Molecular Scale Simulations of the Self–Assembly of Amphiphilic Molecules: Current State-of-the-Art and Future Directions

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Abstract

Gaining an understanding of the self–assembly of amphiphilic molecules has been a goal for experimental, theoretical and computational research in the field of soft matter for approximately a century. In the field of materials modelling, understanding the self–assembly of amphiphilic molecules at experimental conditions has proven to be a challenging problem and has led to several developments that have driven the entire field of computational materials science forward. In this review, we present the current-state-of-the-art in terms of applying all-atom and coarse–grain molecular dynamics simulations in order to study the self–assembly process and the structure that results. Additionally, we present a few of the challenges that still exist with some ideas as to future directions that may be used to overcome them.

Keywords: colloids, polymers, self–assembly, molecular dynamics, all-atom, coarse–grain, implicit solvent models.

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1 Introduction

The self–assembly of amphiphilic molecules (i. e. surfactants, block copolymers and biomolecules) play a critical role in many applications within the fields of nanotechnology, detergency, catalysis, and drug delivery [1–15].

Due to the occurrence of these self–assembly processes in nature and in the above stated industries, the desire to gain an understanding of self–assembly phenomena has been a major driving force for experimental, theoretical and computational soft matter research for nearly a century. As a result, significant progress has been made in understanding that the self–assembly process is largely driven by the solvophilic and solvophobic interactions between the amphiphilic molecules and their environment. These interactions have their origin in the chemical structure of the amphiphilic molecules, which have polar and nonpolar segments that result in there being these distinct regions of the molecules that prefer or dislike contact with the solvent. Therefore as the chemical composition of the amphiphilic molecules changes and becomes more complex, the structures that result from their self–assembly also become more complex and varied. For example, as the concentration of amphiphilic molecules in an aqueous solution increases to a value in excess of the critical micelle concentration (cmc), the structure of the self–assembled aggregate will change from micelles to bilayers to lamellar and then other more complex phases.

The structure of micelles has been the focus of a large amount of research over the last century. In addition to the use of micelles in various industrial applications, they are also present generally throughout the process that results in the formation of more complex supramolecular self–assembled structures [16]. The research done on the structure of the micelles has shown that the aggregation number in a micelle and the size and shape of the micelle are dependent on the structure [17] and concentration [17, 18] of the amphiphilic molecule which is being used as a building block. Additionally, it has been shown that the structure and shape of a micelle can change with the temperature [19, 20], and the solvent environment including the pH [21], ionic strength [21] and the presence and concentration of co-solvents [22] and co-solutes [17, 23, 24]. The structural, dynamic and thermodynamic properties of micellar systems have been studied using a number of experimental techniques including surface tension, microcalorimetry, TEM, cryoTEM, SEM, SAXS, SANS and NMR [25].

More recently computer simulations have been applied to study these systems. In this article, the current state of the art of the simulations that

generally fall within the class of classical molecular dynamics simulations is presented. We introduce the basic field in Section 2, and then look at two large subclasses of the field that have been used to study the self–assembly of amphiphilic molecules: all-atom simulations (Section 3) and coarse-grain simulations (Section 4). Then finally, we present some of the challenges that are remaining when applying these simulations to study these self–assembly processes in Section 5. There are other simulation techniques which are commonly used to study these self–assembly processes and the resulting structures which we are not covering in this review and for those we would direct you to other recent reviews that have covered them including Refs. [26–28].

2 Molecular Scale Simulations

The two most common types of simulations used to study the self–assembly of amphiphilic molecules while taking into account molecular-scale detail are molecular dynamics (MD) and Monte Carlo (MC) simulations. A complete overview of these two methods is beyond the scope of this article, but can be found in any number of textbooks including Refs. [29–32]. In general, the two different methods differ in that MD simulations are deterministic in nature while MC simulations are probabilistic. As a result, MD simulations have an inherent time that allows for time-dependent trajectories, which are produced by solving Newton's equations of motion numerically, to be studied. MC simulations do not have an inherent time scale and instead the trajectories are the result of a random sampling of the energy landscape while searching for the global minimum free energy.

In both types of simulations, the energy of the simulated systems are determined by calculating the interactions between amphiphilic and solvent molecules (and any other molecules/ions in the system) [Note: Throughout this manuscript, when we refer to the 'energy', we are making reference to the potential energy unless otherwise stated.]. In order to do so, a 'force field' is chosen and used in the simulations to determine the total energy of the system (U_{tot}):

$$U_{\mathrm{tot}} = U_{\mathrm{nb}} + U_{\mathrm{b}} \tag{1}$$

where U_{nb} represents the nonbonded terms that are used to define the van der Waals and electrostatic interactions between two molecules and U_{b} represents the bonded terms that govern the local structure of an individual molecule. While there are various functional forms used to determine the intermolecular forces, the most common forms used in simulations of self–assembly of

amphiphilic molecules result in the nonbonded term between atoms i and j being:

$$U_{\mathrm{nb}}(r_{ij}) = 4\epsilon\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{r_{ij}}. \quad (2)$$

In Equation 2, r_{ij} is the distance between atoms i and j, ϵ_{ij} and σ_{ij} are parameters obtained either from experiment or from quantum calculations that represent a characteristic energy and length scale of the interaction between atoms i and j, respectively. Also, q_i and q_j are the partial charges that have been assigned to atoms i and j, which again are determined from experimental and/or quantum calculations.

The intramolecular term is generally defined as:

$$U_{\mathrm{b}}(l, \theta, \phi) = U_{\mathrm{bond}}(l) + U_{\mathrm{angle}}(\theta) + U_{\mathrm{dihed}}(\phi) + U_{\mathrm{improp}}(\phi). \quad (3)$$

In Equation 3, U_{bond} describes the rigidity of covalent bonds formed between two atoms. U_{angle} describes the stiffness of angles that are made up of three atoms i, j, and k which are connected through two bonded pairs i, j and j, k. U_{dihed} describes the preference for a dihedral, or torsion, angle that is made up of four atoms i, j, k, and l, where the angle that is measured is that which is formed between two planes: one defined by atoms i, j, and k and one by atoms j, k, and l. Meanwhile, U_{improp} is generally used to govern the planarity of rings within the molecular structure and is a specific type of dihedral in which one of the four atoms is a central atom and is bonded to each of the three other atoms. With the use of the bond, angle, dihedral and improper terms to govern the structure of a molecule, the nonbonded energy is neglected for covalently bonded first neighbours (often referred to as 1–2 interactions, e.g. the pairs i–j, j–k, and k–l in Figure 1) and second neighbours (1–3 interactions, e.g. the pairs i–k and j–l in Figure 1). Also, the nonbonded energy is scaled for covalently bonded third neighbours (1–4 interactions, e.g. i–l in Figure 1). A cartoon representation of each of the intramolecular terms described briefly above is shown in Figure 1.

The functional forms for the intramolecular terms vary with the force field chosen, but in each term there are a couple of parameters which govern the specific interaction and the values of these parameters are again generally found from experimental or quantum simulation data. The most common families of force fields used in all-atom simulations of the self–assembly of amphiphilic molecules are GROMOS [33], OPLS [34], CHARMM [35–37], AMBER [38] and COMPASS [39]. In coarse–grain simulations, the force fields are generally less transferable than in all-atom simulations

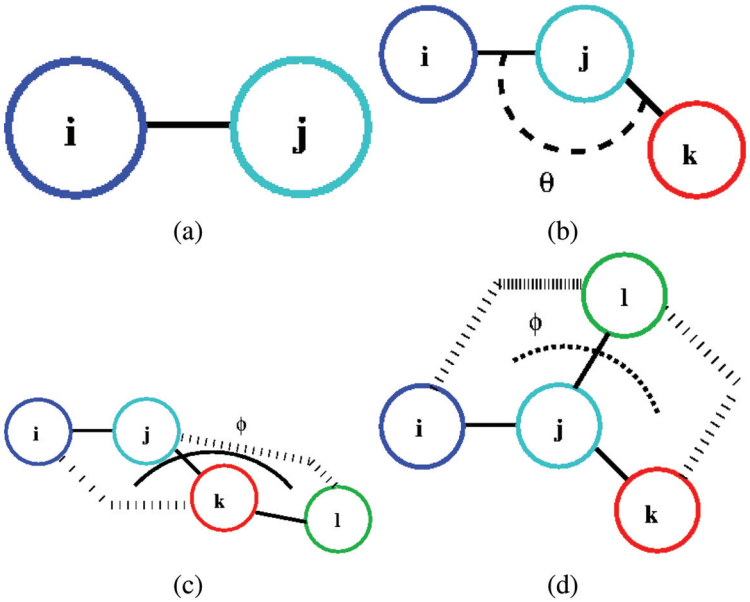


Figure 1 Cartoons of atomic configurations that are modeled by the (a) bond potential (U_{bond}), (b) angle potential (U_{angle}), (c) dihedral potential (U_{dihed}) and (d) improper potential (U_{improp}).

and therefore it is more relevant to discuss approaches to developing coarse–grain force fields than actual families of force fields. We briefly introduce these methods in Section 4. However, there are two general families of coarse–grain force fields that have been used to study the self–assembly of amphiphilic molecules: the MARTINI force field [40, 41] and the ELBA force field [42].

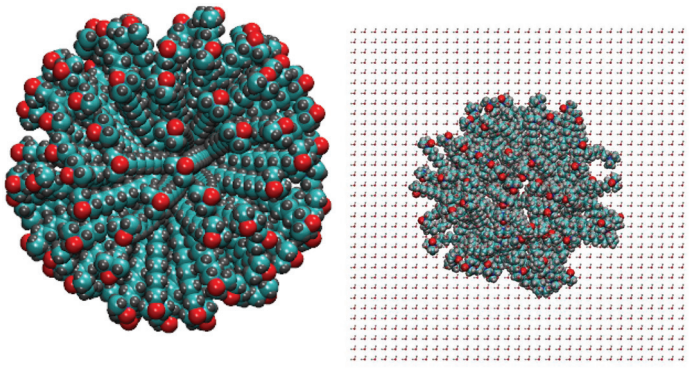
3 All-Atom Simulations

The aggregation of amphiphilic molecules is a phenomenon that is driven by favourable (solvophilic) and unfavourable (solvophobic) interactions between the various parts of the amphiphilic molecules and the solvent environment. Therefore understanding the specific nature of these interactions, and the relative strength of these interactions are key when attempting to develop design rules of building self–assembled structures for a particular application. In all-atom simulations, where each atom of the amphiphilic and solvent molecules is represented explicitly, the role that solvent plays in the self–assembly process, the distribution of the various chemical species within

the aggregates, and the interfacial properties of the aggregates are easily accessible and can be directly measured from the resultant trajectories of the molecules within the simulated system. Additionally, when using MD simulations, the time dependence of the trajectories observed within the simulations are intended to approximate the time scales in the real systems.

Simulating the self–assembly of amphiphilic molecules in solution does present several challenges for all-atom simulations. One main challenge is due to the inherent time scale in the process of self–assembly of these molecules ($\sim 10^{-6}$ s) at experimental concentrations as compared to the time step ($\sim 10^{-15}$ s) that can generally be used in all-atom simulations while still ensuring a stable simulation. This would require simulations to span 10^9 timesteps in order to observe the desired phenomena, and as of yet this length of the simulation is prohibitive for liquid systems. Another challenge presented by these systems is the number of atoms that are necessary in order to study the experimentally relevant concentration ranges ($< 10\mu$M) of the solute molecules. This results in 10^5–10^6 atoms in the simulated system, where often times the ratio of solvent to solute is approximately $10^4 : 1$, which again is pushing the current state-of-art with respect to simulation size obtainable on reasonable amounts of computational resources. These challenges have resulted in various solutions being generated within the framework of all-atom simulations, and have served as additional motivation for advancing the development of novel coarse–graining approaches (which will be discussed in Section 4).

One approach that has been taken to study the structure and interactions that govern the stabilisation of the self–assembled aggregate of surfactant molecules has been to pre-assemble the molecules such that their initial geometry is not too far away from the expected final geometry. With the aid of any one of a number of freely available software packages [43–47], a variety of initial geometries ranging from the simple to quite complex can be built, given that you know the number of molecules that you want to place within that geometry. Therefore, one must know a typical aggregation number for the system of interest from experiment. The general approach that has been taken is shown in Figure 2. First, the molecules are packed into a spherical (or some other geometry) structure, then that structure will be simulated in order to perform an energy minimisation and finally it is immersed into a simulation box with the necessary number of water molecules in order to reproduce the desired concentration. This general approach has been used in numerous all-atom molecular dynamics simulation studies of various surfactants in different solvent environments [48–66]. While these simulations do not



(a) (b)

Figure 2 Snapshots demonstrating the route to generating a pre-assembled configuration for use in an all-atom simulation: (a) the distribution of surfactant molecules within the sphere and (b) then the placement of the minimized structure of the surfactant aggregate into a simulation box of solvent molecules.

provide any information about the actual self–assembly of these aggregates, the detailed descriptions of the interactions which govern the structure of the aggregate and the resulting interfacial properties are very useful in attempting to understand how different chemistries affect these aspects of the aggregates. Additionally, some of the properties that can be calculated (i.e. size, shape and number of solvent molecules per surfactant molecule at the interface of the micelle) can be useful for experimentalists when interpreting or fitting their data as well.

Within the past 20 years, all-atom molecular dynamics simulations have been used to attempt to study the self–assembly process of surfactants by starting with an initial configuration with the surfactant molecules distributed homogenously throughout the simulation system. In order to be able to observe the self–assembly of the surfactant molecules during the course of the simulation, very high concentrations (0.1–1M) of surfactant are generally used as was done for dodecylphosphocholine [67], sodium dodecyl sulfate (SDS) [68, 69] and sodium hexyl sulfate [70]. The phase behavior and transition in shape and size of the aggregates of titratable fatty acids [71] have been studied as the pH of the solution changes using a recently developed replica-exchange constant pH MD scheme.

There have been recent developments which allow the results that are obtainable from atomistic self–assembly simulations to be extended in order to provide information about the critical size and shape at a range of surfactant

concentrations. This has allowed all-atom simulations to be used to predict the cmc. One method which was developed by Sanders *et al.* [72] and recently reviewed in [73] utilises an empirical approach that relates the total surfactant concentration and the free monomer concentration to the cmc. They used this approach to utilize data from atomistic simulations of sodium hexyl, heptyl, octyl and nonyl sulfate surfactants to determine all of the necessary quantities for their empirical approach and then predicted the cmc values, and have shown that the values found from the simulation data generally underpredict the experimental cmc. This method does capture the same chain length dependence of the cmc values as is observed experimentally and also accurately predicts the aggregation numbers for the surfactant with smaller length hydrocarbon chains.

Another approach that has been used to determine the cmc of surfactant mixtures is thermodynamic integration [30] where the free energy of micelle formation is determined from a series of MD simulations of micelles with different aggregation numbers, and this method has showed good agreement with experimental results for SDS [74]. Thermodynamic integration has also been used to study the penetration of methane and water into SDS micelles [75, 76].

Another recent method uses the COSMOmic [77] and COSMO-RS [78–82] models to obtain the free energy of partioning a solute in the interior of a micelle, based on quantum chemistry and statistical thermodynamics, from the atomistic structure of a micelle determined from MD simulations. This approach has been used to study solute partitioning within pure micelles of different surfactants [83–85], mixed micelles [86], and many other applications as reviewed in [87].

4 Coarse–Grain Simulations

While atomistic MD simulations provide a high level of detail in their representation of the simulated system, they possess several intrinsic features which are prohibitive to studying many self–assembly processes that occur on large spatial and temporal scales. Coarse–grain (CG) models address each of these issues by integrating out degrees of freedom of the system and thus providing a simplified model of its physical behavior. The majority of the current state-of-the-art CG models have their origin traced back to the 'bead–spring' coarse–grain model of polymer chains that was introduced by Kremer and Grest in 1990 [88]. Individual atoms are no longer explicitly defined, instead coarse–grain beads represent chemical groups or small volumes of

fluid that interact with each other in a similar way to the atoms in atomistic MD. CG beads within the same molecule interact with each other via bonded interactions which include bond stretching, angle bending and sometimes dihedral and improper angle terms. For non-bonded interactions, a Lennard–Jones potential is most commonly used and has the advantage of having a functional form which is relatively computationally cheap to evaluate. In instances where the non-bonded potential energy function is poorly represented by the Lennard–Jones potential, tabulated potentials are utilised to describe the pairwise interaction whilst preserving the chemical specificity of CG beads. Therefore, the same general terms, which were introduced in Section 2, are used in all-atom and CG models of the molecules, however, the functional form of the various terms may differ.

The energy landscapes of the interactions mentioned above are significantly smoother than their atomistic counterparts. This permits the use of an intergation time step Δt of $\sim 10^{-14}$ s during a CG simulation, which is an order of magnitude larger than that used in all-atom simulations. Therefore with every integration step, the simulated system evolves an order of magnitude further through time in the same amount of computer simulation time when compared to all-atom simulations. This results in increasing the time scale of simulations that can be feasibly conducted to observe the desired self–assembly phenomena. Another consequence of the smoothed energy landscapes is that the frictional forces to which atoms are subjected in all-atom simulations are simply absent in CG simulations. When two chain segments of a molecule pass by each other or get entangled in an all-atom simulation, there will be numerous local minima that must be overcome for the chains to diffuse away from one another. These frictional forces involve interactions between all of the atoms present in the interacting segments of the chains. In a CG simulation, this same process will involve only a small number of different interaction sites which have smooth interaction potentials that will result in a much shorter diffusion time. This results in a speed up of the overall dynamics, which is conducive to observing self–assembly processes within a reasonable amount of computational time. Moreover, the number of interaction sites required to represent a simulated system of a given size will typically be an order of magnitude less than the all-atom representation as a result of the mapping of atoms onto a CG bead (as described in the following subsection).

Hence the CG simulation advantages are three-fold: An integration time step is permitted which is an order of magnitude larger than the upper limit in atomistic MD, the number of interaction sites required to model a system

comprised of a given number of molecules is severely reduced and the system dynamics are sped up due to the absence of friction, which increases diffusion rates. These advantages result in CG simulations being able to access the large time and spatial scale self–assembly processes.

4.1 Mapping from Atomistic Representation to CG Representation

Irrespective of the approach to coarse–graining, the choice of molecular mapping is always the first step and is crucial to determining the success of the model. If too few atoms are grouped into a bead then the model will fail to provide a significant enough speed up compared to atomistic simulations, at the same time if too many atoms are grouped into one bead then the model will not be detailed enough to capture the chemical nature of the molecules. Routinely, an average of four heavy atoms are mapped to one coarse grained bead as this provides a good compromise between achieving a computational speed up whilst retaining chemical detail. Figure 4 shows an example mapping for an amphiphilic block-copolymer consisting of repeated units of poly-ethylene oxide (PEO) and poly-butylene oxide (PBO). Each repeated unit is mapped to one bead. The atomistic representation of this polymer has 401 atoms, the CG representation using the depicted mapping reduces to a mere 38 CG beads.

A polymer with a conveniently sized repeat unit provides a natural choice for mapping. In other cases it may not be so simple, especially when ring structures are involved. Bereau and Kremer recently proposed an automated mapping scheme [89] which finds the optimum mapping of a desired molecule into a coarse–grain representation defined by bead types from the MARTINI force field for coarse–grained molecules [41]. This code works by attempting to minimize an energy function which has a variety of contributions: (a) there is a penalty for any new CG bead introduced; (b) there is a repulsive overlap between CG beads thereby keeping them apart; (c) there is a favorable contribution from an atom being situated close to a CG bead; (d) and finally there is a penalty for any atom not being located within the radius of any CG bead. This method was tested on 22 different compounds and the mappings generated were consistent with those from the original MARTINI force field. Examples of the mapping used within MARTINI to represent dipalmitoylphosphatidylcholine (DPPC), cholesterol and benzene can be seen in Figure 3.

The process of coarse–graining produces a simulation model which is less accurate than atomistic simulations because there is significantly less

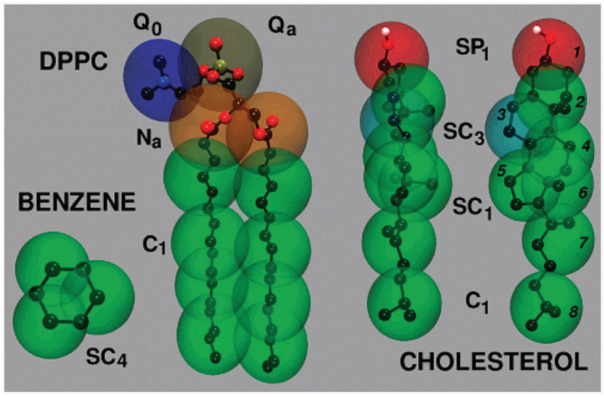


Figure 3 Mapping between the chemical structure and the coarse–grained model for dipalmitoylphosphatidylcholine (DPPC), cholesterol, and benzene [41].

detail contained within the model as a result of combining atoms into a single interaction site. Coarse–grain models are generally unable to capture all of the underlying physical behavior of molecules and therefore, one must decide which features in particular they wish to faithfully reproduce. This decision will affect the parametrisation process because the interaction potentials will be fitted such that they reproduce a set of microscopic structural features such as radial distribution functions (rdfs) which are easily obtained from atomistic molecular dynamics simulations or a set of macroscopic desired properties, e.g. macroscopic thermodynamic properties such as densities, area per lipid headgroup or free energy of solvation which may be obtained from experiment. These two approaches can largely be separated into the two categories of bottom-up (Section 4.2) and top-down (Section 4.3) coarse–graining, respectively.

4.2 Bottom-Up Approaches

Bottom-up approaches use microscopic information about the target system as an input and aim to construct CG interaction potentials which are able to reproduce reference distributions obtained from all-atom simulations. Intramolecular interactions in CG simulations are almost exclusively obtained using bottom-up approaches. For every molecule which is to be coarse–grained, an atomistic simulation of a single molecule in a simulation box full of solvent is performed as a reference. This single molecule simulation system ensures that the bonded distributions aren't affected by non-bonded

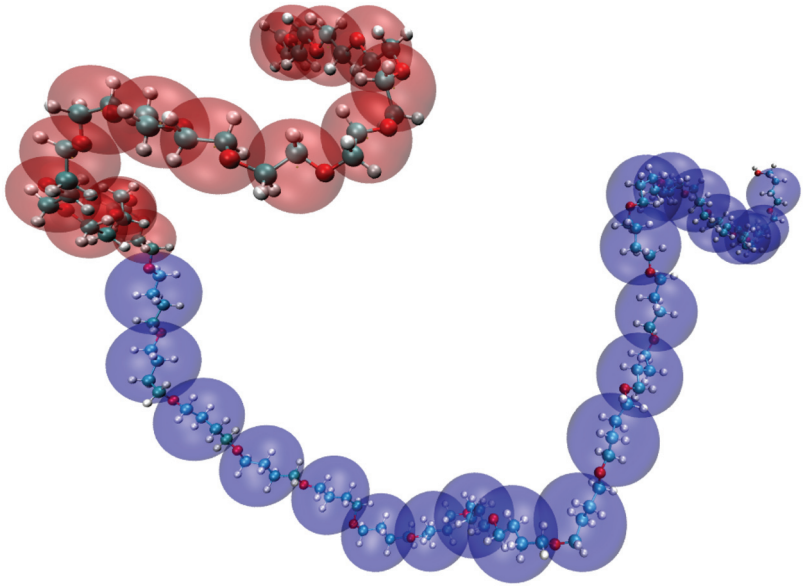


Figure 4 The mapping scheme of polymer PEO_{16}-PBO_{22}. PEO beads are shown in red whilst PBO beads are shown in blue.

interactions arising from interactions with neighbouring solute molecules. Distributions of bond lengths, bond angles and dihedral angles are constructed and then these are used to determine the intramolecular potential energy functions. Operating under the assumption that all bonded degrees of freedom are independent of one another, Gaussian functions can be fitted to each of the bond length l distributions with the functional $P(l) = A\exp\left(-k_{\mathrm{bond}}(l-l_0)^2/2\right)$, from which the values for the effective force constant k_{bond} and equilibrium bond length l_0 for each bond type are obtained, and A is an arbitrary constant. The values obtained from the fitting procedure can be used to characterise a harmonic bond stretching potential function. For bond angle potential energy terms, a similar approach can be taken. It is common to use the distribution of $\cos\theta$ as opposed to θ, such that the bond angle potential takes the functional form:

$$U_{val}(\theta) = \frac{1}{2}k_{\mathrm{angle}}(\cos\theta - \cos\theta_0)^2 \tag{4}$$

where k_{angle} and θ_0 denote the effective force constant and equilibrium angle, respectively. If the distributions are multi-modal i.e. have several maxima, then tabulated functions can be constructed by using a Boltzmann inversion approach.

Bottom-up techniques also exist to construct non-bonded coarse–grained interaction potentials. The most common include: the Inverse Monte Carlo method (IMC) [90, 91], Iterative Boltzmann Inversion (IBI) [92, 93] and Force Matching [94–97]. VOTCA [98] is a software package which focuses on analysing molecular dynamics data for the development of systematic coarse–graining techniques, which allows coarse–graining to be performed using all of the above mentioned bottom-up CG methods (IMC, IBI and FM). STOCK [99] is an online tool which is similar in purpose as VOTCA. These bottom-up CG methods have been used to study a variety of amphiphilic materials including recent studies of lipids [100] and polymers [101–104]

Mirzoev and Lyubartsev [105] used the Inverse Monte Carlo method to construct a coarse–grained force field to model the self–assembly of Dimyristoylphosphatidylcholine (DMPC) lipids into bilayers and vesicles (as shown in Figure 5. They used a rdf inversion to obtain initial guesses for the non bonded potentials between their various different CG beads, then they employed the IMC method to refine these potentials until the rdfs produced by the CG force field were in good agreement with the reference ones. They carried out reference atomistic simulations at four different lipid-water molar ratios and discovered that there is a non-negligible dependence of the effective potentials upon the concentration at which they were generated. This is clear from the differing rdfs obtained at different concentrations and also from the differing behaviour of the force fields obtained. Effective potentials computed at low lipid concentrations produced bilayers with a more ordered structure and lower area per lipid on average. Conversely, the effective potentials obtained from reference simulations at higher lipid concentrations form bilayers with more of a fluid-like structure.

This concentration dependence of the potentials observed by Mirzoev and Lyubartsev exposes a limitation in the construction of CG force fields from structural properties in that the model is only valid for the state point at which it was parameterised. Other studies have demonstrated that the potentials derived from IBI can depend on the phase of a simple lipid [106]. In other instances, potentials for polymers determined by the IBI method have been shown to depend on the chemical environment [93, 107, 108] or the temperature [109, 110] at which they were derived. One recent attempt to addressing this limitation is using the results from all-atom simulations at different states for producing the CG potentials from IBI [111]. However, the state dependence of potentials derived from bottom-up approaches causes the parametrisation process to be lengthy. Additionally, since every pairwise interaction must be separately constructed, adding new components to the

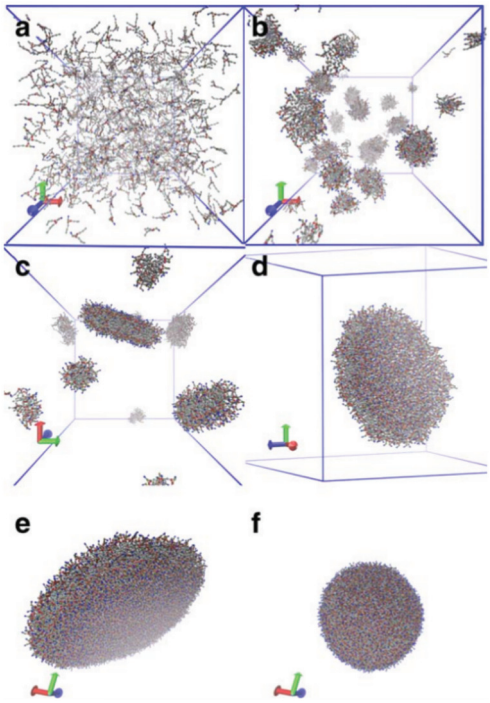


Figure 5 Self–assembly of a vesicle using a CG model with implicit solvent obtained using the Inverse Monte Carlo method by Mirzoev and Lyubartsev [105]. Figures (a)–(d) show the progression of the self–assembly from the (a) initial configuration of lipids within the simulation box to (b) the rapid formation of small semispherical particles to the (c) agglomeration of particles into disc-like structures and (d) finally after 2 μs a large ($\sim$ 1000 lipids) 'pancake' was formed. Whereas, Figures (e) and (f) show the transition of a pre-assembled large 'pancake' structure containing 4000 lipids to a stable spherical vesicle, respectively.

system requires another increasingly lengthy fitting procedure. As a result, top-down approaches have become increasingly popular for building CG models used to study self–assembly.

4.3 Top-Down Approaches

Top-down approaches to coarse–graining aim to provide a set of interaction parameters which will give rise to correct macroscopic thermodynamic properties. One top-down CG approach which has proved to be particulary popular in the biomolecular simulation community is the MARTINI force field, developed by Marrink *et al.* [41]. MARTINI has been parameterised in a systematic

way based upon the reproduction of experimental partitioning free energies between polar and apolar phases of a large number of chemical compounds. While MARTINI has been used largely for biomolecular simulations and there are currently topologies available for many lipids, surfactants, all amino acids as well as many polymers, nanoparticles and a variety of sugars.

The latest version of the force field is comprised of four main types of interaction sites: polar (P), nonpolar (N), apolar (C), and charged (Q). Each of these types are then further subcategorised which allows for a more accurate description of chemical features. Within a main type, the sub types are distinguished by either a letter denoting hydrogen bonding capability (d = donor, a = acceptor, da = both, 0 = none), or by a number indicating the degree of polarity (from 1 to 5, where 1 and 5 represent low and high polarities respectively). All molecules are constructed from these bead types.

Sanders and Panagiotopoulos [112] used the MARTINI model in addition to several other CG models to study the micellisation behaviour of the zwitterionic surfactant dipalmitoyl-phosphatidylcholine (DPC) and the non-ionic surfactant C_8E_4 over microsecond time scales. The instantaneous free surfactant amount was obtained over the simulation trajectory and the average free surfactant concentration after equilibration was taken as the cmc. They used a simple relation to relate cmc to temperature:

$$\ln(cmc) = -\Delta G/kT \tag{5}$$

where ΔG is the Gibbs free energy change of micellisation, k is Boltzmann's constant and T is the temperature. They found that for both single tailed and double tailed surfactants, the MARTINI force field underpredicts the cmc by two orders of magnitude at 298 K, most likely due to the model's approximate treatment of electrostatic interactions. They identified the lack of an orientationally dependent solvent model as a probable explanation for the failure of the simulations to match the experimentally observed nonmonotonic temperature dependence of cmc in aqueous solutions.

The representation of solvent has been an ongoing challenge for the MARTINI force field. In the original version of the force field [40], the freezing temperature of the CG water was too high and the solvent spontaneously froze during simulations as a result of a nucleation event of the solid phase, spreading rapidly through the simulation box. This problem was addressed in the second version of the force field, MARTINI 2.0, by the introduction of antifreeze particles. These have the effect of disturbing the undesirable lattice packing of the original beads used to model water due to their larger diameter. Also,

the interaction strength between antifreeze and water beads was increased to avoid phase separation of antifreeze and water particles.

Since then, a polarisable water model [113] has been introduced into the MARTINI force field. This consists of 3 interaction sites as opposed to the original one site water model. The central particle (W) is neutral and interacts with other particles in the system by means of Lennard–Jones interactions in a similar way as the single site water model did. The additional particles (WP and WM) that are used in the three-site water model are bound to the central particle and carry a positive and negative charge of $+q$ and $-q$ respectively. These additional particles interact with neighbours by electrostatic interaction alone, and lack any LJ interactions. The bond lengths of W-WP and W-WM are constrained to a distance l and interactions between WM and WP particles within the same molecule are excluded. The charged particles can therefore rotate around the W particle. The position of the charged beads determines the dipole moment of the water bead and can vary from 0 (when the charged beads share the same position in space), to $2lq$ (when the charged particles are at the maximum displacement away from each other). The freezing temperature for polarisable water was determined in the same way as for the standard MARTINI water model and was found to be $T_{\mathrm{melt}} = 282 \pm 3$ K which is closer to the correct value. This polarisable model has allowed the MARTINI force field to be applied to studying charged interfaces that may occur when studying cationic or anionic amphiphilic molecules and their self–assembly.

Meanwhile the ELBA force field [42] has been developed by Orsi and Essex to realistically represent the main electrostatic interactions within lipid systems in aqueous solutions. In doing so, they have developed a CG water molecule that is represented by a single spherical particle which has a point dipole in order to capture the well-known dipolar behaviour of the water molecule. This water model has recently been shown to be able to reproduce several fundamental properties of water as accurately as the best all-atom models [114, 115]. Additionally, Orsi and Essex have used charged particles to represent the head group (i.e. the choline group in dioleoylphos-phatidylcholine (DOPC) and distearoylphosphatidylcholine (DSPC) and the amine group in dioleoylphosphatidylethanolamine (DOPE)) and the phosphate group. The glycerol and ester groups of the lipid molecules are then modelled by a point dipole. These models are parameterised in order to reproduce experimental measurements of the area and volume per lipid, the dipole potential and the spontaneous curvature of lipid membranes. This model has been used to simulate the spontaneous formation of the lamellar phase of DOPC lipids and the inverse hexagonal phase of the DOPE

lipids as well as the interactions between DOPC and DOPE lipids in mixed bilayers [116].

4.4 Implicit Solvent Models

Certain self–assembly phenomena (i.e. large multi-lamellar vesicles, vesicle budding, and vesicle fusion) occur on such large spatial and temporal scales that using a solvated coarse–grained simulation model is still too expensive to be realisable. Additionally, when simulating the self–assembly of amphiphilic molecules at experimentally relevant concentrations with CG models, the system sizes are still large (10^4 – 10^5 CG beads) due to the large number of water beads. By removing explicit water, the degrees of freedom of these systems that are largely water would be reduced considerably and therefore enhancing the computational speed of these simulations is possible by employing implicit water models.

Travesset *et al.* developed a relatively simple but very effective implicit solvent model for use with a CG model of block copolymers that include both hydrophobic and hydrophilic blocks [117, 118]. In this simple model, the hydrophobic beads interact with each other and with the hydrophilic beads via the standard Lennard–Jones 12-6 potential (as shown in Equation 2), while the hydrophilic beads interact with one another via the repulsive part of the same equation. These models have been used to model very complex phase transitions of these polymers [117] as well as study the crystals that are formed by the micelles [118].

Another relatively generic CG model with implicit solvent was used by Deserno *et al.* for fluid bilayer membranes [119] in which individual lipid molecules are represented by one head bead and two tail beads. By means of simple pair potentials, these lipid molecules self–assembled into a fluid bilayer state without the presence of explicit solvent. This model gives rise to the expected elastic behaviour on large length scales and its physical properties such as bending stiffness and fluidity can be tuned via a single parameter, w_c, which parameterises the decay range of the interaction between tail beads.

This attractive potential between tail beads is defined as:

$$V_{attr}(r) = \begin{cases} -\epsilon, \ r < r_c \\ -\epsilon \cos^2 \frac{\pi(r-r_c)}{2w_c}, \ r_c \leq r \leq r_c + w_c \\ 0, \ r > r_c + w_c \end{cases} \tag{6}$$

The model is generic in that it lacks chemical specificity, however great insight can be provided into self–assembly processes as well as fusion, bilayer melting

and lipid raft behaviour by tuning the decay range of the attractive interactions between lipid tail beads. Figure 6 shows examples of the complex phases and phenomena that were captured by this model.

Panagiotopoulos and collaborators have developed an implicit solvent model that has been used to model both ionic and nonionic surfactants [120–123]. In their model, the head group is represented by a single coarse–grain bead which has a charge that is equivalent of the net charge of the headgroup of the surfactant. The CH_2 and CH_3 groups within the hydrocarbon chain in the tail of the surfactant are represented by united atoms, where the hydrogens and carbons in one CH_x group are represented by one bead. The solvophobic attraction of the surfactants is concentrated onto the terminal tail bead, while the rest of the hydrocarbon united atoms interact via a standard Lennard–Jones interaction. The solvophobic interaction of the terminal bead has been tuned such that it allows their model of SDS to accurately reproduce the experimentally observed cmc and micelle aggregation numbers. They have used both MD and grand-canonical MC simulations to determine the cmc and aggregation number of various other surfactants as well, while leaving the solvophobic energy parameter unchanged. They have shown that the cmc values and aggregation numbers for cationic tetra- and dodecyltrimethylammonium bromide (TTAB, DTAB) and chloride (DTAC), anionic sodium alkyl

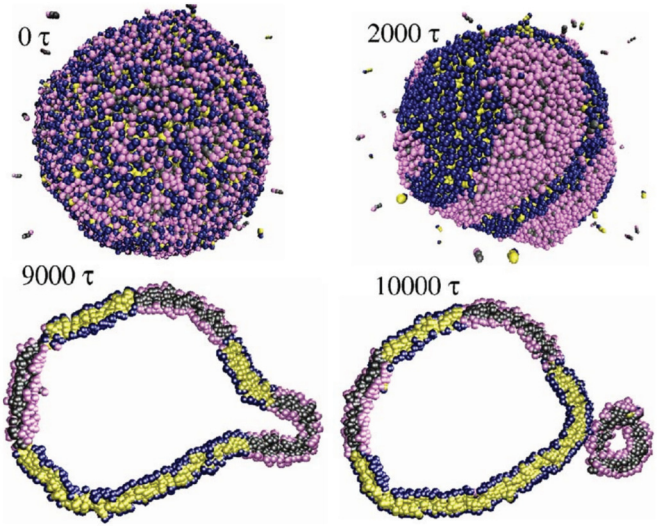


Figure 6 Images of the phase seperation and budding sequence for a mixed vesicle simulated using the generic lipid model proposed by Deserno *et al.* [119].

sulphates and non-ionic PEG surfactants are within reasonable agreement with experimentally observed values.

An implicit solvent version of the MARTINI force field ("Dry" MARTINI) has been constructed by Marrink *et al.* [124]. To account for the lack of explicit solvent, the underlying force field interaction matrix has been modified in order to reproduce numerous properties of lipid membranes including: bending modulus, bilayer thickness, area per lipid, and even coexistence of liquid ordered and disordered domains. In certain applications such as giant unilamellar vesicle formation or membrane tethering, solvent may account for up to 90% of the system [125]. With the absence of solvent, Dry MARTINI leads to a significant speedup for large systems, enabling the simulation of multicomponent membranes containing millions of lipid molecules.

Recently, Wang and Larson used the Dry MARTINI model to simulate SDS [126]. They performed a reparameterisation in order to match the structural and thermodynamic properties of SDS micelles with those from the standard MARTINI model with explicit water. This reparameterisation was achieved by replacing a shifted electrostatic cut-off with particle mesh-ewald (PME) electrostatics with a high dielectric constant ($\epsilon_r = 150$). Wang and Larson performed 12 μs simulations at two different surfactant concentrations (72.8 and 182 mM) at 300 K, which are shown in Figure 7a) and b), respectively. In the snapshots of both simulations, surfactants are assigned colours to depict which micelle they belonged to initially. The second snapshot used to depict each simulation illustrates that the system is in equilibrium because the number of micelles present and micelle size distributions remain unchanged, however surfactant exchange has occurred extensively between the micelles. Also, as is shown in Figure 7a) they observed spherical micelles at lower concentrations of SDS and then they saw the shape of the micelles transition to cylindrical as the concentration of SDS increased (as shown in Figure 7b)) and with added salt.

4.5 Backmapping from CG Model to All-Atom Representation

CG molecular simulations allow us to simulate the self–assembly of large systems and produce equilibrium structures of the aggregates. These trajectories can then be used to select various configurations from along the self–assembly process to convert (often referred to as 'backmapping') to all-atom models in order to obtain the detailed description of the interactions within the system that are not captured within CG models. There are several methods to do this which use atomistic trajectories from previous simulations to fit an atomistic

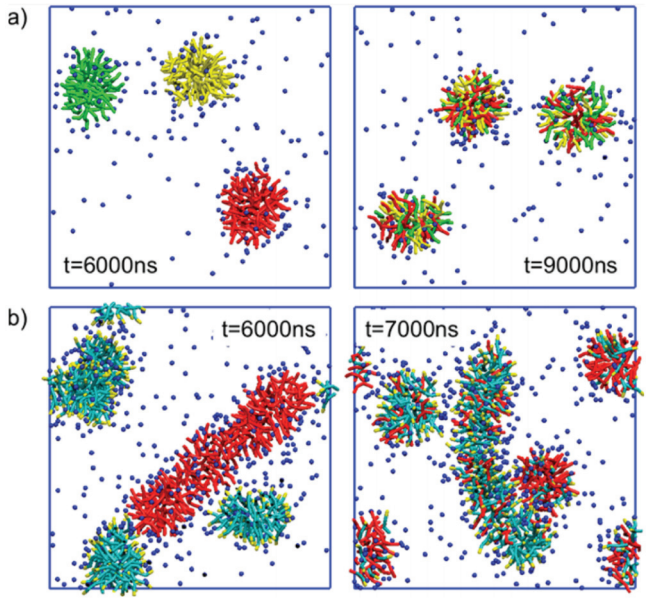


Figure 7 Snapshots of equilibrated SDS micelles in systems with SDS concentrations of (a) 72.8 and (b) 182 mM at 300 K. As can be seen, Wang and Larson observed a transition in the shape of the self–assembled micelles from spheres at lower concentrations (a) to cylinders at larger concentrations (b). [126].

structure to the conformation of the coarse–grain representation based on an energetic criteria [127–130], where the majority of these were developed for application to biological molecules but the general method could be extended to any molecule. Rzepiela *et al.* developed a method that uses a process whose most significant step is to carry out a simulated annealing simulation in which the coarse–grain and all-atom representations of the molecule are linked to one another via restraints [131].

More recently, Brocos *et al.* proposed a positional interpolation/ extrapolation method for the mapping of CG to atomistic resolution [132]. Wassenaar *et al.* created a method that started with a similar approach as was used by Brocos *et al.* and then added a new procedure for reconstructing protein backbones and also has enhanced the generation of local structure within a molecule using a set of geometrical operations [133]. These two approaches provide efficient and versatile methods that can be applied to a diverse combinations of force fields and be applied generally to the majority of molecules found in soft matter.

5 Future Challenges

In this review, we have presented the various advances that have been made in simulation methods, system construction and model development in order to further the understanding of the self–assembly processes of amphiphilic molecules. These advances have been made in order to address the inherent challenges that are presented by studying amphiphilic solutions at experimentally relevant concentrations, which include the large spatial and time scales which are necessary to observe the self–assembly process from molecules in solution to equilibrated aggregates. Additionally, the optimisation of massively parallel MD software packages (i.e. LAMMPS [134], HOOMD-Blue [135, 136], NAMD [137], Gromacs [138], AMBER [139]) to run on state-of-the-art high-performance computing clusters that contain both central processing units (CPUs) and graphics processing units (GPUs) has amplified the enhancements that have resulted from the improved simulation methods to date. However, there is still room for further improvement in a couple of areas that will allow molecular scale simulations to provide further valuable information about the self–assembly process of amphiphilic molecules.

One area in which further work is required to improve the performance of all-atom and coarse–grain simulations of self–assembly in solution is in the improvement/development of force fields that are used. In our group, we have done several studies in which we have carried out MD simulations of short chained phosphocholine (PC) and ceramide lipids in various solvents in collaboration with experimental groups who carry out neutron diffraction enhanced with isotopic substitution [140–143]. These studies have allowed us to directly compare the rdfs for the interactions of various parts of the lipid molecules with their solvent environments to the rdfs determined from the experimental data. In doing so, we have been able to identify some of the interactions which are not well represented by current classical force fields and those that are. While we have not identified the cause of those interactions which are less representative of the experimentally measured interactions, some of them are probably caused by the fact that the force fields that we used were non-polarisable. In a similar collaborative project in which we studied the interactions between proline monomers in concentrated solutions, we found a significant improvement in the agreement between the rdfs found from simulation and experiments when employing polarisable force fields [144]. There has been continual development of polarisable force fields (e. g. [145, 146]) which will allow for simulations to be carried out of more diverse systems. Additionally, further development of polarisable CG force

fields (e.g. [42]) may allow for CG simulations to be increasingly accurate as well.

As was stated previously, backmapping allows scientists to utilise CG simulations to overcome the inherent time and length scale limitations of all-atom simulations and still be able to convert to all-atom simulations at various states of the self–assembly process to get a detailed understanding of the governing interactions. However, further development of methods that would allow for simulations to be used to study the full self–assembly process using atomistic models would be the ideal situation. For example, the development of an accurate implicit solvent model that could be utilised within all-atom simulations would provide a significant enhancement in the length and time scales obtainable as the number of atoms in the simulation would reduce significantly. One approach that could be taken to develop an implicit solven model for amphiphilic molecules is to follow the same approach as has been recently employed for studying peptides in implicit water [147, 148].

Additionally, there is significant scope for developing and employing novel simulation techniques that could be used to simulate the rare-event of the micellisation of the all-atom systems. Recently, Markov state models have been utilised to study the self–assembly of coarse–grain models of viral capsids [149], and may have some promise to continue developing towards simulating more complex systems. One other method that might have significant scope for driving the field forward is that of further development and application of adaptive resolution simulation schemes in which different subregions of a simulated system is represented with different resolution (i.e all-atom for solute molecules and its solvation shells, CG models for the rest of the solvent) [150–153]. Recently, Kreis *et al.* have developed a method in which the atomistic representation is coupled to a low resolution region represented by an ideal gas, which then is the most efficient coarse–grain representation [154]. They show that water can be successfully coupled to an ideal gas and also discuss the challenges that will need to be addressed in order to apply this method more broadly. However, if reasonable solutions to these challenges are found, then one could see how only representing the solvent molecules within the solvation shell of the amphiphilic molecules during the course of the self–assembly process would significantly increase the speed of these simulations.

Therefore, the molecular-scale modelling of the self–assembly of amphiphilic molecules at experimentally relevant conditions is one of the areas that has driven and continues to drive the development of simulation models

and methods. While the progress made to date has allowed for a significant contribution to the understanding of the self–assembly process, there are plenty of challenges which still remain that molecular scale simulations would prove very useful (for one compilation of some of the challenges see Ref. [155]) that will drive further development of the methods and models used.

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