Phase behavior and structure formation in linear multiblock copolymer solutions by Monte Carlo simulation

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The solution phase behavior of short, strictly alternating multiblock copolymers of type \((A_nB_m)_m\) was studied using lattice Monte Carlo simulations. The polymer molecules were modeled as flexible chains in a monomeric solvent selective for block type \(A\). The degree of block polymerization \(n\) and the number of diblock units per chain \(m\) were treated as variables. We show that within the regime of parameters accessible to our study, the thermodynamic phase transition type is dependent on the ratio of \(m/n\). The simulations show microscopic phase separation into roughly spherical aggregates for \(m/n\) ratios less than a critical value and first-order macroscopic precipitation otherwise. In general, increasing \(m\) at fixed \(n\), or \(n\) at fixed \(m\), promotes the tendency toward macroscopic phase precipitation. The enthalpic driving force of phase change is found to universally scale with chain length for all multiblock systems considered and is independent of the existence of a true phase transition. For aggregate forming systems at low amphiphile concentrations, multiblock chains are shown to self-assemble into intramolecular, multichain clusters. Predictions for microstructural dimensions, including critical micelle concentration, equilibrium size, shape, aggregation parameters, and density distributions, are provided. At increasing amphiphile density, interaggregate bridging is shown to result in the formation of networked structures, leading to an eventual solution-gel transition. The gel is swollen and consists of highly interconnected aggregates of approximately spherical morphology. Qualitative agreement is found between experimentally observed physical property changes and phase transitions predicted by simulations. Thus, a potential application of the simulations is the design of multiblock copolymer systems which can be optimized with regard to solution phase behavior and ultimately physical and mechanical properties. © 2008 American Institute of Physics. [DOI: 10.1063/1.2905231]

I. INTRODUCTION

Linear multiblock copolymers, like their diblock analogs, undergo microphase separation when the blocks are sufficiently incompatible. The behavior of these molecules in concentrated solutions and melts has been extensively explored experimentally,1–8 where the main applications of multiblock copolymers have been in the areas of thermoplastic elastomers, blend compatibilizers, and barrier materials. Theoretically, a number of formalisms have been applied toward the description of microphase separation or the order-disorder transition (ODT) in multiblock copolymer melts. Models based on confined chain statistics as developed by Krause,9 Meier,10,11 and Henderson and Williams12,13 and self-consistent mean-field and random phase approximation theories, as proposed by Helfand,14 Zielenksi and Spontak,15 and Ohta and Kawasaki16 have proven to be particularly useful in elucidating relationships between molecular characteristics and microstructural dimensions in the strong-segregation limit, where only fully developed microdomains are considered. In the weak-segregation regime, where microstructure domains are wide, microstructure formation near the ODT was first modeled by Leibler17 in the case of diblock copolymers by using the random phase approximation of de Gennes.18 Benoit and Hadzioannou19 extended the formalism of Leibler17 to calculate the spinodal line for microphase separation. Their work additionally addressed the microstructural characteristics of the microphase separated state to obtain estimates of microdomain periodicity as a function of the number of block pairs per molecule. Kovsalsis and Whitmore20 later employed the functional integral methods of Hong and Noolandi21 to examine the lamellar phase in the weak-segregation limit. Most recently, the mean-field theory of Leibler17 has been adapted by Mayes and Olvera de la Cruz22 to triblock copolymers and later extended by Wu et al.1 to establish an asymptotic relationship for the ODT in symmetric multiblock copolymer melts. Since then, modifications to the formalisms have been proposed to further account for block polydispersity,20,23–25 non-uniform block sequence distribution,23,26,27 and block looping.19,28–31 On the computational side, investigations of multiblock copolymer melts by Houdayer and Muller,32 Dobrynin and Erukhimovich,33 Semler and Genzer,34 and Balazs et al.35 have provided complementary insight into the ODT and resulting microdomain architectures. In general,
predictions from both theoretical and simulation models have yielded good agreement with experimental results.

Investigations of multiblock copolymer phase behavior in dilute, selective solvents have primarily focused on copolymers of low block sequences. To date, the majority of research efforts have been directed toward di- and triblock copolymers, where upon self-assembly, the formation of nearly spherical core-shell type microstructures has been predicted theoretically and demonstrated via experiments and computer simulations. Microstructures based on these architectures have been used in a number of advanced technologies ranging from drug delivery to the patterning of nanosurfaces. More recently, progress in the field of synthetic polymer chemistry has made the preparation of low molecular weight, linear multiblock copolymers with high degree of structural regularity possible. Current experimental research efforts aim to exploit the solution phase self-assembly of low molecular weight multiblock copolymers in novel applications, particularly in the field of protein-based drug delivery. Amphiphilic multiblock copolymers are thought to offer more flexibility in tailoring properties of a delivery system than comparable di- and triblock copolymers. The use of multiple short amphiphilic polymers in one polymer has been shown to prevent the rapid and preferential loss of one polymer type, allowing for modulated drug release profiles and leading to an overall enhanced stability of the microstructure. In general, the multiblock copolymer chains employed in these applications are relatively short, ranging from tetrablocks to decablocks, with individual block sizes below 2000 Da. For example, Bikram et al. have described the formation of multiblock microstructures based on copolymers of poly(ethylene glycol) conjugated to cationic poly(L-lysine) as carriers of therapeutic genes. The multiblock complexes were shown to efficiently encapsulate plasmid DNA into structures with an average particle size of approximately 200 nm. More recently, Quaglia et al. reported the preparation of micron sized protein-loaded particles based on the self-assembly of amphiphilic poly(ethylene glycol)-poly(e-caprolactone) multiblock copolymers. The authors observe significant variability in protein distribution within microparticle interiors and protein release profiles depending on the distribution of poly(ethylene glycol) blocks along the chain. These results suggest that fine control over the structural parameters of amphiphilic linear multiblocks can be employed for the rational design of microstructures for the optimized delivery of diverse therapeutic proteins.

Despite these advances, relatively little is known about the specific effect of block copolymer architecture on phase separation, micellization, and the resulting micellar properties. Experimentally, there is a large parameter space to explore, and it becomes difficult to independently consider the effects of factors such as monomer type, block size, and chain molecular weight on the observed solution phase behavior. In addition, the dilute concentrations at which phase separation has been observed in these systems further complicate experimental investigations, whereby it becomes exceedingly difficult to purely separate equilibrium effects from kinetic influences. For multiblock copolymers, the issue of equilibration becomes more pronounced relative to di- and triblock copolymers. In the regions where microstructure formation takes place, the state of a multiblock chain can become kinetically trapped in one of multiple local minima in the free energy landscape. Similarly, the predictive capabilities of theoretical models in the dilute regime are relatively limited. The complexity of macromolecule association in selective solvents precludes reliable prediction of the structures formed at thermodynamic equilibrium. Consequently, the complexity of the phase diagram, which may include regions of homogeneity, aggregation, gel formation, or precipitation, cannot be accounted fully by theoretical representations. Toward this end, researchers have employed computational methods to explore the rich phase behavior of polymers with complex architectures. Atomistic models in which the solvent is explicitly considered are often too computationally costly and are, thus, only appropriate for the exploration of single microstructure properties. In contrast, coarse-grain models which implicitly account for the solvent are more suitable for phase coexistence calculations.

In this work, we present a Monte Carlo study of the self-assembly of strictly alternating, low molecular weight multiblock amphiphiles of type $A_nB_m$ in dilute solutions, where the solvent is implicitly considered. Because they can be conveniently synthesized experimentally through polymerization methods that employ coupling of diblock chains, compositionally symmetric linear multiblock copolymers offer a simple model upon which relationships between copolymer architecture and solution phase behavior determined via simulations can be validated. In particular, we systematically explore the influence of block size and number of blocks per chain on the tendency toward microstructure formation and macroscopic phase separation.

The manuscript is arranged as follows. In Sec. II, we describe the model and methodologies employed to distinguish between macro- and microscopic phase separations and obtain estimates of critical parameters and aggregation properties. In Sec. III, we present our data and compare our results to available lattice data and to qualitative trends observed experimentally in dilute, nonionic polymer solutions. Finally, we draw some conclusions and suggest physical insights into the general characteristics of phase separation in multiblock solutions, which may be applied to the study of low molecular weight copolymers of more complex architecture.

II. MODEL AND SIMULATION METHOD

The simulation model is designed to represent a solution of a multiblock copolymer of type $A_nB_m$ in a selective solvent. Copolymer architecture is defined by two parameters; the size of the amphiphilic $A$ and $B$ blocks, designated by the subscript $n$, and the number of repeating $(A_nB_m)$ diblock units designated by the subscript $m$. In all systems, the volume fraction of $A$ and $B$ blocks in the chain is held constant and equal to 0.5.

As in previous works, polymers are represented as linear chains of connected sites on a cubic lattice in accordance with the model of Larson et al. Each monomer of the
polymer occupies a single lattice site and all unoccupied sites are considered as solvent. Links between successive segments along the chain are confined along the vectors (0,0,1), (0,1,1), and (1,1,1) and their reflections on the cubic lattice, resulting in a coordination number of 26. Attractions exist between sites along these 26 possible directions. Interactions of strength $e_{AA}$ occur between two solvophilic groups, a solvophilic group and a solvent molecule, and two solvent molecules. Interactions of strength $e_{AB}$ occur between solvophilic or solvent groups and solvophobic groups, while interactions of strength $e_{BB}$ occur between solvophobic groups. The interaction between $B-B$ groups is set to $-2$, and all other interactions are set to $0$. The total interaction between two lattice sites is calculated from pairwise summation of site-site interactions, where all sites have the same mass and interaction range. The simulation model, thus, represents a solution of $(A_n B_m)_m$ chains in a solvent poor for $B$ units and athermal for $A$ units.

We use the grand canonical Monte Carlo method with multihistogram reweighting as described in previous works. Simulations are performed on a simple cubic lattice of dimensions $L \times L \times L$ under periodic boundary conditions. The inverse temperature $\beta = 1/kT$, chemical potential $\mu$, and volume $V = L^3$ are defined per simulation run as input parameters. The temperature, energy, and chemical potential are nondimensionalized by the nearest neighbor interaction strength, while length is nondimensionalized with the lattice spacing of unit size.

Data from multiple runs are combined to obtain a global free energy function according to the methodology proposed of Ferrenberg and Swendsen. This approach is based on performing a number of simulations for a given polymer at selected temperatures and specified chemical potentials to collect particle density and energy probability histograms. Minimization of differences between the predicted and observed histograms is then used for data integration. Once convergence has been achieved, all thermodynamic properties for the system over the range of densities and energies covered by the histograms can be obtained.

Following the convention used in a previous work, the size dependence of the calculated osmotic pressures and phase envelopes for a given amphiphile are used to characterize the nature of the phase transition. In binary systems consisting of a mixture of amphiphile and solvent, where the lattice is fully occupied, the pressure calculated from simulations is equivalent to the osmotic pressure of the amphiphile in the system. For amphiphiles undergoing macroscopic phase separation, the slope of the osmotic pressure within the two-phase region is finite in a finite-size system, and the phase transition is rounded. As the system size is increased, the transition approaches a horizontal line. In addition, the apparent phase diagram is essentially independent of simulation system size away from the critical point. These attributes indicate the presence of a true first-order phase transition. By contrast, for systems undergoing micellization, the osmotic pressure behavior is essentially identical for all system sizes. The slope of the osmotic pressure curve is related to the number of independent kinetic aggregates and is, thus, expected to be finite and independent of system size for systems that form micelles. Correspondingly, there is a strong finite-size effect on the phase envelope.

For systems undergoing microscopic phase separation, or micellization, the critical micelle concentration (cmc) in a simulation can be defined as the volume fraction at which the break in osmotic pressure curve is observed. This volume fraction is indicative of the point at which the first micelle appears in the thermodynamic limit. In practice, the cmc is defined as the volume fraction at which the second derivative of the osmotic pressure curve is a maximum.

In macroscopic phase-separating systems, critical parameter estimates for vapor-liquid phase transitions are made using the mixed-field finite scaling method. According to the finite-size scaling theory, an un-normalized ordering operator combining the number of particles and energy is defined such that a nonuniversal field mixing parameter controls the strength of coupling between energy and density fluctuations near the critical point. The probability distribution of this operator is obtained by combining simulation results of a series of runs performed near the expected critical point using the multihistogram reweighting approach of Ferrenberg and Swendsen. The ordering parameter is then normalized to zero mean and unit variance. Comparison of the resulting distribution to the Ising-class limiting distribution and subsequent optimization to minimize the absolute deviations between the observed and Ising-class distribution yield an estimate of the nondimensionalized critical temperature ($T^*_c$) and chemical potential ($\mu^*_c$).

In all systems, statistical uncertainties for selected conditions were obtained as the standard deviation ($2\sigma$) of results obtained by performing independent runs at identical thermodynamic conditions but varying random number sequences.

III. RESULTS AND DISCUSSION

A. Macro-versus microphase separation

The phase transition behavior of alternating, low molecular weight multiblock copolymers of type $(A_n B_m)_m$ in a solvent selective for block $A$ is systematically investigated as a function of block degree of polymerization ($n$) and number of blocks per chain ($m$). The fraction of $A$ and $B$ monomers per molecule is held constant and equal to 0.5 in all systems studied. The interaction energy parameter is fixed such that the monomer-solvent incompatibility is invariant and is representative of a regime in which $B$ monomers are strongly attractive. The phase transition is, thus, driven by a variation in the temperature, or equivalently, the strength of the attractive potential.

The computed phase and aggregation behaviors for all systems examined in this work are summarized in Table I. Aggregate forming systems are indicated by cells in bold type, while systems undergoing first-order, macroscopic phase separation are designated by cells in nonbold type. The approach employed to distinguish between aggregation and phase separations was briefly explained in the previous section and is primarily based on the finite-size dependence of calculated osmotic pressure versus density as detailed in earlier work by Panagiotopoulos et al. In general, for multi-
blocks of equal molecular weight and overall composition, an increase in the degree of block polymerization reduces the tendency for macroscopic phase separation and favors the formation of aggregates. When the degree of block polymerization is held constant and the number of blocks in a molecule is increased, the driving force toward microphase separation is diminished. A roughly diagonal demarcation line exists between aggregate forming systems and those undergoing macroscopic precipitation. We define a correlation parameter \( \lambda = m/n \) that characterizes the architecture of a molecule of constant composition. The simulations then predict microphase separation for \( \lambda < 1 \) less than a critical value and macroscopic separation otherwise. For \((A,B )_m \) multiblock chains, the critical value of \( \lambda \) is seen to increase with the size of constituent blocks. Systems located near the demarcation lines drawn in Table I will display evidence of the size of constituent blocks. Systems located near the demarcation line will display evidence of the size of constituent blocks. Systems located near the demarcation line will display evidence of the size of constituent blocks.

<table>
<thead>
<tr>
<th>((A,B)_1)</th>
<th>((A,B)_2)</th>
<th>((A,B)_3)</th>
<th>((A,B)_4)</th>
<th>((A,B)_5)</th>
<th>((A,B)_6)</th>
<th>((A,B)_7)</th>
<th>((A,B)_8)</th>
<th>((A,B)_9)</th>
<th>((A,B)_{10})</th>
</tr>
</thead>
</table>

Exploiting the association behavior of multiblock copolymers in dilute, apolar organic solutions is limited. An example is the work by Nie et al. that studied the structure and dynamics of a polystyrene-polybutadiene (PB) pentablock copolymer (S-B-S-B-S) in heptane, a strongly selective solvent for PB and a poor solvent for PS. In dilute solutions, no micellization of the pentablock was detected. Instead, the pentablock copolymer was found to undergo macroscopic phase separation into two liquid phases. By contrast, a structurally similar triblock copolymer (S-B-S) of comparable molecular weight and PS composition experiences microphase separation to yield spherical micelles. This effect can be explained in the framework of the present work. As a first assessment, the enthalpic interaction to the interaction energies in the experimental and simulation systems can be compared. Experimentally, the Flory–Huggins interaction parameter \( \chi \) is determined by using the values of solubility parameters of PS, PB, and \( n \)-heptane \([ \delta_{PS} = 9.1, \delta_{PB} = 8.4, \delta_{h - heptane} = 7.4 \text{ (cal/cm}^3)^{1/2} \text{]} \) and the molar volume of \( n \)-heptane \((243 \times 10^{-24} \text{ cm}^3) \), yielding \( \chi_{\text{heptane,PS}} \approx 217/T \) and \( \chi_{\text{heptane,PB}} \approx 75/T \). Thus, at a temperature of 300 K, the \( \chi \) parameters represent solvent systems poor for PS and good for PB. Comparatively, the interaction set \([ e = e_{AB} -(1/2)e_{AA} -1/2e_{BB}] \) employed in the present simulation model is representative of a solvent system poor for B units \((e_{BB} = -2) \) and athermal for A units \((e_{AA} = 0, e_{AB} = 0) \). This interaction set was selected to match the previous work by Panagiotopoulos et al. to allow comparisons with diblock and triblock copolymers studied earlier. Based on the calculated Flory–Huggins interaction parameters for PS and PB in \( n \)-heptane, interaction energy values \( e_{BB} \approx -1.8, e_{AA} \approx -0.6, \) and \( e_{AB} = 0 \) would instead be required to more accurately reflect critical temperature estimates of PS homopolymer in \( n \)-heptane as well as the quality of the solvent for the PB. Experimentally, the crossover in phase transition from micelle formation to macroscopic phase separation was observed going from S-B-S triblock copolymers to S-B-S-B-S heptablock copolymers. In our simulations, this transition is best represented by \((A,B)_m \) model systems, where a similar crossover is expected to occur for approximate values of \( m \) between 2 and 3. Thus, the qualitative agreement between experimental and simulation results supports the potential application of this simple model to the study of solution phase behavior for multiblocks of more complex architecture.

B. Microscopic phase separation

The behavior of aggregate forming multiblocks is more closely examined here as a function of block size and overall chain length. In Fig. 1, the polymer volume fractions at the cme \((\phi_{\text{cmc}}) \) for \((A,B)_m \) and \((A,B)_m \) aggregate forming systems are plotted as a function of inverse temperature, \( 1/T^* \). Points from simulations are fitted by using an equation of the form

\[
\ln(\phi_{\text{cmc}}) = A + B/T^* \tag{1}
\]

where \( A \) and \( B \) are parameters. In a first-order phase change, parameter \( B \) is proportional to the enthalpy change per chain upon transition from a dilute homogeneous phase to a dense phase, assuming that solution nonidealities can be neglected. While micellization is not strictly a first-order transition, it can be seen that all data in the temperature ranges investigated are well fitted by Eq. (1) \((R^2 \approx 0.999) \). Thus, by analogy, parameter \( B \) in aggregate forming systems

![Fig. 1. Critical micelle concentration \((\phi_{\text{cmc}}) \) as a function of reciprocal temperature \((1/T^*) \) for selected aggregate forming multiblocks as indicated in legend. Points are from simulations, with estimated 2σ statistical uncertainties in measured data represented by error bars. Lines are fitted to points according to Eq. (1).](http://jcp.aip.org/jcp/figure.jsp)
onstrated, stem from excluded volume effects of loop chains entropic contributions, which as will be subsequently dem-
stration. Instead, the instability can be indirectly attributed to shown in Table I, is unlikely to result from inherent dis-
phase separated state with the addition of diblock units, as hence, the observed instability of the microscopic systems. Therefore, for copolymers of equal composition and

fall on the same line as aggregate forming

interestig that simulation data for all values as determined from Eq. parameters of macro-

and dashed line for \( (A_sB_m) \_1 \) and \( (A_sB_m) \_3 \) systems (for \( m > 1 \)).

C. Aggregation properties

Amphiphilic copolymer chains in solution adopt configura-
tions in which interactions of insoluble segments with the solvent are minimized. In amphiphilic multiblock copolymers, competition between intra- and intermolecular as-

sociations allows for a large number of possible chain topologies, in which insoluble segments can adopt loop, bridged, and dangling configurations. The fraction of chains which take on a particular configuration depends on a delicate balance of enthalpic and entropic contributions to the free energy.

In this section, equilibrium properties of aggregates formed by microphase separating multiblock chains are inv-
estigated. The aggregate size from simulations is dependent on both temperature and overall amphiphile concentration \( (\varphi_c) \). To enable comparisons across copolymers of different architectures, \( T^\ast \) is selected to be near the upper temperature limit for aggregate formation as defined in a previous work. \[ T^\ast \] The overall polymer volume fraction at \( T^\ast \) is specified, such that it is approximately twice the value of \( \varphi_c \) for the system under consideration. This ratio is chosen, such that the poly-
mer concentration is as near the cmc as is possible for the simulation system sizes studied. In analyses of the simulation data, we define an aggregate, or equivalently a cluster, as follows. We consider that two solvophobic B monomers be-
long to the same cluster if the distance between them is less than or equal to the interaction range of \( \sqrt{3} \) times the lattice spacing. Once a cluster has been defined, the number of chains comprising the cluster is calculated. Thus, the distri-
Contributions of aggregates are independently computed as a function of solvophobic monomers per aggregate \((N_B)\) and number of chains per aggregate \((N_{\text{chain}})\).

Aggregation parameters for selected microphase separating \((A_3B_3)_m\) and \((A_5B_5)_m\) multiblocks in the dilute regime \((\varphi_*/\varphi_{\text{cmc}} = 2)\) are shown in Table II. Corresponding average aggregate number distributions are illustrated in Fig. 3. As shown, the aggregate number distributions of all multiblock chain types examined exhibit a single, well-distinguished peak, signifying the formation of well-defined aggregates.

The most probable aggregation numbers, denoted as \(N_B^*\) and \(N_{\text{chain}}^*\), are defined by the peak in the Gaussian portion of the respective distribution. To ascertain the effect of diblock repeat units on microstructure properties, the simulation data are grouped into two series, such that \((A_3B_3)_1, 2, 3\) systems are collectively examined, separately from \((A_5B_5)_1, 2, 3\) systems.

<table>
<thead>
<tr>
<th>System</th>
<th>(T^*)</th>
<th>(\varphi_{\text{cmc}})</th>
<th>(\varphi_*/\varphi_{\text{cmc}})</th>
<th>(N_B^*)</th>
<th>(N_{\text{chain}}^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>((A_3B_3)_1)</td>
<td>6.6</td>
<td>0.029 (2)</td>
<td>1.9(2)</td>
<td>61(1)</td>
<td>174 (8)</td>
</tr>
<tr>
<td>((A_3B_3)_2)</td>
<td>6.6</td>
<td>0.011 (1)</td>
<td>2.1(3)</td>
<td>30(1)</td>
<td>168 (8)</td>
</tr>
<tr>
<td>((A_3B_3)_3)</td>
<td>6.8</td>
<td>0.0073(3)</td>
<td>1.8(3)</td>
<td>17(3)</td>
<td>147(10)</td>
</tr>
<tr>
<td>((A_5B_3)_1)</td>
<td>9.1</td>
<td>0.0204(1)</td>
<td>1.9(2)</td>
<td>48(3)</td>
<td>240(20)</td>
</tr>
<tr>
<td>((A_5B_3)_2)</td>
<td>9.1</td>
<td>0.0145(1)</td>
<td>1.8(1)</td>
<td>21(2)</td>
<td>195(20)</td>
</tr>
<tr>
<td>((A_5B_3)_3)</td>
<td>9.1</td>
<td>0.0086(2)</td>
<td>2.5(6)</td>
<td>13(3)</td>
<td>185(45)</td>
</tr>
</tbody>
</table>

**FIG. 3.** (Color online) Representative aggregate size distributions for \((A_3B_3)_m\) and \((A_5B_5)_m\) systems at the conditions of Table II, calculated as a function of solvophobic monomer number \(N_B\) and number of chains \(N_{\text{chain}}\). All points are from simulations.
tems. As can be seen in Table II, for chains of defined block size, self-assembly results in the formation of aggregates for which $N_{\text{chain}}^*$ decreases uniformly as the number of diblock units per chain is systematically varied from 1 to 3. This trend is confirmed for both the $(A_1B_1)_{1,2,3}$ and $(A_2B_1)_{1,2,3}$ series, where each successive addition of a diblock unit results in approximately 50% reduction in the $N_{\text{chain}}^*$ value. By contrast, calculated values of $N_{\text{chain}}^*$ are essentially unaffected by $m$. For instance, the value of $N_{\text{chain}}^*$ for $(A_2B_1)_m$ chains ranges from $147 \pm 10$ to $174 \pm 8$, while for $(A_2B_2)_m$ chains, the value of $N_{\text{chain}}^*$ ranges among $185 \pm 45$ and $240 \pm 20$, where the uncertainty represents $2\sigma$ in measured quantities for multiple runs generated at each condition. Thus, for each series, $N_{\text{chain}}^*$ values are statistically equivalent and independent of the number of diblock units per chain.

The minimum number of chains required to form an aggregate of a given multiblock chain type can be externally calculated based on the value of $N_{\text{chain}}^*$ obtained from simulations, assuming that only intrachain association occurs. For example, in the case of $(A_2B_1)_3$ aggregates, the simulation results indicate that the most probable clusters are composed of approximately $168 \pm 8$ solvophobic $B$ units, as shown in Table II, column 6. Because each $(A_2B_1)_3$ chain consists of six $B$ units, the minimum possible number of chains required to construct an aggregate of this chain type is approximately equal to $28 \pm 2\{168 \pm 8/6\}/$. This value is essentially equivalent to the value of $N_{\text{chain}}^*$ independently determined through simulations, as reported in Table II, column 5. Consequently, we can infer that at low $\phi_r$, the majority of multiblock chains comprising clusters adopt a fully looped configuration in which essentially all solvophobic units of a single molecule participate in the aggregate core. The high probability of loop formation is intuitively attributed to the entropic penalty of chain stretching that would be required for interchain association of insoluble units in solutions of low amphiphilic density. In addition, the enthalpic penalty of solvophobe-solvent interactions associated with dangling chains will limit the frequency of their occurrence.

The average number of chains per diblock micelle is limited according to geometric constraints on the radius, defined by the extended length of the insoluble segment within the micellar core. In the case of multiblock chains, the average aggregate size will be determined by contributions from both insoluble looped segments and extended chain ends within the aggregate core. For chains with a large number of diblock units, contributions from loop segments are expected to dominate. However, when the number of repeat units is low, such as for systems examined in this work, packing of stretched insoluble chain ends within the core is likely to dictate the aggregate size. Because in the core only a few extended chain ends are required to define the spherical aggregate size, the radius of a multiblock aggregate can reach that of the extended solvophobic chain end without a major free energy penalty. Therefore, for chains of specified block size, the mean radius of low molecular weight multiblock copolymer aggregates will, in essence, be determined by the radius of the equivalent diblock micelle. Simulation data in support of this statement are provided in the following section.

Equivalence in mean radii of aggregates across systems of a particular series additionally implies equality in aggregate surface areas and, by extension, aggregation numbers. However, in multiblock copolymers where chains adopt loop configurations to form aggregates, the area occupied by $A-B$ junction sites at the core-corona interface is expected to reduce the surface area available for incorporation of additional chains. The number of $A-B$ junction sites at the interface is related to the number of loops that chains adopt. If, as suggested earlier, chains adopt loop configurations in the dilute regime such that nearly all insoluble segments of a multiblock chain participate in cluster formation, then the number of $A-B$ junction sites at the interface of a cluster should be proportional to the number of $A-B$ junction points per chain. This is clearly evidenced in Table II, where for chains of defined block size, the value of $N_{\text{chain}}^*$ is shown to decrease linearly in proportion to the number of diblock units per chain, thus providing additional support of the predominance of the loop topology of multiblock chains in the dilute regime.

A lower limit on $N_{\text{chain}}^*$ is not easily defined. For the multiblock chains investigated in this work, for which the block size is relatively low, the formation of stable clusters with progressively lower $N_{\text{chain}}^*$ values is preempted by macroscopic phase separation. When the block size is increased, the crossover to macroscopic phase separation is suppressed (see Table I). Consequently, in the limit of sufficiently large block size, the formation of single chain, unimolecular aggregates is predicted by the simulations, in agreement with theoretical scaling predictions by Halperin.

Experimentally, the formation of unimolecular micelles by amphiphilic copolymers has traditionally been observed for dendrimer and graft copolymers in selective solvents. To the best of our knowledge, the formation of unimolecular micelles by linear, strictly alternating multiblock copolymers was only very recently realized. Zhou et al. have reported on the formation of unimolecular micelles by multiblock copolymers based on $N,N$-dimethylacrylamide (PDMA) and $N$-isopropylacrylamide (PNIPAM) in aqueous solutions. More interestingly, the authors demonstrate that when the number of diblock pairs per multiblock chain is fixed (a value of $\approx4$ is reported), the copolymers can self-assemble into either unimolecular micelles or multichain aggregates, depending on the lengths of the PDMA and PNIPAM blocks. These preliminary experimental data are in agreement with the simulation results of our present model and, thus, confirm the influence of multiblock architecture, in particular, block lengths, on copolymer chain self-assembly.

D. Aggregate size, shape, and density distributions

Multiblock chain molecular architecture can impose constraints that force microphase separated aggregates to adopt a number of morphologies, which cannot be predicted a priori. In this section, the geometric characterization of stable multiblock copolymer aggregates is considered. The size and morphology of aggregates are quantified by calculating the radius of gyration, where the radius of gyration tensor is defined by...
The coordinates of the center of mass of an aggregate are given by the sum of the squared radius of gyration, defined as

\[ R^2_{\text{gyr}} = \frac{1}{N} \sum_{k=1}^{N} (x_{i,k} - x_{i,cm})(x_{j,k} - x_{j,cm}), \]

where \( x_{i,k} \) and \( x_{j,k} \) are the \( i \)th and \( j \)th components of the positions of the monomer \( k \) and \( N \) is the total number of monomers in the aggregate. The coordinates of the center of mass of an aggregate are given by

\[ x_{i,cm} = \frac{1}{N} \sum_{k=1}^{N} x_{i,k}. \]

The eigenvalues of the tensor defined by Eq. (2) yield the three principal radii of gyration, ordered such that \( R_1 \leq R_2 \leq R_3 \). The average values of the ordered eigenvalues over all aggregates are computed to produce the average principal radii of gyration, denoted as \( \langle R^2_{1/3} \rangle \), \( \langle R^2_{2/3} \rangle \), and \( \langle R^2_{3/3} \rangle \). In the simulations, the micelles do not have distinct boundaries. As such, their sizes are characterized by the root mean squared radius of gyration, defined as

\[ \langle R_{\text{rms}}^2 \rangle_{\text{mean}} = \left( \langle R^2_{1/3} \rangle + \langle R^2_{2/3} \rangle + \langle R^2_{3/3} \rangle \right)^{1/2}. \]

We describe the morphology of aggregates through calculation of a shape, or asphericity factor \( \alpha_S \), as previously employed,

\[ \alpha_S = \frac{\langle (R^2_1) - \langle R^2_3 \rangle \rangle^2 + \langle (R^2_2) - \langle R^2_3 \rangle \rangle^2 + \langle (R^2_2) - \langle R^2_2 \rangle \rangle^2}{\frac{1}{2} \langle (R^2_1) + \langle R^2_2 \rangle + \langle R^2_3 \rangle \rangle^2}. \]

Values of \( \alpha_S \) can range from 0 for a perfect sphere to a maximum of 1 in the limit of a long, thin cylinder. By using the convention of Kenward and Whitmore, we designate aggregates with asphericity values \( \alpha_S \approx 0.1 \) as spherical.

Calculated mean cluster radii \( \langle R^2_{1/3} \rangle_{\text{mean}} \) for \((A_1B_1)_m\) and \((A_3B_3)_m\) systems at the conditions of Table II are reported in Fig. 4. Only the most probable aggregates, those in the vicinity of \( N^*_\text{chain} \), are considered in this analysis. In general, for chains of specified block size, the addition of diblock units yields only slight increases in radius. Alternatively, when the number of blocks per chain is fixed, \( \langle R^2_{1/3} \rangle_{\text{mean}} \) scales in proportion to the ratio of block sizes in approximate accordance to \( n^{1/3} \), consistent with previously reported\(^{6,7} \) effect of block size on the dimension of diblock copolymer micelles. Thus, as suggested in the previous section, for strictly alternating multiblock chains of equal composition and in the strong-segregation limit, the radius of microphase separated aggregates is primarily governed by the size of the constituent blocks and is relatively independent of the number of blocks per chain. Finally, asphericity values for \((A_3B_3)_m\) aggregates in the vicinity of \( N^*_\text{chain} \) are calculated according to Eq. (5). For all systems investigated, the values of \( \alpha_S \) do not exceed 0.1 and the most prevalent clusters resulting from multiblock chain association are effectively spherical.

The behavior of aggregate forming multiblocks at the limit of micro- to macroscopic phase transition is more closely examined. Multiblocks close to this boundary are expected to display evidence of approaching crossover to phase separation. As an illustration, the aggregate size distributions of \((A_1B_1)_3\) chains are studied. Despite the low amphiphile density considered in Fig. 3(a), the emergence of a second peak at higher aggregation numbers can be detected. We denote this aggregation peak by \( N^*_\text{chain} \), and note that it lies at a value of approximately 60. Principal and mean radii of gyration of \((A_1B_1)_3\) aggregates in the vicinity of \( N^*_\text{chain} \) are reported in Fig. 5(a), along with values for aggregates near \( N^*_\text{chain} \). Ratios of the characteristic lengths for clusters near \( N^*_\text{chain} \) indicate elongation of aggregates in two of the three principal directions, and an \( \alpha_S \) value of approximately 0.22 is calculated for these clusters. The transition to larger aggregates with elongated morphology is also evident in the corresponding snapshot of Fig. 5(b). Accordingly, the transition of stable microstructures to macroscopic phase precipitation is preceded by the broadening of the aggregate size distributions and the formation of clusters of higher aggregation numbers.

We additionally consider the radial density distributions \( \rho(r) \) of \( A \) and \( B \) monomers within aggregates as a function of distance \( r \) from the center of mass. As already reported, the mean radius of the most probable aggregates slightly increases as a function of the number of diblock units per chain, while at the same time, no variation in the aggregation number \( N^*_B \) is detected. When jointly considered, this implies variability in the spatial distribution of monomers within aggregates of different chain types. To better understand this effect, monomer distributions for \((A_1B_1)_m\) clusters are examined at the conditions of Table II, considering only aggregates in the vicinity of the reported \( N^*_\text{chain} \) values. Typical representations of total \( A \) and total \( B \) monomers as a function of \( r \) are shown in Fig. 6(a). In all cases, the density profiles in the aggregate cores (\( r < \approx 2.8 \)) are essentially uniform, and the cores consist almost entirely of \( B \) units surrounded by solvated \( A \) monomers. However, as the number of diblock units per chain increases, the aggregate cores become less defined. The core regions of \((A_1B_2)_3\) and \((A_3B_3)_3\) aggregates exhibit a reduction in \( B \) monomer density as well as a corresponding, nearly equivalent increase in the density of \( A \) monomers. In all cases, the solvent remains the minority component.
The distribution of monomers is alternatively examined by considering the probability that a monomer of type A or type B is located at a distance r from the center of an aggregate. This probability is proportional to the quantity \( r^2 \phi(r) \). Density distributions, plotted as a function of \( r^2 \phi(r) \), are shown in Fig. 6(b). When plotted in this manner, the overlap in the distributions of total A and B monomers in the interfacial region is more clearly discerned. The area of coincidence among the distributions is shown to increase with \( m \).

For \((A_1B_2)_3\) chains, the fraction of total A and B monomers within the area of overlap is approximately 22%, while for \((A_3B_3)_2\) and \((A_3B_3)_3\) systems, the fraction increases to approximately 31% and 36%, respectively. The greater degree of A and B monomer intermingling additionally indicates the formation of aggregates with less defined core-corona structures, larger interfacial regions, and a reduced ability to segregate incompatible monomer types. Accordingly, the demonstrated tendency toward macroscopic phase separation with block addition is attributed to the formation of microstructures, in which steric stabilization of solvent incompatible monomers is significantly diminished. The simulations, thus, suggest that for multiblock chains of low molecular weight blocks, the loss of entropy associated with looping of solvophilic segments becomes prohibitive as the number of blocks per chain is increased and, consequently, precludes the formation of stable aggregates. Finally, the ability to generate stable polymeric aggregates in which the aggregate core polarity (degree of A and B monomer overlap) can be tailored through copolymer architecture offers a highly adaptable platform for drug delivery, particularly for the delivery of peptide and protein therapeutics. The altered chemical and physical nature (i.e., porosity) of microstructure interiors has experimentally been shown to facilitate hydrophilic drug incorporation and modulate the kinetics of drug release. Nonetheless, a deeper understanding of the potential of such copolymer systems requires a careful knowledge of how molecular structure (composition, block length, and architecture) affects the overall microstructure features, influences which can be elucidated through coarse-grained simulations such as those discussed in this work.

**E. Network formation**

The ability of multiblock chains to bridge multiple insoluble segments allows for the formation of connected structures at sufficiently high concentrations. This characteristic feature has been extensively explored for...
multiblock chains in the melt and in solutions of selective solvents. In this work, the qualitative nature of multiblock network formation is examined with respect to the type of thermodynamic phase equilibrium attained in dilute solutions.

As an illustration, representative snapshots of the macroscopic phase separating \( (A_3B_3)_{10} \) system are shown in Fig. 7. The simulation temperature is selected such that it is significantly below \( T^* \), and equilibrium exists between low and high density polymer phases. Interchain bridging of collapsed solvophobic segments can clearly be seen in the low solvophilic density regimes, as illustrated by the corresponding chain distribution plot in Fig. 7(a). Alternatively, at higher \( \phi_r \), the probability of segment bridging increases and a connected network results, as shown in Fig. 7(b). Computationally, the network is characterized as a gel when nearly all the chains in a system have bridging segments, yielding a single cluster spanning the box boundaries in the \( x \), \( y \), and \( z \) directions. With periodic boundary conditions in all three directions, these bridging segments produce an infinitely large three dimensional network or gel. The chain distribution of Fig. 7(b) confirms the presence of a single, relatively monodisperse collection of chains, whose peak coincides with the average number of molecules in the simulation system. Thus, at semidilute concentrations, macroscopic phase separating multiblocks are shown to form swollen gels. Because no aggregates are present in dilute solutions of this system, gel formation results as a consequence of random association of solvophobic segments across collapsed microdomains and not as a consequence of bridging across multichain aggregate cores.

In Fig. 8, representative snapshots of the \( (A_3B_3)_{10} \) micro-structure separating multiblock are presented as a function of \( \phi_r \). At an amphiphile density of approximately 3\% [Fig. 8(a)], interconnections between solvophobic aggregate cores are clearly visible. However, most clusters remain independent and possess a relatively well-defined aggregation number, as evidenced by the peak in the corresponding chain distribution. At an intermediate density [Fig. 8(b)], highly polydisperse clusters of large aggregation numbers dominate, yet the presence of small aggregates can still be detected (indicated by arrow). Above a certain density, which is not quantitatively determined in this work, there are enough bridged segments connecting a sufficient number of aggregates to span the entire simulation system, and gelation occurs. This is signified by the presence of a single peak in the chain distribution, as shown in Fig. 8(c). Qualitative examination of aggregate structure as a function of \( \phi_r \) indicates that the elongated morphology of individual clusters at low \( \phi_r \) [Figure 8(a)] remains relatively unperturbed for the highly interconnected clusters of the gel phase [Fig. 8(c)]. Thus, the gel can be viewed as a swollen array of elongated aggregates connected by bridged chains, where the insoluble domain size is primarily determined by the characteristic scale of the microphase separated aggregate core. These results are qualitatively similar to previous studies in triblock copolymers. However, gels formed by bridging of multiblock copolymer aggregates may be better suited as viscoelastic modifiers
than comparable triblock micellar gels. The increased number of aggregate junctions possible in a multiblock chain may potentially yield a gel of higher elastic modulus and enhanced mechanical properties in contrast to materials with low number of blocks.3,69,83 Finally, the observed variability in solvophobic domain size and distribution in gels of multiblock copolymers depending on the phase transition type in the dilute regime can be exploited in the design of novel drug delivery vehicles, where release kinetics of entrapped drugs can potentially be tailored through specification of gel microstructure.

IV. CONCLUSIONS

In the present study, we have examined the dilute phase behavior of perfectly alternating, amphiphilic $\text{A}_n\text{B}_m$ type multiblock copolymers. We show that a simple lattice model of the multiblock chains can qualitatively account for experimentally observed chain-structure dependence on copolymer solution phase behavior.64,65,73 In particular, when the architecture of chains is characterized through a correlation parameter $\lambda = m/n$, we find that the phase transition behavior of dilute solutions of $(\text{A}_n\text{B}_m)_m$ depends on the value of $\lambda$. For chains of a specified value of $n$, the simulations predict microscopic phase separation below a critical $\lambda$ value and macroscopic phase precipitation otherwise. The location of the critical correlation parameter was shown to increase with the molecular weight of constituent blocks. Alternatively, for chains in which $m$ is specified, our simulations predict a reduction in the enthalpic contribution toward phase separation when the chains are subdivided into greater number of blocks. Thus, diblocks are found to phase separate much more readily than tetrablocks, which, in turn, do so more readily than hexablocks and so on. This tendency is evident in all multiblock chains examined, irrespective of the type of phase transition experienced.

Equilibrium microstructural properties were studied as a function of multiblock chain architecture and amphiphile concentration. In the dilute regime, the formation of well-defined, near spherical, multichain, core-shell type aggregates was predicted for all microphase separating multiblocks studied. Under these conditions, multiblock chains were shown to predominantly adopt loop configurations, such that nearly all insoluble segments of a single chain participate in cluster formation. When the block size is specified, the mean radius of multiblock copolymer aggregates was primarily determined by the characteristic scale of corresponding diblock micelles. As a consequence, characteristic aggregation parameters of the diblock copolymer micelle also defined the mean cluster aggregation numbers of multiblock copolymer aggregates. Calculated values of $N^*_B$ were nearly constant among clusters of multiblock chains with specified block size. Alternatively, $N^*_\text{chain}$ was shown to lin-
the simulations presented in this work is the design of rela-
to the rheological, morphological, and mechanical
often limit systematic analyses of copolymer structural ef-
ferts of the primarily unassociated chains. These distinc-
oscopic phase separating multiblock chains were formed as a
tration, a transient gel was formed, whereby all insoluble
sity and bridging was found. At a sufficiently high concen-
tration as a consequence of bridging across the insoluble
Halperin.66

The unique behavior of multiblock copolymers makes them useful in various fields as thermoplastic elastomers,86 viscoelastic modifiers,1 drug delivery nanostructures,46, 87 and blend compatibilizers.88 However, experimental limitations often limit systematic analyses of copolymer structural ef-
fects on the rheological, morphological, and mechanical properties in dilute solutions. Thus, a practical implication of the simulations presented in this work is the design of relatively low molecular weight multiblock copolymer systems which can be tailored with regard to solution phase behavior, microstructure formation, and gelation properties.

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