Molecular Modeling and Simulation - Exploring Vehicle into Atomistic World

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It has not been 30 years or so for molecular modeling and simulation (MMS) approach, which elucidates scientific problems and provides reliable answers, to be accepted appreciatively in science and engineering communities. By taking advantage of continuous growth of computer technology, MMS field presently greets a new era with help of stopless inventions and developments of theories and simulation methods based on molecular physics and statistical mechanics and thermodynamics. As a result, a wide variety of MMS methods, which are generally distinguished by different scales of time and length, have been developed (see Fig.1). Each method possesses its own merits, thus recently, bridging scaling gaps between methods or co-works among them become common efforts to many researchers in computational fields. Our group particular focuses on the region embracing atomistic to coarse-graining (i.e. meso) scales by using molecular dynamics (MD) and Monte Carlo simulation methods. In this letter, we introduce four different topics spanning bio-and nanomaterials, which are currently engaged in our group with support of the high performance computing (HPC) center at UNIST, to illustrate unlimited possibility in the choice of research subjects and great potentials to benefit various fields of science and engineering.

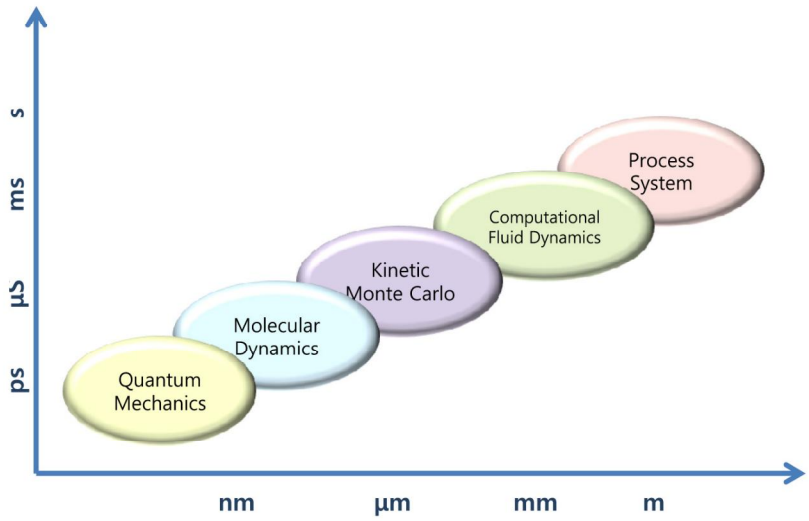

Figure 1 : Multiscale modeling framework based on time and length scales.

1. *Determination of Tertiary Protein Structure and Study of Functional Behaviors*

Among antimicrobial peptides, defensins containing six invariant cysteine residues are of particular interest as they exhibit a broad spectrum of antimicrobial activity against Gram positive and Gram negative bacteria, yeast, fungi and some enveloped viruses. The defensin family can be classified into three different subfamilies (i.e. a, b, q) based on the pattern of six conserved cysteine residues forming three disulfide bridges. The human b-defensins (HBDs) deserves a special attention due to their prominence in potent antimicrobial activity and as a chemo-attractant, thereby playing a key role in innate and adaptive immunity. Their great potentials are found in developing ideal therapeutic drugs as antibiotics and modulators of inflammation, however the less knowledge has been developed for this HBDs subfamily to further study the structural effect on their antimicrobial property; the interaction mechanisms involving membrane depolarization and permeabilization is still a matter of dispute. We aim to resolve this issue via MMS study. First, a stable 3D structure of HBD is found by homology modeling and MD simulation in the absence of experimental structure determined from X-ray or NMR. A typical structure of HBD-28 has been constructed and simulation models HBD_A and D are found by analyzing different sequency alignments of residues. (see Fig. 2) With this predicted model, dimerization is performed by combinatorial arrangements of b-sheets and a preliminary dimer of HBD 28 satisfying thermodynamic conditions is chosen. Then, the dimer is submerged into a buffer solution (i.e. water) to capture detailed molecular interactions against a lipid bilayer. Out of two probable activities of dimer(s), which are either the penetration mode to make a hole into the lipid bilayer or the spreading mode to make a film of dimers on its surface, we found that the latter is the case for HBD 28's antimicrobial behavior by analyzing the landscape of atomistic details built in the phase-space information. This MD treatment is not restricted to HBDs but applicable to mutated proteins, thus a prompt characterization of antimicrobial degree is anticipated prior to real experiments.

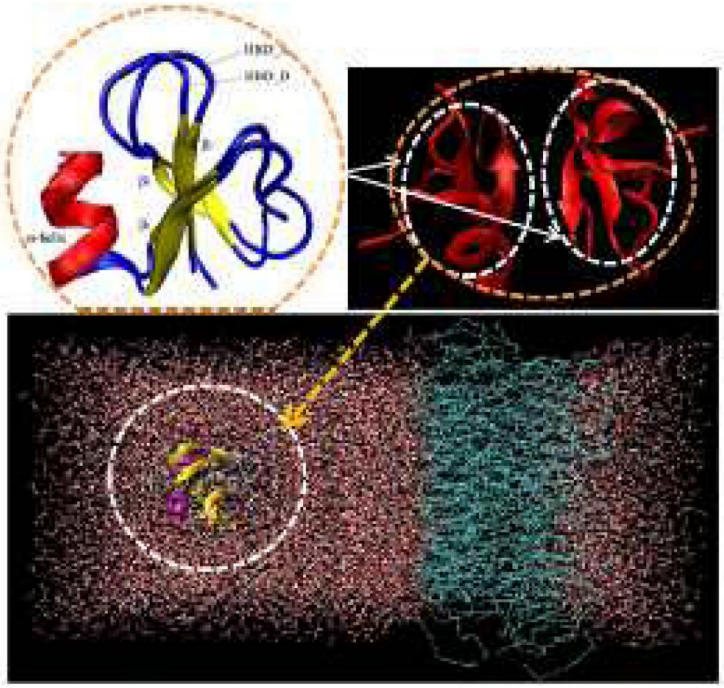

Figure 2 : Models of HBD 28 from homology modeling and MD (top left). Dimerization of HDB 28 via favorable interaction of β-strands (top right). Dimer of HBD 28 in water against lipid bilayer. (bottom)

2. *Synthesis of Advanced Nanocomposites – Cross-Linked Epoxy-Silicate Polymer: Determination of Design and Thermal, Mechanical, and Interfacial Properties*

Advanced engineered materials, including thermosetting epoxy, find a wide range of applications in the space, aerospace, and electronic industries where harsh conditions exist and challenges such as weight minimization and functionality maximization provide obstacles to reaching desired goals to explore new frontiers. There are particularly great interests for improving the ability to tailor a product to meet specific

weight, thermal, optical, mechanical, and electrical requirements where the environment consists of intense thermal cycling and weight constraints. In this regard, we aim to build a reliable MMS framework to enable readily determining phase behaviors and properties of cross-linked epoxy-silicate polymer nanocomposite (PNC) and optimizing the design of its derivative materials through fundamental understanding of intermolecular forces dominating the thermal and mechanical behavior of PNCs. Two underlying objectives are enumerated; construction of building blocks for constituent components of epoxy-silicate PNC and assembly of the building blocks to construct epoxy-silicate PNC through self-crosslinking. Each system under two activities experience intensive treatments of atomistic manipulation to grain high quality and reliability of the simulated system. There exist three main phases in typical production of silicate-PNCs; intercalation (see Fig. 3), flocculation, and exfoliation. Under the annealing process, each of those led to unique materials with improved properties. Detailed simualtion study of interfacial effect on thermal and mechanical nature of the PNCs is a novelty of this subject. In technical viewpoint, this work can provide clear answers to unknown phenomena such as mechanism and state of dispersion and orientation of silicate nanoparticles, confining effects of layered silicate platelets on confined epoxy polymers and their structures, and fatigue-fracture phenomena in different phases of epoxy-silicate PNCs. Most importantly, using simulation as a guide, PNC development can be tailored to fit a particular application, with significant time and cost savings.

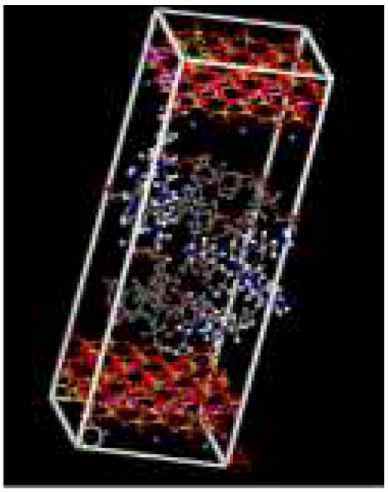

Figure 3 : Localized polymer nanocomposite in the intercalated phase. Two layers of silicate nanoplatelets (red), epoxy (gray), surfactant (blue, long chain), and curing agent (blue, short chain)

3. *Study of Phase and Property of Fluid Particles in Cylindrical Confinement*

The confined systems, within micro- to nanometer of pores in size, have received very much attention due to unusual variation of properties of confined fluids compared to those of bulk. Their practical cases can be found in the fields of capillary condensation, nano-lithography, nano-print, gas adsorption, separation and purification, transport in porous materials, storage, packaging, etc. As an extension study, our interest lies in single-walled carbon nanotube (SWCNT) because it is one of the most prominent materials due to their excellent electrical, mechanical, and structural properties, yet has not been seen as a material equipped with much of inner hollow space. SWCNT is made from a graphite sheet rolled up into cylindrical shape containing a hollow interior (see Fig. 4). Our group sees its potentiality to store atoms or small molecules such as CH_4, H2, H_2O etc, thus aims to figure out the solidification effect, which is exerted by the confining surface depending on different chiralities of CNTs. Phase behaviors and properties of inserted particles in such a small structured-pore have not been extensively studied due to difficulties of controlling confining degree, hydrophobic nature, concentration and so on. Those limitations can be naturally removed in this study since artificial modification of the system (i.e. even unphysical state) is possible. From our preliminary

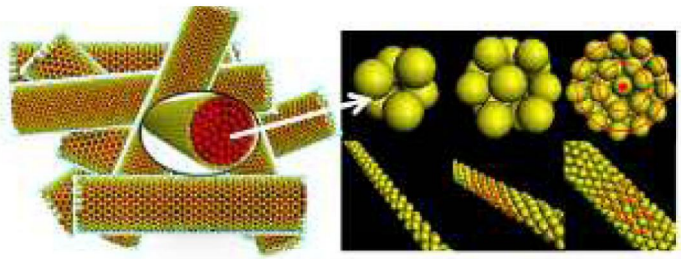

Figure 4 : Fluid particles confined in Carbon Nanotubes with different (m,n). Confined particles are extracted for detailed analysis (right)

study, we found that there exists a small effect of surface chirality on the shift of phase transition from fluid-like to solid-like, but it is minimal compared to variation of diameter. We continuously plan to obtain fundamental aspects of confined fluids influenced by pore size and surface chirality via MD method. This includes the study of subtle change from gas to liquid phase. In this case, the grand-canonical transition-matrix Monte Carlo (i.e. GC-TMMC) will be utilized to capture the phase transition.

4. Assembly of Drug Carrier Nanoparticle using Poly (Butyl-CyanoAcrylate)

The strength of a drug carrier system is greatly reflected in its pharmacokinetics over the conventional preparations. In particular its usage is important for the delivery of vulnerable biotechnologically-derived therapeutic substances into human body. Over past few decades, many experiments have been conducted to investigate the properties and structures of drug carrier systems, which aim to improve their performance. However, it is difficult (not to mention, it's costly) to investigate micro- to nano-scale drug carrier systems fully by experiments when the time-dependent phenomena such as transformation, formation, and dissolution of such system are under consideration. Thus, our group aims to investigate structure, properties, phase behavior (i.e. self-assembly) of drug carrier systems by using a coarse-graining simulation method, dissipative particle dynamics (DPD). The method is designed to illustrate the mesoscale (i.e. comparable to Kinetic Monte Carlo region in Fig.1) phase space, thus a large system can be simulated to depict actual phenomena related to morphology of the drug carrier. In this project, the DPD simulation has been particularly applied to investigate the poly (butyl-cyanoacrylate) (PBCA) drug carrier system (see Fig. 5), which contains surfactant (Lutrol®F68), ethanol, water, and oil (triglycerid), since it can potentially serve as a chemical coat for the drug protection and as a regulatory medium for the release of drug. Also, it is found to be a suitable drug carrier for insulin due to adjustable nature of nanoparticles in agglomeration. In the preliminary study, the nanospherical structure of the PBCA drug carrier system derived from the DPD simulation is found to be in good agreement with the structure determined from NMR analysis as emphasized by dotted-circle lines on the right side in Fig. 5. Thus, our group plans to carry out a systematic study on the PBCA drug carrier system with respect to formation and dissolution as well as transformation in size as functions of composition of constituent chemicals, thermal effect, pressure, and solution environment. since small disturbances to the initial system trigger significant changes of the phase and structure of the drug carrier system (i.e. as indicated in systems directed red arrows in Fig. 5). Subsequently, it is planned that the insulin will be included prior to the formation of the drug carrier to investigate realistic effects on formation and dissolution of the final drug-nanoparticles.

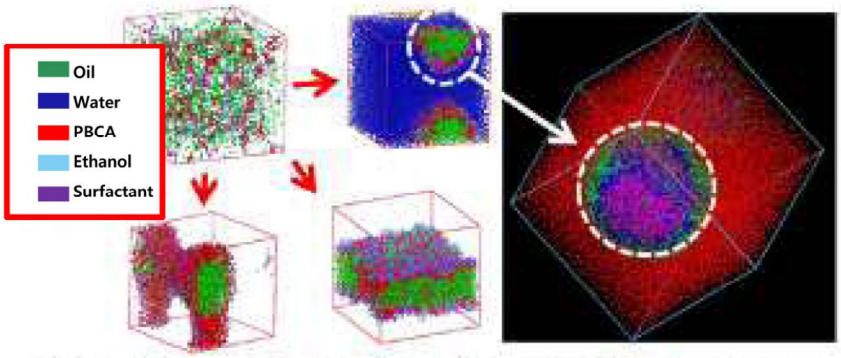

Figure 5 : Coarse-grained particles of oil, water, PBCA, ethanol, and surfactant. Different self-assemblies are observed depending on variables of concentration, polymer's chain length, temperature etc