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Coarse-grained molecular modelling: a powerful approach toward simulations of polymers and biomolecules

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Abstract

On the study of physical phenomena and properties of chemical and biological systems, alongside experimental works, it is also desirable to obtain a molecular understanding of these systems using computer simulations. While experiments are used to explore the physical reality, simulations on the other hand provide unprecedented access to all positions of all particles at all times, leading to a clearer description of the system of interest. Molecular simulation of several-million-atom systems has been now tractable due to the rapid increase of computational power in recent years. Nevertheless, there remain cases where the all-atom simulations alone are not sufficient. Such cases involve modeling of polymeric and biological materials in which their physical phenomena and properties are usually determined by structure and dynamics in a wide range of time and length scales. To deal with this issue, simplified models retaining close connections to the underlying atomistic representations, so-called coarse grained (CG) models, have been introduced. This review provides a background and guide of CG molecular modeling currently used in polymer and biomolecular researches, covering definition, developing techniques, and applications of CG models. An outlook to the future of CG simulations is also presented in this review.

Keywords: coarse-grained models, polymers, biomolecules, molecular simulations

1. Introduction

On the study of physical phenomena and properties of chemical and biological systems, alongside experimental works, it is also desirable to obtain a molecular understanding of these systems using computer simulations. While experiments are used to explore the physical reality, simulations on the other hand provide unprecedented access to all positions of all particles at all times, leading to a clearer description of the system of interest. Typical simulation techniques, e.g. molecular dynamics (MD) and Monte Carlo (MC) simulations, have proven to be very useful for studying wide variety types of materials. To date, most of these simulations are "atomistic" (or "all atom"), meaning that each atom in the simulation corresponds to a single atom in the real system. The quick growth of computer power as predicted by Moore's law [1], combined with a highly efficient parallel programs allow ones to keep expanding time and length scales in their simulations. However, for large molecular systems, atomistic simulations would be computationally very expensive as it is required to calculate force for every single atom. In addition, increase in computational cost would also limit the length of phenomena that one wish to observe. Taking into account the use of high performance computers, the current largest systems that can be handled by particle-based simulations are limited to 10^7 interacting atoms and time scales up to 1 microsecond [2].

Consider soft materials such as polymers and biomolecules, their behavior and properties are usually governed by interactions and processes on a wide range of length and time scales. For example, it would take more than a hundreds of nanoseconds to see the mechanical unfolding process of muscle proteins [3], or to observe budding and fission of micelles from surfactant monolayers, a large number of surfactant molecules containing several million atomic particles, are required to put into the simulation box [4]. From these examples, despite the advent

of high-performance computers, it is not feasible to study these large and slowly relaxing systems using simulations at fully atomistic details.

To access the time and length scales relevant to material properties, coarser models retaining close connections to higher resolution atomistic description, have been introduced. These models are so called "coarse-grained (CG) models", which have been developed especially for studying events that occur on timescales of hundreds of nanoseconds to milliseconds and length scales of hundreds of nanometers to microns. Coarse-grained molecular modellings have striven to improve computational efficiency in polymer and biomolecular simulations and have attracted a significant amount of attention in recent years.

In this review we give the reader a concept of coarse-grained molecular modeling currently used in polymer and biomolecular researches. We describe what a CG model is in section 2. Then, we provide insights into a model building techniques in section 3, and give a state-of-the-art examples demonstrating successful use of CG models in section 4. In section 5 we discuss the current issues of CG model development. We finally conclude with a short outlook on future directions of the CG models.

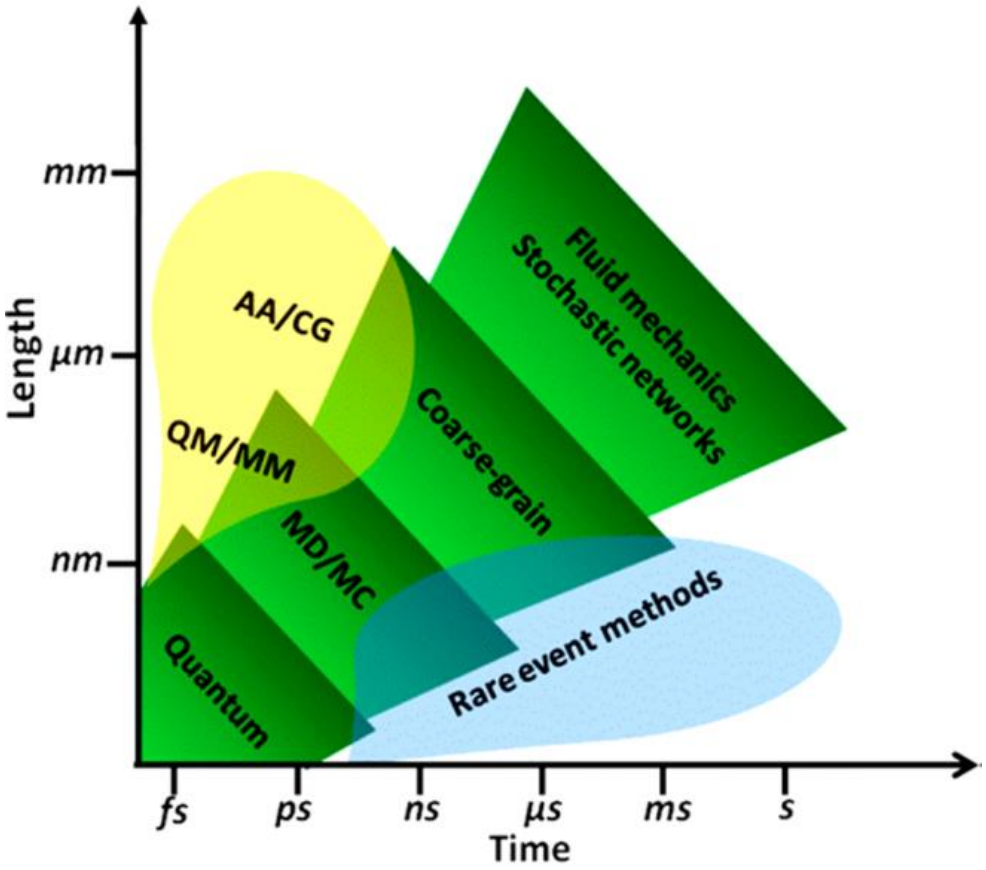

Figure 1 Schematic outline of time and length scales accessible to current simulation methods. The terms QM/MM and AA/CG represent hybrid simulations between quantum mechanics/molecular mechanics and all-atom/coarse-grained techniques, respectively.

2. What is coarse-grained model?

Computational study of materials can be done with different level of accuracy and efficiency, depending on the properties of interest and computational resource one could effort. Current computational techniques with specific time and length scales are illustrated in Figure 1. This begins with highly accurate but computational very demanding *ab initio* calculations (quantum calculations). As the timescale and/or length scale grows, the level of detail in the representation of the system is reduced respectively to all-atom and coarse-grained simulations. The simulations can be simplified further to a highly efficient but very low-detail fluid mechanics method. Bridging between these techniques, also known as "multiscale modeling", i.e. quantum/atomistic or atomistic/coarse-grained simulations can also be done. This hybrid modeling employs a various levels of treatment to achieve both efficiency and accuracy in the simulation. Advanced sampling methods, so-called rare event techniques, allow for sampling of slow processes on long time scales.

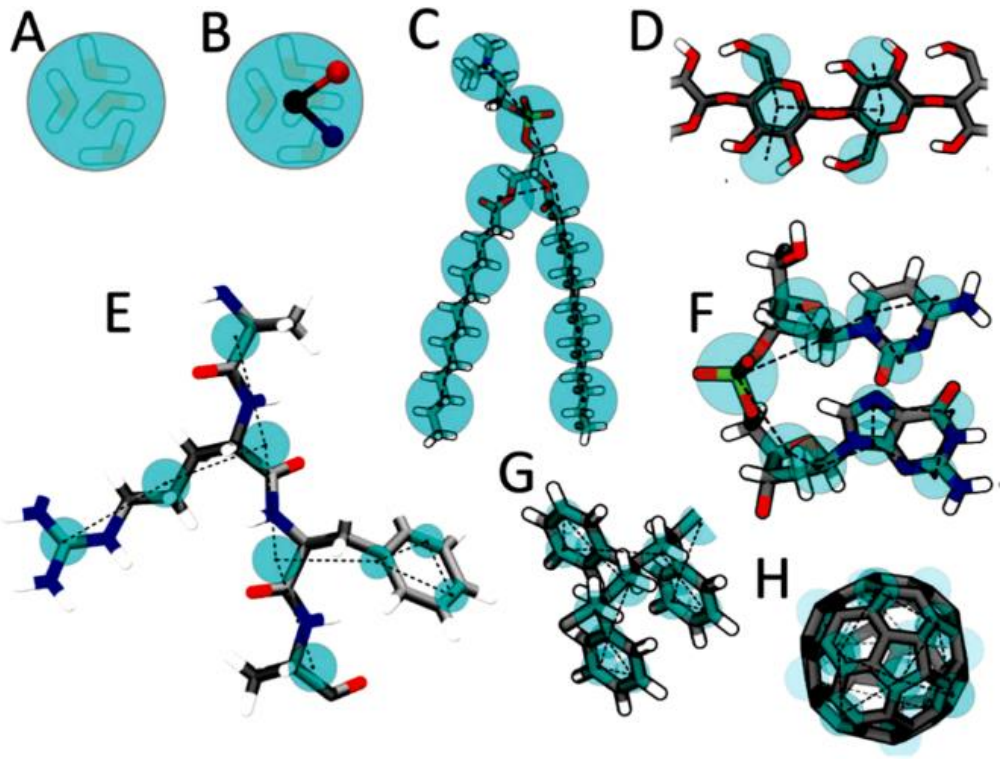

Figure 2 Examples of coarse-grained mapping schemes. (A) Standard water particle representing four water molecules. (B) Polarizable water molecule with embedded charges. (C) DMPC lipid. (D) Polysaccharide fragment. (E) Peptide. (F) DNA fragment. (G) Polystyrene fragment. (H) Fullerene molecule. CG beads are shown as cyan transparent beads overlaying the atomistic structure. Reproduced with permission from Ref [5].

The term "Coarse-grained" is generally used to refer to a simplified representation of more detailed (higher resolution) models. It is normally constructed by systematically reducing the number of degrees of freedom of the molecule under study, while keeping only key important ones, so that the phenomena and the properties being observed still retained. For example, it could be a turning of an all-atom model to an united-atom one (where hydrogens are fused with heavier atoms into single particles), or it could be a lumping of groups of atoms together into a single interaction site (bead or super atom), or it could even be a turning of an explicit solvent model to an implicit one. In most cases, the more detailed system in CG simulation is usually referred to the fully atomistic model. A method of defining a coarse-grain model by replacing groups of atoms/molecules with CG sites is referred to as "a mapping scheme". A typical example, in which an atomistic structure of a molecule is simplified to a chain of beads of a coarse-grained model, is illustrated in Figure 2. Reducing the number of degrees of freedom of the target systems brings three benefits to CG simulations: (i) lower computational cost due to a smaller number of interaction sites compared to atomistic models, (ii) larger simulation time step due to less steep interaction potentials (in the case of dynamics simulations), and (iii) quicker movement of the system through configurational space due to smaller energy barriers and/or a smoother energy landscape. It is by these factors that promote a considerable speed-up in terms of computer time in the coarse-grained simulations compared to their atomistic counterparts. As an example, in a study of adsorption behavior of polyethylene glycol at a water/air interfaces, CG model was shown to provide about 1000 times faster in the equilibration process compared to a similar sized atomistic system [6].

3. Coarse graining techniques

Coarse-graining is a method of converting important information from experiments or from higher resolution simulations into CG potentials (also known as CG force fields or CG interactions). Several coarse-graining techniques have so far been developed for deriving CG potentials, and can essentially be classified into two different approaches. The first route, known as "bottom-up" approach, is a method where CG interactions are derived from structural properties of higher resolution simulations (i.e. from atomistic- or quantum calculations). The systematic ways of doing this are inverse Monte Carlo (IMC) [7], iterative Boltzmann inversion (IBI) [8], force matching (FM) [9] and other related methods. The second route, classified as "top-down" coarse graining, is a method where CG potentials are derived from key experiment data, especially thermodynamic properties. Good examples for this approach include the CG models for biomolecules developed by Klein [4] and Marrink [10] research groups, which used several key properties, e.g. density, compressibility, interfacial tension, and free

energies, to derive interaction potentials. Comparing between the two coarse graining approaches, the bottom-up method was found to be capable of capturing more details of the molecular interaction [2]. However, since CG force fields from this route are usually extracted from atomistic simulation performed at a single thermodynamic state, it found to be less transferable when applying to different simulation conditions compared to those obtained from the top-down approach [11]. In practice, many CG models are developed by using a combination of the bottom-up and the top-down approaches [11]. To give some examples of how CG force fields are derived in detail, a structure-based coarse graining based on IBI technique and that using thermodynamics-based coarse graining, are described below.

3.1. Structure-based coarse graining using IBI technique

The iterative Boltzmann inversion (IBI) procedure, proposed by Muller-Plathe et al. [8], is perhaps the most widely used technique, owing to its conceptually straightforward, allowing any type and number of structural properties as input with relatively fast convergence. This technique has successfully been applied in optimizing effective CG potentials for many polymeric and biomolecular systems. The IBI method essentially consists of three steps, including (i) choosing how to represent the underlying atomistic models with the CG counterparts (mapping), (ii) performing reference atomistic simulation to extract a target structural function(s), and (iii) performing the iteration by repeatedly simulating the system in its CG representation and evaluating the functions of interest. In the iteration step, the coarse-grained potential is refined according to the following scheme:

$$U_{i+1}^{CG}(x) = U_i^{CG}(x) + k_B T \ln\left[\frac{P_i(x)}{P_{target}(x)}\right] \quad (1)$$

The initial guess for the CG potential (U_0^{CG}) used in Equation 1 is usually the potential of mean force (PME) extracted from the simple Boltzmann inversion of the target function. The symbols k_B and T denote Boltzmann constant and temperature at which the potential is derived, respectively. The subscript i denotes the iteration number. According to Equation 1, one can easily see that convergence is reached as soon as the probability distribution function $P(x)$ matches the target distribution function $P_{target}(x)$. Practically, $P(x)$ could represent radial distribution function (RDF), bond length- or bond angle distribution functions. Therefore, the IBI method can be used to derive both nonbonded (from the target RDF) and bonded (from the target bond length and bond angle distributions) potentials. It should be noted that the potentials obtained from this technique are in the numerical (tabulated) form.

3.2. Thermodynamic-based coarse-graining

The thermodynamic-based coarse-graining is typically incorporate a simple analytical form such as a Lennard-Jones (LJ) or the Morse potentials to describe interactions between CG beads. In this approach, the CG force fields are derived by optimizing interaction parameters such that the properties of interests match the target experimental data. A good example is a CG water model by Chiu and co-workers [12], which is developed under the requirements of reproducing the phase changes and coexistence of water. In this model, four molecules of water are grouped into one CG bead, and interactions between these CG beads are described by the Morse potential of a form

$$U(r_{ij}) = \varepsilon\left[e^{\alpha\left(1-\frac{r_{ij}}{R_0}\right)} - 2e^{\frac{1}{2}\alpha\left(1-\frac{r_{ij}}{R_0}\right)}\right] \quad (2)$$

where R_0 is the distance of the minimum energy ε, and α is a parameter that measures the curvature of the potential around R_0. r_{ij} is the distance between pair particles of interest. The smaller the value of α, the softer is the potential. The density of the system is mainly affected by the value of R_0, the cohesive energy by ε, and the compressibility by α. This potential form, therefore, allows a flexibility of tuning the parameters to fit a variety of experimental data. For example, the adjustable parameters R_0 and ε are parameterized to fit the experimental density and heat of vaporization, respectively. In the same way, the selection of the value of α is based on the agreement of the simulated vapor-liquid interfacial tension with the experimental data.

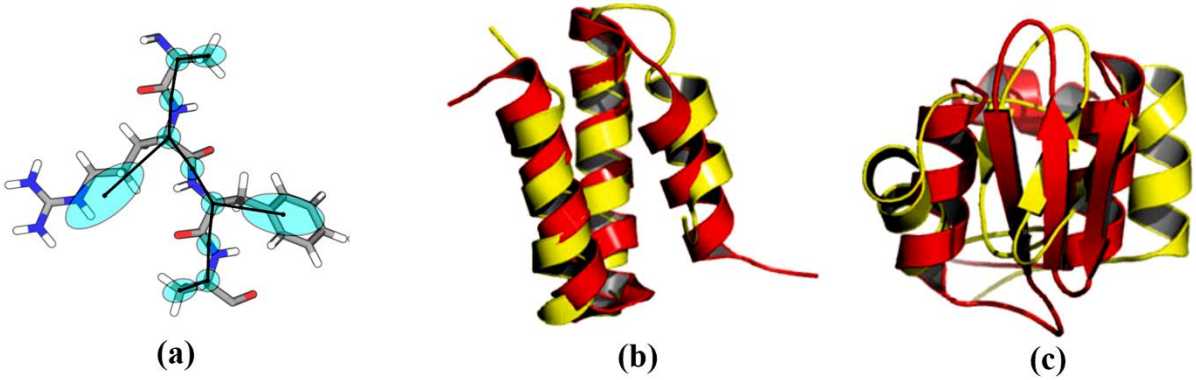

Figure 3 (a) Mapping scheme for CG protein model of an Ala-Arg-Phe-Ala peptide in the UNRES model. Reproduced with permission from Ref (2). (b) and (c) are protein folding structures for three-helix bundle (PDB:X9B) and *α/β* fold (PDB:1WHZ), as predicted using the UNRES CG FF. The native structure is colored red and the predicted structure yellow. Reproduced with permission from Ref [13].

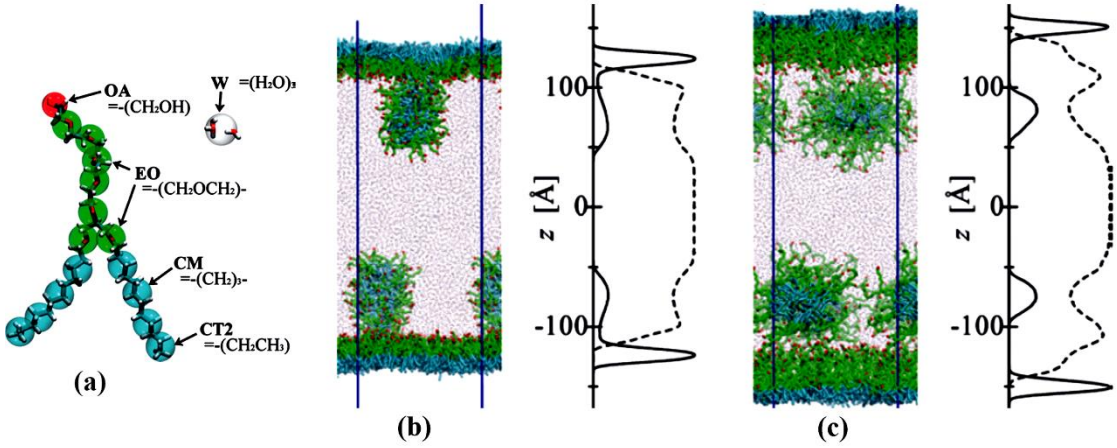

Figure 4 (a) Definition of CG polyethylene glycol lipid and water used in surfactant self-assembly study by Klein and co-workers [4]. (b) and (c) show final snapshots of LIP-5 and LIP-13 monolayer simulations with probability distribution of hydrocarbon (solid line) and water (dashed line) along the normal to the air–water interface. LIP-5 and LIP-13 denote lipids with five-and thirteen ethyleneglycol segments in the headgroup, respectively. Reproduced with permission from Ref [4]. Copyright 2008, Royal Society of Chemistry.

4. CG models and their applications

Applications of CG models range far and wide, covering various fields of material research. To demonstrate how CG models can be used to replace atomistic representations to study important behavior in biomolecular and polymeric systems, some state-of-the-art simulations presented by the pioneer researcher in this field are cherry-picked and discussed below.

4.1. Protein folding

Protein folding is the process by which an unfolded protein resumes its functional shape, known as the native state. Failure to fold into native structure can produce inactive proteins, causing adverse effects such as neurodegenerative, allergies and diseases. Atomistic protein simulations is computationally expensive, and mostly applicable for studying small protein chains. CG models are, therefore, extremely attractive in this field. One of the models that has been widely used to study protein folding as well as other processes relating to protein behavior is the UNited RESidue (UNRES) CG force field developed by Liwo et al. (14). The UNRES models generally consist of two part: (1) the back bone, consisting two CG beads of interacting peptide-group and noninteracting group and (2) the side chain which is a single ellipsoidal bead (see Figure 3a). The UNRES force field is a potential of mean forces (PMFs) extracted from *ab initio* and semi-empirical calculations as well as atomistic simulations of small molecules. So far, the UNRES model has successfully participated in many protein studies, including the structure predictions for a three-helix bundle and a α/β fold [15] and the folding pathway of single- and multichain

proteins [16]. Figure 3b and 3c show protein folding structures for three-helix bundle (PDB:X9B) and α/β fold (PDB:1WHZ), as predicted using the UNRES CG FF [13].

4.2. Surfactant self-assembly

Self-assembled surfactant behavior is among the most studied topic in biomolecular and polymer researches. Despite significant experimental and theoretical works, many aspects of surfactant self-assembly remain poorly understood on the molecular level. The long-time nature and metastability pertinent to surfactant aggregation in solution limits the applicability of all-atom simulations. In this regard, the CG model has found it place in enabling computation of self-assembled surfactants at the mesoscale regime. Klein and coworkers are one of the pioneers in surfactant model development [4] & [17]. Their recent non-ionic surfactant model (see Figure 4a) was found to be very effective at characterizing the surfactant self-assembly in the bulk solution and at air–water and oil–water interfaces [4]. The interaction potentials of the model were optimized using several key properties, including surface/interfacial tension, bulk density, compressibility and hydration/transfer free energy (for parameterizing nonbonded potentials), and distribution functions obtained by all-atom simulations (for deriving bonded potentials). A fast relaxation of the model allows observation of complex phenomena such as budding and fission of micelles from surfactant monolayers (see Figure 4b and 4c) and the repartitioning of surfactants at oil–water interface, which are difficult to detect even in experiments.

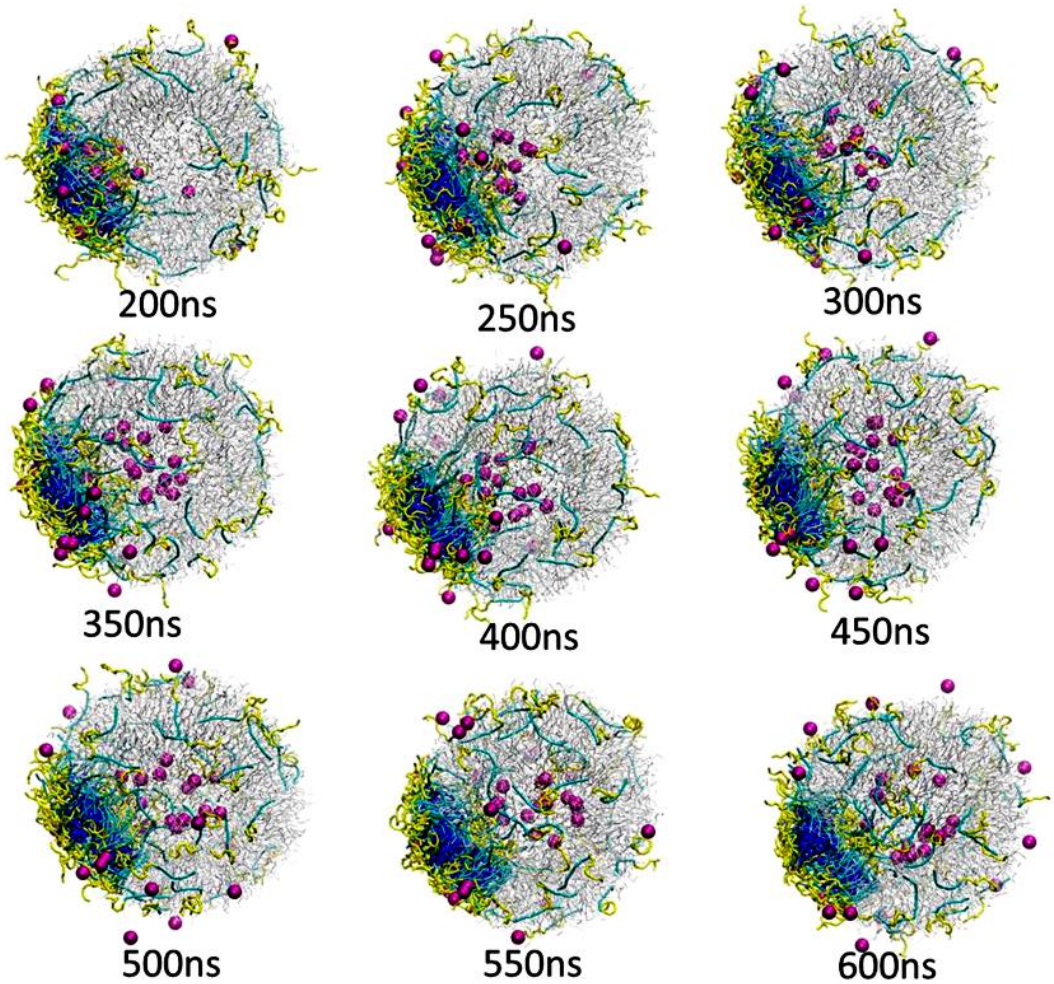

Figure 5 Snapshots of hydrophilic drugs (shown in magenta) transported across the lipid membrane and release inside the inner core of the vesicle. The lipid vesicle is represented in the transparent sticks (gray color) to demonstrate the hydrophilic content penetration inside the vesicle. Polymers are shown in yellow and blue stick representation, while water is not shown for clarity. Simulation time is labelled below each snapshot. Simulation was performed using the CG Martini force field [18]. Reproduced with permission from Ref [18]. Copyright 2013, American Chemical Society.

4.3. Drug delivery systems

Drug delivery systems are technologies for delivery and/or controlled release of therapeutic agents to the targeted location. One of the problems triggering the need of this technology is that bare drug molecules can hardly cross the complex cell membrane to their target. Therefore, design of delivery vesicles that help drug molecules to cross the cell membrane is crucial. Despite numerous experimental studies in this area, a deeper understanding of delivery processes using simulation studies is equally important. Such delivery mechanisms, however, take place at very large length and time scales, and therefore, restricted the use of high resolution simulations. CG simulations, particularly those using the Martini force field, are unique for studying drug delivery [19] & [20]. The Martini force field is one of the most widely used CG force fields in biomolecular simulations. Current Martini model comprises four main types of interaction sites: polar, non-polar, apolar, and charged, which were derived from partitioning free energies between polar and apolar phases of a large number of chemical compounds. Recently, Srinivas and co-workers [18] have employed the Martini force field to study polymeric micelle assisted hydrophilic drug transportation across lipid membrane. Such complex phenomena, including transportation of polymeric micelle across a lipid membrane and releasing of hydrophilic drugs inside the lipid vesicle, have been captured by their CG simulations (see Figure 5). Insights from this study could also help experimentalists to design better delivery vesicles, especially for hydrophilic drug molecules.

4.4. Proton transport in fuel cell membranes

Polymer electrolyte membrane (PEM) fuel cells are energy conversion devices that can deliver high power density with minimal pollution compared to fossil fuels. Decades of research have been invested into understanding the morphology of PEM and its impact on the proton conduction mechanism, the key event that determine the membrane efficiency. Beside experimental studies, simulation efforts have been made to understand the relationship between membrane nanostructure and the proton transport. Such structural information can be learned from atomistic simulations. However, to attain realistic membrane structures which allow for accurate predictions of proton conductivity, the CG representations are necessary. Several CG approaches have been implemented to capture key information, including the water network and the hydrophilic cluster sizes in membranes, which act as a channel for proton transportation. Recently, Voth and co-workers have employed a multiscale approach, combining reactive atomistic simulations with coarse-grained descriptions to address modeling the morphology and transport behavior of a proton in Nafion membrane [21] & [22] (see Figure 6). The complex interplay of morphology, proton distribution, and diffusion coefficients at a length scale beyond capability of atomistic simulations have also been revealed using a combined CG approach with smoothed particle hydrodynamics (SPH) [22]. Moreover, the resulting conductivities calculated for the material were found to agree very well with trends from experiment [22].

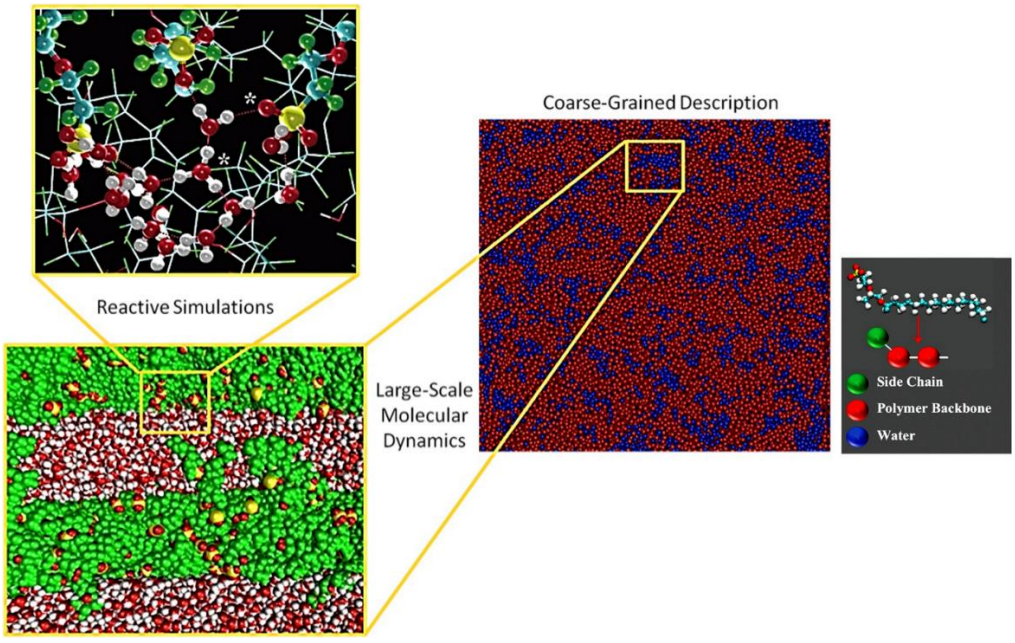

Figure 6 A multiscale approach to modeling proton exchange membranes from atomistic level reactive simulations to coarse-grained descriptions. Red spheres represent the oxygen atoms, white spheres represent the hydrogen atoms, yellow spheres represent the sulfur atoms, and the rest represent the Nafion backbone atoms. Reproduced with permission from Ref [21]. Copyright 2012, American Chemical Society.

5. Current issues of CG model development

Despite the growing diversity of new CG models, there are several consequences of moving from a fully atomistic to a coarse grained description. The most concerning issue for CG model development is a loss of transferability, meaning that the resulting models can only be applied in a narrow range of thermodynamic conditions. Usually, CG potentials were derived from atomistic simulations or experiments at a specific state (e.g. temperature, composition, etc.), and they were found to work well only for this particular condition [23]. Good result is not guaranteed when applying the same model at other state conditions. For example, the CG potential of ortho-terphenyl generated from atomistic simulation at 300 K was unable to reproduce any glass transition temperature at 250 K or above [24], which is in contrast with the atomistic models that give a glass transition at 260 K. The CG model of benzene obtained by reproducing the structural properties of pure liquid state was incapable of representing benzene in dilute aqueous solution [25]. The model did not show benzene aggregation as it was observed in detailed atomistic simulations. These examples are known as "*the representability problem*" [23], addressing that the CG potentials, especially ones obtained from structural-based coarse-graining, are highly specific to the thermodynamic state at which they derived from and cannot be assumed to be transferable to a different set of conditions. Some frameworks, for instance, combining bottom-up and top-down approaches by using multiple reference simulations and/or a variety of experimental data as a target for optimizing CG potentials, have been suggested to improve the model transferability [26]. Minimizing the information loss upon coarse graining [27] and choosing a proper CG mapping schemes [28] can also be done alongside to enhance transferability of CG models. To date, there is still no systematic way of achieving models with degree of transferability comparable to their atomistic counterparts. This topic is still under active development.

Another issue needed to concern for coarse-graining is a lack of compatibility. This problem arises from the fact that most of the current CG models are only parameterized for a specific class of molecules, for instance, proteins, lipids, and surfactants, where key building factors such as the mapping scheme and the interaction forms may not compatible with others. Following the increases in discovering of novel complex materials such as DNA–polymer hybrids [29], peptide surfactants [30], and so on, it is, therefore, desirable to establish generic CG force fields to study these upcoming materials.

6. Summary

Coarse-grained models have gaining a lot of popularity in polymer and biomolecular researches. By systematically reducing the number of degrees of freedom of a system of interest, these simplified models offer a considerable improvement in computational efficiency, allowing observation of long-timescale events not accessible to conventional atomistic simulations. The big challenge in CG model development is to improve the model transferability so that they can work equally well at other set of conditions apart from the state from which they were derived. The continuing increase in computer power will serve atomistic simulations of ever more complex systems. Nevertheless, there will be a certain limit when using these very detailed simulations at the most relevant scales of macromolecular materials. To this end, it is expected in the near future that a new generation of CG force fields with high degree of transferability and compatibility will be created, and then, become the main tool in simulation study of polymers and biomaterials.

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