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Introduction to Computational and Theoretical Studies Focused on Self-Assembly and Molecular Organization

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Self-assembly refers to the bottom-up organization of matter into structures with varying degrees and types of order and underpins the formation of materials such as micelles, molecular, polymeric and colloidal crystals, folded biomolecules, and biological organelles and tissues. Devising "bottom-up" strategies to design materials for novel applications requires a fundamental understanding of the physicochemical principles that govern self-assembly. Recent advancements in the development of novel computational methods and multiscale modeling, coupled with increased access to robust computational resources, have rendered atomistic and mesoscale simulations of the self-assembly of many complex systems possible. The special issue "*Computational and theoretical studies focused on self-assembly and molecular organization*" presents a collection of articles published in a single issue of the journal authored by leaders in the field.

The assembly and disassembly of proteins and other biomolecules into complex structures are pivotal to numerous biological process and are governed by the heterogeneous molecular surface characteristics. Ji et al. introduce a novel hydropathy scale for protein residues based on the collective response of water molecules within a protein's first hydration to increasing temperatures (10.1021/acs.jctc.3c00106). Using molecular dynamics (MD) simulations and Markov State Models, Ghosh et al. probe the mechanism through which α-crystallins inhibit the aggregation of γD-Crystallin, a key structural protein in human lens whose aggregation is thought to result in cataract formation (10.1021/acs.jctc.3c00774).

Liquid−liquid phase separation (LLPS) ensues when proteins segregate into dense (protein-rich) and dilute (solvent-rich) phases, a process that plays a key role in the formation and function of biocondensates that assemble within biological cells and organelles. It is, however, not feasible to study LLPS using conventional atomistic simulations due to their limited accessible time and length scales, necessitating instead suitable coarse-grained (CG) representations of proteins. Zerze optimizes the MARTINI 3 CG force field to accurately reproduce experimental estimates of the transfer free energies between dilute and dense phases of the low-sequence complexity domain of the Fused in Sarcoma protein. The work also emphasizes the sensitivity of the balance between salt screening and salting-out effects to the strength of protein−water interactions (10.1021/acs.jctc.2c01273). In another investigation concerning the MARTINI 3 force field, Vaiwala and Ayappa reparametrize it specifically for the outer lipopolysaccharide membrane of *E. coli* (10.1021/acs.jctc.3c00471). Kapoor et al. devise a CG model of DNA that is compatible with the HPS-Urry, a widely used CG protein force field. Employing this new model, they simulate a full nucleosome, both with and without histone tails (10.1021/acs.jctc.3c00525). Wasim et al. tackle the formidable task of modeling the 4.6 × 10^6-base pair genome of *E. coli* by developing a CG model with a resolution of 500 base pairs, informed by experimental contact maps and RNA-sequencing data. They demonstrate that the chromosome confined within a cell will self-organize into a series of nonoverlapping domains, consistent with experimental observations (10.1021/acs.jctc.3c00118). Hooten et al. employ a bottom-up strategy to construct CG models of triphenylalanine using fully atomistic MD trajectories. They reveal that changing the CG representation of the aromatic side chain from one bead to three beads significantly alters the morphologies of aggregates formed by these short peptides (10.1021/acs.jctc.3c00458).

The self-assembly of polymers into well-organized structures holds significant promise for the fabrication of materials with desired properties and functionalities. For instance, block copolymers (BCPs), i.e., polymers comprising of two or more chemically distinct types of monomers, can self-assemble into structures such as lamellae, cylinders, spheres, and bicontinuous phases, which have found diverse applications in drug delivery, soft lithography, catalysis, and gas storage. Grant et al. introduce a minimalistic, phenomenologically parametrizable CG particle-based model for chiral BCPs to compare BCPs comprised of achiral and chiral blocks, investigating the effect of chirality and chemical disparity on the free energy of disorder−order transition. They find that the helical pitch plays a dominant role in the effective repulsion between the two blocks (10.1021/acs.jctc.3c00680). An emerging area of research in the soft matter community is to understand the self-assembly characteristics of active polymers. Miranda et al. incorporate activity into CG ring polymers by applying a tangential self-propulsion force along the ring backbone. They demonstrate that when confined, active ring polymers self-organize into clusters of slowly moving rings, with faster moving rings dispersed outside such clusters. They observe such self-organization across a broad range of densities and

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confinement gaps, which is triggered once the activity surpasses a critical threshold value (10.1021/acs.jctc.3c00818).

In recent decades, there has been an increased interest in using nanoparticles to assemble complex superlattices. For instance, polymer-grafted nanoparticles have been demonstrated to spontaneously assemble into diverse anisotropic superstructures. Yu and Guo examine the effect of grafting density and polymer chain length on the self-assembly of polymer-grafted nanocrystals with spherical, octahedral, and cubic cores using a CG model. The dynamics of the assembly are tracked via the system crystallinity and orientational order. They find that the directional entropy encoded in the anisotropic cores fundamentally transforms the types of assembled ordered phases (10.1021/acs.jctc.3c00551). Nambiar et al. consider a tunable model of deformable, hinge-like nanoparticles anchored to a planar lipid bilayer via cholesterol molecules. They observe that nanoparticles with higher rigidity induce membrane deformation, facilitating the alignment of their hinges (10.1021/acs.jctc.3c00687). Upah et al. assess the impact of implementation details, such as the employed thermostat, MD time step, potential cutoff, initial configuration, sampling method, and the simulation length, on the potential of mean forces between two gold nanocrystals decorated with thiol chains (10.1021/acs.jctc.3c00749). Rod-shaped particles exhibit a propensity to align and assemble into liquid crystalline phases upon increasing number density or applying shear deformation. Garcia Daza et al. perform microrheology simulations of smectic liquid crystals using a dynamic Monte Carlo approach to determine the magnitude of the friction force experienced by a spherical tracer particle being dragged by a constant force (10.1021/acs.jctc.3c00356). Since the nature of the interactions between individual building blocks dictates their self-assembly behavior, the task of designing target self-assembled structure can be formulated as an inverse design problem wherein the interactions among building blocks are optimized for that purpose. Petix et al. improve the efficiency of the relative entropy minimization approach in inverse design by developing a Chebyshev polynomial interpolation methodology on Smolyak sparse grids (10.1021/acs.jctc.3c00651).

Nanoporous materials represent another class of materials with wide-ranging applications in energy storage, catalyst support, and separation of gases and liquids. Ugwumadu et al. introduce a new simulation protocol designed for generating atomistic models of amorphous nanoporous carbon materials. Their findings reveal that *sp*-hybridized carbon atoms predominantly populate pore surfaces, functioning as active sites for oxygen adsorption (10.1021/acs.jctc.3c00394). Rocha and Vashisth use Langevin dynamics to study the self-assembly of binary mixtures of dumbbell (two-lobe) shaped and various multilobe shaped nanoparticles. Their simulations reveal that the structures assembled from such binary mixtures exhibit markedly higher levels of porosity compared to those formed by monodisperse systems (10.1021/acs.jctc.3c00406).

Surfactants, which are comprised of polar head groups and hydrophobic tails, possess a distinctive capacity for self-assembly both in aqueous solutions and at interfaces. Kanduč et al. devise a self-consistent thermodynamic framework, which, coupled with free energy calculations, offers a comprehensive thermodynamic characterization of the micellization process and the adsorption behavior of surfactants at interfaces (10.1021/acs.jctc.3c00223). The self-assembly of several moieties, such as proteins, lipids, and surfactants, is driven by hydrophobic hydration. Ashbaugh estimates the free energies associated with the removal of water molecules from cavities within aqueous media and introduces a new statistical mechanical framework to relate the computed free energies to water structure within cavities (10.1021/acs.jctc.3c00387). Le et al. investigate the aggregation of kaolinite particles through a multiscale modeling approach, examining their behavior across varying salt concentrations. They use atomistic simulations to estimate effective interactions between kaolinite particles and observe the formation of large kaolinite aggregates in the absence of salt, whereas the presence of salt leads to reduced aggregation (10.1021/acs.jctc.3c00719). Sun and Escobedo study the phase behavior of bolapolyphiles, molecules featuring a rigid rod-like core with hydrophilic ends, decorated with hydrophobic side chains of varying branching patterns. They report the formation of several network phases depending on the molecular architecture and temperature and detail a methodology to characterize the space group, periodic unit cell and the structure factor of such phases, even in the presence of defects and distortions arising from localized disorder or incompatible simulation box sizes (10.1021/acs.jctc.3c00395).

Most self-assembly processes proceed through a nucleation and growth mechanism, and identifying appropriate collective variables (CVs) for nucleation is essential for systematically investigating the kinetics and mechanism of self-assembly. An essential criterion for such CVs is their invariance to translations, rotations, and permutations of chemically equivalent growth units. Deitrich et al. introduce a new approach utilizing graph neural networks to compute nucleation CVs on-the-fly, resulting in an orders-of-magnitude enhancement in computational efficiency (10.1021/acs.jctc.3c00722).

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