

# FORCE FIELD DEVELOPMENT FOR SIMULATIONS OF CONDENSED PHASES

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## *Abstract*

The focus of this review is on development of force fields for simulations of technologically important properties of fluids and materials. Of particular interest are models that can reproduce thermodynamic and transport properties over a broad range of temperatures and densities. Most existing force fields have been optimized to the configurational properties of isolated molecules and thermodynamic or structural properties of liquids near room temperature. Recently developed force fields are now available that also reproduce phase coexistence properties and critical parameters for selected systems, but they are not yet generally applicable to many systems of interest. Simulation methodologies for rapid determination of intermolecular potential parameters from experimental data are discussed. Two key unresolved questions remain, namely how to incorporate polarizability and other non-additive interactions, and the logistics of large-scale efforts to obtain parameters for broad classes of components.

## *Keywords*

Force fields, intermolecular potentials, thermodynamic properties, phase coexistence, critical properties, Monte Carlo simulations, molecular dynamics simulations

## **Introduction**

In 1965, Intel's co-founder Gordon Moore suggested that the computing power of a single chip doubles every eighteen months. We have now experienced several decades of growth in accordance with this statement. Some fundamental barriers to future growth may soon appear (Service, 1997), but today's desktop workstations have the processing power of supercomputers of just a few years ago. Molecular modelers have greatly benefited from this increasing computing power.

Molecular modeling and simulation algorithms have also improved over time. For example, configurational bias Monte Carlo methods (Siepmann and Frenkel, 1992; de Pablo *et al.*, 1992) enable sampling of conformations and free energies of chain molecules with much higher computational efficiency than previous techniques.

Despite progress in computing hardware and simulation methodologies, prediction of properties of interest to industrial applications for condensed phases is not currently practiced on a routine basis. The lack of appropriate intermolecular potential functions is often quoted as *the* most important barrier for application of atomistic simulation methodologies to problems of industrial interest (Thompson, 1999, Table 4-2). A legitimate question is why this is still the case, given that many general force fields are now available that have been optimized to structural, bonding and thermodynamic properties of a large number chemical components. The answer to this question is that many important properties are not currently considered during potential model development. In particular, most generally available force fields have not been tested for their ability to reproduce phase coexistence

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properties of pure fluids and mixtures over broad temperature ranges. Most existing force fields also have not been extensively tested for density or concentration conditions far removed from the pure liquid state at ambient temperature and pressure. Unfortunately, one cannot expect good performance of these force fields at conditions that have not been considered in their development. This, in turn, severely limits the reliability and predictive ability of molecular modeling methods.

The present review focuses on issues related to development of force fields for atomistic simulations of condensed phases, with particular emphasis on phase coexistence and other thermodynamic properties of fluids and amorphous materials. Issues related to force field development from *ab initio* calculations and hybrid methods are addressed by the contributions of M. Parrinello and R. Freisner in this volume.

The plan of this paper is as follows. Currently available general force fields for simulations of fluids are reviewed first. Computational methodologies for the routine determination of force fields accurate over broad temperature and density ranges are presented in the following section. Recently developed potentials for phase coexistence properties are described in detail. Possible additional force field features not included in current potentials and the issue of coordinated model development are discussed in the final section.

### Currently Available General Force Fields

Many force fields for atomistic simulations have been developed over the past decades. No attempt is made in the present paper to provide an exhaustive review of all such efforts. Instead, the main approaches taken by previous researchers are briefly illustrated.

Most current force fields describe bonded interactions by stretching, bending and torsional potentials. The bonded interaction parameters are obtained by fitting to *ab initio* data, usually obtained at the Hartree-Fock level with large basis sets. Partial charges are used for describing electrostatic interactions. In recent years, the Ewald summation technique for handling the long-range character of the electrostatic interactions has become popular.

One approach for describing non-bonded interactions, pioneered in the early work by Jorgensen (1984), non-bonded potential parameters are obtained by fitting experimentally observed liquid densities and enthalpies and structural properties near room temperature. The latest versions of these models are "all-atom" force fields explicitly incorporating hydrogens. Examples include the OPLS (Jorgensen *et al.*, 1996), CHARMM (Mackerell *et al.*, 1995), AMBER (Cornell *et al.*, 1995) and COMPASS (Sun, 1998) force fields. The primary focus of these models is on biological and organic molecules in aqueous solution. As shown in Fig. 1 (from Chen *et al.*, 1998), for simple hydrocarbons, there is good, but not quantitative, agreement between calculated and experimental coexistence curves.

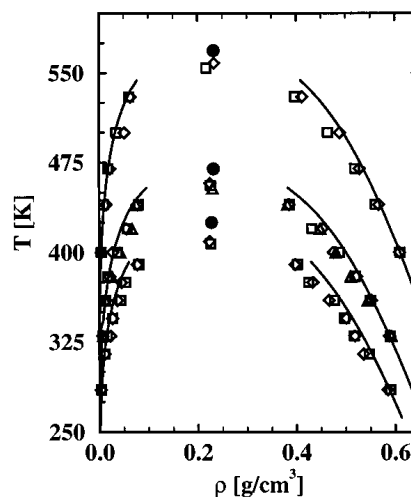


Figure 1. Vapor-liquid coexistence curves for variations of the OPLS all-atom force field for *n*-butane, *n*-pentane and *n*-octane. Points are simulation results and lines are experimental data. Reprinted with permission from Chen *et al.*, 1998. © 1998 American Chemical Society.

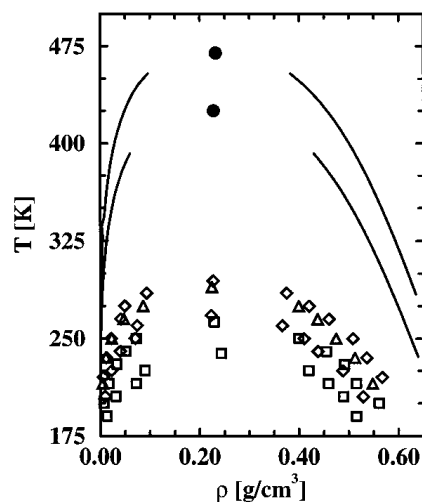


Figure 2. Vapor-liquid coexistence curves for variations of the MMFF force field for *n*-butane and *n*-pentane. Points are simulation results and lines are experimental data. Reprinted with permission from Chen *et al.*, 1998. © 1998 American Chemical Society.

Another approach to obtaining force field parameters is to minimize the deviations between predicted and observed bond lengths, angles, vibrational frequencies, conformational energies, and minimum-energy conformations of clusters. A current example of this approach is the MMFF force field developed by Halgren (1996a-d). Unfortunately, even for simple hydrocarbon systems, this approach can result in completely unrealistic thermodynamic properties, as illustrated by the data in Fig. 2 (from Chen *et al.*, 1998).

The force fields described in this section share several common features. In particular, non-bonded dispersion interactions are described by Lennard-Jones 12-6 potentials. The only exception is the COMPASS force field, which uses a 9-6 potential. Only two-body interactions are included; three- and higher-order interactions are effectively incorporated in the values of the potential model parameters. The errors introduced by this approximation are most pronounced if calculations at densities and temperatures significantly different from the ones used in the parameterization. For example, the value of the dipole moment for the water molecule in these models is significantly higher than the gas-phase value. This is done in order to compensate for polarizability interactions that lead to a higher value of the dipole moment in liquid water, but lead to incorrect values for the second virial coefficient and energy at low densities.

## Computational Methods

This section focuses on computational methodologies that have been found useful for rapid development of intermolecular potential models that can reproduce coexistence properties over a broad temperature range. A more extensive recent review of these methods is available (Panagiotopoulos, 2000a).

### *Gibbs Ensemble Monte Carlo*

The Gibbs Ensemble Monte Carlo simulation methodology (Panagiotopoulos, 1987; Panagiotopoulos *et al.*, 1988; Smit *et al.*, 1989) enables direct simulations of phase equilibria in fluids. Gibbs ensemble simulations are performed in two separate microscopic regions, each within periodic boundary conditions. The thermodynamic requirements for phase coexistence are that each region should be in internal equilibrium, and that temperature, pressure and the chemical potentials of all components should be the same in the two regions. System temperature in Monte Carlo simulations is specified in advance. The remaining three conditions are satisfied by performing three types of Monte Carlo moves, displacements of particles within each region (to satisfy internal equilibrium), fluctuations in the volume of the two regions (to satisfy equality of pressures) and transfers of particles between regions (to satisfy equality of chemical potentials of all components). The method has been frequently used, in combination with configurational bias sampling discussed in the following paragraph, to determine phase diagrams of a large number of fluids. Reviews of the Gibbs method and its applications are available (Panagiotopoulos 1995, 2000a).

### *Configurational Bias Sampling and Expanded Ensembles*

The most common bottleneck in achieving convergence in methods that rely on particle transfers is the prohibitively low acceptance of transfer attempts. For dense

fluid phases, especially for complex, orientation-dependent intermolecular potentials, configurations with "holes" in which an extra particle can be accommodated are highly improbable, and the converse step of removing a particle involves a large cost in energy.

Configurational-bias sampling techniques significantly improve sampling efficiency for Gibbs or grand canonical Monte Carlo simulations. The methods have been reviewed in detail by Frenkel (1995), Frenkel and Smit (1996), and Siepmann (1999). The methods trace their ancestry to biased sampling for lattice polymer configurations proposed by Rosenbluth and Rosenbluth (1955). Development of configurational-bias methods for canonical and grand canonical simulations and for continuous-space models took place in the early 1990's (Frenkel *et al.*, 1992; de Pablo *et al.*, 1992; Siepmann and Frenkel, 1992; Laso *et al.*, 1992).

Configurational-bias methods are based on segment-by-segment insertions or removals of a multisegment molecule. Several trial directions are attempted for every segment insertion, and a favorable growth direction is preferentially selected for the segment addition. This way, the acceptance probability of insertions is greatly enhanced.

For each segment growth or removal step, a correction factor (often called "Rosenbluth weight") is calculated. The product of the Rosenbluth weights of all steps is incorporated in the overall acceptance criterion for particle insertions and removals in order to correct for the bias introduced by the non-random growth along preferential directions.

Another approach for handling multisegment molecules is based on the concept of expanded ensembles (Lyubartsev *et al.*, 1992; Wilding and Müller, 1994; Vortsov-Velyaminov *et al.*, 1996; Escobedo and de Pablo, 1996). Expanded ensembles for chain molecules construct a series of intermediate states for the molecule of interest, from a non-interacting (phantom) chain to the actual chain with all segments and interactions in place. These intermediate states can be semi-penetrable chains of the full length or shortened versions of the actual chain. Estimates of the free energy of the intermediate states are required to ensure roughly uniform sampling, as for thermodynamic and Hamiltonian scaling methods mentioned in the previous section. The advantage of expanded ensembles over configurational-bias methods is that arbitrarily complex long molecules can be sampled adequately, if sufficient computational effort is invested in constructing good approximations of the free energies of intermediate states.

### *Histogram Reweighting Methods*

Early in the history of development of simulation methods it was realized that a single calculation can, in principle, be used to obtain information on the properties of a system for a range of state conditions (McDonald and Singer, 1976; Wood, 1968; Card and Valleau, 1970). However, the practical application of this concept was

severely limited by the performance of computers available at the time. In more recent years, several groups have confirmed the usefulness of this concept, first in the context of simulations of spin systems and later for continuous-space fluids (Wilding, 1995; Panagiotopoulos *et al.*, 1998; Wilding, 1997; Potoff and Panagiotopoulos, 1998).

A histogram reweighting grand canonical Monte Carlo (GCMC) simulation for a one-component system is performed as follows (histogram reweighting for multi-component systems is analogous to the one-component version). The simulation cell has a fixed volume  $V$  and is placed under periodic boundary conditions. The inverse temperature,  $\beta=1/k_B T$  and the chemical potential,  $\mu$ , are specified as input parameters to the simulation. Histogram reweighting requires collection of data for the probability  $f(N, E)$  of occurrence of  $N$  particles in the simulation cell with total configurational energy in the vicinity  $E$ . This probability distribution function follows the relationship

$$f(N, E) = \frac{\Omega(N, V, E) \exp(-\beta E + \beta \mu N)}{\Xi(\mu, V, \beta)} \quad (1)$$

where  $\Omega(N, V, E)$  is the microcanonical partition function (density of states) and  $\Xi(\mu, V, \beta)$  is the grand partition function. Neither  $\Omega$  nor  $\Xi$  are known at this stage, but  $\Xi$  is a constant for a run at given conditions. Since the left-hand side of Eq. 1 can be easily measured in a simulation, an estimate for  $\Omega$  and its corresponding thermodynamic function, the entropy  $S(N, V, E) = k_B \ln \Omega(N, V, E)$  can be obtained by a simple transformation of Eq. 1:

$$S(N, V, E) / k_B = \ln[f(N, E)] + \beta E - \beta \mu N + C \quad (2)$$

$C$  is a run-specific constant. Eq. 2 is meaningful only over the range of densities and energies covered in a simula-

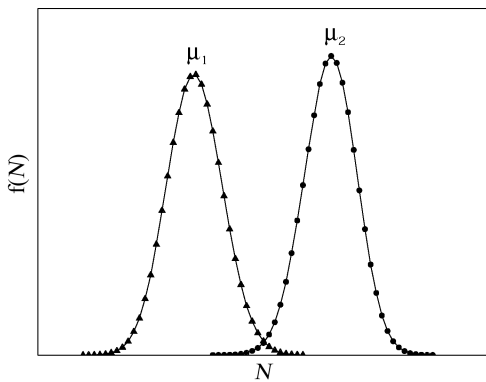


Figure 3. Schematic diagram of the probability  $f(N)$  of occurrence of  $N$  particles for two GCMC runs of a pure component system at the same volume and temperature, but different chemical potentials,  $\mu_1$  and  $\mu_2$ , respectively.

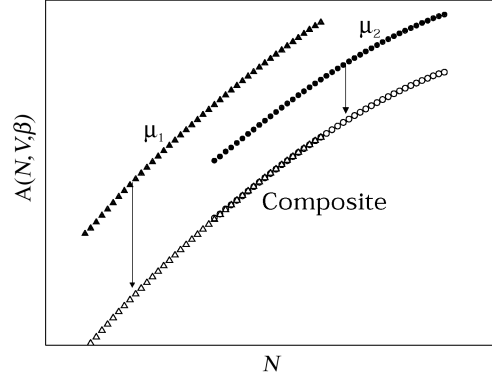


Figure 4. Illustration of the process of histogram transformation and combination. The abscissa is calculated as  $\ln[f(N)] - \beta \mu N$  from the data of Fig. 3.

tion. If two runs at different chemical potentials and temperatures have a region of overlap in the space of  $(N, E)$  sampled, then the entropy functions can be “merged” by requiring that the functions are identical in the region of overlap.

To illustrate this concept, we make a one-dimensional projection of Eq. (1) to show histograms for two runs at different chemical potentials in Fig. 3. There is a range of  $N$  over which the two runs overlap. A transformation analogous to Eq. 2 gives the Helmholtz energy  $A(N, V, \beta)$ , within an additive constant, as shown in Fig. 4. The raw curves for  $\mu_1$  and  $\mu_2$  as well as a “composite” curve formed by shifting data for the two runs by the amount indicated by the arrows are indicated in Fig. 4. The combined curve provides information over the range of particle numbers,  $N$ , covered by the two runs.

Simulation data are subject to statistical uncertainties, which are particularly pronounced near the extremes of particle numbers and energies visited during a run. When data from multiple runs are combined as shown in Fig. 4, the question arises of how to determine the optimal amount by which to shift the raw data in order to obtain a global free energy function. Ferrenberg and Swendsen (1988) provided a solution to this problem that minimizes the differences between predicted and observed histograms. All thermodynamic quantities for the system over the range of densities and energies covered by the histograms can be obtained from the combined histograms.

In the absence of phase transitions or at temperatures near a critical point, the values of all observable quantities are independent of initial conditions, since free energy barriers for transitions between states are small or nonexistent. However, at lower temperatures, free-energy barriers for nucleation of new phases become increasingly larger. The states sampled at a given temperature and chemical potential depend on initial conditions, a phenomenon known as hysteresis. The histogram reweighting method can be applied to systems with large free-energy barriers for transitions between states, if care is taken to link all states of interest *via* reversible paths.

### Thermodynamic and Hamiltonian scaling

Two methods related to histogram reweighting are thermodynamic and Hamiltonian scaling Monte Carlo. Thermodynamic-scaling techniques proposed by Valleau (1991) are based on calculations in the constant pressure ( $NPT$ ), rather than the grand canonical ( $\mu VT$ ) ensemble and provide information for the free energy over a range of volumes, rather a range of particle numbers. Thermodynamic scaling techniques can also be designed to cover a range of Hamiltonians (potential models) in the Gibbs (Kiyohara *et al.*, 1996) or Grand Canonical ensemble (Errington and Panagiotopoulos, 1998).

In their Hamiltonian-scaling form, the methods are particularly useful for optimizing parameters in intermolecular potential models to reproduce experimental data such as the coexisting densities and vapor pressures. Thermodynamic and Hamiltonian scaling methods require estimates for the free energy of the system as a function of conditions, so that the system can be forced to sample the range of states of interest with roughly uniform probability.

### Gibbs-Duhem Integration

Most methods for determination of phase equilibria by simulation rely on particle insertions to equilibrate or determine the chemical potentials of the components. Methods that rely on insertions experience severe difficulties for dense or highly structured phases. If a point on the coexistence curve is known (e.g. from Gibbs ensemble simulations), the remarkable method of Kofke (1993a, 1993b) enables the calculation of a complete phase diagram from a series of constant-pressure simulations that do not involve any transfers of particles. The method enables calculations of solid-fluid coexistence (Agrawal and Kofke, 1995), for which other methods described in this paper are not applicable. The method and its applications have been recently reviewed (Kofke, 1999).

For one-component systems, the method is based on integration of the Clausius-Clapeyron equation over temperature,

$$\left( \frac{dP}{dT} \right)_{sat} = - \frac{\Delta H}{T \Delta V} \quad (3)$$

where “*sat*” indicates that the equation holds on the saturation line, and  $\Delta H$  is the difference in enthalpy between the two coexisting phases. The right-hand side of Eq. 3 involves only “mechanical” quantities that can be simply determined in the course of a standard Monte Carlo or molecular dynamics simulation. From the known point on the coexistence curve, a change in temperature is chosen,

and the saturation temperature at the new temperature is predicted from Eq. 3. Two independent simulations for the corresponding phases are performed at the new temperature, with gradual changes of the pressure as the simulations proceed to take into account the enthalpies and densities at the new temperature as they are being calculated.

### Force Fields for Phase Coexistence Properties

In the recent years, availability of the methods described in the previous section has had an impact on force field model development by enabling determination of parameters that reproduce accurately phase coexistence properties over broad temperature ranges. The performance of models with respect to coexistence properties is of paramount importance for design of separation processes. However, there are many other reasons why such models are highly desirable. In particular, at low temperatures (near the triple point), the chemical potential of the liquid essentially determines the vapor pressure, so that models that do well for phase coexistence also describe accurately the free energy of the dense liquid. Near the critical point, phase coexistence involves phases with densities intermediate between those of a gas and a highly subcritical liquid. The requirements for good performance over a broad range of densities and temperatures are much more severe than the thermodynamic properties at a single temperature and density used in development of many currently available general force fields.

### Hydrocarbons

Hydrocarbon molecules are ubiquitous in industrial processes and form the building blocks of biological systems. They are non-polar and consist of a small number of groups, thus making them the logical starting point for potential model development.

Three accurate united-atom potential sets for  $n$ -alkanes have appeared recently. The TRAPPE (Martin and Siepmann, 1998) and NERD models (Nath *et al.*, 1998) use the Lennard-Jones (12,6) potential to describe non-bonded interactions among methyl and methylene groups, while the model of Errington and Panagiotopoulos (1999) uses the exponential-6 functional form. All three reproduce the experimental phase diagrams and critical points. The exponential-6 model is slightly better with respect to representation of the vapor pressures. Figs. 5 and 6 illustrate the quality of representation of experimental data for the newer optimized models. Deviations from experimental data for the exponential-6 united atom model are comparable to those for a recently developed all-atom TRAPPE model (Chen and Siepmann, 1999).

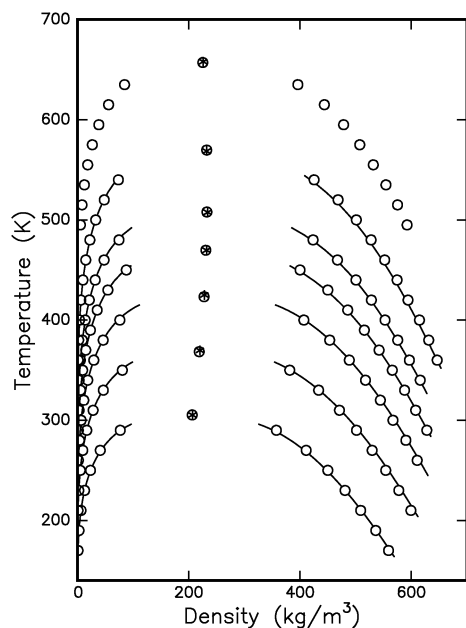


Figure 5. Phase diagrams of selected *n*-alkanes. The curves from bottom to top are for ethane, propane, butane, pentane, hexane, octane, and dodecane. Circles represent simulation results and lines are experimental data. Uncertainties are smaller than the size of the symbols. Reprinted by permission from Errington and Panagiotopoulos, 1999. ©1999, American Chemical Society.

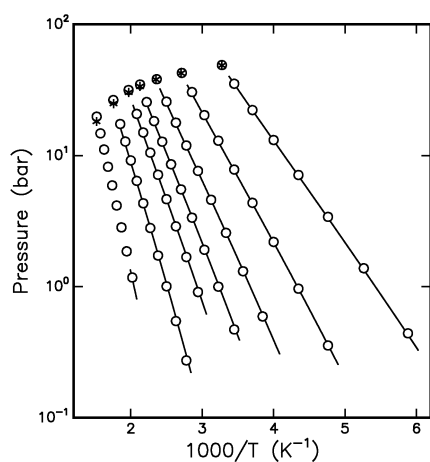


Figure 6. Vapor pressures of selected *n*-alkanes. The curves from right to left are for ethane, propane, butane, pentane, hexane, octane, and dodecane. Symbols are the same as for Fig. 5. Reprinted by permission from Errington and Panagiotopoulos, 1999. ©1999, American Chemical Society.

United-atom potentials for branched alkanes have been developed by Cui *et al.*, (1997), Martin and Siep-

mann (1999) and for  $\alpha$ -olefins by Spyriouni *et al.* (1999).

#### Polar fluids

There have been several recent studies of the phase behavior of polar compounds such as *n*-alkanols (van Leeuwen, 1996), hydrogen sulfide (Kristof and Liszi, 1999) and carbon disulfide (Kristof *et al.*, 1996). However, no transferable force fields that can be used to obtain the phase behavior of polar fluids with reasonable accuracy are currently available. An example of the challenges in predictions of the behavior of polar fluids is provided by Visco and Kofke (1998), who studied two *ab initio* and one empirical potential model for hydrogen fluoride. The *ab initio* models did not model accurately the saturated liquid densities and none of the models predicted correctly the vapor pressure and heat of vaporization as functions of temperature.

#### Water

Because of the importance of water in biological and chemical systems, a large number of models have been proposed for atomistic simulations. Rigid fixed point charge models for water are often used in simulations of biological systems because of their simplicity and reasonable predictions of the structure and thermodynamics of liquid water at ambient conditions. Such models include the TIP4P (Jorgensen *et al.*, 1983), SPC (Berendsen *et al.*, 1981) and SPC/E (Berendsen *et al.*, 1987) models. All represent water as a single Lennard-Jones (12,6) sphere within which are embedded positive and negative charges.

Table 1 compares the critical temperature  $T_c$ , density  $\rho_c$ , and vapor pressure,  $P_{vp}$ , at  $T=373$  K of fixed point charge models for water. The “Exp-6” model (Errington and Panagiotopoulos, 1998) is also a fixed point charge model, but utilizes the exponential-6 functional form for the repulsion and dispersion interactions and was parameterized to the phase coexistence properties. The SPC/E model predicts a critical temperature near the experimental value, but underestimates the vapor pressure (and thus the chemical potential) by more than a factor of two. The SPC model has the correct vapor pressure, but severely underestimates the critical temperature. The TIP4P model has an even lower  $T_c$  and overestimates the vapor pressure. The Exp-6 model does very well for both  $T_c$  and  $P_{vp}$ , and has the closest  $\rho_c$  to the experimental value. However, the Exp-6 model does not do as well as the other models for structure of the liquid, in particular with respect to the oxygen-oxygen pair correlation function. It also has a dielectric constant lower than that the experimental value at room temperature.

Clearly, none of these simple fixed point charge models for water can adequately reproduce thermodynamic and structural properties over a broad temperature range. As also suggested earlier, the inclusion of only two-body interactions also results in a higher “effective” dipole moment relative to the isolated (gas phase) molecule.

Table 1: Comparison of thermodynamic properties of fixed point charge water models. Simulation data are from Errington and Panagiotopoulos (1998) for the SPC, SPC/E and Exp-6 models and from Vlot *et al.*, (1999) for the TIP4P model.

Model	$T_c$ (K)	$\rho_c$ (kg/m <sup>3</sup> )	$P_{VP}$ (bar) at $T=373$ K
SPC	$594 \pm 1$	$271 \pm 6$	$1.0 \pm 0.2$
SPC/E	$639 \pm 2$	$273 \pm 9$	$0.37 \pm 0.06$
TIP4P	$561 \pm 3$	$290 \pm 50$	$1.4 \pm 0.1$
Exp-6	$646 \pm 1$	$297 \pm 5$	$0.95 \pm 0.01$
Experimental	647	322	1.01

Several polarizable models for water are available in the literature, but none seem to be better than the simple fixed point charged models with respect to the coexistence properties and critical parameters (Kiyohara *et al.*, 1998). Some of the newer “fluctuating-charge” models developed from *ab initio* calculations (Stern *et al.*, 1999) have not yet been tested with respect to their phase coexistence behavior. Chen *et al.* (2000) performed an extensive search for optimized parameters for polarizable water models. Two optimized force fields were proposed. The SPC-pol-1 force field yields good saturated vapor and liquid densities, heats of vaporization and dielectric constants but does not represent well the liquid structure. The TIP4P-pol force field yields excellent liquid structures but does not perform well for the coexistence properties near the critical point. Chen *et al.* concluded that “we have to continue our quest for improved water force fields.”

### Mixtures

A key question for all force fields for atomistic simulations is their ability to predict properties of mixtures without use of additional adjustable parameters for the unlike-pair interactions. Extensive phase coexistence data are available for many mixtures, but have not generally been used to validate proposed models. This is primarily because of the difficulties associated with simulations of phase coexistence for mixtures prior to the development of the computational methods discussed in the previous section.

For mixtures of non-polar components such as hydrocarbons or inert gases, there is considerable evidence that the newer force fields optimized to the phase equilibrium properties can be used for reliable predictions of mixture behavior. For example, Fig. 7 illustrates the predicted phase behavior of a mixture of ethane with *n*-heptane (Errington and Panagiotopoulos, 1999). Excellent agreement is obtained with experimental data without use of any mixture parameters.

An important unresolved question is that of combining rules for unlike-pair parameters of the repulsion and dispersion terms. The Lorentz-Berthelot combining rules (arithmetic mean for the diameters and geometric mean for

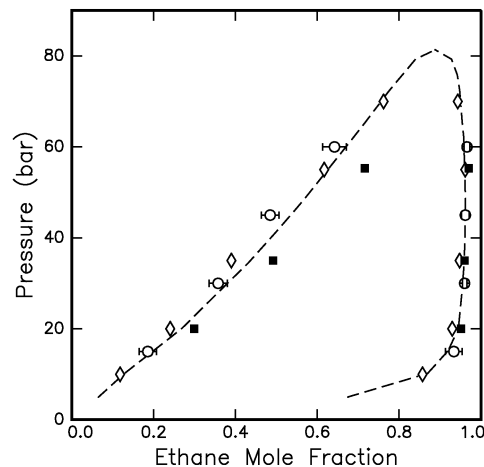


Figure 7. Phase diagram for a mixture of ethane and *n*-heptane at  $T=366$  K. Squares, diamonds and circles are used for the NERD, TraPPE and Exp-6 models, respectively. A dashed line is used for the experimental data. Reprinted by permission from Errington and Panagiotopoulos, 1999. ©1999, American Chemical Society.

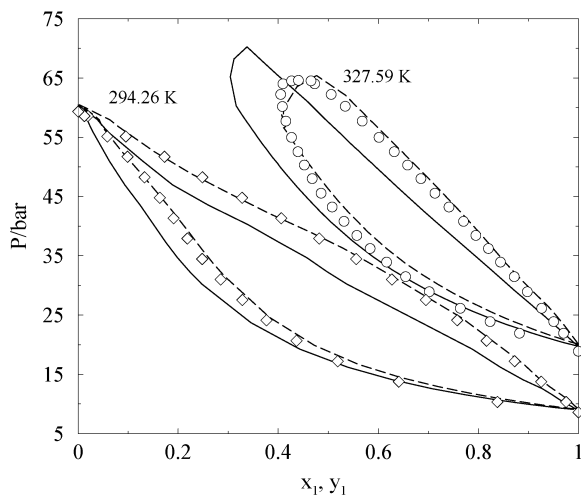


Figure 8. Propane/CO<sub>2</sub> pressure-composition diagram. Experimental data:  $T=327.59$  K (open circles)  $T=294.26$  K (open diamonds). GCMC simulations with the Lorentz-Berthelot (solid line) and Kong combining rules (dashed line). The average statistical uncertainties for the simulation data in pressure and composition are  $\pm 0.47$  bar and  $\pm 0.0050$ , respectively. Reprinted by permission from Potoff *et al.*, 1999. ©1999 Taylor and Francis.

potential well depths) have been used almost universally for unlike-pair parameters in predictive simulations. However, some recent results (Potoff *et al.*, 1999), suggest that different combining rules may be more appropriate for groups that differ significantly in size or polarity. Fig. 8 presents calculations for the pressure-composition diagram of propane with CO<sub>2</sub>. The Kong (1973) combin-

ing rules, which result in less attractive unlike-pair interactions than the Lorentz-Berthelot rules, give better agreement with experimental data for this and similar mixtures. Potoff *et al.* (1999) also find that for mixtures with large differences in polar character between the components, current models do not result in quantitative agreement with experiments.

### Discussion and Future Directions

In this review, I have attempted to summarize the state-of-the-art in force field development for simulations of condensed phases over large ranges of temperatures and densities. A number of computational methods that have been developed over the past few years enable the routine calculation of free energies and phase coexistence properties for model systems. These methods are now being used to obtain optimized intermolecular potentials for many substances. The resulting force fields have not yet attained the level of generality of currently available academic and commercial force fields, and they have not yet been incorporated in standard simulation codes. However, these developments are likely to occur in the near future.

Despite relatively rapid progress, there are many unresolved questions in the area. The first set of questions involve the functional form of the potential models. It is clear that for strongly interacting molecules, such as water, no simple two-body effective potential can quantitatively reproduce both structure and thermodynamics and additional interactions are necessary. The most important of these is likely to be polarizability. Recent methodological developments (Martin *et al.*, 1998; Chen *et al.*, 2000) permit incorporation of polarizability in Monte Carlo calculations with a penalty of a factor of ten in CPU time relative to non-polarizable model calculations. This is still a rather large cost, so the quest for other methods to incorporate polarizability will likely continue.

An interesting new concept that may have some impact on potential model development is the use of finely discretized lattice models suggested by Panagiotopoulos and Kumar (1999) and Panagiotopoulos (2000b). The basic idea is that lattice models can be made to approximate their continuum analogs by increasing the ratio,  $\zeta$ , of particle diameter to lattice spacing. The surprising result is that relatively low values of  $\zeta$  are required for quantitative agreement of the calculated thermodynamic properties between lattice and off-lattice models. For Lennard-Jones and exponential-6 fluids,  $\zeta=10$  results in agreement between lattice and continuum calculations for the phase envelope and critical parameters to within narrow statistical uncertainties. Even the structure of the fluids, which would have been expected to show some lattice artifacts, is identical between the two systems. The advantage of the finely discretized models is numerical speed. For ionic systems, the speed advantage is a factor of up to 100, while for the Lennard-Jones and exponential-6 interactions a factor between 10 and 20. A recent paper (Kumar,

2000) illustrates how this concept can be used to obtain quantitatively accurate lattice models for hydrocarbons.

Finally, a barrier to rapid force field development and testing with respect to free energies and phase coexistence predictions has been the lack of availability of portable, high quality codes appropriate for this purpose. Multiple groups (primarily academic) have been active in this area, but there has been relatively limited coordination and exchanges of data and codes.

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