of two. Therefore, when evaluating the significance of the results in Sec. 1.4.2, it should be remembered that the uncertainties in the normalized fluctuations are determined only to this limited precision.

Finally, we validate the formula Eq. (1.21) for the combined mean \bar{r} and its uncertainty estimate $\bar{\Sigma}$ defined by Eq. (1.26). This validation is important because the quantities \bar{r} and $\bar{\Sigma}$ are used to determine the value and uncertainty of the average micelle shapes' curvature ratios, which will be examined in Sec. 1.4.2. The validation is done by comparing the combined mean \bar{r} with the combined set of all shape samples, as described in Sec. 1.3.5. In Fig. 1.16, we show a plot of the statistic χ_ℓ^2 , defined in Eq. (1.29), for the low-contrast micelle with 848 core beads. The χ_ℓ^2 fall within the expected range, and the ℓ -average of χ_ℓ^2 is 1.5. The difference between this value and the ideal value of 1 suggests that the error in the combined mean may be slightly underestimated. From Fig. 1.16, this underestimation seems to be worst for low ℓ modes.

1.4.2 Shape features

Finally we discuss our findings concerning the shape features discussed in Sec. 1.3.6. To study quantitatively the dependence of micelle shape on composition already apparent in Table 1.1, we plot in Fig. 1.17 the curvature ratios and normalized fluctuations of these shapes, as well

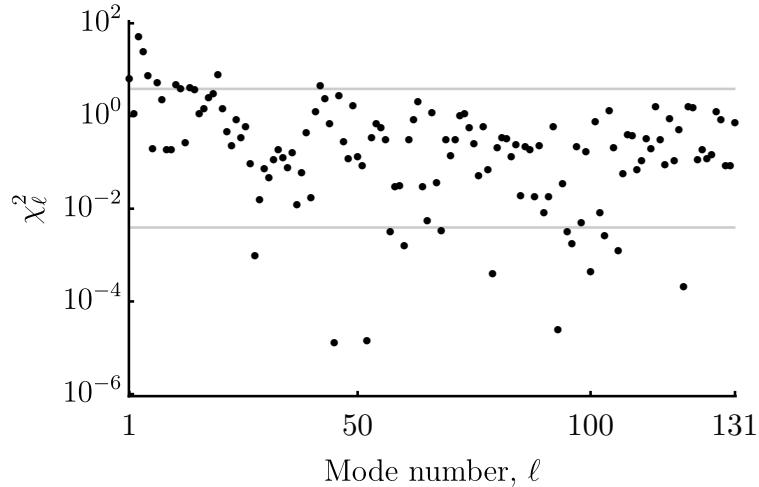
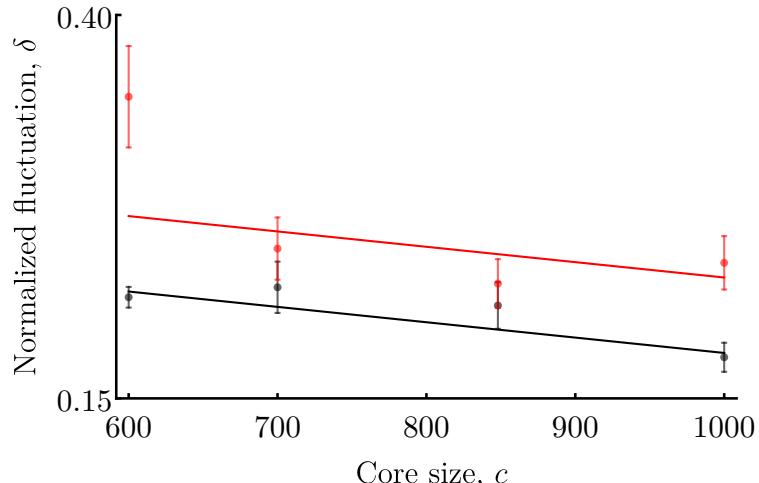


Figure 1.16: Plot of χ_ℓ^2 defined in Eq. (1.29) vs mode number ℓ . The two horizontal gray lines demarcate the 90% confidence interval.

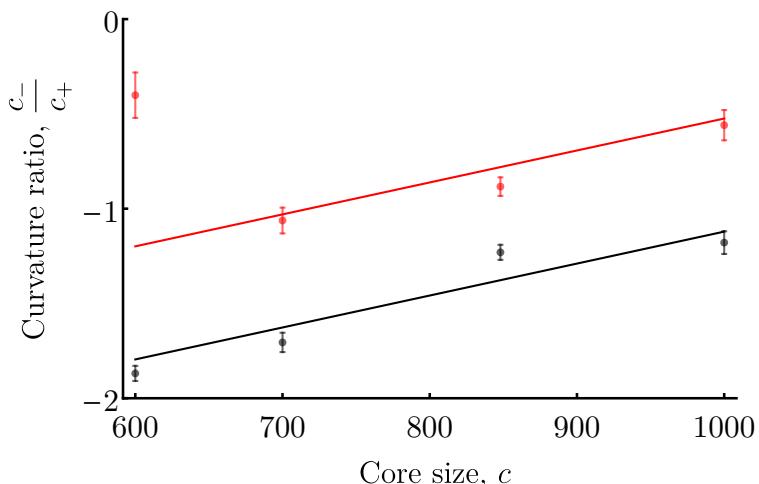
as a fit to a simple linear model. Several trends are revealed by these plots. The curvature ratio becomes more negative (meaning that the dimple becomes more pronounced) as the asymmetry ratio becomes more negative (meaning the solvophobic-rich diblocks become even more solvophobic). This confirms our intuition explained in Sec. 1.2.2 that the curvature should be positively correlated with the asymmetry ratio.

Another trend is that as the size of the core is increased, the curvature ratio becomes more positive (meaning that the dimple becomes less pronounced). We propose the following explanation for this behavior. We note that an increase in the core size increases the volume of the micelle. This increased volume could be accommodated either by an increase in the perimeter, reducing the density of diblock ‘‘surfactant’’ on the surface and thereby presumably increasing the micelle surface tension, or by making the micelle more circular, thereby making the curvature ratio more positive. In practice, we expect both of these happen to some extent, and so increasing the core size would both increase the surface tension and make the curvature ratio more positive.

The normalized fluctuations are less precisely determined, but trends are still apparent. The data show that the normalized fluctuations decrease as the solvophobic-rich diblocks become more solvophobic. This effect could also be explained in terms of a competition



(a)



(b)

Figure 1.17: Plots of normalized fluctuation δ and curvature ratio c_- / c_+ vs micelle composition. The micelle compositions are those of Table 1.1. In (a), δ is plotted against the size of the micelle core. Black (red) points represent high (low) contrast micelles. The data are fit to a model containing only constant and gradient terms: $\delta = \delta_0 + m_c c + m_r r$, with c being the number of core beads and r being the solvophobic-rich diblock asymmetry ratio (defined in Eq. (1.2)). Best fit parameters are found to be $m_c = (-1.0 \pm 0.3) \times 10^{-4}$ and $m_r = 0.37 \pm 0.08$. The reduced chi-squared for this fit is 1.9. The curvature ratio is treated analogously in (b). The best fit parameters for the curvature ratio are given by $m_c = (1.7 \pm 0.1) \times 10^{-3}$ and $m_r = 4.5 \pm 0.3$. The reduced chi-squared for this fit is 14. After omitting the outlier at a core size of 600 and $n_{\text{int}} : n_{\text{ext}} = 27 : 4$, the reduced chi-squared drops to 4.4.

between the preferred perimeter and preferred curvature. As the solvophobic-rich diblocks become more solvophobic, the dimple becomes more pronounced, which we propose leads to an increase in perimeter and consequently surface tension. This increased surface tension would then decrease the amplitude of shape fluctuations. Also, the data suggest that micelles with more core have lower normalized fluctuations, although the size of this effect is on the same order of the uncertainty. We have argued in the previous paragraph that increasing the core should increase surface tension. In addition to reducing the dimple, this increased tension should also reduce fluctuations, explaining the trend.

We note one more feature in the data: the low-contrast micelle with 600 has a significantly more positive curvature ratio than the trend line of Fig. 1.17(b) predicts. Although we are not sure how to explain this, we suspect this behavior is related to the onset of a transition reported in [52] involving the buckling of a two-dimensional vesicle wall upon decreasing the vesicle’s interior volume. If the energy barrier associated with buckling was high enough to preclude a buckling event from occurring within a simulation, then our observation, previously noted in Sec. 1.4.1, of two well-defined, but inconsistent micelle shape averages could be explained. In any event, this data point is an interesting starting point for further investigation.

Having described our results, we now note that they afford some degree of predictive power. We have observed a range of curvature ratios extending approximately from -0.5 to -1.8 exhibiting a mostly regular dependence on micelle composition. Therefore if a micelle with curvature ratio in the observed range is to be constructed, the data provide a way to determine which micelle composition gives the desired curvature ratio. In this way, we have demonstrated that micelle shape design is possible using our design mechanism.

1.5 Discussion

The work presented in this paper is only a first demonstration that our micelle design mechanism can provide for fine control of a micelle shape. Only two aspects of the micelle

composition were changed, and only two aspects of the micelle shape were studied. Further, the system we studied was only two-dimensional and the problem of malformed micelles was deferred completely. In this section, we address these issues in order to clarify the significance of our results: we describe other aspects of micelle composition to vary; we suggest additional features of the thermal shape distribution to control; we suggest a few alternate schemes for bonding the micelle's constituent diblocks with the idea that they may be more effective at preventing malformed shapes; and we discuss how the results presented in this work may be extended to three dimensions and what challenges may arise. Finally, we discuss how our results are relevant to the applications mentioned in the introduction.

1.5.1 Further variation of micelle composition

In this work, the effect of only two aspects of micelle composition was studied, and some speculative explanations of the observed behavior were given. In future work, other aspects of micelle composition may be varied, extending the range of observed micelle shapes and giving further insight into the factors affecting micelle shape. For example, only the asymmetry of the solvophobic-rich diblocks were studied; the effect of varying the solvophilic-rich diblocks could also be studied. Another aspect of the micelle composition to address is the length of the diblocks. In this work, we filled the micelle surface with diblocks of a specific chosen length, and chose the asymmetry of these diblocks to produce the desired curvature. However, there is freedom in choosing the length of the diblocks: the micelle surface could be filled using a larger number of shorter diblocks, holding fixed the imprinted preferred curvature profile. A third way of altering the micelle composition is to introduce another species of diblock. In the micelle shapes presented in Sec. 1.4, there were three regions of significantly different curvature: the concave dimple, the weakly convex surface opposite the dimple, and the strongly convex surface adjacent the dimple. Since these micelles only contain two species of diblock, the observed micelle shapes seem to be at odds with our stated design strategy, wherein the diblock's preferred curvature dictates the surface curvature. We

expect that the mismatch between the imprinted curvature and the realized curvature represents a frustration which may affect the dynamics (e.g., fluctuations) of the micelle. To test this expectation, one could introduce a third species of diblock to better match the realized micelle curvature, and study the resulting micelle shapes.

1.5.2 Additional shape features to control

Just as there are many ways to alter the micelle composition, there are many aspects of the micelle shape to control. Here we list three extensions to the shape control demonstrated in this work. First, instead of the curvature ratio of the average shape illustrated in Fig. 1.12, one could study other quantities characterizing the average shape. In fact, the difference metric Δ_{int} , defined in Eq. (1.10), provides a way of quantifying the similarity to any chosen target shape. Second, we chose a static set of interaction parameters in our model; however, applications may require exposing the micelle to varying environments (having variations of e.g., temperature, pH, or salt concentration). On the one hand, such a varying environment would presumably make it difficult to ensure a fixed micelle shape. On the other hand, there emerges a challenge of designing a micelle that assumes different designed shapes depending on its changing environment. Lastly, we have found evidence of a micelle exhibiting two metastable shapes in a single environment. In this case, there is a breakdown in the representation of the micelle shape as a Gaussian distribution fluctuating about a single mean. Instead, one could categorize the observed micelle shapes into clusters (each representing a metastable micelle shape), and find the mean shape in each cluster and the transition rates between the clusters. Further, each metastable shape presumably may be designed by changing the micelle composition.

1.5.3 Ensuring micelles are well-formed

In Sec. 1.1.3, we identified one challenge associated with our shape-design strategy as the stability challenge of ensuring that the micelles are well formed: that the diblocks keep their

intended relative positioning on the micelle surface. We chose to sidestep discussion of this challenge, and instead focus only on the shape control of well-formed micelles. However, without some way of ensuring micelles remain well formed, the shapes of the well-formed micelles seem to be of limited importance. In this section, we give examples of what can be done to ensure micelles remain well formed.

If there are a number of micelles dispersed in a solvent, one way a micelle can fail to be well formed is to coalesce with another micelle. In our work, we avoid this failure mode by including only one multiblock copolymer in a simulation, but the applications we imagine involve many coexisting micelles, in which case coalescence must be prevented. Coalescence and transfer of material between micelles is a phenomenon that already occurs for conventional micelles made of diblock copolymers, and it has been found both through simulations [53–55] and experiments [42, 56, 57] that the composition of a micelle’s constituent diblocks can be used to control the micelle’s equilibrium size. Therefore, we expect that it is possible to choose diblock compositions so that large aggregates composed of coalesced single-polymer micelles are thermodynamically unstable.

Alternatively, even a single micelle may become malformed, either by diblocks rearranging on the surface as was the case for Fig. 1.11(a) or by solvophobic blocks exiting the micelle interior to a second solvophobic region disconnected from the micelle interior as was the case for Fig. 1.11(b). It is possible that altering the polymer interactions (e.g., changing the immiscibility of the solvophobic monomers) is sufficient to suppress these failure modes.

If altering the polymer interactions is not sufficient or practical, other bond topologies besides the linear one used in this work, while perhaps harder to synthesize, might be effective. One could imagine a solvophobic backbone chain with solvophilic (and perhaps solvophobic) side chains; in fact, these bond schemes have been considered theoretically in [16]. Alternatively, the backbone chain could be solvophilic. Even more intricate possibilities are a solvophobic backbone chain with diblock side chains or even branched side chains where the degree of branching can be used to control the curvature. Examples of alternate bond

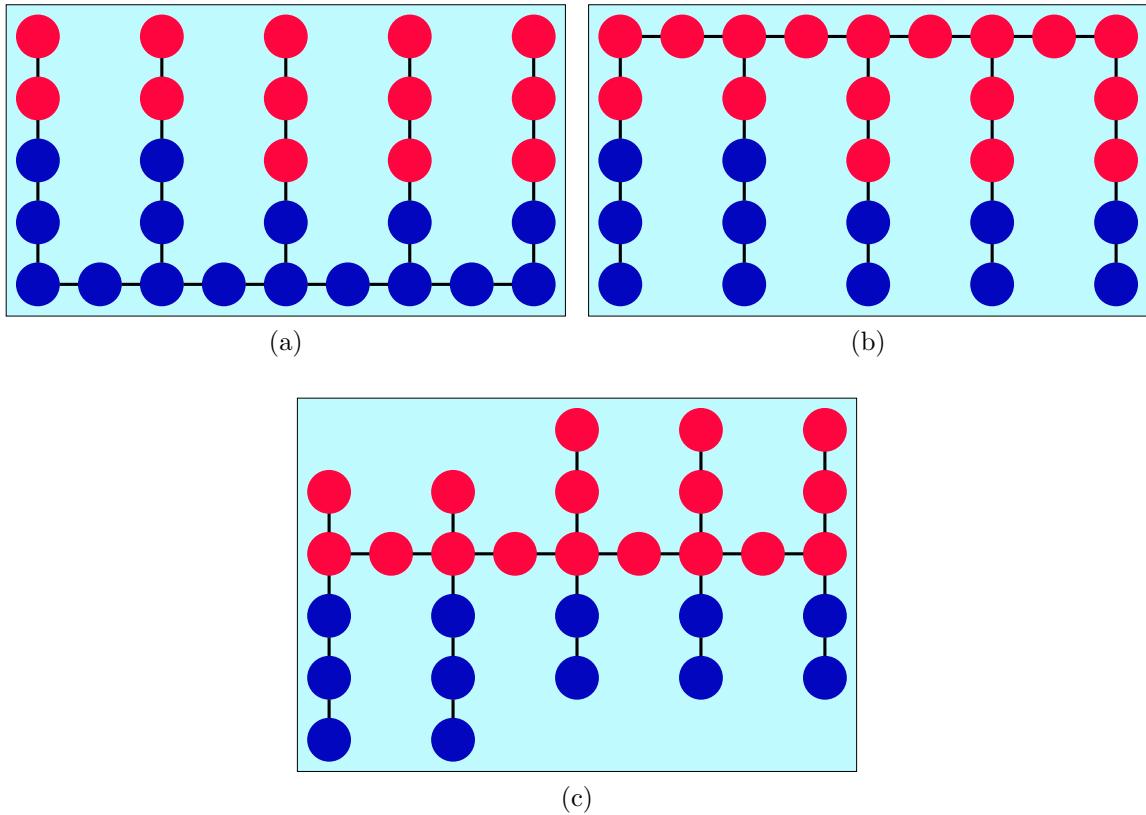


Figure 1.18: Schematics of alternate bond topologies for single-polymer micelles. The color scheme is the same as that of Fig. 1.2. In (a), diblocks have been attached as side chains to a solvophobic homopolymer. In (b), the diblocks are instead attached on their solvophilic ends to a solvophilic homopolymer. Lastly, in (b), the diblocks are represented as a pair of side chains attached to a solvophilic homopolymer chain.

topologies are shown in Fig. 1.18. In any case, we imagine that the effect of a diblock's spontaneous curvature on the shape of a well-formed micelle is mostly independent of the bond scheme used to make the micelle well formed, so that these two problems may be studied independently.

1.5.4 Implications for three-dimensional micelles

In this work, a polymer model having only two dimensions was chosen, as has often been done [58–62]. Two-dimensional simulations have the advantage of being both computationally less demanding and easier to visualize. Despite the simplicity gained by moving to two dimensions, the polymer behavior nonetheless is closely analogous to the three-dimensional case.

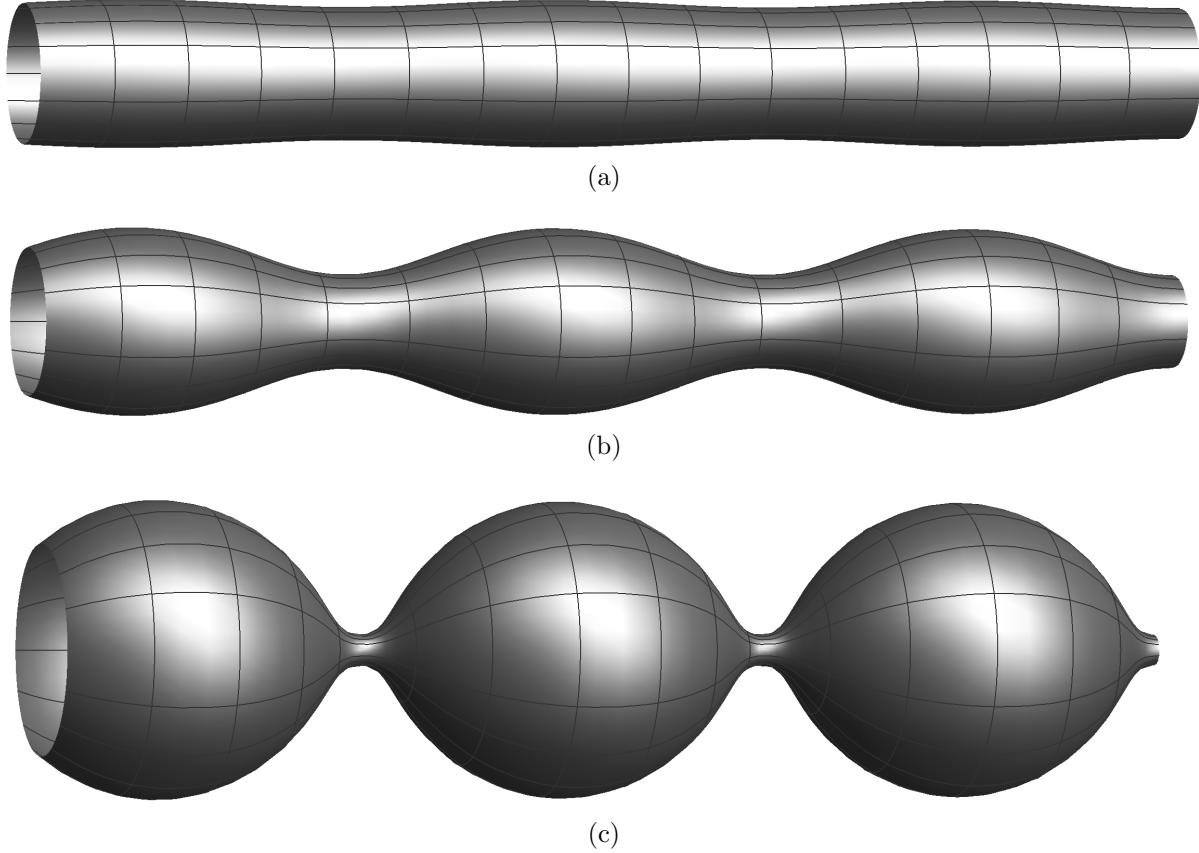


Figure 1.19: Plots of three unduloids interpolating between a cylinder and a string of spheres. Each surface shown in (a), (b), and (c) has a uniform mean curvature, and furthermore the three curvatures are the same. In fact, these shapes can be continuously deformed into one another with the mean curvature held fixed.

For example, we observed that our two-dimensional polymers exhibit a well-defined density, surface tension, and a preferred mean square displacement per monomer, as is the case in a three-dimensional system. Since these are the primary ingredients that set the micelle surface's preferred curvature [40], it is expected that a three-dimensional micelle surface ought to be influenced by the constituent polymer compositions similar to the two-dimensional micelles considered here. For example, we expect that making a patch of solvophobic-rich diblocks on the surface of a micelle with spherical topology would cause the micelle to form a concave dimple.

Although we expect the degree of shape control demonstrated in this work to be indicative of what is possible in three dimensions, we must admit that the extra dimension reduces the

potential for additional control offered by our shape-design strategy, as we now explain. In two dimensions, a curve is completely specified by its curvature at every point, and therefore a unique shape may be determined by imposing a preferred curvature at each point. In three dimensions, to lowest order in the curvature, the local bending energy U_{bend} per unit of the micelle surface area is [63] given by

$$U_{\text{bend}} = 2k(H - c_0)^2 + \frac{\bar{k}}{2}K, \quad (1.35)$$

where H and K are the mean and Gaussian curvatures, c_0 is the spontaneous mean curvature, and k and \bar{k} are moduli governing the mean and Gaussian curvature, respectively. While we expect that the local spontaneous mean curvature parameter c_0 can be set by the local diblock composition at the surface, a surface is described by not one, but two principal curvatures at each point. Thus a micelle shape is underspecified by the mean curvature profile induced by diblocks on the micelle surface. For example unduloids [64] are a family of distinct shapes all having the same mean curvature profile (examples shown in Fig. 1.19). The diblocks having mean curvature compatible with the unduloid in Fig. 1.19(b) will likewise have a mean curvature compatible with Fig. 1.19(c), so neither one of these shapes can be designed if diblocks affect only the preferred mean curvature. Even if full control of the shape is not possible in three dimensions, some degree of control is undoubtedly possible. For example, we expect it is possible to design a micelle having a dimpled shape analogous to the one considered here. Characterizing this control represents an interesting direction for future research.

Another difficulty with extending the shape-design mechanism is that a more sophisticated bond scheme is necessary to enforce the relative positioning of the diblocks on the surface of the micelle. Indeed, three-dimensional amphiphilic linear multiblock copolymers and polymers with side chains have been simulated [65], and while rough shape control has been demonstrated, the junction points do not arrange themselves on the micelle surface

in an organized manner, so the fine control we seek does not seem possible. Instead, the polymer may need to be realized in the form of a branched polymer. One possibility is to first form a cross-linked polymer network of a roughly spherical shape, and then graft onto the network surface diblocks of the desired compositions. There remains a question of how to create the cross-linked polymer network with chemically distinct surface regions necessary to graft specific species of polymer to specific regions on the surface. We hypothesize that such a network could be created either by growing outward from a multifunctional core such as a silsesquioxane [66] or by growing inward from an external, rigid scaffold such as a protein cage [67]. In either case, after the network is formed, the original core or scaffold could be disassembled, leaving only the flexible polymer network.

1.5.5 Relevance to applications

We now discuss how our results could be used to address the applications discussed in the introduction. One application was to use shape-designed micelles as drug carriers. It has been found that the carrier shape can affect how much drug can be loaded into the micelle [6]. Also, it has been found that nanoparticle shape can affect where in the body (e.g., in which organ) the particles accumulate [68–72]. Our shape-design mechanism therefore may potentially be used to optimize the loading capacity or biodistribution of a micelle drug carrier. Additionally, it was found that carrier shape flexibility affects how quickly the drug is cleared from the body [72–75]. Thus control not only of micelle shape, but also flexibility may be relevant to drug delivery applications.

Another application was the lock and key mechanism. In [10], the assembly of concave objects, similar to the ones designed in this work, was studied. It was found that in the presence of depletants, ensembles of these objects could be made to aggregate. It was further found that the size of the concave feature affects the aggregation: the concave curvature of the dimple must match the convex curvature of the object to which it will bind. Since the micelles studied in this work are dimpled in a similar way, it is natural to ask if they can

participate in the same selective aggregation behavior.

1.6 Conclusion

Molecular dynamics simulations were used to study the fluctuating shape of a polymeric micelle at finite temperature in two dimensions. The micelle was constructed from a single, linear, multiblock copolymer. A globular state with the multiblock's junction points sequentially ordered around the micelle perimeter is often maintained during the course of the simulation when such a state is used as the initial configuration. We introduced and validated statistical methods for quantitatively characterizing such a globular micelle shape in the presence of strong thermal fluctuations. Using these methods, we demonstrated the effectiveness of a strategy where the multiblock is viewed as a collection of diblock copolymers joined end to end, and the asymmetry of these diblocks is selected to dictate the micelle surface curvature. Specifically, we found that positioning solvophobic-rich diblocks preferring concave curvature on the micelle surface caused the formation of a concave dimple in the surface region occupied by these diblocks. Further, the strength of the dimple is controlled by both the asymmetry of these diblocks and the size of a homopolymer core segment located in the micelle interior. In addition to the strength of the dimple, the asymmetry of the solvophobic-rich diblocks and the size of the core segment affected the amount of fluctuations in the micelle shape.

This work is a modest step in the direction of making shape-controlled micelles based on modulated preferred surface curvature. Many caveats and shortcomings were noted, such as the metastability of our simulated micelles and the two-dimensional nature of the simulation. Nevertheless, we have found that micelle shape can be controlled by the constituent diblock composition. In future work, the micelle shape-design strategy could be studied in three dimensions where it is as yet unclear how precisely polymeric micelles' shapes could be controlled. Additionally, research must be done to determine what is necessary and sufficient to ensure the thermal stability of the designed micelle.

CHAPTER 2

FEASIBILITY OF RATIONAL SHAPE DESIGN

2.1 Introduction

Micelles are self-organized aggregates occurring in a solvent, and consisting of two chemically incompatible regions: the exterior of the micelle, occupied by solvophilic material which is miscible with the solvent, and the interior of the micelle, containing solvophobic, immiscible material. The chemical dissimilarity between the micelle interior and exterior allow the micelle to transport material which would normally be immiscible in the solvent. This is what makes micelles effective in their perhaps best-known role as detergents. A related application is to use micelles as a drug carrier, with the drug payload residing in the interior of the micelle. It has been found that a drug carrier's shape affects aspects of the drug carrier's performance such as where in the body (e.g., into which organ) the drug payload is deposited [68–72]. A second application where micelle shape may be important concerns micelles aggregating together to form higher-order structures of various shapes such as cubes, pyramids, or long chains [76–79]. The shape of these aggregates might be controlled through the shape of the constituent micelles.

Because of the importance of micelle shape, it would be useful to have a rational design scheme to create micelles of a precisely tailored shape. A good rational design scheme would identify a few key control parameters governing how the micelle is synthesized, and these control parameters would have a well-behaved effect on the micelle shape. Ideally, the effect of the control parameters would be so regular that, given the observed shapes from a small number of control parameter values, the relationship between shape and control parameters could be accurately determined by a naive linear model.

In this work, we characterize the performance of such a scheme wherein the micelle consists of a single, linear, multiblock copolymer (i.e., a polymer containing solvophilic and solvophobic monomers segregated into multiple homogeneous blocks), and the number of

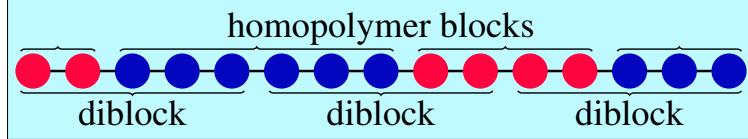


Figure 2.1: Two different views of a linear multiblock copolymer composed of two species of monomer, shown in red (light gray) and blue (dark gray). In the first view, the multiblock is considered a collection of homopolymer segments. In the second view, it is considered a sequence of diblocks joined end to end. Figure reproduced from [1].

these blocks and their lengths, which we collectively refer to as the “micelle composition”, are used as control parameters to set the micelle shape. We study the design scheme by simulation, which, for simplicity, is performed in two dimensions, a choice we will justify in Sec. 2.4. In a previous paper [1], we demonstrated that this scheme can indeed be used to produce a micelle of a nonstandard dimpled shape, and we showed, by varying two aspects of the micelle composition, that the micelle shape could be controlled. In this paper, we go beyond merely demonstrating that it is possible to control the micelle shape: we select several control parameters governing the micelle composition, and we assess the regularity of the micelle’s shape dependence on these parameters. We seek to determine if the micelle’s shape dependence can be explained by a straightforward rationale and whether this dependence is simple enough that it may be represented by a naive linear model.

To better motivate which aspects of the micelle composition we vary in this work, we now give a more detailed description of the rationale underlying our shape-design scheme. The key idea is to view the multiblock copolymer not as a sequence of homopolymer blocks joined together, but rather as a sequence of diblocks. Thus two homopolymer blocks are joined at a diblock junction point, and adjacent diblocks are joined to each other in the middle of a homopolymer segment, as illustrated in Fig. 2.1. With this view in mind, we now give an explanation, illustrated in Fig. 2.2, of how the diblocks’ block lengths may affect the micelle shape. In solution, the solvophilic blocks are located at the exterior of the micelle, while the solvophobic blocks compose the micelle interior. Thus, the diblock junction points occupy the boundary separating the two regions. It is well-known that such an interface containing

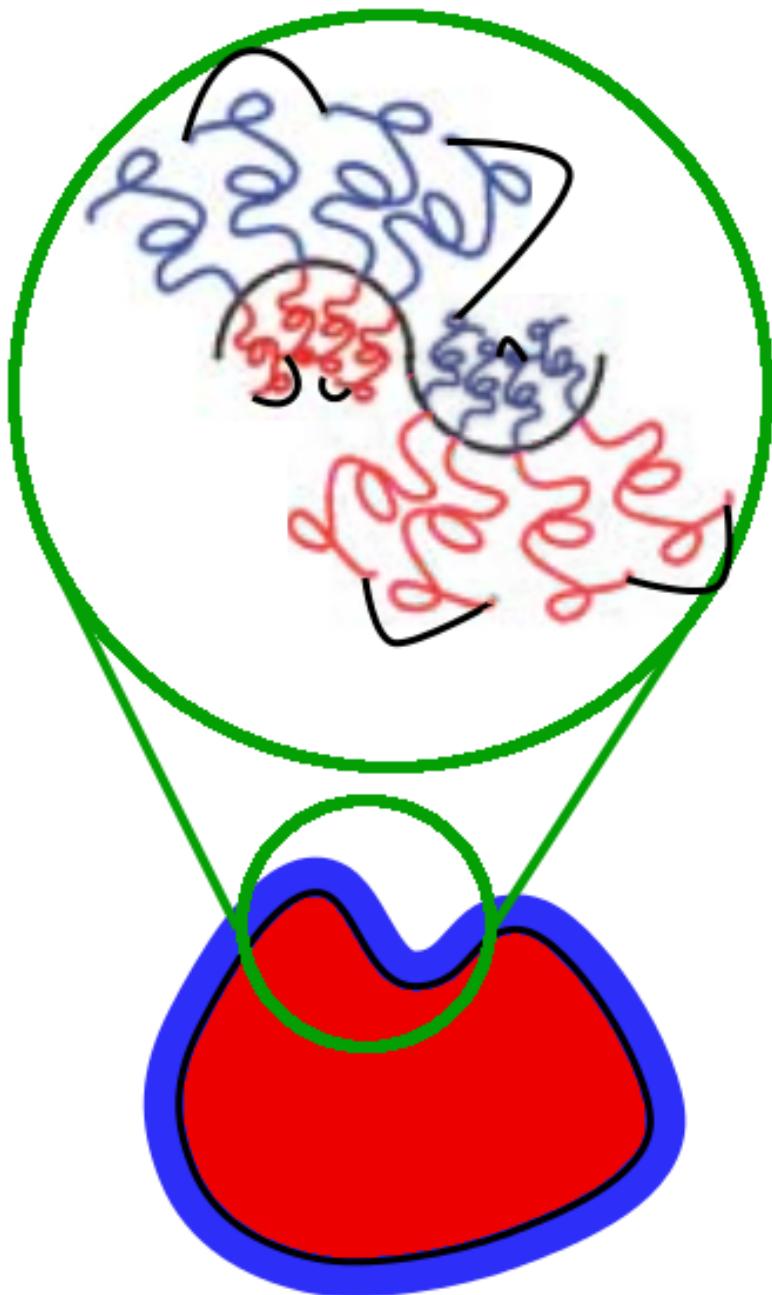


Figure 2.2: Illustration of shape-design rationale. The multiblock, viewed as a collection of diblocks, exhibits a configuration where the junction points of the diblock lie on the micelle surface. Diblocks of different composition, and therefore different spontaneous curvatures, cause a nonuniform surface curvature, giving the micelle its desired shape. The relative positioning of the diblocks is enforced by joining them end to end. Figure reproduced from [1].

diblocks has a spontaneous curvature depending on the diblocks' compositions and chemical properties [40]. By this reasoning, we may judiciously choose the diblock lengths at each point on the micelle surface to imprint a spontaneous curvature profile giving rise to the desired shape.

We have now explained why the multiblock is viewed as a collection of diblocks, but we have not explained why these diblocks must be joined together as opposed to simply being allowed to aggregate as in a typical self-assembled micelle composed of diblock amphiphiles. The diblocks are joined in order to prevent them from diffusing across the micelle surface, since such diffusion would erase the intended spontaneous curvature profile. Nevertheless, as will be indicated in Sec. 2.2, the multiblock structure of the polymer often fails to ensure the intended diblock arrangement on the surface. To eliminate these failures something further must be done, but an in-depth study of this issue is beyond the scope of the present work. Instead, we simply discard the problematic micelles. A justification for discarding the problematic micelles and proposals for how they may be completely eliminated in future work are given in Sec. 2.4.

In the rest of this paper, we describe an assessment of the performance of this design scheme. In Sec. 2.2, we describe how we simulate single-polymer micelles: we identify a micelle composition that assumes a nonstandard shape; we select five aspects of the micelle composition as suitable control parameters; and we choose two features of the micelle shape whose dependences on the control parameters are to be assessed. In Sec. 2.3, the results of varying our chosen aspects of micelle composition are presented, and the effect on the shape features is examined. In Sec. 2.4, we discuss the implications of our results for the practicality of the shape-design scheme presented in this paper, and we revisit unresolved issues mentioned in Sec. 2.1 and Sec. 2.2. In Sec. 2.5, we conclude.

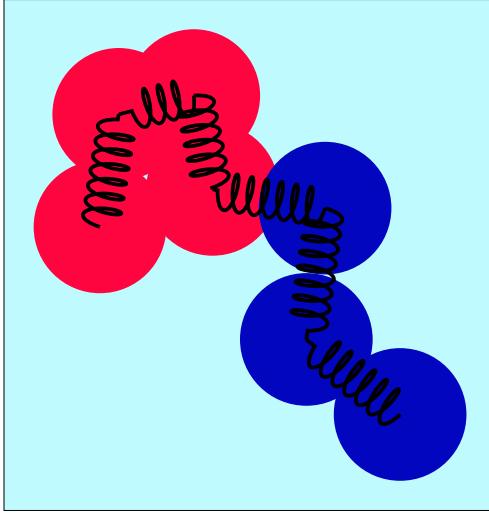


Figure 2.3: Schematic of a short diblock copolymer as represented in our model. This copolymer consists of seven beads: four solvophobic beads, shown in red (light gray), and three solvophilic beads, shown in blue (dark gray). Harmonic springs connect beads adjacent along the polymer. The light blue background represents the implicit solvent.

2.2 Methods

To assess our shape-design scheme, we simulate micelles of various compositions and compare the resulting shapes. However, before simulations can be performed, a physical model for the micelles must be selected. A detailed description of our model and simulation method is given in [1]. We now present the most relevant features starting with the model.

We choose a simple coarse-grained bead-spring model with implicit solvent (similar to those of [43–46]) because our shape-design mechanism should not depend on details of the interactions of the polymer constituents. A polymer molecule is represented as a linear sequence of beads with consecutive beads joined by harmonic springs, as illustrated in Fig. 2.3. There are two species of beads: solvophilic beads, which interact with other beads through only a short-range repulsion, and solvophobic beads, which experience an additional longer-range attraction with other solvophobic beads because of their immiscibility with the solvent. The particular values of the interaction parameters and the simulation’s temperature are chosen to replicate macroscopic behavior of real polymer.

This model is simulated at constant temperature using the LAMMPS molecular dynamics

package [47]. At regular intervals of the simulated time, the simulation records the junction points' positions, defined as the midpoint between adjacent beads of opposite species. Because we are interested only in the overall shape of the micelle and not the individual positioning of each bead, these junction points provide sufficient data for our purposes.

We refer to each list of junction point positions as a “shape”, denoting it by a blackboard bold symbol (e.g., \mathbf{r}). Therefore, each shape \mathbf{r} has the form

$$\left(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_i, \dots, \mathbf{r}_{N_j} \right), \quad (2.1)$$

where N_j is the number of junction points in the micelle and each \mathbf{r}_i is a two dimensional junction point position. The output of the simulation is a time sequence of such shapes: \mathbf{r}_α , $\alpha = 1, 2, \dots, N_s$, where N_s is the number of sampled shapes.

After the simulation runs are complete, the shape sequences are further analyzed. We summarize the resulting sequence \mathbf{r}_α of shapes by its average $\bar{\mathbf{r}}$, the shape variance matrix Σ of dimension $2N_j \times 2N_j$ characterizing the variance shape's thermal fluctuations, and another $2N_j \times 2N_j$ variance matrix $\bar{\Sigma}$ representing the uncertainty in the mean shape $\bar{\mathbf{r}}$.

For a given micelle composition, we run several simulations. Despite the bonds joining adjacent diblocks, roughly half of the simulations result in poorly formed micelles where the diblocks do not keep their intended positioning on the surface. Since we are interested in the behavior of our shape-design scheme, which depends on the diblocks maintaining their intended positioning, we exclude any poorly formed micelles from further analysis. Concretely, we reject any simulation run whose average micelle either has two neighboring junction points separated by more than forty percent of the median distance between adjacent junction points, or whose the shortest closed path connecting all the junction points does not have the intended ordering. In Sec. 2.4, we explain why the exclusion of these poorly formed micelles is justified. We combine the results of the remaining simulations to make a best estimate of $\bar{\mathbf{r}}$, Σ , and $\bar{\Sigma}$.

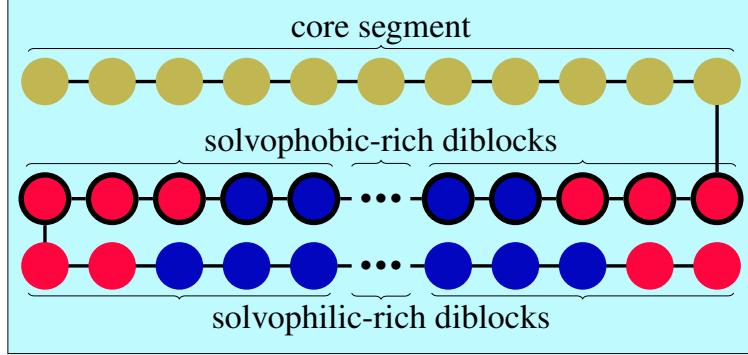


Figure 2.4: Schematic of multiblock bond architecture. Tan (top row) and red (light gray, bottom rows) disks represent solvophobic beads, while blue disks (dark gray, bottom rows) represent solvophilic beads. Black segments represent bonds between beads. The multiblock begins with a core segment composed of solvophobic beads shown in tan and occupying the top row. To this segment solvophobic-rich diblocks, outlined in black as in Fig. 2.5, are successively attached end to end. Lastly solvophilic-rich diblocks are attached end to end. The “•••” symbols represent further diblocks not shown. Figure adapted from [1].

Having described how the micelles are simulated, we now describe which micelle compositions to simulate in order to examine their effect on micelle shape. We start with a reference micelle composition previously shown in [1] to produce a micelle of nonstandard dimpled shape. Then we select several parameters of this micelle composition to be changed.

The basic design of the copolymers simulated in this work is shown in Fig. 2.4. The key feature of the design is that the micelle contains two species of diblock having a common length but distinguished by their composition: a “solvophobic-rich” species of diblock, having relatively more solvophobic beads and therefore favoring a more negative, concave curvature, and a “solvophilic-rich” species of diblock, having relatively more solvophilic beads and therefore favoring a more positive, convex curvature. This contrast in preferred curvature is designed to cause the formation of a dimple. The linear copolymer begins with a long sequence of solvophobic beads, which forms a “core” to be situated in the micelle’s interior. To one end of this core segment are joined end-to-end a sequence of solvophobic-rich diblocks. To the free end of this sequence of solvophobic-rich diblocks, we attached a sequence of solvophilic-rich diblocks. The micelle has 700 core beads, 12 solvophobic-rich diblocks each containing 27 solvophobic beads and 4 solvophilic beads, and 55 solvophilic-rich

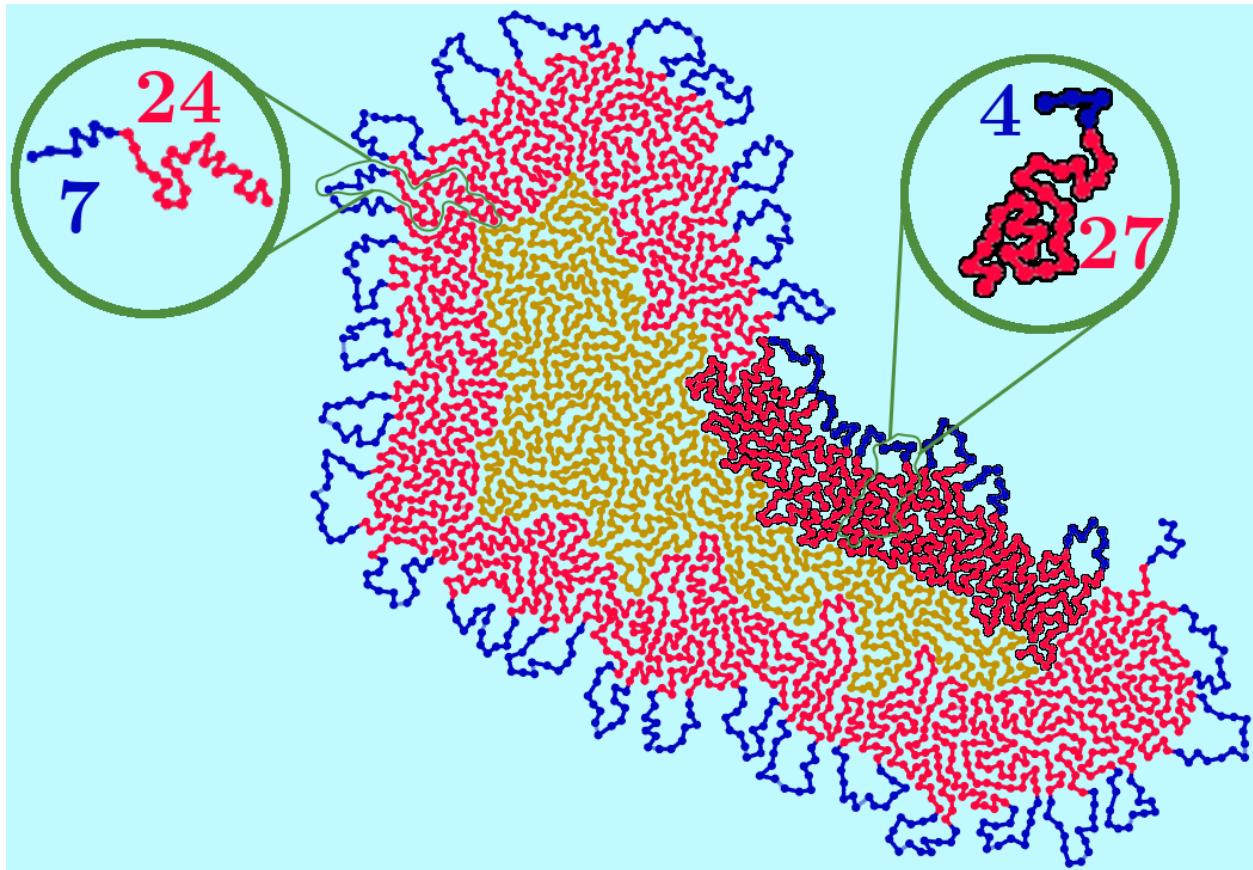


Figure 2.5: A typical configuration of the reference micelle during the course of a simulation. The red (light gray) beads are solvophobic; the blue (dark gray beads on micelle exterior), solvophilic. The tan beads (dark gray beads in micelle interior), which constitute the micelle core, are also solvophobic. The micelle is constructed from two types of diblocks, termed solvophobic-rich and solvophilic-rich. The solvophobic-rich diblocks, outlined in black, are located near the dimple.

diblocks each containing 24 solvophobic beads and 7 solvophilic beads. A chemical formula representing this monomer sequence is $R_{700}(R_{27}B_4B_4R_{27})_6(R_{24}B_7B_7R_{24})_{27}R_{24}B_7$, where R represents a solvophobic monomer and B represents a solvophilic monomer. A typical thermal configuration of a micelle having the reference composition is illustrated in Fig. 2.5.

Next, we describe our chosen control parameters—parameters of the micelle composition that we alter to control the micelle’s shape. A good control parameter must have a well-behaved effect on the micelle shape, and, further, its effect on micelle shape ought to be predictable using a simple rationale. Accordingly, we will describe each parameter’s anticipated effect as it is introduced. The first parameter we define is the number of core beads, N_{core} , having a value of 700 for the reference micelle composition; it can be used to set the enclosed volume of the micelle without affecting the surface properties. Two additional parameters concerning the number of beads in the micelle are the numbers of solvophobic-rich (N_- , the “−” reflecting that these diblocks prefer a relatively negative, concave curvature) and solvophilic-rich (N_+ , the “+” reflecting that these diblocks prefer a relatively positive, convex curvature) diblocks in the micelle, which we expect to set the preferred perimeter of their respective regions of the micelle surface without directly affecting either region’s preferred curvature. These parameters have the values of $N_- = 12$ and $N_+ = 55$ for the reference micelle composition. The two final parameters concern the compositions of the solvophobic-rich and solvophilic-rich diblocks. We keep the length of either species of diblock fixed at 31, changing only the relative amount of the two species of beads (that is, the asymmetry of the diblock). The asymmetry of a diblock containing n_{phobic} solvophobic beads and n_{philic} solvophilic beads is quantified by the “asymmetry ratio” r defined by

$$r = \frac{n_{\text{philic}} - n_{\text{phobic}}}{n_{\text{philic}} + n_{\text{phobic}}}. \quad (2.2)$$

The asymmetry ratio of several model diblocks is illustrated in Fig. 2.6. We denote the asymmetry ratio of the solvophobic-rich diblocks and solvophilic-rich diblocks by r_- and r_+ ,

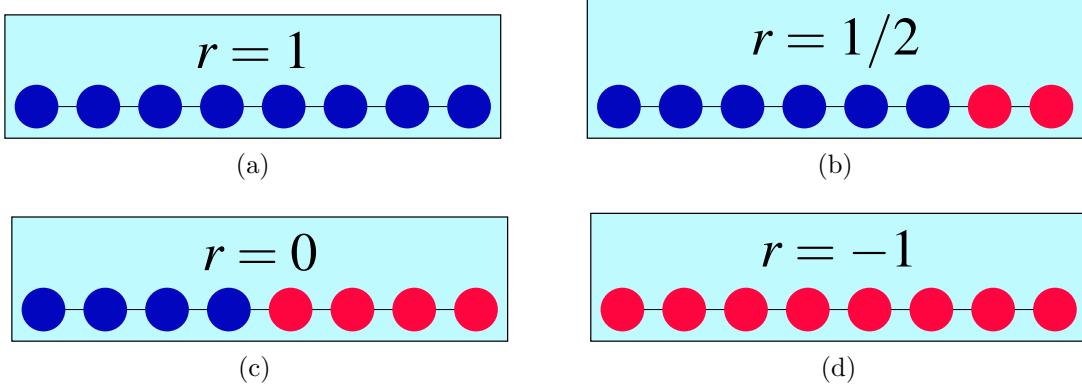


Figure 2.6: Several diblocks (or, in the extreme cases where only one species of bead is present, homopolymers) and their asymmetry ratios r defined in Eq. (2.2). Solvophobic beads are shown in red (light gray), and solvophilic beads, in blue (dark gray).

respectively. By definition, solvophilic-rich diblocks have a larger asymmetry ratio, so that r_- and r_+ satisfy $r_- < r_+$. These two parameters provide a way to control the spontaneous curvature of their respective regions of the micelle surface while only weakly changing the preferred perimeter. Specifically, we expect that the more positive a diblock's asymmetry ratio, the more positive its associated preferred curvature.

Having described how the micelle compositions are changed, we now describe what features of the resulting thermal micelle shape distribution we study. A graphical representation of the average shape \bar{r} , shape sample variance Σ , and variance in the mean shape $\bar{\Sigma}$ characterizing the micelle shape distribution is shown in Fig. 2.7. In previous work [1], we have validated that the mean shapes are reproducible and the errors in the mean shape are indeed consistent with the variability in the mean shape between simulation runs. However, since the average shape \bar{r} , shape sample variance Σ , and variance in the mean shape $\bar{\Sigma}$ are high-dimensional objects, we choose, for the sake of concreteness, to look at only two scalar shape features summarizing these quantities, which we soon define: the curvature ratio, characterizing the strength of the average shape's dimple, and the normalized fluctuation, characterizing the size of thermal shape fluctuations.

The curvature ratio $\frac{c_-}{c_+}$, illustrated in Fig. 2.8, is defined as the shape's average signed curvature c_- in the region occupied by the solvophobic-rich diblocks divided by the average

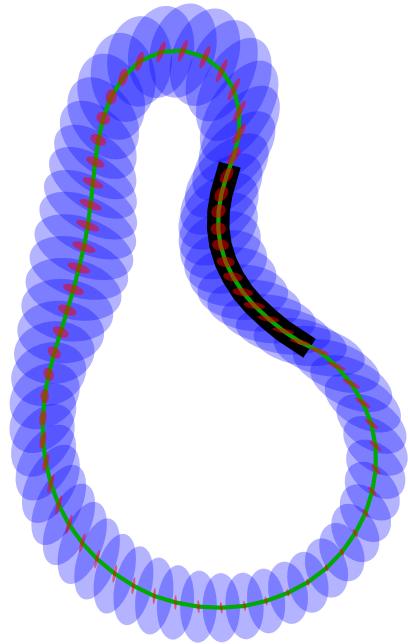


Figure 2.7: A graphical representation of the average shape \bar{r} , the shape fluctuations Σ , and the uncertainty in the average shape $\bar{\Sigma}$ of the reference micelle. The average shape \bar{r} is represented as a green curve (passing through the midline of shaded region) connecting the average position of the junction points. The curve segments connecting solvophobic-rich diblocks are outlined in black. The shape fluctuations Σ are represented by a large blue ellipses surrounding each junction point indicating the 40% confidence region (corresponding to one standard deviation) for the junction point's position during the course of the simulation. The uncertainty in the mean shape is represented similarly with smaller red ellipses indicating the confidence region for the mean junction point position.

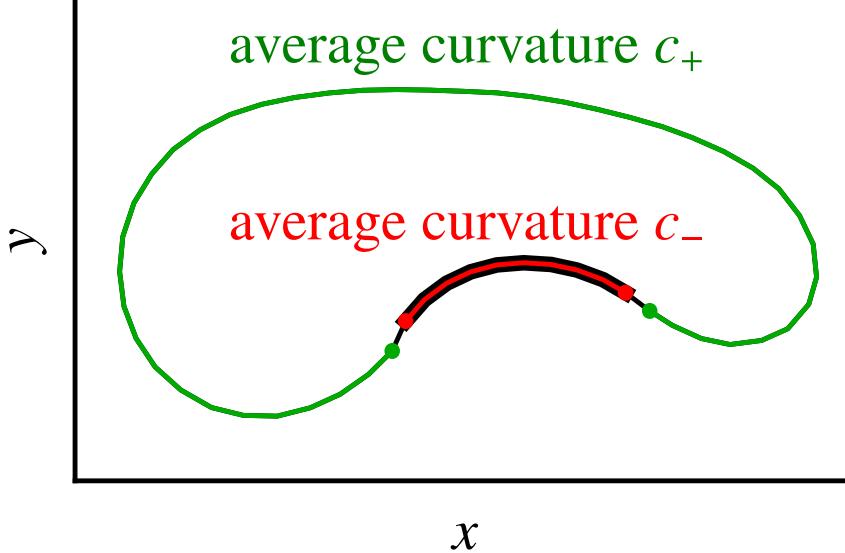


Figure 2.8: Illustration of curvature ratio definition. The region occupied by solvophobic-rich diblocks is shown in red, and its average signed curvature (having a negative value in this case) is denoted by c_- . By contrast, the region occupied by solvophilic-rich diblocks is shown in green, and its average curvature is denoted c_+ . The curvature ratio is defined as the ratio c_-/c_+ . Figure reproduced from [1].

signed curvature c_+ in the region occupied by the solvophilic-rich diblocks. Thus a circle has a curvature ratio of one, and negative curvature ratios indicate the presence of a concave dimple, with increasingly negative curvature ratios indicating stronger dimples.

The normalized fluctuation δ is defined by the formula

$$\delta = \sqrt{\frac{\text{Tr } \Sigma}{2N_j R_g^2}}, \quad (2.3)$$

where R_g is the radius of gyration of the average shape \bar{r} . Intuitively, the factor $\sqrt{\frac{\text{Tr } \Sigma}{2N_j}}$ may be interpreted as the root-mean-square length of the semi-axes of the blue ellipses shown, for example, in Fig. 2.7 (the blue ellipses being the one standard deviation confidence regions for the sampled position of the junction points). The normalized fluctuation is a scalar measure of the size of the shape fluctuations, normalized so as not to scale with the number of junction points or overall spatial extent of the micelle shape.

The uncertainties in these two shape features can, like the values themselves, be estimated

from the micelle shape distribution statistics \bar{r} , Σ , and $\bar{\Sigma}$. Since the curvature ratio depends only on the mean shape \bar{r} , its uncertainty can easily be inferred from the error in the mean $\bar{\Sigma}$. However, our estimate for the uncertainty in the normalized fluctuation is more subtle; we refer the reader to [1] for a description and validation of this uncertainty estimate.

2.3 Results

In this section, we show the dependence of the two shape features $\frac{c_-}{c_+}$ and δ on the five micelle composition parameters N_{core} , N_- , N_+ , r_- , and r_+ introduced in Sec. 2.2. To speak to the question we raised in Sec. 2.1 of whether this observed dependence is explained by a straightforward rationale, we give simple arguments accounting for the observed behavior in terms of the micelle surface’s tension and bending energy. The adequacy of our proposed explanations, as well as what these results imply about the feasibility of a naive design strategy will be discussed in Sec. 2.4.

We are not so much concerned with the exact numerical values of the composition parameters as we are with how the micelle shape qualitatively depends on them. Therefore, to simplify discourse, we normalize the composition parameters by their values for the reference micelle, and we denote the normalized values with a hat ($\hat{\cdot}$). For example, the normalized amount of core \hat{N}_{core} is given by $N_{\text{core}}/700$, since the reference micelle composition has 700 core beads. Similarly, the normalized number of solvophilic-rich chains is given by $\hat{N}_+ = N_+/55$, since the reference micelle composition has $N_+ = 55$, etc.

To frame the explanation of our observed results, we first explain what one might naively expect. The shape dependence can be thought of as a function from the five-dimensional space of micelle composition parameters to the two-dimensional shape feature space. In this work, we start from a base micelle composition and change different aspects of the micelle composition (in other words, moving in different directions in micelle composition space) and observe the resulting change in the shape features (in other words, how the resulting shape changes in shape feature space). A naive expectation, which must be borne out for

\hat{N}_{core}	14%	29%	43%	57%	71%	86%
\hat{N}_{core}	100%	114%	129%	143%	157%	171%
\hat{N}_{core}	186%	200%	214%	286%	357%	

Table 2.1: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) as a function of the number of core beads N_{core} . As the number of core beads increases, the shapes become more circular, and, as illustrated by the size decrease of the blue ellipses and the fluctuations decrease.

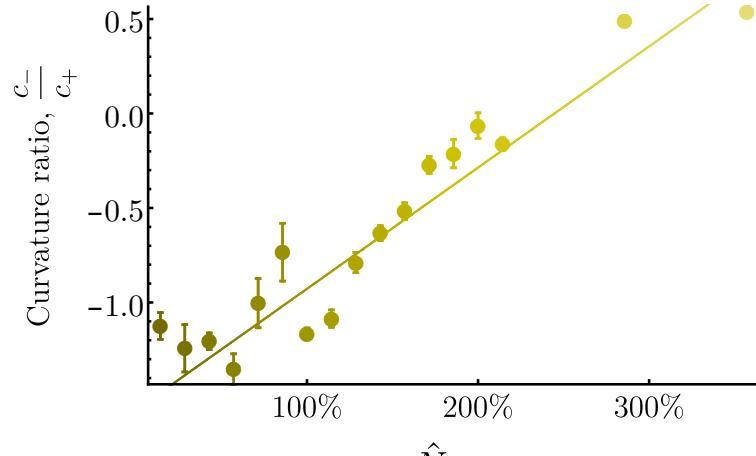
small changes in the micelle composition, is that the micelle shape change depends linearly on the change in micelle composition. In the typical case, we expect the map to have full rank so that it is possible to change the curvature ratio without changing the normalized fluctuation and vice-versa through appropriate changes to the micelle composition. Then by the rank-nullity theorem [80], there must be three directions in the micelle composition space (typically not corresponding to a change in any single composition parameter) that lead to no change in the shape features. Since we expect the three null directions to have no relationship to the axes defined by the five composition parameters, we expect the five composition parameters to each change the shape features in a unique direction in the two-dimensional shape feature space. We will compare our results to these expectations after presenting the results.

We begin by examining the shape features' dependence on the number of core beads N_{core} while holding the other four composition parameters fixed. Table 2.1 shows the average shapes, fluctuations, and uncertainties in the average shapes resulting from varying

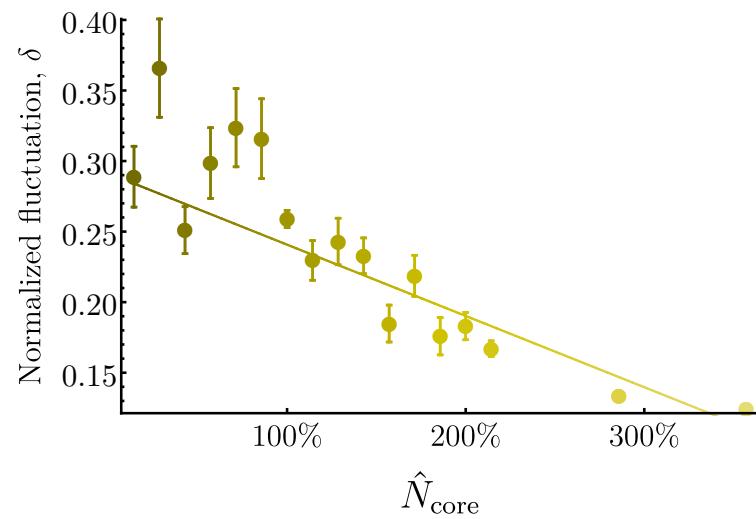
the number of core beads N_{core} . It is apparent from these results that the effect of increasing N_{core} is to make the shapes more circular and decrease their fluctuations. The character of these trends can be studied more precisely by plotting the shape features $\frac{c_-}{c_+}$ and δ against N_{core} , which we do in Fig. 2.9. In this figure, it is clear that the shape features generally follow the trend apparent from Table 2.1, and, excluding the largest values of N_{core} , the dependence of the shape features on N_{core} is roughly linear. The largest two values of N_{core} indicate smaller slopes than the other data, consistent with the expectation that for large N_{core} , the curvature ratio should approach unity and the normalized fluctuations should go to zero. Thus the data resulting from varying N_{core} show a moderately sized domain of linearity.

Next we present in Fig. 2.10 the dependences of the shape features on each of the five micelle composition parameters. There are two types of trends that result from varying a micelle composition parameter: the first type of trend, shown in Fig. 2.10(a), is where the fluctuation increases as the dimple becomes more pronounced (i.e., curvature ratio becomes more negative); the second type of trend, shown in Fig. 2.10(b), involves the opposite relationship between the shape features, with the fluctuation instead decreasing as the dimple becomes more pronounced. The first type of trend results from varying N_{core} and N_+ , while the second type of trend results from varying r_- , r_+ , and N_- .

We now propose an explanation for why varying N_{core} and N_+ (the shapes resulting from varying N_+ are shown in Table 2.2) both cause the normalized fluctuation and the strength of the dimple to respond in the same direction. Since increasing N_{core} tends to increase the size and therefore the perimeter of the micelle, and decreasing N_+ decreases the number of diblocks on the micelle perimeter, either of these changes tends to decrease the density of diblocks on the micelle surface. As the surface density of the diblocks is decreased, we expect their surfactant-like effect to be reduced so that the surface tension of the micelle would increase. This surface tension increase should have two effects. The first effect is to reduce fluctuations in the micelle shape, and the second effect is to make the micelle shape



(a)



(b)

Figure 2.9: Plots of (a) the curvature ratio $\frac{c_-}{c_+}$ and (b) the normalized fluctuation δ , with standard errors indicated, as a function of \hat{N}_{core} , the number of core beads N_{core} divided by the number of core beads in the reference micelle. Also plotted is a line of best fit to the data. The lightness of the points and the fit line is set by the value of \hat{N}_{core} . (While the color is redundant in this plot, it is included to introduce the pattern used in Fig. 2.10.) The curvature ratio shows a fairly regular increasing trend (meaning the micelle shape becomes more circular) with the number of core beads, while the normalized fluctuation shows a decreasing trend. To assess the linearity of these trends, linear fits are performed to both sets of data.

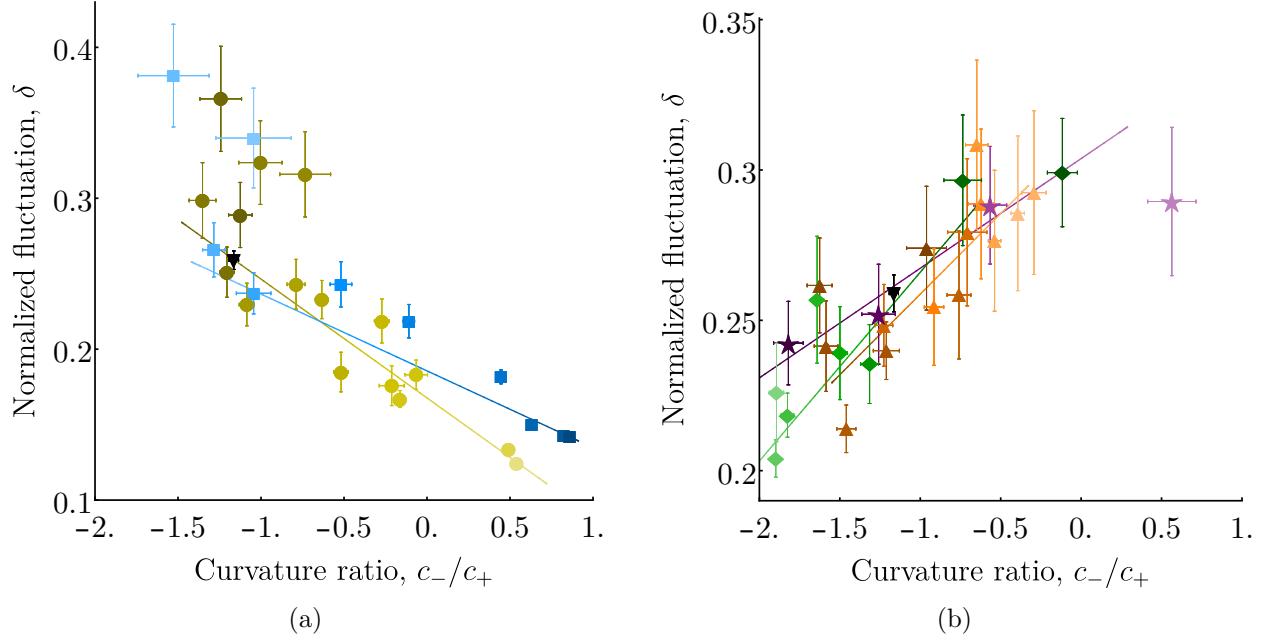


Figure 2.10: Scatter plots showing curvature ratios and normalized fluctuations exhibited by micelles of several compositions. Each micelle composition has been obtained by changing one of the following parameters from the reference micelle value (the black downward-pointing triangle near $\frac{c_-}{c_+} = -1.2$, $\delta = 0.26$): (a) N_{core} (yellow circles) or N_+ (blue squares); or (b) N_- (orange upward-pointing triangles), r_- (purple stars), or r_+ (green diamonds). The lightness of the data point represents the value of the parameter, with lighter points indicating larger values of the parameter in the manner of Fig. 2.9. To guide the eye and to assess linearity, we plot linear fits of the shape feature dependence on each of the five micelle composition parameters. To reduce crowding of the data, the five micelle compositions are partitioned into two plots according to the slope of the data resulting from varying the parameter.

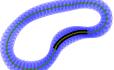
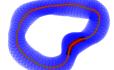
\hat{N}_+	45%	55%	64%	73%	82%	91%
						
\hat{N}_+	100%	109%	118%	127%	136%	
						

Table 2.2: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) as a function of \hat{N}_+ , the number of solvophilic-rich diblocks expressed as a percentage of the reference micelle value. As the number of solvophilic-rich diblocks increases, the shapes become less circular and the fluctuations increase.

more circular, reducing the strength of the dimple. Thus we expect that increasing N_{core} or decreasing N_+ both decreases the fluctuations (i.e., decreases δ) and decreases the strength of the dimple (i.e., makes $\frac{c_-}{c_+}$ more positive). By this reasoning, changing either N_{core} or N_+ would cause $\frac{c_-}{c_+}$ and δ to change in opposite directions, consistent with the negative slope in Fig. 2.9.

Having discussed the two micelle composition parameters which affect the normalized fluctuation and the dimple strength in the same way, we now discuss the remaining three composition parameters, where the responses of the shape features are opposite to each other as shown in Fig. 2.10(b). First we propose explanations for the results of varying asymmetry ratio r_- of the solvophobic-rich diblocks, those designed to sit at the micelle's dimple. The resulting shapes are shown in Table 2.3. For values of r_- closer to zero (i.e., more symmetric diblocks), the solvophobic-rich diblocks are very similar in composition to the solvophilic-rich diblocks, and so their preferred curvatures are similar, which we expect to result in a weak dimple (i.e., $\frac{c_-}{c_+}$ should become less negative). If the dimple is weak, then the shape should be nearly circular, so that less perimeter is required to enclose the same amount of volume, and indeed we expect that the volume enclosed by the micelle depends only weakly on the diblock composition so that micelle perimeter does decrease. A decrease in perimeter

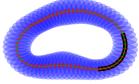
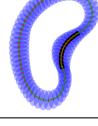
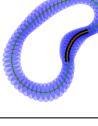
\hat{r}_-	74%	83%	91%	100%	109%	117%
						

Table 2.3: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) as a function of \hat{r}_- , the asymmetry ratio of the solvophobic-rich diblocks expressed as a percentage of the reference micelle value. As the solvophobic-rich diblocks become more asymmetric, making a sharper contrast with the solvophilic-rich diblocks, the shapes become less circular, the fluctuations decrease.

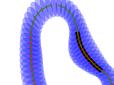
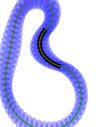
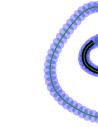
\hat{r}_+	135%	124%	112%	100%	88%
					
\hat{r}_+	76%	65%	53%	41%	29%
					

Table 2.4: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) as a function of \hat{r}_+ , the asymmetry ratio of the solvophilic-rich diblocks expressed as a percentage of the reference micelle value. As the solvophilic-rich diblocks become less asymmetric, making a sharper contrast with the solvophobic-rich diblocks, the shapes become less circular and the fluctuations decrease.

causes a higher density of diblocks and since we expect the diblock composition only weakly affects the preferred density of diblocks, we therefore expect a lower surface tension, leading to greater shape fluctuations (i.e., an increase in δ). We conclude that r_- should change $\frac{c_-}{c_+}$ and δ in the same direction, as observed.

The key point to the above argument was that the difference between the asymmetries of the micelle's two species of diblock determines how circular the micelle shape is. In the case we discussed, this asymmetry contrast was controlled by changing r_- , but it could just as well been controlled by changing r_+ (results shown in Table 2.4). Therefore, as the solvophilic-rich diblocks are made more asymmetric, they become more similar to the solvophobic-rich

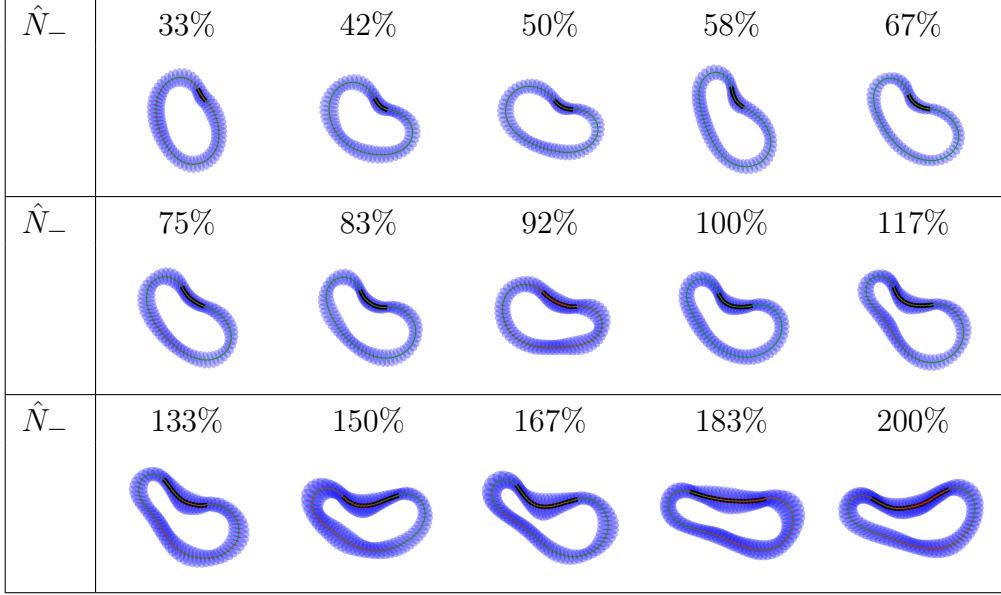


Table 2.5: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) as a function of \hat{N}_- , the number of solvophobic-rich diblocks expressed as a percentage of the reference micelle value. As the number of solvophobic-rich diblocks beads increases, the shapes become less circular and the fluctuations increase.

diblocks, and so we expect the shapes to become more circular and to fluctuate more. Thus, like r_- , r_+ should affect $\frac{c_-}{c_+}$ and δ in the same direction.

The results of varying the number of solvophobic-rich diblocks N_- (see Table 2.5) mostly follow the same trend as the results of varying the diblock asymmetries r_+ and r_- , but a different explanation is required. In this case we expect decreasing N_- to decrease the density of diblocks on the micelle surface, thereby increasing the surface tension and decreasing the fluctuations as measured by δ . However, decreasing N_- also decreases the length of micelle perimeter that has to deform in order to achieve its preferred curvature. Therefore, we expect micelles with small N_- may have a more strongly curved dimple, so that $\frac{c_-}{c_+}$ becomes more negative. By this reasoning N_- , like r_+ and r_- , would affect $\frac{c_-}{c_+}$ and δ in the same direction.

While the results of varying the number of solvophobic-rich diblocks N_- do mostly follow a smooth trend, we note one nonmonotonic feature of this data. The simulated micelle with

the smallest N_- (four solvophobic-rich diblocks), which according to the trend of the data should have the most extreme dimple, actually has a less pronounced dimple than even the base micelle. One might hypothesize that there is a minimum number of solvophobic-rich diblocks needed to nucleate a dimple. Whatever the case, this nonmonotonicity that a naive linear model explaining the micelle shape may not be sufficient for shape design.

In the preceding results, we have varied a single parameter of the micelle composition to observe the effect on two micelle shape features and have seen that the data lie on only two trend lines. This contradicts our expectation that each composition parameter change the shape features in a unique direction in shape feature space. Instead, we find that three shape composition parameters change the micelle shape in the same direction, meaning that at the level of a linear approximation, there are two independent combinations of these three parameters which have no effect on the micelle shape. The other two composition parameters also change the micelle shape features in a common direction, so that there would be one combination of the parameters which have no effect on the micelle shape features.

To produce a micelle shape not falling on either of the two trends, it is necessary to change multiple micelle composition parameters at once. For ease of shape design, we would hope that the effect of simultaneously changing two composition parameters could be naively inferred by linearly extrapolating from the individual effects of the parameters. While the effects of varying individual micelle composition parameters were not independent as we expected, they were indeed often roughly linear. If linearity of the shape dependence is assumed, then the effect of varying any combination of micelle composition parameters can be inferred from the data presented above. One can then determine precisely how to change the composition parameters to produce a desired shape change (e.g., to reduce normalized fluctuations while holding the curvature ratio fixed). Additionally, by determining which composition parameters have no effect on the shape, one has freedom in picking the composition parameters. This freedom may be used to choose the most convenient parameters resulting in a desired shape. To test if things are this simple in practice, we have performed

\hat{N}_{core}	100%	114%	129%	143%	157%
\hat{N}_{-}	33%	42%	50%	58%	67%
	A blue-outlined shape with a small indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a larger indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a significant indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a deep indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a very deep indentation on the left and a green line showing the curvature profile.
\hat{N}_{core}	171%	186%	200%	214%	
\hat{N}_{-}	75%	83%	92%	100%	
	A blue-outlined shape with a deep indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a very deep indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a deep indentation on the left and a green line showing the curvature profile.	A blue-outlined shape with a very deep indentation on the left and a green line showing the curvature profile.	

Table 2.6: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) for micelles interpolating between the $\hat{N}_{\text{core}} = 214\%$ composition of Table 2.1 and the $\hat{N}_{-} = 33\%$ composition of Table 2.5. The shape features associated with these data are plotted in Fig. 2.11.

simulations where two micelle composition parameters are varied simultaneously.

In the first set of simulations, N_{core} and N_{-} are varied to interpolate between the $\hat{N}_{\text{core}} = 214\%$ and $\hat{N}_{-} = 33\%$ data points of Table 2.1 and Table 2.5. The simulated shapes are shown in Table 2.6.

To get a closer look on the effect on the shape features, we plot in Fig. 2.11 the curvature ratios and normalized fluctuations for the shapes in Table 2.6 as well as the results of individually varying N_{core} and N_{-} . We see that the interpolating micelle compositions produce shape features that mainly lie along the trend of the data set where just N_{core} is varied, contrary to the naive expectation that these shape features should be a linear combination both of the shapes feature resulting from varying N_{core} as well as those resulting from varying N_{-} . To explain this, we hypothesize that the micelles with a large value of N_{core} have a surface tension so large that the change in spontaneous curvature profile caused by changing N_{-} does not have a noticeable effect on the micelle.

In the second set of simulations, N_{+} and r_{+} are varied to interpolate between the $\hat{N}_{+} = 136\%$ and $\hat{r}_{+} = 53\%$ data points of Table 2.2 and Table 2.4. The simulated shapes are shown

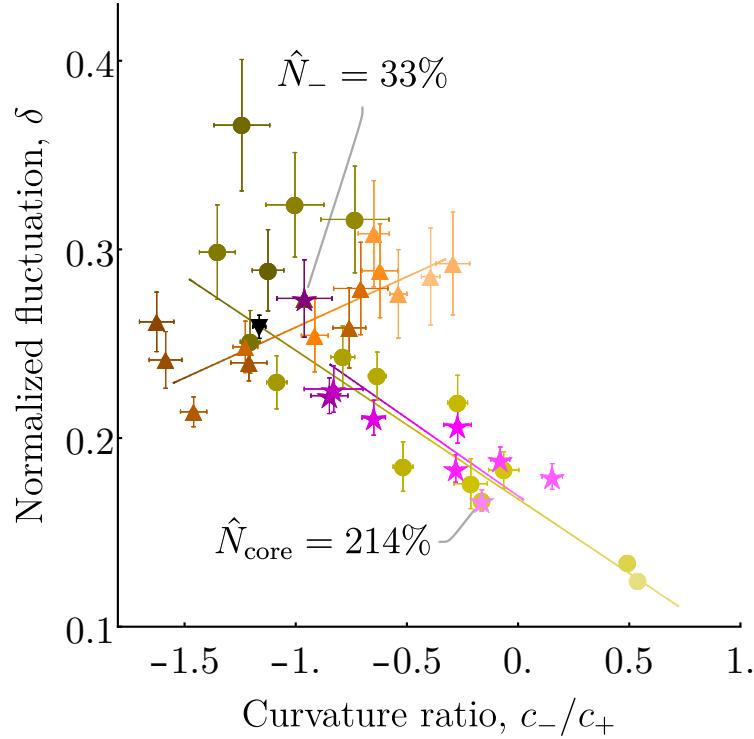


Figure 2.11: Scatter plot showing the curvature ratios and normalized fluctuations of the data shown in Table 2.6 (magenta stars). The scatter plot and the fit lines are made in the style of Fig. 2.10, and the data sets from varying only N_{core} (yellow circles) and only N_{-} (orange upward-pointing triangles) are reproduced in this figure. Notice that for the data set where only N_{-} is changed, the micelle with the smallest value of \hat{N}_{-} , namely 33%, has a weaker dimple than, and therefore appears to the right of, the reference micelle (downward pointing black triangle). By contrast, most other shapes from micelles with $\hat{N}_{-} < 100\%$ have stronger dimples than the reference micelle and therefore appear to its left. Despite this variation in micelle shape caused by changing N_{-} , the magenta points, representing a simultaneous variation in both N_{core} and N_{-} , follow the same trend as the yellow points representing a variation only in N_{core} .

\hat{N}_+	100%	109%	118%	127%	136%
\hat{r}_+	53%	65%	76%	88%	100%
					

Table 2.7: Mean micelle shapes, thermal fluctuations, and errors in mean micelle shapes (illustrated in the manner of Fig. 2.7) for micelles interpolating between the $\hat{N}_+ = 136\%$ composition of Table 2.2 and the $\hat{r}_+ = 53\%$ composition of Table 2.4. The shape features associated with these data are plotted in Fig. 2.12.

in Table 2.7. For a more quantitative view of the effect on the shape features, we plot in Fig. 2.12 the curvature ratios and normalized fluctuations of both the shapes in Table 2.6 and the previously discussed shapes of Table 2.2 and Table 2.4 which resulted from individually varying N_+ and r_+ .

Ideally, the shape features would linearly, or at least monotonically, interpolate between the two extreme cases. Taking error bars into account, the data are nearly consistent with a monotonic increase in fluctuations from the $\hat{r}_+ = 53\%$ data point to the $\hat{N}_+ = 136\%$ data point. However, the curvature ratio dependence is unambiguously nonmonotonic.

To see how the dependence might not be monotonic, consider first the $\hat{r}_+ = 53\%$ micelle composition, which has the largest asymmetry contrast of the simulated data shown in Table 2.7 and the fewest diblocks on the micelle perimeter. On the one hand, the strong asymmetry contrast should lead to a strong dimple, but on the other hand, the decrease in the number of diblocks should lead to a higher surface tension and consequently a smaller dimple. Next consider the micelle composition at the other extreme, having the largest number of diblocks with $\hat{N}_+ = 136\%$. In this case, there should be a low surface tension, as evidenced by this micelle's large normalized fluctuation, which allows for a larger dimple, but also a low asymmetry contrast which would lead to a smaller dimple. The nonmonotonicity we observe is that there are intermediate micelles showing a stronger dimple than both of the extreme cases.

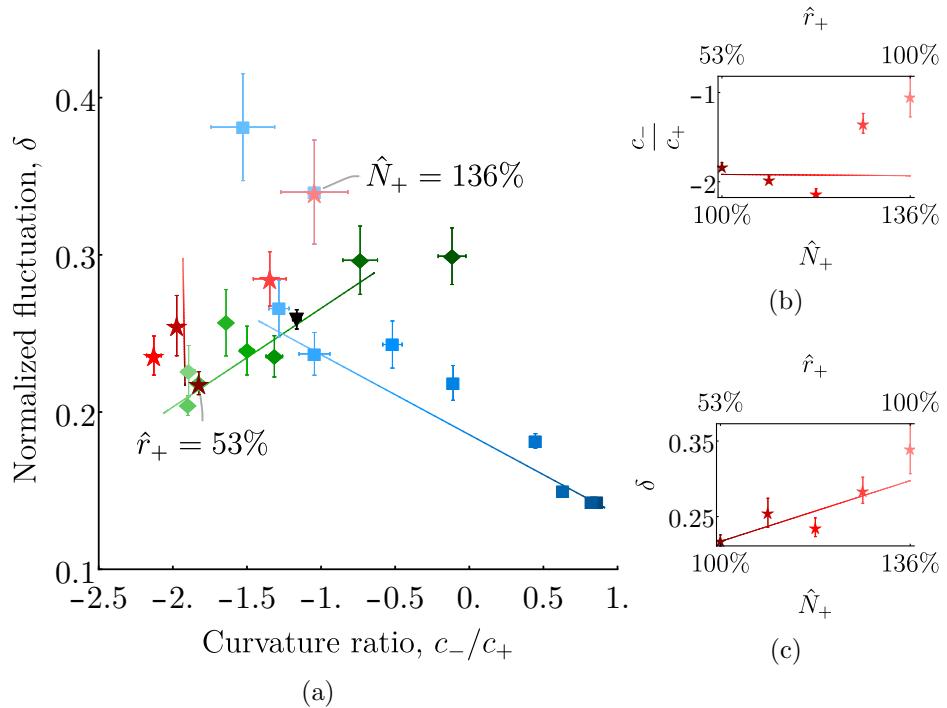


Figure 2.12: (a) Scatter plot showing the curvature ratios and normalized fluctuations of the data shown in Table 2.7 (red stars). The scatter plot and the fit lines are made in the style of Fig. 2.10, and the data sets from varying only \hat{N}_+ (blue squares) and only \hat{r}_+ (green diamonds) are reproduced in this figure. The data from Table 2.7 exhibit a nonmonotonic variation in the curvature ratio, leading to the linear fit of the shape feature dependence on our chosen combination of \hat{N}_+ and \hat{r}_+ to have almost no variation in $\frac{c_-}{c_+}$ (resulting in a vertical fit line), despite the significant variation shown by the data. (b) and (c) individual dependences of $\frac{c_-}{c_+}$ and δ , respectively, on the simultaneous variation in \hat{N}_+ and \hat{r}_+ of Table 2.7 (i.e., red stars of (a)), plotted in the style of Fig. 2.9. (b) provides a clear visualization of the nonmonotonicity in $\frac{c_-}{c_+}$ and the resulting near constancy of the best fit.

We hypothesize that as we move from the first extreme with a large asymmetry contrast and fewer diblocks to the opposite extreme, there comes a critical micelle composition where the increasing preferred perimeter set by the number of diblocks becomes large enough to completely accommodate the preferred curvature of the dimple. Micelles with more diblocks and less asymmetry contrast than this critical composition do not benefit from the increased perimeter from the diblocks, and instead have a decreasing dimple strength set by the decreasing asymmetry contrast. On the other hand, micelles with less diblocks and more asymmetry contrast than the critical composition experience both an increased surface tension and an increased preferred curvature. As evidenced in Fig. 2.11, the surface tension has a larger effect on the dimple strength, and so we expect dimple strength diminishes. By this logic, there should be a maximum dimple strength near the critical composition, and so the curvature ratio dependence should be nonmonotonic. In any event, this example shows that a linear interpolation is insufficient to approximate the behavior of the shape features between two micelle compositions, since nonmonotonic behavior is possible.

2.4 Discussion

In Sec. 2.3, we showed how the micelle shape features depended on the composition parameters. In this section, we discuss what implications these results have for the central questions of our work, namely whether a micelle may feasibly be designed using the rationale presented in Sec. 2.1. We begin by discussing if the micelle shape dependence is sufficiently regular to allow for arbitrary shape features to be designed using only a naive strategy. Next, we address a shortcoming of this work mentioned in Sec. 2.1, which is that the micelles shapes are only metastable. We explain why the statistics of the metastable shapes examined here are meaningful and discuss what might be done to stabilize the micelles in practice. Lastly, we justify why the two-dimensional simulations considered here are relevant to practical applications which necessarily have three-dimensions.

In the introduction, we set a goal of identifying good control parameters to design the

shape of the micelle. Such control parameters ought to have a simple, easily understandable effect. Indeed, in Sec. 2.3, we found a smooth variation in the micelle shape features, and we were able to give plausible physical explanations of the observed behavior involving the volume enclosed by the micelle, the surface tension resulting from extension of the micelle perimeter, and the bending energy associated with the curvature of the micelle perimeter. The explanations were not explicitly verified because it is difficult to define and independently measure the bending energies and surface tensions of the fluctuating, asymmetric micelles considered in this work. However, we found that the shape dependence was significantly non-linear and produced nonmonotonicities in some cases, and therefore the dependence cannot be quantitatively explained for the purposes of shape design by simple physical arguments or a naive linear model. Therefore, if an accurate model of the relationship between the control parameters and the micelle shape is desired for facilitation of shape design, something more must be done.

One approach is to create Hamiltonian whose degrees of freedom are the junction points and which contains terms for the bulk compression of the micelle interior and the stretching and bending of the micelle surface. It would be necessary to perform a series of simulations to determine a mapping between the micelle composition and the parameters of the simplified Hamiltonian. Once this mapping is determined, the simplified model, having far fewer degrees of freedom, would give a much simpler and less computationally intensive way of understanding how the micelle shape depends on the micelle composition.

Alternatively, if one desires to design a single specified micelle shape, the required micelle composition could be found by some nonlinear optimization strategy, such as a genetic algorithm. Such machine learning algorithms have been applied to the design of material properties in a number of contexts [81–84].

So far, we have considered only micelles which exhibited the intended positioning of diblocks on the surface, which we call well formed, even though as noted in Sec. 2.2, micelles resulting from our simulation often did not have this property. We now give a justification

for considering this seemingly biased sample. Our justification is based on the fact that the well-formed micelles are metastable, meaning that the micelles have a significant chance of surviving the length of a simulation without forming a defect in the diblock arrangement, but there is a finite probability to form a defect from which the micelle would never recover. With this in mind, it is natural to investigate the thermodynamic statistical properties of the well-formed micelles, and the appropriate statistical weight to each micelle configuration in this subensemble is found simply giving equal weight to each well-formed micelle while discarding the others.

However, if this statistical analysis is to be meaningful for practical applications, something must be done to enforce that the micelles be well formed. We view this problem as separate from the question of how the micelle composition affects the shape of the well-formed micelles, but we believe there are a few promising approaches to solving this problem. One approach is to change the interaction parameters of the system. The choice of parameters used in this work was motivated by the desire to have a lower energetic barrier for bead rearrangements allowing shorter simulation times, but this has the drawback of facilitating diblock rearrangements on the micelle surface. Stronger interactions may increase the energetic penalty for micelle defects, greatly reducing their occurrence. Another approach is to make the two species of monomers composing the solvophobic-rich diblocks different from the two species composing the solvophilic-rich diblocks. Such a difference between the two types of diblocks could promote their segregation on the micelle surface, thereby enforcing their intended positioning.

Beyond changing the interaction parameters of the system, a further approach is to alter the polymer architecture with the idea that a different bond topology would better stabilize the well-formed micelles. Whatever approach is taken to solve this problem, we don't expect it to significantly alter the shape dependences observed in this work, as these are a basic result of the polymer nature of the micelle.

In practical applications, the design problem considered in this work must be solved

in three dimensions. However, we have chosen to conduct two-dimensional simulations, as has often been done [58–62]. We argue that since the physics affecting micelle shape (compressibility, surface tension, spontaneous surface curvature) are qualitatively unchanged, the dependence on the micelle composition of a similar three-dimensional shape, such as a dimpled sphere, should be similar. In general, one can imagine many more target micelle shapes beyond a dimpled sphere. In contrast to two-dimensional shapes, the three-dimensional target shapes are described by two principal curvatures at each point on the surface. The diblock composition on the surface, however, specifies only a mean curvature at each point to lowest order [63]. Therefore we expect that the profile of diblock compositions over the micelle surface is not in general sufficient to completely control the micelle shape in three dimensions, so that full shape control would be harder or perhaps impossible in three dimensions. However, some shape control must be possible, and studying the extent of this shape control is an interesting direction for future research.

2.5 Conclusion

We have described a micelle shape-design scheme, and shown its capacity to control the average shape and fluctuations of a micelle in thermal equilibrium. We began with a reference micelle composition producing a moderately dimpled micelle, and varied, one by one, several aspects of the reference micelle composition to examine the effect on the thermal micelle shape. We studied two features of the micelle shape in particular, and found that the dependences were somewhat smooth, but significantly nonlinear and sometimes nonmonotonic. Additionally, simulations were conducted where two aspects of the micelle composition were changed simultaneously, with the result that the combined effect of changing two parameters could not easily be deduced by looking at the individual effects on the micelle. Plausible rationales were given to explain these results. Even though the relationship between the micelle composition and shape may not satisfactorily be characterized by a naive linear relationship, we believe more sophisticated methods to characterize the relationship

are nonetheless possible, and we proposed examples. We expect the principles that govern our simple two-dimensional model to extend to three dimensions, and therefore that our results provide evidence that a similar design scheme should work to produce three dimensional shape-designed micelles.

APPENDIX A

MODEL

This section is devoted to providing a precise description of the pair potentials governing the two species of beads. In our system of units described in Sec. 1.2.1, the bond interaction $U_{\text{bond}}(d)$ felt by two adjacent beads displaced by a distance d is given by

$$U_{\text{bond}}(d) = d^2. \quad (\text{A.1})$$

The form of the nonbonded interaction U_{nb} is more complicated. This interaction is the sum of two terms. One term is a stiff repulsion U_r enforcing that no two beads have the same position. Following [43], we take an interaction whose strength is proportional to the size of the overlap region of the beads. Therefore the stiff repulsion is given by

$$\frac{U_r(d)}{P_r D_r^2/2} = \cos^{-1} \left(\frac{d}{D_r} \right) - \frac{d}{D_r} \sqrt{1 - \frac{d^2}{D_r^2}}, \quad (\text{A.2})$$

where D_r is the maximum range of the repulsive interaction, P_r is a constant setting the strength of the interaction, and again d is the distance between the bead centers. For simplicity, we simply take the same value of P_r and D_r to govern all pairs of beads. In addition to this stiff repulsion, there is an attraction $U_a(d)$ between solvophobic beads of the same form as Eq. (A.2), but with a longer interaction range D_a , and a negative strength parameter P_a . For the sake of reproducibility, we present the values we chose for these parameters; the values are $D_r = 2.015873$, $P_r = 8.870637$, $D_a = 4$, and $P_a = -0.378$. $U_a = 4.75$. The form of the pair potential and the specific parameter values were chosen to produce a homopolymer with favorable kinetics and physically reasonable thermodynamic properties (density, compressibility, surface tension, etc.), as will be seen in Appendix C. Plots of the pair potentials are shown in Fig. A.1. We did not perform an extensive search of functional forms for the pair potential, and the precision of the quoted parameter values

was not necessary to produce a physically reasonable polymer; instead, the large number of digits resulted from reparameterizing the interaction potential. Therefore we expect that a pair potential having either an alternate functional form or parameter values different by a few percent would still lead to physically reasonable behavior. Still, sufficiently poorly chosen parameters may cause undesirable behavior such as all beads collapsing to a single position or glassy dynamics.

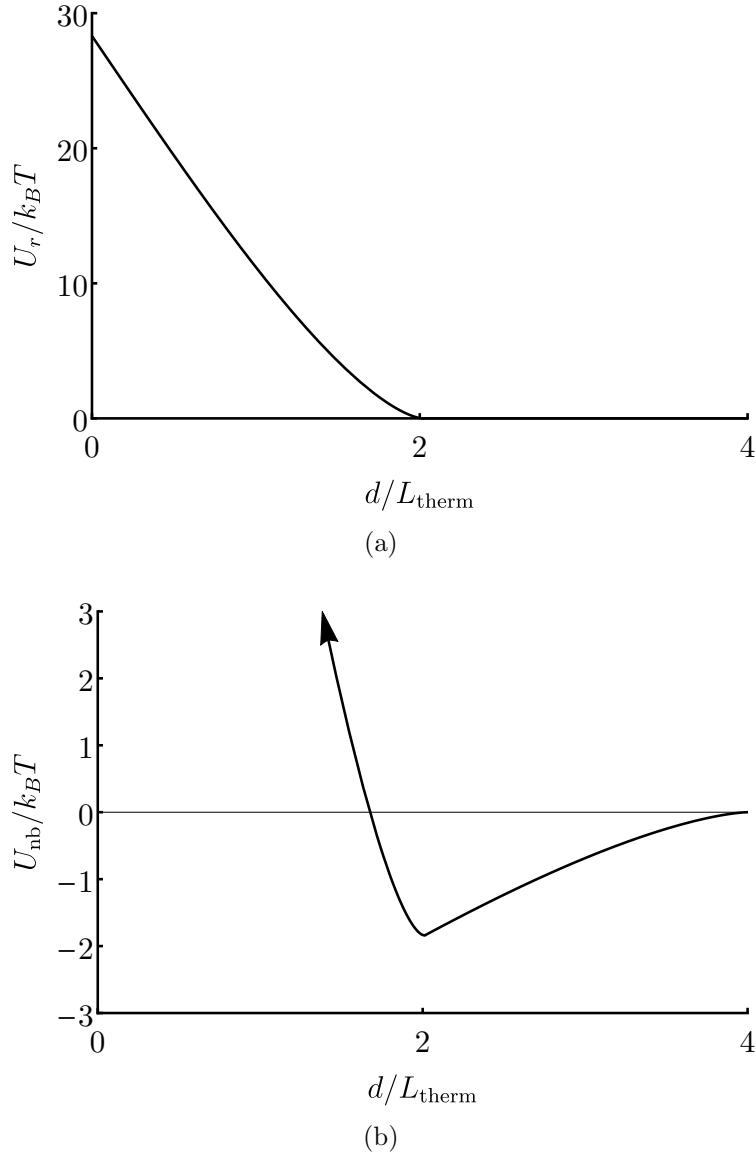


Figure A.1: Plots of nonbonded interaction potential. Energies and lengths have been nondimensionalized using $k_B T$ and L_{therm} respectively, as described in the second paragraph of Sec. 1.2.1. In (a), the purely repulsive interaction potential U_r of Eq. (A.2) for a bead pair containing a solvophilic bead is plotted. In (b), the interaction potential for two solvophobic beads is plotted. This interaction potential contains an attractive term in addition to the repulsive potential U_r plotted in (a).

APPENDIX B

SIMULATION METHOD

To determine the average micelle shape resulting from this model, we perform a constant temperature molecular dynamics simulation using LAMMPS [47]. Although LAMMPS is a molecular dynamics simulator, meaning it essentially works by calculating forces from the potentials and then using Newton’s second law to get the accelerations from these forces, it provides for running simulations of a fixed number of particles “ n ” at constant temperature “ t ” and either constant volume “ v ” or pressure “ p ”, through its `fix nvt` and `fix npt` commands, respectively. Since we are interested in obtaining a thermal ensemble of configurations, these are exactly the commands we used to time-evolve the system. There are two parameters for the `fix nvt` command: a timestep and a time constant `Tdamp` setting how quickly the simulation thermalizes the system. Additionally, for constant pressure simulations, there is an additional time constant `Pdamp` determining how quickly the volume in a constant pressure simulation responds to an unbalanced pressure. To specify these time constants, we must express them in terms of our time unit, which, referring to our the system of units described in Sec. 1.2.1, is $\sqrt{\frac{mL_{\text{therm}}^2}{k_B T}}$, where m is the mass of a bead, L_{therm} is the root-mean-square extension of the harmonic spring in thermal equilibrium, k_B is Boltzmann’s constant, and T is the temperature of the simulation thermostat. From this expression, it can be shown that the time unit is equal to T_{dimer}/π , where T_{dimer} is the oscillation period of two beads connected by a spring and isolated from the thermal bath. In terms of this unit of time, we found after some experimentation that setting the timestep to 0.003 and setting `Tdamp` and `Pdamp` to 0.5 allows for efficient and numerically stable simulation.

Another detail of the simulation is the initialization. In all cases, the initial bead velocities were chosen from a thermal distribution at the temperature of the simulation thermostat.

APPENDIX C

VALIDATION

In this section, we verify that our model and simulation method, described in detail in Appendices A and B, produce physically reasonable results in cases where the expected behavior is known. One such case is a homopolymer melt: a system consisting of a dense phase of polymers all made from the same single species of bead (in our case, solvophobic). The melt ought to have a well-defined density, compressibility, and surface tension. Additionally, the density and mean square end to end distance of the polymer ought to have an expected dependence on the number of monomers in the polymer. In addition to verifying that the simulation is consistent with these expectations, we also test for quantitative agreement between the melt properties and those of real polymer; specifically, we compare with poly-(dimethylsiloxane) (PDMS). A comparison of our system with PDMS is apt because both systems are only weakly insoluble.

First we consider the melt density. We simulate a periodic homopolymer system, shown in Fig. C.1, at zero pressure. In this case, the equilibrium density is the number of beads divided by the average volume of the system. Multiple independent simulations for different chain lengths n were run in order to find the dependence of the simulated density d on chain length and compare this dependence to theoretical expectations. Theoretically, the density is expected to reach a finite value d_∞ as the chain length goes to infinity. For large values of the chain length, the dependence of the density on the chain length $d(n)$ can be expanded in the small parameter $1/n$:

$$d(n) = d_\infty + \frac{a}{n}, \quad (\text{C.1})$$

where a is a parameter representing how strongly the density depends on the chain length. We find that our data are indeed well fitted by this functional form, as seen in Fig. C.2.

Having found the equilibrium density at zero pressure, we may also find the equilibrium density at finite pressure. The response of the density to an applied pressure is characterized

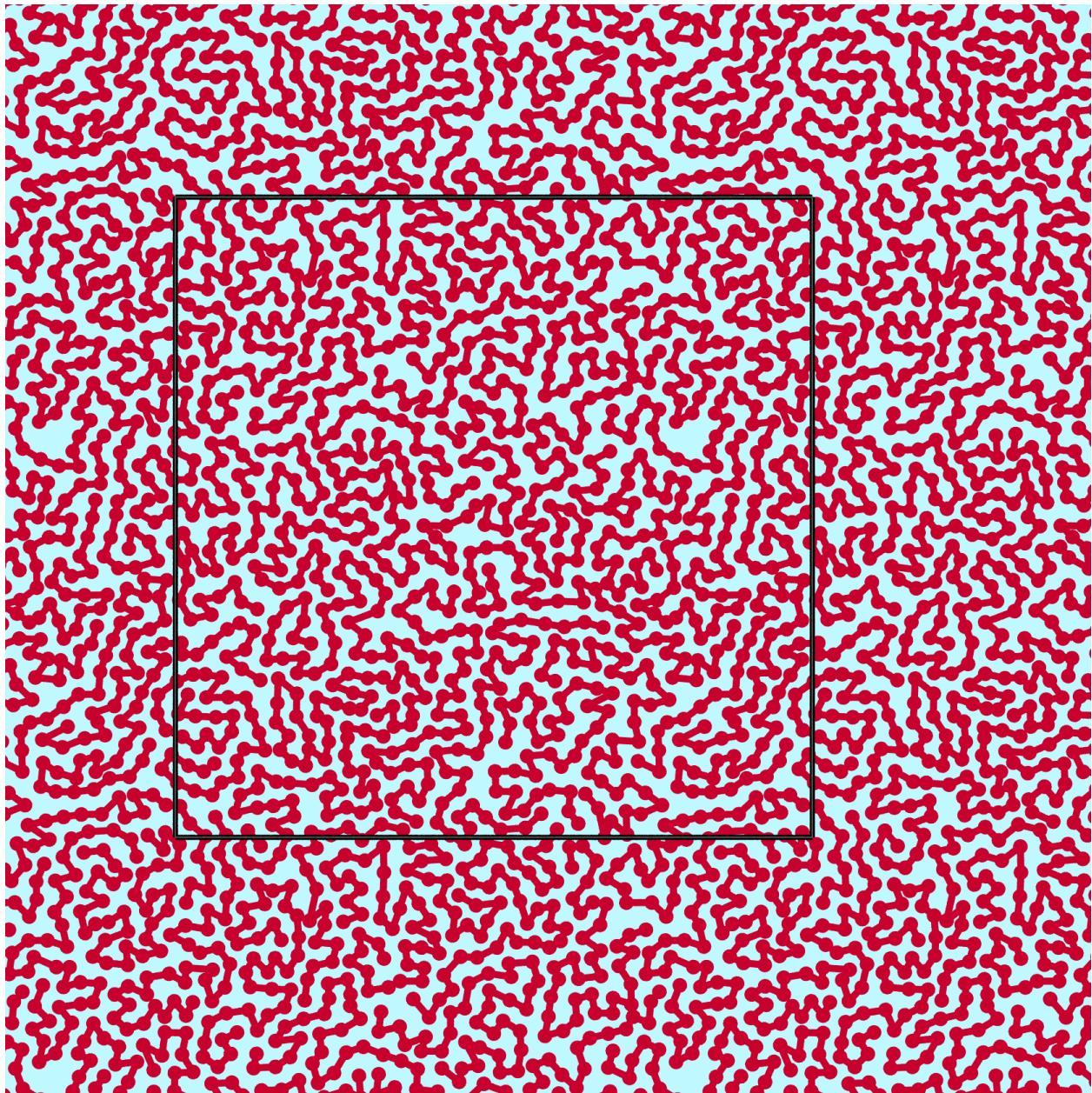


Figure C.1: Visualization of simulated homopolymer melt. The simulated system contains 30 solvophobic homopolymer chains, each having 35 beads, shown as red disks. The springs connecting adjacent beads are shown as red segments. The system is periodic, its boundary indicated by the black square.

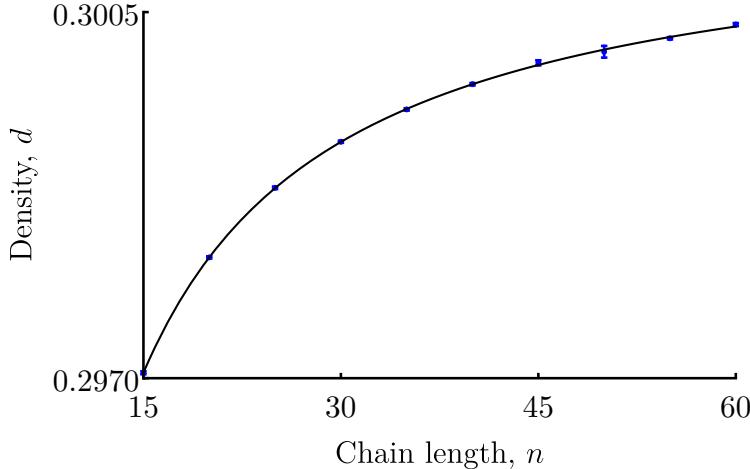


Figure C.2: Solid curve: expected functional form Eq. (C.1), fitted to the simulation values shown as points. The resulting reduced chi-squared is 0.5, indicating that this functional form is consistent with the data. The best-fit value of d_∞ is 0.30146 ± 0.00001 .

by the compressibility, denoted β . Alternatively, β may be determined by analyzing the density fluctuations at constant pressure. If the simulation produces a proper Boltzmann ensemble, these two ways of determining the compressibility ought to agree. Indeed, the compressibilities determined from these two methods do in fact agree, as can be seen in Fig. C.3.

In Fig. C.3(b), there are two outliers exhibiting anomalously large fluctuations, and therefore excluded from the compressibility analysis. Since these outliers could not be reproduced, they were replaced by data from repeated simulations. In any case, the outliers represent only small fluctuations in density (less than one percent). Additionally, the average density observed from these two simulations is consistent with the trend exhibited by the rest of the simulations, as shown in Fig. C.2. This suggests that the samples are incompletely equilibrated for purposes of determining these small fluctuations, even though they are well equilibrated for determining the density. Consequently, we conclude that care is needed when estimating the magnitude of, and uncertainty in, a physical quantity's thermal fluctuations. Accordingly, we provide validation of our estimates of micelle shape fluctuations in Sec. 1.4.1.

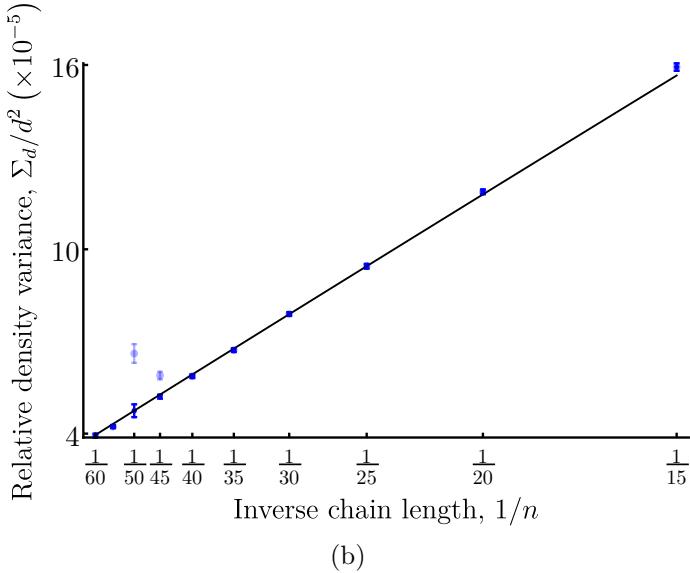
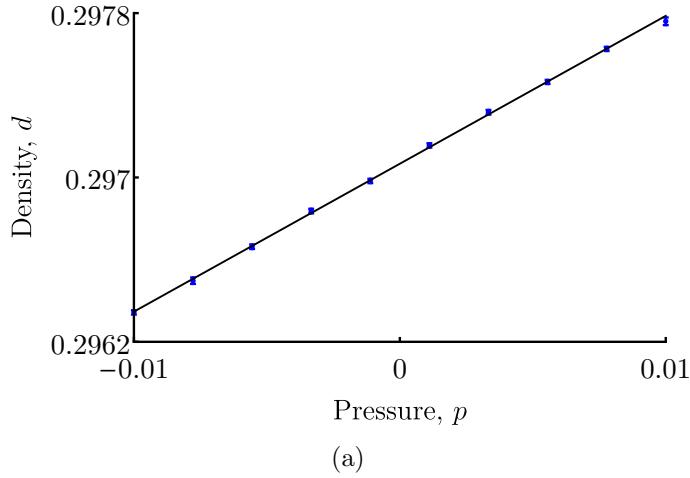


Figure C.3: Two independent fits to determine the compressibility β . In (a), the density d of the homopolymer system of Fig. C.1 with 30 polymer chains and 15 beads per chain is plotted against the applied pressure (data points). The solid line shows a fit of the functional form $d(p) = d_0(1 + \beta p)$ to the data, which yields a compressibility β of 0.242 ± 0.002 , and reduced chi-squared of 0.65. In (b), data from the same simulations of Fig. C.2 are plotted. The variance of the sampled densities, normalized by the square density $d(n)^2$ found from the fit of Fig. C.2, are plotted against the reciprocal of the chain length. Two systems having 45 and 50 beads per chain produced anomalous results, which could not be reproduced after several attempts. These anomalous results are shown as partially transparent data points, and the solid data points at the same chain lengths are results from representative repeats of the simulation. A fit of the expected functional form $\beta d(n)/(N_c n)$ to the data excluding the outliers was performed, where N_c is the number of chains (namely, 30) in the simulation. The fit gives a best-fit compressibility of 0.2372 ± 0.0007 , and the chi-squared of the fit is 1.4.

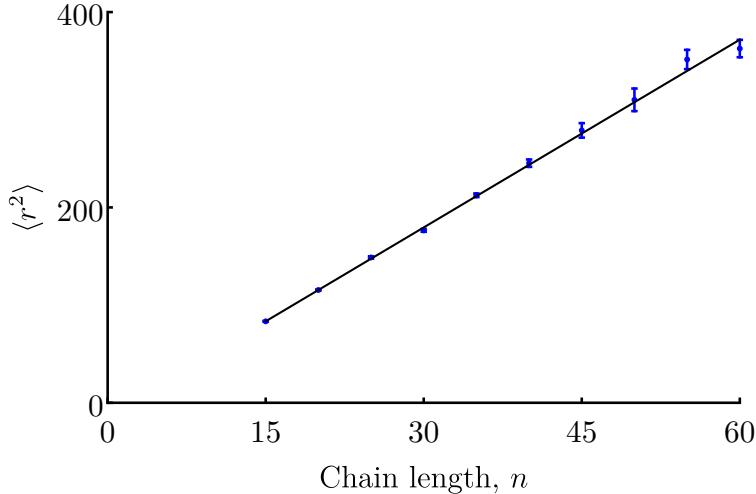


Figure C.4: Plot of the mean-square end-to-end chain distance $\langle r^2 \rangle$ as a function of chain length for the same systems of Fig. C.2 and Fig. C.3(b). The data are fit to a the theoretical expectation given in Eq. (C.2), resulting in a best-fit value of b^2 equal to 6.41 ± 0.05 and a reduced chi-squared of 1.1.

In addition to the density, the mean-square end-to-end chain distance $\langle r^2 \rangle$ also has an expected dependence on chain length [85]

$$\langle r^2 \rangle(n) = b^2 n + \langle r^2 \rangle_0, \quad (\text{C.2})$$

where b^2 is a parameter giving the size of each bead's contribution to the mean-square end-to-end distance, and $\langle r^2 \rangle_0$ is a subleading correction. As can be seen in Fig. C.4, our data does match this expectation well.

The final property of our system considered here is its interfacial tension with the solvent, which we determine using a simulation cell of fixed volume and two free surfaces, as shown in Fig. C.5. Since the simulation has two surfaces, the surface tension is half of the force transmitted across the simulation cell. Because we know the inter-bead forces as a function of bead position, calculating the transmitted force in the simulation is a simple matter. We expect a well-defined surface tension independent of the number of chains in the simulation, and indeed this is what we find, as can be seen in Fig. C.6.

Having verified that the homopolymer melt behavior matches theoretical expectations,

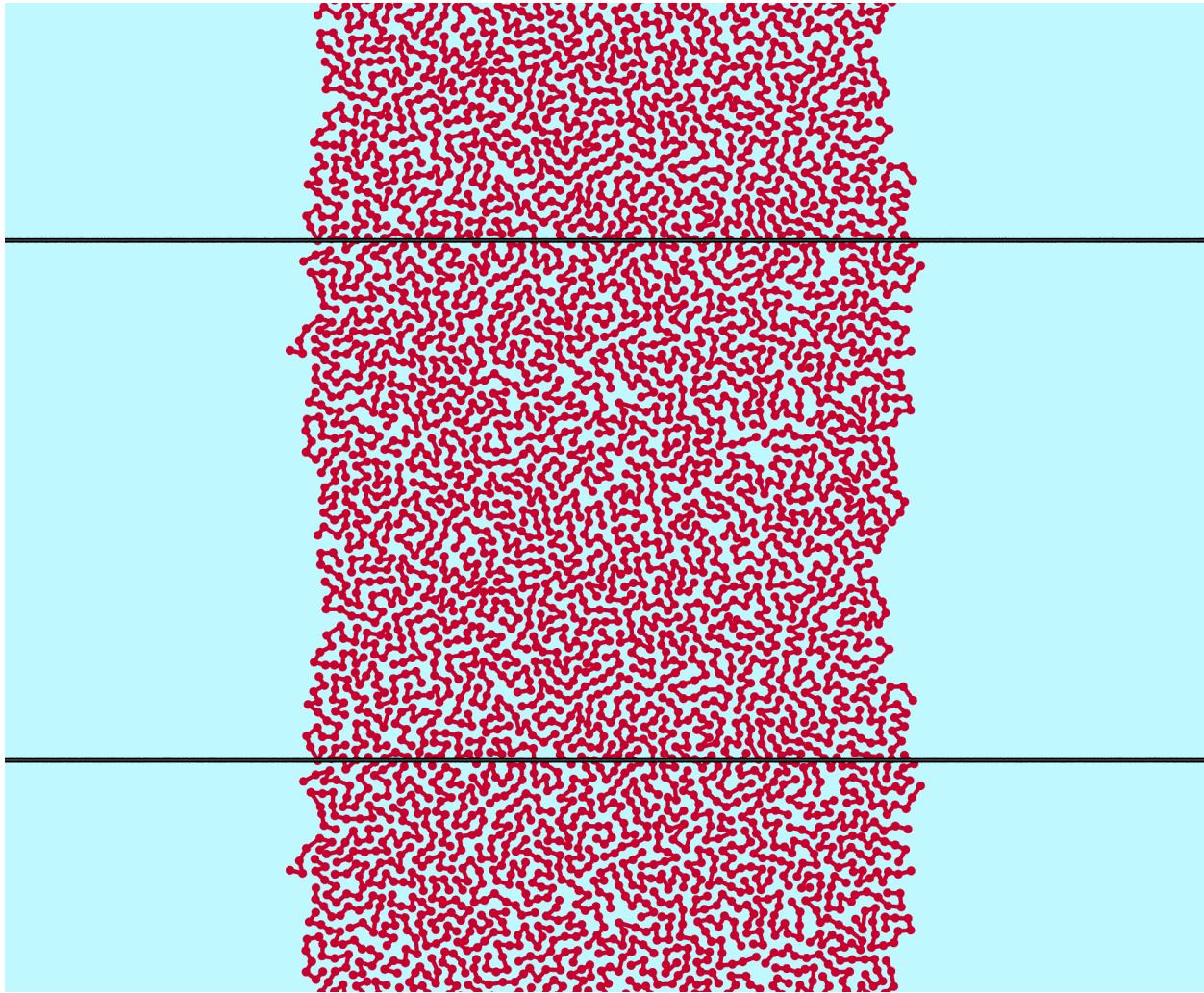


Figure C.5: Typical configuration of a strip of homopolymer in (implicit) solvent. The simulated system contains 143 solvophobic homopolymer chains, each having 15 beads, shown as red disks. The springs connecting adjacent beads are shown as red segments. The system is periodic in one direction, and the fixed periodic boundaries are shown as black lines.

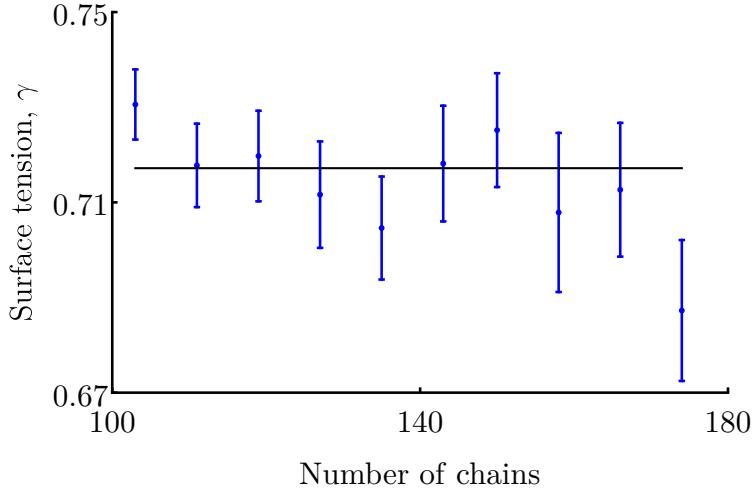


Figure C.6: Plot of inferred surface tensions vs number of chains for system simulated in the geometry of Fig. C.5. A best fit to a constant yields a surface tension of 0.717 ± 0.003 . The reduced chi-squared of the fit is 1.1, indicating that the data are consistent with the surface tension being independent of the number of chains in the system, as theoretically expected.

we may ask if the actual values of the density, compressibility, and mean-square end-to-end distance per monomer are similar to those of a real polymer. We compare to poly-(dimethylsiloxane) at room temperature. To form a basis for comparison, we must make contact between simulation units and the physical units in which PDMS is measured. One correspondence of units may be set by identifying the temperature of the simulation with the room temperature. Another correspondence can be made by identifying the Kuhn length [86], which we denote by ℓ_K , of the model system with that of PDMS. To compare the number density of the simulated system with PDMS, it is necessary to specify the number of dimethylsiloxane monomers corresponding to one simulated bead. We make the choice that one Kuhn segment in the simulation ought to correspond to one Kuhn segment of PDMS. The mean square bond length l^2 of our simulation is 3.2, so the number of beads per Kuhn segment b^2/l^2 is equal to 2.0, and the Kuhn length b^2/l is 3.6. Using the correspondences we have just described, physical properties of our simulation and those of PDMS are tabulated in Table C.1.

From Table C.1, we see that the density, compressibilities, and surface tensions of our

Quantity	Unit	PDMS value	Value in simulation
Kuhn segment density	ℓ_K^{-d}	2.5	1.9
Compressibility	$\frac{\ell_K^d \times 10^{-3}}{k_B T}$	4.0	19
Surface tension	$\frac{k_B T}{\ell_K^{d-1}}$	5.6	2.6

Table C.1: Properties of our simulated homopolymer system compared with those of poly-(dimethylsiloxane). Since only comparison of nondimensional ratios are meaningful, we express its properties in a system where the unit of length is the Kuhn length ℓ_K , the unit of energy is thermal energy $k_B T$, and the amount of polymer is measured by the number of Kuhn segments. Nondimensionalized this way, the values of the density are similar, but our simulated system has a lower surface tension and higher compressibility. The physical properties of PDMS needed to calculate the values in this table may be found in [87–89].

simulated system are all on the same order of magnitude of those of PDMS, validating that our simulated system has properties similar to a real polymer. Further, the nature of the difference of the two systems' properties can be partially explained: our simulated system's compressibility is higher than that of PDMS, and its surface tension is lower. This is explained by our tuning of the interaction parameters of our model to create a “soft” system with a low energy barrier for bead rearrangements, leading to shorter simulation times. With this in mind, we conclude that our model polymer is reasonably similar to PDMS, if a little softer.

APPENDIX D

EQUIVALENCE OF TWO DEFINITIONS OF MEAN SHAPE

To justify our definition Eq. (1.15) of $\bar{\mathbf{r}}$, we show that it is equivalent to an alternative notion of average. The alternative definition involves first rotating the shapes so that the summed pairwise square differences are minimized, and then simply taking an arithmetic average. In symbols, we define the minimizing rotation angles $\check{\theta}_\alpha$ by

$$(\check{\theta}_1, \dots, \check{\theta}_{N_s}) = \arg \min_{(\theta_1, \dots, \theta_{N_s})} \sum_{\alpha, \beta=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{R}_{\theta_\beta} \mathbf{r}_\beta), \quad (\text{D.1})$$

and then we define the arithmetic average $\tilde{\mathbf{r}}$ of the shapes by

$$\tilde{\mathbf{r}} = \frac{1}{N_s} \sum_{\alpha=1}^{N_s} \mathbf{R}_{\check{\theta}_\alpha} \mathbf{r}_\alpha. \quad (\text{D.2})$$

To transform Eq. (D.2) into a form more similar to Eq. (1.15), we use a standard identity relating the expected square differences between two independent samples to the expected square difference of a single sample to the mean¹:

$$\frac{1}{N_s^2} \sum_{\alpha, \beta=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{R}_{\theta_\beta} \mathbf{r}_\beta) = 2 \frac{1}{N_s} \sum_{\alpha=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \frac{1}{N_s} \sum_{\beta=1}^{N_s} \mathbf{R}_{\theta_\beta} \mathbf{r}_\beta). \quad (\text{D.3})$$

In fact we can proceed further by recognizing that the arithmetic mean minimizes the sum of square differences. Using this fact to transform the right hand side of Eq. (D.3), we obtain

$$\frac{1}{N_s^2} \sum_{\alpha, \beta=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{R}_{\theta_\beta} \mathbf{r}_\beta) = 2 \frac{1}{N_s} \min_{\mathbf{a}} \sum_{\alpha=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{a}). \quad (\text{D.4})$$

Using this identity (and ignoring an unimportant multiplicative factor of $2N_s$), we may

1. Recall if X and Y are two independent, identically distributed random variables, then (using $\langle \dots \rangle$ to denote expected value) $\langle (X - Y)^2 \rangle = \langle X^2 - 2XY + Y^2 \rangle = 2(\langle X^2 \rangle - \langle X \rangle^2) = 2\langle (X - \langle X \rangle)^2 \rangle$. This identity applies in our case because $\Delta_{\text{ext}}(X, Y)$ is of the form $(X - Y)^2$.

transform Eq. (D.1) into

$$(\check{\theta}_1, \dots, \check{\theta}_{N_s}) = \arg \min_{(\theta_1, \dots, \theta_{N_s})} \min_{\mathbf{a}} \sum_{\alpha=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{a}). \quad (\text{D.5})$$

From this equation, we see that the $\check{\theta}_\alpha$ result from performing a double minimization of $\sum_{\alpha=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{a})$ with respect to both the θ_α and \mathbf{a} . Now we have already stated above Eq. (D.4) that the minimizing \mathbf{a} must be the arithmetic average given by Eq. (D.2), so that we may simply write

$$\begin{aligned} \tilde{\mathbf{r}} &= \arg \min_{\mathbf{a}} \min_{(\theta_1, \dots, \theta_{N_s})} \sum_{\alpha=1}^{N_s} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{a}) \\ &= \arg \min_{\mathbf{a}} \sum_{\alpha=1}^{N_s} \min_{\theta_\alpha} \Delta_{\text{ext}}(\mathbf{R}_{\theta_\alpha} \mathbf{r}_\alpha, \mathbf{a}) \\ &= \arg \min_{\mathbf{a}} \sum_{\alpha=1}^{N_s} \Delta_{\text{int}}(\mathbf{r}_\alpha, \mathbf{a}) \\ &= \bar{\mathbf{r}}, \end{aligned} \quad (\text{D.6})$$

where the second line is obtained by noting that each term in this sum of square differences depends on only one $\mathbf{R}_{\theta_\alpha}$, and the third and fourth lines are obtained by applying the definitions Eq. (1.10) and Eq. (1.15) respectively. We conclude that the two notions of average $\bar{\mathbf{r}}$ and $\tilde{\mathbf{r}}$ are indeed the same.

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