Perspective

Molecular Simulations in Chemical Engineering: Present and Future

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Introduction

The first direct simulations of phase equilibria for simple molecules (argon) were performed slightly over a decade ago (Panagiotopoulos, 1987). Today, calculations of phase behavior for multicomponent mixtures of engineering importance are no longer surprising (e.g., Nath et al., 1998; Escobedo, 2000; Chen et al., 2001; Zervopoulou et al, 2001), simulations of phase transformations of solids under extreme conditions of pressure and temperature are now feasible (Lacks, 2000), studies on the rheological response of lubricants under enginelike conditions are increasingly common (McCabe et al., 2001), and the structure and thermodynamic properties of large polymeric molecules can be determined reliably from simulations (Karayiannis et al., 2002).

Molecular simulations have made enormous strides in recent years, and are gradually becoming a ubiquitous tool in many fields of science and engineering. It is partly due to the ever-increasing speed of computers and, perhaps to a larger extent, to the development of new methods for simulation of complex fluids and materials. Chemical engineers have been responsible for many of the developments and applications of molecular simulations. In this Perspective, the status of this field is reviewed briefly, as well as some of the areas that hold the greatest promise for future development.

A molecular simulation generally consists of a computer realization of a system in which actual molecular configurations are used to extract structural, thermodynamic and dynamic information (Frenkel and Smit, 2002). The term "configuration" denotes a set of Cartesian coordinates (and momenta in the case of dynamic simulations) for all the atoms or molecules that constitute a system. The quality of this information depends strongly on the number of uncorrelated configurations available for subsequent analysis. At the heart of a molecular simulation lie the methods employed to generate them. In molecular dynamics, Newton's equations of motion are integrated to generate a trajectory for the system of interest. In Monte Carlo methods, probability distribution functions dictated by statistical mechanics are sampled to generate distinct configurations.

This article focuses on simulation of systems described by classical force fields, noting that an area of intense research is concerned with bridging the gap between classical and quantum descriptions, and even between quantum and macroscopic models (Sum and Sandler, 1999). It is also centered on Monte Carlo (MC) methods, as opposed to molecular dynamics (MD) techniques; MC methods are not as widely used by the engineering community as MD, yet hold perhaps the greatest potential impact.

Classical MD methods are relatively robust and general. These attributes have led to the widespread availability of commercial and public domain software for MD simulations. These calculations follow the natural dynamics of a system, and the resulting trajectories typically last a few tens of nanoseconds; unfortunately, for fluids or materials of engineering importance, many phenomena of interest occur on much longer time scales. The diffusion coefficient of a gas through a polymeric glass is on the order of 10^{-13} cm^2/s, which implies that, on average, in a nanosecond-long simulation a gas molecule would only travel a fraction of an Angstrom—too small a distance to generate any meaningful statistical information. While several "acceleration" techniques have been proposed over the last several years (e.g., Voter et al., 2002), many orders of magnitude must be bridged before MD can be used to study micro- or millisecond processes.

Monte Carlo methods usually rely on acceptance/rejection algorithms. Starting from an initial configuration, random perturbations of the system are proposed (e.g., by performing random displacements of the atoms about their original positions). By "accepting" only some of the resulting random configurations, one can construct an ensemble of those distributed according to well-defined functions of the energy, temperature, and other relevant thermodynamic variables (these functions are dictated by statistical mechanics).

Monte Carlo methods do not have the all-purpose appeal of MD, tending to be system-specific. MC algorithms vary widely depending on the system of interest, and they are not well suited for study of time-dependent processes. These techniques are designed to sample representative microstates (snapshots or configurations) of a system at equilibrium; macroscopic properties are found as the average of microscopic quantities measured over the ensemble of snapshots. In general, MC is as effective as one's ability to sample such microstates. The challenge of sampling configuration space is best exemplified by the "protein folding" problem, where an algorithm must somehow be capable of identifying a restricted number of folded states out of countless configurations.

This challenge arises in the simulation of most complex systems. Ionic and polymeric materials, for instance, are well known cases where "relaxation" to equilibrium is difficult due to trapping in local energy minima. Sampling techniques that have been proven effective for a given system can be completely useless for another. While such a specialization is a problem, it also provides an oppor-

tunity for development of system-specific methods for fluids or materials that could not be studied otherwise. In a sense, the key for designing improved and effective MC methods thereby lies in the ability to capitalize on our physical understanding of a system to overcome its particular ergodicity problems.

Present and Future Applications

Table 1 summarizes some of the conventional simulation methods that have found widespread use, along with representative novel methods that appear promising at addressing some of the challenges associated with complex systems. This table provides only an overview of various techniques and applications available in the literature. It also illustrates the rate at which new methods are being developed and the variety of systems that are amenable to study by molecular simulation.

In general, advanced Monte Carlo methods can be classified into three categories. The various entries in Table 1 are color-coded according to the category. This discussion is facilitated by viewing the free energy surface or landscape of a complex system as consisting of deep minima separated by large barriers. In the first category (red in Table 1), elaborate schemes are devised to artificially eliminate the high-energy barriers that preclude good sampling of configuration space. An example of this type of method is provided by the so-called "multicanonical ensemble" technique, which systematically smoothes out a rugged free energy landscape by assigning artificial weights to states or configurations that would otherwise never be visited.

In the second category (blue in Table 1), highly creative Monte Carlo "moves" are designed to help the system "jump" over free energy barriers. An example of this type of moves is provided by the double-bridging Monte Carlo technique (Karayiannis et al., 2002), in which entire pieces of two long polymer molecules are excised and reconnected, thereby altering significantly the connectivity of a configuration and the overall shape or conformation of the molecules.

The third category of MC methods (green in Table 1) aims to maximize the amount of statistically relevant information that can be extracted from a finite set of calculations. An example of this type of technique is provided by histogram reweighting approaches (Ferrenberg and Swendsen, 1989), in which entire distributions (as opposed to only average values) are collected during a simulation. These distributions can be subsequently recombined and manipulated to generate thermodynamic and structural information over wide ranges of conditions from a relatively small number of simulations. These three categories are not mutually exclusive and,

Table 1. Overview of Methods for Molecular Simulation with Classical Force Fields

Basic Goal Space	Established Methods	Emerging Methods	Typical areas of Application
Simulate dynamics, evolution of a system	Molecular dynamics (MD) in various std. Ensembles	Hyperdynamics, Self-guided MD, Multiscale & parallel implementations	Peptide and protein modeling, Polymer dynamics, Dynamics of fluids near glass transition, "billion"-atom simulations
	Brownian dynamics	various flow situations, external fields, & anisotropic hydrodynamic interactions	Polymer chain dynamics in solution, DNA dynamics
		Multiscale variants coupled with macroscopic flow	Polymer melt processing, crystallization
		Diffusive particle dynamics (DPD)	Block copolymer phase segregation, micellar formation
	Kinetic Monte Carlo Methods	Implementations not requiring a-priori table of events	Coarse-grained modeling of surface deposition, crystallization, and folding events
Identifying equilibrium states, Structure, thermo-dynamic properties	Lattice models; e.g., bond-fluctuation model	Novel lattices that closely mimic continuum space	Ionic systems, protein folding, meso-scales
	Biased Monte Carlo methods in various ensembles	New methods for chain systems, rebridging of chains, cluster moves in hydrogen-bonding systems, polarizable models	Long chain melts and blends, hydrogen-bonding and ionic systems
	Simulated tempering, Multicanonical Sampling, Parallel tempering or replica exchange	combinations of these methods	Biological molecules, peptides, proteins, zeolites, porous media, polymers, atom clusters
Identifying mechanisms via free energy landscape	Umbrella sampling methods	Multidimensional mapping via ad-hoc order parameters	Nucleation in liquids and solids
Phase equilibrium calculations	Interfacial methods, Gibbs ensemble, Gibbs-Duhem integration	methods for solid-fluid coexistence, variants based on grand canonical ensemble	Phase transitions in confined spaces, micellar phases, liquid crystals, "complete" phase diagrams
Mapping/extrapolating point-wise data	Taylor-series expansions, Histogram reweighting	Extensions to various ensembles, finite-size analysis	Numerous systems, critical points, ionic species, Polydisperse polymers, etc.
Mapping out entire regions of thermo-dynamic space		Density of states method	Numerous systems including polymers and biopolymers

in fact, some of the more courageous simulations to date have involved combinations of several MC techniques.

In the chemical engineering literature, molecular simulations have been extensively used as a means to generate "pseudo-experimental" data. Such simulation studies generally develop and validate a force field by reproducing experimental data and can often provide predictions under conditions that complement available data (Chen and Mathias, 2002).

Recent applications of Monte Carlo simulations employing classical force fields cover wide-ranging phenomena such as vapor-liquid equilibria for hydrocarbons (Martin and Siepmann, 1998; Nath et al., 1998; Errington and Panagiotopoulos, 1999), isoenthalps (Escobedo and Chen, 2001), freezing of solids (Malanoski and Monson, 1999; Polson and Frenkel, 1999), phase-transitions in pores (Radhakrishnan et al., 2002), adsorption of gases in solid matrices (Muller et al., 2000; Sarkisov and Monson, 2000), partitioning of hydrocarbons in zeolites (Macedonia and Maginn, 1999; Calero et al., 2001), determination of zeolite structures (Falcioni and Deem, 1999), structure and properties of polymers (Karayiannis et al., 2002), as well as the thermophysics of water (Errington and Debenedetti, 2001), polar substances, and hydrogen-bonding fluids (Visco and Kofke, 1999; Chen et al., 2001; Shah et al., 2002).

The cornerstone for this type of applications is the force field. Some aspects of a force field can be determined from electronic structure calculations, but further optimization by analysis of experimental data is generally required to improve the predictive capability of a model.

While applications aimed at filling in the gaps in physical and chemical data are boundless, the future of simulation methods may lie instead in applications aimed at the discovery of new phenomena or the elucidation of the physics that govern the behavior of novel systems. In cases where controlled laboratory experiments are too difficult or impossible, simulations can be used to construct virtual experiments for study of complex systems. Similarly, in situations where experimental results are ambiguous or indirect, simulations provide an ideal complement for precise interpretation of laboratory data. Such applications, even though more fundamental in nature, could have a significant impact in the hands of scientists and engineers.

Although accurate force fields offer obvious advantages to discovery-driven simulations, coarse-grained models can be more appropriate when physical understanding is the focus and computational demands create a bottleneck. Such science-driven simulations are not new, as they have been reported ever since the inception of molecular simulation (e.g., to elucidate the role of entropy in phase transitions via the study of hard-sphere and hard-rod systems). But many recent studies have mainly served as a proof-of-the-concept of what is potentially achievable (Escobedo, 2001).

Many studies have been reported on the use of MC methods as a discovery tool in nanofabrication processes, in materials science, or in biological research, to name a few. In fact, one could argue that several of the studies referenced above regarding pseudo-experimental data generation also include an element of "discovery." Instead of a long list of applications, two recent examples are detailed that illustrate how simulations can be used to elucidate problems of interest to chemical engineers: the catastrophic collapse of photoresist structures encountered in lithographic nanofabrication processes, and the study of an atypical antibody and the key interactions that govern the structure of its binding site.

Recent work has established that the mass transport and glass transition behavior of polymeric materials in nanoscopic structures can differ significantly from that of the bulk. A *structure* in this case is defined as a physical construct (e.g., a film, a line, or a post). These structures are important in a wide variety of applications, most notably in lithographic nanofabrication processes (Cao et al., 2000). The origin of these differences is not well understood and is a subject of considerable debate. Less is known about the mechanical properties of nanoscopic structures, although it is precisely these properties that pose the most immediate and significant challenges to the future success of nanofabrication processes. Characterizing experimentally the mechanical properties of polymeric nanoscopic structures is particularly challenging; molecular simulations are playing an important role by providing striking qualitative predictions of elastic behavior in such systems.

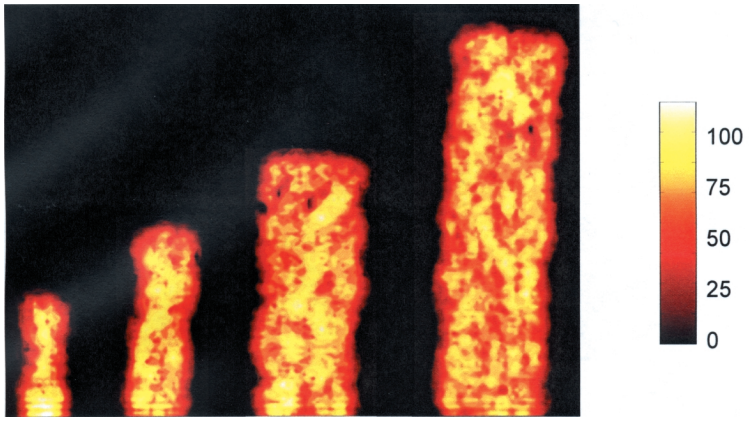

Figure 1. Cross-section of local mechanical constants of nanoscopic polymeric structures as a function of size.
The color code is used to depict the constants as a percentage of the bulk value. The structures consist of polymer molecules supported on a crystalline substrate.

The challenge for simulations has been twofold. Generating representative configurations for glassy systems has required development of new theoretical constructs and new sampling techniques (Debenedetti and Stillinger, 2001, Wang and Landau, 2001, Yan et al., 2002), and the nature of the problem has required that new ways be developed for calculation of local stresses and elastic moduli (Todd et al., 1995, Van Workum, 2002). Recent simulations of glassy, thin polymer films and nanoscopic structures (Boehme and de Pablo, 2002), for example, indicate that the bending modulus of ultra-small polymer walls or lines is considerably smaller than that of the bulk material. This loss of mechanical strength could have adverse effects for future lithographic nanofabrication processes at the scale of tens of nanometers. That work has also shown that such lines are mechanically inhomogeneous at the scale of a few nanometers (Van Workum, 2002).

Figure 1 shows a cross section of several glassy, polymeric nanostructures of different sizes; the structures are infinitely long in the direction perpendicular to the page and are supported at the bottom by a crystalline substrate. The width of the largest structure is approximately 20 monomer diameters, and the molecules consist of 16 monomers connected by flexible bonds. The aspect ratio of the struc-

tures is approximately four. The color code is used to represent normal mechanical constants as a percentage of the bulk value. For a simple, homogeneous material, one expects to have a mechanical continuum with uniform mechanical properties throughout the sample. For glassy nanostructures, however, the picture that emerges from simulations is different. Distinct domains are observed having large or low mechanical constants and having characteristic dimensions of approximately 2 to 4 monomer diameters. The occurrence of these domains raises questions about the ability of continuum mechanics to describe nanoscopic, amorphous polymeric glassy structures, and it will be interesting to develop formalisms capable of bridging the molecular representation outlined here with continuum treatments for solid deformation processes.

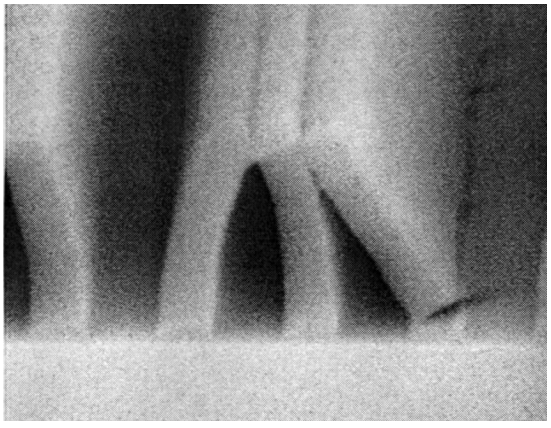

Figure 2. Collapse of polymeric structures (lines) during processing.
The width of the structures is approximately 100 nm, and their aspect ratio is 5.

Near the surfaces of the structure, the mechanical constants (e.g., the bending modulus) are much lower than in the bulk of the system; this leads to an overall loss of mechanical stability of polymeric structures having characteristic dimensions of tens of nanometers. It is experimentally observed that polymer lines of comparable dimensions do exhibit a propensity to "collapse" during wet processing (see Figure 2). While such collapse can be partially attributed to the capillary forces exerted by rinse solvents, the size-induced plastification as evidenced by simulations is likely to play an important role in this problem. These findings could, in turn, have an impact on our ability to mass-produce nanoscopic structures out of polymeric glasses; by understanding the origin of this loss of mechanical strength, one could proceed to engineer materials or approaches that circumvent collapse.

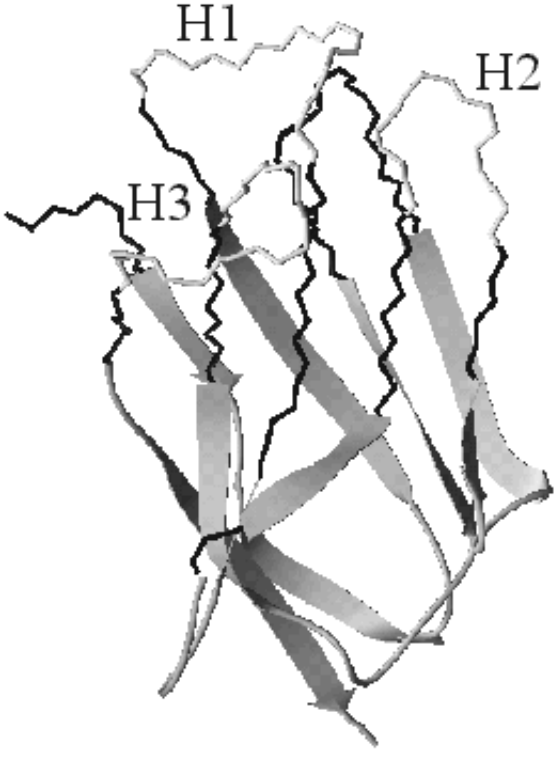

Figure 3. Main-chain atoms of the llama HC-V domain solved by X-ray diffraction (Spinelly et al., 1996).
The loops are shown as gray lines and proximal framework regions as black lines.

In the general area of biophysics, MC molecular simulations have been extensively applied to biopolymers such as peptides and proteins (e.g., Wu and Deem, 1999; Skolnick and Kolinski, 1999; Mitsutake et al., 2001; Rathore and de Pablo, 2002). The engineering of antibodies for novel applications in medicine, separations, and catalysis is an area where MC methods can play an important role. The binding site of a typical mammalian antibody is composed of six "loops" or hypervariable regions where mutations tend to concentrate (loops H1, H2, H3 belong to the heavy chain, and, L1, L2, and L3 to the light chain). A common approach to predict loop structures is to use a knowledge-based (KB) method that relies on homology rules derived from solved protein structures. The canonical structure model (Al-Lazikani et al., 1997) assumes that the main chain structures of the antibody loops (except H3) depend on loop length, as well as on a few key residues located at specific sites. They, therefore, typically adopt one of a limited number of structures.

Camelid antibodies are unique in that their antigen-binding site often has only three loops (H1, H2, and H3). They represent the smallest such structure produced in nature. Camelid antibodies have brought new challenges to KB methods; known extensions of the canonical structure model (Decanniere et al., 2000) have had limited success. These molecules also provide new opportunities to enrich our understanding of the structure-function relationship in antibodies.

The loops of an uncomplexed llama heavy-chain V domain (HC-V) have been recently studied by molecular simulation (Fenwick and Escobedo, 2002). In the crystal structure (see Figure 3), these loops adopt conformations inconsistent with the predictions of KB methods. To simulate this system in solution, a novel MC method was implemented that uses: (1) an MD engine (Brooks et al., 1983) for its ability to handle atomistic level detail and allow global "moves"; (2) hybrid MC (Mehlig et al., 1992) so that MD can be readily combined with other MC schemes; and (3) a generalized replica-exchange method (Yan and de Pablo, 1999; Sugita et al., 2000) that constructs a multibox ladder wherein beneficial conformational changes generated at ergodic states (e.g., at high temperatures and softer constraints) can trickle down to the nonergodic states of interest.

While standard MD gets trapped in local minima states (near the initial "guess" structure), this MC method is able to relax the system to equilibrium. Although simulated structures were consistent with

the known crystal structure (see Figure 4), they show more than one preferred conformational state for loops H1 and H3. Such atypical conformational freedom of H1 may confer this antibody added adaptability during complex formation to compensate for the lack of a light chain. Through the analysis of simulated structures, which contain more detail than the crystal structure, a number of key interactions were identified that may explain the poor predictions of KB models; e.g., the presence of uncommon aminoacids in the H1 region appears to induce noncanonical features in the structures of H2 (via steric effects) and H3 (via an inter-loop salt-bridge). A more complete picture of structural determinants of Camelid antibody loops could be made via *in-silica* site-directed mutagenesis.

Where do we go from here?

Just as for fluid mechanics, where analytical theories have been gradually surpassed by numerical solutions capable of describing more complex situations, a similar trend is occurring in statistical mechanics, where numerical solutions (i.e., molecular simulation methods) are gradually becoming the technique of choice to describe systems of ever-increasing realism and complexity. Discovery-driven, rather than data-driven, simulations are likely to have the largest impact on the development of improved or novel technologies. The challenge for future applications of molecular simulation, as either a "pseudo-experimental" data generator or a discovery tool, lies in developing more sophisticated algorithms capable of handling the increasing complexity and size of the systems. In this context, *tailor-made*, smart MC methods appear more promising than *all-purpose* MD techniques. Only a decade ago, it would have been difficult to anticipate that phase equilibria for complex, multicomponent mixtures could be predicted accurately from simulations. Such calculations are still demanding, but they are no longer perceived to be out of the ordinary. What used to be a novel way of predicting phase behavior has become a more conventional application of simulations.

In chemical engineering, molecular simulations will likely impact both traditional areas and emerging fields. Indeed, as discussed before, molecular simulations can play an important role in the growing fields of biomolecular engineering and in nano-science and technology, where device sizes are coincidentally becoming commensurate with those amenable to simulation. Chemical engineers have traditionally been in the business of molecular transformations. Science and engineering have given us an unprecedented ability to manipulate small structures and even individual molecules. This ability will give rise to new opportunities and new questions. Molecular simulations are uniquely positioned to help answer some of these questions and help guide the design of novel, molecular-scale processes. Accurate force fields will still be necessary and, in some cases (e.g., in the study of chemical reactions), it will be necessary to resort to quantum-mechanical levels of description. But calculations that may now seem to be far-fetched could soon become routine applications of simulations.

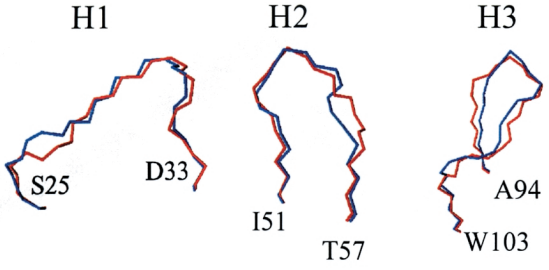

Figure 4. Comparison of the H1, H2, and H3 loops from a representative sample of the most populated states in an MC simulation (gray lines) with the corresponding loops in the crystal structure (dark lines).
Their root mean squared distances are 0.83, 1.02, and 1.51 Å, respectively. The alpha-numeric symbols at the bottom denote the aminoacids at the loop bases.

In the study of truly macroscopic systems, a different challenge lies in developing "multiscale" approaches that can integrate modeling tools capable of describing a system over a wide range of length and time scales (Maroudas, 2000, Jendrejack et al. 2002, Abraham et al., 1998). We are already seeing important advances in the multiscale modeling of solids and non-Newtonian fluids. With continuing progress, some of these methods will become standard in commercial software, and practicing engineers will eventually be able to use these for development, design and operation of the chemical engineering processes of the future.

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