

HIGHLIGHT

Computer Simulation of Aqueous Block Copolymer Assemblies: Length Scales and Methods

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ABSTRACT: Atomistic, coarse-grain, and mesoscopic computer simulation methods applied recently to the study of block copolymer assemblies in solution are reviewed. At the atomic level, particle-based simulations have provided insight into specific interactions such as hydrogen bonding between polymer and water.

Coarse-grain models have given a generalized view of the conformations of polymer chains in solvents of different qualities by grouping clusters of atoms into effective interaction sites. Mesoscopic self-consistent field theory allows for the study of the phase diagram of block copolymers in water using a mean-field continuum description.

Advances in and results with these methodologies are presented along with present challenges. © 2006 Wiley Periodicals, Inc. *J Polym Sci Part B: Polym Phys* 44: 1907–1918, 2006

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INTRODUCTION

Copolymers which are composed of at least one hydrophilic and one hydrophobic block have been widely seen in experiments to self-assemble in water to yield a variety of morphologies. The two driving forces for organization are the difference in solubility of the blocks and the constraint imposed by the chemical linkage between the blocks. Polymers used thus far for the hydrophobic block(s) include inert polyethylene (PEE), polystyrene (PS) and polybutadiene (PBD), and degradable polylactic acid (PLA) and polycaprolactone (PCL), while common hydrophilic blocks are polyacrylic acid (PAA), polymethyl-oxazoline (PMOXA), and polyethylene oxide (PEO), the latter of which is widely used for biological applications. Explicit computer simulations of such polymeric systems can be a challenge because of the high molecular weights intrinsic to polymers, as well as the need for explicit water and large system sizes. Nonetheless, the challenges across various length scales (Fig. 1) are beginning to be met as highlighted here.

Classically, the relative lengths of the blocks can be described by a packing parameter defined as v/a_0l_c , where v is the volume of the hydrophobic segment, a_0 is the effective cross-sectional area of the hydrophilic group, and l_c is the chain length of the hydrophobic block normal to the interface.¹ A packing parameter less than 1/3 is characteristic of spherical micelles; a value between 1/3 and 1/2 gives cylindrical micelles; a value between 1/2 and 1 corresponds to vesicles; lamellae form at a value of 1, and inverted structures are observed at values greater than 1. In addition, other morphologies have been observed, such as tubules, Y-junctions, onions and hollow shells. The mechanisms of assembly for many of these morphologies are still

unclear and are under investigation by many groups. For example, it has been proposed that vesicles formed by diblock copolymers are thermodynamically stabilized by segregation of polydisperse chains to the inner or outer leaflet of the membrane, based on their hydrophilic-to-hydrophobic block length ratio.^{2,3} Computer simulations can help elucidate morphological determinants, including the effects of polydispersity and other variables on mechanisms of self-assembly.

The diversity of structures obtainable from aqueous block copolymer assemblies are already too numerous to elaborate, but many have inspired a focus on biological application. Crosslinked di- and triblock copolymer vesicles can be used to prepare hollow nanospheres for the controlled release of an encapsulated drug in the bloodstream.^{4,5} Channel-forming transmembrane proteins have been incorporated within triblock copolymer planar membranes⁶ and vesicles.⁷ Responsive nanocapsules can be fabricated containing these

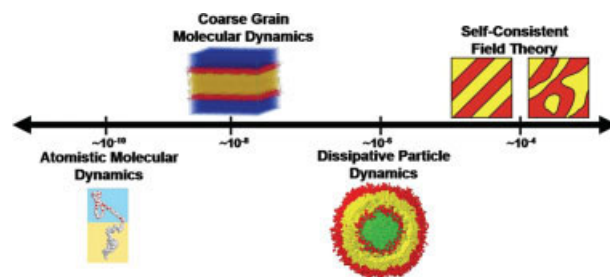


Figure 1. Length scales accessible (in meters) with different computer simulation methods for polymeric systems. The atomistic scale allows for the simulation of solvated single chains, a coarse-grain description can be used for simulation of a membrane patch, DPD permits the simulation of entire vesicles, and SCFT gives access to complex morphologies.

channels, and these have great potential for targeted drug delivery and diagnostics.⁸ In addition, experiments on the incorporation of several channel-forming peptides into diblock copolymer membranes of various thicknesses have been used to study the effects of hydrophobic mismatch on the activity of these proteins.⁹ Work on PEO-PEE vesicles has confirmed their capabilities to encapsulate proteins,¹⁰ as well as their long-term stability in the blood plasma and nontoxicity to cells. By combining encapsulation strategies with membranes decorated with transmembrane protein channels, block copolymer vesicles have been used as nanoreactors.^{7,11} These function by allowing substrates into the vesicle under reversible voltage gating of the channels, where they are acted upon by an encapsulated enzyme. Another promising direction for controlled release is to use a degradable hydrophobic block which causes destabilization of the assembly with time. Oxidation of polypropylene sulfide (PPS) changes its nature from hydrophobic to hydrophilic, resulting in the breakup of vesicles constructed from PEO-PPS-PEO triblock copolymers.^{12,13} Hydrolysis of PLA changes the preferred conformation of PEO-PLA diblock chains, making them more surfactant-like. This results in poration and hydrophobic or hydrophilic drug release from worm-like micelles or vesicles.¹⁴⁻¹⁷ Even though the experimental settings are usually complex, computer simulations can play an important role in gaining detailed insights into structures and also in offering new design strategies.

Many applications are enabled by the improved mechanical properties that block copolymers impart to the assemblies over their lipid counterparts. Experimental characterization of block copolymer assemblies includes measurements on toughness, elasticity and bending rigidity, permeability and fluidity, interfacial viscosity, as well as their dependence on variables such as block length and crosslinking. Pipette aspiration results¹⁸ showed that diblock copolymer membranes have similar area expansion moduli as lipid membranes, but their toughness (defined as the stored energy at which membrane rupture occurs) extends to $\sim 20\%$ area strain, while lipid membranes can support strains of only $\sim 5\%$. A study¹⁹ on the bending rigidity of diblock copolymer membranes reported a quadratic scaling with increasing hydrophobic thickness, with values similar to that of lipid membranes for comparable molecular weights. The shear viscosity was found to be about 500 times larger than that of lipid membranes.²⁰ The ability to increase the hydrophobic thickness makes block copolymer membranes less permeable to water than lipid membranes.¹⁰ Electroporation and other rupture techniques have allowed for studies of the dynamics of pore healing and more generally the deformation and hydrodynamic behavior of diblock copoly-

mer vesicles.²¹ FRAP studies¹⁸ of probe molecules in diblock copolymer membranes have shown a decrease in the mobility parallel to the membrane plane with increasing molecular weight. At high molecular weights, chain entanglement leads to a crossover from Rouse to reptation dynamics, strongly influencing diffusivity. Computer modeling, along with theory and experiment, can perhaps provide a unified view and a set of general rules for the behavior of segregated block copolymer systems.

This review provides a summary of some of the computer modeling work aimed at understanding block copolymer assemblies in solution. These efforts fall naturally into categories that are defined by the level of resolution used to describe the interactions between the molecules, since they provide different information about the system according to the limitations and assumptions made in each technique. Each category is briefly described in the following sections, along with a summary of published work. The second section treats work done with computer simulations at the atomistic level, the third section presents coarse-grained approaches, and the fourth section reviews work done with self-consistent field (SCFT) theory calculations. The final section concludes with a summary of accomplishments and challenges that need to be overcome to make significant advances.

ATOMISTIC LEVEL

In atomistic modeling, all the atoms in the system are explicitly represented and the interactions are usually quantified by potentials for chemical bonds, bond angles, dihedral angle torsions, electrostatics, and nonbonded (Van der Waals) interactions. The nonbonded interactions are often described using pairwise Lennard-Jones potentials, bonds and angles are described by harmonic potentials, torsions are usually represented with a truncated Fourier series, and electrostatics by Coulomb potentials. Two widely used parameter sets are CHARMM²² and Amber,²³ but these are both optimized for biological systems near 300 K and do not treat certain functional groups needed to model synthetic polymers. OPLS²⁴ is a more appropriate choice for the simulation of block copolymer systems, because it was built for modeling organic molecules.

Given the atoms and interactions, molecular dynamics (MD) involves solving Newton's equations of motion for a collection of atoms with the force obtained from the net gradient of the potentials. Monte Carlo (MC) methods involve sampling configuration space for a collection of atoms in a manner consistent with the desired ensemble (e.g., canonical, isothermal isobaric, etc.). Frenkel and Smit²⁵ and Allen and Tildesley²⁶ are standard references of choice for these techniques. For atomistic detail, MD is a more appropriate technique, since MC becomes inef-

ficient when dealing with dense multicomponent systems. Although implicit solvent can be used, nearly all atomic level studies explicitly include solvent molecules.

Given the length- and timescale limitations of atomistic simulations, very few studies have been done on block copolymer systems using atomistic MD (AMD) before the 1990s, with the systems usually consisting of a single polymer chain in implicit solvent. One of these studies was done by Duca and Hopfinger,²⁷ in which simulations were performed to look at the interactions between negatively charged copolymers in different concentrations of Ca^{2+} counterions at 300 K. The aqueous environment was incorporated through a uniform dielectric constant. The energetics of the polymer-counterion interactions and the role of chain conformational flexibility on these interactions were reported. An unusually strong binding interaction was reported between one of the copolymers studied and Ca^{2+} , for which structure-binding analysis led to the identification of a specific Ca^{2+} binding sequence and geometry that appeared responsible for the strong counterion association.

In the last few years, improvements in both hardware and software have made it possible to increase the capabilities of atomistic simulations. Although the systems sizes are still restricted to a few polymer molecules in explicit solvent, they provide insights into very specific interactions that cannot be accounted for with coarse-grain models. Longhi et al.²⁸ used AMD simulations to look at dilute aqueous solutions of a 50-unit oligomer model for the thermoresponsive polymer poly(*N*-isopropylacrylamide) at temperatures below and above its lower critical solution temperature (LCST) in water. They showed that at 310 K (above LCST), the oligomer exhibits a more compact conformation than at 300 K (below LCST), in qualitative agreement with experiments, and that it is surrounded by a smaller number of first-hydration-shell water molecules. Another AMD study investigated the association of hydrophobically end-capped polyethylene oxide urethane resin (HEUR) as a function of the number of hydrocarbons on both ends and it revealed that the association of a HEUR micelle is affected not only by hydrophobicity but also by chain flexibility.²⁹

Many computational studies have focused on the behavior of PEO because of the multiple biological applications that seem to reflect its unique solution properties in water. This is due mainly to its structural similarity with water, strong hydrogen bonding to the ether oxygen atoms, and high flexibility and mobility in aqueous solution. Anderson and Wilson³⁰ described the organization of PEO-based copolymers at the air/water interface. They used AMD trajectories to construct density profiles that could be directly compared to experimental neutron reflectivity data over a wide range of polymer surface concentrations. Previously, experimental neutron reflectivity data for such systems

could only be deduced through the fitting of structural parameters (layer composition and thickness). The simulation reflectivity data showed excellent agreement with experiments at low surface concentrations, while agreement at high concentrations was significantly better than in a previous model that neglected water.³¹ Also, as the surface concentration of the molecule was increased, the authors were able to observe a transition of the PEO block from a pancake conformation to the brush conformation. More recently, another study³² on self-transformable sulfonated PEO acrylate diblock copolymer (PEO- $\text{SO}_3\text{A/OA}$) entrapped into polysulfone membranes revealed that increasing the density of PEO chains attached to a hydrophobic surface increases the hydration of the surface by stabilizing the water structure in its vicinity.

In general, computer simulations at the atomistic level are necessary to gain insight into detailed interactions such as hydrogen bonding, polymer-solvent interactions, and specific conformational effects (e.g., *cis/trans* isomerization). However, another use for AMD simulations can be to provide intramolecular data, useful as input in the parameterization of coarse-grain models.

COARSE GRAIN

A wide variety of coarse-grain models have been developed to simulate block copolymer systems on length scales that are far larger than can be accessed using atomistic models. Coarse-grain models involve representing a group of atoms by a single sphere. In view of this simplification, the full chemical details of the molecules cannot be retained. However, effective interactions among the spheres can be chosen to mimic some key features of the real polymer chain. The representation of a collection of atoms, with considerable internal flexibility, by a single site leads to softer interaction potentials between sites which also permit large timesteps to be used. Since the number of particles is reduced by at least an order of magnitude, and since the interactions are simpler and more computationally efficient, coarse-grain models have become a popular tool in the polymer community over the last two decades. These models allow for an explicit connection between the molecular and continuum descriptions, first demonstrated perhaps by Goetz et al.³³ for mechanical properties of membranes. Even with the increase in efficiency over atomistic models, severe limitations on the sizes and timescales accessible still exist, and therefore, early studies focused on block copolymers were mostly reported for “short” chains, for example, block lengths from 2 to about 30.

Reports in the literature typically focus on AB block chains, where the A block is hydrophilic (or, more generally, “solvophilic”) while interactions between the solvent and the B block are less favorable. The two main families

of models employed have been off-lattice models and lattice models. One lattice model by Larson and coworkers^{34,35} is prototypical and uses a fully occupied simple cubic lattice in which a site interacts equally with all 26 sites that lie within one lattice spacing in each of the three directions. Sites can be oil-like or water-like, and amphiphiles are constructed by linking together a number of water-like and oil-like sites. Oil–oil and water–water contacts are equally favorable while oil–water ones are unfavorable. The interactions were defined by only one parameter χ ($\chi = \epsilon z/k_B T$, where z is the coordination number of the lattice), which established the difference in energy between the favorable contacts and the unfavorable contacts. We focus below on the off-lattice models, which are typically more versatile and realistic, although the lattice models are usually more efficient.

Many of the off-lattice coarse-grain models are similar to those adopted by Smit and coworkers^{36–38} as a variation on a model developed earlier by da Gama and coworkers.^{39,40} These models employ nonbonded potentials which consist of a Lennard-Jones potential that is truncated and shifted in energy, so that the potential U is zero at the point of truncation. Beyond this point, the conservative forces ($f = -\nabla U$) vanish. For A–A or B–B interactions, the truncation distance is chosen to be large, for example, 2.5σ , so that the site–site interactions can be attractive. For A–B interactions, the truncation distance is chosen to be at the minimum of the full Lennard-Jones potential, yielding a shifted potential that is purely repulsive.

Dissipative particle dynamics (DPD) is similar to MD in its use of coarse-grain models except that dissipative and random forces act between particles as well as the usual conservative ones. While intended to mimic the influences of neglected degrees of freedom, the dissipative and random forces also collectively serve as a thermostat. The atomistic-to-coarse grain mapping is usually similar to that in MD and MC. All of the forces employed in typical DPD simulations conserve momentum, and hydrodynamic interactions are correctly represented. Warren⁴¹ recently reviewed the technique. Many improvements have been implemented within the DPD framework in the last few years, such as modifications in the integrators to eliminate the sensitivity to timestep size⁴² and extension beyond the usual constant volume ensemble to a constant pressure ensemble.⁴³

Murat and Grest were perhaps the first group to incorporate polymer–solvent interactions by performing MD simulations using a coarse-grain model with a mapping of one monomer per site and a coupling to a heat bath.⁴⁴ Different aspects of polymer–solvent interactions were examined: polymers of different lengths in good solvent conditions grafted on a flat surface at different values of surface coverage,⁴⁵ interactions between two parallel surfaces with end-grafted polymers,⁴⁶ polymer chains grafted on cylindrical surfaces under good solvent conditions,⁴⁷ polymeric

brushes in solvents of varying qualities,⁴⁸ and properties of dendrimers under varying solvent conditions.⁴⁹ This work would later become useful in the development of self-assembly of AB copolymers.

In 1996, Semenov and coworkers published one of the first papers on self-assembly of polymeric amphiphiles.⁵⁰ In this study, the polymers were represented as chains of either 4 or 8 units (each representing statistical segments of the real polymer molecule rather than monomers). One of the end units was B-type (hydrophobic) while the rest of the molecule was A-type (hydrophilic), and the chains were immersed in a good solvent for the A monomers. At this point, the models used to describe the molecular interactions were rather simple and arbitrary, partly for computational efficiency but also because limited knowledge concerning the corresponding molecular forces was available. Trajectories were generated by using both MD and Monte-Carlo schemes. The size and shape of the micellar core was observed to depend on the radius of interaction of the B groups, r . If the value of r was comparable to the chain length, micelles of nearly spherical shape emerged, while a decrease in r induced a sharp polymorphic transition of the micellar core from the spherical shape to a disk-like (bilayer-like) shape. This result is consistent with behavior in the superstrong segregation regime. The authors provided a theoretical explanation of the simulation results⁵¹; for a fixed micelle size (aggregation number), the shape of the core is determined mainly by a balance between the interfacial energy and the free energy of the defects. If the interfacial term is dominant, then the free energy minimum should correspond to a minimum of the surface area of the micellar core, thus implying a spherical geometry of the core. Alternatively, when the energy of defects is dominant, it is the number of defects that should be minimized. Later, Khalatur and Khokhlov, coauthors with Semenov in the papers mentioned earlier, published a study on the micelle stability and thermodynamics of micelle formation in the presence of low-molecular-weight additive particles attracted to the core of the micelle.⁵² Equilibrium configurations were observed with the additive particles concentrating in the core of the micelle, in analogy with a hydrophobic drug loading into a micelle.⁵³ As predicted by theory,⁵¹ loading of the additives caused a deformation of the originally spherical micellar shape because of: (i) the usual statistical fluctuations that are characteristic of any liquid-like space-limited objects and (ii) the effect of the intracore structural defects, that is insertions of chain A groups inside the core. In terms of the thermodynamic stability of micelles, they showed that stable micellar aggregates occur only at temperatures near the condensation temperature for the pure additive particles and that incorporation of additive particles inside the micellar core increases the “critical” temperature of the core disintegration. Also, under the conditions close to the condensation

temperature of low-molecular-weight particles, the association equilibrium shifts drastically to the formation of large aggregates within the solvent-swollen core.

An MD study of diblock copolymers in the melt lamellar phase⁵⁴ reported the dependence of the parallel and perpendicular components of the diffusion coefficient on both block lengths and on the interaction between blocks. For diblocks of length $N = 40$ ($1N_e$) and 100 ($3N_e$), where N_e is the entanglement length of the homopolymer melt, the diffusion constant parallel to the interface was found to remain constant, while the perpendicular component was strongly suppressed upon increments in the interaction parameter, in agreement with theoretical predictions based on the Rouse model. For even longer chains (N_e up to 400), a strong reduction of entanglement effects was observed, but results for the diffusion coefficient were inconclusive for this chain length because of the long relaxation times required.

An MC study⁵⁵ on micelle formation of block copolymers in selective solvent sought to elucidate how geometric properties of micelles, as well as mean aggregation number $\langle n \rangle$, depend on the total chain length N when all the other variables are held fixed. Previous theoretical efforts had predicted, by assuming infinite chain length and strong segregation, that $\langle n \rangle$ increases with some power law for large N , with the exponent differing among the various theories. For N varying from 4 to 32, Binder reported a scaling of $R \propto N_B^{1/3}$ but, after comparing with various experimental works, concluded that there are several regimes where somewhat different power laws apply if N_A, N_B are both large. When N_A and N_B are small, the behavior does not seem universal; however, all studies agreed that the aggregation numbers in the micelles are fairly small, and the transition at the critical micelle concentration (cmc) is rather gradual. Comparisons to theory could not be done because of the discrepancy in the ranges of N studied.

Another study on the effects of block composition on the micellization behavior of ABA and BAB triblock copolymers in a solvent selective for block A done by Kim and Jo⁵⁶ showed formation of thermodynamically stable micelles with well-defined cmc values at all compositions. By measuring the standard enthalpy of micelle formation, the authors showed that the driving force toward micellization becomes weaker when the length of the insoluble block is decreased. Wijmans et al.⁵⁷ followed upon this result in their study of triblock copolymers in solution at concentrations well above the cmc to account for the experimentally observed density dependence of structural properties. In particular, they found that for “weakly segregating” triblock copolymers, the size of the micelles depends noticeably on the amphiphile concentration. At high volume fractions, they found that the structure of the amphiphilic system can be mapped onto that of a high density, monodisperse hard-sphere fluid, even when the micellar system itself was found to be quite polydisperse. On the

other hand, the same model failed to describe low-density systems. They concluded that it is incorrect to assume that the scattering intensity of such micellar systems can be represented by the product of a density-dependent hard-sphere structure factor and a density-independent form factor.

Panagiotopoulos et al.⁵⁸ used the Larson model to investigate the micellization *versus* phase separation behavior of diblock and triblock copolymers in solvent. It was reported that, for the cases studied, each system either micellizes or phase separates, but never both. This result, which disagrees with the experimentally observed behavior, where the same aqueous surfactant solution shows both phase separation and micellization under different conditions, was attributed to the inability of the model to properly incorporate the unusual solvation properties of water. The surfactant volume fraction at the cmc was found to increase with increasing temperature, giving positive values of the heat of micellization. For surfactant architectures close to macroscopic phase separation, the cluster size distributions were broad and extended to very large aggregation numbers, indicating the presence of elongated micellar aggregates. BAB triblock systems showed phase separation over a broader range of parameter space than that of the ABA triblock.

Another finding of Kim and Jo⁵⁶ was that high B fraction leads to the formation of micelles with cylindrical shape. This morphology was also observed and studied by Termonia⁵⁹ by using lattice MC on diblock copolymers. The sphere-to-cylinder transition was described in terms of a packing parameter that depends on the relative cross sections of the two blocks. The cross section could thus be varied either by a change in one of the block lengths or by the hydrophilic block being allowed to adopt an ordered conformation (e.g., helical). This effect was confirmed by a Brownian Dynamics²⁶ study which looked at the role of the head group size in amphiphilic self-assembly for a bead-spring model of flexible amphiphiles.⁶⁰ It was shown that the cmc increases for larger size of the hydrophilic head segment and that amphiphiles with larger heads form micelles with a very sharp cluster distribution.

Around 2002, various groups began to incorporate increasing detail in the models. Even though model parameters (interaction energy, force constant, radius of interaction, mass, volume) were still chosen in a somewhat arbitrary way, added details included explicit water^{59,61,62} and bending potentials to account for three-body interactions.⁶² More capable computers enabled also an increase in the number of particles in the systems (although chain lengths remained short), and as a consequence, other types of morphologies, apart from the spherical micelles, such as worms and vesicles, could be observed. Maiti et al.⁶² observed different morphologies on the self-assembly of supramolecular aggregates of model surfactant oligomers in an aqueous medium by using a coarse-grained model

with NPT MD simulations. They studied the effect of the degree of oligomerization x (number of hydrophobic tails) and surfactant concentration c on the nature of the self-assembly, as well as on the micelle size distribution. They reported a decrease in the cmc with increasing x . When increasing c , both two-tail and three-tail surfactant systems exhibited a transition from spherical micelles to cylindrical micelles. With further increase in c , these cylindrical micelles transformed into extremely long “worm-like” or “thread-like” micelles. In addition, at intermediate concentration, the formation of closed-loop micelles (vesicles) was observed. No differences were found in the behavior of the self-diffusion coefficients for two-tail and three-tail surfactant solutions.

By using DPD, Yamamoto et al. could capture some of the mechanisms for spontaneous vesicle formation of amphiphilic molecules in aqueous solution.⁶¹ In the DPD simulation, starting from both a randomly dispersed system and a bilayer structure of the amphiphile, spontaneous vesicle formation was observed through the intermediate state of an oblate micelle or a bilayer membrane. The mechanism consisted of fluctuations in the membrane that encapsulate water particles with eventual sealing to form a vesicle. They tracked the hydrophobic interaction energy between the amphiphile and water as a function of time and observed a decrease in this quantity as the vesicle formed. They also compared timescales for vesicle formation for single-tail and two-tail amphiphiles, finding faster kinetics for the two-tailed amphiphiles than for the single-tailed ones. The same method was also applied to study the budding and fission dynamics of two-component vesicles.⁶³ By changing the strength of the interactions between the amphiphiles forming the vesicle, it was possible to make them segregate into domains (rafts) within the membrane. These domains caused deformations in the membrane that, when large enough, caused fission of the vesicle into two or more smaller vesicles formed from either one of the amphiphile types.

In 2004, a series of papers were published from a collaboration between the experimental group of Discher and the computational group of Klein^{64–67} in which a coarse-grain MD model for polyethyleneoxide–polyethylene (PEO–PEE) was developed and applied to compute morphologies and physical properties of assemblies in water. The model was built to replicate a collection of data obtained from both experimental and atomistic computer simulation methods.⁶⁴ Each polymer coarse-grain site represents one monomer (three heavy atoms, on average), and a water site represents three molecules. The mass of each site was determined from its constituent atoms, while the interaction energies (ϵ 's) and radii of interaction (σ 's) were chosen to replicate the experimental bulk density and surface tension of the species, respectively. Also, the intramolecular structure of the polymers was incorporated by add-

ing harmonic bonds and bends for which the force constants (k_x 's and k_θ 's) and equilibrium values (x_0 's and θ_0 's) were chosen to replicate the first and second moments of the bond and angle distributions obtained from atomistic MD simulations.

The model replicated the experimentally observed phase behavior of PEO–PEE diblock copolymers in water—an initially random configuration of diblock copolymers in water self-assembled into a bilayer, cylindrical micelle, or spherical micelle, depending on the hydrophilic-to-hydrophobic block length ratio (f_{EO}) chosen for the molecules.⁶⁵ Also, simulations done on the triblock copolymer PEO–PEE–PEO in water have shown assembly into “tube”-like structures in which 38% of the molecules appear arranged in a linear configuration, spanning the membrane of the tube, while the rest of the chains acquired a hairpin configuration.⁶⁷

The model was used to study the effects of block length on different physical properties of the bilayer configuration, such as the area elastic modulus, the scaling of the hydrophobic core thickness, and the lateral chain mobility.⁶⁵ The scaling of the hydrophobic core thickness with hydrophobic block length in the bilayer configuration agreed with experimental results reported¹⁸ on bilayers in the same block length regime as the simulations. The simulation data was also used to calculate the absolute value of the bilayer's area elastic modulus and it was found to be independent of the block length; both of these results were in good agreement with the experimental view. The experimental diffusivity of the diblocks was compared with data collected from the simulations on the amount of entanglement between the two leaflets of the bilayer, suggesting a shift in diffusivity behavior from the Rouse regime (low molecular weight) to a regime dominated by entanglements.

In exploring the biological applications of diblock copolymer vesicles, Klein and Discher also published studies on the effects of adding diblock copolymers to lipid membranes⁶⁶ and on the incorporation of protein-like channels into diblock copolymer membranes.⁶⁷ In the former study, the concentration of PEO–PEE diblocks in a lipid membrane was varied from 0 to ~40 wt %, along which a configurational transition was observed for the PEO block going from a pancake-like configuration (low concentrations) to a brush-like configuration. Also, changes in the lipid area per molecule and the membrane thickness were observed as a function of concentration. In the latter study, by mimicking a membrane protein with a cylindrical pore, the effect of inclusions on PEO–PEE diblock copolymer membranes of different thicknesses was studied. The study revealed that chain flexibility, combined with hydrophobic mismatch, has two important consequences on membrane–channel interactions: (1) accommodating the protein inclusions of various thicknesses and (2) blocking water permeation of the pore. In general, the model has demonstrated that

membranes built from low-molecular-weight diblock copolymers behave more like a lipid membrane, but the experimental diblock copolymer membranes behave differently because of the significantly higher molecular weights.

More recently, the groups of Klein and Discher, in collaboration with Lipowsky's group, published a new coarse-grain model for PEO-PEE,⁶⁸ this time in the DPD framework. Because of the simpler interactions, DPD allows an increase in system size sufficient to simulate entire vesicles while still maintaining the diblock molecular weight within the experimental range. The PEO-PEE model was built, as before, using experimental surface tension and density data together with atomistic MD intramolecular structural information. Building the model required the introduction of a density-based atomistic-to-coarse-grain mapping to obtain a physically realistic description of the system. After introducing these changes to the DPD framework, the resulting DPD model for PEO-PEE gave values for the membrane area expansion modulus and the power-law scaling of the hydrophobic core thickness that were in excellent agreement with the experimental values. In addition, mechanisms of poration via osmotic swelling were explored with this model.

SELF-CONSISTENT FIELD THEORY

Given the high molecular weight of block copolymer systems, equilibration and sampling time becomes an issue, even though these systems are truly soft and morphologically malleable. An additional route has therefore been to model the polymers using SCFT. Such field theories offer the important advantage of providing simple intuitive explanations for its predictions and the speed with which numerical results can be generated. In equilibrium theory, the standard approach is to solve a variant of Gaussian chain self-consistent field (SCF) equations for a fixed geometry (e.g., spherical or lamellar). The free energy is then minimized within a mean field approximation. Predictions of the phase behavior can be made using the SCF model. These methods are limited by certain approximations which are necessary to make the problem tractable. One disadvantage of the method is that the calculations are based on equilibrium between an isolated aggregate and a homogeneous polymer-solvent mixture. Fluctuations of the individual assemblies are not considered, and interactions between aggregates are accounted for in a rather crude manner. The method is therefore less suited to study the collective behavior of systems containing many fluctuating assemblies. Moreover, defects cannot be described because of the symmetry imposed by the geometrical constraint.

Dynamic variants of SCFT combine Gaussian mean-field statistics with a coarse-grained Ginzburg-Landau model for time evolution of conserved order parameters.

The model describes collective relaxation by stochastic diffusion equations. The dynamics of the morphologies is controlled by thermodynamic forces obtained from the mean-field theory, a linear diffusion operator, and thermal noise. The method is often used for the description of the kinetics of self-assembly as well as the resulting morphologies by quenching a system with an initially homogeneous density distribution. The evolution of the mesoscale structures are obtained directly from the density field. Continued algorithmic improvements have allowed for the 3D mesoscale study of complex polymer solutions⁶⁹ and, hence, the simulation of vesicle formation.⁷⁰ Shear conditions, which are industrially important, have also been incorporated into the method.⁷¹

Evers et al. developed a version of SCFT for the adsorption of block copolymers from a multicomponent mixture.⁷² The grand canonical theory uses a lattice between two parallel plates, where each lattice site can be occupied by a polymer or a solvent bead. The equilibrium structure is determined by minimizing the free energy over the various possible lattice conformations, where a mean-field approximation is applied within each lattice layer. Equations are derived for the calculation of conformational probabilities, the segment density profiles, and the free energy. Comparisons are made between the adsorbed structure of diblock copolymers and the structure of diblocks with terminally anchored chains. Systematic differences are found, but overall the structures are similar, with the adsorbing block lying flat on the surface and the nonadsorbing block protruding far into the solution.⁷² The method has also been successfully used in colloidal applications, for example, to describe the (repulsive) interaction between two adsorbed layers of diblock copolymers.⁷³ Micelle formation can also be modeled with this theory by choosing a spherical lattice.⁷⁴

Linse and Bjorling generalized this theory by extending it to the case where the polymer segments possess internal degrees of freedom.⁷⁵ The use of internal states results in effective segment-segment interaction parameters, which are temperature and density dependent. Results obtained with this method have been carefully compared with experimental data for a variety of aqueous copolymer systems. The prominent increase in pluronic (PEO-polypropylene oxide-PEO) absorption from an aqueous solution is captured as the temperature is raised to the cloud point. For the temperature-dependent micellization of aqueous pluronic systems, qualitative agreement with experiment has been obtained for the decrease in the cmc, the increase in the mean aggregation number, and the increase in the micellar size with increasing temperature.⁷⁶ Agreement was also obtained for the dependence of the air/water interface surface tension on the triblock volume fraction,⁷⁷ and the phase behavior of three-component pluronic/dextran/water systems agrees with experiment.⁷⁸ Finally, density profiles

of PEO homopolymers at an air/water interface have been compared to neutron reflectivity measurements; the shape and extension of the chains into the water subphase agree well with the experimental data, but the predicted surface excess is too large.⁷⁷

Additional studies done by other groups with this type of model include the study by Guerin and Szeleifer on the cmc and the micellar size distribution as a function of the A and B block lengths and temperature.⁷⁹ The hydrophobic region was found to be more compact for longer hydrophobic blocks and for lower temperatures. Another study on polymer brushes dissolved in a good solvent⁸⁰ showed very good agreement with experimental results for PS but not for PEO. The deviations from theory and experiment for PEO were attributed to specific interactions between polymer and solvent. In an attempt to incorporate specificity in the molecular interactions in SCFT, Dormidontova⁸¹ introduced a modification in the free-energy expression to account for the PEO–water and water–water hydrogen-bonding interactions. The temperature and concentration dependence of the average fraction of hydrogen bonds between PEO and water were found to be in good agreement with experimental or MD simulation data. Also, comparisons were made to experimental data on the temperature behavior of the second virial coefficient and the effective interaction parameter. The decrease of the virial coefficient with temperature is caused by the balance of the opposing effects of water–PEO and water–water hydrogen bonding. The phase diagram for PEO of different molecular weights in water was calculated using experimentally reported data for the energy and entropy of association and very good quantitative agreement was achieved at reproducing the closed-loop regions of phase coexistence.

Dynamical SCFT studies have reproduced the phase behavior of concentrated aqueous pluronic systems. In agreement with experiment, the classical morphologies were all observed by varying the concentration in a small interval (50–70%): lamellar, bicontinuous, hexagonal, and micellar.⁶⁹ The self-assembly into vesicles of ABA triblock copolymers in dilute solution was also reproduced by Zhu et al.⁸² A number of complex vesicles, such as global, elongated, and necklace-like vesicles, were obtained with both experiments and SCFT calculations. Vesicle formation has also been observed from diblock copolymers in water with dynamic SCFT by the group of Doi.⁷⁰

Many SCFT studies have focused on the effects of polydispersity on various properties such as the cmc,⁸³ micellar size,^{83,84} and vesicle stability.⁸⁴ The cmc was found to decrease by several orders of magnitude while the aggregation number increased when the polydispersity of pluronic polymers in water was increased.⁸³ Also, close to the cmc, the micelles were found to predominantly form from the longest components (low cmc chains). The strong temperature dependence of the cmc and of the aggregation number

was only marginally affected by polydispersity.⁸³ When investigating the effects of polydispersity on the structure of diblock copolymer vesicles in dilute solution, it was found that larger polydispersity favors the formation of smaller vesicles.⁸⁴ This polydispersity effect was attributed to the segregation of copolymers according to their chain lengths to the inner and outer monolayers of the vesicle membrane, in good agreement with experimental results. Polydispersity was also found to affect the surface activity of triblock copolymers at the air–water interface.⁷⁷ The calculations showed that below the cmc, the longest and most surface active component dominates the distribution of chains at the interface. However, above the cmc, the long polymers self-assemble preferentially in the water subphase, depleting the solution of these components, and hence reducing the adsorbed amount of the long polymers at the interface. Although it is clear that polydispersity can affect properties of the assemblies, a study on vesicle formation from ABA triblock copolymers in dilute solution showed that polydispersity does not determine the overall morphology.⁸²

The effects of temperature on the phase behavior and dynamics of aqueous pluronic solutions have been studied using dynamic SCFT.^{85,86} Both studies reported that increasing temperature decreases the rate of phase separation and has a strong influence on the phase behavior in terms of preferred morphologies and periodicity of the assemblies.

Initial efforts toward biological applications deal with loading of a hydrophobic drug in the interior of block copolymer micelles. Dynamic SCFT has been specifically used to study the interaction of haloperidol with aqueous pluronic copolymers.⁸⁷ The drug is modeled as a water site with a different solubility parameter. The simulations, in agreement with experimental TEM data, show an increase in the core size and deformation of the micellar shape upon loading of the drug. The simulations also show a broader size distribution and a larger aggregation number for the loaded micelles.

CONCLUSIONS

Aqueous block copolymer systems have gained much interest in the scientific community in recent years because of the flexibility they offer for a multitude of applications in both the materials science and biomedical fields. As more experimental results are reported, more questions also arise with respect to the behavior of these systems. Computer simulations have helped answer some of these questions and seem poised to continue in this capacity as better computational techniques are developed and faster machines become available.

In this review, we have presented a summary of the answers that computer simulations have provided so far,

categorized by the time- and length scales accessible to each of the techniques.

At the atomistic level, MD simulations have provided considerable insight into specific interactions that depend sensitively on the chemical nature of the functional groups involved. As with other systems in which one of the components is water, the behavior of aqueous block copolymer systems will sometimes be dominated by hydrogen bonding interactions with water. Atomistic computer simulations can provide this level of detail and, additionally, provide data for the parameterization of coarse-grain models. Better force-fields for polymers, especially in a biological setting, need to be developed.

At the coarse-grain level, studies have focused on providing a generalized view of the conformations of polymer chains in solvents of different qualities. Although recent models have been constructed using experimental and AMD data, most of the models used are still generic (toy models) and need to be refined to make them more realistic in both their chemical and physical details.

At the mesoscopic level, SCFT has been able to reproduce the experimentally observed phase behavior of aqueous block copolymer systems with minimal contamination from finite size effects. This allows for the study of high concentration (e.g., bicontinuous) phases without serious problems from periodic boundary conditions, and allows for a proper account of micelles, whose size can fluctuate significantly around the mean aggregation number. It remains a challenge to properly treat hydrodynamics and to extend the method to systems in which specific correlations are important.

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