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Molecular Simulations in Macromolecular Science

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Abstract Molecular simulations are now an essential part of modern chemistry and physics, especially for the investigation of macromolecules. They have evolved into mature approaches that can be used effectively to understand the structure-to-property relationships of diverse macromolecular systems. In this article, we provide a tutorial on molecular simulations, focusing on the technical and practical aspects. Several prominent and classical simulation methods and software are introduced. The applications of molecular simulations in various directions of macromolecular science are then featured by representative systems, including self-assembly, crystallization, chemical reaction, and some typical non-equilibrium systems. This tutorial paper provides a useful overview of molecular simulations in the rapid progress of macromolecular science, and suggests guidance for researchers who start exploiting molecular simulations in their study.

Keywords Molecular simulation; Coarse-grained molecular dynamics; Multi-scale method; Polymer physics

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INTRODUCTION

The development of computer simulation has a long and rich history. Initially, electronic computing machines were utilized for the development of nuclear weapons and code-cracking during the Second World War.[1] Until the early 1950s, electronic computers became partly available for nonmilitary use and this provided the fundamental conditions for the progress of computer simulations. In March 1952, Metropolis was interested in having as broad a spectrum of problems as possible tried on the Los Alamos MANIAC (Fig. 1 top left).[2] This may be the origin of computer simulation applied in various disciplines.

With the development of computer technology, it has become possible to characterize the static and dynamic properties of chemicals by molecular simulation, which has revolutionized the means of studying chemical problems and played a crucial role in the advance of chemistry. The algorithms and programs can only be written by researchers and the CPU was applied to calculate in the early stage of the molecular simulations due to the limitation of the technology. However, since computing capability continues to increase at an astonishing rate with the rapid improvement of computer hardware and the enormous enlargements in data storage, the development of molecular simulation has been greatly promoted. Up to now, various software packages have been exploited to make simultaneous use of both CPU and GPU available in a system, providing extremely high performance compared to the programs based on CPU only.[3,4] Due to the superior computational capability at a fraction of the cost and power consumption as compared with CPUs (as shown in Fig. 1 top right), GPUs are increasingly taken as main processors in simulations and supported by well-known software packages, such as DL-POLY,[5] AMBER,[6] LAMMPS,[7] NAMD,[8] HOOMD-blue,[9] GALAMOST,[10] and GROMACS.[11] These sophisticated commercial and open-source software packages are convenient to use with clear graphics and robust functionality.

Both observation and comprehension are necessary for science. The theory that mainly relies on approximation was the only way to understand and predict the properties of a molecular substance before the advent of molecular simulation.[12] The subject of how simulations are related to physical theory is raised. The simulation is built on fundamental theoretical principles, but it is a more elaborate calculation that attempts to avoid several approximations. The benefit of molecular simulation is that it may be used to verify existing theories, while also pointing out the direction for the development of new theories. Besides, molecular simulation outcomes can be equivalent to numerical solutions of complex systems that the theory cannot address analytically. As a result, molecular simulation can handle far more intricate systems and a wide variety of problems than theories.[1] Additionally, there is no doubt that molecular simulations are essential for making it easier to interpret experimental data at the microscale. It not only can acquire results consistent with those of experiments but also enables the inference of macroscopic properties relevant to experimental interests. Particularly when experiments are expensive or challenging due to the harsh conditions, simulation is a crucial addition to laboratory investigations. Therefore, experiment, molecular simula-

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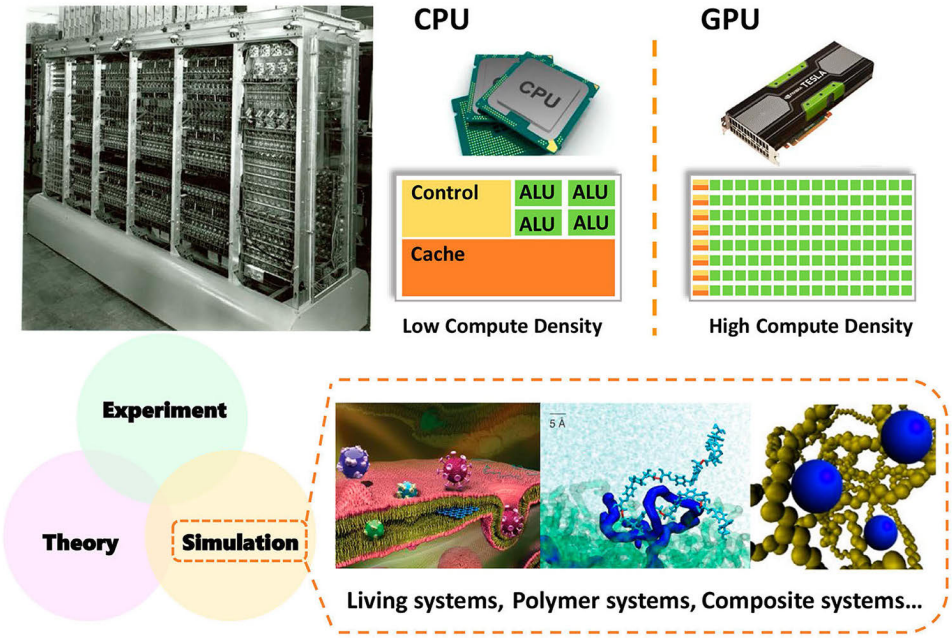

Fig. 1 Top: The first electronic computer Los Alamos MANIAC and the schematic illustration of CPU and GPU. Bottom: Experiment, simulation, and theoretical study are the three imperative methods. Simulation can be utilized to deal with scientific problems of various systems, such as living systems,[14] polymer systems,[15] and composite systems. (Reproduced with permissions from Refs. [14, 15]; Copyright (2020, 2018), The Royal Society of Chemistry and American Chemical Society).

tion, and theoretical study are the three imperative approaches to observing and comprehending physical and chemical problems, which have been well illustrated and described in a previous editorial.[13]

In this tutorial, we will provide a brief overview of molecular simulation, concentrating mostly on technical and practical aspects. Our intention here is to essentially explain the fundamentals of molecular simulation for both professionals and beginners who want to perform simulations. In the next section, several mainstream simulation techniques, relevant research systems, and the corresponding software packages are introduced. Several applications are then described as examples to illustrate how molecular simulations solve chemical issues. This tutorial offers a useful overview of molecular simulations in macromolecular science and provides direction for researchers who desire to utilize molecular simulation.

SIMULATION METHODS AND SOFTWARE

In this section, we briefly describe a variety of simulation and calculation techniques widely used to study and predict the structures, properties, and controlling mechanisms of macromolecules.[16] According to the temporal and spatial scales of their application systems, the techniques can be classified into three primary categories: quantum chemical calculations, atomistic simulation, and coarse-grained simulation. Among these three methods, quantum chemical calculation mostly focuses on the tiniest temporal and spatial aspects relating to the electron. Atomistic simulation typically concentrates on issues at the nanoscale and millisecond scales, and a particle corresponds to a specific real atom. By contrast, the coarse-grained (CG) simulation ignores all atom-level information, which is commonly employed to investigate mesoscale problems and universal laws. In the following parts, the specific methods of each technique together with their fundamental principles, advantages/disadvantages, and software will be detailed.

Quantum Chemical Calculations and Software

In quantum chemical calculations, the movement and the impact of the electron are primarily taken into account. First principle calculation is one of the representative quantum chemical calculation methods, which considers the electronic and the nuclear degree of freedom separately.[17] This method only requires the nuclear charge of the atom and a few simulated environmental parameters as inputs, and all properties are derived by solving the Schrodinger equation without using any empirical parameters. As a result, the merit of using first principle calculation is that the outcome is more accurate and takes less intervention. However, due to the low computational efficiency, a new approach known as density functional theory (DFT) is proposed, which is based on the first principle calculation.[18] DFT transforms the complex many-body problem of interacting electrons and nuclei into a coupled set of one-particle (Kohn-Sham) equations, which are computationally much more manageable. This theory allows parameter-free calculations of all ground-state physical observables and nowadays becomes one of the most useful methods. In general, quantum chemical calculations can be used in significant studies involving the electron, such as the comprehension and development of catalytic processes in enzymes and zeolites,

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electron transport, solar energy harvesting and conversion, drug design in medicine, as well as many other issues in science and technology. Both GAUSSIAN and VASP are mature software packages for quantum chemical calculations. One piece of commercial Windows/Linux software called Material Studio also contains a module that enables users to investigate issues in the gas phase, solvent, surface, and solid environments by quantum chemical calculations. Researchers who are not proficient with Linux or programming may use this software.

Atomistic Simulation and Software

The classical atom-level molecular simulation has emerged as one of the most fascinating and popular ways to improve our understanding of molecular processes in material science and living systems. This type of approach can address many tasks related to the nanometer and nanosecond scales of macromolecules (as shown in Fig. 2). All-atom simulation is a remarkably powerful method of presenting information at atomistic resolution since in the atomistic simulation, one particle stands for one specific atom. However, due to the effectiveness of algorithms and the current computing power, it can only be used to simulate microscale systems.[19–22]

Molecular dynamics (MD) method

MD simulation method is the undisputed tool for all-atom simulation. The deterministic classical equations of motion serve as the basis for the atomic movements in MD simulation. Thus, MD technique is an effective approach to providing information about the dynamic properties of many-particle systems. In addition, there might be 30 different atom types to consider and several hundred different intra- and inter-molecular potentials to fit in a complicated system. The force field (FF) refers to the functional forms used to characterize the intra- and inter-molecular potential energy of a collection of atoms, and the corresponding parameters that will determine the energy of a given configuration. The most popular all-atom simulation FFs created for various systems and properties are AMBER, CHARMM, OPLS-AA, and CVFF. AMBER FF is mainly developed for studying the biomolecules, such as proteins, nucleic acids, and polysaccharides.[23] CHARMM force field can treat various macromolecules, including organic molecules, polymers, biochemical molecules, *etc*.[24] The structure, configuration energy, and free energy obtained by this FF are often compatible with the experimental value. OPLS-AA FF was developed for the computations on organic liquids, dilute aqueous solutions, hydrogen bonding, and ion-water complexes, and has provided a set of functions to describe the nonbonded interactions for proteins in crystals or aqueous solutions.[25] The most accurate calculations of the structure and binding energy are one of the main features of the CVFF FF.[26] For molecular simulation, choosing a suitable FF is a crucial step. There are two basic ways to select the best FFs. The first is scrutinizing the FFs employed in the studies for analogous chemicals or systems. Normally, the recommended choices from other papers are designed to work well and have been extensively tested. The other is, based on the purpose of developing various FFs, selecting the one that comes the closest to your actual objective. One item that needs to be kept in mind is to avoid a "mix and match" strategy for different components of various FFs. The majority of software packages for atomistic-level MD simulation include the documents of various FFs, such as Material Studio, GROMACS, LAMMPS, NAMD, and AMBER. MD simulation can be implemented by modifying the control script, defining the parameters, and using commands to start a simulation run.

Coarse-grained Simulation and Software

Since the amount of computation increases exponentially with the number of particles, using large numbers of atoms to embody all molecular details can be extremely time-consuming. A typical kind of simulation for accessing long-time scales in

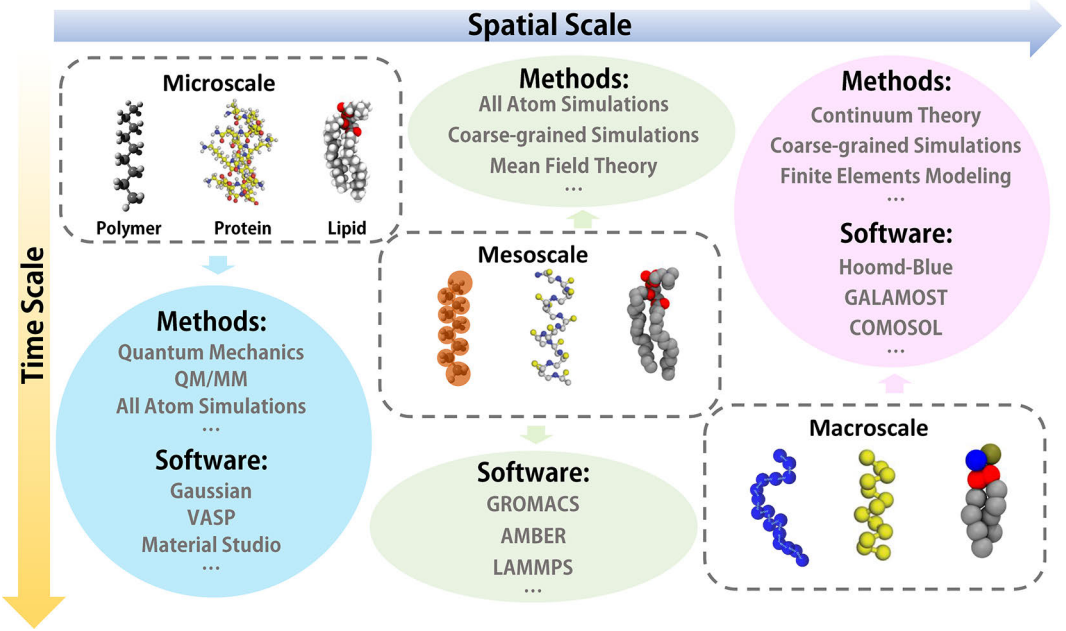

Fig. 2 Schematic representations of the multiscale approaches. (Reproduced with permissions from Refs. [27, 28]; Copyright (2019, 2012) American Chemical Society, Springer Science+Business Media LLC).

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macromolecule simulations is the coarse-grained simulation. Also, from the increase in the accessible timescales, it is possible to infer the comparable rise in the accessible system sizes. In the CG model, one particle represents a region of fluid that encompass at least several atoms or chemical groups, which is large on a molecular scale but still macroscopically small. Compared to atomistic simulation, CG simulation with simplicity and efficiency makes it an excellent tool for investigating properties at mesoscopic scale and obtaining insight into universal molecular mechanisms.

Monte Carlo (MC) method

MC simulation is the earliest developed computer simulation method by von Neumann, Ulam, and Metropolis at the end of the Second World War. Different from MD method, the foundation of MC is statistical mechanics that a determinate problem can be equivalently substituted into a probabilistic simulation. Hence through massive stochastic sampling, the average of a selected statistical ensemble can be easily obtained.[29] However, in general, the probability that the targeted structures appear is quite low. Directly computing the ensemble average by random sampling is not practical. Thus, in order to improve the efficiency of MC simulation, a variety of important sampling techniques are used according to diverse systems and requirements. Besides, the most important feature of MC method is that the free energy can usually be obtained readily. MC method only considers the configuration space, eliminating the momentum part, it is often used to study systems in equilibrium. In addition to equilibrium properties, the Monte Carlo idea can also be exploited to tackle dynamical properties that consider an activation barrier on both sides of detailed balance, reflecting as the prefactor of Metropolis sampling algorithm, which is called kinetic Monte Carlo. Generally, MC method is implemented by writing your own programs in FORTRAN, C/C++, or MATLAB to accomplish the desired simulations. HOOMD-blue also can perform hard particle MC simulations of a variety of shape classes.

Dissipative particles dynamics (DPD) method

DPD method is one of the typical coarse-grained simulation methods which incorporates hydrodynamic effects directly. Compared to MC method, DPD method can obtain the kinetic process of particle motion. Moreover, different from the force field in MD, in DPD, all particles interact by three pairwise forces: the conservative force, the dissipative force, and the random force.[30,31] The thermodynamic properties are determined by the conservative force that depicts the compatibilities of components, usually specified with Flory-Huggins χ-parameters.[32] This connection is a considerable mapping between the DPD model and Flory-Huggins theory at fixed density. Therefore, one of the most notable advantages of DPD method is that the interactions between different components can be readily considered based on thermodynamic parameters in experiments, making DPD a more realistic simulation method. Moreover, in DPD, a larger integration time step can be utilized, leading to the reduction of computing times. Thereby DPD method enlarges the spatial and temporal scales of systems that molecular simulation can study. Currently, DPD has become one of the most widely used simulation methods for investigating complicated macromolecular systems with polymers, nanoparticles, or biological components. Material Studio, GALAMOST, HOOMD-Blue, and LAMMPS can carry out the DPD method.

Brownian dynamics (BD) method

Going beyond mesoscopic models of solute, further coarse-graining can be accomplished by averting the direct simulation of the fluid altogether. In BD, solvent particles are implicit, leading to a dramatic reduction in the number of particles, greatly improving the simulation efficiency.[33] However, in contrast to MD and DPD methods, the limitation of BD method is that the hydrodynamic effect is usually neglected.[34] GALAMOST, HOOMD-blue, and LAMMPS are all suitable for conducting the BD simulation.

APPLICATIONS

Molecular simulation is a powerful tool that can be exploited to examine various macromolecular systems under a variety of conditions. This section concisely introduces several applications of molecular simulation by four typical problems, *i.e.*, self-assembly, crystallization, chemical reaction, and non-equilibrium systems, as examples. At the same time, the appropriate simulation methods for each issue are further discussed, so as to provide the fundamental guidance for the simulation studies of these issues.

Self-assembly

Self-assembly occurs naturally in many systems and is an important practical strategy for creating ensembles of nanostructures. It is a process in which the components are autonomously organized without human intervention from disorder into ordered patterns or structures.[40] The simulation findings and the experimental data are compared by using the self-assembly of the grafted-nanoparticles as an example to demonstrate the accuracy and dependability of the simulation results. According to composition, the grafted nanoparticles can microphase separate into a variety of morphologies (Fig. 3a top). The grafting chain length and grafted density directly affect the assembled structures.[35] The phase diagram concerning grafted chain length and the number of grafted chains was acquired from the MC simulation (Fig. 3a bottom left), which is consistent with that of experiments (Fig. 3a bottom right).

Additionally, understanding various self-assembly principles and regulation rules from the microscopic perspective is greatly aided by molecular simulation. On the one hand, molecular simulation is a powerful approach to identifying novel structures and revealing regulation rules of molecular self-assembly under the influence of molecular components, topology, charge, mass, interaction, surface properties, polarizability, and various complicated factors.[41] DPD is used, for instance, to examine how the length of the middle block and compatibility between the two copolymer blocks affect the self-assembly of H-shaped polymers. The study demonstrated that both parameters have a significant impact on polymer aggregation and internal phase separation, and the phase diagram is displayed in Fig. 3(b).[36] On the other hand, molecular simulation can make the micro-mechanism and kinetic processes of self-assembly visible.[42] Utilizing a fused dihydrofolate reductase (DHFR) dimer tethered by flexible peptide linkers, highly stable 2D nanorings can be produced for the assembly of biomolecular when induced by bivalent enzyme inhibitors (bis-MTX), as shown in Fig. 3(c). At the

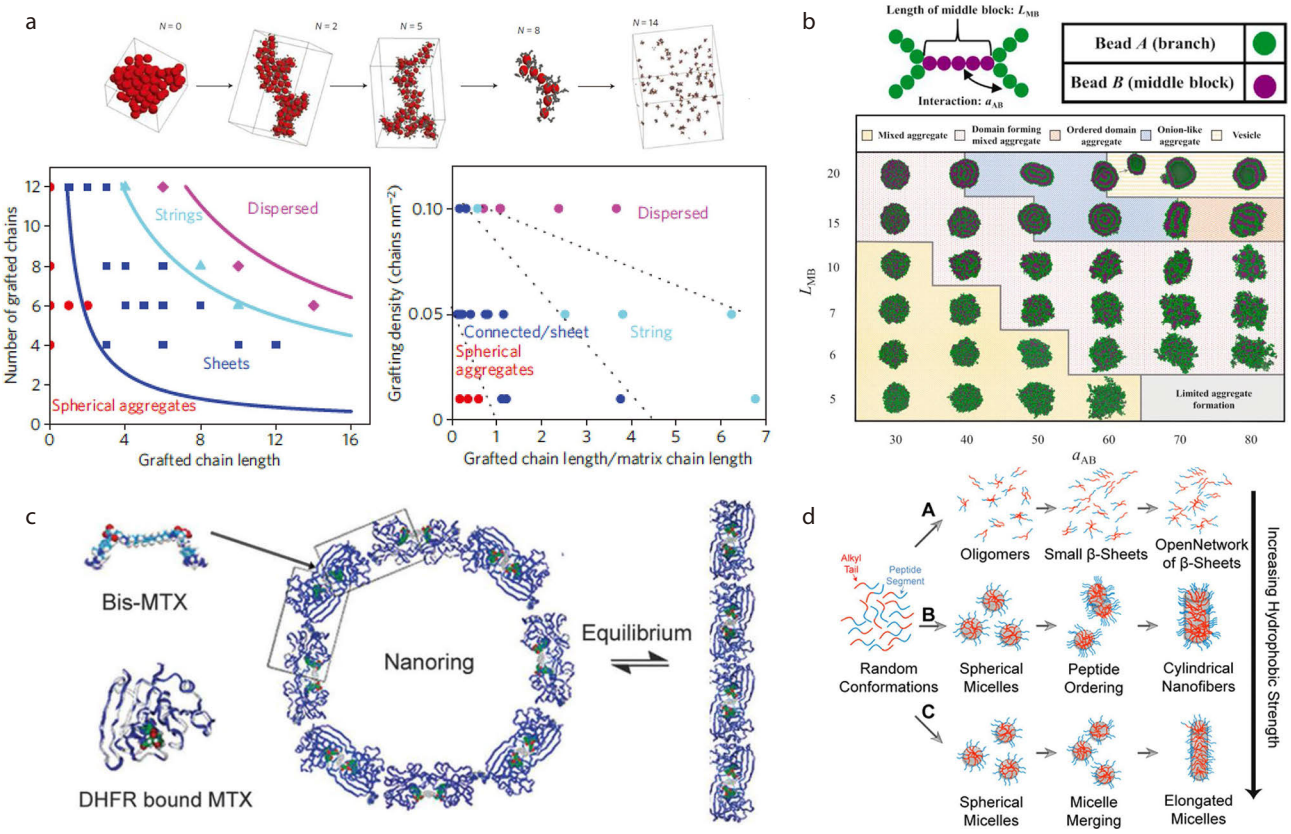

Fig. 3 (a) Simulation predictions and comparison of simulation to experiments. Top: Simulation snapshots for particles with six uniformly spaced grafts, going from bare particles forming spherical aggregates, to flattened cylinders with N=2; branched cylinders with thinner arms N=5; sheets with N=6 not shown); long strings with N=8 (only one string shown); short chains with N=10 (not shown); and isolated particles with N=14. Bottom left: Results of simulations at different grafting densities. Red symbols: spheres, dark blue: sheets, light blue: strings, magenta: well-dispersed particles. Bottom Right: Experimental 'morphology diagram' of polymer-tethered particles mixed with matrix polymers. Red symbols represent spherical aggregates, blue symbols are sheets and interconnected structures, cyan symbols are short strings and purple symbols are dispersed particles. The lines that separate the different regions are merely guides to the eye.[35] (b) Phase diagram showing the different aggregate morphologies obtained from H-shaped block copolymer architecture as a function of middle block length (LMB) and interaction parameter a_{AB}. Six main regions of the phase diagram are identified: mixed, domain forming mixed, ordered domain, onion-like and vesicle-like aggregates, as well as, a region where only limited aggregate formation is observed.[36] (c) The individual components and proposed assembly mechanisms of the bisMTX and DHFR2 system. The conformational flexibility of the growing chain and thermodynamics of its connections will regulate the balance between cyclic and linear oligomers.[37,38] (d) Schematic diagram of three kinetic mechanisms proposed by simulation results.[39] (Reproduced with permissions from Refs. [35, 38 and 39]; Copyright (2009, 2016 and 2015), Springer Nature, The Royal Society of Chemistry, and American Chemical Society).

atomistic level, MD simulation can directly explain the assembly mechanism and provide precise assembled structures.[37,38] Furthermore, the distinctive kinetic mechanisms based on the solvent conditions can also be identified using discontinuous MD, which produces diverse nanostructures at moderate temperatures (Fig. 3d).[39] In summary, MD and DPD are more appropriate and frequently utilized for self-assembly investigations. One of the causes is that both methods can provide accurate assembly structures in a relatively short computational time. In addition, both approaches can display the dynamic process and evolution pathway of the assembly. However, it is unquestionable that the choice of simulation method should depend on the desired properties. MC method and the combination of two or more methods are also general approaches to investigating the special properties or mechanisms of self-assembling systems.

Crystallization

For nearly a century, researchers have been studying the intricate phenomena of crystallization in polymers. A unique perspective on polymer crystallization has been provided by simulations,[43–45] which can reveal molecular mechanisms of nucleation, growth, and the associated free energy barriers during the very early stages of crystallization.[46] A spinodal liquid–liquid phase separation is demonstrated in polymeric materials when they are rapidly cooled into an unstable region of the phase diagram, according to MD simulation with the united atoms model (as shown in Fig. 4a). The underlying mechanism for crystallization is general for a broad range of polymers, including poly(ethylene terephthalate), polyethylene, poly(ether ketone), isotactic polypropylene and poly(ethylene naphthalate).[47] Moreover, complicated systems and conditions like shear-induced polymer crystallization and confined crystallization can be realized by simulations. The formation

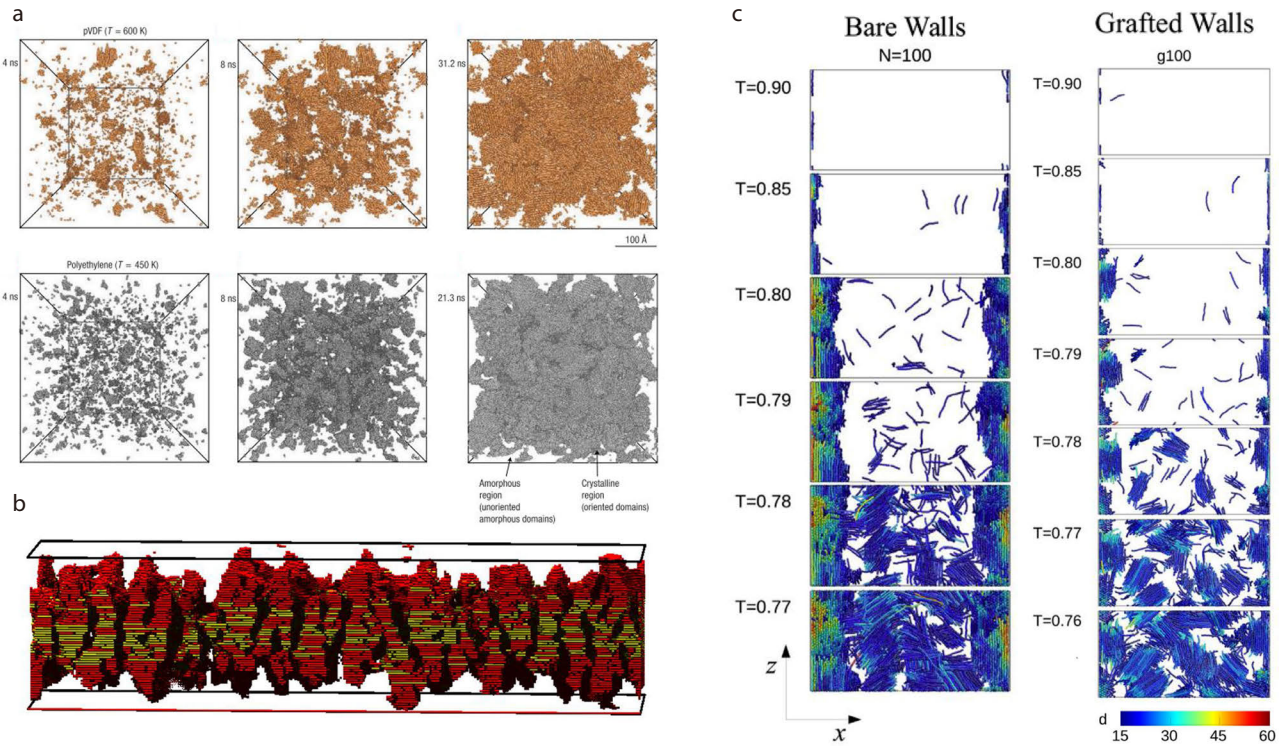

Fig. 4 (a) Snapshots from the MD simulations showing the evolution of the spinodal-assisted crystallization process for the polar (orange 'atoms') and nonpolar (grey 'atoms') polymer models at a temperature of 600 K (top) and 450 K (bottom), respectively. Only the oriented domains are explicitly shown (the unoriented amorphous domains are the white space in each panel). Top: The ordering evolution for the polar polymer, where the times are 4, 8 and 31.2 ns, respectively. Bottom: The ordering evolution for the nonpolar polymer, where the times are 4, 8 and 21.3 ns, respectively.[47] (b) Snapshot of the shish-kebab structure at 4000 MC cycles during isothermal crystallization. The yellow cylinders represent the crystalline bonds of the long-chain component, while the red cylinders represent those of the short-chain component.[48] (c) Snapshots of crystalline segments between two bare walls and grafted walls during continuous cooling, respectively. Here, different colors denote different stem lengths (d) and we only display crystalline segments with $d \geq 15$ for a clear visualization. T=0.9 corresponds to T=495 K. The coordinate axes and the color legends are displayed at the bottom.[49] (Reproduced with permissions from Refs. [47, 48 and 49]; Copyright (2006, 2018 and 2017) Nature Publishing Group, American Chemical Society, and Elsevier Ltd.).

process of shish-kebab crystallites in a driven field with Poiseuille-flow-like gradient forces presumably generated around the shear layer of melt fracture was studied using MC simulation of a binary blend of short and long polymers. Furthermore, it illustrated the synergetic coil-extension and segregation tendencies of long-chain fractions upon precursor formation, which lead to a discontinuous crystalline structure along the shish, as shown in Fig. 4(b).[48] MD simulations for the polymer crystallization in confinement show that the crystallization in the case of bare walls typically consists of surface-induced processes close to the walls, followed by homogeneous nucleation in both the boundary and middle regions (Fig. 4c, left). In the case of grafted walls, however, portions of polymer chains residing close to the walls are adhesive to the surfaces and become permanent graft points (Fig. 4c, right).[49] In general, MD and MC methods are often adopted to study crystallization. MC method can provide the equilibrium states in terms of free energy, while MD method can show the kinetic process of crystallization.

Chemical Reaction

Chemical reactions are one of the most essential topics in chemistry, and a variety of simulations can be used to investigate issues related to them.[50] Ab initio is considered to simulate phenomena like electron transfer by describing chemical reactions at the electron level in terms of quantum mechanics. Thus, it is possible to explore reaction mechanisms, including the intermediate state, which enhances our understanding of chemical processes.[51] The Reax FF is created in MD simulation to represent chemical reactions, which is a general bond-order-dependent FF that provides accurate descriptions of bond breaking and formation.[52–54] The failure of the poly(dimethylsiloxane) polymer (PDMS) at high temperatures and pressures as well as in the presence of various additives are examined at the atomic level from MD simulations using Reax FF (Fig. 5a-I).[55] Moreover, polymerization-induced self-assembly (PISA) at the mesoscale has become more popular recently. PISA, in general, is a procedure that can be utilized to synthesize amphiphilic block copolymers by inducing soluble initiators or macro-CTAs (macromolecular chain-transfer agents) in specific solvent conditions. During the process, the newly generated hydrophobic block gradually gains dominance with the growth of its length in polymerization. The characteristic microscopic self-assembly structures were generated using the DPD approach in combination with a stochastic reaction model, which also revealed the dynamic routes of their development (Fig. 5a-II).[56] In a word, if the anticipated properties of chemical reactions are related to the electron transfer, the quantum chemical calculation method and VASP or Gaussian software

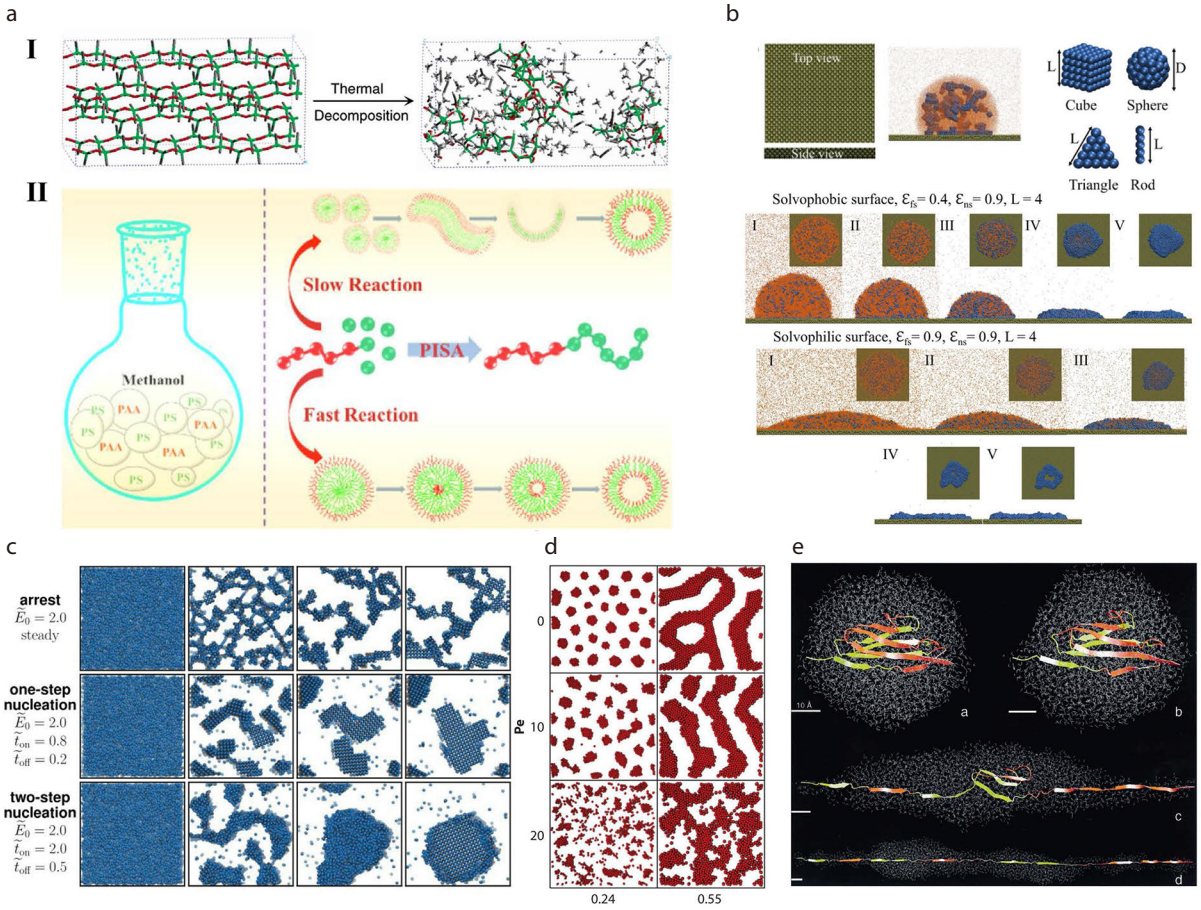

Fig. 5 (a) I. Initial and final configuration of the 3500K MD simulation of PDMS at a density of 1.227 g/cm^3.[55] II. Schematic illustration of the possible pathway of the assembly transition during the PISA process with slow and fast polymerization.[56] (b) Snapshots showing the top view and side view of the surface. Different shapes of NPs used in simulations, cube, sphere, triangle, and rod, each having length (*L*) or diameter (*D*), which in the case of sphere is equal to 5. Snapshots showing the shape of the nanofluid droplet, with rod shaped NPs, with time during evaporation on the solvophobic and solvophilic surface, having different images I, II, III, IV, and V, showing the snapshots at different time 0τ, 5000τ, 10000τ, 15000τ, and 50000τ, respectively. The green, orange, and blue colors represent the surface, solvent, and NPs, respectively.[58] (c) Snapshots over time of perfectly conducting dispersions at φ=0.20 (volume fraction) evolving *via* different kinetic mechanisms. Suspensions begin as a homogeneous, disordered fluid (first column) and evolve for 1000τ_D (last column). The middle columns show the snapshots at intermediate time points. However, the selection of intermediate time points are not the same among rows.[59] (d) Self-propelled spheres. Left: snapshots at φ=0.24, Right: φ=0.55. From top to bottom: Pe=0, 10, 20. The dimensionless Péclet number is used to characterize the degree of self-propulsion of the particles, defined as $\mathrm{Pe}=\left(v_p\sigma\right)/D$, where v_p is the magnitude of the axial propelling velocity, σ is the particle diameter, and D is the translational diffusion coefficient. At Pe=10, meso-phases of living clusters are observed at lower densities, and living stripes are seen at higher densities.[60-61] (e) The intermediate stages of pulling simulations. The protein domain I27 (residues 1–88) is drawn in cartoon representation with the two β-sheets presented in different colors, and water molecules are drawn in line representation.[62] (Reproduced with permissions from Refs. [55, 56, 58, 59, 61 and 62]; Copyright (2005, 2019, 2019, 2019, 2016 and 1998) American Chemical Society, American Chemical Society, AIP Publishing, American Chemical Society, The Royal Society of Chemistry, The Biophysical Society).

need to be adopted. However, in chemical reactions, if only the bonding and unbonding processes are concerned, the MD simulations with Reax FF or the stochastic reaction model are the better choices.

Non-equilibrium Systems

Complex non-equilibrium problems can also be studied through molecular simulation.

(1) Evaporation. The structural and thermodynamic characteristics of the liquid-vapor interface are of fundamental interest for a wide range of technological implications.[57] MD simulations of Lennard-Jones particles have been performed to analyze the self-assembled structure of nanoparticles (NPs) when nanofluid droplets evaporate over a heated surface. Various NP shapes for the nanofluid are taken into consideration in this work, including a sphere, cube, triangle, and rod. The structure of the NP deposit created following evaporation is assessed in relation to the strength of solvent-surface and NP-surface contact, as well as the size and shape of the NPs (Fig. 5b).[58]

(2) External field. Dynamic assembly processes governed by external filed, in which the interactions among particles are externally controlled and vary over time, offer a promising method to address the propensity of materials to arrest in undesirable metastable states.[63] An effective strategy of active

assembly for dispersions of polarizable dielectric or paramagnetic nanoparticles can be achieved by toggling an external electric or magnetic field, which induces attractive particle interactions, on and off cyclically over time. According to computational models for these active assembly processes, cyclically toggling the external field causes the growth of colloidal crystals at substantially quicker rates and with significant defects than for assembly in a steady field (Fig. 5c).[59]

(3) Active systems. Active materials represent a novel class of condensed matter allowing for the formation of dynamic, global structures that are out of equilibrium through the combination of motile elements.[64] The simulations give us unlimited access to the spatial and temporal resolution of the mechanics of propulsion. Additionally, the experimental findings may be very precisely replicated by the simulation of active nanoparticles.[65] The phase behavior of self-propelled spherical and dumbbellar particles interacting *via* microphase separation generating potentials can also be studied using simulations. Results demonstrate that it is possible to drive the formation of two new active states under the appropriate circumstances: a spinning cluster crystal, which is an ordered mesoscopic phase with spinning crystallites of finite size as lattice sites, and a fluid of living clusters, which is a two-dimensional fluid where each "particle" is a finite size living cluster (Fig. 5d). [60–61]

(4) Macromolecules under tension. The simulation of steered molecular dynamics (SMD), a particular kind of MD simulation, applies a directing vector to a molecule or protein in order to study its response to external forces, mimicking the process of atomic force microscopy (AFM).[66,67] It is frequently employed to calculate the free energy or to comprehend the kinetics and the structural determinants of biomolecular processes[68] such as the transition between different conformations of DNA, folding and unfolding of proteins, ligand binding to receptors and enzymes, and transport of small molecules through channels.[69] By stretching the protein titin Ig domains in solution, for instance, using SMD method, the resulting force-extension profiles exhibit the dominating peak which can be exploited to analyze the structures of proteins (Fig. 5e).[62] Various software, such as GROMACS and LAMMPS, can implement SMD simply by adjusting the parameters in the control scripts.

In brief, molecular simulation can be utilized to observe and study a wide range of complicated non-equilibrium processes. However, due to the intricacy of problems and the reality that it heavily depends on the specific systems and phenomena, it is best to decide on the proper simulation method case-by-case. Sometimes one even needs to develop in-house programs to achieve the goal. Therefore, performing a non-equilibrium simulation demands a clear research objective as well as an appropriate simulation method.

SUMMARY

This tutorial article covers several elementary aspects necessary for molecular simulation. Since computer hardware and simulation technologies have progressed so rapidly, molecular simulation no longer only can solve basic and conventional chemistry problems, but also puts a spotlight on a variety of complicated systems.

For a specific scientific problem, the first step in beginning a simulation is to design the simulation systems, including the construction of rational initial models and the verification of the temporal and spatial scales. The following stage is to concentrate on simulation methods and the optimum FF selection. Then, the proper software is chosen, bearing in mind both the computation efficiency and the method. After setting the appropriate parameters, the simulation is finally prepared to run. Above all, for molecular simulations, the applicability of the force field, the computational efficiency, the accuracy of the simulation method, and the rationality of the initial structure are the primary factors that determine whether a simulation protocol is successful or failed.

At present, one of the main challenges of molecular simulation is to improve the simulation model's accurate construction and parameterization by incorporating experimental results. The field of molecular simulation is still undergoing tremendous growth today. Another challenge is to supply a drastic speedup of algorithms and software. If considerable efforts could be made in the future in software package expansion and the creation of simulation techniques, it must be more convenient for researchers to conduct molecular simulations. With this in mind, the key issues in more fields will be resolved through molecular simulation in the future.

BIOGRAPHY

Li-Tang Yan received his Ph.D. in polymer physics and chemistry at Tsinghua University in 2007. Then he went to Bayreuth University in Germany as a Humboldt Research Fellow. In 2010, he joined Prof. Anna Balazs' group at University of Pittsburgh in USA as a Postdoctoral Research Fellow. He returned to Tsinghua University as a faculty from May 2011, and now is a full professor with tenure. He leads a polymer theory and physics group working on polymer theory and simulation, soft condense matter physics, biophysics and nonequilibrium physics.

Conflict of Interests

The authors declare no interest conflict.

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