Application of molecular dynamics simulation in self-assembly

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Abstract: During the past few years, numerous studies have been done in self-assembly. Among most of these studies, Molecular Dynamic Simulation is widely used to construct the experiment model. This work firstly introduced three practical applications of MD simulation in self-assembly. Then, two main kinds of simulation are discussed including all-atom simulation and coarse-grained simulation, together with the way of thoughts before the simulation start. It is found that researchers always start with the whole analysis of the substances that need to be studied. It helps to confirm the appropriate model that can apply in the simulation naturally. Besides, depended on the principles that need to be studied, the way of establishing the simulation system varies, ranging from separation experiment in both types of simulation to the change of essential parameters. Furthermore, the adoption of L-J potential in MD simulation proves to be a wise option on account of its convenient and simple model. It is remarkable that, considering some small details like the differences between implicit and explicit solution, classical Martini force field is replaced by Dry Martini force field.

1. Introduction

Molecular dynamics simulation is an excellent tool for prognosticating the way that atoms in different molecular systems move with the time coursing depended on a generic model of the interactions between atoms governed by physics. The basic concept of MD simulation is evident. It is feasible that, with the positions of all the atoms given, the forces exerted by all other atoms on each atom can be calculated. Newton’s laws of motion can be used here to predict the position of every atom in space as a function of time. The forces are calculated repeatedly over a period of time, so that the position and velocity of each atom can be updated. Generally, Trajectory obtained from the simulation clearly shows the distribution of atoms at each stage of the simulation.

Self-assembly, also called ordering, is a well-known phenomenon where individual particles in a system spontaneously organize to form ordered structures. [1] Weak and non-covalent interactions often contribute to such process. Self-assembly tends to be controlled by the functionalization of the particle surface or particles’ physical characteristics, or via the exertion of magnetic fields. For example, an external shear force can cause unidirectional ordering of lamellar bilayers formed by a polymeric surfactant, resulting in the formation of anisotropic hydrogels, which can be used as artificial muscles. [2] Besides, the behaviors of self-assembly usually happen in the cases like protein folding and the formation of cytomembrane. Thus, during the biophysical processes, one can capture the self-assembled structures.

It is no uncommon that researchers usually observe the colloidal self-assembly via the MD simulations. However, although numerous studies have been done in this field, the understanding of the recapitulative train of thought when it comes to how to combine the MD simulation with the self-assembly, still needs to be consummated. In this work, three applications of MD simulation in
colloidal self-assembly are discussed including their individual research methods and some necessary preconditions and theories.

2. Application

2.1 MD simulation study of polyoxyethylated alcohols self-assembly in emulsion systems [3]

According to the paper, although numerous researches have been conducted to illustrate the effect on properties of the emulsion, the process that AEO self-assembled in water or oil systems seems vague to perceive. Besides, the understanding of the internal interactions between the branching structure made up of hydrophilic groups and self-assembly remains incomplete. Considering that MD simulation is an efficient method in the research of the structure of interface, especially oil/water. CGMD simulation, which are derived from the MARTINI force field, is adopted in view of its capability that it can carry large-scale calculation. However, CGMD turns out to be lacking accuracy. Therefore AAMD, also called all-atom molecular dynamic simulation, is used which is of great precision. With the aid of the multiscale combination of two kinds of MD simulation, it is possible that two simulation approaches complement each other, so that both can give full play to individual advantages.

GROMACS is chosen as the platform to do all the simulations. \( C_{12}E_x \) (\( x=4,6,8,10,15, \) and \( 20 \)), which is CmEn conventionally, is the oil-soluble part of Alcohol ethoxylate (AEO). It serves as the nonionic surfactant in the AAMD simulation with the oil component octane which is both described via the AA model. Moreover, the simple point charge extended model is applied in water molecules. As for the CGMD simulation, MARTINI force field plays the role of explaining the single particle combined by an atomic cluster. Besides, the simulation naturally integrates other components into the CG models, depending on the principles of single chemical groups like volumes and types.

Furthermore, in order to do the research, simulation system is a must. Thus, two kinds of simulation systems are designed to analyze two cases, including the comparison of AA model and CG model in the environment of biphasic interfaces without co-surfactants and components that distribute stochastically in advance under the CG model. Both cases are demonstrated by the diagram in Fig.1. It is worth mentioning that, considering the process of the simulation in mixed system is 10 times longer compared with the biphasic interfaces, the data are collected in the second half of the simulation for the sake of the equilibrium state of the whole system. Even more to the point, by applying the VMD, also called Visual Molecular Dynamics software, the visualization of all simulations can be achieved.

Fig.1. Diagrams of three simulation systems:(A) and (B) show the biphasic interfaces under AA model and CG model respectively; (C) shows the stochastically distributed system under the CG model

2.2 Role of repulsive forces on self-assembly behavior of amyloid β-peptide (1-40): MD simulation approach [4]

\( \text{Aβ40} \) protein has the tendency to aggregate, which is the focus of a certain number of scientific studies in view of its significance in demonstrating the reason behind Alzheimer’s disease. However, due to the restrictions like temperature the heterogeneity occurs in the process of aggregation and the failure
of applying the NMR and X-rays in the experiment that analyze the monomer structure and oligomers of β amyloid, the researches in this area seems hard to be productive. Therefore, the necessary data of Aβ is obtained indirectly from other methods, like scanning TEM and FTIR method, which is used to capture the information about the mass of molecules and the secondary structures, respectively.

Among those methods, it is the transformation in the expression of potential that matters a lot. Numerous studies have been carried out in order to control the hydrophobic forces, which is generally the contributing factor during the procedure of Aβ protein folding. It is remarkable that the Lennard-Jones potential is widely used in various research models, due to its universality. Even more to the point, the participation of L-J potential naturally introduces the MD simulations which construct the whole experiment structure. It is not uncommon that L-J potential has been adopted in many molecular dynamic simulations due to its simple analytic form. However, collisions in repulsion are arisen from the adoption of L-J potential part which is unavoidable. Studies have been done to develop new methods, so that the collisions can be weakened or eliminated. For example, in a new potential conducted by a research, the repulsion part is separated from the whole to demonstrate the flexibility of protein. Besides, Gaussian model works as the tool for expressing the attraction part. With the help of the combination of two aspects, the researches are simplified.

As for Aβ40, the transition is made on the method from the idea of separation to the approach of doing adjustment of the repulsion term exponent, which is an essential parameter in Lennard-Jones potential. Reasons are as follows. Parameters like bond length and angles is impossible to migrate away from other restrictions. That explains the narrow applications in the method of separating the repulsion part and attraction part completely, including the practice in simple fluids. Therefore, in the complex system, such method turns out to be less effective. Hanley demonstrated some differences between the complex system and the simple system in fluids via such method. [5] The specific expression of L-J potential is as follows:

\[ u_{LJ}(r) = 4\varepsilon \left( \frac{\sigma}{r} \right)^m - \left( \frac{\sigma}{r} \right)^6 \]

The m in the expression ranges from 8 to 12. It represents the changes of the repulsion term. Therefore, OPLA-AA/L and GROMOS96 turn out to be the suitable and basic force fields through the simulation. Particularly, the adjustment of the repulsion term usually cast an influence on different force fields. Thus, the comparison between the effect on two different force fields is also taken into consideration.

2.3 Coarse-grained molecular dynamics simulation of the interface behavior and self-assembly of CTAB cationic surfactants [6]

Surfactant is a substance that significantly reduces the surface tension of the target solution. It has a fixed hydrophilic and oleophilic group, which can be arranged directionally on the surface of the solution. The molecular structure of the surfactant is amphiphilic. One end is a hydrophilic group, the other end is a hydrophobic group. Hydrophilic groups are often polar groups, such as carboxylic acid. Particularly, under certain thermodynamic conditions, the surfactant in water solution has to tendency to self-assemble. Such processes produce various structures. However, many studies although have been done on this theme, it remains incomplete in the understanding of surfactant self-assembly. Therefore, researches seem necessary to refine the theory. Since the self-assembly of surfactant takes place at the molecular level, MD simulation turns out to be a suitable option to carry out the research. Nevertheless, the commonly used AA model proves to be unqualified for such a mission. Mainly because the appropriate time and length scales which are used to study the principles of surfactants and micelles, are widely divergent with the AA model. Thus, sights are turned on the CG models. It is also called the molecular dynamic simulations of coarse-grained models. By reducing the degrees of freedom, the simulation time can be studied much longer than using the classical atomic model (all-atomic model). Besides, with the help of the increasingly advanced computational power, CG models are widely used for molecular modeling of biomolecules of various granularity levels.

Here, CTAB (Hexadecyl trimethyl ammonium Bromide) is chosen as the surfactant for the
experiment. CTAB is a cationic surfactant. It has good surfactivity and stability. It is usually used to produce gargles, disinfectants and deodorants. Like other surfactants, CTAB also has the characteristics that one of its ends has a hydrophilic group and the other has a hydrophobic group. The specific structure is demonstrated in Fig.2. To make the simulation more accurate, both AA model and CG model are applied in the research including the behaviors of CTAB in explicit aqueous solvents via two models and the CTAB in implicit aqueous solvents via CG model.

Fig.2. (A) shows the structure of CTA+ surfactants. (B) explains the difference between the AA model and CG model on CTAB. CG model is characterized by the brown and blue spheres, while all the small single atoms in the spheres make up the AA model. C1 is the hydrophobic headgroup and the Q0 is the hydrophilic tail.

Worth reminding that MARTINI force field is also applied in the CG model of CTAB in implicit aqueous solvents. However, instead of the classical MARTINI force field, the Dry Martini with a CG force field is adopted, which is illustrated by Clément Arnarez et al. [7] Specifically, considering the implicity of aqueous solvents, changes should be made on the interaction strength while the expression of force fields remains unchanged.

3. Conclusion
In this review, we investigated three practical applications of molecular dynamic simulation in self-assembly. We also summarized their train of thoughts about how to reach a natural integration between the MD simulation and the self-assembly. We described the all-atom MD simulation and its characteristics like more accuracy and suitable for small time scales model. Meanwhile, we also introduced the coarse-grained MD simulation which mainly focuses on the basic features of particles and neutralize the less important part in order to simplify the experiment procedures. Also, due to such advantages, CGMD simulations are more suitable for experiments with large time and length scales. It is found that, among the various CG models, the one that combined with the MARTINI force fields proves to be more efficient. Besides, we introduced the Lennard-Jones potential. Because of its convenience, it is often used to describe the interaction of overlapping wave functions in gas properties, scattering model and molecular models. Description of inert gas atoms made by L-J potential is particularly accurate and the interactions between neutral atoms or molecules are also a good approximation. Therefore, it is always applied in various molecular dynamic simulations.

Two main analytical approaches are described. The first is the idea of separation. Since the substances to be studied are on the molecular level so that we can use the MD simulation. Then, because the AA model and CG model focus on different essentials, both models are carried out at the same time, respectively. Finally, a comparison and summary are made between the results of two ways of simulations. Another way of thought is employed when L-J potential is adopted in MD simulation. In case of the model combined with the L-J potential, collisions caused by repulsive forces are inevitable. In order to counteract or mitigate the collisions, we have to change the repulsion term exponent. Thus, the results of simulation tend to be more precise.
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