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Recent Contributions of Statistical Mechanics in Chemical Engineering

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Some of the recent advances that have been made by chemical engineers in the field of statistical mechanics, as well as some of the new products and processes that have resulted from these advances, are reviewed. New approaches to molecular dynamics, Monte Carlo, quantum mechanics, master equations, hierarchical methods, liquid state theory, and field theory are discussed. Applications and commercial results in the microelectronics, biotechnology, pharmaceutical, and chemical process industries are highlighted.

Introduction

Statistical mechanics is the basis with which we seek to understand and predict natural phenomena on the molecular level. There is a long history of emphasis on thermodynamics in chemical engineering. Only in the last 20 years, however, has statistical mechanics become a major focus within chemical engineering. In the past decade, graduate student research has exploded with the adoption of computational statistical mechanics. The number of chemical engineering faculty in the U.S. engaged in molecular-level simulation as their primary area of research has risen from a handful a decade ago to roughly 40 now (Cummings et al., 1997). The number of chemical engineering faculty specializing in quantum-mechanical calculations has risen from essentially zero to about ten. Finally, the number of chemical engineering faculty engaged in field-theoretic approaches to statistical mechanics has risen from zero to roughly four.

Statistical mechanics has begun to make an appearance in graduate education programs. The majority of the "top ten" programs require a course in statistical mechanics, and almost all offer one as an elective. In contrast, statistical mechanics has not yet made a substantial impact on undergraduate education. A number of programs offer an undergraduate elective course in statistical mechanics, but a typical undergraduate student in chemical engineering receives exposure to this subject only within a physical chemistry class. This has implications when recruiting students to graduate research programs, where we often may be forced to describe statistical mechanics as a type of modern thermodynamics.

The purpose of this review is to highlight some of the advances that have been made within statistical mechanics in the last decade. Attention has purposely been focused to ad-

vances made by chemical engineers. This is done to emphasize the impact of statistical mechanics developed by chemical engineers on the field of chemical engineering. A large body of work, present within physical chemistry and condensed matter physics, will go mostly unmentioned. Deep, conceptual insights from various aspects of statistical mechanics that have led to new, predictive capabilities will be discussed. In addition, some specific products and processes that have resulted from statistical mechanics research will be mentioned. Specific fruits of the research in statistical mechanics are shown in *italic*. These *italicized items* are specific examples of new products or processes within companies, not academic laboratories, that have resulted from fundamental research in the last decade. The conclusion contains a more exhaustive list of applications from the chemical process industries.

This review is organized primarily by the methods of statistical mechanics, rather than by the fields of application, to emphasize the importance of fundamental insights in the creation of new products and processes. Various means of simulating classical dynamics for molecular systems of interest to chemical engineers are discussed first. The commercialization of a new line of surfactants from such molecular dynamics research is mentioned. Many effective methods that chemical engineers have invented for the computational calculation of equilibrium properties of molecular systems are discussed next. Drug design, plant optimization, and crystal structure determination are mentioned as unique example applications. A case study illustrates how the theory of statistical mechanics can be used to determine the crystal structures of zeolitic materials. Some of the uses of quantum me-

chanics in chemical engineering are mentioned. Applications in the fields of catalysis and process design are cited. Analytical and numerical master equation approaches, are discussed next. Applications in X-ray diffraction and transdermal drug delivery are mentioned. Hierarchical methods that can simulate large molecular systems to long times by a combination of accurate atomistic simulation methods with more "coarse-grained" methods are discussed. The growing use of classical liquid state theory within chemical engineering is reviewed. The density functional approach to liquid state properties is discussed. Some of the field-theoretic work in chemical engineering is next reviewed. Finally, some of the recent applications of statistical mechanics to molecular biology and the biotechnology industry are discussed. To illustrate the tremendous future potential of this field for chemical engineering, some important recent work from chemists has been included. Many examples in drug design, combinatorial synthesis, and pharmacogenomics are listed to emphasize the significance of this field for chemical engineers. Finally, a list of applications of molecular simulation from the chemical process industries is given and conclusions are drawn.

Molecular Dynamics

Following the motion of individual molecules through space is one of the most natural atomic-level simulations to perform on a computer. This procedure requires nothing more than integrating Newton's equation of motion

$$F_i = m_i \ddot{r}_i, \qquad (1)$$

with which we are all familiar. From this simulation, which is a molecular dynamics simulation, we gather information about the molecular system of interest. We learn about both the dynamics of the system, and, for a long enough simulation, the average properties of the system. The results are relatively simple to interpret, because our intuition is trained to understand classical motion from an early age. Of course, since we are studying atomic-level phenomena, it is more appropriate to use quantum mechanics rather than classical mechanics. In view of the difficulty in performing quantum calculations, however, we may content ourselves with the approximate results provided by classical mechanics. Essentially all implementations of molecular dynamics simply follow the classical trajectories of atoms predicted by Eq. 1 and ignore quantum effects. To calculate the force on each atom, F_i, we need a force field. Standard forms of force fields for molecular systems have been derived over the years. These force fields provide the internal energy associated with a given arrangement of the atoms within a system. The force on each atom is then given as the gradient of this internal energy

$$F_i = \nabla_{r_i} U(r_1, \ldots, r_N). \qquad (2)$$

Derivation of force fields transferable between different molecular systems and valid over wide ranges of temperature and density remains an active area of research. The major challenge of molecular dynamics is to integrate Newton's law to long periods of time. Characteristic time scales associated with molecular motions are in the femtoseconds, yet often we

may be interested in phenomena in the picosecond or even second time scale. The stiffness of the differential equations, which results from the disparate time scales of the various intramolecular and intermolecular motions, makes numerical integration of Newton's law difficult. At the present time, for fully atomistic simulations, we are unable to access times significantly beyond the one-hundred picosecond range.

Simple examples

The straightforward molecular dynamics method, even though limited to investigation of phenomena on the picosecond time scale, is quite powerful. A large number of physical phenomena of interest to chemical engineers have been investigated by this method in the past decade. These investigations can be roughly broken down into those that were primarily interested in the dynamics of the system under study and those that were primarily interested in the structure.

Zeolites are microcrystalline materials widely used in the chemical industry as catalysts, sorbents, and ion-exchange materials. Figure 1 shows three zeolites that are commonly used in these applications. Essentially all of the applications of zeolites are limited by diffusion; hence, transport within zeolites has been an active area of research. Below are a few examples selected from these studies.

Alkanes in zeolites are a natural case to study due to the importance of zeolites in petroleum cracking operations. An interesting phenomenon, observed experimentally with some controversy, is resonant diffusion, where the diffusivity of long-chain alkanes depends in a nonmonotonic fashion on the chain length. The Maginn group has undertaken the challenge of observing this phenomenon by molecular simulation (Runnebaum and Maginn, 1997). Resonant diffusion was, indeed, observed in their simulation of long-chain alkanes in silicalite, although the effects were not as dramatic as in the original experiments. Zeolites used in catalytic operations produce a complex reaction product mixture during operation, and the transport properties of such mixtures are of importance to the overall performance. The Snurr group has undertaken model studies of diffusion in binary mixtures in silicalite (Snurr and Kärger, 1997). The molecular dynamics calculations produced diffusivities in agreement with pulsed-field-gradient NMR measurements. Detailed mechanistic information was derived from these studies. For example, with a mixture of methane and CF_4, methane was found to adsorb preferentially in the ziz-zag channels, while CF_4 was found to adsorb preferentially in the straight channels. Anisotropic diffusion was observed as well in this noncubic material.

The transport properties of zeolites are limited not only by internal diffusion but also by access to the internal pore network from the surface. The effect of surface barriers on kinetics is relatively simple to estimate when the windows that allow reactants to enter the interior of a zeolite catalyst are taken to be rigid. Molecular dynamics allows one to estimate the importance of fluctuations in the windows, and the Glandt group has used molecular dynamics to study the effects of these breathing modes (Ford and Glandt, 1995a,b). Dynamics of the windows is most significant when the size of the reactant (or product) is comparable to that of the window. In this case, the species can pass through the window only when fluctuations open the window beyond its average size. The
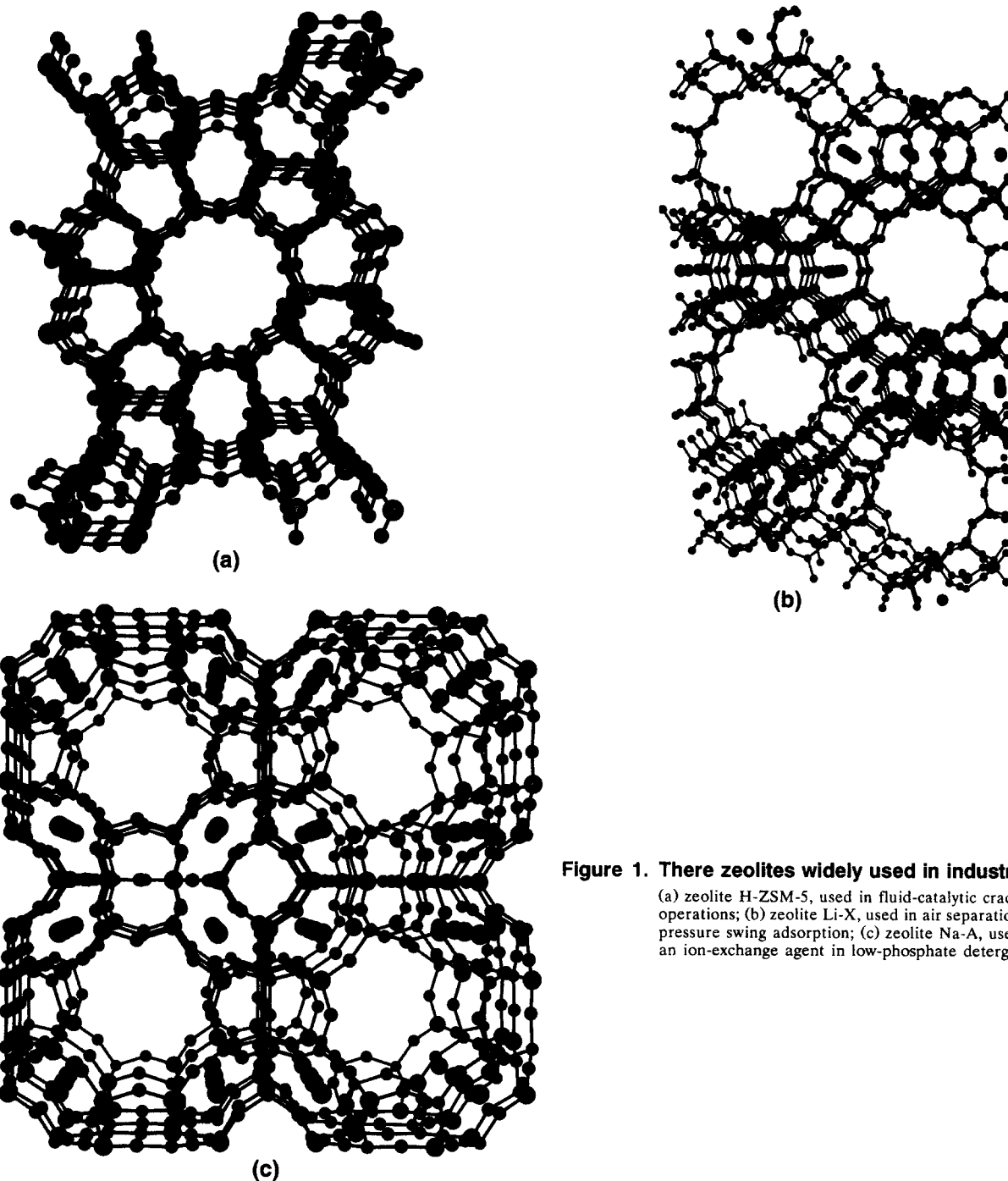
Figure 1. There zeolites widely used in industry.

(a) zeolite H-ZSM-5, used in fluid-catalytic cracking operations; (b) zeolite Li-X, used in air separation by pressure swing adsorption; (c) zeolite Na-A, used as an ion-exchange agent in low-phosphate detergents.

same effect is significant for diffusion of reactants within the zeolite, which occurs also by cage-to-cage hopping through windows. I have estimated that the kinetic window effect can increase the effective size of windows in zeolites by at least 0.5 Å, which is roughly the same order of magnitude as observed in experiments (Deem et al., 1992).

The kinetics of heterogeneous reactions on metal surfaces is an important area for chemical engineering. While the re-

action event itself must be studied with quantum mechanical calculations, transport of physisorbed or chemisorbed reactants on the surface may be reliably studied by classical means. The Fichthorn group has used molecular dynamics to look at the diffusion of n-alkanes on platinum surfaces (Huang et al., 1994). The alkanes were found to stay relatively closely bound to the surface with occasional rotations of parts of the molecule off the surface. The dominant mechanism for diffu-

sion was found to be overall rotation and translation of the molecules within the surface plane. Important dynamical corrections to simple transition state theory for the dynamics were identified in these detailed calculations.

Fluid mechanics is another traditional area of strength within chemical engineering, and analysis of the continuum Navier-Stokes equations is the traditional approach. Calculation of the transport coefficients and boundary conditions, however, is intrinsically a molecular problem. Among the many studies, an interesting example of what molecular dynamics can teach us comes from the work of the Troian group (Thompson and Troian, 1997). This simulation examined the slip/no-slip boundary conditions for a simple fluid near a rough surface. The traditional Navier slip boundary condition was found to be a low-shear limit of a more general nonlinear relation between slip and local shear rate and surface roughness. Determination of general results such as this from specific studies is one of the most prized goals of simulation research.

As a final example of a dynamical study, I mention a study by the Debenedetti group on glassy fluids (Speedy and Debenedetti, 1996). Supercooled fluids are metastable, and their properties cannot be calculated by normal equilibrium thermodynamic calculations. One must, in principle, know the detailed dynamics of glassy systems to predict their properties. Molecular dynamics, of course, is suited to perform exactly these types of studies, although the accessible time scales are rather short. By studying a model tetravalent fluid, the Debenedetti group was able to investigate how the glass transition depends on the rate at which the fluid is cooled (Speedy and Debenedetti, 1996). For sufficiently slow cooling, the transition was found to be independent of the quench rate. This result is significant because it indicates that, in this limit, the properties actually do not depend on the detailed kinetics: the glass transition becomes an ideal transition in a type of generalized thermodynamics.

The thermodynamics and kinetics of zeolite synthesis is an active area of research. As an example of the use of molecular dynamics to determine a primarily structural property, I mention an investigation of the thermodynamics of ZSM-11 synthesis from amorphous silica by the Bell group (Shen et al., 1997). The challenge was to calculate the Gibbs free energy of formation of the zeolite from the amorphous silica and tetraalkylammonium hydroxide precursors. The overall free energy change was broken down into pieces through the use of thermodynamic cycles. Many of these pieces could be estimated from previously available experimental data. Some significant energy and entropy changes, however, were unavailable, and these were estimated by straightforward molecular dynamics calculations. The overall prediction was impressively accurate and correctly predicted that three tetrabutylammonium cations and one tetrapropylammonium cation occupy each unit cell on average.

Surfactants are widely used within the chemical process industries, and they have received intensive scrutiny within the statistical mechanics community under the name "complex fluids." These are difficult molecules to study via molecular dynamics, since the natural dynamics occurs rather slowly. The Smit group overcame this limitation by studying a model surfactant, with a softer potential energy surface, that allowed simulations to rather long times (Smit et al., 1990).

These simulations, and others, provided substantial insight into how surfactants reduce interfacial tension. *In fact, Shell Chemical subsequently commercialized new classes of Gemini surfactants based on this research (Cummings et al., 1997).*

It is well known that solids-handling is an important part of most chemical processing operations, typically occurring in up to 50% of processing steps. Perhaps less appreciated is that the synthesis of the solid particles in the first place deserves study in the context of minimizing solids-handling operations. For example, a different synthesis of a particulate product may eliminate some of the solid processing steps, such as breakup and grinding, required by a less efficient, traditional synthesis of the particulate precursor. Molecular dynamics has been employed by the Zachariah group to study small silicon particles such as might be produced in an aerosol reactor (Zachariah et al., 1996). These simulations showed that even for nanometer-sized clusters, the behavior was similar to that of bulk amorphous silica. No dramatic effects were seen as the cluster size was reduced because of the similarity between the surface and bulk contributions to the overall energy.

As a final example, I mention a study by the Rutledge group of the conformal relaxation of defects in the α-phase of poly(vinylidene fluoride) (Carbeck and Rutledge, 1996). On the time scales accessible to molecular dynamics, relaxation occurred by translation and rotation of the alkane chain segments. These motions allowed for the transport of small voids and impurities, which further relax the material. Unfortunately, additional collective relaxation phenomena happen on even longer time scales, and so molecular dynamics cannot provide a complete description of the relaxation of this material.

Nonequilibrium molecular dynamics

Molecular dynamics can be used to study many types of dynamical processes, even those not at equilibrium conditions. Such studies are often called nonequilibrium molecular dynamics (NEMD) to distinguish them from standard applications of molecular dynamics. The nonequilibrium system under study can either be a steady-state system or a non-steady-state system. The most common application of NEMD is to study the steady-state transport properties of systems near equilibrium. A common example would be flow through a membrane pore under a pressure gradient, as shown in Figure 2. By studying systems under infinitesimal driving forces, one can calculate all the traditional transport coefficients, such as slip coefficients, viscosity, diffusivity, and permeability. This approach provides a more transparent calculation of these quantities than does the traditional Green-Kubo correlation function approach. Moreover, NEMD can study systems far from equilibrium, where linear transport theory breaks down.

The viscosity of simple fluids, a parameter needed within the Navier-Stokes equations, is of fundamental interest in chemical engineering. A variety of model calculations has been undertaken to calculate viscosities of simple fluids by the NEMD technique. The Gubbins group has used NEMD to study the viscosity of model simple fluids confined within small slits (Akhmatskaya et al., 1997). Excellent agreement with sophisticated dynamic liquid-state theories was achieved.
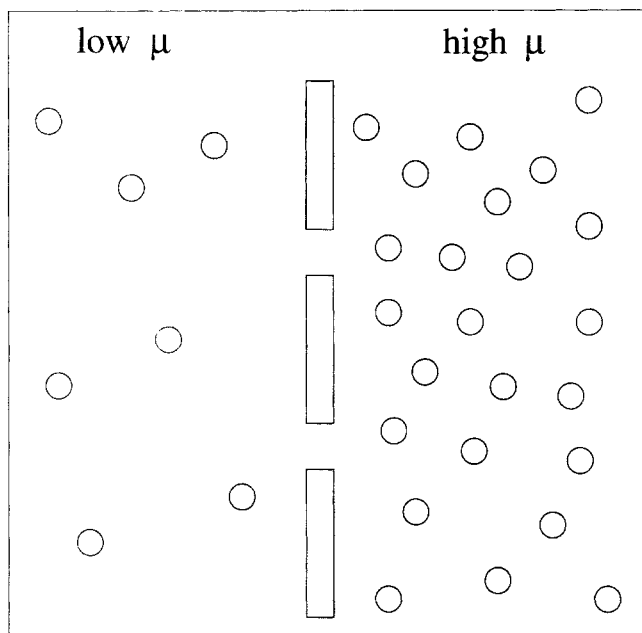
Figure 2. Two different reservoirs at two different chemical potentials.

A net flow through the membrane occurs due to the chemical potential gradient.

Viscosities up to 50% higher than bulk values were observed in nanometer-sized slits. Effects such as wall motion, fluid-wall attraction, and temperature gradients are easily studied in this approach. Pressure-driven membrane flow has been investigated by the MacElroy group (MacElroy, 1994). By simulating flow through a membrane channel connecting two reservoirs at different chemical potentials, permeabilities can be calculated. The increased viscosity in small pores shows up as a reduction in the permeability. In addition, slip flow is a significant component of the overall flow rate, even for dense fluids. These are just some of the many insights into molecular-scale phenomena that simulation can provide.

The viscosity of complex fluids, such as polymer mixtures, has recently begun to be investigated. The Klein group has pioneered some of these NEMD methods. Shear viscosities of alkanes ranging from decane to propylheptane were studied (Mundy et al., 1996). It was found that force fields fit to equilibrium critical phenomena were able to predict reliably linear transport coefficients. This is an important conclusion, as it implies that these simple force fields can be used to gain insight into complex phenomena, such as tribology and lubrication. Some care must be used in these simulations, both in extrapolating data from simulations for finite driving forces to the linear response regime and in the method used to solve Newton's equations (Mundy et al., 1995). Some of these challenges have been addressed by the de Pablo group (Xu et al., 1997; Khare et al., 1996). It was found that polymer melts confined to thin layers, such as would occur under some lubrication operations, have very different rheology than bulk melts. Both temperature and slip effects are important. The polymers themselves reorient and stretch in the fields produced by the flow, and, taking slip into account, the viscosity is found to increase with decreasing film thickness.

Ab-initio molecular dynamics

One of the challenges of molecular dynamics lies in the calculation and parameterization of the internal energy in Eq. 2. Force fields have traditionally been analytical forms containing parameters to be fit from quantum mechanical calculations or experiment. This fitting is somewhat arbitrary and introduces both systematic and random errors into the calculation. One might imagine, instead, simply performing the quantum calculation of the internal energy "on the fly" while solving Newton's equations. This approach, developed by Car and Parrinello, is called *ab-initio* molecular dynamics (Car and Parrinello, 1985). This approach provides the "exact" internal energy associated with any given configuration of the atoms. Of course, this quantum calculation of the energy is a difficult calculation. Most often a type of approximate density functional theory is used in this calculation, and so the internal energy calculation is not "exactly" a solution of the nonrelativistic Schrödinger equation. Computational limitations have further restricted application of this method to relatively small systems. This approach is still making the approximation of classical mechanics for the motion of the atomic nuclei. This assumption, the Born-Oppenheimer approximation, is the same one that is assumed in normal molecular dynamics. The advantage of *ab-initio* molecular dynamics is in the better calculation of $U(r^N)$.

Relatively few groups are using *ab-initio* molecular dynamics within chemical engineering. This will change as systems of interest to chemical engineers are being studied. The Frenkel group has studied the laser annealing of defects in silicon by this method (Sivestrelli et al., 1997). Defect annealing is a crucial step in the fabrication of silicon wafers for high-performance electronics. It is clear that when defects move, silicon-silicon bonds must break and form. For this reason, *ab-initio* molecular dynamics, which can accurately treat such events, would be expected to provide much more reliable results than would a classical calculation. In this study, the melting of the silicon lattice was found to be driven both by plasma annealing without vibrational excitation and by normal, vibration-mediated thermal melting.

Ab-initio studies of small biomolecules have also begun to appear. Quantum effects are important in this case to get the best possible treatment of formation and breakage of hydrogen bonds. Simulations of peptides in both vacuum and solvent show that a primary effect of solvent-induced hydrogen bonds is to break secondary structure (Samuelson et al., 1997). For this reason, more extended structures are observed in the aqueous phase, and free energy barriers between different conformations are lowered.

Remaining challenges in molecular dynamics

From these examples, we can see the tremendous impact that molecular dynamics has had, and will continue to have, in chemical engineering. Two glaring problems remain, however. The first is the time scale problem: one would like to design algorithms that would allow one to simulate to times longer than nanoseconds with today's computers. The second is the length scale problem: one would like to be able to simulate systems larger than a few million atoms so as to reach the bulk, thermodynamic limit. Advanced integration methods, derived from sophisticated operator splitting, Hamilto-

nian approaches to classical dynamics, have begun to address the time-scale problem (Tuckerman et al., 1992). Some of the NEMD simulations of polymers mentioned above employed this multiple time step approach. In addition, simulations of biomolecules have begun to appear that employ this approach (Tobias et al., 1993). These multiple time-step methods, however, gain us less than an order of magnitude in the time scales that we can address for systems of interest to chemical engineers. The length-scale problem is alleviated somewhat by domain-decomposition techniques that are possible on parallel computers. Solution of the time- and length-scale problems is one of the most active areas of chemical engineering research in molecular dynamics methods development. Recognition within chemical engineering of the importance of these two issues is documented by their prominent mention in the recent NSF CTS workshop on "Future Directions in Molecular Modeling and Simulation" (Cummings et al., 1997). One hope is that a combination of analytical, field-theoretic methods (discussed below) and computer simulation may allow us to bridge the temporal and spatial scales.

Equilibrium Monte Carlo

In contrast to molecular dynamics, Monte Carlo seeks to determine only the equilibrium properties of a system. No information about the dynamics of the system can be calculated in a standard Monte Carlo calculation. All that a Monte Carlo simulation attempts to do is to sample the relevant equilibrium probability distribution. For example, for a system with a constant total number of particles, temperature, and volume, a classical Monte Carlo simulation would sample the Boltzmann distribution

$$P(r_1, \ldots, r_N) = Z^{-1} \exp\left[-U(r^N)/(k_B T)\right], \quad (3)$$

where k_B is Boltzmann's constant, and Z is the configurational partition function that normalizes the probability distribution. Here U is the internal energy of the system, which is (to date) always calculated from a classical force field. Averages of any molecular property, say G, are given by averages over this distribution

$$\langle G \rangle = \frac{\int dr^N G(r^N) \exp\left[-U(r^N)/(k_B T)\right]}{\int dr^N \exp\left[-U(r^N)/(k_B T)\right]}. \quad (4)$$

A Monte Carlo simulation accomplishes this task by producing a series of molecular configurations $r^N(1)$, $r^N(2)$, ... Each particular configuration occurs with the Boltzmann probability, and so molecular averages can be computed as simple averages over the configurations produced in the Monte Carlo run

$$\langle G \rangle \approx \frac{1}{M} \sum_{\alpha=1}^{M} G\left[r^N(\alpha)\right]. \quad (5)$$

A Monte Carlo calculation, in effect, performs the integrals in Eq. 4 in a weighted fashion: it gathers more samples where the integrand is larger. Moreover, the calculation is performed without the need for explicitly computing the value
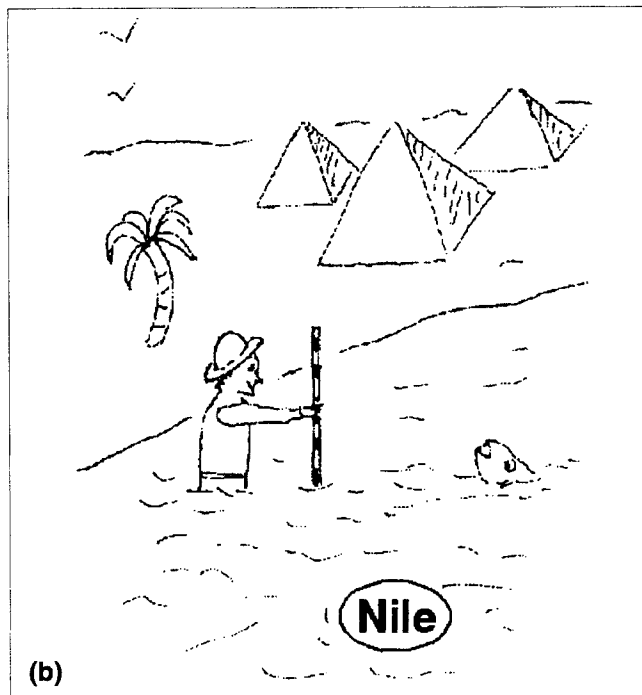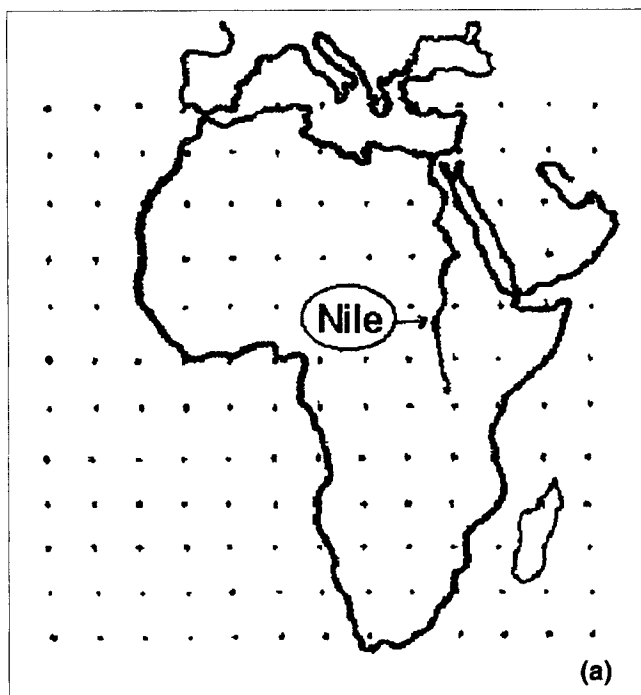

Figure 3. Two ways to measure the depth of the Nile.

An unweighted scheme (a) samples uniformly over the geography, only occasionally sampling the Nile, which is the area of interest. A weighted scheme (b) samples only in the area of interest and, thereby, achieves a much greater accuracy for the same amount of effort. Used with permission from Frenkel and Smit (1996).

of the configurational partition function. The difference between unweighted and weighted sampling is shown in Figure 3.

Because a Monte Carlo simulation is required only to sample the Boltzmann distribution, and not to satisfy the more restrictive Newton's equations, it can be much more efficient in sampling molecular configurations than can be molecular dynamics. A Monte Carlo simulation is allowed to make highly unphysical moves that would never occur in the natural dynamics. In fact, if one knows some properties of the system to be simulated, one can incorporate this information into the design of highly efficient, biased moves. Technically, all that is required is that the proposed biased move (1) lead to a Markov process, (2) lead to ergodic and regular sampling, and (3) satisfy balance or detailed balance (Parisi, 1988). Chemical engineers have been the leaders in the past decade, ahead of physicists and physical chemists, in the construction of such efficient Monte Carlo schemes for molecular systems. Increases in efficiency exceeding 10^5 have been achieved for complex zeolitic, polymeric, and biological systems.

Grand canonical Monte Carlo

Among the more interesting systems to chemical engineers are systems with adsorption. That is, we are often interested in open systems, where the number of molecules inside our control volume can change. The ensemble in statistical mechanics that corresponds to an open system with constant temperature, volume, and chemical potential is the grand canonical ensemble. The probability of occurrence of a given molecular configuration is a generalization of Eq. 3 to include a dependence on the number of total molecules. Monte Carlo methods have been designed to sample this distribution. This approach is often called grand canonical Monte Carlo (GCMC). I here mention some of the applications of this method over the last decade.

Adsorption within advanced carbon materials has been a topic of particular interest. Microporous carbons have interesting adsorption isotherms, due to both the guest-host energetic interactions and the tortuous internal geometry of the host. The Gubbins group has examined the effect of pore diameter on the thermodynamic and structural properties of model fluids (Suzuki et al., 1997). It was found, for example, that the properties of CCl_4 adsorbed in nanometer-sized carbon pores change from those of a liquid to those of a plastic crystal as the pore size is reduced. A variety of experimental probes, such as solid-state NMR and X-ray diffraction, have shown similar types of increased order for fluids such as nitrogen, water, and benzene adsorbed in small pores. Single-walled carbon nanotubes, first discovered by Iijima (Iijima and Ichihashi, 1993) and Kiang and coworkers (Bethune et al., 1993) are a form of nanometer-sized carbon fibers. Figure 4 shows the structure of a typical carbon nanotube. The adsorption properties of carbon nanotubes seem to be unique. Single-walled carbon nanotubes, for example, appear to be nearly ideal hydrogen storage media (Dillon et al., 1997). Grand canonical Monte Carlo simulations have been performed to study the adsorption of model fluids, such as argon and nitrogen, in carbon nanotubes of varying diameters (Maddox and Gubbins, 1995). The adsorption properties were found to depend on the detailed structure of the nanotubes,
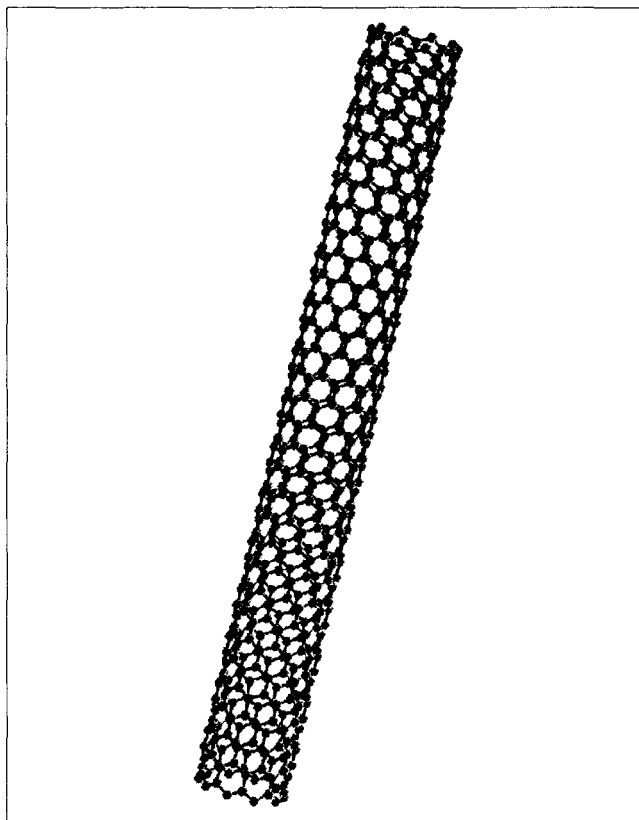

Figure 4. Typical carbon nanotube.

This tube has the "zig-zag" structure with a radius of approximately 7 Å.

such as radius, helicity, and chirality. The temperature for capillary condensation was found, as well, to depend on the pore length.

Activated carbons are an older class of materials, widely used as catalysts and sorbents. Many of the properties depend on the details of the charged, "activating" sites within the material. The Glandt group has undertaken the challenge of modeling this random charge distribution, by considering activated carbon to be made from platelets with uniform dipolar charge at the edge (Segarra and Glandt, 1994). The heterogeneity of the charge distribution was found to influence dramatically the sorption properties. Adsorption isotherms of methane and ethane were accurately predicted from a charge distribution obtained by a fit to the experimental isotherm of water. Related studies were performed by the Gubbins group (Müller et al., 1996). In these simulations, the active sites were found to play an important role in nucleating water clusters within the carbon material. At high enough loadings, the water clusters percolated throughout the material. A typical percolated water cluster in a pore of activated carbon in shown in Figure 5. Most of the peculiar properties of water adsorption in activated carbon can be explained by this percolation of water clusters. Insights such as this can be obtained only by detailed molecular modeling.

By the nature of the method, grand canonical Monte Carlo breaks down for complex fluids at high density, where it becomes difficult to insert molecules. An extension of the method, due to the Gubbins and Panagiotopoulos groups, to
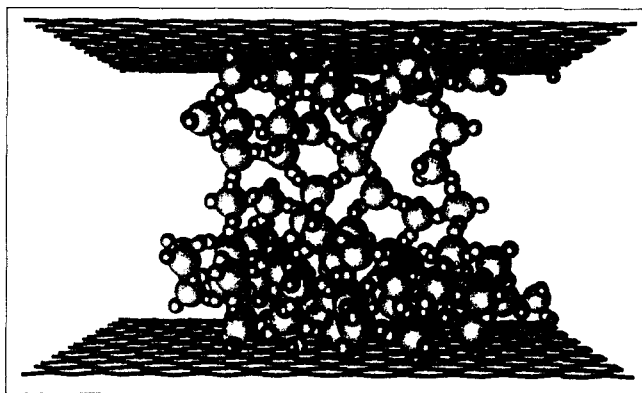
Figure 5. Typical configuration from a grand canonical Monte Carlo simulation of water in 2-nm-wide activated carbon pore at 300 K and 0.0631 P_{sat}.

Used with permission from Müller et al. (1996).

calculate the chemical potential of chain molecules is called the chain increment method (Vega et al., 1994). This approach calculates the incremental chemical potential to add one additional monomer to a polymer chain. The overall chemical potential of the polymer is then assumed to be proportional to the length of the chain multiplied by the incremental chemical potential. This method has proven successful in determining the phase behavior of simple polymer melts (Sheng et al., 1996; Spyriouni et al., 1997).

Gibbs-Duhem integration

Phase equilibria are of substantial interest to chemical engineers, and they are one of the tougher calculations to perform. Fluid-solid equilibria are particularly difficult to calculate because of the long equilibration times of the solid-fluid interface. Explicit simulations of the fluid-solid interface can, of course, be avoided through the calculation of chemical potentials. Absolute chemical potentials, however, are not cheap to calculate. An efficient method for determining an entire liquid-solid phase boundary is the Gibbs-Duhem integration method of Kofke. This method integrates the Clausius-Clapeyron equation over temperature to determine the phase boundary from a single liquid-solid equilibrium point and several constant pressure simulations of the liquid and solid phases (Kofke, 1993a,b, 1998; Agrawal and Kofke, 1995). The method is applicable to other types of equilibria with long equilibration times. As an example, the de Pablo group has used Gibbs-Duhem integration to determine phase behavior of polymeric melts (Escobedo and de Pablo, 1997a).

Configurational biased Monte Carlo

A problem common to all standard Monte Carlo methods is that it is difficult to generate a new molecular configuration $r^N(\alpha + 1)$ substantially different from an old molecular configuration $r^N(\alpha)$. This limitation, which is particularly severe for the interesting case of complex molecules or fluids at high density, means that the Monte Carlo scheme is not efficiently sampling all of the configurations naturally adopted by the system under study. As mentioned above, the effi-

ciency of a Monte Carlo scheme can be improved if one incorporates *a-priori* knowledge about the behavior of the system into the simulation.

The configurational bias Monte Carlo (CBMC) of Frenkel, Smit, and de Pablo is a first step along these lines (Frenkel et al., 1992; Frenkel and Smit, 1992; de Pablo et al., 1992). In this approach, one does not simply try a random displacement of one of the atoms, as in standard Metropolis Monte Carlo. Instead, one tries several random displacements and, in a statistical fashion, preferentially accepts moves that lead to lower energies. Polymer configurations are modified by an extension of this procedure. First, part of the polymer is removed. Then, each monomer that was removed is reattached by repeating the multiple-trial procedure. Figure 6 illustrates the method for a polymer melt. The CBMC method introduces a bias in the transition probability, and a modified acceptance criterion is used to correct for this bias. Interestingly, a "reverse move" is required so as to satisfy detailed balance.

The configurational bias technique is tremendously powerful. It has been used to solve via simulation many problems previously considered impossible (Smit, 1996a). For example, the phase behavior of long-chain alkanes, of interest to the petrochemical industry, can now be studied (Smit, 1995, 1996a,b; de Pablo, 1995; Escobedo and de Pablo, 1997b). Mixed monolayer systems, of interest biologically as well as in adhesion, coating, and lubrication applications, have been examined (Siepmann and McDonald, 1992). One can use simulations such as these, for example, in an attempt to design mixed monolayers with specific wetting, adhesion, or membrane-transport properties.

The adsorption of alkanes in zeolites is important in catalytic cracking operations, and the relevant dynamics occurs on a time scale not accessible to molecular dynamics. This is a complex system, essentially at high density, and standard Monte Carlo methods are unable to predict adsorption isotherms for long-chain alkanes. The configurational bias method provided some of the first simulation data for alkanes longer than decane. The conformations of hydrocarbons within the channels of several important zeolites were elucidated (Smit and Maesen, 1995; Bates et al., 1996a; Maginn et al., 1995). The phenomenon of commensurate freezing, wherein alkanes with chain lengths commensurate to the periodicity of a channel are preferentially adsorbed, was studied. Longer chains were found to unkink upon adsorption and locate preferentially in straight channels in structures with interpenetrating straight and zig-zag channels. Heats of adsorption were calculated (Bates et al., 1996b). Strong adsorption was found for all simple hydrocarbons, with the heat of adsorption increasing for longer chains and smaller pores. An application of configurational bias Monte Carlo by my group to solve zeolite structures will be mentioned below.

Clays are a related material of substantial importance as drilling fluid additives. Pillared clays are of importance as catalyst and adsorption hosts. Clays are also used in purification operations and as cosmetic bases. Smit performed an impressive configurational bias calculation that elucidated the anomalous swelling properties of montmorillonite (Karaborni et al., 1996). One, three, five, and so on layers of intercalated water were found to be stable between the layers of the clay, in agreement with experiment. Even numbers of water layers
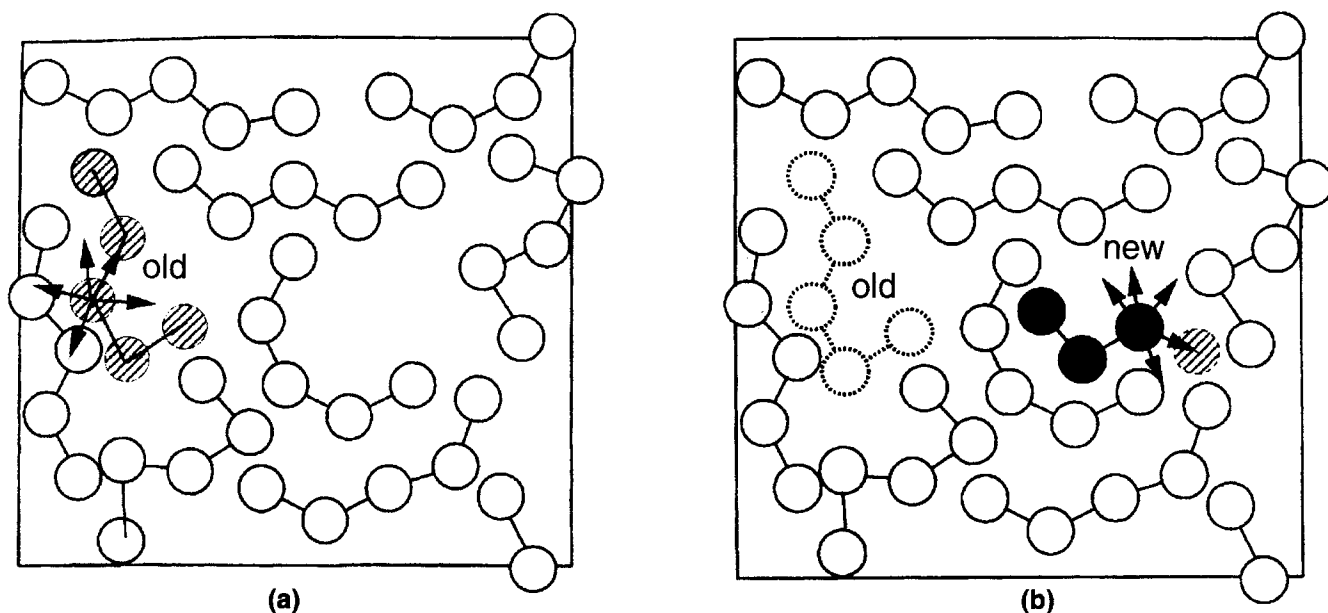
Figure 6. Regrowth step of the configurational bias method for: (a) retracing the old configuration; (b) generating a new configuration.

Arrows indicate the set of random trial displacements. Used with permission from Frenkel and Smit (1997).

were not found, due to an interesting competition among the energetics of water adsorption within the clay, water-clay hydrogen bonds, and water-water hydrogen bonds. These simulations allow one to conclude that this delicate interplay between molecular interactions is responsible for the anomalously facile swelling of this clay.

Finally, biological molecules are a ripe area for application of configurational bias methods. Molecular biology, and the resulting industry of biotechnology, is discovering increasingly powerful tools for the manipulation of genetic and protein structure and function. Configurational bias Monte Carlo provides a powerful tool with which to study the molecular basis of much of biological function. As an example, I have developed a concerted rotation, configurational bias method to study cyclic peptides (Deem and Bader, 1996), using the methods of Theodorou, Frenkel, Smit, and de Pablo for alkanes as an inspiration (Dodd et al., 1993; Frenkel et al., 1992; Frenkel and Smit, 1992; de Pablo et al., 1992). This method was able to sample the relevant body-temperature degrees of freedom for cyclic peptides, a feat not possible with previous Monte Carlo or molecular dynamics methods. *The method has applications in the process of diversity drug design. It is used, for example, by CuraGen Corporation in this context.*

Gibbs ensemble

The discovery of the Gibbs ensemble method by Panagiotopoulos was a watershed event in the simulation of fluid-fluid phase equilibria (Panagiotopoulos, 1987). This approach manages to calculate a fluid-fluid phase equilibrium without considering either an explicit interface or an absolute chemical potential. This is accomplished by considering two reservoirs. One reservoir contains the fluid in phase α and the

other contains the fluid in phase γ. An equal chemical potential in these two reservoirs is maintained by particle exchange moves. Figure 7 illustrates these moves. The Gibbs ensemble method, and various refinements, have allowed simulation of complex fluid-fluid equilibria for the first time.

Some of the first simulations were of simple fluid phases. Early simulations considered the phase behavior of the Lennard-Jones fluid (Panagiotopoulos, 1992a). These accurate simulations revealed previously unappreciated behavior of this well-studied system. For example, it became apparent that the critical properties of simple fluids calculated from simulation are extremely sensitive to the parameters of the force field and to the cutoff method employed. This discovery eventually led to the current interest in the determination of force fields valid over wide ranges of temperature and density (Cummings et al., 1997). The Gibbs ensemble was shown to be clearly superior to both grand canonical and test particle Monte Carlo methods (Panagiotopoulos, 1992b). Real, simple systems were also examined. The Smit group, for example, used the Gibbs ensemble method to determine the vapor-liquid curve of methanol (van Leeuwen and Smit, 1995). The first simulation of a complex hydrocarbon mixture was performed by de Pablo and Prausnitz (1989).

The Gibbs ensemble method was quickly combined with the configurational bias method. This allowed simulation of the phase behavior of polymer melts. An early simulation by the Smit group determined the critical behavior of alkanes up to C_{48} (Smit et al., 1995), a calculation impossible with any prior simulation method. Liquid-liquid equilibria for confined fluids in random porous media is of importance in gel chromatography, adsorptive separation, and enhanced oil recovery. The Glandt group undertook model simulations in an effort to elucidate fundamental molecular phenomena of confinement (Gordon and Glandt, 1996). Various processes
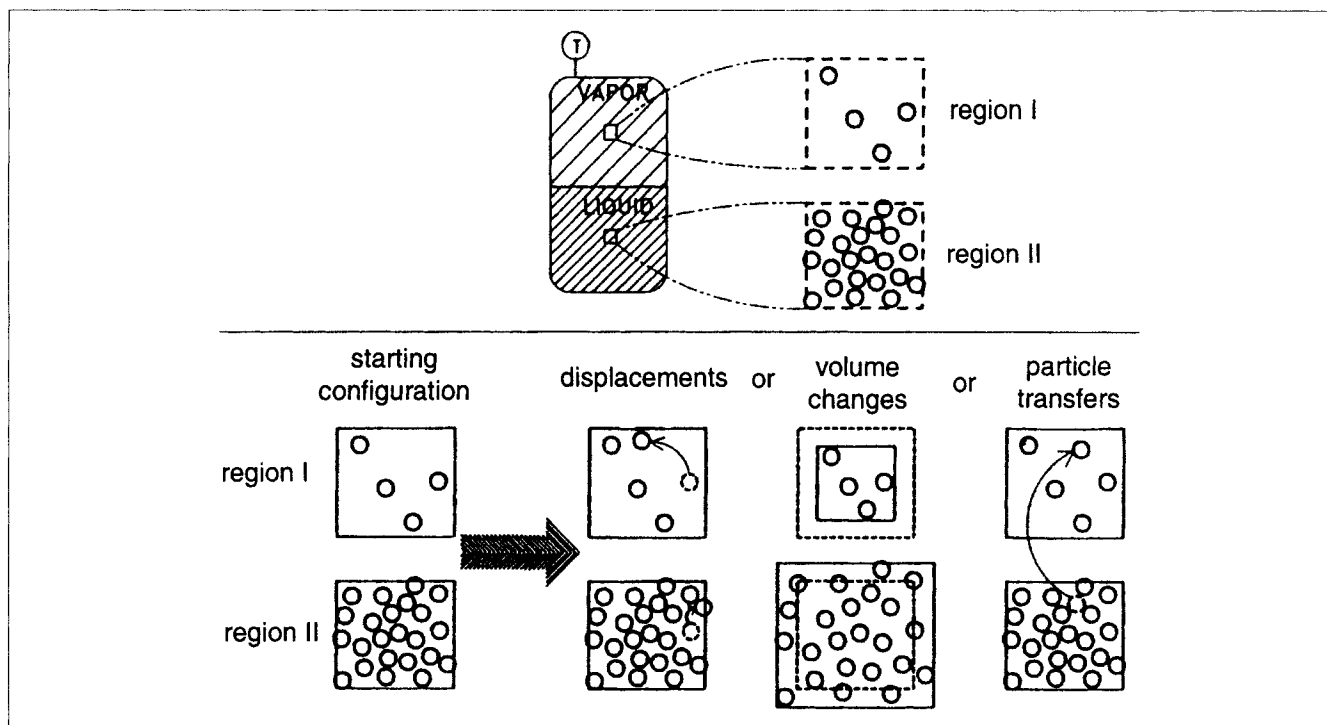
Figure 7. Trail moves in the Gibbs ensemble method.

Used with permission from Panagiotopoulos (1992a).

were identified in these detailed simulations, including capillary condensation and adsorption/desorption hysteresis. More exotic behaviors were also observed, including prewetting phenomena and layering transitions.

Semi-grand ensemble and reactive Monte Carlo

Chemical engineers are often interested in systems that are not only complex, but also reacting. One of the first methods to handle polydisperse, or reacting, systems was the semi-grand ensemble from the Glandt group (Briano and Glandt, 1984; Kofke and Glandt, 1987). A polydisperse system was modeled as a reactive system, in which individual polymers could change chemical identity by changing their degree of polymerization. The fundamental variables that were used to characterize the system were the temperature, density, and ratios of activity coefficients of all the species. The method is generally useful for simulating complex mixtures (such as hydrocarbons) or phase equilibria. This approach is more physically motivated than the traditional "lumping" approach of the petrochemical industry. The Klein group has pursued this idea with various studies of hydrocarbon mixtures (Campbell and Klein, 1997). Theodorou has used these ideas to construct a variable connectivity Monte Carlo method for polymer melts (Pant and Theodorou, 1995). Such a method is necessary to overcome the extremely severe topological constraints that occur in these systems. That is, the natural dynamics that never permits chains to cross leads to extremely long, glassy relaxation behavior in polymer melts. A combination of the semi-grand ensemble and a geometrical rebridging technique resulted in a method that was able to sample conformation space effectively for this complex system. A re-

lated, expanded ensemble technique has been developed by the de Pablo group for the simulation of polydisperse polymer melts (Escobedo and de Pablo, 1996).

These seminal works were extended specifically to consider reactive mixtures, rather than multicomponent mixtures generally (Johnson et al., 1994; Smith and Triska, 1994). Specific systems considered include nitric oxide dimerization (Johnson et al., 1994) and formation of NO from O_2 and N_2 (Smith and Triska, 1994). These methods can be used for chemically reactive mixtures, as well as for associating fluids. The original approaches failed at high density due to the use of a simple grand-canonical-like insertion step. Incorporation of a biased Monte Carlo scheme would lead to a successful method at high densities. These methods require knowledge of the possible reactions *a priori*, and so they fail for associating mixtures for which the important clusters are not known. The authors note, for example, that they were unsuccessful at improving the equilibration behavior of methanol or water.

Monte Carlo as an optimization technique

Monte Carlo also has applications as an optimization tool. Simulated annealing is one of the more powerful techniques for optimization of an objective function with many local minima. It was first invented by Kirkpatrick, Gelatt, and Vecchi as a technique for optimization of the wiring layout of chip designs at IBM (Kirkpatrick et al., 1983). It has since seen usage in an enormous variety of fields. *As one example in classical design, I mention the work of Marco Duran at Exxon Corporate Research in the optimization of plant designs.*

One of the most exciting areas of applied synthetic chemistry is the design of tailored materials with custom proper-

ties. Custom design of zeolites is one of the more active examples of this approach within chemical engineering. There are two fundamental challenges in this approach: first, simply to determine the structure of a newly-made zeolite, and second, to design a zeolite structure with desired structural and chemical properties. The first problem is nontrivial because zeolites are usually synthesized as small crystallites, less than 5 μm. As such, single-crystal X-ray diffraction cannot be performed, and only powder diffraction data can be collected. Unfortunately, there is no direct method for inverting a powder diffraction pattern to determine a structure. Zeolites continue to be synthesized at a furious pace. Perhaps soon, the techniques of diversity synthesis will be introduced to the field, with a tremendous explosion in the number of synthetic zeolites. The second challenge is difficult because, although there are a large number of possible zeolite structures, there are also many topological and geometrical constraints that limit which arrangements of atoms with useful chemical properties can be made as zeolites. A means of automatically generating all possible structures consistent with the desired properties and with being "zeolite-like" would be desirable.

We have has tackled these challenges with a simulated annealing approach (Deem and Newsam, 1989, 1992) (see Case Study). At least five other groups have used a preliminary implementation to solve new zeolite structures (Li et al., 1993; Akporiaye et al., 1996a,b,c; Nenoff et al., 1993; Campbell et al., 1998; Vaughan, 1998). *Corporate and academic researchers use the structural information provided by this approach not only to understand the performance of newly synthesized catalysts but also to propose rational syntheses of homologous materials with tailored performance.* We have recently developed a significantly enhanced method that makes use of biased Monte Carlo in a parallel tempering scheme that rigorously satisfies detailed balance (Falcioni and Deem, 1998). *Molecular Simulations, Inc., has set up a contract research program to apply this powerful approach to structure determination for its customers in the materials science area.*

This Monte Carlo approach to structure determination can be generalized to other microcrystalline materials. For example, one can determine the structure of molecular crystals from powder diffraction data (Newsam et al., 1992). *Pharmaceutical companies are using this approach to determine the structure of small organic drugs from low-quality, small crystals.*

Quantum Mechanics

Quantum mechanics is the most basic theory with which we seek to predict and to understand nature. Quantum mechanics solves Schrödinger's equation

$$H\Psi_\nu = E_\nu\Psi_\nu, \qquad (6)$$

to determine the ground state energy E_0, as well as excited states for any molecular system of interest. As previously mentioned, this is an expensive calculation. There are two main methods to solve this equation, direct wave function methods and density functional theory. Typically, the wave function approach is more accurate but it is limited to smaller systems.

One can do quantum statistical mechanics, in which thermal averages are calculated as averages over quantum states

$$\langle G \rangle = \frac{\sum_\nu G_\nu \exp[-E_\nu/(k_B T)]}{\sum_\nu \exp[-E_\nu/(k_B T)]}, \qquad (7)$$

where G_ν is the value of the property G in state ν. The most efficient numerical means of performing such calculations is path integral Monte Carlo. Alternatively, one can correct classical simulations with perturbation theory in Planck's constant to obtain a semi-classical approximation (Lacks and Rutledge, 1994).

Commercial quantum codes are widely used in the industry by chemical engineers involved in process design. Thermochemistry of reactions is one of the most common calculations [For a review, see (Irikura and Frurip, 1996)]. Advanced applications abound in the chemical processing, microelectronics, and defense industries. In many of these applications, both thermodynamics and kinetics are needed. For example, for reactor design, one might want to know enthalpies of reaction. For design of chemical vapor deposition, plasma etching, or surface cleaning applications, one might want to know the kinetics of surface reactions. For aviation applications, one might want to know the combustion kinetics of jet fuel in the presence of inhibitors or other additives. *Many processes have been optimized with such calculations, including catalytic conversion of methane to methanol, styrene process design, light naphtha desulfurization, and decomposition of Teflon (Irikura and Frurip, 1996).*

It is fair to say that most activity within chemical engineering in the quantum field has been in the application of quantum methods to systems of engineering interest. One of the more interesting areas of study has been the attempt to relate chemical function to structure for zeolitic materials. High accuracy is, in principle, needed for reliable rational catalyst design (Cummings et al., 1997). In addition, one should appreciate that zeolites are typically synthesized under kinetic control, and so simple energetic calculations may not be predictive in the synthesis step. It seems, however, that the approximate energetic calculations currently feasible do provide insight into the structure/function relationships in zeolites.

Several properties of zeolites have been examined. One of the more basic properties is the location of the aluminum species within the zeolite framework. Semi-empirical calculations have shed light on this issue for H-ZSM-5, particularly on the importance of local structural relaxation (Lonsinger et al., 1991). Related *ab-initio* molecular orbital calculations have investigated the origin of hydrophobicity in VPI-5 (Kitao and Gubbins, 1994). Specific Al sites were found to bind water strongly, and this information was helpful in the interpretation of solid-state NMR measurements. Ammonia adsorption in H-ZSM-5 has been studied with density function calculations (Kyrlidis et al., 1995). Finally, the thermochemistry of NO_x decomposition over Cu-ZSM-5 was studied by a statistical mechanical analysis of quantum calculations (Trout et al., 1996).

Master Equation Approaches

I now turn to dynamical methods that, while still based on molecular principles, do not entail following the motion of all atoms within a system at all times. The basic method, often
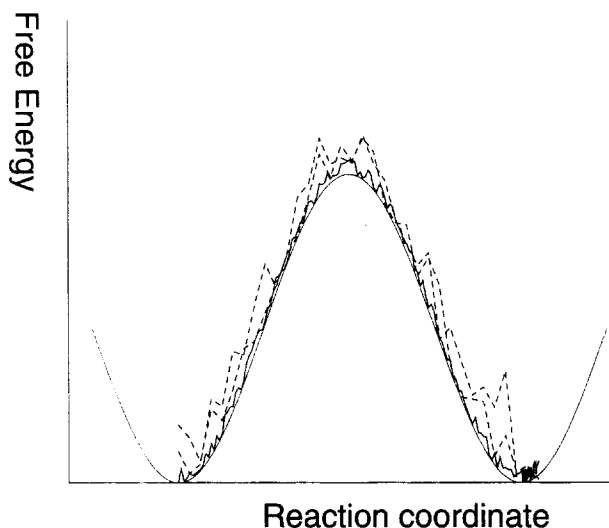
called transition state theory, works for systems that tend to spend substantial amounts of time within localized states and only rarely tend to jump between these states. The overall, long-time behavior can be described simply in terms of the rates of jumping between the states. Mathematically, this is achieved by writing a master equation that describes how the probability of being in a given state changes with time

$$\frac{dP_\alpha(t)}{dt} = \sum_\gamma \left[\tau^{-1}_{\gamma \to \alpha} P_\gamma - \tau^{-1}_{\alpha \to \gamma} P_\alpha \right], \qquad (8)$$

where $\tau^{-1}_{\alpha \to \gamma}$ is the rate at which transitions from state α to state γ are made. Identifying the states and determining the values of the transition rates are the challenges to application of this method.

As one very direct application of the master equation approach, I mention the calculation of diffraction patterns from zeolites with planar faults. The structures of zeolites (and clays) are often made of two-dimensional sheets connected along a third direction to make a crystal. One particular crystal structure might be made of three types of layers, arranged in the order "abcabcabc...." Often, however, the order of the layer stacking is not fixed, but random. For example, the layers might arrange in the order "bacaacb...." Figure 8 shows the random stacking sequences that can occur in the zeolite frameworks FAU and EMT. This random stacking can be described by a master equation, where the states identify which layer is present, the transition rates identify the probability of making a transition from layer type α to layer type γ, and time indexes the position of the layer in the third direction. All properties of the material are then defined as statistical averages over an ensemble of crystallites obeying these statistics. The calculation of the powder diffraction pattern of such an ensemble is of particular interest. In collaboration with others, I have developed a recursive method to perform these statistical calculations. *The resulting DIFFaX program is used worldwide by scientists in chemical process companies and academia to calculate diffraction intensities from crystals containing planar defects (Treacy et al., 1991).*

Transition state theory

Implementation of the master equation approach for a system with a small number of states and transition rates can be done analytically. This method is often called transition state theory. Subtleties associated with the definition of the transition rates exist. Basically, the rates tell us how often a system makes a transition that changes the state of the system from state α at time t to state γ at time $t + \delta t$. There is a subtlety, which is what value of δt should we use? If we use $\delta t \to 0$, we obtain the traditional transition state theory. If we use a small, but nonzero, value for δt, we obtain a theory that is dynamically corrected for recrossing events. Figure 9 shows the basic concept of a reaction barrier and recrossing events.

Snurr, Theodorou, and Bell used simple transition state theory to predict the diffusion of benzene in silicalite (Snurr et al., 1994a). Uncertainty in the definition of the states, and lack of correction for dynamical recrossings, lead to predicted diffusion coefficients too low by several orders of magnitude. Earlier work by June, Bell, and Theodorou used a

(a)

(b)

Figure 8. (a) Possible stacking of a crystal with only two layer types; (b) sheets connecting sodalite cages to form a predominantly hexagonal (*bss* = EMT) or a predominantly cubic (FAU) material.

Probabilities of the transitions are denoted by α_{ij}. Used with permission from Treacy et al. (1991).

Reaction coordinate

Figure 9. Two trajectories on a free energy surface (thin solid).

The first trajectory (thick solid) successfully completes the reaction. The second trajectory (thick dashed) recrosses the barrier, and does not successfully react. Recrossings such as this lead to a dynamic correction to simple transition state theory.

dynamically-corrected transition state theory to achieve better agreement with experiment for the diffusion of xenon and SF$_6$ in silicalite (June et al., 1991). More recent work by Auerbach (Auerbach, 1997) for benzene diffusion in Na-Y zeolites was able to obtain fairly good agreement between experimental diffusivities and an analytical theory, at least at low loadings.

Transition state theory has also been used to examine diffusion on metal surfaces. Such diffusion is of interest to chemical engineers because of its importance in heterogeneous catalysis. The Fichthorn group derived analytical expressions for diffusion of n-butane on Pt(111) and Cu(001) metal surfaces (Raut and Fichthorn, 1997). Such expressions may be of use in the design of nanometer-scale devices and reactors.

Crystallization kinetics of simple fluids has been tackled via computer simulation. One of the first new expressions for the dynamical correction since the original work of Bennett and Chandler is described in a recent publication (Ruiz-Montero et al., 1997). The new form will prove useful in computer studies of crystallization, ion association reactions, and diffusion in solids. This method was, in fact, used in simulation studies of crystal nucleation of Lennard-Jones fluids. Interestingly, although the stable crystalline form is face-centered cubic, the initial crystallite nuclei are body-centered cubic. These simulations emphasized the importance of detailed computer simulations: classical nucleation theory was shown to underestimate substantially the size of the critical nuclei and to underpredict by two orders of magnitude the kinetic prefactor for nucleation.

Finally, recent work on transdermal drug delivery can be understood in terms of transition state theory. The Langer and Blankschtein groups have shown that a combination of chemical enhancers and ultrasound is effective in transporting drugs through the skin (Johnson et al., 1996). *Drugs such as corticosterone, dexamethasone, estradiol, lidocain, testosterone, progesterone, and caffeine were shown to be effectively transported through the skin.* The enhancement provided by ultrasound was understood as a disordering of the outermost layer of the skin. The cavitation induced by ultrasound in this layer increased the effective permeability of the drugs by decreasing the free energy barrier to passage through the skin. An enhancement ratio predicted by simple theory without adjustable parameters was found to be in good agreement with the experimental data (Mitragotri et al., 1995).

Rare event dynamics: kinetic Monte Carlo

In complex systems, it is difficult to catalog all possible states and all possible transitions *a priori*. To avoid explicit consideration of all these states, a Monte Carlo procedure that simulates the Poisson process implied by the master equation can be employed. It is also difficult to calculate the dynamical corrections with an analytical theory. Molecular dynamics can be used to calculate these corrections explicitly (since the time during which we explicitly follow trajectories to look for recrossing events δt is usually on the order of picoseconds).

Diffusion in zeolites has been a common topic of study, due to the fundamental importance of reactant and product transport in the chemical process industry and due to the long time scales associated with this motion. The Auerbach group has carried out an extensive series of simulations. Reorientation rates of benzene, which result from both rotation within a single cage and intercage hopping, have been studied (Auerbach and Metiu, 1997). The diffusivity was found to decrease with decreasing Si:Al ratio, most likely because of the overall slowing down effect of the disordered Al sites. The diffusivity was found not to be especially sensitive to the pattern of disorder in the zeolite, whereas the benzene orientational randomization was. Using this insight, one can extract information about the structure of the disorder from solid-state NMR experiments. Additional simulations calculated benzene diffusivities in Na-Y that were in good agreement with experimental NMR data (Auerbach and Metiu, 1996). Interesting effects due to disorder were found. For example, creation of a new binding site within the zeolite can either increase or decrease the diffusivity of a reactant, depending on whether the new site binds weakly or strongly to the reactant (Auerbach et al., 1996). Dynamic Monte Carlo has been used to study the effect of reactivity on diffusivity in ZSM-5 (Trout et al., 1997). Interestingly, the overall reaction rate is optimized by a finite fraction of reactive sites, due to a delicate balance between reduced diffusivity and increased reactivity as the density of reactive sites is increased. Insights into guest-host interactions, such as those gathered from these simulations, should help in the design of advanced materials.

The Weinberg group has studied various aspects of surface reactions with dynamical Monte Carlo. Surface reactions are a natural candidate for the dynamic Monte Carlo approach, since reactants typically adsorb onto well-defined sites on the surface (Kang and Weinberg, 1995). It has been known for some time that the kinetics of even simple reactions do not follow the simple law of mass action. [They do not even follow the more sophisticated reaction diffusion equation (Park

and Deem, 1998a; Deem and Park, 1998a).] Correlations between the reactants lead to discrepancies with all but the most sophisticated analytical theories. Monte Carlo, on the other hand, is adept at uncovering the exact behavior of complicated heterogeneous reactions. The Weinberg group has used this approach to elucidate the kinetics of a wide variety of systems, ranging from temperature-programmed desorption spectra (Meng and Weinberg, 1994, 1995) to precursor mediated kinetics (Kang et al., 1990) to molecular beam epitaxy (Nosho et al., 1996; Meng and Weinberg, 1996). In these early simulations (Kang and Weinberg, 1992), the Poisson process implied by the master equation was modeled only approximately since the random waiting times were replaced by averaged time increments (see Elston and Doering, 1996).

Hierarchical Modeling

So far, I have described computer simulation methods that cover a wide range of spatial and temporal scales. In order of increasing scale, these methods are quantum mechanics, molecular dynamics, Monte Carlo, and master equation methods. There is typically a connection between the more detailed approach and the less detailed. For example, quantum mechanics is used to calculate the force fields used in molecular dynamics. Molecular dynamics is used to calculate the dynamical corrections required in the master equation approach. Would it not make sense to combine all these length scales within one simulation technique? Such an approach is called a hierarchical method. Chemical engineers have a natural advantage in the design of such methods, given their broad educational background that ranges from quantum mechanics to continuum theories. The search for such methods is one of the most active areas of fundamental simulation research in chemical engineering (Cummings et al., 1997).

Hierarchical methods are, fundamentally, used to bridge large spatial and temporal scales. Spatial length scales can be explicitly bridged by domain decomposition techniques on large parallel computers, but hierarchical methods imply a coarse graining of the problem, not simply an efficient computational decomposition. Intuitively, hierarchical methods seek to join the atomic and continuum theories in an efficient fashion. Even large parallel computers do not allow access to long time scales. Hierarchical methods are needed to match continuum or stochastic dynamics with exact, short-time molecular dynamics. A general hierarchical method would seek to combine quantum mechanics, atomistic simulations, Brownian or Stokesian dynamics, and transport equations.

Defects in silicon

Jump dynamics of point defects in solids was the original application of Charles Bennett's seminal 1975 article on a dynamically-corrected transition state theory (Bennett, 1975). A tremendous number of simulations have since been performed, but I mention a few recent simulations of defect transport in silicon as examples of hierarchical methods. Maroudas and Brown studied impurity transport in silicon semiconductors (Maroudas and Brown, 1993). The approach was to identify fundamental mechanisms and rates of transport by detailed atomistic calculation. The various levels of
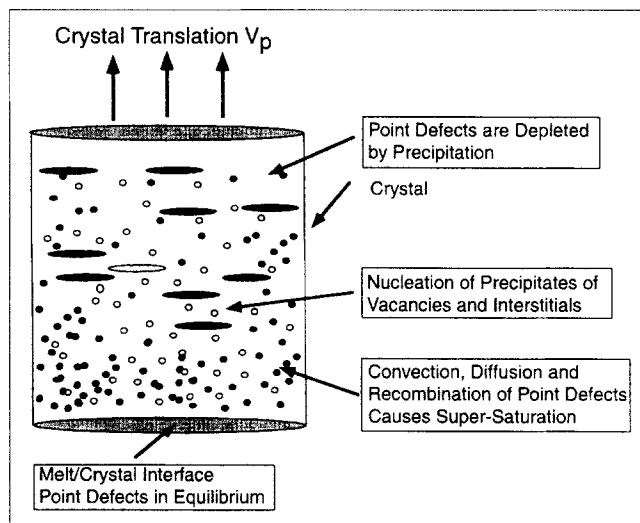

Figure 10. Mechanisms governing the distribution of defects within a growing cylindrical crystal.
Reprinted with permission from Brown et al. (1994).

this hierarchical approach are shown in Figure 10. These rates and events were then simulated via dynamic Monte Carlo and continuum theories (Brown et al., 1994). Recent multimillion-atom simulations have been performed with the explicit aim of determining the parameters that should enter a coarse-grained model of defect dynamics (Bulatov et al., 1988; Zhou et al., 1988). Control of microdefects in silicon wafers is still a major, unsolved problem, and methods such as these will eventually be of help.

Alkane diffusivities in zeolites

Diffusivity of long-chain alkanes in zeolites is a good example of a problem that requires hierarchical methods. The relevant dynamics occurs on such long-time scales that conventional molecular dynamics provides almost no information (for an exception, see Runnebaum and Maginn, 1997). Yet, as chemical engineers, we are interested in the diffusivity, since it influences such operations as fluid catalytic cracking, hydrocarbon separation, and catalytic dewaxing. Coarse-grained models of both the alkane and the zeolite have been developed (Snurr et al., 1994b; Maginn et al., 1995). Natural new variables for the alkane are the head and tail positions. There is an effective force between the head and tail and an effective friction of the alkane within the zeolite channels. The friction is different for straight and zig-zag channels and for transitions between channels. (All this may sound quite similar to the concept of friction factors for fluid flow in pipes!) The effective force and mobility matrix for the head and tail elements were calculated from detailed, atomistic simulations (Maginn et al., 1996). These parameters were then input to a dynamic Monte Carlo simulation. The resulting dynamical approach was several orders of magnitude faster than explicit molecular dynamics calculations with the difference becoming more dramatic for longer chain molecules. Interestingly, the required time step in the dynamic Monte Carlo was roughly constant with chain length, since the friction is pro-

portional to the chain length. The diffusivity is limited by the dynamics of the head and tail exploration for chain lengths up to C_{20}. Beyond this, friction effects along the chain are expected to play a role and to decrease substantially the overall diffusivity.

An even more coarse-grained approach was taken to capture the effects of reactivity on diffusion in microporous media (Alvarado et al., 1997). The atomistic system was mapped onto an effective resistor network. The resulting network system was found to be well approximated by an effective reaction diffusion partial differential equation. This work provides a clear demonstration of hierarchical modeling from a detailed atomic-scale model all the way to the continuum.

Stokesian dynamics

Stokesian dynamics is a method to study dynamics of particles in fluids without an explicit consideration of the solvent molecules. Particle suspensions and dispersions, for which this technique is suited, often occur in chemical engineering. Typical examples include slurries, composites, ceramics, colloids, and polymer and protein suspensions. Stokesian dynamics can be used to calculate the properties of diffusion, sedimentation, flocculation, and rheology in these systems. This approach is hierarchical, because high-frequency degrees of motion have been integrated out. One solves the resulting Langevin equation (Brade and Bossis, 1988)

$$m_i \cdot \frac{dV_i}{dt} = F_i^H + F_i^P + F_i^B. \tag{9}$$

Here m_i is the generalized mass tensor of particle i, V_i is the generalized velocity of particle i, F_i^H is the hydrodynamic force on particle i, F_i^P is the external force on particle i, and F_i^B is the random, Brownian force on particle i due to the random, thermal motion of the solvent. Exact calculation of the hydrodynamic interaction is expensive, and clever approximations that are feasible to implement on a computer have been developed (Brady and Bossis, 1988).

Stokesian dynamics simulations have revealed fundamental features of fluids in confined geometries. For example, the phenomenon of shear thickening was found to be related to the formation of clusters of particles (Brady and Bossis, 1988). Approximations inherent in macromolecular integral equation theories of various levels of sophistication have been clarified by comparison with explicit Stokesian dynamics simulations (Bergenholtz and Wagner, 1997). Elongational and orientational properties of polymers in flows have been investigated (Evans and Shaqfeh, 1996). For example, the properties of forced flow of xanthan gum in porous media have been examined. The results have implications for the food and agricultural industry, as well as for enhanced oil recovery. Flows of polymers in more general forms of disordered media have been examined (Mosler and Shaqfeh, 1997). Sedimentation and fluidization, which are of importance in the silting of rivers, formation of secondary rocks, and design of chemical reactors and waste treatment plants, have been studied. Exact numerical prediction of these quantities is important as a primary test of integral equation theories (Rutgers et al., 1995).

Connection with field-theoretic approaches

There is an intimate relation between hierarchical methods and field theoretic methods. Field theory is a sophisticated technique of statistical mechanics that can represent phenomena that occur on long spatial and temporal scales. One can derive, as well, field theories that are exact for any molecular system. In principle, field theory should be the natural vehicle through which to derive hierarchical methods. Some limited progress along these lines has been made. I have derived field-theoretic approximations for dynamics in disordered media (Deem and Chandler, 1994c; Deem, 1995). The theory contains parameters that can be determined by atomic-level simulations. A combination of the two approaches, which might be viewed as a computational version of singular perturbation theory, should lead to a comprehensive theory of transport in materials such as disordered zeolites. This specific example, and a more general framework, however, remain to be demonstrated.

Liquid State Theory

An accurate theory for the structure of simple liquids was one of the major accomplishments of statistical mechanics in the 1970s. The theories of Weeks, Chandler, and Anderson (WCA) (Chandler et al., 1983), Chandler and Anderson (RISM) (Chandler and Anderson, 1972), and Schweizer and Curro (PRISM) (Schweizer and Curro, 1997) now provide an analytical means to calculate detailed structural properties of a wide range of fluid systems. Liquid state theory has been extended to cover the critical region, using ideas from a renormalization group theory (Parola and Reatto, 1985; White and Zhang, 1995). Lue and Prausnitz have recently generalized the method to multicomponent mixtures (Lue and Prausnitz, 1988). These theories are now accepted within the chemical engineering community. The old equation-of-state approach has been, or can be, replaced by these approaches and their associated closure relations. Correlations of data, when necessary, can now be done in terms of the direct correlation functions $c(r)$ instead of parameters in equations of state. Madden-Glandt theory provides a means of examining the structure of liquids in the microporous materials of interest to chemical engineers (Thompson and Glandt, 1996). Liquid state theory has been extended to complex fluid mixtures, such as disordered bicontinuous phases (Deem and Chandler, 1994a,b).

Fundamental aspects of the hydrophobic effect have been investigated since the original work of Pratt and Chandler (1977). Recent approaches by the Paulaitis group have focused on the importance of the hydrophobic effect for surfactant self-assembly, protein folding, and molecular recognition by biological membranes. An information theoretic approach, assuming Gaussian statistics, has been developed (Paulaitis, 1997). The proximity equations that have been developed appear to give the structural properties of water in good agreement with simulation and experimental data. This agreement is impressive, given the difficulty that liquid state theories have traditionally had with aqueous systems. In principle, this proximity approach should be related to the more basic liquid state theories (Chandler, 1993), although the exact field-theoretic connection remains to be made. Lue and Blank-
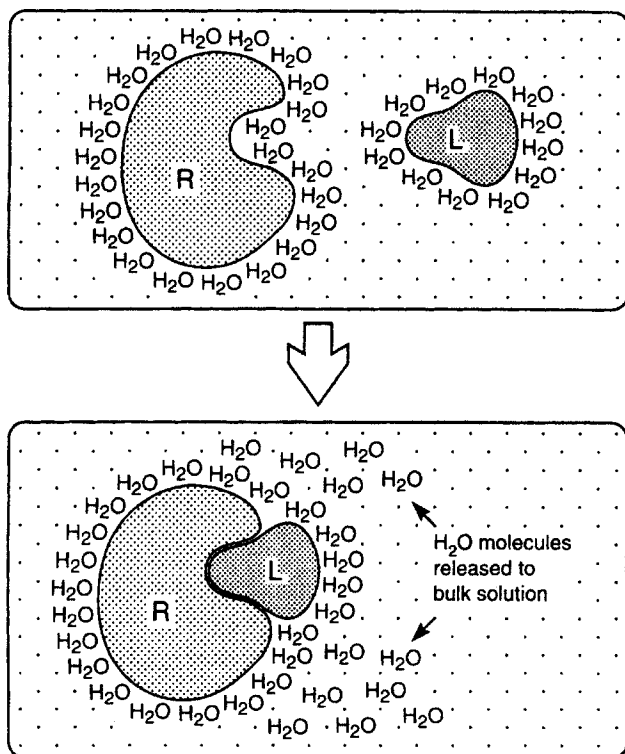
Figure 11. Receptor molecule (R) binding to a ligand molecule (L).

Reprinted by permission from *Nature* (Israelachvili and Wennerström, 1996).

schtein have made some progress along these lines (Lue and Blankschtein, 1995).

Perhaps, some of the most impressive applications of these theories have been to biological systems. The importance of liquid-mediated forces in these systems has been emphasized by Israelachvili and Wennerström (1996), and Figure 11 shows the basic concept involved. A liquid state theory for protein partitioning in aqueous systems has been derived (Lue and Blankschtein, 1996). With such a theory, one can rationally tune protein partitioning by changing the pH, polymer type and mass, and salt. Blanch and Prausnitz have detailed this approach for salting out of proteins such as ovalbumin and lysozyme (Coen et al., 1995; Chiew et al., 1995; Curtis et al., 1998), as well as for adsorption of proteins in hydrogels (Sassi et al., 1996). While not as accurate as explicit simulations, these analytical theories allow one to gain enough insight into the fundamental principles to design, for example, protein separation methods.

Classical Density Functional Theory

Classical density functional theory is another approach to the structure of liquids. Liquid state theory is expressed in terms of the correlation functions of the liquid of interest. Density functional theory, on the other hand, directly considers the average density of a liquid of interest. Density functional theory is most often used to examine the properties of fluids near walls or in confined media. In principle this the-

ory can be made exact, that is, to agree perfectly with atomistic simulations. In practice, however, density functional theory is somewhat less accurate than liquid state theory due to technical approximations made in the calculation of local entropy terms.

The Gubbins group has used density functional theory extensively to study fluids in confined geometries. Large effects on confined fluids have been found due to the fluid-wall interaction (Cracknell et al., 1995). Many fundamental features have been elucidated, such as surface-driven phase transitions, selective adsorption, adsorption/desorption hysteresis, and novel transport properties. This type of nonlocal density functional theory can be used to predict adsorption in real materials, design materials with tailored properties for advanced applications, and invert experimental data to determine pore-size distributions. As these authors mention, though, this theory is not always a good substitute for simulation. In particular, they show that if the structure of a heterogeneous microporous material is not properly accounted for, inaccurate results may be produced. For example, while nonlocal density function theory with a simple geometric model works well for the adsorption of methane and ethane in activated carbon, in some cases the inhomogeneity of the material and pore swelling become important. As another example, these authors show that by assuming a smooth wall for the mesoporous material MCM-41, one underpredicts the average pore size when using nonlocal density functional theory to invert experimental nitrogen adsorption data.

Model studies have been carried out for Lennard-Jones fluids in pores (Sliwinska-Bartkowiak et al., 1997). Reduced critical temperatures are typically found with a shift in the liquid-gas coexistence curve towards the species more attracted to the pore wall. A variety of additional phenomena are found, such as capillary condensation, layering transitions, and wetting transitions. The reduced geometry of the pore substantially affects properties such as melting, solid-solid and liquid-liquid phase transitions, and impurity solubility. Practical applications of this work on liquid-liquid transitions in confined media abound in the areas of oil recovery, lubrication, coating technology, and pollution control. The dramatic changes of solubility upon confinement are important in the dispersion of pollutants in the soil, removal of trace contaminants from soil and water, and lubrication.

Kusaka, Wang, and Seinfeld have used used density functional theory to address fundamental issues in ion-induced aerosol nucleation (Kusaka et al., 1995a,b). The importance of ionic and dipolar effects on the nucleation rate was clearly shown. Puzzling dependencies of the nucleation rate on the sign of the ion inducing the nucleation were explained as resulting from asymmetric distributions of charge within the nucleating particles. Differences of up to two orders of magnitude in the nucleation rate were found to result from such asymmetric charge distributions.

In lubrication applications one is interested, as well, in the dynamics of confined fluids. Pozhar and Gubbins have developed a dynamic version of density functional theory (Pozhar and Gubbins, 1991, 1993). This theory is able to calculate the local transport coefficients, such as viscosity, for various geometries. It was found that, as expected, the local transport values can be approximated by the values at the locally-averaged density. This approximation is only rough, however, and

the full theory gives a more reliable estimate. The theory predicts a generalized slip relation at the wall, in addition to producing a sort of generalized Navier-Stokes equation for confined fluids. The theory is in impressive agreement with atomistic simulation data down to pores a few atoms wide.

Field Theory

Field theory, as typically used, is a means for making predictions from a coarse-grained description of the system of interest. Within a field theory, average properties are calculated by averages over coarse-grained variables, not the detailed positions of all the atoms

$$\langle G \rangle = \frac{\int \mathcal{D}\Psi G[\Psi]\exp\{-H[\Psi]\}}{\int \mathcal{D}\Psi \exp\{-H[\Psi]\}}, \qquad (10)$$

where Ψ is a coarse-grained variable. Field theory is useful, because it is naturally suited to analyze systems with dynamics that occurs on very long spatial or temporal scales. Such systems are exceedingly expensive to analyze via computational means. Moreover, field theory provides analytical results, which are easier to use in design applications than are numerical data. The main applications of field theory within chemical engineering have been to polymer structure, copolymer order-disorder transitions, and chemical kinetics.

Static field theory

Field theoretic approaches to polymer structure were developed by physicists such as de Gennes, des Cloizeaux, Edwards, and others in the 1960s and 1970s. These methods have been applied and extended to the more detailed polymeric systems of interest to chemical engineers, initially by the Fredrickson group (Bates and Fredrickson, 1990). I mention two examples as representative of the many structural calculations that have been performed. Surface enrichment has been studied in polymer blends by field theoretic means (Donley et al., 1997). The combined effects of entropic packing and enthalpic binding were found to determine the surface segregation of polymer blends. A connection between the field theoretic approach and polymer RISM was made. The effect of chain flexibility on the scattering function of a polymer melt has been investigated (Marques and Fredrickson, 1997). Both the bulk and surface properties of semidilute solutions of these flexible molecules were calculated. Mean field theory has progressed to the point where it can be routinely applied by experimentalists (Matsen and Bates, 1996). Very good agreement is now found between the prediction of fully-implemented mean field theory and experiment.

A great many of the static properties of polymeric systems have been calculated with these field theoretic methods. As one specific example, I mention some of the work on elastic constants of various phases. The lamellar phase has been of particular focus. Figure 12 provides an illustration of the lamellar phase. Moduli for compression and extension of lamellar diblocks have been calculated (Wang, 1994). The de-
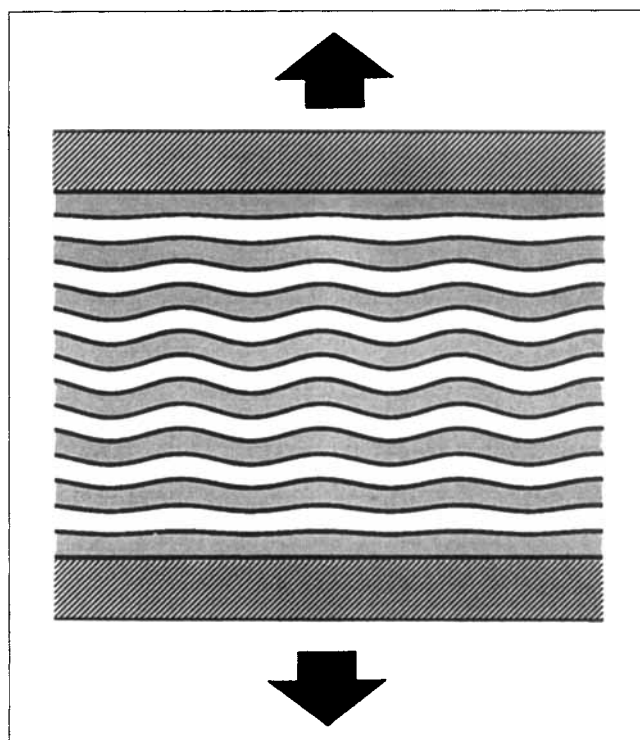

Figure 12. Cross-sectional view of layer undulation (induced by tension) in a lamellar diblock copolymer phase.

The A phase is shown as gray, and the B phase is shown as white. With permission from Wang (1994).

pendence on the blockiness of the copolymers has been examined with architectures that lead to looser packing of the lamellar layers leading to smaller dynamic compressibilities (Chakraborty and Fredrickson, 1994). The anomalous elasticity of smectic-A liquid crystals has been calculated via a mapping to the KPZ equation (Golubovic and Wang, 1994).

One of the more common applications of diblock copolymers is as surfactants and stabilization agents. One example is the stabilization of colloidal particles by adhesion of polymers on the surface. Figure 13 shows how polymers grafted to colloids prevent flocculation. The thermodynamics of the adsorption of diblocks on colloidal particles has been examined (Qiu and Wang, 1994). The density and stabilization properties of the adhered polymers can be modified by changing the length of the polymers, by changing the statistics of each block within the diblock, or by changing the size of the colloidal particle. One may even envision using selective diblock adhesion as a means to separate particles of varying size. More generally, diblocks can be used to lower the surface tension between two liquid or polymer phases. The spreading characteristics of liquids on such diblock films have been investigated (Martin et al., 1996). Studies such as these could well be studying the behavior of water drops on a new-waxed car finish!

An extensive body of work has been done by the Fredrickson and Bates groups on the order/disorder transitions that can occur in diblock copolymer systems (Bates and Fredrickson, 1990). As a recent example, I mention work on model
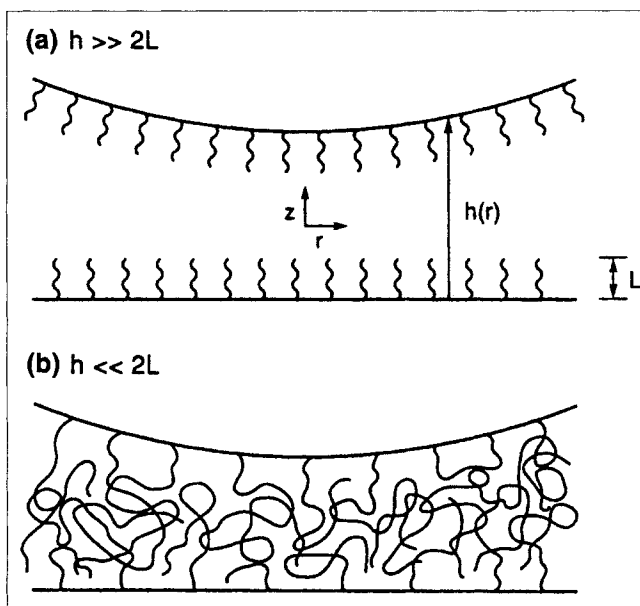
Figure 13. Polymer chains grafted to surfaces in a good solvent.

When the polymer chains overlap, there is a force pushing the surfaces apart. Used with permission from Frederickson and Pincus (1991).

hesion, and food protection, one often has a random heteropolymer in contact with a surface. The various adsorption and desorption transitions that can occur with a smooth surface, and how they depend on pH, polymer composition, and temperature, have been examined (Gutman and Chakraborty, 1995, 1996). Surface ordering induced by confinement has been examined (Gutman and Chakraborty, 1994). Adsorption transitions occurring near a disordered surface exhibit additional control mechanisms, such as pattern matching (Srebnik et al., 1996; Bratko et al., 1997). As intuitively expected, highest adsorption occurs when the statistics of the surface disorder and heteropolymer randomness are compatible.

Dynamic field theory

More recently, there has been an effort to look at long-time dynamics, rather than just statics, with field theory. Polymer rheology, polymer phase transitions, and polymer reactions have all received recent attention. In addition, fundamental work has been done showing that the traditional reaction diffusion partial differential equations are not correct for bimolecular surface reactions.

Work has been done to understand lubrication forces in polymeric systems. Seminal studies looked at the drainage of polymer layers adhered to and confined between plates (Fredrickson and Pincus, 1991). Frequency-dependent elastic and dissipative constants were calculated. Such theory provides a guide with which to design molecules for lubrication, molding, and coating applications.
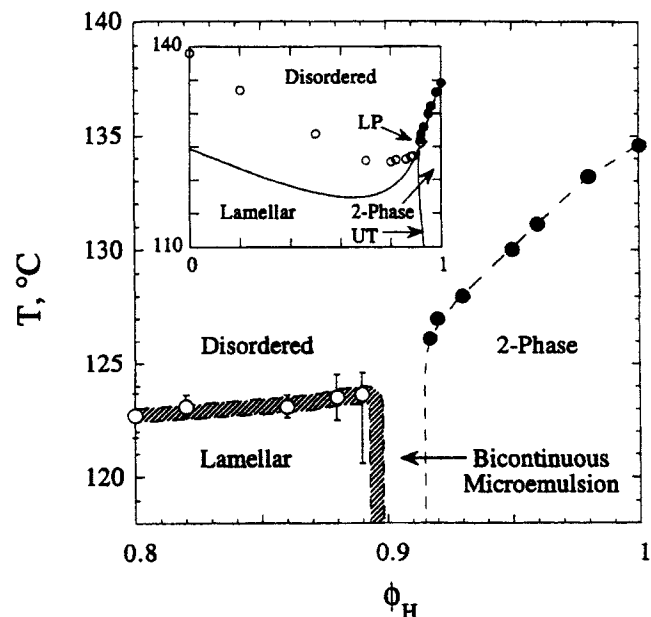
disordered bicontinuous phases. Disordered bicontinuous phases have been known for some time to occur in oil, water, and surfactant systems, but only recently has this phase been observed for long block copolymers (Bates et al., 1997). This phase is fluctuation induced, and it appears where simple mean field theory predicts an isotropic Lifshitz point. It seems that the mean field theory breaks down for the real system in three dimensions, and instead of the Lifshitz point, the disordered bicontinuous phase occurs. Figure 14 compares the theoretical predictions with experimental results for a high-molecular weight copolymer blended with thermodynamically incompatible homopolymers. That one can predict where this phase occurs, as a function of molecular architecture, density, temperature, and so on, with a simple, analytical theory is significant. This predictive ability is expected to lead to the design of new polymeric materials with useful mechanical, electrical, optical, or barrier properties. The Wang group has investigated triblock systems in an effort to provide similar theoretical guidance for the design of advanced molecular systems with nanoscale features (Zheng and Wang, 1995).

Recent work by the Chakraborty group has focused on the even more exotic phases and behavior that can occur in random heteropolymeric systems. Random heteropolymers in disordered media have been studied (Chakraborty and Shakhnovich, 1995). Replica methods were used to identify a low-temperature phase in which the heteropolymer adopts one of a few conformations consistent with the structure present in the random media. At higher temperatures, normal, protein-like folding occurs in which, again, only a few orientations are adopted. Between these two limits, and at much higher temperatures, the heteropolymer is able to access very many configurations. For applications such as microelectronics, automotive lubrication, high-performance ad-

Figure 14. Experimental phase behavior of a symmetric mixture of PE-PEP copolymer and PE and PEP homopolymers.

The volume fraction of homopolymer is given by ϕ_H. A mean-field calculation is shown in the inset. The two lines of critical points (solid) converge on an isotropic Lifshitz point. The predicted isotropic Lifshitz point does not exist, and the experimental system adopts, instead, a bicontinuous phase. Used with permission from Bates et al. (1997).

The kinetics of various order-order and order-disorder transitions in block copolymer systems has been studied (Fredrickson and Bates, 1996). Some of this work has addressed the question of what happens in an experimental system after a rapid temperature change is made (Qi and Wang, 1996, 1997). Typically, the system will undergo a change from one phase to another. Interestingly enough, the system often passes through nontrivial intermediate phases. Figure 15 shows how the lamellar phase crosses over to the hexatic phase after a temperature quench. The dynamics of this process has implications for the stability, or metastability, of the more exotic block copolymer phases.

The kinetics of the polymerization process itself has received attention (Fredrickson, 1996). The diffusion-controlled polymerization reaction for diblocks is interesting because as the reaction occurs, the growing polymers microphase separate. The effects of flow on reactions have been studied (Kolb et al., 1997). Flow typically slows down intrapolymer reactions through an elongation of the polymer chain. Conversely, flow typically speeds up interpolymer reactions through an increase of the center-of-mass diffusivity of the polymer.

I now turn to review the work by my group on transport-limited reactions in two dimensions. This is an interesting topic for chemical engineers. Moreover, chemical engineers, with their intuition into chemical kinetics, have an advantage over physicists in tackling this problem. Substantial progress has been made in understanding the behavior of bimolecular reactions in two dimensions.

Surface reactions in two dimensions show a variety of interesting behaviors. Simple systems, such as oxidation of CO on single crystal Pt(110), show surprisingly rich behavior (Graham et al., 1994), ranging from spirals and standing waves to chemical turbulence (Eiswirth and Ertl, 1995; Jakubith et al., 1990). Qualitatively, the difference between two and three dimensions is that diffusive mixing is less effective in two dimensions. With less mixing, transport limitations become more significant, and this leads to a breakdown of the law of mass action in two dimensions. Surprisingly, even the traditional reaction diffusion partial differential equation is also
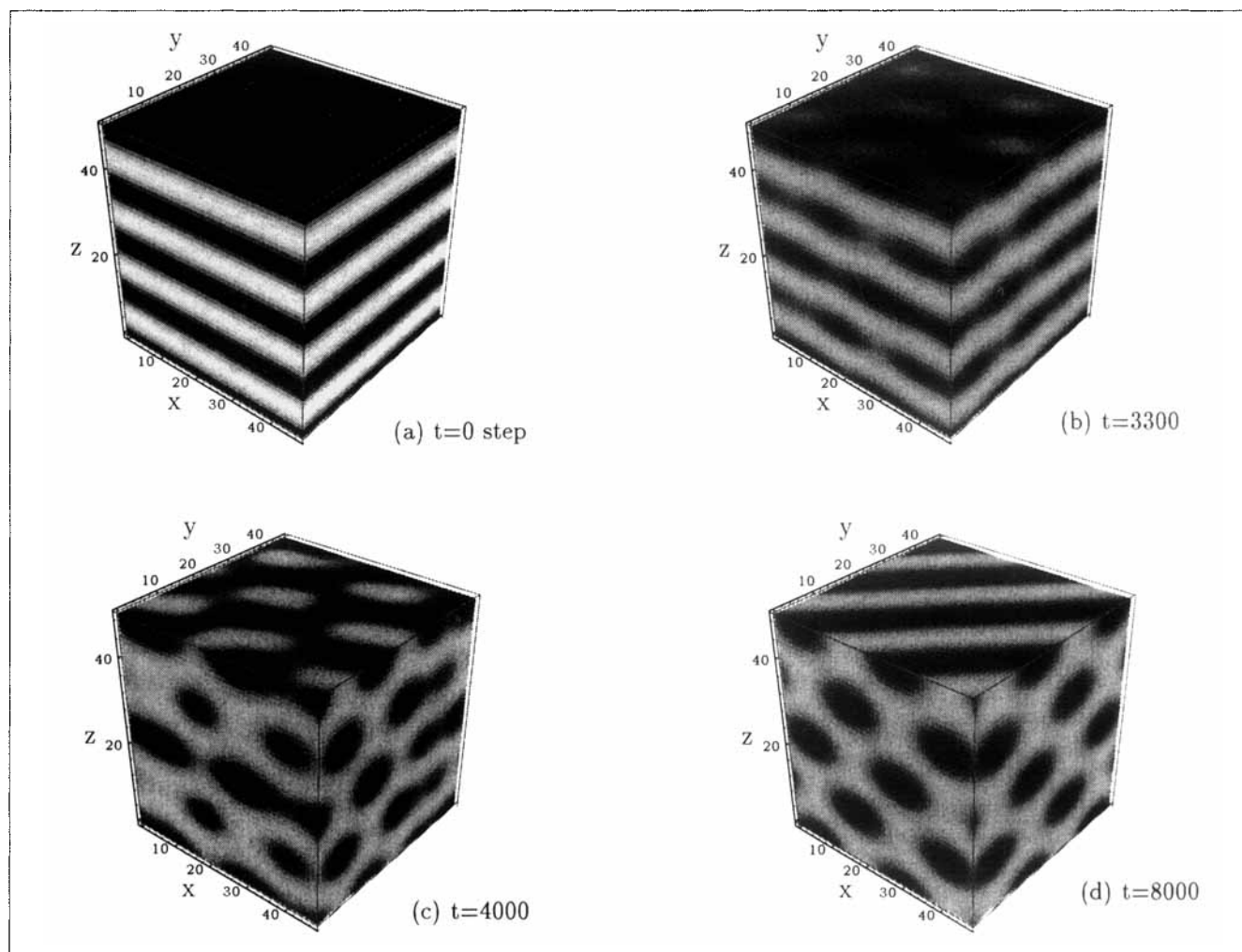

Figure 15. Evolution of the lamellar phase to the hexagonal phase in a weakly segregated diblock copolymer system.

Used with permission from Qi and Wang (1997).

qualitatively wrong in two dimensions. The reaction diffusion equation fails, because it is a type of mean field theory and two dimensions is the upper critical dimension for bimolecular kinetics, below which mean field theory fails.

Two-dimensional reactions occur in many contexts. The most familiar one is heterogeneous catalysis. However, there are many other cases of 2-D kinetics. Defect annealing in thin films is one example of a bimolecular annihilation reaction that occurs in two dimensions. Annealing of line defects in 3-D solids is another example. Reactions occurring within thin fluid films in another example.

The kinetics of the simplest reactions, even though not predictable by the reaction diffusion equation, is known, and field theoretic methods are not needed. For reactions that occur within disordered media, however, the kinetics is essentially unknown. Field theoretic methods are ideally suited to predict the long-time kinetics of such reactions. We have pursued this approach, mapping a master equation description of the kinetics onto a field theory. We found the asymptotic, long-time reactant concentrations by using a field-theoretic renormalization group analysis.

The two-dimensional bimolecular annihilation reaction $A + A \rightarrow \emptyset$ in the presence of random impurities was analyzed (Park and Deem, 1998a). We found that certain types of disorder lead to anomalous kinetics in the long time limit: $c_A(t) \sim bt^{\delta - 1}$. This kinetics results because the disorder forces the system into the (sub)diffusion controlled regime, where the mean-square displacement grows sublinearly with time as $\langle r^2(t) \rangle \sim at^{1 - \delta}$ and in which the kinetics must become anomalous. Computer simulations are in perfect agreement with the field-theoretic predictions (Chung and Deem, 1998).

The long-time behavior of the $A + B \rightarrow \emptyset$ reaction in two dimensions was examined, and a universal exponent and prefactor were found in the absence of disorder (Deem and Park, 1998a). It was shown, again, that certain types of disorder lead to a (sub)diffusion-limited reaction and a continuously variable decay exponent. Pattern matching between the reactant segregation and the disorder was not strong enough to affect the long-time decay.

The dynamics of the two-dimensional ion-dipole pairing reaction $A^+ + B^- \overset{\lambda}{\underset{\tau}{\rightleftharpoons}} AB$ was analyzed in the presence of disorder (Park and Deem, 1998b). Sufficiently singular disorder forces the critical temperature of the Kosterlitz-Thouless-Berezinskii fixed point to be nonuniversal. This disorder leads to anomalous ion pairing kinetics with a continuously variable decay exponent. Sufficiently strong disorder eliminates the transition altogether. For ions that are chemically reactive, anomalous kinetics with a continuously variable decay exponent also occurs in the high-temperature regime. The Coulomb interaction inhibits reactant segregation, and so the ionic $A^+ + B^- \rightarrow \emptyset$ reaction behaves like the nonionic $A + A \rightarrow \emptyset$ reaction.

Finally, two-dimensional reactive turbulent flow, a subject of long-standing and great interest to chemical engineers, was analyzed. The behavior of the reactions $A + A \rightarrow \emptyset$ and $A + B \rightarrow \emptyset$ occurring in turbulent flow in two dimensions was analyzed (Deem and Park, 1998b). A variety of interesting behavior was found, including, in the presence of potential disorder, decay rates faster than that for well-mixed reactions. This
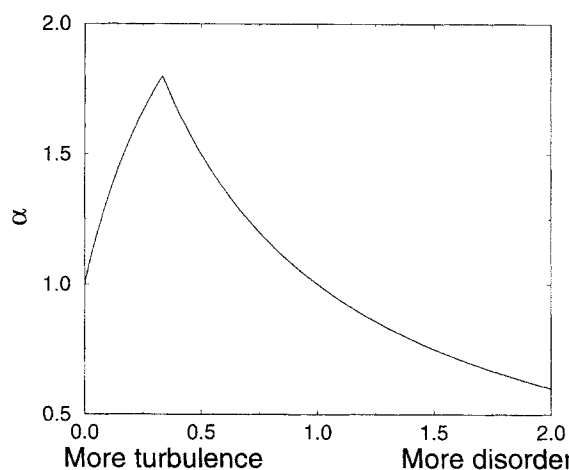

Figure 16. Decay exponent for the $A + A \rightarrow \emptyset$ reaction in the presence of isotropic turbulence and potential disorder.

The concentration decays as $c_A(t) \sim (\text{const})t^{-\alpha}$. Decay exponents greater than unity correspond to reaction rates faster than that for well-mixed reactants (Deem and Park, 1998b).

"superfast" decay is shown in Figure 16. This superfast reactivity has implications for the design of microreactors, such as might be constructed with MEMS technology.

Applications in Biotechnology

I conclude with some examples of the application of statistical mechanics to the biotechnology and pharmaceutical industry. To date, very little academic chemical engineering research in statistical mechanics has been done on problems of interest to these industries. A much greater emphasis has been placed upon the older chemical process and materials industries. There is significant research activity to be done in
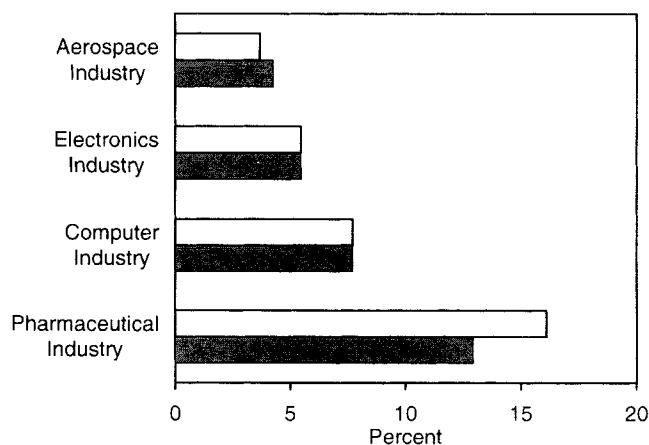

Figure 17. R&D investments as a percentage of sales for some high-technology industries in 1991 (light) and 1993 (dark).

Adapted from Boyd (1997).

the new fields, however. As shown by Figure 17, the pharmaceutical industry makes the largest investment in research and development relative to sales of any of the high-technology industries. The chemical, petrochemical, and materials industries make relative investments substantially smaller than those shown in this Figure. In these last sections, which are intended to be forward looking, I mention some areas where statistical mechanics can have an impact and some of the successes that have been achieved to date.

Drug design

Rational design of drugs has been a goal of theoretical medicine chemists since the early 1980s. To date, it remains true that no successful drug has yet been designed by purely computational methods (Boyd, 1998a). *There are roughly thirty pharmaceuticals, however, whose discovery benefited in some way from computer simulation (Boyd, 1998a)*. One of the earliest examples is the antibacterial norfloxacin. The carbonic anhydrase inhibitor dorzolamide hydrochloride, which is a treatment for glaucoma, benefited from classical and quantum methods of ligand design. Molecular modeling played a role in the discovery of the acetylcholinesterase inhibitor donepezil hydrochloride. The angiotensin II receptor antagonist losartan sodium was discovered with the help of molecular modeling of the octapeptide angiotensin II. Molecular modeling aided in the discovery of the migraine drug zolmitriptan. A variety of inhibitors to HIV-1 have been discovered with the help of computer simulation, including indinavir sulfate, nelfinavir mesylate, saquinavir, and rintonavir. It is worth mentioning one failure of the computational approach: the exhaustive studies of inhibitors to dihydrofolate reductase have yet to lead to any effective anti-cancer or anti-infective therapeutics.

Several of these computer studies have been in the context of mapping a peptide inhibitor onto a more drug-like organic molecule. The viability of this approach is emphasized by the recent successes with minimized proteins (Cunningham and Wells, 1997). *The concerted rotation, configurational bias method (Deem and Bader, 1996) is used by the biotechnology company CuraGen in this context.*

These examples illustrate that while relatively few drugs (roughly 1%) are discovered by academia, many of the methods for such discovery are developed in academia (Boyd, 1997). Tremendously challenging intellectual issues remain within this field, which is ripe for incorporation within chemical engineering. As one example, I mention the importance of understanding, predicting, and overcoming multidrug-resistant diseases (Boyd, 1997). The rapidly increasing cost of drug discovery (roughly $359 million and 8–12 years as of 1990) and the rapidly increasing research and development expenditures (see Figure 18) makes this area ripe for process improvement, at which chemical engineers are so adept.

As a final example, I mention the recent work of the Zukoski group on the crystallization of proteins (Rosenbaum and Zukoski, 1996; Rosenbaum et al., 1996). X-ray crystallography is still the primary means for high-resolution structure determination of protein crystals. Structure is crucially important for understanding the molecular basis of protein function. Crystallization is still, unfortunately, an essentially
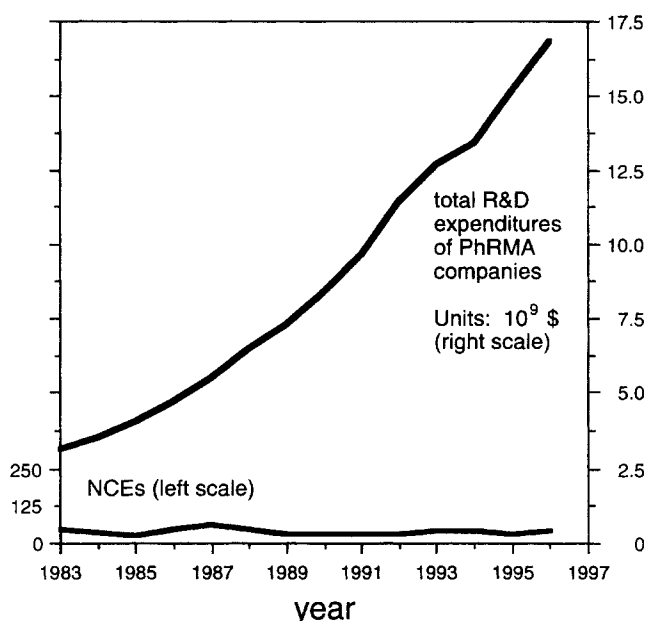

Figure 18. Money spent on pharmaceutical research and number of new chemical entities (NCEs) introduced worldwide.

Reprinted with permission from Boyd (1998b).

Edisonian endeavor, where many different crystallization conditions are examined in the hopes of finding one that works. The results of many such experiments have been successfully correlated to second virial coefficients and a single prototypical phase diagram. With such predictive understanding of the crystallization process, one may hope to design better crystallization schemes. A recent example is the predicted enhancement of nucleation in the vicinity of a metastable fluid-fluid critical point (ten Wolde and Frenkel, 1997). Enhancement of the nucleation rate without increasing the crystal growth rate is key to the production of high quality crystals (see Figure 19).

Combinatorial chemistry

Combinatorial chemistry was developed in the field of molecular biology, and later in organic chemistry, as a means of creating a large library of diverse molecules that can be screened or selected for those molecules with a particular property of interest. Stemmer (1994) has recently provided a greatly enhanced method for the discovery of protein molecules with improved function. His insight was to generalize the process of antibody recombination and maturation to all possible protein molecules (Marks et al., 1992). With this approach, many molecules of interest to chemical engineers can be made to function better, including proteases, lipases, amylases, cellulases, specialty chemicals, drugs, and remediation agents (Patten et al., 1997). *This method has been used by MAXYGEN to optimize enzymes, a fluorescent protein tag, antibody expression, arsenate resistance genes, atrazine degradation enzymes, DNA repair molecules, and antibiotic deprotection (Patten et al., 1997).* Future applications include protein phar-
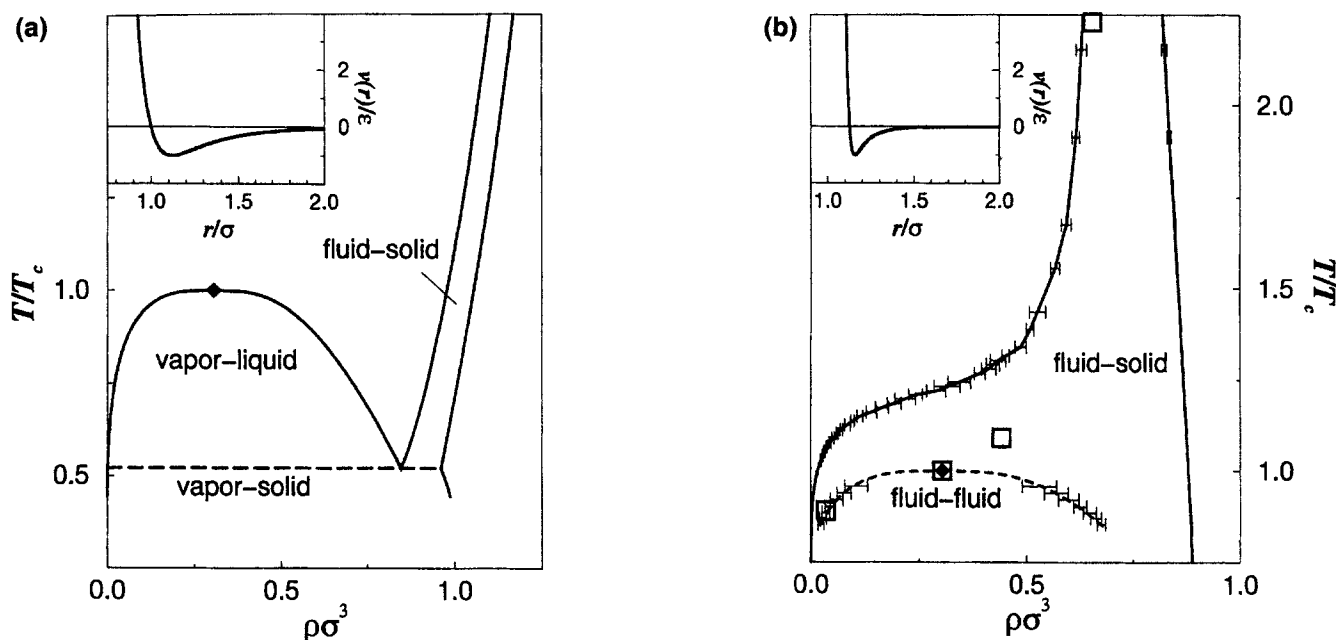
Figure 19. Typical phase diagram: (a) simple molecular substance; (b) protein-like substance.

Temperature is reduced by the critical temperature T_c and the density is reduced by the effective diameter of the particles σ. The dashed curve in (b) traces the metastable fluid-fluid coexistence. Near the pseudo-critical point on this dashed curve, the crystal nucleation rate is enhanced while the crystal growth rate is still modest. Reprinted with permission from ten Wolde and Frenkel (1997).

maceuticals, small molecule pharmaceuticals, gene therapy, DNA vaccines, recombinant protein vaccines, viral vaccines, and viruses with evolved functions. This work has begun to catch the attention of biochemical engineers, and the Arnold group has made contributions in this area (Zhao et al., 1998; Arnold, 1998). The Khosla group has developed an alternative route, designing combinatorial biosynthesis approaches for the construction of polyketide libraries (Khosla and Zawada, 1996; Jacobsen et al., 1997).

Significant opportunities exist for the application of statistical mechanics to this burgeoning area. The basic idea of combinatorial methods is to search sequence space so as to identify regions of protein space that have desirable chemical function. There are several molecular biological parameters in the method, such as how long to make the DNA pieces to be shuffled, how many homologous genes to shuffle, and how high a point mutation rate to select (Stemmer, 1995; Zhang et al., 1997). Optimization of these parameters is a natural task for chemical engineers. Design of better methods is a more ambitious task, which we have recently tackled (Bogarad and Deem, 1998).

While combinatorial chemistry was not invented by researchers in the field of statistical mechanics, it is fair to say that perhaps it should have been! The design of effective methods for searching composition space is similar in concept to the design of effective Monte Carlo methods for searching configuration space, at which chemical engineers have shown great aptitude. Some significant work has been done on the analysis of these methods (Kauffman, 1993; Kauffman and Macready, 1995). It is notable that one of the strongest present chemical-engineering proponents of combinatorial chemistry in the solid state, Henry Weinberg at

SYMYX Technologies, has taught graduate statistical mechanics for the last twenty-five years! Significant opportunities exist for chemical engineers to develop and to apply these synthesis and screening techniques to the discovery of new materials with useful functions. Possible applications abound in the fields of catalysis, sensors, coatings, and microelectronics. *As an important, recent example, I mention the discovery of a new high-dielectric material that may be used in future generations of DRAM chips (Vandover et al., 1998).*

Pharmacogenomics

One of the ideas of pharmacogenomics is that it would be very useful to monitor the molecular processes that take place in an individual as a drug regimen is carried out. With such information, one could correlate, on the molecular level, the effectiveness of a drug therapy as a function of disease state. One means of monitoring the molecular processes within an individual is to measure the levels at which various proteins are expressed in different tissues. This could be done by sequencing the genetic material expressed in the tissues, which requires very-high-throughput screening. This approach might appear to be impractical, since one knows that sequencing of the entire human genome will take more than a decade. All one really wants to know in pharmacogenomics, however, is the concentration of each of the roughly 100,000 proteins that naturally occur within the body. This is a much simpler problem: simply perform, say, 300,000 measurements whose results depend on the level of protein expression and invert the data to determine the protein concentrations. Genetic methods for performing such measurements exist. *Of the many present methods, I mention the gene chip approach of Affymetrix*

Table 1. Selected Applications Implemented by Some CPI Companies*

Company	Areas of Successful Application
Air Liquide	Design of zeolites for O_2/N_2 separation
Air Products & Chemicals	Adhesives and adsorption
Albemarle	Flame retardants and lubricants
Amoco	Homogeneous and heterogeneous catalysis, thermochemistry, and process parameters
ARCO	Chemicals and polyester weatherability
BASF	Surfactant lamellae and micelles
BP	CH_4 adsorption
Chevron	Gas hydrates, lubricants, and anti-corrosives
Dow	Polymers, thermochemistry, reaction networks, and ΔH_{rxn} (safety)
Dow-Corning	Silicone chemistry
DuPont	Homogeneous and heterogeneous catalysis, thermochemistry, and agricultural chemicals
Exxon R&E	NO_x kinetics, elementary and networked reactions, and zeolites
Hercules	Polysaccharide rheology
IBM	Polymers and coatings
Lubrizol	Hydrocarbon-Cl_2 reactions and anti-corrosives
General Motors	Monolithic catalysts
Phillips	Catalysts and gas hydrates
Procter & Gamble	Design of detergent enzymes
Royal Dutch Shell	Diffusion in porous media
Schlumberger	Setting of drilling cements
Shell USA	Solvent separations, catalysis, and surfactants
Union Carbide	Homogeneous catalysis and material properties
Xerox	Modification and development of photocopying materials

*Used with permission from Cummings et al. (1997).

(Fodor, 1997; Lipshutz et al., 1995), the hybridization approach of Hyseq (Drmanac et al., 1998; Milosavljević et al., 1996), and the quantitative expression analysis of CuraGen, to which I contributed. The design and optimization of these statistically based methods is an ideal area for chemical engineers.

A related and ubiquitous goal of bioinformatics is to perform very-high-throughput DNA sequencing. The same methods as above can be adapted for this purpose (Lipshutz and Fodor, 1994). However, one can also imagine using the traditional Sanger sequencing approach in radical designs. The "NanoNiagara" device of CuraGen is one such example (Deem et al., 1996; Bader, 1997; Mulhern et al., 1996; Bader, 1998). Similar devices have recently been described by other groups (Ertas, 1998; Duke and Austin, 1998).

Conclusion

To quote from Daan Frenkel and Berend Smit, computer simulation is now an "essential tool in the design of novel materials" (Frenkel and Smit, 1997). The tools of statistical mechanics are not limited to the study of argon: They can be and are now used on real materials of interest to the chemical process industry (Smit, 1995). Table 1, compiled by Phillip Westmoreland from discussions held each year at the annual AIChE meeting, lists just some of the successes that various companies have had with these methods. Several successes in the pharmaceutical industry, with aggregate sales in the hundred-billion dollar range, have already been mentioned.

I would like to close with three thoughts. First, the impressive list of industrial successes of statistical mechanics was the result of significant, fundamental advances in quantum mechanics, molecular dynamics, and Monte Carlo simulation methods. Second, analytical methods are not now irrelevant in light of these powerful simulation methods. The significant analytical advances in our ability to predict the structure and dynamics of polymers, properties very difficult to simulate directly, have only recently been developed, and industrial applications will surely follow. Finally, statistical mechanics has a significant role to play in shaping new methods of materials design, such as combinatorial materials synthesis.

Notation

$c_A(t)$ = concentration of species A at time t
$\mathfrak{D}\Psi$ = functional infinitesimal
E_ν = quantum energy in state ν
H = Hamiltonian (classical or quantum)
m_i = mass of atom i
$P_\alpha(t)$ = probability of being in state α at time t
r_i = position of atom i
$\ddot{r}_i$ = acceleration of atom i
t = time
Ψ_ν = quantum energy in state ν

Literature Cited

Agrawal, R., and D. A. Kofke, "Solid-Fluid Coexistence for Inverse-Power Potentials," Phys. Rev. Lett., 74, 122 (1995).

Akhmatskaya, E., B. D. Todd, P. J. Daivis, D. J. Evans, K. E. Gubbins, and L. A. Pozhar, "A Study of Viscosity Inhomogeneity in Porous Media," J. Chem. Phys., 106, 4684 (1997).

Akporiaye, D. E., H. Fjellvag, E. N. Halvorsen, T. Haug, A. Karlsson, and K. P. Lillerud, "UIO-6—A Novel 12-Ring AlPO4, Made in an Inorganic-Organic Cation System," Chem. Comm., 13, 1553 (1996a).

Akporiaye, D. E., H. Fjellvag, E. N. Halvorsen, J. Hustveit, A. Karlsson, and K. P. Lillerud, "UIO-7—A New Aluminophosphate Phase Solved by Simulated Annealing and High-Resolution Powder Diffraction," J. Phys. Chem., 100, 16641 (1996b).

Akporiaye, D. E., H. Fjellvag, E. N. Halvorsen, J. Hustveit, A. Karlsson, and K. P. Lillerud, "The Synthesis and Structure Solution of UIO-7, A New Molecular-Sieve," Chem. Comm., 5, 601 (1996c).

Alvarado, V., H. T. Davis, and L. E. Scriven, "Effects of Pore-Level Reaction on Dispersion in Porous Media," Chem. Eng. Sci., 52, 2865 (1997).

Arnold, F. H., "Design by Directed Evolution," Acc. Chem. Res., 31, 125 (1998).

Auerbach, S. M., "Analytical Theory of Benzene Diffusion in Na-Y Zeolite," J. Chem. Phys., 106, 7810 (1997).

Auerbach, S. M., and H. Metiu, "Modeling Orientational Randomization in Zeolites: A New Probe of Intracage Mobility, Diffusion and Cation Disorder," J. Chem. Phys., 106, 2893 (1997).

Auerbach, S. M., and H. I. Metiu, "Diffusion in Zeolites via Cage-To-Cage Kinetics: Modeling Benzene Diffusion in Na-Y," J. Chem. Phys., 105, 3753 (1996).

Auerbach, S. M., L. M. Bull, N. J. Henson, H. I. Metiu, and A. K. Cheetham, "Behavior of Benzene in Na-X and Na-Y Zeolites: Comparative Study by ^{2}H NMR and Molecular Mechanics," J. Phys. Chem., 100, 5923 (1996).

Bader, J. S., "Programmable Nanoscale Engines for Molecular Separation," NIST ATP Program, 96-01-0141 (1997).

Bader, J. S., "A Nanoscale, Liquid-Phase DNA Separation Device Based on Brownian Rachets," paper K14.09, APS Meeting, Los Angeles (1998).

Bates, F. S., and G. H. Fredrickson, "Block Copolymer Thermodynamics—Theory and Experiment," *Ann. Rev. Phys. Chem.*, **41**, 525 (1990).

Bates, F. S., W. W. Maurer, P. M. Lipic, M. A. Hillmyer, K. Almdal, K. Mortensen, G. H. Fredrickson, and T. P. Lodge, "Polymeric Bicontinuous Microemulsions," *Phys. Rev. Lett.*, **79**, 849 (1997).

Bates, S. P., W. J. M. van Well, and R. A. van Santen, "Location and Conformation of n-Alkanes in Zeolites: An Analysis of Configurational-Bias Monte Carlo Calculations," *J. Phys. Chem.*, **100**, 17573 (1996a).

Bates, S. P., W. J. M. van Well, R. A. van Santen, and B. Smit, "Energetics of n-Alkanes in Zeolites: A Configurational-Bias Monte Carlo Investigation into Pore Size Dependence," *J. Amer. Chem. Soc.*, **118**, 6753 (1996b).

Bennett, C. H., *Diffusion in Solids: Recent Developments*, J. J. Burton and A. S. Norwick, eds., Academic Press, New York (1975).

Bergenholtz, J., and N. J. Wagner, "Self-diffusion in Dispersions of Charged Colloidal Spheres by Generalized Hydrodynamics," *Physica A*, **235**, 34 (1997).

Bethune, D. S., C.-H. Kiang, M. S. deVries, G. Morman, R. Savoy, J. Vasquez, and R. Beyers, "Cobalt-Catalyzed Growth of Carbon Nanotubes with Single-Atomic-Layer Walls," *Nature*, **363**, 605 (1993).

Bogarad, L., and M. W. Deem, "Hierarchical Combinatorial Evolution in Protein Space," (1998).

Boyd, D. B., "Computer-Aided Molecular Design," *Encyclopedia of Library and Information Science*, A. Kent and C. M. Hall, eds., Marcel Dekker, New York (1997).

Boyd, D. B., "Is Rational Design Good for Anything?," *Rational Drug Design*, M. R. Reedy and A. L. Parrill, eds., Amer. Chem. Soc., Washington, DC (1998a).

Boyd, D. B., "Innovation and the Rational Design of Drugs," *CHEMTECH*, **28**, 19 (1998b).

Brady, J. F., and G. Bossis, "Stokesian Dynamics," *Ann. Rev. Fluid Mech.*, **20**, 111 (1988).

Bratko, D., A. K. Chakraborty, and E. I. Shakhnovich, "Recognition between Random Heteropolymers and Multifunctional Disordered Surfaces," *Chem. Phys. Lett.*, **280**, 46 (1997).

Briano, J. G., and E. D. Glandt, "Statistical Thermodynamics of Polydisperse Fluids," *J. Chem. Phys.*, **80**, 3336 (1984).

Brown, R. A., D. Maroudas, and T. Sinno, "Modeling Point Defect Dynamics in the Crystal Growth of Silicon," *J. Crystal Growth*, **137**, 12 (1994).

Bulatov, V., F. F. Abraham, L. Kubin, B. Devincre, and S. Yip, "Connecting Atomistic and Mesoscale Simulations of Crystal Plasticity," *Nature*, **391**, 669 (1998).

Campbell, D. M., and M. T. Klein, "Construction of a Molecular Representation of a Complex Feedstock by Monte-Carlo and Quadrature Methods," *Appl. Catal. A*, **160**, 41 (1997).

Campbell, B. J., G. Bellussi, L. Carluccio, G. Perego, A. K. Cheetham, D. E. Cox and R. Millini, "The Synthesis of the New Zeolite, ERS-7, and the Determination of its Structure by Simulated Annealing and Synchrotron X-ray-Powder Diffraction," *Chem. Comm.*, **16**, 1725 (1998).

Car, R., and M. Parrinello, "Unified Approach for Molecular-Dynamics and Density-Functional Theory," *Phys. Rev. Lett.*, **55**, 2471 (1985).

Carbeck, J. D., and G. C. Rutledge, "A Method for Studying Conformational Relaxations by Molecular Simulation: Conformational Defects in α-Phase Poly(vinylidene fluoride)," *Macromol.*, **29**, 5190 (1996).

Chakraborty, A. K., and G. H. Fredrickson, "Elastic Constants for Random Block Copolymers in the Strong Segregation Limit: Effects of Sequence Distribution," *Macromol.*, **27**, 7079 (1994).

Chakraborty, A. K., and E. I. Shakhnovich, "Phase Behavior of Random Copolymers in Quenched Random Media," *J. Chem. Phys.*, **103**, 10751 (1995).

Chandler, D., "Gaussian Field Model of Fluids with an Application to Polymeric Fluids," *Phys. Rev. E*, **48**, 2898 (1993).

Chandler, D., and H. C. Andersen, "Optimized Cluster Expansions for Classical Fluids. II. Theory of Molecular Liquids," *J. Chem. Phys.*, **57**, 1930 (1972).

Chandler, D., J. D. Weeks, and H. C. Andersen, "van der Waals Picture of Liquids, Solids, and Phase-Transitions," *Science*, **220**, 787 (1983).

Chiew, Y. C., D. Kuehner, H. W. Blanch, and J. M. Prausnitz, "Molecular Thermodynamics for Salt-Induced Protein Precipitation," *AIChE J.*, **41**, 2150 (1995).

Chung, W.-J., and M. W. Deem, "Numerical Observation of Disorder-Induced Anomalous Kinetics in the $A + A \rightarrow \emptyset$ Reaction," *Physica A*, in press (1998).

Coen, C. J., H. W. Blanch, and J. M. Prausnitz, "Salting Out of Aqueous Proteins: Phase Equilibria and Intermolecular Potentials," *AIChE J.*, **41**, 996 (1995).

Cracknell, R. F., K. E. Gubbins, M. Maddox, and D. Nicholson, "Modeling Fluid Behavior in Well-Characterized Porous Materials," *Acc. Chem. Res.*, **28**, 281 (1995).

Cummings, P. T., B. K. Peterson, C. K. Hall, M. Neurock, A. Z. Panagiotopoulos, and P. R. Westmoreland, "NSF Workshop: Future Directions in Molecular Modeling and Simulation: Fundamentals and Applications," NSF Technical Report, http://flory.engr.utk.edu/nsf.html/final-report.html (1997).

Cunningham, B. C., and J. A. Wells, "Minimized Proteins," *Curr. Opin. Struct. Biol.*, **7**, 457 (1997).

Curtis, R. A., J. M. Prausnitz, and H. W. Blanch, "Protein-Protein and Protein-Salt Interactions in Aqueous Protein Solutions Containing Concentrated Electrolytes," *Biotech. Bioeng.*, **57**, 11 (1998).

de Pablo, J. J., "Simulation of Phase Equilibria for Chain Molecules," *Fluid Phase Equil.*, **104**, 195 (1995).

de Pablo, J. J., and J. M. Prausnitz, "Phase Equilibria for Fluid Mixtures from Monte-Carlo Simulation," *Fluid Phase Equil.*, **53**, 177 (1989).

de Pablo, J. J., M. Laso, and U. W. Suter, "Estimation of the Chemical Potential of Chain Molecules by Simulation," *J. Chem. Phys.*, **96**, 6157 (1992).

Deem, M. W., "Field-Theoretic Approximations for Normal Diffusion in Random Velocity Fields," *Phys. Rev. E*, **51**, 4319 (1995).

Deem, M. W., and J. S. Bader, "A Configurational Bias Monte Carlo Method for Linear and Cyclic Peptides," *Mol. Phys.*, **87**, 1245 (1996).

Deem, M. W., and D. Chandler, "Charge Frustrated Model of Bicontinuous Phases," *Phys. Rev. E*, **49**, 4268 (1994a).

Deem, M. W., and D. Chandler, "Formation of Interfaces in Bicontinuous Phases," *Phys. Rev. E*, **49**, 4276 (1994b).

Deem, M. W., and D. Chandler, "Classical Diffusion in Strong Random Media," *J. Stat. Phys.*, **76**, 911 (1994c).

Deem, M. W., and J. M. Newsam, "Determination of 4-Connected Framework Crystal Structures by Simulated Annealing," *Nature*, **342**, 260 (1989).

Deem, M. W., and J. M. Newsam, "Framework Crystal Structure Solution by Simulated Annealing: Test Application to Known Zeolite Structures," *J. Amer. Chem. Soc.*, **114**, 7189 (1992).

Deem, M. W., and J.-M. Park, "The Effect of Static Disorder and Reactant Segregation on the $A + B \rightarrow \emptyset$ Reaction," *Phys. Rev. E*, **57**, 2681 (1998a).

Deem, M. W., and J.-M. Park, "Reactive Turbulent Flow in Low-Dimensional, Disordered Media," *Phys. Rev. E*, **58**, 3223 (1998b).

Deem, M. W., J. M. Newsam, and J. A. Creighton, "Fluctuations in Zeolite Aperture Dimensions Simulated by Crystal Dynamics," *J. Amer. Chem. Soc.*, **114**, 7198 (1992).

Deem, M. W., J. S. Bader, G. Mulhern, and J. M. Rothberg, "Device for Liquid-Phase Sequencing of DNA," paper 84a, AIChE Meeting, Chicago (1996).

Dillon, A. C., K. M. Jones, T. A. Bekkedahl, C. H. Kiang, D. S. Bethune, and M. J. Heben, "Storage of Hydrogen in Single-Walled Carbon Nanotubes," *Nature*, **386**, 377 (1997).

Dodd, L. R., T. D. Boone, and D. N. Theodorou, "A Concerted Rotation Algorithm for Atomistic Monte-Carlo Simulation of Polymer Melts and Glasses," *Mol. Phys.*, **78**, 961 (1993).

Donley, J. P., D. T. Wu, and G. H. Fredrickson, "On the Control of Surface Enrichment in Polymer Blends and Copolymers," *Macromol.*, **30**, 2167 (1997).

Drmanac, S., D. Kita, I. Labat, B. Hauser, C. Schmidt, J. D. Burczak, and R. Drmanac, "Accurate Sequencing by Hybridization for DNA

Diagnostics and Individual Genomics," *Nature Biotech.*, **16**, 54 (1998).

Duke, T. A. J., and R. H. Austin, "Microfabricated Sieve for the Continuous Sorting of Macromolecules," *Phys. Rev. Lett.*, **80**, 1552 (1998).

Eiswirth, M., and G. Ertl, in *Chemical Waves and Patterns*, R. Kapral and K. Showalter, eds., Kluwer, Dordrecht (1995).

Elston, T. C., and C. R. Doering, "Numerical and Analytical Studies of Nonequilibrium Fluctuation-Induced Transport Processes," *J. Stat. Phys.*, **83**, 359 (1996).

Ertas, D., "Lateral Separation of Macromolecules and Polyelectrolytes in Microlithographic Arrays," *Phys. Rev. Lett.*, **80**, 1548 (1998).

Escobedo, F. A., and J. J. de Pablo, "Expanded Grand Canonical and Gibbs Ensemble Monte Carlo Simulation of Polymers," *J. Chem. Phys.*, **105**, 4391 (1996).

Escobedo, F. A., and J. J. de Pablo, "Pseudo-Ensemble Simulations and Gibbs-Duhem Integrations for Polymers," *J. Chem. Phys.*, **106**, 2911 (1997a).

Escobedo, F. A., and J. J. de Pablo, "Phase Behavior of Model Polymeric Networks and Gels," *Mol. Phys.*, **90**, 437 (1997b).

Evans, A. R., and E. S. G. Shaqfeh, "The Conformation of Semi-rigid Polymers during Flow through a Fixed Fiber Bed," *J. Non-Newtonian Fluid Mech.*, **64**, 95 (1996).

Falcioni, M., and M. W. Deem, "A Biased Monte Carlo Scheme for Zeolite Structure Solution," *J. Chem. Phys.*, in press (1998).

Fodor, S. P. A., "Massively Parallel Genomics," *Science*, **277**, 393 (1997).

Ford, D. M., and E. D. Glandt, "Steric Hindrance at the Entrances to Small Pores," *J. Memb. Sci.*, **107**, 47 (1995a).

Ford, D. M., and E. D. Glandt, "Molecular Simulation Study of the Surface Barrier Effect. Dilute Gas Limit," *J. Phys. Chem.*, **99**, 11543 (1995b).

Fredrickson, G. H., "Diffusion-Controlled Reactions at Polymer-Polymer Interfaces," *Phys. Rev. Lett.*, **76**, 3440 (1996).

Fredrickson, G. H., and F. S. Bates, "Dynamics of Block-Copolymers —Theory and Experiment," *Ann. Rev. Mat. Sci.*, **26**, 501 (1996).

Fredrickson, G. H., and P. Pincus, "Drainage of Compressed Polymer Layers: Dynamics of a Squeezed Sponge," *Langmuir*, **7**, 786 (1991).

Frenkel, D., and B. Smit, "Unexpected Length Dependence of the Solubility of Chain Molecules," *Mol. Phys.*, **75**, 983 (1992).

Frenkel, D., and B. Smit, *Understanding Molecular Simulation: From Algorithms to Applications*, Academic Press, San Diego (1996).

Frenkel, D., and B. Smit, "Simulation of Phase Coexistence for Complex Molecules," *Comput. in Phys.*, **11**, 246 (1997).

Frenkel, D., C. G. A. M. Mooij, and B. Smit, "Novel Scheme to Study Structural and Thermal Properties of Continuously Deformable Molecules," *J. Phys.: Condens. Matter*, **4**, 3053 (1992).

Golubovic, L., and Z.-G. Wang, "Kardar-Parisi-Zhang Model and Anomalous Elasticity of Two- and Three-Dimensional Smectic-A Liquid Crystals," *Phys. Rev. E*, **49**, 2567 (1994).

Gordon, P. A., and E. D. Glandt, "Liquid-Liquid Equilibrium for Fluids Confined within Random Porous Materials," *J. Chem. Phys.*, **105**, 4257 (1996).

Graham, M. D., I. G. Kevrekidis, K. Asakura, J. Lauterbach, K. Krischer, H. H. Rotermund, and G. Ertl, "Effects of Boundaries on Pattern Formation—Catalytic Oxidation of CO on Platinum," *Science*, **264**, 80 (1994).

Gutman, L., and A. K. Chakraborty, "Surface-Induced Ordering for Confined Random Block Copolymers," *J. Chem. Phys.*, **101**, 10074 (1994).

Gutman, L., and A. K. Chakraborty, "A Field Theory of Random Heteropolymers near Solid Surfaces: Analysis of Interfacial Organization and Adsorption-Desorption Phase Diagram," *J. Chem. Phys.*, **103**, 10733 (1995).

Gutman, L., and A. K. Chakraborty, "Exotic Transitions of Random Heteropolymers Interacting with Solid Surfaces," *J. Chem. Phys.*, **105**, 7842 (1996).

Huang, D., Y. Chen, and K. A. Fichthorn, "A Molecular-Dynamics Simulation Study of the Adsorption and Diffusion Dynamics of Short n-Alkanes on Pt(111)," *J. Chem. Phys.*, **101**, 11021 (1994).

Iijima, S., and T. Ichihashi, "Single-Shell Carbon Nanotubes of 1 nm Diameter," *Nature*, **363**, 603 (1993).

Irikura, K. K., and D. J. Frurip, "Symposium on Computational Thermochemistry," ACS Technical Report, http://www.nist.gov/compchem/irikura/irikura.html (1996).

Israelachvili, J., and H. Wennerström, "Role of Hydration and Water Structure in Biological and Colloidal Interactions," *Nature*, **379**, 219 (1996).

Jacobsen, J. R., C. R. Hutchinson, D. E. Cane, and C. Khosla, "Precursor-Directed Biosynthesis of Erythromycin Analogs by an Engineered Polyketide Synthase," *Science*, **277**, 367 (1997).

Jakubith, S., H. H. Rotermund, W. Engel, A. Vonoertzen, and G. Ertl, "Spatiotemporal Concentration Patterns in a Surface Reaction—Propagating and Standing Waves, Rotating Spirals, and Turbulence," *Phys. Rev. Lett.*, **65**, 3013 (1990).

Johnson, J. K., A. Z. Panagiotopoulos, and K. E. Gubbins, "Reactive Canonical Monte Carlo—A New Simulation Technique for Reacting or Associating Fluids," *Mol. Phys.*, **81**, 717 (1994).

Johnson, M. E., S. Mitragotri, A. Patel, D. Blankschtein, and R. Langer, "Synergistic Effects of Chemical Enhancers and Therapeutic Ultrasound on Transdermal Drug Delivery," *J. Pharm. Sci.*, **85**, 670 (1996).

June, R. L., A. T. Bell, and D. N. Theodorou, "Transition-State Studies of Xenon and SF_6 Diffusion in Silicalite," *J. Phys. Chem.*, **95**, 8866 (1991).

Kang, H. C., and W. H. Weinberg, "Dynamic Monte Carlo Simulations of Surface-Rate Processes," *Acc. Chem. Res.*, **25**, 253 (1992).

Kang, H. C., and W. H. Weinberg, "Modeling the Kinetics of Heterogeneous Catalysis," *Chem. Rev.*, **95**, 667 (1995).

Kang, H. C., C. B. Mullins, and W. H. Weinberg, "Molecular Adsorption of Ethane on the Ir(110)-(1×2) Surface: Monte Carlo Simulations and Molecular Beam Reflectivity Measurements," *J. Chem. Phys.*, **92**, 1397 (1990).

Karaborni, S., B. Smit, W. Heidug, J. Urai, and E. van Oort, "The Swelling of Clays: Molecular Simulations of the Hydration of Montmorillonite," *Science*, **271**, 1102 (1996).

Kauffman, S. A., and W. G. Macready, "Search Strategies for Applied Molecular Evolution," *J. Theor. Biol.*, **173**, 427 (1995).

Kauffman, S. K., *The Origins of Order*, Oxford University Press, New York (1993).

Khare, R., J. J. de Pablo, and A. Yethiraj, "Rheology of Confined Polymer Melts," *Macromol.*, **29**, 7910 (1996).

Khosla, C., and R. J. X. Zawada, "Generation of Polyketide Libraries via Combinatorial Biosynthesis," *TIBTECH*, **14**, 335 (1996).

Kirkpatrick, S., C. D. Gelatt, and M. P. Vecchi, "Optimization by Simulated Annealing," *Science*, **220**, 671 (1983).

Kitao, O., and K. E. Gubbins, "Theoretical Studies on VPI-5. Origin of the Hydrophilicity," *Chem. Phys. Lett.*, **227**, 545 (1994).

Kofke, D. A., "Gibbs-Duhem Integration—A New Method for Direct Evaluation of Phase Coexistence by Molecular Simulation," *Mol. Phys.*, **78**, 1331 (1993a).

Kofke, D. A., "Direct Evaluation of Phase Coexistence by Molecular Simulation via Integration along the Saturation Line," *J. Chem. Phys.*, **98**, 4149 (1993b).

Kofke, D. A., "Semigrand Canonical Monte-Carlo Simulations: Integration Along Coexistence Lines," *Adv. Chem. Phys.*, **105**, 405 (1998).

Kofke, D. A., and E. D. Glandt, "Nearly Monodisperse Fluids: I. Monte Carlo Simulations of Lennard-Jones Particles in a Semigrand Ensemble," *J. Chem. Phys.*, **87**, 4881 (1987).

Kolb, A., C. M. Marques, and G. H. Fredrickson, "Flow Effects in the Polymer Cyclization Reaction," *Macromol. Theory Simul.*, **6**, 169 (1997).

Kusaka, I., Z.-G. Wang, and J. H. Seinfeld, "Ion-Induced Nucleation. II. Polarizable Multipolar Molecules," *J. Chem. Phys.*, **103**, 8993 (1995a).

Kusaka, I., Z.-G. Wang, and J. H. Seinfeld, "Ion-Induced Nucleation: A Density Functional Approach," *J. Chem. Phys.*, **102**, 913 (1995b).

Kyrlidis, A., S. J. Cook, A. K. Chakraborty, A. T. Bell, and D. N. Theodorou, "Electronic Structure Calculations of Ammonia Adsorption in H-ZSM-5 Zeolites," *J. Phys. Chem.*, **99**, 1505 (1995).

Lacks, D. J., and G. C. Rutledge, "Simulation of the Temperature Dependence of Mechanical Properties of Polyethylene," *J. Phys. Chem.*, **98**, 1222 (1994).

Li, H.-X., M. E. Davis, J. B. Higgins, and R. M. Dessau,

"Aluminophosphate Molecular-Sieves Comprised of Hydrated Triple Crankshaft Chains," *J. Chem. Soc., Chem. Comm.*, **4**, 403 (1993).

Lipshutz, R. J., and S. P. A. Fodor, "Advanced DNA Sequencing Technologies," *Curr. Opin. Struct. Biol.*, **4**, 376 (1994).

Lipshutz, R. J., D. Morris, M. Chee, E. Hubbell, M. J. Kozal, N. Shah, N. Shen, R. Yang, and S. P. A. Fodor, "Using Oligonucleotide Probe Arrays to Access Genetic Diversity," *Biotechnique*, **19**, 442 (1995).

Lonsinger, S. R., A. K. Chakraborty, D. N. Theodorou, and A. T. Bell, "The Effects of Local Structural Relaxation on Aluminum Siting within H-ZSM-5," *Catal. Lett.*, **11**, 209 (1991).

Lue, L., and D. Blankschtein, "Applications of Integral-Equation Theories to Predict the Structure, Thermodynamics, and Phase-Behavior of Water," *J. Chem. Phys.*, **102**, 5427 (1995).

Lue, L., and D. Blankschtein, "A Liquid-State Theory Approach to Modeling Solute Partitioning in Phase-Separated Solutions," *Ind. Eng. Chem. Res.*, **35**, 3032 (1996).

Lue, L., and J. M. Prausnitz, "Thermodynamics of Fluid Mixtures Near to and Far from the Critical Region," *AIChE J.*, **44**, 1455 (1998).

MacElroy, J. M. D., "Nonequilibrium Molecular Dynamics Simulation of Diffusion and Flow in Thin Microporous Membranes," *J. Chem. Phys.*, **101**, 5274 (1994).

Maddox, M. W., and K. E. Gubbins, "Molecular Simulation of Fluid Adsorption in Buckytubes," *Langmuir*, **11**, 3988 (1995).

Maginn, E. J., A. T. Bell, and D. N. Theodorou, "Sorption Thermodynamics, Siting, and Conformation of Long n-Alkanes in Silicalite as Predicted by Configurational-Bias Monte Carlo Integration," *J. Phys. Chem.*, **99**, 2057 (1995).

Maginn, E. J., A. T. Bell, and D. N. Theodorou, "Dynamics of Long n-Alkanes in Silicalite: A Hierarchical Simulation Approach," *J. Phys. Chem.*, **100**, 7155 (1996).

Marks, J. D., H. R. Hoogenboom, A. D. Griffiths, and G. Winter, "Minireview: Molecular Evolution of Proteins on Filamentous Phage," *J. Biol. Chem.*, **267**, 16007 (1992).

Maroudas, D., and R. A. Brown, "Calculation of Thermodynamic and Transport Properties of Intrinsic Point Defects in Silicon," *Phys. Rev. B*, **47**, 15562 (1993).

Marques, C. M., and G. H. Fredrickson, "Rigid Gaussian Chains I—The Scattering Function," *J. Phys. II France*, **7**, 1805 (1997).

Martin, J. I., Z.-G. Wang, and M. Schick, "Effects of Polymer Brush Self-Assembly on Spreading and Thin Film Stability," *Langmuir*, **12**, 4950 (1996).

Matsen, M. W., and F. S. Bates, "Unifying Weak- and Strong-Segregation Block Copolymer Theories," *Macromol.*, **29**, 1091 (1996).

Meier, W. M., and D. H. Olson, *Atlas of Zeolite Structure Types*, Elsevier, Boston, http://www-iza-sc.csb.yale.edu/IZA-SC/Atlas/AtlasHome.html (1996).

Meng, B., and W. H. Weinberg, "Monte Carlo Simulations of Temperature Programmed Desorption Spectra," *J. Chem. Phys.*, **100**, 5280 (1994).

Meng, B., and W. H. Weinberg, "Theoretical and Simulation Studies of Recombinative Temperature Programmed Desorption," *J. Chem. Phys.*, **102**, 1003 (1995).

Meng, B., and W. H. Weinberg, "Dynamical Monte Carlo Studies of Molecular Beam Epitaxial Growth Models: Interfacial Scaling and Morphology," *Surf. Sci.*, **364**, 151 (1996).

Milosavljević, A., S. Savković, R. Crkvenjakov, D. Salbego, H. Serrato, H. Kreuzer, A. Gemmell, S. Batus, D. Grujić, S. Carnahan, T. Paunesku, and J. Tepavčević, "DNA Sequence Recognition by Hybridization to Short Oligomers: Experimental Verification of the Method on the *E. coli* Genome," *Genomics*, **37**, 77 (1996).

Mitragotri, S., D. A. Edwards, D. Blankschtein, and R. Langer, "A Mechanistic Study of Ultrasonically-Enhanced Transdermal Drug Delivery," *J. Pharm. Sci.*, **84**, 697 (1995).

Mosler, A. B., and E. S. G. Shaqfeh, "The Conformation Change of Model Polymers in Stochastic Flow Fields: Flow through Fixed Beds," *Phys. Fluids*, **9**, 1222 (1997).

Mulhern, G. T., J. S. Bader, and J. M. Rothberg, "Novel Microfabricated and Liquid-Phase Techniques for DNA Sequencing and Fragment Analysis," *Abs. Pap. Amer. Chem. Soc.*, **212**, 157 (1996).

Müller, E. A., L. F. Rull, L. F. Vega, and K. E. Gubbins, "Adsorption of Water on Activated Carbons: A Molecular Simulation Study," *J. Phys. Chem.*, **100**, 1189 (1996).

Mundy, C. J., J. I. Siepmann, and M. L. Klein, "Decane under Shear: A Molecular Dynamics Study using Reversible NVT-SLLOD and NPT-SLLOD Algorithms," *J. Chem. Phys.*, **103**, 10192 (1995).

Mundy, C. J., M. L. Klein, and J. I. Siepmann, "Determination of the Pressure-Viscosity Coefficient of Decane by Molecular Simulation," *J. Phys. Chem.*, **100**, 16779 (1996).

Nenoff, T. M., W. T. A. Harrison, G. D. Stucky, J. M. Nicol, and J. M. Newsam, "The Crystal-Structure of a New Sodium Zinc Arsenate Phase Solved by Simulated Annealing," *Zeolites*, **13**, 506 (1993).

Newsam, J. M., M. W. Deem, and C. M. Freeman, "Direct Space Methods of Structure Solution from Powder Diffraction Data," in *Accuracy in Powder Diffraction II (NIST Special Publication)*, E. Prince, J. K. Stalick, and R. J. Hill, eds., National Institute of Standards and Technology, Bethesda, MD (1992).

Nosho, B. Z., V. Bressler-Hill, S. Varma, and W. H. Weinberg, "Effects of Strain on Island Scaling Studied by Monte Carlo Simulations," *Surf. Sci.*, **364**, 164 (1996).

Panagiotopoulos, A. Z., "Direct Determination of Phase Coexistence Properties of Fluids by Monte-Carlo Simulation in a New Ensemble," *Mol. Phys.*, **61**, 813 (1987).

Panagiotopoulos, A. Z., "Direct Determination of Fluid Phase Equilibria by Simulation in the Gibbs Ensemble: A Review," *Mol. Simulation*, **9**, 1 (1992a).

Panagiotopoulos, A. Z., "Molecular Simulation of Phase Equilibria: Simple, Ionic and Polymeric Fluids," *Fluid Phase Equil.*, **76**, 97 (1992b).

Pant, P. V. K., and D. N. Theodorou, "Variable Connectivity Method for the Atomistic Monte Carlo Simulation of Polydisperse Polymer Melts,," *Macromol.*, **28**, 7224 (1995).

Parisi, G., *Frontiers in Physics: Statistical Field Theory*, Vol. 66, Addison-Wesley, Redwood City, CA, p. 343 (1988).

Park, J.-M., and M. W. Deem, "Disorder-Induced Anomalous Kinetics in the $A + A \rightarrow \emptyset$ Reaction," *Phys. Rev. E*, **57**, 3618 (1998a).

Park, J.-M., and M. W. Deem, "Ionic Reactions in Two Dimensions with Disorder," *Phys. Rev. E*, **58**, 1487 (1998b).

Parola, A., and L. Reatto, "Hierarchical Reference Theory of Fluids and the Critical Point," *Phys. Rev. A*, **31**, 3309 (1985).

Patten, P. A., R. J. Howard, and W. P. C. Stemmer, "Applications of DNA Shuffling to Pharmaceuticals and Vaccines," *Curr. Opin. Biotech.*, **8**, 724 (1997).

Paulaitis, M. E., "Molecular Thermodynamics of Hydrophobic Effects," *Curr. Opin. Coll. Interf. Sci.*, **2**, 315 (1997).

Pozhar, L. A., and K. E. Gubbins, "Dense Inhomogeneous Fluids: Functional Perturbation Theory, the Generalized Langevin Equation, and Kinetic Theory," *J. Chem. Phys.*, **94**, 1367 (1991).

Pozhar, L. A., and K. E. Gubbins, "Transport Theory of Dense, Strongly Inhomogeneous Fluids," *J. Chem. Phys.*, **99**, 8970 (1993).

Pratt, L. R., and D. Chandler, "Theory of the Hydrophobic Effect," *J. Chem. Phys.*, **67**, 3683 (1977).

Qi, S., and Z.-G. Wang, "Kinetic Pathways of Order-Disorder and Order-Order Transitions in Weakly Segregated Microstructured Systems," *Phys. Rev. Lett.*, **76**, 1679 (1996).

Qi, S., and Z.-G. Wang, "Kinetics of Phase Transitions in Weakly Segregated Block Copolymers: Pseudostable and Transient States," *Phys. Rev. E*, **55**, 1682 (1997).

Qiu, X., and Z.-G. Wang, "Competing Adsorption and Micellization of Diblock Copolymers: Effects of Colloidal Sizes," *J. Coll. Interf. Sci.*, **167**, 294 (1994).

Raut, J. S., and K. A. Fichthorn, "Diffusion Mechanisms of n-Butane on Pt(111) and Cu(001): Unique Molecular Features," *J. Vac. Sci. Technol. A*, **15**, 1542 (1997).

Rosenbaum, D. F., and C. F. Zukoski, "Protein Interactions and Crystallization," *J. Cryst. Growth*, **169**, 752 (1996).

Rosenbaum, D. F., P. C. Zamora, and C. F. Zukoski, "Phase-Behavior of Small Attractive Colloidal Particles," *Phys. Rev. Lett.*, **76**, 150 (1996).

Ruiz-Montero, M. J., D. Frenkel, and J. J. Brey, "Efficient Schemes to Compute Diffusive Barrier Crossing Rates," *Mol. Phys.*, **90**, 925 (1997).

Runnebaum, R. C., and E. J. Maginn, "Molecular Dynamics Simulations of Alkanes in the Zeolite Silicalite: Evidence for Resonant Diffusion Effects," *J. Phys. Chem.*, **101**, 6394 (1997).

Rutgers, M. A., J.-Z. Xue, E. Herbolzheimer, W. B. Russel, and P. M. Chaikin, "Crystalline Fluidized Beds," *Phys. Rev. E*, **51**, 4674 (1995).

Samuelson, S., A. Hughes, and G. J. Martyna, "Solvent, Force Field, Temperature and Quantum Effects on the Folding Free Energy Surface of Blocked Alanine Tripeptide," *J. Chim. Phys.*, **94**, 1503 (1997).

Sassi, A. P., H. W. Blanch, and J. M. Prausnitz, "Phase Equilibria for Aqueous Protein/Polyelectrolyte Gel Systems," *AIChE J.*, **42**, 2335 (1996).

Schweizer, K. S., and J. G. Curro, "Integral-Equation Theories of the Structure, Thermodynamics, and Phase-Transitions of Polymer Fluids," *Adv. Chem. Phys.*, **98**, 1 (1997).

Segarra, E. I., and E. D. Glandt, "Model Microporous Carbons: Microstructure, Surface Polarity and Gas Adsorption," *Chem. Eng. Sci.*, **49**, 2953 (1994).

Shen, V., K. Watanabe, and A. T. Bell, "Theoretical Analysis of the Thermodynamics of ZSM-11 Zeolite Synthesis," *J. Phys. Chem. B*, **101**, 2207 (1997).

Sheng, Y.-J., A. Z. Panagiotopoulos, and S. K. Kumar, "Effect of Chain Stiffness on Polymer Phase Behavior," *Macromol.*, **29**, 4444 (1996).

Siepmann, J. I., and I. R. McDonald, "Monte Carlo Simulations of Mixed Monolayers," *Mol. Phys.*, **75**, 255 (1992).

Sivestrelli, P. L., A. Alavi, M. Parrinello, and D. Frenkel, "Structural, Dynamical, Electronic, and Bonding Properties of Laser-Heated Silicon: An *ab initio* Molecular-Dynamics Study," *Phys. Rev. B*, **56**, 3806 (1997).

Sliwinska-Bartkowiak, M., S. L. Sowers, and K. E. Gubbins, "Liquid-Liquid Phase Equilibria in Porous Materials," *Langmuir*, **13**, 1182 (1997).

Smit, B., "Molecular Simulation of Thermodynamic Properties: From Argon to Long-Chain Paraffins," *Ind. Eng. Chem. Res.*, **34**, 4166 (1995).

Smit, B., "Computational Physics in Petrochemical Industry," *Physica Scripta*, **T66**, 80 (1996a).

Smit, B., "Molecular Simulations of Fluid Phase Equilibria," *Fluid Phase Equil.*, **116**, 249 (1996b).

Smit, B., and T. L. M. Maesen, "Commensurate 'Freezing' of Alkanes in the Channels of a Zeolite," *Nature*, **374**, 42 (1995).

Smit, B., A. G. Schlijper, L. A. M. Rupert, and N. M. van Os, "Effects of Chain Length of Surfactants on the Interfacial Tension: Molecular Dynamics Simulations and Experiments," *J. Phys. Chem.*, **94**, 6933 (1990).

Smit, B., S. Karaborni, and J. I. Siepmann, "Computer Simulations of Vapor-Liquid Phase Equilibria of n-Alkanes," *J. Chem. Phys.*, **102**, 2126 (1995).

Smith, W. R., and B. Triska, "The Reaction Ensemble Method for the Computer Simulation of Chemical and Phase Equilibria I. Theory and Basic Examples," *J. Chem. Phys.*, **100**, 3019 (1994).

Snurr, R. Q., and J. Kärger, "Molecular Simulations and NMR Measurements of Binary Diffusion in Zeolites," *J. Phys. Chem.*, **101**, 6469 (1997).

Snurr, R. Q., A. T. Bell, and D. N. Theodorou, "Investigation of the Dynamics of Benzene in Silicalite Using Transition-State Theory," *J. Phys. Chem.*, **98**, 11948 (1994a).

Snurr, R. Q., A. T. Bell, and D. N. Theodorou, "A Hierarchical Atomistic/Lattice Simulation Approach for the Prediction of Adsorption Thermodynamics of Benzene in Silicalite," *J. Phys. Chem.*, **98**, 5111 (1994b).

Speedy, R. J., and P. G. Debenedetti, "The Distribution of Tetravalent Network Glasses," *Mol. Phys.*, **88**, 1293 (1996).

Spyriouni, T., I. G. Economou, and D. N. Theodorou, "Thermodynamics of Chain Fluids from Atomistic Simulation—A Test of the Chain Increment Method for Chemical-Potential," *Macromol.*, **30**, 4744 (1997).

Srebnik, S., A. K. Chakraborty, and E. I. Shakhnovich, "Adsorption-Freezing Transition for Random Heteropolymers near Disordered 2D Manifolds due to Pattern Matching," *Phys. Rev. Lett.*, **77**, 3157 (1996).

Stemmer, W. P. C., "Rapid Evolution of Protein *in vitro* by DNA Shuffling," *Nature*, **370**, 389 (1994).

Stemmer, W. P. C., "Searching Sequence Space," *Biotechnol.*, **13**, 549 (1995).

Suzuki, T., K. Kaneko, and K. E. Gubbins, "Pore Width-Sensitive Filling Mechanism for CCl_4 in a Graphitic Micropore by Computer Simulation," *Langmuir*, **13**, 2545 (1997).

ten Wolde, P. R., and D. Frenkel, "Enhancement of Protein Crystal Nucleation by Critical Density Fluctuations," *Science*, **277**, 1975 (1997).

Thompson, A. P., and E. D. Glandt, "Polymers in Random Porous Materials: Structure, Thermodynamics, and Concentration Effects," *Macromol.*, **29**, 4314 (1996).

Thompson, P. A., and S. M. Troian, "A General Boundary Condition for Liquid Flow at Solid Surfaces," *Nature*, **389**, 360 (1997).

Tobias, D. J., G. J. Martyna, and M. L. Klein, "Molecular Dynamics Simulations of a Protein in the Canonical Ensemble," *J. Phys. Chem.*, **97**, 12959 (1993).

Treacy, M. M. J., J. M. Newsam, and M. W. Deem, "A General Recursion Method for Calculating Diffracted Intensities from Crystals Containing Planar Faults," *Proc. Roy. Soc. A (London)*, **433**, 499 (1991).

Trout, B. L., A. K. Chakroborty, and A. T. Bell, "Analysis of the Thermochemistry of NO_x Decomposition over CuZSM-5 Based on Quantum Chemical and Statistical Mechanical Calculations," *J. Phys. Chem.*, **100**, 17582 (1996).

Trout, B. L., A. K. Chakraborty, and A. T. Bell, "Diffusion and Reaction in ZSM-5 Studied by Dynamic Monte Carlo," *Chem. Eng. Sci.*, **52**, 2265 (1997).

Tuckerman, M., B. J. Berne, and G. J. Martyna, "Reversible Multiple Time Scale Molecular-Dynamics," *J. Chem. Phys.*, **97**, 1990 (1992).

van Leeuwen, M. E., and B. Smit, "Molecular Simulation of the Vapor-Liquid Coexistence Curve of Methanol," *J. Phys. Chem.*, **99**, 1831 (1995).

Vandover, R. B., L. D. Schneedmeyer, and R. M. Fleming, "Discovery of a Useful Thin-Film Dielectric Using a Composition-Spread Approach," *Nature*, **392**, 162 (1998).

Vaughan, D. E. W., in preparation (1998).

Vega, L. F., A. Z. Panagiotopoulos, and K. E. Gubbins, "Chemical Potentials and Adsorption Isotherms of Polymers Confined between Parallel Plates," *Chem. Eng. Sci.*, **49**, 2921 (1994).

Wang, Z.-G., "Response and Instabilities of the Lamellar Phase of Diblock Copolymers under Uniaxial Stress," *J. Chem. Phys.*, **100**, 2298 (1994).

White, J. A., and S. Zhang, "Renormalization Group Theory of Nonuniversal Thermal Properties of Fluids," *J. Chem. Phys.*, **103**, 1922 (1995).

Xu, Z., R. Khare, J. J. de Pablo, and S. Kim, "On the Calculation of Transport Properties of Polymer Melts from Nonequilibrium Molecular Dynamics," *J. Chem. Phys.*, **106**, 8285 (1997).

Zachariah, M. R., M. J. Carrier, and E. Blaisten-Barojas, "Properties of Silicon Nanoparticles: A Molecular Dynamics Study," *J. Phys. Chem.*, **100**, 14856 (1996).

Zhang, J.-H., G. Dawes, and W. P. C. Stemmer, "Directed Evolution of a Fucosidase from a Galactosidase by DNA Shuffling and Screening," *Proc. Nat. Acad. Sci. USA*, **94**, 4504 (1997).

Zhao, H., L. Giver, Z. Shao, J. A. Affholter, and F. H. Arnold, "Molecular Evolution by Staggered Extension Process (StEP) *in vitro* Recombination," *Nature Biotech.*, **16**, 258 (1998).

Zheng, W., and Z.-G. Wang, "Morphology of ABC Triblock Copolymers," *Macromol.*, **28**, 7215 (1995).

Zhou, S. J., D. L. Preston, P. S. Lomdahl, and D. M. Beazley, "Large-Scale Molecular-Dynamics Simulations of Dislocation Intersection in Copper," *Science*, **279**, 1525 (1998).

Case Study: Zeolite Structure Determination

Question: What is the crystal structure? (What are the positions of the silicons?)

Answer: Determine by sampling an energy function to find structure consistent with experimental data and with being zeolite-like (Figure A1).

How: Use statistical mechanics.

• Define a cost-function (Hamiltonian) to minimize
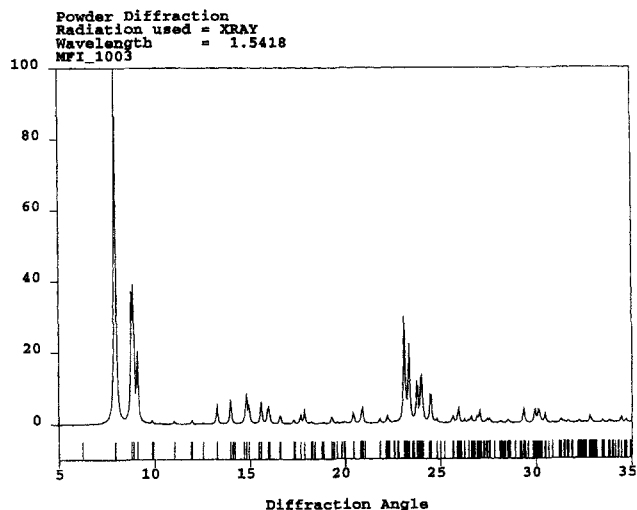$$H = H_{geom} + R_{exp}^2.$$

Figure A1. Powder diffraction pattern of an unknown material.
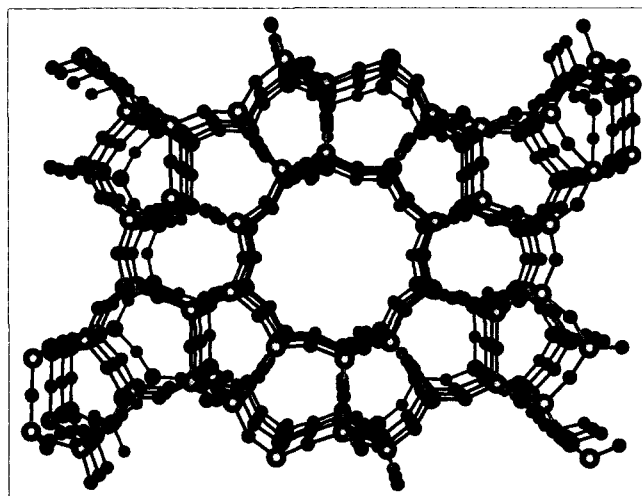

Figure A2. Crystal structure of ZSM-5.

• The Hamiltonian measures the reasonableness of the silicon positions, as well as the match to the experimental powder diffraction pattern.

• Sample all possible configurations with $p \propto \exp(-H/T)$.

• Use parallel tempering to get minimum energy structure.

The crystalline material is ZSM-5 (Figure A2). This is the most complex known zeolite, with 12 unique T-atoms, and requires powerful methods to solve (Falcioni and Deem, 1998).