A Graduate Course on
MULTI-SCALE MODELING OF SOFT MATTER*

FRANCISCO R. HUNG, KEITH E. GUBBINS
   Chemical Engineering Department, North Carolina State University • Raleigh, NC 27695-7095
STEFAN FRANZEN
   Department of Chemistry, North Carolina State University • Raleigh, NC 27695-8204

Theory and simulations play an important role in chemical engineering, chemistry, and physics. They provide a link between the microscopic features of a system and its macroscopic properties. Molecular simulations can be used as "computational experiments" to get information that would be very difficult or impossible to get in a laboratory, and they can also assist in the analysis of experimental results. Moreover, simulations provide a way to test theories and thus determine their range of validity.[1,2]

A number of problems of current interest require insight on many length scales, ranging from angstroms (subatomic and atomic scales: electron rearrangement, bond breaking and formation) up to macroscopic scales (bulk material properties). For example, intermolecular interactions have length scales on the order of nanometers, and the microscopic structure of some phases can involve length scales on the order of tens of nanometers, microns, millimeters and even larger, depending on the nature of the molecules present in the system. In a similar way, the corresponding time scales of the dynamic processes associated with these phenomena can range from femtoseconds to milliseconds, reaching seconds or even hours in some cases. Examples of systems exhibiting such a wide range of length and time scales are polymeric and colloidal systems, self-assembly of surfactants on surfaces, biological systems, and chemical reactions in nonideal or nano-structured environments (liquid solutions, supercritical fluids, porous media, micelles, composites, etc.).

Problems such as these require a multi-scale approach in which *ab initio*, atomistic, and meso-scale methods are combined. No single model or simulation algorithm can cover this range of length and time scales. Figure 1 illustrates the length and time scales presently accessible to the main groups of computational methodologies. This figure was constructed

assuming that calculations are performed for a maximum of one week on the Blue Horizon (IBM SP3) supercomputer at the San Diego Supercomputer Center (SDSC), which has a maximum speed of 1.728 Tflops.[3] More and more approximations are introduced as we move from *ab initio* algorithms to the continuum level: larger length and time scales are handled efficiently, but at the cost of reduced accuracy and loss of fine structure. Electronic structure is lost in atomistic simulations, and atomistic detail is lost in meso-scale simulations. An important challenge and an active area of research in modeling of soft matter is how to link the different methods available to cover the whole range of length and time
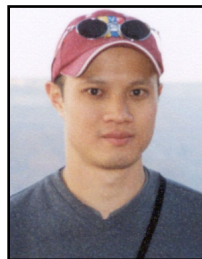
Francisco R. Hung received his BS (1996) and MS (1999) in chemical engineering at Universidad Simón Bolívar in Venezuela. He was Assistant Professor in the Department of Thermodynamics and Transport Phenomena at Universidad Simón Bolívar before coming to North Carolina State University, where he is currently a chemical engineering PhD candidate.

Keith E. Gubbins is the W. H. Clark Distinguished University Professor at North Carolina State University, where he has been since 1998. He obtained his PhD at the University of London and has been a faculty member at the University of Florida and Cornell University prior to joining North Carolina State University.

Stefan Franzen is Associate Professor of Chemistry at North Carolina State University. He has a BS degree from University of California, Berkeley, and a PhD from Stanford University. He was a Peace Corps Volunteer Teacher in Kenya, EMBO Fellow at École Polytechnique in Palaiseau, France, and Director's Fellow at Los Alamos National Laboratory, prior to joining the faculty at NCSU.

---

scales of interest (see, *e.g.*, [4-8] and references therein). In addition, a common criticism from industry is that our PhD graduates are too specialized and have insufficient knowledge of modeling methods outside of their own specialization. In an industrial setting, the researcher is expected to be able to choose the most appropriate method for studying and solving a new problem and to apply it and get results quickly. Therefore, students need to have familiarity with the full range of tools available for theoretical and modeling work.

In the Spring Semester of 2004 we offered a new graduate course in multi-scale modeling of soft matter. Most of the students taking the course were from chemistry and chemical engineering, and the course was also offered via video transmission to students from the University of North Carolina at Chapel Hill. The aim of this course is to provide a background on the computational methods available at the different scales, at a level suitable for graduate students whose primary research interests are experimental as well as theoretical. Students in the class are asked to work problems using web-based modules illustrating the different theoretical and simulation approaches for a variety of problems. This paper presents an overview of the most important features of the course, including the basis, applicability, and strengths and weaknesses of the methods. Examples of some of the computational exercises are presented and discussed. The course material is posted on the course website at <http://gubbins.ncsu.edu/che597b/> and includes PowerPoint slides and videos of the lectures, as well as links to the web modules containing the computational exercises proposed.

COURSE STRUCTURE

The course syllabus is presented in Table 1. The course is suitable for students who are already familiar with classical thermodynamics, and differential and inte-
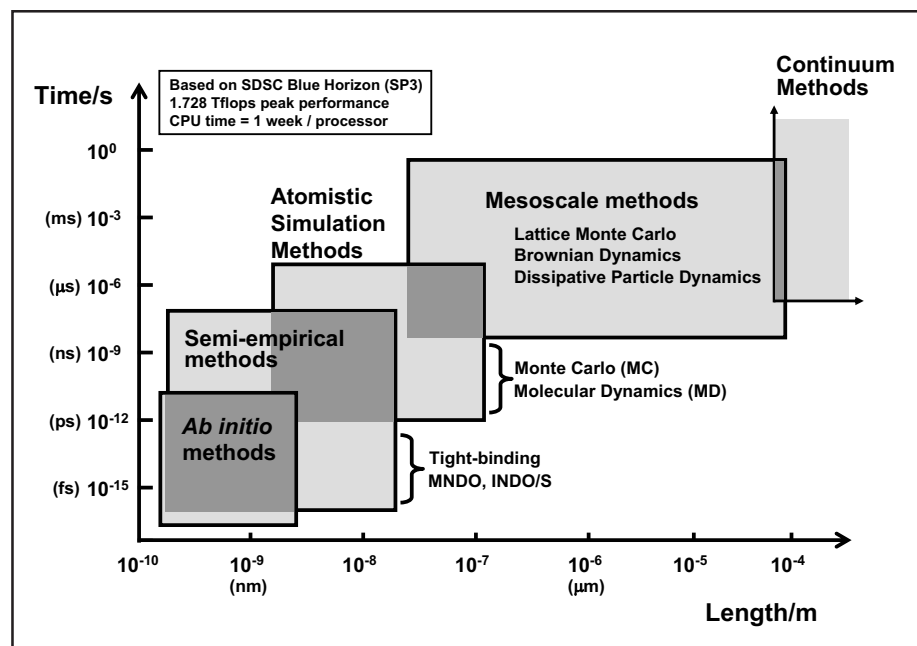
Figure 1. Length and time scales accessible to different molecular simulation methods. We assume that the calculations are performed for a maximum of one week on the Blue Horizon IBM SP3 supercomputer at the San Diego Supercomputer Center (SDSC), which operates at a maximum speed of 1.728 Tflops.

TABLE 1
Course Syllabus

Lecture	Topic
1.	Introduction; electronic, atomistic, mesoscale modeling; examples
2.	*Ab initio* methods; Schrödinger equation; Born-Oppenheimer approximation
3.	*Ab initio* methods; Hartree-Fock method; density functional theory (DFT)
4.	*Ab initio* methods; density functional theory (DFT) and applications; semi-empirical methods
5.	Introduction to semiclassical statistical mechanics
6.	Canonical ensemble; partition function, thermodynamics
7.	Factoring the partition and distribution functions
8.	Distribution functions and correlation functions
9.	Uniqueness theorem; reverse Monte Carlo
10.	Statistical mechanics in the grand canonical ensemble
11.	Intermolecular forces
12.	Composite pair potentials and force fields
13.	Force field parameterization
14.	General features of molecular simulation; Monte Carlo algorithm; Metropolis method
15.	Monte Carlo simulation; canonical ensemble, isothermal-isobaric ensemble, grand canonical ensemble
16.	Monte Carlo simulation and phase equilibria (I); Gibbs ensemble Monte Carlo; determination of chemical potentials; thermodynamic integration
17.	Monte Carlo methods and phase equilibria (II); Gibbs-Duhem integration method; overview of other Monte Carlo methods
18.	Molecular dynamics
19.	Molecular dynamics; calculation of dynamic properties; constraint dynamics
20.	Mesoscale methods; lattice Monte Carlo
21.	Mesoscale methods; Langevin dynamics, coarse graining, and Brownian dynamics
22.	Mesoscale methods; Brownian dynamics and dissipative particle dynamics
23.	Statistical mechanics of inhomogeneous fluids; interface, surface tension, adsorption
24.	Density functional theory (DFT) of interfaces
25.	Adsorption, fluids in pores, phase equilibria in confined systems
26.	Colloids
27.	Biological systems (I)
28.	Biological systems (II)
29.	Special topics; multiscale molecular modeling of chemical reactivity (I)
30.	Special topics; multiscale molecular modeling of chemical reactivity (II)

gral calculus. The course has no formal exams. The students are asked to work on the proposed computational modules, and to complete a term paper project on a free topic related to the course. The course consisted of four groups of lectures:

1. **Electronic (subatomic) scale:** *ab initio* and semi-empirical methods (lectures 1-4)
2. **Atomistic scale:** semiclassical statistical mechanics, intermolecular forces, Monte Carlo and Molecular Dynamics methods (lectures 5-19)
3. **Meso-scale:** Lattice Monte Carlo, Langevin Dynamics, coarse graining, Brownian Dynamics and Dissipative Particle Dynamics (lectures 20-22)
4. **Applications:** phase equilibria of bulk and confined systems, adsorption and interfaces, colloids, biological systems and chemical reactions (lectures 23-30)

Since there is presently no suitable text for such a course, material was taken from several sources. The text by Leach[9] covers parts of the material in Section 1, much of Section 2, and parts of Section 4. Additional references for Section 1 (*ab initio* and semi-empirical methods) include the books by Jensen,[10] Szabo and Ostlund,[11] Parr and Yang,[12] and Koch and Holthausen.[13] The section on semiclassical statistical mechanics is covered in Gray and Gubbins[14] and McQuarrie,[15] and more advanced aspects of Monte Carlo and Molecular Dynamics methods are covered in the monographs of Allen and Tildesley[1] and Frenkel and Smit.[2] Meso-scale methods (Section 3) are covered briefly in Frenkel and Smit,[2] and in more detail in monographs by Zwanzig[16] and Mazo.[17]

The first three groups of lectures covered the theoretical basis of the methods, followed by a description of the most relevant theoretical and modeling tools, their strengths and

TABLE 2
Pros and Cons of the Different Modeling Tools Described in this Course

Methods	*Main Idea*	*Pros*	*Cons*
Electronic scale: *ab initio*	Calculate properties from first principles solving the Schrödinger equation numerically	• Can handle processes that involve bond breaking/formation, or electronic rearrangement (*e.g.*, chemical reactions) • Methods offer ways to systematically improve on the results, making it easy to assess their quality • Can (in principle) obtain essentially exact properties without any input but the atoms conforming the system	• Can handle only small systems, on the order of 10^2 atoms • Can only study fast processes, usually on the order of 10 ps. • Approximations are usually necessary to solve the equations
Electronic scale: semi-empirical	Use simplified versions of equations from *ab initio* methods (*e.g.*, treating explicitly only the valence electrons); include parameters fitted to experimental data	• Can also handle processes that involve bond breaking or formation, or electronic rearrangement • Can handle larger and more complex systems than *ab initio* methods, often of the order of 10^3 atoms • Can be used to study processes on longer timescales than can be studied with *ab initio* methods, on the order of 10 ns	•Difficult to assess the quality of the results • Need experimental input and large parameter sets
Classical atomistic scale: Molecular Dynamics (MD), Monte Carlo (MC)	Use empirical or *ab initio* derived force fields, together with semi-classical statistical mechanics to determine thermodynamics (MC, MD) and transport (MD) properties of systems. Semi-classical statistical mechanics equations are solved "exactly"	• Can be used to determine the microscopic structure of more complex systems, on the order of 10^5 - 10^6 atoms • Can study dynamical processes on longer timescales, on the order of 1 μs	• Results depend on the quality of the force field used to represent the system • Many physical processes happen on length- and timescales inaccessible by these methods, *e.g.*, diffusion in solids, many chemical reactions, protein folding, micellization
Meso-scale	Introduce simplifications to atomistic methods to remove the faster degrees of freedom, and/or treat groups of atoms ("blobs of matter") as individual entities interacting through effective potentials	• Can be used to study structural features of complex systems on the order of 10^8 - 10^9 atoms • Can study dynamical processes on timescales inaccessible to classical methods, up to seconds	• Can often describe only qualitative tendencies; the quality of quantitative results may be difficult to ascertain • In many cases, the approximations introduced limit the ability to physically interpret the results
Continuum (not covered in this course)	Assume that matter is continuous and treat the properties of the system as field quantities. Numerically solve balance equations coupled with phenomenological equations to predict the properties of the systems	• Can in principle handle systems of any (macroscopic) size and dynamic processes on longer time scales	• Require input (viscosities, diffusion coefficients, parameters required in equations of state, etc.) from experiment or from a lower-scale method; they can be difficult to obtain in some cases • Cannot explain results that depend on the electronic or molecular level of detail

weaknesses, and the kind of problems studied with them. In addition, ways to link results obtained using methods at different scales are described and discussed when appropriate. The last section of the course covers the use of the different methodologies in various applications. The main idea of each one of the group of methods described in this course, as well as their most important advantages and disadvantages, are summarized in Table 2. We included continuum methods in Table 2 for completeness, although these modeling tools are not covered in this course. These methods are applied at the macroscopic scale and usually involve solving the equations of material and energy balance, coupled with phenomenological (constitutive) equations, to predict the properties of the systems assuming that matter is continuous. The most important continuum methods are usually studied in detail in a number of courses in chemical engineering.

At the electronic (subatomic) scale, we discussed both *ab initio* and semi-empirical methods. The purpose of the *ab initio* methods (Table 2) is to calculate properties from first principles using quantum mechanics.[5,9-11] The nature of the atoms comprising the system is provided as input, and the time-independent Schrödinger equation is then solved numerically for a given many-atom system

$$\hat{H}\Phi = E\Phi \tag{1}$$

where Φ represents the wave function of the many-atom system, E is the total energy, and $\hat{H}$ is the Hamiltonian operator. For the general case of a system of N electrons and M nuclei, the Hamiltonian operator is[5,11]

$$\hat{H} = -\sum_{i=1}^{N}\frac{1}{2}\nabla_i^2 - \sum_{I=1}^{M}\frac{1}{2M_I}\nabla_I^2 - \sum_{i=1}^{N}\sum_{I=1}^{M}\frac{Z_I}{r_{iI}} + \sum_{i=1}^{N-1}\sum_{j=i+1}^{N}\frac{1}{r_{ij}} + \sum_{I=1}^{M-1}\sum_{J=I+1}^{M}\frac{Z_I Z_J}{R_{IJ}} \tag{2}$$

where the indices i,j,... refer to the electrons and the indices I,J,... refer to the nuclei. The symbol ∇_i^2 is a Laplacian operator with respect to the coordinates of electron i, and ∇_I^2 is a Laplacian operator with respect to the coordinates of the nucleus I. The first term in Eq. (2) represents the electronic kinetic energy; the second term is the nuclear kinetic energy. The remaining three terms are the Coulomb interactions between the nuclei and the electrons, between electron pairs and between nucleus pairs, respectively. Equation (2) is written in atomic units.[5,11]

Some of the basic elements common to most *ab initio* methods are introduced during the lectures. We also briefly explore some of the most common approaches to finding approximate solutions to Eq. (1), and discuss their advantages and limitations (Table 2). Density functional theory (DFT) is an alternative approach covered in class that permits one to obtain reasonably accurate results for complex systems. The main difference between DFT and the methods mentioned

before is that the fundamental variable is not the wave function Φ but the electronic density $\rho(\mathbf{r})$.[5,10,12,13] The energy functional $E[\rho]$ in DFT includes terms accounting for the kinetic and potential energy of both electron-nucleus and electron-electron interactions. The latter accounts for the potential energy of the Coulomb interaction and the so-called exchange-correlation potential energy.[5,10,12,13] Applications, examples, advantages and limitations of DFT are discussed.

An alternative and less rigorous approach to the electronic problem is provided by the semi-empirical methods (Table 2), which are briefly discussed. In these algorithms,[5,9,11] the many-electron problem is simplified in some way (*e.g.*, by treating explicitly only the valence electrons), and then some parameters obtained from experiment or higher quality *ab initio* calculations are included in order to get good results. The main advantages and disadvantages of such methods (Table 2) are discussed. Semi-empirical methods are particularly useful for dealing with large systems (*e.g.*, biomolecules, chemical reactions in complex systems) where the more computationally demanding *ab initio* methods are impossible to apply due to limited computing power. On the other hand, the semi-empirical methods are not truly *ab initio* methods, since they make use of experimental information to obtain their results.

Before introducing the two main classical atomistic simulation methods (Molecular Dynamics and Monte Carlo; see Table 2), we include some lectures discussing semiclassical statistical mechanics, intermolecular forces and commonly used force fields and models to describe intra- and intermolecular interactions. In atomistic simulation methods,[1,2,9] empirical or *ab initio* derived force fields are used, together with semiclassical statistical mechanics, to determine thermodynamic and/or transport properties of the system of interest. In general, the (mechanical) properties of a system, such as internal energy, pressure and surface tension, depend on the positions and momenta of the N particles that form the system. In Molecular Dynamics (MD), the molecules move naturally under their own interaction forces; the positions and velocities of each atom or molecule are followed in time by numerically solving Newton's equations of motion

$$\frac{d^2 x_i}{dt^2} = \frac{F_{x_i}}{m_i} \tag{3}$$

which describe the motion of a particle with mass m_i along one coordinate x_i, F_{xi} being the force acting on the particle in that direction (due to the presence of other molecules, or external forces). The average of a (mechanical) property A can be determined as

$$A_{average} = \lim_{\tau\to\infty}\frac{1}{\tau}\int_0^\tau A\left[\mathbf{p}^N(t),\mathbf{r}^N(t)\right]dt \tag{4}$$

where $\mathbf{p}^N(t)$ and $\mathbf{r}^N(t)$ represent the N momenta (p_1, p_2, ..., p_N) and positions (r_1, r_2, ..., r_N), respectively, at time t. In Monte Carlo, we determine average properties from an ensemble, rather than a time, average

$$\langle A \rangle = \int\int d\mathbf{p}^N d\mathbf{r}^N A\left(\mathbf{p}^N, \mathbf{r}^N\right) P\left(\mathbf{p}^N, \mathbf{r}^N\right) \qquad (5)$$

where $P(\mathbf{p}^N, \mathbf{r}^N)$ is the probability density of finding a molecular configuration with momenta $\mathbf{p}^N$ and positions $\mathbf{r}^N$. The probability density is given by the statistical mechanics of the system.[1,2,9] In MC, a random number generator is used to stochastically perturb a system (by randomly moving the molecules, changing the volume of the system, etc.). In order to generate an ensemble of configurations distributed according to $P(\mathbf{p}^N, \mathbf{r}^N)$, only a fraction of these perturbations are accepted. According to the ergodic hypothesis,[1,2,9] the time average and ensemble averages are equal, so $A_{average} = \langle A \rangle$. The main features of MD and MC are introduced in this group of lectures, together with their extension to different ensembles, derivation of the acceptance criteria, a description of some of the more advanced MD and MC techniques, and some typical applications of these methods.

Soft matter often consists of large, massive particles (*e.g.,* polymers, colloids, surfactants, proteins, etc.) in a sea of small, light particles (solvent). In such systems the time scales involved for the large and small particles are very different. In the meso-scale methods (Table 2), simplifications to classical atomistic methods are introduced (coarse-graining) to remove the faster degrees of freedom and/or treat groups of atoms as individual entities interacting through effective potentials. One example of such methods is lattice Monte Carlo simulations,[2,9,18] in which molecules or groups of atoms occupy discrete positions on a lattice; the simulations are computationally more efficient than those using atomistically detailed continuum models. Other meso-scale methods covered are Brownian Dynamics and Dissipative Particle Dynamics,[1,2] which are based on the Langevin equation for the dynamics of the large particles[16,17]

$$m\mathbf{a}_i(t) = \mathbf{F}_i(t) = \sum_{j\neq i} \mathbf{F}_{ij}^C - \gamma\mathbf{v}_i(t) + \sigma\varsigma_i(t) \qquad (6)$$

where m is the mass of the particles, $\mathbf{a}_i(t)$, $\mathbf{v}_i(t)$, and $\mathbf{F}_i(t)$ are the acceleration, velocity and force, respectively, for particle i, $\mathbf{F}_{ij}^C$ is the conservative (solvent-mediated) force acting on the large particle i due to another large particle j, and γ is the friction coefficient on the big particles due to the presence of small particles. The last term in Eq. (6) is a "random force" introduced to account for the Brownian motion due to collisions between the small particles and the large particle, and must be included to ensure that the equipartition theorem is obeyed at long times.[1,2,16,17] The noise amplitude is σ, and

$\varsigma_i(t)$ is a Gaussian random variable. The noise amplitude σ and the friction coefficient γ are related via the fluctuation-dissipation theorem.[1,2,16,17]

The connection between results from modeling methods in different scales via "upscaling" or "downscaling" approaches are introduced. The "upscaling" approach is deductive: results from a lower-scale calculation are used to obtain potentials and parameters for a higher-scale method. Examples mentioned in class are the calculation of properties from atomistic and/or meso-scale simulations, such as phenomenological coefficients (*e.g.*, viscosities, diffusivities), for later use in a continuum model; fitting of force-fields using *ab initio* results, for later use in atomistic simulations; deriving the potential energy surface for a chemical reaction, to be used later in atomistic MD simulations; deriving coarse-grained potentials for "blobs of matter" from atomistic simulation, to be used in meso-scale simulations. In contrast, the "downscaling" approach is inductive and involves using higher-scale information (often experimental) to build parameters for lower-scale methods. This is more difficult, due to the non-uniqueness problem. For example, atomistic simulation results lack any electronic detail, and meso-scale simulations do not contain atomistic detail; thus, there is no unique way to reintroduce such detail and go to the lower level. Some examples of downscaling are the fitting of two-electron integrals in semi-empirical electronic structure methods to experimental data (ionization energies, electron affinities, etc.) and fitting of empirical force fields to reproduce experimental thermodynamic properties, *e.g.*, second virial coefficients, saturated liquid density and vapor pressure.

PROBLEM SETS AND WEB MODULES

A practical approach to the instruction of modern topics in theory and simulation must rely on hands-on experience with computers and software, illustrating the application of some of the methods covered in class to a number of practical problems. We have used commercial software from Accelrys Inc., with a graphical user interface (Insight II) for the setup and analysis of most of the simulations. This approach decreases the amount of time required on software-specific issues. In addition, some of the simulation exercises are based on home-made programs done by members of our research groups. We have defined two groups of applications, one based in methods at the electronic scale and the other studying applications at classical atomistic scales. So far we have not included any group of applications in meso-scale simulations, but we are working in order to include some of them in future offerings of this course. In each module, the students run a small calculation that takes approximately 10 minutes (or less) of CPU time, which helps them understand the process of setting up a calculation and submitting the job on a com-

puter with a batch queue. The elementary (starting) modules can be tackled in less than 2 hours, even for students who lack basic computer skills. The advanced modules can take three hours or longer. Since some students were not familiar with UNIX operating systems (or even with command-line computing), we provided a help menu on the course website describing basic operations such as file transfer, editing and storing data.

Quantum chemistry applications

We chose to focus on density functional theory (DFT) [5,10,12,13] since it is widely used and provides reasonably accurate results with fair computational costs for complex systems. Some of the proposed DFT modules include

- *Water (starting module)*
- *Polymers*
- *Surface adsorption*

In the water module, the students are asked to determine the values of properties such as bond lengths and angles, charges and dipole moment, and force constants for stretching and bending. These are parameters required in typical force field parameterizations and can also be compared to experimental values. Moreover, these results can be compared

(a)

(b)
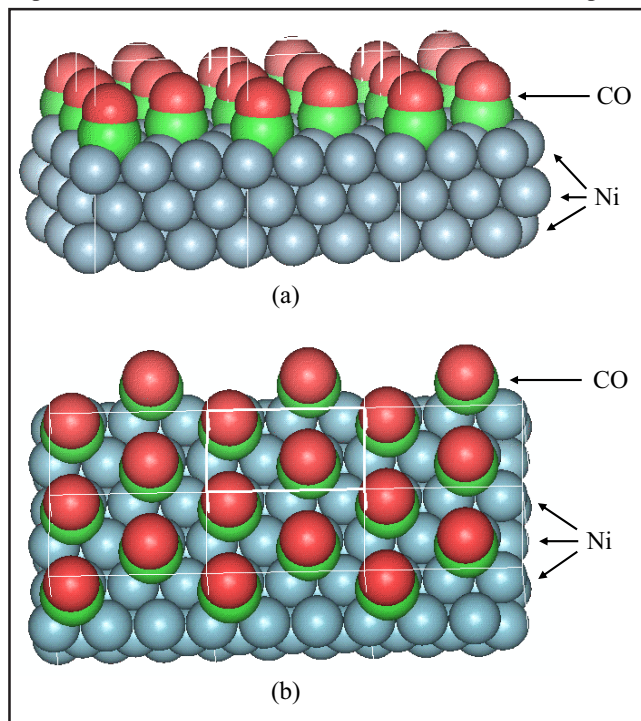
Figure 2. DFT applied to surface adsorption. Depiction of adsorption of carbon monoxide (CO) on Ni(111). (a) Lateral view, and (b) top view. The distance between the adsorbate layer of CO and the Ni surface is 1.2 Å.

later with those obtained from simulations of water using classical force fields, which is included in the atomistic group of applications. The form of the molecular orbitals for water can also be examined from the DFT calculations. Beyond water, the students can progress to more advanced calculations including geometry optimization for polymers and surface adsorption.

In the polymer module, the elastic constants such as the bulk and Young's modulus can be calculated for crystalline polymers such as polyethylene.[19,20] The surface adsorption module involves calculation of the adsorption energy of small molecules (diatomics, amines, thiols, etc.), on a range of metals (Au, Ag, Pt, Pd, Ru, etc.).[21] The suggested example is the adsorption of carbon monoxide on Ni(111),[22,23] which is depicted in Figure 2. In addition, the vibrational frequencies of adsorbed CO can be compared to those exhibited by a free molecule of carbon monoxide.

Classical atomistic applications

Some of the proposed modules in this group of applications include

- *MD and MC simulation of Lennard-Jones argon (starting module)*
- *MD simulation of liquid water*
- *Reactive Monte Carlo (RxMC) study of the ammonia synthesis reaction (bulk fluid phase)*
- *Quench dynamics of cyclic peptide analog of Leu-enkephalin*

In the starting module, the students are asked to perform both MD and MC simulation of Lennard-Jones (LJ) argon in the canonical ensemble. The students perform simulations at different temperatures, calculate typical fluid properties (*e.g.,* internal energy, pressure, heat capacity, radial distribution function), and compare the results from both methods. The self-diffusion coefficient is also determined from the MD simulations using both the velocity autocorrelation function and the mean square displacement, and the results from both methods are compared.

In the water module, the students are asked first to equilibrate two hydrogen-bonded water molecules, using the transferable intermolecular potential TIP3P, in a very low-density gas phase, and then to estimate the energy of formation of the hydrogen bond and the angle between the two associated water molecules. These two results can be compared with experimental values. Following this, the students perform MD simulations of liquid TIP3P water at room temperature and determine properties such as internal energy, heat capacity, self-diffusion coefficient, di-

pole autocorrelation function, and the radial distribution functions O-O, O-H, and H-H, comparing to experimental values when possible.

The constant pressure version of the Reactive MC (RxMC) method[24] is used in one of the modules to determine the equilibrium state of a mixture of N_2, H_2 and NH_3 in the bulk, reacting according to $N_2 + 3H_2 \Leftrightarrow 2NH_3$, at high temperatures and pressures. The typical trial moves attempted in a RxMC simulation are summarized in Figure 3(a). The molecular models were the same as those used recently by Turner, *et al.*,[25] and are depicted in Figure 3(b). The molecular constants used to calculate the partition function for this reactive mixture (N_2, H_2 and NH_3) are all found in McQuarrie's text.[15] Close agreement with the experimentally measured conversions of ammonia in the bulk phase is expected to be achieved with RxMC.[25]

The protein folding problem is one of the central issues in bioscience and biotechnology today. While the problem is enormously complicated, a simple demonstration of the thermodynamic and statistical issues is exemplified by the application of quench dynamics in the study of the folding transition of a cyclic hexamer peptide, which is shown in Figure 4. This molecule is hydrophobic and can penetrate cell membranes; then, the cyclic peptide is hydrolyzed and drugs such as Leu-enkephalin[26-28] can be released inside the cell. Therefore, such a system can be used as a drug delivery system model. To understand the peptide relative membrane permeability, we must first search the thermodynamically accessible states. To accomplish this, the peptide is heated and equilibrated at high temperatures (*e.g.*, 500 K) to overcome any isomerization barriers. A number of peptide conformations are selected, quenched (progressively cooled to lower temperatures) and equilibrated. The resulting structures represent local minimum conformations, and their relative energies map out the thermally accessible conformations of the peptide. Three families of structures are expected to be found: folded, unfolded and intermediate. The folded structure (Figure 4) has two hydrogen bonds, shown in Figure 4 as the N-H··O=C distances of 2.07 Å and 2.09 Å. The folded structure has a β-sheet fold, as shown by the side view. The unfolded structure (Figure 4) has no hydrogen bonds (N-H··O=C distances of 4.35 Å and 4.42 Å), has a crowned morphology, and the side view shows that the structure is more similar to an extended chain, rather than to a β-sheet. The intermediate structure has only one hydrogen bond and combines features of both of the previously described structures. This particularly simple example illustrates how computational modeling of folding transitions is possible using a relatively simple model. The structures obtained from quench dynamics simulations can then be used to compute vibrational

frequencies using density functional theory methods, obtaining results in agreement with experimental trends.[29]

CONCLUDING REMARKS

The main objective of this course is to make students familiar with the most important computational methods available at different scales (electronic, atomistic and meso-scale), and to illustrate how they can be applied to some problems of current interest. The course was offered for the first time in Spring 2004, and we plan to further develop it for future offerings. We are currently working to include a group of computational exercises on meso-scale simulations in the course, and thus provide practical examples of modeling at all the different scales covered in this course. In addition, we plan to include practical exercises linking the results from methods at different scales, via upscaling or downscaling. This is an active research area at present, and it is important for a course of this kind to be up to date. Both the course outline and computational modules need to be continually updated in order to cover the most recent and interesting methodologies and applications.

ACKNOWLEDGMENTS
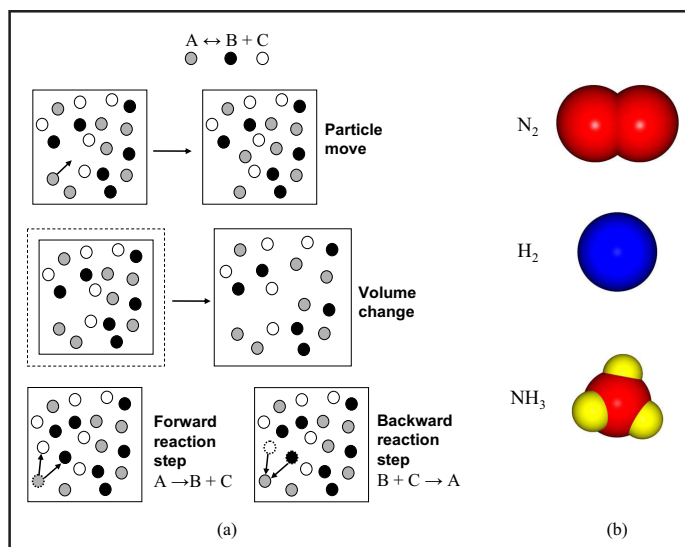
***Figure 3.*** *Reactive Monte Carlo (RxMC) module: (a) illustration of the RxMC typical moves for a reaction A ↔ B + C: particle move, volume changes, forward and backward reaction steps; and (b) schematic representation of the model molecules studied. Nitrogen was represented by a two-site LJ molecule, with the addition of three point charges chosen to account for its quadrupole. The hydrogen molecule was treated as a single LJ sphere, and the model for NH_3 consisted of one LJ plus negative point charge site to represent the nitrogen, and three positive point charges to represent the three hydrogens. No LJ sites were used to account for the hydrogens on the ammonia molecules.*

versity and the University of North Carolina at Chapel Hill who took this course, for their patience, support, feedback and motivation. We gratefully acknowledge Professors David A. Kofke (University at Buffalo, The State University of New York) and Sharon C. Glotzer (University of Michigan), for kindly providing us full access to their respective course materials. We thank Erik E. Santiso, who prepared the material and lectured the classes about chemical reaction modeling. We also would like to thank Henry Bock, Naresh Chennamsetty and Supriyo Bhattacharya, for their help in the preparation of the lectures about meso-scale simulations. It is a pleasure to thank Professors Ken Thomson (Purdue University) and C. Heath Turner (University of Alabama), for kindly providing the data for Figures 1 and 3 of this paper.

REFERENCES

1. Allen, M.P., and D. J. Tildesley, *Computer Simulation of Liquids*, Clarendon Press, Oxford (1987)
2. Frenkel, D., and B. Smit, *Understanding Molecular Simulation* 2nd Ed., Academic Press, San Diego, CA (2002)
3. Information taken from http://www.npaci.edu/BlueHorizon/. 1 Tflop = 10^{12} floating point operations per second.
4. de Pablo, J.J., and F. A. Escobedo, "Molecular Simulations in Chemical Engineering: Present and Future," *AIChE J.,* **48**, 2716 (2002)
5. Santiso, E.E., and K. E. Gubbins, "Multi-Scale Molecular Modeling of Chemical Reactivity," *Mol. Simul.*, in press (2004)
6. Maroudas, D., "Multiscale Modeling of Hard Materials: Challenges and Opportunities for Chemical Engineers," *AIChE J.,* **46**, 878 (2000)
7. Glotzer, S.C., and W. Paul, "Molecular and Mesoscale Simulation Methods for Polymer Materials," *Annu. Rev. Mater. Res.,* **32**, 401 (2002)
8. Abraham, F.F., J. Q. Broughton, N. Bernstein, and E. Kaxiras, "Spanning the Length Scales in Dynamic Simulation," *Comp. Phys.,* **12**, 538 (1998)
9. Leach, A.R., *Molecular Modelling. Principles and Applications* 2nd Ed., Prentice-Hall, Harlow (2001)
10. Jensen, F., *Introduction to Computational Chemistry*, John Wiley and Sons, Chichester (1999)
11. Szabo, A., and N. Ostlund, *Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory*, Dover, New York (1996)
12. Parr R.G., and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford (1989)
13. Koch, W., and M.C. Holthausen, *A Chemist's Guide to Density Functional Theory*, Wiley-VCH, Weinheim (2000)
14. Gray, C.G., and K.E. Gubbins, *Theory of Molecular Liquids*, Clarendon Press, Oxford (1984)
15. McQuarrie, D.A., *Statistical Mechanics*, University Science Books, Sausalito (2000)
16. Zwanzig, R., *Nonequilibrium Statistical Mechanics*, Oxford University Press, New York (2001)
17. Mazo, R.M., *Brownian Motion*, Clarendon Press, Oxford (2002)
18. Panagiotopoulos, A.Z., "On the Equivalence of Continuum and Lattice Models for Fluids," *J. Chem. Phys.,* **112**, 7132 (2000)
19. Miao, M.S., M.L. Zhang, V.-E. van Doren, C. van Alsenoy and J.L. Martins, "Density Functional Calculations on the Structure of Crystalline Polyethylene at High Temperatures," *J. Chem. Phys.,* **115**, 11317 (2001)
20. Bruno, J.A.O., N.L. Allan, T.H.K. Barron, and A.D. Turner, "Thermal Expansion of Polymers: Mechanisms in Orthorhombic Polyethylene," *Phys. Rev. B,* **58**, 8416 (1998)
21. Franzen, S., "Density Functional Calculation of a Potential Energy Surface for Alkane Thiols on Au(111) as Function of Alkane Chain Length," *Chem. Phys. Lett.,* **381,** 315 (2003)
22. Doll, K., "Density Functional Study of Ni Bulk, Surfaces and the Adsorbate Systems Ni(111)($\sqrt{3}$ x $\sqrt{3}$)R30º-Cl, and Ni(111)(2x2)-K,", *Surf. Sci.,* **544**, 103 (2003)
23. Shah, V., T. Li, K.L. Baumert, H.S. Cheng, and D.S. Sholl, "A Comparative Study of CO Chemisorption on Flat and Stepped Ni Surfaces Using Density Functional Theory," *Surf. Sci.,* **537**, 217 (2003)
24. 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)
25. Turner, C.H., J.K. Johnson, and K.E. Gubbins, "Effect of Confinement on Chemical Reaction Equilibria: The Reactions $2NO \Leftrightarrow (NO)_2$ and $N_2 + 3H_2 \Leftrightarrow 2NH_3$ in Carbon Micropores," *J. Chem. Phys.,* **114**, 1851 (2001)
26. Wang, B., K. Nimkar, W. Wang, H. Zhang, D. Shan, O. Gudmundsson, S. Gangwar, T. Siahaan, and R. T. Borchardt, "Synthesis and Evaluation of the Physicochemical Properties of Esterase-Sensitive Cyclic Prodrugs of Opioid Peptides Using Coumarinic Acid and Phenylpropionic Acid Linkers," *J. Pept. Res.,* **53**, 370 (1999)
27. Dudowicz, J., K.F. Freed, and M. Y. Shen, "Hydration Structure of Met-Enkephalin: A Molecular Dynamics Study," *J. Chem. Phys.,* **118**, 1989 (2003)
28. van der Spoel, D., and H.J.C. Berendsen, "Molecular Dynamics Simulations of Leu-Enkephalin in Water and DMSO," *Biophys. J.,* **72**, 2032 (1997)
29. Maness, S.J., S. Franzen, A.C. Gibbs , T.P. Causgrove and R.B. Dyer, "Nanosecond Temperature Jump Relaxation Dynamics of Cyclic β-Hairpin Peptides," *Biophys. J.,* **84**, 3874 (2003) ❏
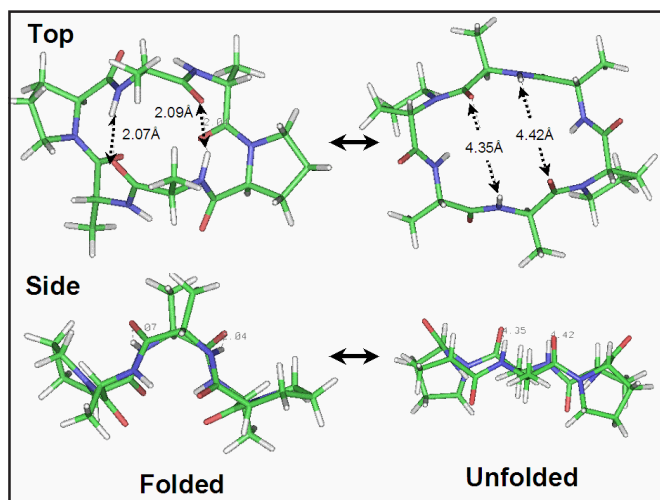
Figure 4. Quench Dynamics module. Depiction of the folded and unfolded structures obtained from quench dynamics simulations of a model cyclic hexamer peptide. Two hydrogen bonds are observed in the folded structure (N-H¨O=C distances of 2.07 Å and 2.09 Å, top view), which has a β-sheet fold (side view). The unfolded structure exhibits a crowned morphology with no hydrogen bonds (N-H¨O=C distances of 4.35 Å and 4.42 Å, top view), and an extended-chain morphology (side view). The structures obtained from quench dynamics simulations can be used to compute vibrational frequencies using density functional theory methods. The trends in the vibrational frequency of the folded and unfolded structures agree with experimental results.