SLAB-GEOMETRY MOLECULAR DYNAMICS SIMULATIONS: DEVELOPMENT AND APPLICATION TO CALCULATION OF ACTIVITY COEFFICIENTS, INTERFACIAL ELECTROCHEMISTRY, AND ION CHANNEL TRANSPORT

by

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Methods of slab-geometry molecular dynamics computer simulation were tested, compared, and applied to the prediction of activity coefficients, interfacial electrochemistry characterization, and ion transport through a model biological channel-membrane structure. The charged-sheets, 2-D Ewald, corrected 3-D Ewald, and corrected particle-particle-particle-mesh (P³M) methods were compared for efficiency and applicability to slab-geometry electrolyte systems with discrete water molecules. The P³M method was preferred for long-range force calculation in the problems of interest and was used throughout.

The osmotic molecular dynamics method (OMD) was applied to the prediction of liquid mixture activity coefficients for six binary systems: methanol/n-hexane, n-hexane/n-pentane, methanol/water, chloroform/acetone, n-hexane/chloroform, methanol/
chloroform. OMD requires the establishment of chemical potential equilibrium across a semi-permeable membrane that divides the simulation cell between a pure solvent chamber and a chamber containing a mixture of solvent and solute molecules in order to predict the permeable component activity coefficient at the mixture side composition according to a thermodynamic identity. Chemical potential equilibrium is expedited by periodic adjustment of the mixture side chamber volume in response to the observed solvent flux. The method was validated and shown to be able to predict activity coefficients within the limitations of the simple models used.

The electrochemical double layer characteristics for a simple electrolyte with discrete water molecules near a charged electrode were examined as a function of ion concentration, electrode charge, and ion size. The fluid structure and charge buildup near the electrode, the voltage drop across the double layer, and the double layer capacitance were studied and were found to be in reasonable agreement with experimental findings.

Applied voltage non-equilibrium molecular dynamics was used to calculate the current-voltage relationship for a model biological pore. Ten 10-nanosecond trajectories were computed in each of 10 different conditions of concentration and applied voltage. The channel-membrane structure was bathed in electrolyte including discrete water molecules so that solvation, entry, and exit effects could be studied. Fluid structure, ion dynamics, channel selectivity, and potential gradients were examined. This work represents the first such channel study that does not neglect the vital contributions of discrete water molecules.
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1 INTRODUCTION

1.1 Slab Geometry

The ability to solve chemical engineering problems often hinges on the understanding of chemistry that occurs at interfacial boundaries such as in heterogeneous catalysis and vapor-liquid equilibrium. A common assumption that is used to simplify these problems requires that the system be infinite and somewhat homogeneous in two of the three directions (labeled the $x$ and $y$ directions throughout this work), with the interfacial boundary in the third direction (labeled the $z$ direction throughout this work). We refer to this physical description as an “infinite slab geometry,” or simply “slab geometry.” For our purposes, slab geometry simply means that there are abrupt changes in the system when moving in the $z$ direction and relative homogeneity when moving in the $x$ and $y$ directions. We depict a simple slab-geometry system in Figure 1.1 that caricaturizes a small section of an infinite slab of gas molecules confined between two rigid walls.

This work deals with molecular simulations performed in slab geometry. The planar walls containing the fluid present unique problems in simulations. In this work, the problems associated with simulations in slab geometry are examined and remedied where possible. Three very different but important applications of simulations in slab geometry are then studied using appropriate slab-geometry methodologies.
1.2 Molecular Dynamics

The ability to solve chemical engineering problems often requires an understanding of the chemical interactions that occur on the molecular level. Unfortunately, current molecular-level microscopy technology cannot produce a complete description of the molecular-level world. Even though specialized microscopes have produced some atomic structure images, questions about dynamics on the molecular level remain unanswered. However, molecular simulations can be used to model matter on the molecular scale, enabling simulation of angstrom-level events on a femtosecond ($10^{-15}$ second) time scale. We call these simulations molecular dynamics, or MD simulations, because the dynamical motions of model molecules are calculated from classical mechanics using model forces between the molecules. Molecular models are mathematical representations that are used in MD simulations to represent the intermolecular interactions and characteristics of the real molecules. Simple molecular models capture the fundamental molecular-level physics remarkably well.
Given a configuration of molecules and a mathematical representation of interactions between molecules in the simulation as a function of intermolecular distance and orientation, the force on each molecule can be computed and its acceleration determined. New positions and velocities for each molecule can be generated, and the system can be moved forward through time as this process is repeated. The time evolution must be done by numerical integration since the exact solution for the N-body problem is untenable.

In practice, most MD simulations of molecules treat the atomic nuclei of the molecule as intermolecular interaction centers while holding the atoms of the molecule together using rigid bond constraints. In this way, intermolecular interactions are treated as a function of inter-atomic distance only, and molecular orientation effects are treated implicitly as the molecule’s atoms move relative to each other. Usually bond-length vibrations can be neglected without much loss of simulation accuracy.

Pair-wise additivity is also generally assumed wherein multi-body effects are neglected. In other words, for the case of a three-body interaction, it is assumed that the overall interaction between molecules A, B, and C can be adequately represented by the three pair interactions, A with B, B with C, and A with C. It is assumed that the presence of C doesn’t interfere with the A-B interaction. This assumption is computationally expedient and produces relatively little error, because in general, the model parameters themselves have been regressed from experimental data using this assumption.

Working with chemical simulations rather than with real chemicals is attractive for safety reasons and cost considerations. As long as the molecular models adequately represent their real counterparts, simulations can be performed at any temperature or
pressure and in essentially any imaginable environment. It soon becomes evident that computational power is the primary limitation. Even though microprocessor technology continues to improve exponentially, demand on computational resources will always outstrip availability.

Given computational restraints, ingenious methods have been devised to make the most efficient use of CPU time. Likewise, much effort in this work has been expended on computational efficiency considerations, and several creative approaches are presented in the methodology sections.

One ingenious method for the efficient use of computational resources is the application of periodic boundary conditions. Rather than enclosing the simulated molecules in a simulated container, they are allowed to interact with the periodically repeating image of the simulation cell’s contents. Thus, a molecule on the extreme right edge of the simulation cell “feels” molecules to its right that are the image of molecules on the extreme left edge of the simulation cell. And if a molecule on the right edge of the simulation cell moves still further right, it instantaneously jumps to the left edge of the simulation cell. In this way, several hundred molecules behave as if part of a bulk fluid extending infinitely in all directions.

1.3 Interfacial Chemistry and Slab-Geometry MD

Although MD simulations are best suited for the study of a system that can be considered to extend infinitely in all directions, most important chemical and biological processes occur at interfaces. In this work, we study problems of interfacial chemistry that can be represented by a slab-geometry simulation. Simulation of slab geometry differs from regular molecular dynamics simulation in that there are specific boundary
conditions in the direction perpendicular to the slab. For example, the simulation may have a rigid wall, an artificial force field, or a phase boundary in that direction. Unfortunately, the assumptions that are regularly used in MD simulations do not necessarily apply to the case of slab-geometry MD. We will deal with several slab-geometry methodology problems in this work.

One such slab-geometry difficulty lies in the calculation of the long-range intermolecular interactions. It cannot be assumed that long-range forces for a slab-geometry system behave the same way as they do in a simple MD system. Another difficulty lies in the use of the previously mentioned periodically repeating images that are sometimes used to represent the forces exerted by the fluid beyond the primary simulation cell. In Chapter 2, we discuss these difficulties in more detail, and compare several methods of long-range force calculation in slab-geometry MD. Subsequent chapters apply the most efficient and reliable methods examined in Chapter 2 to the problems of interest discussed in the following section.

1.4 Problems of Interest

This work examines three problems of current scientific interest by slab-geometry molecular dynamics computer simulation, and is divided into three parts that represent the research fields: activity coefficient prediction, interfacial electrochemistry, and ion transport through biological channels. Although each of the three parts is very different in terms of real-world application of the knowledge gained, they are unified in that all three can be studied using slab-geometry molecular dynamics methodologies. Chapter 2 deals with the calculation of long-range intermolecular forces for slab-geometry molecular dynamics systems. Chapters 3, 6, and 10 contain introductory information
specific to each of the three research areas to which we have applied the principles of slab-geometry simulations. Specific methodology and simulation results are given in Chapters 4-5, 7-9, and 10. A brief introduction to each of the three problems is given in the following paragraphs.

Chemical engineering requires precise and specific information about the properties of pure substances and mixtures across a range of possible state points in order to design chemical processing equipment. Some of these chemical properties are easily measured and predicted, while others are difficult and expensive to measure and even harder to predict. Among the difficult properties are those that are entropic in nature, such as activity coefficients. Activity coefficients are a measure of component non-idealities in a mixture. In other words, they give information about how the activity of a given chemical species differs in the mixture from the ideal-solution activity which is its concentration. Like most thermophysical properties, the chemistry that determines this non-ideality described by the activity coefficient occurs at the molecular-level and is therefore best examined at that level. As will be shown later in this chapter and in Chapter 3, molecular dynamics is well suited for the prediction and study of activity coefficients and related properties.

Molecular-level electrochemistry can also be studied efficaciously by molecular dynamics. Questions that electrochemistry researchers have grappled with for decades are beginning to be answered by simulations of model systems. Although simplified models that neglect the molecular nature of solvents have yielded increased understanding of electrochemical phenomena, it is becoming increasingly clear that discrete solvent molecules must be included in order to further advance our
understanding. Ion solvation effects, ion charge effects, ion size effects, and temperature
effects are all examinable by molecular simulation. In this study, we explore the voltage
drop across electrolyte solution double layers at charged electrode surfaces. Specifically,
using molecular dynamics we look at double-layer capacitance as a function of
temperature, the effect of ion concentration and electrode charge on the voltage drop
across the double layer, and how ion size affects fluid structure near the electrode surface.
A more thorough introduction is given in Chapter 6.

Perhaps more fascinating to the scientific community at large is the molecular-
level study of critical life processes. Here, we study one such process that is found in
every living organism: the transport of ions through channels found in cell membrane
walls. Ion-selective channels regulate a myriad of biological processes. Our ability to
manipulate these processes is directly tied to our understanding of what is happening on
the molecular-level. Again, this problem is well suited for study by molecular dynamics.
2 LONG-RANGE FORCES IN SLAB GEOMETRY

2.1 Intermolecular Coulombic Interactions

Many molecular models include point charges placed at sites (atomic centers or the center of the heavy atom of a group of atoms) that represent the average electron cloud distribution about the molecule. These sites interact with sites on other molecules according to Coulomb’s Law,

\[ F_{ij} = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}^2}, \]

where \( F_{ij} \) is the force vector acting between the two sites along the vector \( r_{ij} \) that points from site \( i \) to site \( j \), \( q_i \) is the point charge at site \( i \), \( q_j \) is the point charge at site \( j \), and \( \varepsilon_0 \) is the permittivity constant. Although the force interactions dampen quickly with distance (\( \sim r^{-2} \)), the number of interactions grows in proportion to the volume (\( \sim r^3 \)), yielding a net contribution to the total force acting on site \( i \) proportional to the contributing distance (\( \sim r \)). But the forces acting on a site perfectly counterbalance when the charge distribution around that site is radially symmetric. This is certainly not true at small \( r \), and only approximately true at large \( r \), in certain cases. If one assumes radial symmetry of the charge distribution beyond a cutoff distance, \( r_{\text{cut}} \), interactions beyond \( r_{\text{cut}} \) can be neglected. But many slab-geometry systems (especially those studied in Chapters 6-10) feature charge build-up at an interface, entirely invalidating the radially symmetric charge distribution assumption. Therefore, we must consider long-range coulombic interactions.
If we took a brute force approach to calculating the coulombic interactions, we
would compute the force acting on particle $i$ according to

$$F_i = \sum_{j=1}^{\infty} \frac{q_i q_j}{4 \pi \varepsilon_0 r_{ij}^2}.$$  \hfill (2.2)

This is clearly impossible because it would require simulating an infinite number of
molecules.

### 2.2 Long-range Force Calculation Methods

Many alternatives have been proposed to approximate long-range interactions for
systems with slab geometry, each varying in reliability and computational demand.$^{1-10}$ In
Section 2.3, we will compare two of these techniques: the 3-D Ewald summation method,
with the correction term, (EW3DC) as outlined by Yeh and Berkowitz,$^5$ and the charged-
sheets method (CS), which was originally proposed by Torrie and Valleau.$^6-8$

Besides EW3DC and CS, other methods for approximating long-range
interactions for systems of slab geometry have been developed. Pollack and Glosli$^{10}$
indicate that the particle-particle-particle-mesh method ($\text{P}^3\text{M}$) and the fast multipole
method (FMM) can both be adapted to slab geometry, and that both are generally more
efficient than Ewald summation methods. They favor $\text{P}^3\text{M}$ as the most efficient and the
easiest to implement of the methods. We discuss application of the $\text{P}^3\text{M}$ method to slab
geometry in Section 2.4.
2.3 Comparison of the Charged-Sheets and the Corrected 3-D Ewald Methods

2.3.1 The 3-D Ewald Summation with Slab-Geometry Correction

Perhaps the most widely used method for the approximation of long-range potentials acting beyond the primary cell is the Ewald sum method.\textsuperscript{11-12} This method was developed to model long-range interactions in a periodically repeating crystalline structure. Although the method introduces periodicity into what should be an amorphous system (see Figure 2.1), it has been shown to model the structure and properties of real liquids reasonably well when a primary cell of sufficient size is used (i.e., on the order of 100 - 10,000 particles).\textsuperscript{6,11-12}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ewald_fluid.png}
\caption{2-D rendition of an Ewald fluid that models an infinite amorphous fluid as a periodically repeating fluid.}
\end{figure}

Even though the Ewald sum method was originally developed for systems that are periodic in all three directions, Parry and others\textsuperscript{1-3} have developed the equations
necessary for a slab geometry; i.e., a 2-D Ewald method (EW2D). The equation for the total Coulombic energy is given by

\[ U = \frac{1}{4\pi \varepsilon_0} \sum_{\mathbf{m}} \sum_{i=1}^{N} \sum_{j=1}^{N} q_i q_j \frac{1}{2} \frac{\text{erfc}(\alpha \mathbf{r}_{ij} + \mathbf{m})}{|\mathbf{r}_{ij} + \mathbf{m}|} + \frac{1}{4\pi \varepsilon_0} \sum_{i=1}^{N} \sum_{j=1}^{N} q_i q_j \sum_{h>0} \frac{\pi \cos(\mathbf{h} \cdot \mathbf{r}_{ij})}{2hA} \]
\[ \times \left\{ \exp(hz_{ij}) \text{erfc}\left(\frac{\alpha z_{ij} + \frac{h}{2\alpha}}{2}\right) + \exp(-hz_{ij}) \times \text{erfc}\left(-\frac{\alpha z_{ij} + \frac{h}{2\alpha}}{2}\right) \right\} \]
\[ - \frac{1}{4\pi \varepsilon_0} \sum_{i=1}^{N} \sum_{j=1}^{N} q_i q_j \left[ \frac{\pi}{A} \text{erf}(\alpha z_{ij}) + \frac{1}{\alpha \sqrt{\pi}} \exp[-(\alpha z_{ij})^2] \right] - \frac{1}{4\pi \varepsilon_0} \frac{\alpha}{\sqrt{\pi}} \sum_{i=1}^{N} q_i^2, \]

where \( \mathbf{m} \) is the lattice vector \((m_xL_x, m_yL_y, 0)\) with cell integers \(m_x\) and \(m_y\) and simulation cell lengths of \(L_x\) and \(L_y\) in the \(x\) and \(y\) directions, \(\mathbf{h}\) is the reciprocal lattice vector given by \(((2\pi m'_x)/L_x, (2\pi m'_y)/L_y, 0)\) with integers \(m'_x\) and \(m'_y\), \(A\) is the surface area of the cell at the slab surface, \(L_x \times L_y\). The number of \(\mathbf{m}\) and \(\mathbf{h}\) vectors and \(\alpha\) are adjustable parameters chosen for computational efficiency. The dagger following the first summation symbol indicates the omission of the \(i = j\) term when \(\mathbf{m} = 0\); i.e., direct self-interactions within the primary cell are excluded. The force on each particle is equal to the negative of the gradient of the potential energy contribution for that particle:

\[ F_i = -\nabla U_i. \tag{2.4} \]

Spohr\(^4\) showed that the regular 3-D Ewald method (EW3D) almost reproduces the EW2D results, provided that the box length in the \(z\) direction is about five times larger than the box length in the lateral directions and that there is empty space of sufficient thickness in the basic periodic box. The EW3D method is computationally more efficient than EW2D since it does not involve a double sum in reciprocal space. Recently Yeh and
Berkowitz\textsuperscript{5} have shown that the EW3D can be modified to produce results in even better agreement with EW2D. The potential energy equation for EW3D is

\[ U = \frac{1}{4\pi\varepsilon_0} \sum_{\mathbf{n}} \sum_{i,j}^N q_i q_j \left( \frac{1}{2} \frac{\text{erfc}(\alpha |r_{ij}| + \mathbf{n})}{|r_{ij}| + \mathbf{n}} + \frac{1}{\varepsilon_0 V} \sum_{k > 0} \frac{1}{k^2} \exp \left( \frac{-k^2}{4\alpha^2} \right) \right) \times \left( \sum_{i=1}^N q_i \cos(\mathbf{k} \cdot \mathbf{r}_i) \right)^2 + \left( \sum_{i=1}^N q_i \sin(\mathbf{k} \cdot \mathbf{r}_i) \right)^2 \right) - \frac{1}{4\pi\varepsilon_0} \frac{\alpha}{\sqrt{\pi}} \sum_{i=1}^N q_i^2, \]  

(2.5)

where \( V \) is the simulation cell volume given by \( L_x \times L_y \times L_z \), \( \mathbf{n} \) is the lattice vector given by \((n_x L_x, n_y L_y, n_z L_z)\) with integers \( n_x, n_y, \) and \( n_z \), \( \mathbf{k} \) is the reciprocal lattice vector given by \( ((2\pi n'_x)/L_x, (2\pi n'_y)/L_y, (2\pi n'_z)/L_z) \) with integers \( n'_x, n'_y, \) and \( n'_z \). Again, the dagger indicates the omission of the \( i = j \) term when \( \mathbf{n} = 0 \).

The EW3DC method consists of the modification of EW3D to account for the slab geometry, and necessitates the elongation of the primary cell in the \( z \) direction (perpendicular to the slab), and the addition of a correction term to remove the forces due to the net dipole of the periodically repeating slabs. Walls are erected in the \( x-y \) plane that confine the fluid to a fraction of the simulation cell. An empty space of three to five times the space of the fluid-occupied region is left between the repeating slabs to dampen out inter-slab interactions. With this large empty volume between the slabs, only the leading dipole term needs to be removed in order to isolate each of the individual slabs.
This dipole correction term consists of an additional energy term

$$U_c = \frac{1}{2\varepsilon_0 V} M_z^2,$$  \hspace{1cm} (2.6)

which leads to the z-component force given by

$$F_{i,z} = -\frac{q_i}{\varepsilon_0 V} M_z,$$  \hspace{1cm} (2.7)

where $M_z$ is the net dipole moment of the simulation cell in the $z$ direction.

### 2.3.2 The Charged-Sheets Method

Torrie and Valleau\textsuperscript{6-8} suggest an alternative approach to calculating long-range coulombic interactions for slab-geometry systems that is computationally inexpensive, easy to implement, and does not introduce any periodicity into the system. Only long-range forces in the $z$ direction are approximated, and long-range forces in the $x$ and $y$ directions are assumed to be negligible. We shall call this method the charged-sheets method (CS) because of its use of infinite sheets of charge to represent long-range interactions in the $z$ direction beyond the primary cell (see Figure 2.2). The original CS by Torrie and Valleau\textsuperscript{7} uses uniformly spaced sheets with a surface charge that corresponds to a time- and space-averaged charge distribution of the central cell. Since information from previous configurations is used, calculations performed using the original CS are not rigorous Markov-chains. Here, we use a more rigorous version of CS as given by Boda, Chan, and Henderson,\textsuperscript{9} where each particle has a corresponding charged sheet representing charges acting from outside of the primary cell.
For a primary cell with \( L_x = L_y = L \), the potential energy calculated using CS is given by

\[
U = \frac{1}{4\pi\varepsilon_0} \left\{ \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} q_i q_j \left[ r_{ij} - \frac{\pi}{2} \right] + \sum_{i=1}^{N} \sum_{j=1}^{N} [u(i, j, \infty) - u(i, j, L)] \right\},
\]  

\[2.8\]

\[
u(i, j, W) = \frac{q_i q_j}{W^2} \left\{ 4W \ln \left( \frac{0.5 + r_1(z, W)}{r_2(z, W)} \right) - 2|E(z, W)| \right\},
\]

\[2.9\]

\[
E(z, W) = 2\pi - 4 \arctan \frac{4|E(z, W)|}{W},
\]

\[2.10\]

\[
r_1(z, W) = \sqrt{0.5 + \left( \frac{z}{W} \right)^2},
\]

\[2.11\]

\[
r_2(z, W) = \sqrt{0.25 + \left( \frac{z}{W} \right)^2}.
\]

\[2.12\]

In the above, \( z = z_i - z_j \) and is the \( z \) component of the distance between charges \( i \) and \( j \) and \( W \) is a dummy variable that can be replaced with \( L \) or \( \infty \).

Figure 2.2. Cartoon of a central simulation cell surrounded in the \( x \) and \( y \) directions by infinite sheets of charge that exert \( z \)-directional force on the charged particles that are in the simulation cell. (Some of the sheets have been cut away for easier visualization.)
While CS is much less computationally demanding than EW3DC, it should be recognized that it was developed for systems without solvent molecules, and has usually been applied to larger simulation cells in which screening within the primary cell is more effective. With the exception of a study by Boda et al., this is the first study of which we are aware in which CS is used for a system containing discrete polar molecules. In the study of Boda et al., difficulties were encountered in dissolving the ions in the dipolar hard-sphere solvent. Those difficulties might be due, in part, to the use of CS.

2.3.3 Simulation Details

In order to test the effectiveness of EW3DC and CS, simulations of idealized ions using both methods were performed on systems with a molecular solvent and compared. The SPC/E model for water was chosen as the solvent and the idealized ions were assigned Lennard-Jones (LJ) parameters identical to the LJ parameters for the oxygen-oxygen interaction in the SPC/E model, as well as a charge of $\pm e$, where $e$ is the magnitude of the electron charge.

All simulations were performed at 298.15 K with a constant ratio of 25 water molecules per anion-cation pair (~3 M). A wall of LJ atoms was held rigid at $z = 0$ Å and a wall of LJ atoms was held rigid at $z = 27.58$ Å. Wall atoms were placed on a square lattice, at 1.5 Å intervals, and each ion was given an LJ $\sigma = 1.5$ Å, and an LJ $\epsilon/k = 50$ K. In addition, the walls were charged to 0.1 C/m$^2$ by giving each wall atom a partial charge of $\pm 0.0140434$ e. Initial configurations were chosen as a random distribution of water molecules, anions, and cations.

Two system sizes were tested using both EW3DC and CS. The first, smaller system consisted of 600 water molecules, 24 cations, and 24 anions. The slab geometry
was $25.5 \times 25.5 \times 27.58$ Å, and 289 ions were fixed in place on a square lattice to represent each wall. The second, larger system consisted of 1200 water molecules, 48 cations, and 48 anions with a slab geometry given by $36.062 \times 36.062 \times 27.58$ Å. In this case, the square lattice forming the walls was rotated 45 degrees so that the wall atoms would line up on the periodic boundaries; 578 cations were fixed at $z = 0$ Å, and 578 anions were fixed at $z = 27.58$ Å to form the walls. The length of the periodic box in the $z$ direction was set at 78 Å in EW3DC calculations for both system sizes.

For each simulation size and method, at least 10 simulations were performed, each from a unique random configuration of the mobile particles. Each simulation lasted approximately 200 ps after approximately 20 ps of equilibration. Results shown below are averages over the simulation runs.

### 2.3.4 Simulation Results

Density profiles, as obtained using the two different system sizes and two different long-range-force calculation methods, are shown in Figs. 2.3 and 2.4 (cation distribution and anion distribution, respectively). As can be seen, the four cases are not equivalent. First of all, we note that the EW3DC runs do show considerably less contact adsorption than the CS runs.

The EW3DC results show a slight system size dependence, mostly in the first layer of cations and anions, while the CS results show a strong dependence on system size, especially in those first layers. Large peaks of anions and cations appear near the walls for the smaller simulation results obtained using CS. As the system size is increased, the magnitudes of these peaks diminish and begin to resemble the EW3DC results.
Figure 2.3. Cation density profiles for the four cases. The traces are for the smaller system using EW3DC (thin solid line), larger system using EW3DC (thick solid line), smaller system using CS (thin dotted line), and larger system using CS (thick dotted line).

Figure 2.4. Anion density profiles for the four cases. The traces are for the smaller system using EW3DC (thin solid line), larger system using EW3DC (thick solid line), smaller system using CS (thin dotted line), and larger system using CS (thick dotted line).
2.3.5 Forces between Two Particles

To investigate the cause of the peak anomalies in the CS results near the wall surfaces, calculations of the total force on individual particles were made. This kind of direct comparison of forces has been utilized previously as a simple and effective way to elucidate the differences between various long-range force calculation methods.\textsuperscript{4,5,15,16} Figure 2.5 shows a comparison between the forces acting in the $z$ direction between two oppositely charged particles as computed using a bare coulomb potential, EW2D, EW3DC, and CS. Here, the same box geometry as Spohr\textsuperscript{4} and Yeh and Berkowitz\textsuperscript{5} was used for comparison purposes ($L = L_x = L_y = 18$ Å and $L_z = 90$ Å). The EW3DC and EW2D methods give excellent agreement in this case, while CS is almost, but not exactly, the same. Figure 2.6 shows a comparison of forces parallel to the slab surface ($F_y$) as calculated by EW3DC and CS, with the same box geometry as before. As can be seen, the forces calculated by EW3DC smoothly go to zero at $L/2$. This is because periodically repeating images of the particles are equidistant in both directions for this case, and therefore their forces perfectly counterbalance. On the other hand, CS produces a discontinuous jump in the calculated force as the minimum-image convention is applied at $L/2$, because CS uses truncation in the $x$ and $y$ directions, rather than periodically repeating images. Both methods are only approximations to the infinitely extended non-periodic slab. However, the discontinuous step in the lateral force of CS, the size of which depends on system size, is less satisfactory than the behavior of EW3DC, where the lateral force approaches zero at $L/2$. 
Figure 2.5. Comparison of the force acting between two oppositely charged point charges in a two-dimensionally periodic system as calculated using EW2D or EW3DC (———), CS (×), and the bare coulombic potential (--------). The scale is chosen for comparison with Fig. 4 of Ref. 4 and Fig. 8 of Ref. 5.

Figure 2.6. Comparison of the \( y \) component of force (parallel to the slab surface) acting between two oppositely charged point charges as calculated using EW3DC (———) and CS (×).
2.3.6 Discussion of the Comparison between CS and EW3DC

The CS simulation results clearly show strong system size dependence. One simple explanation for this observation is that the forces in the $x$ and $y$ directions as calculated by CS are discontinuous at $0.5L$. Since the comparison is between two systems, one containing 600 water molecules and one containing 1200 water molecules, of different $L$, the magnitude and location of the force discontinuity is not the same.

The discussion of the interaction forces between two point charges (Figs. 2.5 and 2.6) indicates that the large size dependence of CS is not so much due to the force in the $z$ direction as those in the $x$ and $y$ directions. Obviously, the larger the discontinuous jump in the lateral forces, the larger is the effect on the density profiles in Figs. 2.3 and 2.4. Although we did not explicitly study larger CS systems, we expect CS to yield results more similar to the EW3DC case as $L$ increases.

It is noteworthy that the forces in the $x$ and $y$ directions acting between an ion pair as calculated by EW3DC are also dependent upon the size of the simulation cell, but are not discontinuous at $0.5L$. The artificial periodicity in the $x$ and $y$ directions causes this problem, and is endemic to the infinite slab geometry. The slight discrepancy between the 600-water-molecule and 1200-water-molecule EW3DC density profiles is perhaps due to this periodicity. Torrie and Valleau\textsuperscript{7} likewise blame “spurious periodicity” for various unphysical results produced by Ewald-type lattice sums.

Periodicity in the $x$ and $y$ directions would not be eliminated by using EW2D instead of EW3DC. Yeh and Berkowitz\textsuperscript{5} clearly demonstrate excellent agreement between EW2D and EW3DC in their work. Based on their conclusions, we can safely assume that EW2D calculations would show good agreement with our EW3DC
calculations, and that system size effects that are observable in EW3DC calculations would also be evident in EW2D calculations.

As pointed out earlier, previous applications of CS have been limited to primitive model calculations with no explicit solvent molecules at low ionic concentration (except for the study by Boda et al.\textsuperscript{14}). Neglect of explicit solvent molecules allows for use of a much larger simulation cell. Coulombic interactions for such a system are “screened” and therefore have much shorter-range effects, which explains why earlier studies involving CS produced satisfactory results which were shown to be reasonably independent of system size.\textsuperscript{6-8} A simulation that includes solvent particles requires roughly two orders of magnitude more particles in order to simulate a system with the same number of ions as that of a system with solvent treated through the dielectric parameter. Thus, a much smaller simulation box must be used, given a fixed amount of available computation time. Smaller simulation boxes require a shorter truncation distance for the long-range interactions in the $x$ and $y$ directions. These truncations, in turn, can cause a distortion in the $z$-direction density profiles as seen in Figs. 2.3 and 2.4. Correct calculation of the long-range forces in the $x$ and $y$ directions using CS for a system that includes solvent molecules would necessitate the use of a very large system size --- on the order of 10,000 solvent molecules or more --- and becomes computationally prohibitive.

Performing molecular dynamics simulations using discontinuous forces between particle pairs as necessitated by CS also causes an artificial heating that must be counteracted by a thermostat.\textsuperscript{17-18} In addition, the unnatural discontinuity requires the use of an unusually small time step to step through the discontinuity.
2.3.7 Conclusion of the Comparison between CS and EW3DC

Due to the problems associated with using CS for the approximation of long-range forces in the $x$ and $y$ directions in electrolyte systems containing polar solvent molecules, its use is generally not recommend for systems containing explicit water molecules. Although EW3DC is computationally more demanding than CS for a system of equal size, there is no abrupt minimum-image discontinuity in the $x$ and $y$ directions. Thus, we conclude that EW3DC is preferred over CS for use in simulations that contain solvent molecules. However, special circumstances may warrant use of CS in order to save computer time (i.e., interactions between wall particles and bulk particles where $x$ and $y$ symmetry cancels any force discontinuities).

Even with EW3DC, caution must be used in system size selection in order to not introduce artifacts into simulation results. Figures 2.3 and 2.4 show that EW3DC does exhibit slight system size dependence. Due to the representation of an amorphous system by a periodic fluid as is required by EW3DC, we recommend the use of a simulation cell that is as large as feasible in order to mask the periodicity.

2.4 The Slab-Geometry-Corrected $P^3M$ Method

Recently, mesh routines have been developed,\textsuperscript{19-24} which present a way to perform long-range Coulombic force calculations that is more efficient than the traditional Ewald summation method. Of the mesh routines, the particle-particle-particle-mesh ($P^3M$) routine developed by Hockney and Eastwood\textsuperscript{19} has been shown to be the most efficient for a given accuracy level.\textsuperscript{23-24} In this work, we modify $P^3M$ for application to slab geometry, as suggested by Pollock and Glosli\textsuperscript{25} and similar to the 3-D Ewald summation modification used by Yeh and Berkowitz.\textsuperscript{5} We show that this
implementation of the slab-“corrected” P$^3$M method, or P$^3$MC as we shall call it, gives results in very good agreement with regular Ewald summation methods, yet at a fraction of the cost.

Many methods for approximating long-range coulombic interactions have been devised, including the charged-sheets method,$^6$-9 the modified reaction field,$^{26}$-29 Ewald sums,$^1$-5,$^{30}$-31 the fast multipole method,$^{10}$,$^{32}$-$^{34}$ and mesh methods.$^{19}$-$^{24}$ In Section 2.3, we showed that the charged-sheets method is inadequate for correctly modeling strong long-range coulombic interactions for systems with discrete solvent molecules. Ewald summations appear to be adequate, yet computationally expensive, and multipole methods are even more costly for systems of a reasonable size.$^{10}$ Mesh methods, particularly P$^3$M, present the most flexible and reliable alternative.$^{10}$,$^{23}$-$^{24}$ Deserno and Holm give an excellent analysis of the various mesh methods,$^{23}$ along with useful recommendations for P$^3$M implementation.$^{24}$ We have followed their recommendations and adopted their notation in the following.

### 2.4.1 P$^3$MC Implementation

We demonstrate implementation of the P$^3$MC method using the same system set-up as in the simulations of Section 2.3.3. We use Fourier space, or $i\mathbf{k}$, differentiation to calculate the intermolecular forces from the electrostatic energies, and a seventh-order assignment scheme ($P = 7$) to assign the charges to the mesh. Calculation of the optimal influence function, $\hat{G}_{\text{opt}}$ of Hockney and Eastwood,$^{19}$ is done at the beginning of each run and therefore presents no additional run-time overhead. The cutoff for the Lennard-Jones (LJ) interactions, and the real-space Coulombic interactions is set at $r_{\text{max}} = 10$ Å, and the mesh size is set at $16 \times 16 \times 64$ in the $x$, $y$, and $z$ directions, respectively. With a
corresponding fixed box size of 25.5 Å × 25.5 Å × 85.1232 Å, and the total number of ions and water molecules fixed at 1000, the optimum value of \( \alpha \) is estimated to be 0.3007. We estimate the average error in our force calculations to be on the order of \( 10^{-5} \) dimensionless force units, according to the estimation method and dimensionless force units of Deserno and Holm.\(^{23}\) Although not as precise as an Ewald sum, the amount of error introduced by this implementation of \( P^3M \) is very reasonable. Extreme accuracy is not needed, especially when considering other possible sources of error in the MD simulation, such as the use of a randomly fluctuating thermostat, or a discrete time step (e.g., 2.5 fs).

In order to account for the slab geometry, we include an empty space, equal to the size of the fluid-occupied space, between repeating slabs of fluid, and a correction term to damp out inter-slab interactions. With the implementation of this correction, the 3-D, periodically repeating simulation closely approximates the simulation of an isolated 2-D slab of finite thickness, as shown by Yeh and Berkowitz.\(^5\)

### 2.4.2 \( P^3MC \) Reliability Tests

To confirm the reliability of our \( P^3MC \) implementation, we compare calculated forces with those calculated using the EW3DC method. In particular, we calculate the force between two oppositely-charged particles along with their periodic images in slab geometry. For easy comparison, we consider the same case as presented in Figs. 2.5 and 2.6. As seen in Figs. 2.7 and 2.8, the \( P^3MC \) and EW3DC calculations are visually indistinguishable. For Fig. 2.7, the difference between the two calculations was less than 0.013\% in all cases, with an average difference of 0.002\%. Even though deviation was up to 1\% in the case of Fig. 2.8, percent deviation is less meaningful here, since the
absolute value of the force approaches zero. The absolute difference between the two calculations on the scale of Fig. 2.8 was always less than $10^{-4}$, which represents a very small amount of error. We have also performed a test case simulation of the smaller system size as described in Section 2.3.3, and we found the ion and water density profiles to be in good agreement with the EW3DC results presented in Section 2.3.4.

With the chosen mesh parameters, our P$^3$M algorithm was approximately four times faster than the corresponding Ewald algorithm. It should be noted that the flexibility of P$^3$M allows for more exact force calculations if desired. The use of a tighter mesh would clearly be more precise, but more CPU intensive.

![Graph](image)

Figure 2.7. Comparison of the force acting between two oppositely charged point charges in a two-dimensional-periodic system as calculated using EW3DC (line), and P$^3$MC (diamonds). The scale is chosen for comparison with Fig. 2.5.
Figure 2.8. Comparison of the $y$ component of force (parallel to the slab surface) acting between two oppositely charged point charges as calculated using EW3DC (line) and P$^3$MC (diamonds). The scale is chosen for comparison with Fig. 2.6.

2.5 Conclusion

The P$^3$MC method is a well-defined and efficient way to model coulombic interactions for large slab-geometry electrolytic systems. Its flexibility and adaptability make it an attractive way to account for long-range intermolecular interactions at the accuracy level and speed that the user desires. This method is clearly the best of those currently available.

The P$^3$M method without the correction term can be used for simulations where it is adequate to model the system as non-isolated periodically repeating slabs of fluid with periodic boundary conditions in all three directions, such as will be discussed in Chapters 3-5 and Chapters 10-12. When it is necessary to model the system as an isolated slab of fluid, the periodic boundary condition is not applied in the direction perpendicular to the
slab surface, and the P\(^3\)MC method is used (P\(^3\)M with the correction term). Such is the case for the work described in Chapters 6-9.
References


3 OMD BACKGROUND INFORMATION

3.1 The Prediction of Activity Coefficients

For decades, scientists and engineers have sought to predict activity coefficients and excess thermodynamic properties based upon molecular-level chemical characteristics. Accurate excess properties are essential to today's chemical process industry. The design and control of chemical processing equipment such as separation units, reactors, and heat exchangers can be no better than the estimated values of the thermodynamic properties used.

But how can accurate estimates for the values of chemical properties for thousands of pure substances and every conceivable mixture at every conceivable state point be obtained? It is unlikely that it could ever be done entirely by experiment. The ability to predict the values of thermodynamic properties with knowledge of only the most fundamental characteristics of the components involved is the most desirable way to cover the entire spectrum of possibilities.

Accurate estimates of activity coefficients are essential to the chemical process industry and are key to the description of other excess thermodynamic properties. It is therefore very desirable to be able to accurately predict them and the temperature, composition, and pressure dependencies that link them to the other excess properties. For example, partial molar excess enthalpy, $\overline{H_i}^{ex}$, and partial molar excess volume, $\overline{V_i}^{ex}$, are
related to the temperature and pressure dependencies of activity coefficients, $\gamma_i$, as follows:

$$\left( \frac{\partial \ln \gamma_i}{\partial T} \right)_{P_x} = -\frac{\overline{H}^e_i}{RT^2}, \quad (3.1)$$

$$\left( \frac{\partial \ln \gamma_i}{\partial P} \right)_{T_x} = \frac{\overline{V}^e_i}{RT}, \quad (3.2)$$

Because of their importance, activity coefficients have been extensively studied.

Data compilations of activity coefficients have been obtained from binary vapor-liquid equilibria for use by industry. Extensive work on correlation of these activity coefficients and study of the theory of mixture non-idealities have produced correlations that can represent the composition dependence of activity coefficients using only two or three parameters regressed from the experimental data. However, no accurate method for the prediction of activity coefficients from first principles, without the use of system-specific adjustable parameters, has been developed. To date, group contribution methods come the closest to the goal of being both predictive and accurate. Group contribution methods are based on the ad hoc form of a correlation equation, but use additive, tabulated constants for the interactions between the various constituent chemical groups of the compounds' structures to replace the adjustable parameters in the correlation. These tabulated group contributions were themselves obtained from a large global database regression of numerous compounds.

The UNIFAC (Universal Functional Group Activity Coefficient) method is the most commonly used group contribution method for predicting activity coefficients in use today. When experimental data and correlations are unavailable, designers generally fall back on this purely predictive method. Unfortunately, the method yields results of
inconsistent accuracy since molecular arrangement of the groups, induction effects, and simultaneous multiple-site interactions are completely ignored. Furthermore, UNIFAC does not model the temperature dependence of activity coefficients with accuracy sufficient to obtain excess enthalpy data from Equation 1. Independent sets of regressed parameters are required for the prediction of excess enthalpy and excess Gibbs energy.

As computer speed and availability continue to increase, the possibility of predicting thermodynamic properties by simulating substances on the molecular level has gained acceptance. These simulations use models of real molecules to mimic the molecule's size, shape, charge distribution, and interactions. Various methods for determining thermodynamic properties can be employed based upon how such simulated molecules interact with each other. Thermodynamic integration, particle insertion, particle growing, and osmotic molecular dynamics (OMD) are the methods currently en vogue for the prediction of entropic-related properties by computer simulation. This work focuses on the OMD method, which requires a simulation cell of slab geometry.

With the advent of high-speed computers and the development of molecular-based simulation strategies, the question remains: can accurate mixture activity coefficient information be predicted from molecular simulations? The goal of this work is development of such a molecular-based predictive method. Furthermore, because the method is grounded in rigorous physics, it is anticipated that its capabilities would not only include quantitative calculations of activity coefficients in binary and multi-component mixtures, but also that those values would be thermodynamically consistent. This would mean that predicted values would exhibit the correct temperature and pressure dependence and that related excess properties (see Eqs. 1 and 2) could also be
obtained. The following sections review the basic concepts, advantages, and disadvantages of several methods that predict activity coefficients or phase equilibrium. Section 3.2 deals with traditional approaches to phase equilibrium determination while Section 3.3 deals with computer simulation methods.

3.2 Traditional Methods of Activity Coefficient Determination

3.2.1 Experimental Measurement

By far the most common and most accurate way to determine activity coefficients is by measuring them experimentally. Methods of experimental determination include measurement of vapor-pressure lowering, boiling point elevation, freezing point depression, and osmotic pressure. However, the most common experimental techniques for activity coefficient determination involve measurements of phase equilibrium (generally liquid-liquid or vapor-liquid).

By measuring the system pressure, temperature, liquid mole fractions, and vapor mole fractions of a vapor-liquid equilibrium system, the experimentalist can determine activity coefficients using the following vapor-liquid equilibrium relation,

\[ \gamma_i = \frac{y_i P \phi_i}{x_i P_{i, \text{sat}} \phi_{i, \text{sat}} PF_i}, \]  

(3.3)

where \( \gamma_i \) is the activity coefficient of component \( i \), \( P \) is the system pressure, \( P_{i, \text{sat}} \) is the saturation vapor pressure of component \( i \) at the system temperature, \( \phi_i \) is the vapor phase partial fugacity coefficient, \( \phi_{i, \text{sat}} \) is the saturation vapor phase fugacity coefficient, \( PF_i \) is the Poynting correction factor, and \( x_i \) and \( y_i \) are the liquid and vapor mole fractions of component \( i \), respectively. The mole fractions, system temperature, and system pressure
can be measured directly. The variables $\phi_i$ and $\phi_{i\text{sat}}$ can be calculated using an equation of state that adequately represents the vapor phase, $P_{i\text{sat}}$ can be obtained from vapor pressure correlations, and $PF_i$ is obtained from

$$PF_i = \exp\left[\int_{P_{i\text{sat}}}^{P} \left(\bar{V}_{i}^{(L)} / RT\right) dP\right],$$

(3.4)

where $\bar{V}_{i}^{(L)}$ is the liquid molar volume of pure component $i$. The Poynting correction factor, $PF_i$ can be taken as unity or can be estimated given the variation of the liquid molar volume with pressure.

Activity coefficients determined in this manner can be trusted to the degree suggested by the combined error associated with the collected data, the equations of state, the vapor pressure correlations, and the liquid molar volume correlations. The activity coefficients can be verified for consistency by using various forms of the Gibbs-Duhem relation:

$$\sum x_i d \ln \gamma_i = -\frac{H_{ex}}{RT^2} dT + \frac{\bar{V}_{ex}}{RT} dP,$$

(3.5)

For example, for a binary system data can be checked for consistency using the integral test for isothermal data,

$$\int_{0}^{1} \ln \frac{\gamma_1}{\gamma_2} dx_1 = 0,$$

(3.6)

where the excess volume term has been neglected. Huge data banks of thermodynamically-consistent, experimentally-determined activity coefficients attest to the importance of accurate, reliable values for use in industrial design. Experimentally-determined activity coefficients are by far the most widely used in the chemical process industry today.
Once determined, activity coefficient data are generally fitted to one of the more popular correlation equations: Margules, van Laar, Wilson, T-K-Wilson, NRTL, or UNIQUAC. These equations vary widely in their complexity and ranges of applicability. However, the Wilson and NRTL equations are considered the best overall correlation equations.

Activity coefficients obtained from experimental measurement and fitted to empirical correlations are sufficiently accurate for most industrial applications. The question then becomes, why not continue to determine activity coefficients in this manner? The measurements are expensive, labor intensive, and not free of error. Experimentally-determined activity coefficients give limited information about why non-idealities are observed. Moreover, activity coefficient data cannot be extrapolated far from the state point at which the data were taken, and they are difficult or impossible to obtain at extreme temperatures and pressures. Experimental determination of activity coefficients for each component in all mixtures across the range of possible temperatures and pressures would be a monumental task indeed.

3.2.2 Group Contribution Methods

Is it possible to predict activity coefficients based on the constituent components' sizes and interaction contributions? Many macroscopic thermodynamic properties such as heat capacity and enthalpy of formation have been successfully linked to molecular structure. Researchers have adopted a similar strategy in an attempt to predict activity coefficients. The most successful methods are the ASOG \(^1\) and the UNIFAC methods. \(^2\) These methods are readily programmable, and are able to yield activity coefficients from minimal information.
The ASOG method predicts a component's activity coefficient based upon its size relative to the other components and upon a summation of temperature-dependent group-interaction contributions. The UNIFAC method follows a similar strategy and is more widely used. Both methods require empirical parameters representing all of the possible group interactions present in the mixture, and because more parameters have been regressed for the UNIFAC method, it is generally the favored method.

Group contribution methods have found widespread use in activity-coefficient estimation when more reliable experimental data are unavailable. Activity coefficients obtained in this fashion are not always of acceptable accuracy. Serious design of chemical process equipment requires a more accurate approach that incorporates effects due to shape, simultaneous multiple-site interactions, and interactions based upon the specific mixture rather than generalized interactions. A predictive method that can distinguish between shape differences (such as in \(n\)-hexane and cyclohexane, or \(p\)-dichlorobenzene and \(o\)-dichlorobenzene); include induction effects due to the presence in the molecule of multiple groups; predict activity coefficients at different temperatures, pressures, and compositions; and also account for other important natural subtleties found in non-ideal multi-component mixtures is highly desirable.

3.3 **Activity Coefficient Prediction by Computer Simulation**

Computer simulations appear to be a viable way to predict thermodynamic properties. Computer simulations can model size, shape, and induction effects. Models used in the simulations mimic real fluids and can therefore represent multi-site simultaneous interactions, multi-component mixtures, and temperature and pressure
effects. As noted in Chapter 1, computer simulations are only limited by available computational power and the ability of the mathematical models to represent real fluids.

It is probable that precise activity-coefficient predictions can be obtained through computer simulations. Computer simulations have no difficulty with multi-component systems and are unhindered at extreme temperatures and pressures. Simulations present a viable alternative method for predicting thermodynamic properties, and show great potential as a means of providing a clean and efficient way to link molecular structure to excess properties.

Some thermodynamic properties are easily related to the mechanical variables of the system through statistical mechanics. For example, temperature is related to the average kinetic energy of the molecules. Additionally, it has been extensively shown that non-entropic properties can be accurately predicted by computer simulation. However, entropic-related properties have proven to be more challenging since they are more difficult to tie to the mechanical variables of the simulation. Regardless of the difficulty, the potential benefits associated with linking these important thermodynamic properties with molecular level information have fueled continued study. Several methods have been suggested and developed and will be discussed herein.

3.3.1 Thermodynamic Integration

Thermodynamic integration\textsuperscript{8-12} utilizes the fact that energy and enthalpy can be readily computed from the mechanical variables of a simulation while Gibbs energy and related properties cannot. If an activity coefficient is known at a given state point, and one wishes to obtain the activity coefficient at a different state point, the Gibbs-Helmholz equation (Eq. 3.1) can be used. A series of simulations are run between the reference
temperature and the desired temperature, and the enthalpy is calculated for each simulation. Results are then numerically integrated to obtain the activity coefficient at the state point of interest. This method has no difficulty at high densities, but many CPU-intensive simulations are needed to obtain a single state point, and a value of the activity coefficient at the reference temperature is required.

3.3.2 Widom’s Particle Insertion Method

Particle insertion methods can determine entropic-related properties from a single simulation and are therefore more efficient and sometimes more practical than integration methods. The method of inserting test particles into a configuration of particles was developed by Widom.\textsuperscript{13} The test particles need not actually be inserted, but the potential energy of the proposed insertion is determined and used to calculate the excess chemical potential,\textsuperscript{14} which in turn can be related to the activity coefficient in the case of mixtures.

Widom's method has been shown to be accurate at low-to-moderate densities, but it deteriorates at high densities due to the difficulty of inserting particles. Especially difficult are large molecules that need to be inserted at various configurations into a system at a liquid density. Unfortunately, the activity coefficients that are of most interest are for relatively complex structured molecules at liquid densities. However, several interesting modifications of Widom's particle insertion method have been shown to be moderately successful in obtaining entropic-related excess properties. Some of the most relevant to this work are briefly outlined in the following sections.
3.3.2.1 Particle Deletion Schemes

If a series of particle insertions into a configuration of particles can be used to calculate chemical potentials, why not remove particles that are already part of that configuration to test the chemical potential? Numerous researchers\textsuperscript{15-20} have fallen into this attractive trap because it avoids the problem of difficult particle insertions. It is a trap because the sampling is biased in favor of low-energy configurations, and that bias cannot be removed because the high-energy configurations are\textit{never} sampled in such a scheme.\textsuperscript{21-22} These high-energy configurations do not occur naturally but must be sampled in order to avoid biasing. Researchers are also lulled into a false sense of security as the sampling converges to a plausible, yet wrong answer.

Umbrella sampling,\textsuperscript{23-26} double-wide umbrella sampling,\textsuperscript{27} and Bennett’s method\textsuperscript{28} all rely partially on particle removal. Kofke and Cummings\textsuperscript{21-22} assert that all methods that include particle deletion steps are highly prone to systematic error, and recommend using only staged insertion methods (staged in the direction of decreasing entropy).

3.3.2.2 Staged Insertion Methods

Large molecules need not be inserted all at once into a dense liquid phase in order to extract activity-coefficient information from the simulation. Many attempts have been made to devise an accurate step-wise insertion method because of its clear computational efficiency advantage over a one-stage tactic. The simplest staged-insertion methods first calculate the probability of finding a cavity in the liquid structure, and then perform insertions only in cavities of sufficient radius.\textsuperscript{29-32} Others grow polymer chains into the solution one \textit{mer} at a time.\textsuperscript{33-38} More recent methods insert weakly-interacting molecules
that are relatively easy to insert, and then gradually turn on inter-molecular interactions until the normally-interacting molecule is completely inserted. These methods all have merit and have been used successfully, yet are still very CPU intensive.

### 3.3.2.3 Distribution-Histogram Methods

A promising class of methods that relies partially on particle insertion is the distribution-histogram class. Histogram reweighting methods particularly have grown in popularity. The important configuration space is sampled at the low energy end by the particles that already are part of the liquid structure and at the high energy end by particle insertion. The gap between the distributions is bridged by a process similar to interpolation. The interpolative nature of these methods enhances their ability to produce accurate chemical potential calculations at a lower cost than for other methods that rely on insertion. However, this class of methods requires further development, especially in identifying the proper functional forms on which to base the interpolations for the systems of interest.

### 3.3.2.4 Osmotic Molecular Dynamics with Insertion

Powles, Holz, and Evans also recognized the practical limitations of inserting particles in an already-dense fluid. They therefore proposed a method that only necessitates the insertion of particles into regions of low density, while capable of determining the chemical potential of very dense fluids. They divide the simulation cell into slabs using an external force field which maintains a density differential in the system while allowing chemical equilibrium to exist. At equilibrium, the entire system is at the same chemical potential. Particles are inserted into the low-density slabs only, thus
avoiding the problem of inserting particles into high-density regions. The chemical potential is calculated for the low-density slab and taken as equivalent to the chemical potential in the high-density slab at equilibrium conditions. Using this method Powles, et al. successfully determined the chemical potential of very dense Lennard-Jones (LJ) fluids at various temperatures.

### 3.3.3 Osmotic Molecular Dynamics

Yet another method for the determination of chemical potentials was proposed by Rowley et al.\textsuperscript{47} This method, developed independently but at the same time as Powles’ method, uses alternating slabs of fluid between a semi-premeable membrane and the principle of equivalent chemical potential at equilibrium for molecules to which the membrane is permeable. This method differs from Powles’ since no particle insertions are required. Chemical potential is calculated entirely from the mechanical variables of the naturally-moving molecular dynamics simulation; it is therefore free from the need to insert molecules. The simulation cell is divided into slabs of pure solvent and slabs of mixed solvent and solute by a simulated membrane. Once equilibrated, time-averaged properties are recorded, and the activity coefficient is calculated from the osmotic pressure difference, the mixture mole fraction, and the simulation temperature. This method is the computer simulation analog of the osmotic pressure experiment sometimes used to measure activity coefficients; thus the name, "osmotic molecular dynamics."

Chemical potentials of pure LJ fluids were computed using this method at high densities and various temperatures with encouraging results. Later publications by Rowley et al. extend the method to include the calculation of activity coefficients for mixtures\textsuperscript{48} and for structured molecules.\textsuperscript{49}
Byrk, Patrykiejew, Pizio, and Sokolowski\textsuperscript{50} adapted the OMD method to reacting mixtures and included additional membranes in their simulation to produce four distinct fluid regions. The novel idea of producing four distinct fluid regions is valuable in that four activity coefficients can be produced from a single simulation.

Although OMD is a promising new technique for the determination of activity coefficients, there are several disadvantages associated with it. First, it relies upon the establishment of osmotic equilibrium, and consequently can require a long equilibration period due to slow mass transfer rates. Another disadvantage is the necessity of bulk fluid representation in the slabs of fluid between membranes. In other words, the method requires the measurement of fluid properties that are undistorted by the membranes, and represent fluid characteristics that would be present in a much larger macroscopic experiment. Consequently, only central regions of fluid that are undistorted by the membranes are used in the property calculations. In practice the density distribution across the simulation cell is carefully monitored to ensure that membrane-perturbed regions of fluid are excluded from property calculations.

3.4 Conclusions about Activity Coefficient Determination Methods

In the quest for accurate activity-coefficient determination, several methods have been discussed. Experimental measurement is the preferred method of determination in terms of accuracy and reliability. Yet, the purely predictive methods are becoming a viable, less-expensive, and more versatile alternative. Group contribution methods like UNIFAC allow predictive activity-coefficient determination, but are not extremely reliable. Computer simulation methods inspire hope that a more reliable method of
linking molecular-level properties to macroscopic entropic-related properties can be developed.

Of the computer simulation methods explored, all have merit, but the OMD method is of interest here because of its dependence upon slab geometry and its freedom from inefficient particle insertions. Furthermore, the OMD method does not require multiple simulations for a single state point.

Although activity coefficients for Lennard-Jones fluids and other idealized systems have been produced, it has not yet been shown that activity coefficients can be accurately predicted for any desired system by computer simulation. It would be an enormous technological advance if a universal method for the accurate prediction of multi-component activity coefficients could be developed.
References

4 OMD METHODOLOGY

4.1 OMD Thermodynamics

As discussed in the previous chapter, activity coefficients can be determined by osmosis experiments in which a pure liquid solvent is separated from a liquid mixture of solvent and solute by a semi-permeable membrane, permeable only to solvent molecules. The activity coefficient is calculated according to the thermodynamic identity,

\[ \ln \gamma_i = -\ln x_i - \frac{1}{RT} \int_{P_0}^{P_0 + \Delta P_{osm}} \tilde{V}_i dP \]

(4.1)

where \( \gamma_i \) is the activity coefficient of the permeable component (solvent) at \( x_i \), the mole fraction of permeable component in the mixture. \( P_0 \) is the pressure on the pure solvent side of the membrane, and \( P_0 + \Delta P_{osm} \) is the pressure on the liquid mixture side of the membrane. The molar volume of solvent, \( \tilde{V}_i \), is left inside the integral and considered to be a function of pressure.

Traditionally, osmosis experiments have only been performed using real chemicals, and have been limited by the impracticality of finding membranes that are permeable to the desired solvent and not to the desired solute and are able to withstand huge pressures. In contrast, simulated membranes are simply programmed to be perfectly permeable to solvent molecules only, and to be immovable.
4.2 Membrane Interactions

We used an artificial fixed-in-space membrane that is permeable only to solvent molecules and of the same functionality as that given by Rowley et al. Rowley et al. used the OMD method to calculate activity coefficients for Lennard-Jones (LJ) fluid mixtures, and modeled the interaction between the membrane and solute particles as a one-dimensional, LJ potential truncated at the potential-well minimum and shifted up in energy by $\varepsilon$, the LJ energy interaction parameter. This provided a continuous, purely repulsive potential based on the distance of the particle from the membrane. Their method was modified in this study to accommodate heterogeneous interaction sites on larger structured molecules. Each site $i$ on solute (impermeable) molecules was set to interact with the membrane according to the following force formula:

$$F_i(z) = 24 \varepsilon_i \sigma_{i,j}^6 \left[ 2 \left( \frac{\sigma_{i,j}}{z} \right)^6 - 1 \right] \text{ for } z < 2^{\frac{1}{5}} \sigma_{i,j}$$

(4.2)

and

$$F_i(z) = 0 \text{ for } z \geq 2^{\frac{1}{5}} \sigma_{i,j}$$

(4.3)

where $z$ is given by

$$z = 2^{\frac{1}{5}} \sigma_{i,j} - d$$

(4.4)

and $d$ is the perpendicular distance between the molecule’s center of mass and the membrane surface. The value of $d$ is defined to be positive only after the center of mass of the solvent molecule has passed through the membrane, and is negative otherwise (no interaction).
Although the value of the activity coefficient obtained from OMD simulations is independent of the form of the purely repulsive potential chosen for the solute-membrane interactions (the membrane must simply be semi-permeable), using a soft repulsive force like Equation 4.2 avoids impulses that can occur with harder potentials during the finite time step associated with the numerical integration of the equations of motion. The form of Equation 4.4 is chosen so that a molecule uniformly feels the repulsion when it crosses the membrane surface. The repulsion is exerted on all sites simultaneously, regardless of the molecule’s orientation.

4.3 Slot Definition

The simulation cell must be of adequate length in the $z$ direction (perpendicular to the membrane surface) to allow the formation of a fluid region that is isolated from, and independent of, the artificial membrane. Even though the chosen membrane described above is relatively undistruptive of the natural liquid structure, a volume of fluid within a fixed distance from the membrane is excluded from property calculations to ensure that only fluid that is not disrupted by the membrane surface is used to predict the activity coefficient. But it is desirable to choose small values for the $z$ direction box dimensions in order to minimize the time required for diffusion and equilibration. For the purposes of this work, the central “slot” region of undistorted fluid was defined as all molecules with center of mass at least 10 Å away from the membrane surface. Benchmark tests that will be discussed later in this chapter confirm that this distance is sufficient for the molecules of this study. Smaller distances were attempted, but proved to introduce error into the calculation.
4.4 Thermostatting

Precise temperature control of the system is crucial to obtaining accurate activity coefficient predictions. Thermostatting of the entire simulation cell to the set-point temperature does not guarantee that the individual slot regions will be held at precisely the desired temperature, especially since the membrane artificially adds energy to the system in the excluded volume regions. We independently thermostat the slot and adjacent exclusion volumes of each half-cell to ensure uniform temperature at the set-point throughout.\(^2\)

The population of molecules pertaining to any given slot or exclusion volume is updated every 100 time steps, at which point the net momentum of that population of molecules in each direction is set to zero by velocity rescaling, followed by an additional velocity rescaling that fixes the population at the set-point temperature. A Gaussian thermostat\(^3\) is used to hold each population’s temperature constant between updates. The zeroing of net momenta ensures that a net drift of the population that can accumulate in OMD simulations does not produce an erroneously high temperature measurement.\(^4\) One degree of freedom is removed from the translational temperature calculation formula,

\[
T = \frac{\sum_i m_i v_i^2}{k(3N - NRDF)},
\]

where \(T\) is the temperature, \(m_i\) and \(v_i\) are the mass and velocity of molecule \(i\), \(k\) is the Boltzmann constant, \(N\) is the number of molecules in the population, and \(NRDF\) is the number of removed degrees of freedom. One degree of freedom is removed due to the thermostat. In a regular MD simulation, momentum is conserved in all three directions for the thermostatted population; so three additional degrees of freedom must be
removed. However, in an OMD simulation, the thermostatted population is continually changing; new populations have not been previously thermostatted to the set-point temperature. Also, momentum is not conserved for the thermostatted populations since the molecules of each slot and exclusion volume interact with the membrane and/or molecules outside that region.

4.5 Osmotic Pressure Calculation

The system temperature has a strong effect on the system pressure and on the osmotic pressure difference. Prediction of activity coefficients by Eq. 4.1 is extremely sensitive to the precise determination of the equilibrium osmotic pressure difference, \( \Delta P_{osm} \). Although this pressure difference can be found by taking the difference between the pressure found on the mixture side of the membrane (Side A) and the pressure found on the solvent side of the membrane (Side B) as calculated using the virial equation, this procedure is computationally expensive, yields large instantaneous fluctuations in the calculation of \( \Delta P_{osm} \), and is prone to error. We have found that this method of finding \( \Delta P_{osm} \) is especially prone to error if discontinuous molecular models (cutoff fluids) are used.

A far better way to determine \( \Delta P_{osm} \) is by simply finding the average force that the membrane exerts to hold impermeable molecules on the mixture side and then dividing that planar force by the membrane surface area,

\[
\Delta P_{osm} = \frac{F_{mem}}{A_{mem}}. \tag{4.6}
\]

We use this method of finding \( \Delta P_{osm} \) throughout this work.
4.6 Force Calculations

The molecular models used in this work include LJ and coulombic interactions. The LJ interactions and real-space contributions to the coulombic interactions were truncated at $r_{\text{cut}} = 10$ Å. Long-range coulombic interactions were computed in reciprocal space according to the particle-particle-particle-mesh (P$^3$M) methodology that is described in detail elsewhere.$^{5-8}$ Reciprocal space forces were determined by $i\mathbf{k}$ differentiation (differentiation in Fourier space), and $\alpha$, which determines the partition of the calculation between real and reciprocal space, was recalculated at each volume change according to the rules given by Deserno and Holm$^8$ in order to optimize calculation accuracy. The P$^3$M optimal influence function was also updated at each volume change.

4.7 Fast Equilibration

Previously, the primary difficulty associated with the OMD method has been the difficulty of establishing chemical potential equilibrium across the membrane due to slow mass-transfer rates. In this work, it was found that the problem of slow mass transfer could be greatly mitigated by preemptively changing the volume (and thus the pressure) on the mixture side (Side B) once a net migration of solvent is detected. Net mass transfer of the solvent from the pure-solvent side (Side A) to Side B or visa versa is prohibited by continually rescaling $z$-directional velocities of the solvent molecules so that the net migration across the membrane is zero. The chemical potential driving force producing the net migration is eliminated by increasing or decreasing the Side B volume in proportion to the observed flux. In this way, chemical potential equilibrium across the membrane is achieved, while net mass transfer is prohibited. Pressure is judiciously applied to prevent flux across the membrane.
The right half of Side A is grouped with the left half of Side B into “Region 1,” and the left half of Side A is grouped with the right half of Side B into “Region 2.” (See Figure 4.1.) Then, at each time step, the \( z \)-directional velocities of permeable molecules in Region 1 are summed and added to the negative of the sum of the \( z \)-directional velocities of permeable molecules in Region 2. This sum is divided by the number of permeable molecules to produce the net flux signal, \( \phi \),

\[
\phi = \frac{\sum v_1 - \sum v_2}{N_{\text{permeable}}}.
\]  

(4.7)

The value of \( \phi \) is recorded, and then eliminated by subtracting \( \phi \) from the \( z \)-directional velocities of all permeable molecules in the simulation cell. By adjusting these velocities, net mass transfer of solvent between Sides A and B is artificially prohibited, but the chemical potential driving force that produced the flux still must be nulled.

Figure 4.1. The OMD simulation cell is divided by a semi-permeable membrane into Side A (left of the central membrane) and Side B (right of the central membrane). Permeable-molecule \( z \) velocities from Region 1 (gray area) are added to the negative of the permeable-molecule \( z \) velocities from Region 2 (white area) to determine the net flux of solvent. The \( z \)-direction box length of Side B, \( L_{z_B} \), is gradually adjusted until the net flux is brought to zero. Meanwhile, flux is artificially prohibited by rescaling permeable-molecule \( z \) velocities.
Before being reset for the next time step, the recorded value of $\phi$, which represents the instantaneous flux, is added to the time-averaged flux accumulator, $\Phi$, which continues accumulation for an arbitrary, pre-determined length of time (a period of 100 time steps was used in this work). A net chemical potential driving force can be detected above the natural, noisy, random fluctuations of the flux only if a very large sample is obtained. Time-averaging helps, but is insufficient. A sufficiently-strong flux signal can be obtained by performing multiple simulations in parallel and averaging the value of $\Phi$ between them. Details about this parallel processing technique are given in Section 4.8.

At the end of the accumulation cycle, the grand average for $\Phi$ is used to determine the new value for $L_z^B$ according to the proportional control scheme,

$$L_z^{B_{\text{new}}} = L_z^{B_{\text{old}}} (1 + K\Phi),$$

where $K$ is an arbitrary gain constant that was chosen to be about 0.05 s/m for this work. Whenever $L_z^B$ is changed, the $z$ positions of the molecules on Side B are scaled to fit the new $L_z^B$. By changing $L_z^B$, the volume on Side B of the simulation cell is adjusted, which in turn increases or decreases the pressure on Side B, and eliminates the net chemical potential driving force. In practice, very gradual and continuous changes of $L_z^B$ (~0.01% every 100 time steps) achieve chemical potential equilibrium after several thousand time steps.

In addition to dramatic reductions in equilibration time, this technique allows the user to hold the mixture-side composition of constituent components fairly constant throughout the duration of the simulation --- net flux of solvent through the membrane is
forced to zero --- leaving the pressure difference across the membrane as the only variable affecting the prediction of the activity coefficient. It becomes clear that chemical potential equilibrium between Sides A and B has been achieved once this pressure difference converges to a constant value. (See Figure 4.2.)

4.8 System Size Considerations and Parallel Processing

Ideally, one would perform OMD simulations using a system of only a few hundred molecules in order to minimize CPU time requirements. Unfortunately, large instantaneous fluctuations of pressures and mole fractions require that we use a much

Figure 4.2. Time progression of a typical OMD simulation (Run 10 of Section 4.9). From top to bottom, the ratio of the Side B volume to the Side A volume (left axis), the osmotic pressure difference (right axis), and the mixture mole fraction (left axis) are shown. Chemical potential equilibrium is achieved within roughly 20,000 time steps, as evidenced by the constant values of the plotted variables.
larger system. One might argue that a small system run over a large amount of time would be preferable to a large system run over a small amount of time. However, a large spatial sample of the desired phase space is much better than a large temporal sample due to the long time-persistence of local anomalies in the local fluid structure. Also, a large system can be broken down into many small sub-systems, or members of the same canonical (NVT) ensemble, and run simultaneously on a parallel processor or on a bank of networked machines.

We have chosen a small system size of 200-1000 molecules for each independent ensemble member in the simulations that we have performed. Depending upon the desired accuracy, we have used 10-200 members ($N_{members}$) of the ensemble that can be performed in parallel. The parallel simulation procedure that we have adopted is as follows:

1) Each member of the canonical ensemble is moved forward a fixed amount of time ($t_{cycle}$), independent of the other ensemble members. Each ensemble member shares a common $N$, $V$, $T$, and simulation cell geometry (cell length in the $x$ and $y$ directions, $L$; Side A cell length in the $z$ direction, $L_A$; and Side B cell length in the $z$ direction, $L_B$).

2) Once each of the $N_{members}$ of the ensemble reaches the end of the cycle time, each of the needed properties, $\Delta P_{osm}$, $x_i$, and the flux ($\Phi$), is computed as the ensemble average.

3) At this point, $L$ is scaled to control the pure-solvent density on Side A to the desired liquid density, and $Lz_B$ is scaled according to Equation 4.8.
4) The new $L$ and the new $L_{zB}$ are applied to each of the $N_{members}$ of the ensemble, molecular positions are rescaled to the new box geometry, and a new cycle begins.

Chemical potential equilibrium is achieved once the variables of interest reach constant values, such as clearly occurs after 20,000 time steps in Figure 4.2. Property collection for activity-coefficient determination can then begin.

4.9 Methodology Validation

Once an OMD code has been written, and the methodology implemented, it is essential to test the methodology on a problem for which the answer is known. Fortunately, such a problem is readily available for testing the OMD methodology: any pure solvent in itself is ideal and OMD should yield an activity-coefficient prediction of unity across the entire composition range. Molecules that are chemically identical are tagged as either solvent or solute molecules, and simulations are performed at various compositions. This is a good test of the OMD methodology since it is highly unlikely that the two terms on the right hand side of Equation 4.1 will be equal and opposite across the entire composition range, yielding $\ln \gamma_i = 0$ everywhere, unless the method is valid.

We performed a set of simulations using the methodology described in this chapter to predict the activity coefficients across the composition range for a simple non-polar fluid of LJ spheres similar to liquid methane. To save computer time for this test case, a radial cutoff for the LJ interactions was set at 6 Å and the intermolecular LJ potential was shifted up so that there was no discontinuity at the cutoff. The LJ $\sigma$ was set at 3.73 Å, and the LJ $\varepsilon/k$ was set at 147.96 K. A set of 200 ensemble members was
moved forward through time according to the scheme outlined in Section 4.8, with each ensemble member consisting of 1000 of these LJ spheres. The simulations were performed at 111.7 K and a pure solvent density of 22 mol/L, with a time step size of 3 fs. All simulations were run for at least 20,000 time steps before property collection began. Each data point required approximately two days of CPU time on one CPU of an SGI Origin 2000 supercomputer.

Results of this test are given in Table 4.1 and shown graphically in Figure 4.3. The simulations yielded an activity coefficient prediction very near unity for all 10 of the independent test cases. Wilson equation parameters that were regressed to fit this data are $\Lambda_{12} = \Lambda_{21} = 0.999$. Infinite-dilution activity coefficients calculated using the resultant parameters are both 1.003. These numbers suggest the level of precision that can be expected in activity-coefficient prediction using the system parameters and methodology outlined above. A perfect prediction would have given $\ln \gamma_i = 0$ for all ten runs shown in Table 4.1, $\Lambda_{12} = \Lambda_{21} = 1$, and infinite-dilution activity coefficients of unity.

It is recommended that future OMD simulation algorithms be subjected to a similar test before being used for activity-coefficient prediction. The data given here can act as a benchmark for demonstrating improvements in OMD efficiency and accuracy. It is expected that with further methodology improvements, parameter optimization, and algorithm enhancements, more precise answers will be obtainable given a fixed amount of available CPU time.
### Table 4.1. OMD test case simulation results.

<table>
<thead>
<tr>
<th>Run</th>
<th>$x_i$</th>
<th>$\Delta P_{osm}$ (MPa)</th>
<th>$-\ln(x_i)$</th>
<th>$-\frac{1}{RT} \int \frac{P_0 + \Delta P_{osm}}{P_0} , dP$</th>
<th>$\ln \gamma_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9512</td>
<td>1.03</td>
<td>0.0500</td>
<td>-0.0502</td>
<td>-0.0001</td>
</tr>
<tr>
<td>2</td>
<td>0.9029</td>
<td>2.11</td>
<td>0.1022</td>
<td>-0.1027</td>
<td>-0.0005</td>
</tr>
<tr>
<td>3</td>
<td>0.8534</td>
<td>3.23</td>
<td>0.1585</td>
<td>-0.1570</td>
<td>0.0016</td>
</tr>
<tr>
<td>4</td>
<td>0.8054</td>
<td>4.46</td>
<td>0.2164</td>
<td>-0.2167</td>
<td>-0.0003</td>
</tr>
<tr>
<td>5</td>
<td>0.7558</td>
<td>5.75</td>
<td>0.2800</td>
<td>-0.2786</td>
<td>0.0014</td>
</tr>
<tr>
<td>6</td>
<td>0.7084</td>
<td>7.18</td>
<td>0.3448</td>
<td>-0.3470</td>
<td>-0.0022</td>
</tr>
<tr>
<td>7</td>
<td>0.6594</td>
<td>8.63</td>
<td>0.4165</td>
<td>-0.4162</td>
<td>0.0003</td>
</tr>
<tr>
<td>8</td>
<td>0.6104</td>
<td>10.25</td>
<td>0.4936</td>
<td>-0.4930</td>
<td>0.0005</td>
</tr>
<tr>
<td>9</td>
<td>0.5622</td>
<td>11.98</td>
<td>0.5759</td>
<td>-0.5746</td>
<td>0.0013</td>
</tr>
<tr>
<td>10</td>
<td>0.5141</td>
<td>13.90</td>
<td>0.6654</td>
<td>-0.6646</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

![Figure 4.3. OMD activity coefficient prediction for a pure LJ fluid in itself. The symbols represent the individual simulation runs (the components are identical) and the lines represent the Wilson equation fit of the data. If the data set were perfect, all points and both lines would lie along the line at $\ln \gamma_i = 0$.](image-url)
References


2. E. S. Eriksen, Activity Coefficients and Excess Properties of Non-polar Binary Mixtures as Predicted by Osmotic Molecular Dynamics (Brigham Young University, Provo, Utah, 1999), pp. 31-35.

3. M. Henrichsen, Application of Osmotic Molecular Dynamics to Structured Molecules (Brigham Young University, Provo, Utah, 1996), pp. 31-34.


OMD RESULTS

5.1 Model Fluids

The OMD method has previously been used to predict activity coefficients for mixtures of LJ spheres and for mixtures of structured molecules made up of homogeneous LJ spheres. In this work, we establish the utility of the OMD method for the prediction of activity coefficients for model fluids containing heterogeneous site interactions and polar groups represented by distributed point charges. We use the OMD method to predict activity coefficients for model fluids representing six classes of liquid binary mixtures that have industrial significance: methanol/n-hexane, n-hexane/n-pentane, methanol/water, chloroform/acetone, n-hexane/chloroform, and methanol/chloroform. The represented classes of binaries are A/NP, NP/NP, A/A, NA/NA, NP/NA, and A/NA, respectively, where NP is a non-polar component, A is an associating component, and NA is a non-associating component.

Molecular models for methanol, water, chloroform, acetone, n-hexane, and n-pentane were obtained from the literature. Values for the model parameters are given in Table 5.1. The repulsion and dispersion potentials were represented in the models with united-atom, pair-wise additive, site-site, LJ potentials located at all heavy-atom nuclei. Lorenz-Berthelot combining rules were used to obtain values for all interactions between heterogeneous interaction sites. Point charges located at nuclear centers were used to model the permanent dipole interactions for water, methanol, chloroform, and acetone.
Table 5.1. Model fluid parameters.

### Intermolecular Interactions

<table>
<thead>
<tr>
<th>Group</th>
<th>(\sigma) (angstroms)</th>
<th>(\varepsilon/k) (K)</th>
<th>q (e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-O (acetone)</td>
<td>2.960</td>
<td>105.750</td>
<td>-0.4240</td>
</tr>
<tr>
<td>-CH(_3) (acetone)</td>
<td>3.910</td>
<td>80.570</td>
<td>+0.0620</td>
</tr>
<tr>
<td>-C (acetone)</td>
<td>3.750</td>
<td>52.870</td>
<td>+0.3000</td>
</tr>
<tr>
<td>-CH (chloroform)</td>
<td>3.800</td>
<td>40.285</td>
<td>+0.4200</td>
</tr>
<tr>
<td>-Cl (chloroform)</td>
<td>3.470</td>
<td>151.068</td>
<td>-0.1400</td>
</tr>
<tr>
<td>-CH(_3) (n-hexane)</td>
<td>3.905</td>
<td>88.070</td>
<td>0.0000</td>
</tr>
<tr>
<td>-CH(_2) (n-hexane)</td>
<td>3.905</td>
<td>59.380</td>
<td>0.0000</td>
</tr>
<tr>
<td>-CH(_3) (methanol)</td>
<td>3.740</td>
<td>105.200</td>
<td>+0.2650</td>
</tr>
<tr>
<td>-O (methanol)</td>
<td>3.030</td>
<td>86.500</td>
<td>-0.7000</td>
</tr>
<tr>
<td>-H (methanol)</td>
<td>0.000</td>
<td>0.000</td>
<td>+0.4350</td>
</tr>
<tr>
<td>-CH(_3) (n-pentane)</td>
<td>3.905</td>
<td>88.070</td>
<td>0.0000</td>
</tr>
<tr>
<td>-CH(_2) (n-pentane)</td>
<td>3.905</td>
<td>59.380</td>
<td>0.0000</td>
</tr>
<tr>
<td>-O (water)</td>
<td>3.169</td>
<td>78.178</td>
<td>-0.8476</td>
</tr>
<tr>
<td>-H (water)</td>
<td>0.000</td>
<td>0.000</td>
<td>+0.4238</td>
</tr>
</tbody>
</table>

**Torsional Potential (n-hexane and n-pentane)**

<table>
<thead>
<tr>
<th>(a_0)</th>
<th>(a_1)</th>
<th>(a_2)</th>
<th>(a_3)</th>
<th>(a_4)</th>
<th>(a_5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1116</td>
<td>1462</td>
<td>-1578</td>
<td>-368</td>
<td>3156</td>
<td>-3788</td>
</tr>
</tbody>
</table>

The method of auxiliary bond constraints was used to model the planar acetone molecule. In all cases, bond lengths and angles were fixed at their equilibrium positions.

Molecular models for alkanes generally include torsional potentials that affect the angle between two sites in the alkane chain that have two other sites between them. This “dihedral angle” is defined as the angle that is formed between the two sites when the molecule is projected onto a plane such that the two intervening sites coincide and form the vertex. The torsional potentials for \(n\)-hexane and \(n\)-pentane were modeled as a
function of dihedral angle $\phi$ with the Ryckaert-Bellemans cosine series,\(^8\)

$$
\frac{u_{i\alpha\gamma}(\phi)}{k} = \sum_{i=0}^{5} a_i \cos^i(\phi),
$$

(5.1)

and the coefficients shown in Table 5.1. All three dihedral angles in $n$-hexane and both dihedral angles in $n$-pentane were assumed to be equivalent and given by the Ryckaert-Bellemans values.

### 5.2 Activity Coefficient Parameter Regression

Once the OMD simulation has been properly equilibrated, and the raw data subsequently collected, the activity coefficient of the solvent at the mixture composition can be calculated according to Equation 4.1. Each simulation yields a single point on the activity-coefficient-versus-composition curve (for one of the components). We have performed five OMD simulations for each component of the six binary mixtures.

Activity coefficients for both components along the entire composition range were then correlated by regressing activity-coefficient model parameters that best fit the OMD simulation data. This procedure smooths the predicted data and incorporates thermodynamic consistency in the form of Equation 3.5.

We have chosen to use the Wilson equation as our activity-coefficient model since it is widely regarded as reliable and robust for correlating binary vapor-liquid equilibrium for most common substances. Hirata, Ohe, and Nagahama outline a procedure for regressing Wilson equation parameters that is very simple and successful.\(^9\) We have used their method with the following objective function to be minimized for the
$n = 16$ simulation data points for each binary mixture:

$$O.F. = \sum_{i=1}^{n} (Q_{simulation} - Q_{Wilson})^2_i$$  \hspace{1cm} (5.2)

where

$$Q = x \ln \gamma_{solvent},$$  \hspace{1cm} (5.3)

and $x$ is the mole fraction of solvent (permeable component).

5.3  Reliability Tests

The magnitude of the objective function is indicative of the error in the fit and hence the accuracy and thermodynamic consistency of the raw data obtained from the simulations. Alternatively, each component’s activity coefficient curve can be regressed independently in order to perform the integral test for thermodynamic consistency. Or, individual raw data points can be compared in pairs using the differential test for thermodynamic consistency.

Ideally, we would like to compare our results with other simulations that use the same molecular models but different methods of chemical potential determination. However, the scarcity of simulation generated activity-coefficient predictions for model binary mixtures of structured molecules in the literature makes such a comparison difficult, if not impossible. Most available data in the literature were obtained using the Gibbs Ensemble Monte Carlo method, which predicts vapor-liquid equilibrium rather than directly predicting the activity coefficients as is done with OMD. Results cannot be compared directly. Rather than attempt such a comparison with other computer simulation techniques, for the purposes of this work we simply test the reliability of the
OMD results using the self-consistency error analysis discussed above. We also compare our results with experimentally measured activity coefficients.\textsuperscript{10-15}

5.4 Results

Figures 5.1-5.6 show OMD-predicted and experimentally-measured activity coefficients for the six systems investigated in this study. In each case, \( \ln \gamma \) is plotted versus mole fraction of component 1. OMD-predicted activity coefficients closely follow experimentally-measured activity coefficients for the methanol/\( n \)-hexane system and for the \( n \)-pentane/\( n \)-hexane system, and the prediction method clearly distinguishes between the nearly ideal \( n \)-pentane/\( n \)-hexane system and the highly non-ideal methanol/\( n \)-hexane system. This is truly remarkable when one considers that no empirical data about the binary mixtures were used to perform this calculation; only the simple molecular models and the Lorenz-Berthelot combining rule were used.

For the four remaining systems, the agreement is much poorer. The very small deviation between the solid points in the figures representing OMD-predicted data and the lines representing the Wilson equation fit indicates the good thermodynamic consistency of the data without further analysis. By definition, the Wilson equation activity coefficient model ensures thermodynamic consistency, and the points clearly fall along the lines.
Figure 5.1. Activity-coefficient comparison for the methanol (1) / n-hexane (2) system at 35 °C. Open symbols represent experimentally measured activity coefficients, solid symbol represent OMD predictions, and the lines represent the OMD data fit to Wilson parameters.

Figure 5.2. Activity-coefficient comparison for the n-pentane (1) / n-hexane (2) system at 25 °C. Symbols are the same as in Fig. 5.1.
Figure 5.3. Activity-coefficient comparison for the acetone (1) / chloroform (2) system at 25 °C.\textsuperscript{12} Symbols are the same as in Fig. 5.1.

Figure 5.4. Activity-coefficient comparison for the chloroform (1) / \textit{n}-hexane (2) system at 25 °C.\textsuperscript{13} Symbols are the same as in Fig. 5.1.
Figure 5.5. Activity-coefficient comparison for the chloroform (1) / methanol (2) system at 35 °C. Symbols are the same as in Fig. 5.1.

Figure 5.6. Activity-coefficient comparison for the methanol (1) / water (2) system at 25 °C. Symbols are the same as in Fig. 5.1.
The thermodynamic consistency of the OMD predictions, along with the methodology validation shown in Section 4.9 suggests that the disagreement between experimentally measured activity coefficients and OMD predicted activity coefficients lies in the molecular models. This is not surprising, considering the simplistic empirical models that were used. Especially suspect are the LB cross-parameters that were used to model the cross interactions between heterogeneous pairs of interacting sites.

Although agreement between OMD predicted phase equilibrium and experimental phase equilibrium is not good enough to lend credence to OMD-predicted activity coefficients over commonly-used methods for activity-coefficient prediction such as UNIFAC, these results do show that OMD activity-coefficient prediction is possible and at least qualitatively accurate for distinguishing between fairly ideal and highly non-ideal mixtures. And unlike UNIFAC, activity coefficients predicted via computer simulation rely solely upon the underlying molecular physics and require no group contribution assumptions.

What about computer simulation methods other than OMD? To our knowledge, it has not yet been demonstrated that other computer simulation methods for phase equilibrium prediction would be able to compare with the OMD predictions presented here. Insertion methods would be especially inefficient at inserting \( n \)-hexane or \( n \)-pentane molecules into a dense liquid. Other methods also present great difficulties or inefficiencies. It is also noteworthy that OMD activity-coefficient predictions are not limited to phase boundaries.

Although these results leave much to be desired in terms of accurate activity-coefficient prediction, they represent perhaps the best way available today to predict
activity coefficients from first principles. Further advances in microprocessor technology, further improvement of the OMD method, and further development of more accurate molecular models will certainly improve prediction reliability.
References


2. E. S. Eriksen, *Activity Coefficients and Excess Properties of Non-polar Binary Mixtures as Predicted by Osmotic Molecular Dynamics* (Brigham Young University, Provo, Utah, 1999), pp. 31-35.


6 INTRODUCTION TO MOLECULAR DYNAMICS INTERFACIAL ELECTROCHEMISTRY

6.1 Interfacial Electrochemistry

The study of interfacial electrochemistry has wide application to the fields of electrochemistry, geochemistry, biology, colloidal science, and surface science. Key processes include electroplating, corrosion, catalysis, energy storage, and ion transport through cell membranes. Most of the important chemistry that occurs in these processes occurs at the electrolyte-solid interface. Knowledge of the structure and energetics at interfaces greatly enhances our ability to manipulate chemical processes that occur in both man-made and biological applications.

6.2 Double-Layer Theory

The fluid near the electrochemical interface is called the double layer (DL), which has reference to the build-up of ions in a layer in the fluid or mobile phase to effectively neutralize the distributed charge at the electrode surface. The layer of ions can be further divided into inner and diffuse layers. The inner layer can be thought of as the region that is inaccessible to the ion nucleus due to the finite size of the ions. Even though the actual application of the inner layer and the diffuse layer to DL theory has only a modest foundation in reality, the whole topic of fluid structure near electrochemical interfaces has become known as DL theory.
The original DL theory was developed nearly a century ago by Gouy and Chapman.\textsuperscript{1-2} Their theory treats the solvent as a continuum with a dielectric constant equal to that of the real solvent. Gouy-Chapman theory treats the ions as simple point charges through the use of a Poisson-Boltzmann equation. In 1924, Stern\textsuperscript{3} modified the Gouy-Chapman theory to include the inner layer that is inaccessible to the ion centers. This modified Gouy-Chapman theory recognizes that the finite size of the ions keeps the ionic centers away from the wall, but still treats the ion-ion interactions like point charges. More recent DL theory accounts for the finite size of the ions for both the ion-wall interactions and the ion-ion interactions through the use of sophisticated integral equation theories that have been applied to the DL geometry.\textsuperscript{4-7} However, these theories still use the continuum solvent of the primitive model. Further work improved the primitive model by treating the solvent as discrete particles.\textsuperscript{8-9} But even in this work, solvent molecules were necessarily very simplistic, and not considered an adequate representation of solvent molecules in a real electrolyte solution.

6.3 Computer Simulation of the Electrochemical Interface

Clearly, the key to further advances in DL theory lies in computer simulation. Much more sophisticated models for ions, solvent molecules, and electrode surfaces can be readily included in a computer model, whereas these complexities are difficult or impossible to include in the more traditional methods. Moreover, with advances in microprocessor technology and simulation methodology, computer simulation is becoming the preferred investigative tool for DL electrochemistry.

Pioneering work in the area of computer simulation of the electrical DL was performed by Torrie and Valleau twenty years ago.\textsuperscript{10-12} They showed that computer
simulation results could be used to test the Gouy-Chapman theory and the more recent improvements. The limited computational power and algorithm availability of the time necessitated the use of a continuum solvent in conjunction with the primitive model and approximate long-range coulombic interactions in their calculations. Only recently have researchers begun to perform DL computer simulations that include discrete solvent molecules and therefore adequately model all parts of the DL: the inner layer, the diffuse layer, and the bulk electrolyte region that is completely shielded from the electrode.\textsuperscript{13-15}

### 6.4 Double-Layer Concepts of Interest

In Chapters 7-9, we will focus on a few key concepts that have generally been of most interest to DL researchers. Of specific interest is the liquid structure near the electrode surface. What is the water density at the electrode surface? Are the water molecules there all specifically oriented? Do the ions adsorb onto the surface of the electrode, or are they kept away from the surface by a layer of water molecules? What is the ion concentration at the surface of the electrode, and how does that compare to the ion concentration in the bulk? Are the ions solvated, or partially solvated at the electrode surface? What is the width of the DL? Does the size of the ions matter? These and other questions can be answered by calculating the average density distribution of the various species as a function of distance from the electrode surface. The density distribution is obtained by filling histogram bins at periodic intervals using “snapshots” of the \( z \) positions of the various species. This histogram produces a time-averaged density distribution of each species as a function of distance from the electrode surface. Care is taken to ensure that the simulation has come to equilibrium prior to the collection of data.
From the density distribution data, one can calculate the charge distribution, the potential profile, and the capacitance of the DL. The capacitance is a measure of the energy stored in the DL, and is of particular interest. Specifically, how does the DL capacitance vary with a change in the electrode surface charge or the ion concentration?

Given the time-averaged density distribution of each species as a function of distance from the electrode surface, the relative potential as a function of distance across the DL, $\phi(z)$, can be calculated using

$$\phi(z) = \frac{1}{\varepsilon_0} \int_{-\infty}^{t} \sum \rho_i(z') \phi(z-t') dt' ,$$

where $\varepsilon_0$ is the permittivity constant, infinity is a point far from the electrode in the bulk fluid region, $\rho_i(z)$ is the charge density of species $i$ at distance $z$ from the electrode, and $t$ is the dummy variable of integration. Please note that this formula applies only to the case of an electrostatic system at equilibrium with spatial charge distribution homogeneity in all but the $z$ direction. Also note that electro-neutrality must exist in the bulk fluid such that $d\phi/dz = 0$ at $z = \infty$. The DL capacitance, $C$, is given by

$$C = \frac{\sigma}{\phi(0)} ,$$

where $\sigma$ is the electrode surface charge density, and $\phi(0)$ is the total potential drop across the DL.
References

7  LOW EFFECTIVE TEMPERATURE PROPERTIES OF THE ELECTROCHEMICAL INTERFACE

7.1  Introduction

The distinction between effective and absolute temperature is important when dealing with electrochemical interface properties. Systems of molten salt have high absolute temperatures, but low effective, or reduced temperatures, where the reduced temperature is $T^* = \frac{\varepsilon d k T}{q^2}$, $d$ is the ionic diameter, $q$ is the ionic charge, and $k$ is the Boltzmann constant. Molten salts may have an absolute temperature of thousands of degrees, but an $\varepsilon \approx 1$, giving an effective temperature similar to that of an aqueous system at low absolute temperatures, because $\varepsilon = 78.5$ for the aqueous system. Both systems can have low effective temperatures and exhibit similar behavior for the capacitance. For example, a system with divalent ions would exhibit behavior similar to a system with monovalent ions with a much lower absolute temperature. The effective temperature is the important variable.

Recently, Boda et al.\textsuperscript{1} have studied low effective temperature anomalies in the properties of the electrochemical interface. They showed that under certain circumstances, a decreasing DL capacitance with decreasing temperature is observed. The restricted primitive model (RPM) was used, where the ions were represented by charged hard spheres of equal diameter, $d$, and the solvent was represented by a uniform dielectric constant, $\varepsilon$. 
The correct representation of long-range coulombic interactions is of the utmost importance in studying interfacial electrolyte systems. In Chapter 2, we compared the charged-sheets method\textsuperscript{3-7} (CS) of modeling these interactions with the corrected 3-D Ewald method\textsuperscript{8} (EW3DC), and found EW3DC to be more reliable than CS for the calculation of long-range coulombic interactions. Due to this finding, it is worth repeating the calculations of Boda et al., in which CS was used, to ensure that this somewhat surprising capacitance temperature relationship is not an artifact of the CS method employed.

The observed decrease in DL capacitance with decreasing temperature in the low effective temperature region is an anomaly for which a quantitative theoretical treatment is not yet available. This behavior contradicts predictions of the Gouy-Chapman theory and the mean spherical approximation, even though these theories predict behavior in agreement with simulation results at higher effective temperatures.

7.2 Simulation Details

We have performed molecular dynamics (MD) simulations similar to the Monte Carlo (MC) simulations of Boda et al.\textsuperscript{1} However, the EW3DC method was used rather than CS, and oppositely-charged walls with an equal number on anions and cations were used, rather than similarly-charged surfaces balanced by an unequal number of anions and cations. Oppositely-charged surfaces should give equivalent results to those produced using similarly-charged surfaces as long as there is sufficient separation distance between the walls to allow neutral fluid formation in the central bulk fluid region of the simulation cell.
Canonical (NVT) simulations were performed with a simulation cell of dimensions $L \times L \times H$, and $H = 20d$. Box length, $L$, was allowed to vary between $15d$ and $17d$ to give the desired bulk density. In all cases, 100 anions and 100 cations were placed between the hard walls at $z = 0$ and $z = H$.

As in the work of Boda et al., reduced variables are defined as $\sigma^* = \sigma d^2 / q$, $\rho^* = \rho d^3$, $C^* = \sigma^* / \phi^*$, and $\phi^* = \phi d / q$, where $\sigma$ is the wall surface charge density, $\rho$ is the bulk density, $C$ is the integral capacitance and $\phi$ is the potential drop across the DL.

Parameters identical to those in case $c$ of the work by Boda et al. were used: $\sigma^* = 0.00765$, $\rho^* \sim 0.04$, $\varepsilon = 78.5$. Simulations were performed at $T^* = 1/25, 2/25, 3/25, 4/25, 8/25, \text{and} 16/25$ ($T = 20, 40, 60, 80, 160, 320$ K for monovalent ions with $d = 4.25$ angstroms and $\varepsilon = 78.5$).

Ten repetitions, each lasting 1 ns after an initial 50 ps equilibration period were performed at each of the six temperatures. Each of the repetitions used a unique and randomly selected starting configuration for ion placements and initial velocities. Density profiles were then taken as an average of the ten repetitions in each case.

The MD equations of motion were integrated using a fourth-order Gear predictor-corrector scheme, with a time step size of 2.5 fs. As required by RPM, hard sphere overlaps between time steps were treated as elastic collisions, with the appropriate changes in ion positions and velocities. All force interactions, including the long-range EW3DC interactions were updated at each time step.

7.3 Results and Discussion

As can be seen in Figure 7.1, the results produced in this study using MD and EW3DC agree well with the results produced by Boda et al. using MC and CS.
Discrepancies between the two data sets are smaller than their combined statistical error. The same increase in capacitance with increasing temperature in the low effective temperature region is observed.

Why is there a change in slope in the $C^*$ vs. $T^*$ plot when going from the low effective temperature region to the high effective temperature region (see Figure 7.1)? It arises from a change in the dominance of two competing effects. At high effective temperatures, thermal energy dominates, and the DL thickness increases with increasing temperature. A thicker DL causes a higher potential and a lower capacitance. At sufficiently low effective temperatures, ion-ion interactions become more important as thermal energy becomes insufficient to separate ion pairs. The usual DL build-up at the electrode surface (see Figure 7.2) is replaced by “drying” at the electrode surface (see Figure 7.3) as ion-ion interactions become increasingly dominant. The DL thickness increases with the decreasing temperature in the low effective temperature region as ion pairing increasingly prevails and causes increased drying at the electrode surface. This unusual behavior of decreasing capacitance with decreasing temperature for the RPM is therefore not an artifact of the calculation method, and the CS method was valid for this case.

### 7.4 Conclusions

We have shown that for this system, CS, MC calculations yield the same results as EW3DC MD calculations within statistical uncertainty. Our calculation also shows that the use of CS by Torrie and Valleau$^{3-5}$ is justified for the system of interest to them. Assumptions inherent in the use of CS seem to be valid when used with RPM; however,
CS should not be used in systems with discrete solvent molecules and $\varepsilon = 1$ as shown in the work of Crozier et al.\textsuperscript{2}

![Figure 7.1. Capacitance as a function of effective temperature. Boxes are the MC CS simulation results by Boda et al., and $\times$’s are the MD EW3DC simulation results of this work. System parameters are $\sigma^* = 0.00765$, $\rho^* \sim 0.04$, and $\varepsilon = 78.5$.](image1)

![Figure 7.2. Density profile of ions along the $z$ axis (perpendicular to the electrode, $z^* = z/d$) for $T^* = 16/25$. The thick line represents the counterions, and the thin line represents the coions. System parameters are $\sigma^* = 0.00765$, $\rho^* \sim 0.04$, and $\varepsilon = 78.5$.](image2)
Figure 7.3. Density profile of ions along the $z$ axis (perpendicular to the electrode, $z^* = z/d$) for $T^* = 2/25$. The thick line represents the counterions, and the thin line represents the coions. System parameters are $\sigma^* = 0.00765$, $\rho^* \approx 0.04$, and $\varepsilon = 78.5$. 
References


8 ELECTROCHEMICAL INTERFACIAL PROPERTIES OF EQUAL-SIZED IONS IN A MOLECULAR SOLVENT

8.1 Introduction

In this chapter, we present simulation results obtained using the $P^3$MC method dealing with the effect of electrode charge and ion concentration on the potential drop across the DL of an aqueous electrolyte solution at a solid atomistic surface. We note the similarity of our results with the experimental force measurements of Israelachvili et al.\(^1\) and the x-ray scattering findings of Toney et al.\(^2\) In addition, we compare our findings with the predictions of traditional interfacial electrochemistry theories as well as with the findings from other simulation work.

8.2 Simulation Details

Simulations were performed at three ion concentrations, 0 M, 0.25 M, and 1 M, each at four electrode surface charges, 0, ±0.1, ±0.2, and ±0.3 C/m\(^2\). Previous studies that included discrete solvent molecules considered only higher ionic concentrations. In all cases, an equal number of monovalent anions and cations of equal size were used, and opposite walls were given equal and opposite charges for an electrostatically neutral system. The well-known SPC/E model of water was used,\(^3\) and the mobile ions were given LJ parameters identical to the SPC/E oxygen-oxygen parameters. Initially, the water molecules and ions were randomly distributed throughout the occupied half of the simulation cell between the two oppositely charged electrode surfaces, which consisted of
single layers of a square lattice of fixed-in-space wall ions centered at 1.5 Å intervals. Each wall ion was assigned LJ parameters of $\sigma_{\text{LJ}} = 1.5$ Å and $\varepsilon/k = 50$ K, along with a partial charge corresponding to the desired electrode charge density.

Canonical ensemble (NVT) simulations were performed with the temperature set at 25 °C and the volume chosen to give a bulk density of approximately 60 mol/L. A somewhat high density was chosen in order to ensure that bulk liquid water would be present in all of the cases without the need to adjust the volume for the individual runs. The simulations were allowed to equilibrate for 50 ps prior to the density profile accumulation period of 200 ps (80,000 time steps of 2.5 fs each). Twenty repetitions, each with a unique starting configuration, were performed at each state point of interest in order to obtain adequate ensemble averaging and smooth ion density distribution profiles. Each repetition required approximately 16 hours of CPU time on a 32 node SGI Origin 2000 supercomputer.

8.3 Results and Discussion

We present in Figs. 8.1-8.3 water and ion $z$ direction (perpendicular to the electrode) density distribution profiles for the 12 cases studied at various surface charges, $\sigma$. No ions are present in Fig. 8.1, and the water density profiles are omitted from Figs. 8.2 and 8.3 for clarity. Water density profiles for Figs. 8.2 and 8.3 are essentially identical to the water density profiles of Fig. 8.1 with the corresponding electrode surface charge. In all cases, the positively-charged electrode is on the left, and the negatively-charged electrode is on the right. Flat, neutral density profiles seen in the central regions of all of the plots indicate the presence of completely-shielded bulk electrolyte fluid. The presence of the bulk fluid shows that the positive and negative electrodes are isolated and
enables us to examine the entire shielding layer of fluid at either electrode.\textsuperscript{4-5} The oxygen and hydrogen profiles are quite smooth in the central region, but the ionic profiles are less smooth due to the greater statistical uncertainty. Other authors have also noted this problem.

Even in the absence of ions or electrode surface charge, we see a pronounced difference between bulk and interfacial water characteristics (see Fig. 8.1, top panel). Other studies confirm this finding,\textsuperscript{6-10} and point out that the difference is even more pronounced as the electrode is charged.\textsuperscript{2,4,8-10} Especially encouraging is the agreement between these MD results and force measurements of Israelachvili \textit{et al.}\textsuperscript{1} and the x-ray scattering findings of Toney \textit{et al.}\textsuperscript{2} They found, contrary to commonly-used theories, such as the Gouy-Chapman (GC) theory,\textsuperscript{11-12} that the water is ordered in layers extending several molecular diameters from the electrode. They also observed strong dipole orientation near the charged surfaces. The oxygen and hydrogen water profiles presented here agree, at least qualitatively, on these points. Earlier theoretical studies of electrochemical interfaces using simpler molecular solvents also show this effect.\textsuperscript{8-10}

Despite the generally good agreement between these MD results and the experimental findings of Toney \textit{et al.},\textsuperscript{2} we also note a disagreement concerning the density of water next to the charged surface. While the experimental findings indicate that the density of water next to the surface is much higher than the bulk water density, our results indicate no such effect. This is in agreement with other MD simulation results\textsuperscript{13-14} even though different electrode models were used. We refer the reader to the paper by Yeh and Berkowitz\textsuperscript{14} for a discussion of this discrepancy between the simulation and experimental results. They cast doubt on the validity of the experimental
Figure 8.1. Oxygen (solid line) and hydrogen (broken line) average density distribution as a function of distance from the center of the simulation cell. The positive and negative electrodes are centered at –21.28 Å and 21.28 Å, respectively. Bulk anion and cation concentrations are 0 M.
Figure 8.2. Cation (solid line) and anion (broken line) average density distribution as a function of distance from the center of the simulation cell. The positive and negative electrodes are centered at −21.28 Å and 21.28 Å, respectively. Bulk anion and cation concentrations are 0.25 M.
Figure 8.3. Cation (solid line) and anion (broken line) average density distribution as a function of distance from the center of the simulation cell. The positive and negative electrodes are centered at –21.28 Å and 21.28 Å, respectively. Bulk anion and cation concentrations are 1 M.
results due to the extremely high density of water next to the surface that was supposedly measured by the experiment.

Without ions present, one might expect a pure solvent to behave similarly at equally- and oppositely-charged electrodes, but the lack of symmetry of the water molecules about all axes of rotation introduces asymmetry in the density profiles, as can be seen by comparing the left and right hand sides of the plots of Fig. 8.1.

Surprisingly, the addition of ions does little to change the water density distributions. Except in the extreme case of ±0.3 C/m², the ions make very small contributions to the charge shielding of the electrode when compared to the contribution of the water molecules. Potential plots at varying ion concentration of the same moderate electrode charge show insignificant differences (see Fig. 8.4). Only for the physically extreme case of ±0.3 C/m² is a significant deviation with change in ion concentration observed. It is well known from experiment¹⁵ that the potential and capacitance show strong ion concentration dependence as well as electrode charge dependence at low ionic concentrations. This phenomenon was not observed in our simulations. It may be necessary to go to concentrations well below 0.25 M to observe this phenomenon. This, regrettably is exceedingly demanding of computer resources.

It is also well known that an ion’s size has a strong influence on its solubility, and hence its adsorptivity onto the surface of an electrode. Even though the sizes of the cations and anions were chosen to be equal for the purposes of this study, the asymmetric charge distribution of the water molecules causes asymmetric anion and cation behavior.
Figure 8.4. Potential drop across the DL (from the middle of the slab to the electrode surface) as a function of surface charge density and bulk ion concentration. The triangles, X’s, and squares represent 0 M, 0.25 M and 1 M bulk anion and cation concentrations, respectively.

The cations are clearly more easily adsorbed onto the electrode surface, which also suggests better anion solvation, and slower anion transport. At zero charge we observe no wall contact adsorption of either species, and at ±0.3 C/m² both species are strongly adsorbed to the electrode surfaces.

Also evident at large surface charges is the well-known fact that the concentration of ions at a charged electrode can be much larger than the bulk ion concentration. The bottom panes of Figs. 8.2 and 8.3, which correspond to an electrode charge of ±0.3 C/m², show peaks of electrode-adsorbed ions at concentrations of more than two orders of magnitude larger than the corresponding bulk ion concentrations.

Figure 8.5 shows the potential drop across the DL as a function of distance from the electrode surface. Theories, such as the GC theory, that do not consider the molecular nature of the solvent, are unable to predict the oscillatory pattern seen here. More
sophisticated theories do show this effect.\textsuperscript{8-10} Even in the case of no charge, and no ions, this oscillatory pattern is clearly evident as seen in Fig. 8.5. A comparison between the bottom two panes of Fig. 8.5 is also noteworthy, since it demonstrates how the asymmetric nature of the solvent molecules dramatically affects the potential drop across the DL. Even though the electrode surface charges are equal and opposite, the plots are radically different. Although the potential drop across the DL seems to be only mildly affected by ion concentration, it is strongly affected by electrode charge (see Fig. 8.4.).

8.4 Conclusions

Unlike many previous DL simulations, the molecular nature of the solvent was not neglected here, and it was found that the water molecules were responsible for most of the potential drop across the DL and that ion concentration had little effect. Due to the charge distribution and shape of the water molecules, very different behavior was observed at equally- and oppositely-charged electrodes. With the models used here, the cations more easily adsorbed to the electrode surface than the anions, which indicates better solvation of the anions by the water molecules. Given sufficient electrode charge, contact adsorption of either species occurred. In fact, at very high charge, the ion concentration profile shows a peak at the electrodes in excess of 100 times the value of the bulk ion concentration. Overall, results of this MD study were in good qualitative agreement with experimental findings, and what is found in earlier, less sophisticated theoretical results. Further study that includes more sophisticated molecular and electrode models is required before DL capacitance at electrode surfaces can be fully understood.
Figure 8.5. Potential drop from the neutral bulk fluid to the electrode surface as a function of distance from the electrode surface. Bulk anion and cation concentrations are 0 M.
References


9 THE EFFECT OF ION SIZE ON DOUBLE-LAYER STRUCTURE

9.1 Introduction

In Chapter 8, we reported simulations on the structure and electrochemical properties of a model aqueous electrolyte system in which the cations and anions were of equal size. More specifically, the water molecules were modeled with the well-known SPC/E model and the mobile ions were assigned Lennard-Jones (LJ) parameters identical to those for the oxygen-oxygen interactions. In effect, then, all of the dispersion interactions were equivalent.

Often the ability or inability of ions to contact adsorb is explained in terms of the hydration energy for the ion, which itself is a strong function of ion size. The model used in the previous chapter was chosen to isolate concentration and electrode charge effects upon DL structure from any ion size dependency. In this chapter, we report the complementary study in which the LJ potential, particularly the size parameter, for the cation and anion are independently varied for a given concentration (1 M) and electrode charge (±0.1 C/m²).

9.2 Simulation Details

Other than changes in ion sizes, simulation details here are the same as those given in Section 8.2. The effect of ion size (more correctly, the effect of the LJ parameter σ) was studied in comparison to the reference case of equal-sized anions and cations. Case 1 constitutes the reference of equal-size ions, and the LJ parameters for both anions
and cations were set equal to those used for the oxygen atoms in the SPC/E water model. This corresponds to the same model used by Crozier et al.\textsuperscript{1} Cases 2 through 4 explore the effect of ion size on fluid structure relative to this reference while maintaining $\varepsilon/k$ identical for all ions. The LJ parameters corresponding to each case are provided in Table 9.1. The cation $\sigma$ value for Case 2, "small cation," and the anion $\sigma$ value for Case 3, "large anion," are values used by Spohr\textsuperscript{3} to model $\text{Na}^+$ and $\text{Cl}^-$ ions, respectively. Case 4 is the combined case of "smaller cation and larger anion." The last case, Case 5, utilizes the model used by Spohr for aqueous NaCl, including different $\varepsilon$ values and assigned cross interactions that differ from the arithmetic mean values. Since water is by far the most abundant species in the simulations, the oxygen-cation and oxygen-anion interactions are expected to dominate in determining fluid structure; ion-ion interactions will have little effect at the concentration considered here.

Bond angles and bond lengths were constrained to their equilibrium values using Gaussian mechanics.\textsuperscript{4-6} Likewise, a Gaussian thermostat was used to maintain the simulation temperature at 25°C. Drift of bond lengths and angles due to numerical round-off was corrected using a proportional feedback mechanism. Equations of motion were integrated using a fourth-order Gear predictor-corrector scheme.

### Table 9.1. Anion and cation LJ parameters for the five cases studied.

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<td></td>
<td></td>
<td>$\sigma$</td>
<td>$\varepsilon/k$</td>
<td>$\sigma$</td>
<td>$\varepsilon/k$</td>
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<tr>
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</table>
Ions and water molecules were randomly distributed at the beginning of each run, and an equilibration period of 50 ps was performed prior to the property collection period of 200 ps (80,000 time steps of 2.5 fs each). Twenty repetitions, each with a unique starting configuration, were performed for each of the five cases in order to obtain sufficient ensemble averaging and smooth ion density distribution profiles. Each repetition required approximately 16 hours of CPU time on a 32 node SGI Origin 2000 supercomputer.

9.3 Results and Discussion

Results from the simulations are shown in Figs. 9.1 – 9.4 for the average density profiles of anions, cations, oxygen atoms and hydrogen atoms, respectively. In each case, the upper figure represents the absolute density profile and the lower figure represents the deviation of the density from that of the reference case.

It is also of interest to compare the peaks in the diffuse portion of the DL near the cathode in Fig. 9.2. The second peak height is enhanced by about the same magnitude as the contact adsorption peak is decreased when the cation is made smaller. In all the cases studied, multiple layers of cations are formed in response to the cathodic charge, but the third peak is more insensitive to the change in ion size as a reduction in the first peak tends primarily to elevate the second peak.
Figure 9.1. Anion density (top) and density deviation from Case 1 (bottom) as a function of distance from the anode. The individual lines represent Case 1 (thick line), Case 2 (circles), Case 3 (squares), Case 4 (triangles), and Case 5 (crosses).
Figure 9.2. Cation density (top) and density deviation from Case 1 (bottom) as a function of distance from the anode. See Fig. 9.1 caption for explanation of symbols.
Figure 9.3. Oxygen atom density (top) and density deviation from Case 1 (bottom) as a function of distance from the anode. See Fig. 9.1 caption for explanation of symbols.
Figure 9.4. Hydrogen atom density (top) and density deviation from Case 1 (bottom) as a function of distance from the anode. See Fig. 9.1 caption for explanation of symbols.
The most significant effect of ion size is seen in Fig. 9.1 for Cases 3 and 4 where the increased anion size produces a 20-fold increase in local anion density near the anode, or positive, surface. In the reference case, only the cation contact adsorbs even though both ions are the same size. This is probably because the two positive point charges fixed at the hydrogen atom centers in the water molecule can more strongly hydrate the anion. However, in the larger anion cases, the anion is seen to strongly contact adsorb, presumably facilitated by the weaker coulombic hydration of the larger anion. This contact adsorption is accompanied by a replacement of adsorbed water molecules on the anode as evidenced by the substantial decrease in the water peak shown in the bottom of Fig. 9.3.

A decrease in the cation size produces a similar effect at the cathode, or negative electrode, where the modest contact adsorption peak for Case 1 decreases significantly with a decrease in cation size as can be observed in Fig. 9.2. Note by comparing Case 3 to the reference and Case 4 to Case 2 (in Fig. 9.2) that the contact adsorption peak for the cation is affected by an increase in anion size independent of cation size. Cation contact adsorption is enhanced by increased anion size. This counter-ion effect may be associated with an increased ion pairing as the larger anions become less tightly hydrated. Evidence of this is seen in Fig. 9.1 where a small peak of anions appears near the cathode (at the same location as the large cation peak in the DL) for the case of large ions accompanied by significant increase in water density in the first three peaks near the cathode in Fig. 9.3. It may also be caused by the significantly enhanced water density in the three peaks near the cathode produced by the increased anion size and shown in Fig. 9.3. In either...
case, it is clear that significant structural effects are produced at the cathode by the substantial anion contact adsorption that occurs at the anode in the larger anion cases.

The strong adsorption of water at both electrode surfaces is the main feature of Figs. 9.3 and 9.4. The extremely high adsorption peak is consistent with the behavior observed by many others.1,2,7-10 As mentioned above and illustrated in the bottom of Fig. 9.3, the large anion cases show reduced water density at the anode and much increased densities in the three cation layers near the cathode. In spite of the contact adsorption enhancement for the cation by the increased size of the anion, most of the cations are still hydrated as can be concluded from the fact that the contact adsorption peaks in Fig. 9.2 are approximately that of the bulk solution (1 M) with the second peak height roughly four times that density. On the other hand, with the larger anions contact adsorbed there are very few water molecules that get between the anion and the electrode as evidenced by the size and sharpness of the peak.

When compared to the other four cases, Case 5 serves as a check of the previous observations. Although the cation-cation and anion-anion $\sigma$ values are the same as Case 4, the oxygen-cation and oxygen-anion $\sigma$ values used by Spohr3 to model aqueous NaCl solutions are utilized instead of values obtained from the arithmetic-mean combining rule. Although the $\varepsilon$ values are also slightly different, the oxygen-ion $\sigma$ values are expected to dominate the fluid structure. In this case, the oxygen-cation $\sigma$ value is slightly smaller than Cases 2 and 4 and the oxygen-anion $\sigma$ value is closer to Cases 1 and 2 than to 3 and 4. As can be seen in Fig. 9.1, the anion profile for Case 5 is very similar to the reference case. Fig. 9.2 shows that the smaller oxygen-cation $\sigma$ value completely removes the contact adsorption as the cation becomes too tightly hydrated to allow
cations to reach the cathode surface. Note that there is a concomitant increase in both of
the solvated ion peaks relative to the reference case near the cathode. The elevation of the
first peak is most likely due to the fact that there is no contact adsorption to partially
neutralize the cathode charge at shorter distances and the smaller size of the hydrated ions
(note that the peak is also shifted toward the cathode). However, because of the size of
the hydrated ions and the ion self repulsions, the concentration of cations in the first layer
can not become large enough to fully neutralize the cathode’s charge and so the second
peak is also significantly enhanced. Trends for Case 5 in Figs. 9.3 and 9.4 are also
consistent with these explanations of the effects of $\sigma$ values.

We have also calculated the potential in the solution as a function of distance
from the anode. This was done by integrating from the center of the cell outward toward
the two electrode surfaces, using the local number density of charges $\rho_i q_i g_i(z)$, where $q_i$ is
the charge on site $i$, $\rho_i$ is the bulk site density and $g_i$ is the site-wall correlation function.
The potential, $\phi$, as a function of position in the fluid is then calculated from\(^{11}\)

$$\phi(z) = -\sum_i \rho_i q_i \int_z^\infty (z-z')g_i(z')dz'. \quad (9.1)$$

Figure 9.5 shows this function for the five cases considered in this work. The ion
size is seen to have little impact on the potential profile. Indeed, the ions themselves do
not affect the potential as much as the water molecules. The asymmetry observed at the
two electrode surfaces is due to the charge separation in the water molecule; i.e.,
hydrogen sites in the SPC/E model have a positive charge, but no size. The hydrogen
sites can therefore approach the electrode more closely than the oxygen atom. As can be
seen from Fig. 9.5, the surface potential is primarily neutralized by the water molecules
in the first layer and there is little difference between the five cases studied in this region. Further dampening of the potential in the next few layers is slightly a function of the ion size, but again the water dipoles at this concentration tend to dominate the shielding of the potential.

![Graph showing electrostatic potential as a function of distance from the anode. The individual lines represent Case 1 (thick line), Case 2 (———), Case 3 (— — —), Case 4 (· · · · ·), and Case 5 (— · — · —).](image)

Figure 9.5. Electrostatic potential as a function of distance from the anode. The individual lines represent Case 1 (thick line), Case 2 (———), Case 3 (— — —), Case 4 (· · · · ·), and Case 5 (— · — · —).
9.4 Conclusions

We have performed molecular dynamics simulations of 1 M model electrolytes in SPC/E water between two electrified surfaces. The effects of ion size have been studied by independently varying the LJ size parameter of the individual ions relative to the reference case of equal-size anions and cations. The full effect of long-range Coulombic interactions has been included through a highly-efficient P^3MC method applied to a slab-geometry simulation cell.

The molecular nature of the solvent in conjunction with the size of the ions was found to significantly impact the DL structure near the electrode surfaces. With equal-size ions, some cation contact adsorption occurs, but anions do not contact adsorb. However, a small increase in anion size leads to substantial anion adsorption at the anode, expelling some of the adsorbed water molecules. This is because the larger anion can not be tightly hydrated by water molecules. The increased anion size also enhances cation contact adsorption at the cathode. A decreased cation size further diminishes cation contact adsorption. These size effects propagate changes in fluid structure into the diffuse layer, where the height of two or three density peaks can be affected. However, the main dampening of the electrostatic field occurs near the electrode surface due to adsorbed water molecules. The observed size effects are compatible with explanations based on the assumed strengths of hydration for different size ions. Results of simulations on a model aqueous NaCl solution produced results consistent with these conclusions.
References

10 MODEL CHANNEL ION CURRENT CALCULATIONS

10.1 Introduction

Many molecular dynamics (MD) studies have been performed with atomistic models of ion channels during the past two decades.\textsuperscript{1-2} These have focused primarily on the structures of the channels and the energetics and dynamics of their contents, which consist of explicit waters and one or a few ions in the channel with no applied potential. In the past few years, this type of study has dramatically intensified\textsuperscript{3-13} with the discovery of the crystal structure of a bacterial potassium channel\textsuperscript{14} which is expected to serve as a prototype for the structures of voltage-gated channels. These computations have drawn attention to the structure and reduced diffusion coefficients of waters in the confined space and have demonstrated some of the energetic components responsible for ion selectivity in biological channels, but generally do not attempt to simulate ion flow in the aqueous baths outside the channel or the process of channel entry.

The equilibrium properties of ions in channels have also been studied recently using statistical mechanics and simulation approaches with simplified channel models.\textsuperscript{15-22} For instance, based on the mean spherical approximation, the excess chemical potential for binding divalent ions relative to monovalent ions in a confined space with constrained charges helps explain the selectivity of a voltage-gated calcium channel for Ca\textsuperscript{++} over Na\textsuperscript{+}.\textsuperscript{23} The result, which identifies space/charge competition as the mechanism of binding selectivity, has been confirmed by canonical ensemble Monte Carlo
simulations used to determine the distribution of ions between a cylindrical bath surrounding a periodically infinite “channel” containing confined negative charges.\textsuperscript{24-26}

Efforts to examine the flow of ions into and through channels have been carried out using Nernst-Planck,\textsuperscript{27-30} Poisson-Nernst-Planck simulations,\textsuperscript{31-37} and Brownian dynamics (BD).\textsuperscript{38-44} These simulations treat ions as point charges or spheres, respectively, and the water as a viscous continuum dielectric in order to speed simulation processing. The BD simulations are superior to the Nernst-Planck and Poisson-Nernst-Planck simulations for narrow pores because the volumes of the ions are considered.\textsuperscript{45-46}

From extensive studies of current-voltage-concentration relationships with BD, it is clear that substantial radial dipole potentials are required to offset the dielectric boundary effects in order for ions to enter channels like the nicotinic acetylcholine receptor (NACHR),\textsuperscript{42} that the dipoles in pore lining of the KcsA potassium channel allow the observed multiple occupancy and permeability of the channel,\textsuperscript{41} and that the constriction zone in OpmF porin channels presents an energy barrier that is responsible, rather than selective vestibule occupancy, for the observed channel selectivity.\textsuperscript{43}

Perhaps more importantly from a methodological point of view, these BD studies have begun to address a central issue about boundary conditions: how to treat the connection to the essentially infinite bath and membrane found in experimental conditions. Im et al.\textsuperscript{43} use grand canonical Monte Carlo (GCMC) steps in two thin slabs of solution 15 Å from the membrane surfaces to maintain constant chemical potential in the baths and BD steps to simulate ion flow through the baths and channel. This approach demonstrates a key issue: the ion occupancy of the volumette near the entry and
exit of the channel fluctuates considerably and is a Poisson distributed random variable if interactions between particles are neglected.\textsuperscript{21,43}

Furthermore, the dynamics of ion permeation have been illuminated and shown in some cases to differ from expectations based on preconceptions about free energy profiles and transport over energy barriers. For instance, potassium entry into the cytoplasmic end of a smooth-walled model of the KcsA potassium channel is only weakly (rather than linearly) dependent on cytoplasmic $[K^+]$ and is strongly dependent on membrane potential.\textsuperscript{41} Both of these results are counterintuitive from the point of view of near-equilibrium permeation theory (i.e. rate theory)\textsuperscript{47} because collisions of cytoplasmic ions with the channel are expected to rise linearly with concentration\textsuperscript{48} and to be relatively independent of applied potential due to the conductive nature of the bath.\textsuperscript{49}

Also interesting in the Chung et al.\textsuperscript{41} study was the observation that an ion reaching the top of an energy barrier in the potassium channel has a drift velocity 10-fold higher than expected based on bulk diffusivity. This type of kinetic effect is overlooked in near-equilibrium theory. We will show a qualitatively similar ballistic effect during ion exit for the fixed atomistic polar model channel used here, but speculate that it is caused here by the explicit water in the channel.

BD simulations may suffer from neglect of the volume and molecular polarization of water molecules, especially as they mediate interactions between ions within the channel, between ions and the channel walls, and between ions in the channel and ions near the channel entry. It is therefore desirable to consider the effects of solvent and ion momentum explicitly. This requires a small system size, but is shown here to be feasible with periodic boundary methods that allow continuous flow without ion repositioning.
The explicit solvation allows careful examination of water and neighboring ion distribution effects on ion entry into, passage through, and departure from the channel. A constant electric field, corresponding to that expected from a pair of planar electrodes at finite separation from the membrane, is applied to all charged atoms. As shown in a preliminary report, the voltage applied across the entire system becomes, on average, the membrane potential. The periodic image cells represent, to a limited extent, the infinite bath. The images in the z direction allow ion occupancy fluctuations in the volumette bathing the channel as ions partition randomly between the entry and exit compartments and as ions and water molecules flow through the channel. The occupancies can be expected to be approximately binomially distributed, which approximates the Poisson distribution well even for modest populations of ions. Also, the ion concentrations at the x, y, and z boundaries are held constant at the desired bulk level by this mechanism. A Gaussian thermostat is used to prevent system heating from the periodic boundary conditions and applied field with resultant flow. We refer to this particular form of non-equilibrium MD (NEMD) as applied-field MD.

The model channel and membrane system that we use is simple, consisting of a rigid atomic pore with polar walls (i.e. partial charges on the pore atoms) and internal diameter similar to that of NACHR\textsuperscript{47} embedded in a rigid, uncharged membrane. The rigid membrane helps prevent accumulation of momentum along the axis of channel flow and enhances computational efficiency, which, together with the small size of the system and the P\textsuperscript{3}M Ewald sum electrostatics, made it feasible for us to carry out such lengthy simulations.
10.2 Computational Methods

10.2.1 Model System

Applied-field NVT NEMD simulations were performed using a $25 \times 25 \times 55$ Å (in the $x$, $y$, and $z$ directions respectively) simulation box with periodic boundary conditions in all three directions. Rigid, fixed-in-space, model membrane walls consisted of neutral Lennard-Jones (LJ) spheres placed on square lattices at $z = 15$ Å and $z = 40$ Å. Center-to-center spacing of the LJ spheres in the $x$ and $y$ directions was set at 2.5 Å, and the LJ parameters for each were set at $\sigma = 2.5$ Å and $\varepsilon/k = 60$ K, with cross interactions between the mobile particles calculated using the standard Lorentz-Berthelot (LB) rules. A 4-sphere $\times$ 4-sphere section centered at $x = y = 12.5$ Å in each 10-member $\times$ 10-member wall was removed to form the entrance to the channel structure.

The model channel structure was formed using eleven twenty-member rings of LJ spheres with the same parameters as those assigned to the membrane spheres. Rings were given a center-to-center diameter of 10.625 Å, which yields an internal diameter for the channel of 8.125 Å (after subtracting two atomic radii, or $\sigma$). In addition to the LJ parameters, each channel sphere was assigned a partial charge of $-0.5 \, e$, $+0.5 \, e$, $-0.35 \, e$, or $+0.35 \, e$ in a repeating pattern around each identical twenty-member ring ($e$ being the elementary charge). The partial charges were designed to simulate those commonly used for the peptide units in proteins$^{51}$ and approximately simulate the polarity of a backbone-lined channel such as the gramicidin channel or the P region of the potassium channel. These spheres were also held rigid at even spacing around the perimeter of each ring, with each ring centered at $x = y = 12.5$ Å and placed at 2.5 Å intervals along the $z$ axis from $z = 15$ Å to $z = 40$ Å, forming a tube connecting the two membrane walls. Each
successive ring was rotated 9° about the z axis relative to the previous ring in order to produce a helical pattern of charge distribution along the tube as shown in Figure 10.1. The positioning of the membrane and channel spheres rendered the walls impermeable to the mobile atoms. The remainder of the volume of the simulation cell was accessible to the mobile particles making up the aqueous electrolyte solution.

Figure 10.1. Snapshot of the 1 M NaCl in SPC/E water simulated system showing the channel and membrane structure. Sodium and chloride ions are the large green and blue spheres, respectively. Neutral membrane atoms are drawn as transparent light blue spheres, while the charged atoms comprising the channel walls are depicted as small spheres for ease in viewing channel contents. The small black, blue, yellow, and white channel wall spheres carry charges of –0.5, -0.35, 0.35, and 0.5 e respectively. True system and species dimensions are given in the text.
Because we used explicit ions and water molecules, the pairwise coulombic interactions between nonbonded atoms were computed based on the permittivity of free space. With explicit ions and water molecules, dielectric properties arise from dipole moments and there is no need to modulate electrostatic forces with postulated dielectric constants. Thus, the effective dielectric constant of the bath is that of SPC/E water-based saline solution, and that of the membrane region is unity. The electrolyte solution consisted of a combination of SPC/E water molecules, Na\(^+\) ions, and Cl\(^-\) ions. SPC/E water was used rather than TIP3P water because in preliminary simulations with 1.0 M NaCl in TIP3P water we found that the ions had a strong tendency to form ion pairs and clusters.

The LJ and coulombic interaction parameters for the model water molecules and model ions were those used by Spohr, and are repeated in Table 10.1 for convenience. Note the cross parameters differ from those that would be derived from the LB rules.

Table 10.1. Electrolyte solution Lennard-Jones parameters.

<table>
<thead>
<tr>
<th></th>
<th>(\sigma) (Å)</th>
<th>(\varepsilon/k) (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-O</td>
<td>3.169</td>
<td>78.187</td>
</tr>
<tr>
<td>O-Na(^+)</td>
<td>2.876</td>
<td>62.724</td>
</tr>
<tr>
<td>O-Cl(^-)</td>
<td>3.250</td>
<td>62.724</td>
</tr>
<tr>
<td>Na(^+)-Na(^+)</td>
<td>2.730</td>
<td>43.001</td>
</tr>
<tr>
<td>Na(^+)-Cl(^-)</td>
<td>3.870</td>
<td>20.512</td>
</tr>
<tr>
<td>Cl(^-)-Cl(^-)</td>
<td>4.860</td>
<td>20.186</td>
</tr>
</tbody>
</table>

10.2.2 Simulation Procedure and Details

Ten sets of ten simulations were performed using the model system described above. Systems containing a nominal ion concentration of 0.5, 1 or 2 M were each tested at 0.55, 1.1 or 2.2 V externally applied potential, as well as a tenth set at 0.5 M, and 0.0
V. The exact numbers for the nominal concentrations were 608 water molecules, 4 Na\(^+\) ions, and 4 Cl\(^-\) ions for the 0.5 M case; 600 water molecules, 8 Na\(^+\) ions, and 8 Cl\(^-\) ions for the 1 M case; and 584 water molecules, 16 Na\(^+\) ions, and 16 Cl\(^-\) ions for the 2 M case. These systems were close to experimental liquid densities and, as shown below, had reasonable ion and water mobilities.

Each of the 100 runs consisted of 1 ns of equilibration time followed by 10 ns of data collection using a time step of 2.5 fs. Each run was performed on a single CPU of a 64-node SGI Origin 2000 supercomputer and required approximately two weeks of CPU time. Mobile particle positions were stored at 2.5 ps intervals (every 1000 time steps) for analysis by a post-processor program.

An electric field producing the membrane potential was uniformly applied in the \(z\) direction to all mobile particles in the simulation cell, whether in the bath or in the channel, producing the specified potential drops across the 55 Å simulation cell. Because of the external electric field we expect to see some charge build-up in the form of an electrochemical DL at both membrane walls. It will be shown later that as an ensemble average, this DL does indeed form in accordance with expectations from the membrane capacitance, neutralizes the electric field in the reservoir region, and, under opposition from channel water, magnifies the field across the membrane. The combination of the applied field and the response of the mobile particles yields, approximately and on average, the expected constant electric field across the membrane and zero field in the conductive baths, resulting in a membrane potential equal to the drop in the applied potential across the unit cell.
Previous work$^{54-56}$ shows that proper simulation of the electrochemical DL requires adequate representation of long-range electrostatic interactions, including those acting beyond the dimensions of the primary simulation cell. As in previous chapters, we handle the long-range interactions in this slab-geometry problem using the P$^3$M method because of its demonstrated flexibility and superiority to other mesh Ewald methods.$^{57}$ We follow the implementation recommendations of Deserno and Holm.$^{57-58}$

P$^3$M implementation details are as follows. A seventh-order charge assignment function was used along with a 16-point $\times$ 16-point $\times$ 64-point grid in the $x$, $y$, and $z$ directions, respectively. All LJ interactions and real-space coulombic interactions were truncated at $r_{\text{cut}} = 10$ Å. The reciprocal-space portion of the Coulombic interactions was determined by 1) assignment of the charges to the mesh according to the seventh-order charge assignment function, 2) transformation of the charged mesh to Fourier space using a fast Fourier transform, 3) multiplication by the optimal influence function to determine the potential at each mesh point, 4) $i\mathbf{k}$ differentiation in each direction to find the respective electric fields, 5) inverse fast Fourier transform back to real space for fields in all three directions, 6) assignment of the mesh-based electric fields back to the particles according to the same seventh-order charge assignment function, and 7) computation of the reciprocal-space force contribution on each particle given the electric field and the charge on each particle. For our model system, $\alpha$, the parameter that divides the P$^3$M calculation into real- and reciprocal-space contributions, was set at a constant value of 0.3028 Å$^{-1}$ according to the optimization scheme of Deserno and Holm.$^{58}$ The optimal influence function was computed only once for each run (at the beginning).
Gaussian bond and temperature constraints were used,\textsuperscript{59-60} with feedback correction to remove numerical drift error. In all cases, the system temperature was maintained at 25º C. A fourth-order Gear predictor-corrector integration scheme was used to integrate the equations of motion.

10.3 Results

As implied above, the applied field is oriented such that it drives the mobile positively-charged atoms towards higher values of z, and negatively-charged atoms towards lower values of z, and rotates water molecules so that their hydrogens are at higher $z$ values than their oxygens. In the plots used here, the $z$ position is measured from the left-hand periodic boundary. The membrane is centered in the simulation cell between $z$ values of 15 and 40 Å.

10.3.1 Ion Trajectories

The $z$ coordinates of all the ions in the system are shown as a function of time during the simulation period for one of the conditions tested, (2 M NaCl, 0.55 V total applied potential) in Figure 10.2. The ten 10-ns runs have been concatenated into one trace for the purposes of this figure (and Figure 10.3). Thus some ion passage trajectories that appear to terminate or initiate abruptly in mid channel really represent events occurring at the concatenation boundary. Because of the large applied potential, the ion motions along the $z$ direction within the channel are quite uniform with minor fluctuations. Nine complete Na\textsuperscript{+} passages and one Cl\textsuperscript{-} passage (starting at 50 ns) can be observed, with the Cl\textsuperscript{-} passing in the opposite direction (from high to low $z$), as expected.
Figure 10.2.  Na\(^+\) (Ø) and Cl\(^-\) (×) ion \(z\) positions as a function of time for the case of 2 M NaCl with 0.55 V applied potential. Symbols appear at 100 ps intervals. The ten runs of 10 ns each are plotted consecutively for a total of 100 ns of simulation time.

The passages appear to occur randomly in time, as expected for a stochastic process. Occasional visits of Cl\(^-\) ions at the negatively polarized interface (40-43 Å) and of Na\(^+\) ions at the positively polarized interface (12-15 Å) can be identified in Figure 10.2 (and 10.3). In Figure 10.2, these partly represent capacitative charge, but in many cases they are due to partial channel entries, especially where the ions get closer than \(\sigma\) (~2.5 Å) to the membrane sphere centers at \(z = 15\) Å and \(z = 40\) Å. In the baths (\(z = 0-10\) Å and \(z = 45-55\) Å), the ions appear to be uniformly distributed. The Na\(^+\) cannot be distinguished from the Cl\(^-\) in the bulk, but visual inspection of the trajectories did not reveal obvious ion pairing, cluster formation, or separation of cations from anions in the bulk.
The trajectories of just the channel ions are shown in Figure 10.3 for nine of the ten conditions studied (all except for the case of no applied potential). For the purpose of computing channel currents, partial passages are included so that passages truncated at a 10 ns boundary are not neglected. At the lowest applied potential and concentration (0.55 V, 0.5 M case), only two crossings were observed, so the counting error, assuming ion crossing to be a Poisson process, is large. Under conditions of higher concentration or voltage, however, the counting error is more reasonable. The trajectory slopes are steeper at the higher voltages and thus the passage times are shorter. Partial entries of both Na\(^+\) (z>15 Å) and Cl\(^-\) (z<40 Å) are numerous, roughly as common as successful Na\(^+\) passages. Here, there is no chance that any of the symbols represent capacitative charges at the interface because such deep penetrations into the channels are completely prohibited by van der Waals interactions with the fixed membrane spheres. Partial entries appear to reach greater penetrations at lower voltages, probably because such penetrations would be likely to convert to complete passages at the higher potentials. Although it is difficult to distinguish on these plots because they are compressed in the time axis, diffusive motion is evident at the lowest applied potential (0.55 V), especially in the crossing between 90 and 95 ns in the 1M NaCl case. No pair-wise crossing (multiple occupancy) can be readily discerned, although a few very brief occurrences of multiple occupancy were recorded at high voltage (see below for a tabular summary of crossing rates and occupancies).
Figure 10.3. Time evolution of sodium (○) and chloride (×) ion $z$-positions within the channel, drawn at 2.5 ps intervals. Breaks in the data occur at 10 ns intervals representing the ten individual runs. Rows are in order of increasing applied voltage (from top to bottom: 0.55 V, 1.1 V, 2.2 V). Columns are in order of increasing ion concentration (from left to right: 0.5 M, 1 M, 2 M).
The current flowing process for a single channel has been analyzed extensively for gramicidin channels in terms of a simple model.\textsuperscript{61-64} The current flowing through the channel and the bath are assumed to be constant while an ion is passing through the channel and zero between passages. Here, we have computed the current as a function of time from the net charge displacement within the channel per unit time divided by channel length:

\[ i = \frac{\sum q_j \Delta z_j}{tL} \]  

(10.1)

where \( i \) is the calculated current, \( q_j \) is the charge on ion \( j \), \( \Delta z_j \) is the net–displacement of ion \( j \) within the channel during time \( t \), and \( L \) is the channel length. The shapes of these ion passing currents and their relationship to the charge fluctuations in the bath, or bath currents, is shown for one case in Figure 10.4. The channel currents are generally positive, although one Na\textsuperscript{+}–mediated counter-example occurs at 48 ns. The charge fluctuations in the bath (dotted lines) are correlated with the channel currents. Between passages, bath current fluctuations are of the same order of magnitude as the channel currents, \( \pm 150 \) pA. During passages, they retain approximately the same magnitude, but close inspection reveals that they are mostly positive.
Figure 10.4. Channel (boxes) and reservoir (crosses) current versus time for the 2 M and 1.1 V applied potential case. Data points represent the average current during that 1 ns of simulation time. As in Figures 10.2 and 10.3, the 10 ns time periods are demarcated by the vertical grid lines, and are data from independent runs. Note the strong positive correlation between the channel current and the reservoir current.

For the data in Figure 10.4, the total charge transfer computed from the channel currents during the simulation (the integral under the solid curve) is $35.4 \times 10^{-19}$ coul. Within the statistical limitations of the results, this is equal to the net charge transfer in the bath, $38.1 \times 10^{-19}$ coul and corresponds to an average channel current of 35.4 pA (Table 10.2). The amplitude and frequency of bath current oscillations are undoubtedly a function of the system geometry. Bath current fluctuations should be reduced if the bath size is increased.

For our model channel, the time-course of the channel current during a single ion passage is not rectangular, both because of random fluctuations and because the velocity tends to increase as the ion approaches the exit. This is seen in Figure 10.5, which shows the average velocity of Na$^+$ as a function of $z$ position at each of the three applied
potentials utilized for 2 M NaCl. The velocity starts at 2-3 m/s for 0.55 and 1.1 V, 4-5 m/s for 2.2 V. For the lowest voltage, it remains relatively constant throughout the passage, until it nears the exit (38 Å), at which point it undergoes an abrupt increase up to ~16 m/s (39 Å) and then falls back to <5 m/s as the ion becomes abreast of the outer ring of channel atoms and membrane atoms (40 Å), and finally to near 0 m/s as the ion enters the bath. At the higher applied fields, the ion gains momentum as it passes through the channel. At 2.2 V, it does not appear to reach a limiting velocity. Although the higher potentials are not physiologically reasonable, they show that, under certain conditions, the ionic drift may deviate from a steady state. This might also occur at lower voltages, for instance, if the water in the channel were more mobile than in the present case, where the polarity of the channel walls may retard water motions.

Figure 10.5. Average net velocity of sodium ions as a function of z coordinate. Data is shown for the 2 M NaCl cases at 0.55 V (◊), 1.1 V (●), and 2.2 V (×). The arrows in this and subsequent figures (10.7-10.10) mark the entry and exit of the channel.
Statistics taken from the trajectories for all of the 10 cases are given in Table 10.2. The first two columns contain the independent variables for the 10 cases. The average time for passage through an entry region (including failed entries) extending from 12.5-17.5 Å, through the interior from 17.5-37.5 Å, and through an exit region of the channel from 37.5-42.5 Å are given in three rows per cell in the third column. These are calculated from the inverse of the mean ion velocities in these regions. The passage time for the four-fold longer interior step is 0.32 – 2.24 ns, generally less than four times the entry step passage time and much more than four times the exit step passage time, contrary to what one would expect if ion velocity were constant throughout the passage. The long average entry passage time reflects the fact that many ions penetrate only a short distance into the channel and then return out of the channel, reducing the population-average forward velocity. The short average exit passage time is due to rapid acceleration of the ion as it approaches the exit. This is apparent in Figure 10.5 and we have also observed this acceleration in trajectory animations (data not shown). The animations suggest that cation exit may be facilitated by the approach of single Cl\(^-\) atoms to the channel exit. Bulk water orientation, increasing ion momentum under constant applied force, and other potential energy effects may also contribute to the Na\(^+\) acceleration at the channel exit. From Figure 10.5 it is clear that the ion’s forward momentum is quickly dissipated in the bulk electrolyte. Passage times through all three regions decrease with increasing applied potential but are independent (to within statistical errors) of bath concentration.
Table 10.2. Mean entry (12.5 < $z$ < 17.5 Å), passage (17.5 < $z$ < 37.5 Å), and exit (37.5 < $z$ < 42.5 Å) times for Na$^+$ ions, average current as measured in the channel region (15 < $z$ < 40 Å) and bulk reservoir region, and occupancy probabilities for the ten cases tested. Probabilities are defined as the total time that the system was found in a given state divided by the total simulation time, where the occupancy states were: no ions, one Na$^+$ ion, one Cl$^-$ ion, one Na$^+$ and one Cl$^-$, or two Na$^+$ ions in the channel region. On no occasion did more than one Cl$^-$ or more than two ions occupy the channel.

<table>
<thead>
<tr>
<th>Conc. (mol/L)</th>
<th>V (volts)</th>
<th>$t_{entry}$ (ns)</th>
<th>$t_{pass}$ (ns)</th>
<th>$t_{exit}$ (ns)</th>
<th>$i$ (pA)</th>
<th>$P(0)$</th>
<th>$P(Na^+)$</th>
<th>$P(Cl^-)$</th>
<th>$P(Na^++Cl^-)$</th>
<th>$P(2 Na^+)$</th>
</tr>
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<td>.00</td>
<td>.996</td>
<td>.004</td>
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<td>.021</td>
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<td>0.05</td>
<td>19.7</td>
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<td>.091</td>
<td>.001</td>
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</tr>
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<td>0.12</td>
<td>8.52</td>
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<td>.002</td>
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</tr>
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<td>0</td>
</tr>
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<td>0.03</td>
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<td>69.1</td>
<td>.800</td>
<td>.174</td>
<td>.019</td>
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<td>0</td>
</tr>
<tr>
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<td>0.63</td>
<td>1.12</td>
<td>0.12</td>
<td>18.1</td>
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<td>.852</td>
<td>.137</td>
<td>.010</td>
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<td>0</td>
</tr>
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<td>.001</td>
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</tr>
<tr>
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<td>0.04</td>
<td>99.5</td>
<td>98.8</td>
<td>.740</td>
<td>.203</td>
<td>.047</td>
<td>.007</td>
<td>.003</td>
</tr>
</tbody>
</table>

126
The channel currents, calculated from Equation 10.1, and bulk currents calculated from the same equation but using the length of the bath for \( L \), are given in the fourth column of Table 10.2. For reference, 1 pA = 0.625 crossings from 15-40 Å per 100 ns. Although the standard deviations for the currents are not presented, we note that they were much smaller for the channel currents than for the bulk currents. However, both have an uncertainty due to counting errors associated with the Poisson process of channel crossings, which can be deduced from the square root of the number of observed crossings. For the lower concentration, the counts limit our certainty of passage frequency to an order of magnitude, so we do not focus on detailed patterns in the currents. Rather, we simply note that the channel and bulk currents generally agree to within a few pA of statistical fluctuation, as expected from Kirchhoff’s current law,\textsuperscript{65} and they generally increase with applied potential and concentration.

The next 5 columns of Table 10.2 present the average time fractions for the occupancy states for the main channel region (15-40 Å). Although the accuracies of these numbers are limited only by the frequency with which we saved trajectory frames, their usefulness for describing the steady state probabilities of occupancy depends on the underlying statistics of the random processes of ion entry and exit. Because in the best case (2 M, 2.2 V) we only observed ~62 crossings, the accuracy of such Poisson statistics is only of the order of 10%. We therefore show them only to suggest trends, but we feel that detailed kinetic analysis of the results (in terms of discrete step models, for instance) is unwarranted with this data set. The channel is primarily occupied by water only (no ions) or by one Na\(^+\). Occasional occupancy by Cl\(^-\), Na\(^+\) and Cl\(^-\), or two Na\(^+\) ions are noted, especially at 2 M and 2.2 V, but it is obvious that the model channel is primarily
selective for Na\(^+\) and is a single- rather than multiple-occupancy channel. Double Cl\(^-\) and triple occupancy were never observed.

For narrow cylindrical channels, for example gramicidin, saturation in the current-voltage relation at high voltages\(^{66}\) suggests that the rate of ion entry is essentially voltage-independent, presumably because the electric field in the conductive bath is negligible; but translocation (and, to a lesser extent, exit from the channel) are expected to increase substantially with voltage. This combination leads to the prediction that channel occupancy should decrease as applied potential is increased. We note an opposite trend here, at least for differences between 0.55 and 1.1 V. Na\(^+\) occupancy ranges from .021 to .302, increasing with concentration as expected (because the entry rate is expected to be proportional to the bath concentration), but also increasing strongly with voltage at each concentration. This implies that the entry rate must be strongly voltage dependent, more so than translocation and exit from the channel at these voltages. This voltage dependence of entry also appears when the average time between productive entries is calculated (data not shown). We have also examined whether we should expect more double occupancy, given the average time between entry and average passage time for ions in the channel. Although it appeared that for the highest voltage and concentration we should (data not shown), we feel that the statistics are not adequate to make this case with certainty for this data set and the apparent lack of multiple occupancy may be an artifact of the lateral periodic images (images in the x and y directions), so we defer analysis of this point.

The average ionic current through the channel is shown as a function of total applied potential in Figure 10.6. As expected, the current increases with applied potential
and with concentration of the bathing ion. Although the current-voltage relationship \(I-V\) appears to be superlinear in 1 M and 2 M NaCl and sigmoidal in 0.5 M NaCl, the large size of the error bars prevent detailed assertions about the \(I-V\) shapes. Therefore, we have chosen just to draw a spline curve through the points as an eye guide, rather than to fit a simplified model function. The important finding is that current does increase with voltage and concentration as expected.

### 10.3.2 Ion/Water Structure

The current flow through the channel is related to the charge structure throughout the system, that is the positions of ions and water dipoles. As a description of this structure, Figure 10.7 gives the average localized density of each of the four charged...
Figure 10.7. Average density of the various species as a function of $z$ for the 0.5 M and 1.1 V applied potential case. The SPC/E water density is divided into O (thick solid line) and H (thick dotted line) species and is seen above the chloride ion (thin solid line) and sodium ion (thin dotted line) density distributions. For improved viewing, ion densities were multiplied by different factors, namely $j = 1.0$ (O), 0.5 (H), 10.0 (Na$^+$), and 10.0 (Cl$^-$). Moreover for the channel region ($15 \text{ Å} < z < 40 \text{ Å}$), all densities were multiplied by an additional factor of twelve, because only roughly 8.3% of the volume in that region was accessible to the particles.

species as a function of $z$ for the 100 ns simulation at 0.5 M, 1.1 V. For each point, the local density (in units of moles/liter) is calculated from the average occupancy of a narrow slab centered at that point. In the region of the bulk and the interface, the volume accessible to the mobile atom centers is taken as that of a square slab 25 Å on a side (parallel to the x-y plane) and of thickness (in the $z$ dimension) of 0.025 Å. In the region of the channel ($15 < z < 40 \text{ Å}$), the cross-sectional area of a right cylinder approximately in contact with the van der Waals surface of the channel atoms, 51.85 Å$^2$, is used to define the volume accessible to the mobile atoms in the channel. This is an arbitrary volume, because the different atom species differ in their van der Waals parameters, but serves to normalize the density calculation for the sake of comparison between channel
and bulk. During this simulation, the channel was occupied only by water molecules
90.8% of the time and by Na\(^+\) (and water) 9.1% of the time (Table 10.2), so the profile
primarily reflects the state of the unoccupied channel. \([\text{Na}^+]\) and \([\text{Cl}^-]\), plotted at ten
times their actual values, are 0.5 M in the bulk, but \([\text{Na}^+]\) rises above 0.5 M near the
membrane on the left \((6 < z < 8 \text{ Å})\) whereas \([\text{Cl}^-]\) falls below. In contrast, \([\text{Cl}^-]\) rises
slightly above and \([\text{Na}^+]\) falls below on the right \((45 < z < 47 \text{ Å})\). The asymmetry
between cation and anion concentration continues up to the channel entrance, defined as
the planes of the membrane atom centers at 15 and 40 Å. Of course, the excess average
of cations on the left and anions on the right cannot be detected in any single frame, but
represents a probability density constituting the capacitative charge on the membrane. In
this case, the average net charge is \(+1.29 \times 10^{-6} \text{ coul/cm}^2\) \((0.54 \text{ e})\) on the right and \(-1.62
\times 10^{-6} \text{ coul/cm}^2\) \((-0.63 \text{ e})\) on the left, corresponding to a specific capacitance, \(Q/VA\), of
2.74 \(\mu\text{F/cm}^2\) for the membrane. This value can be compared to 0.30 \(\mu\text{F/cm}^2\) using a
thickness of \(d = 30 \text{ Å}\) (which takes into account the membrane interface atom radii) and
is higher than is usually observed for planar bilayers experimentally. However, one
cannot tell from the charge density averaged over the \(x\) and \(y\) dimensions of the slab
whether it primarily represents charging of the membrane or accumulation near the
channel entry and exit. A certain amount of accumulation is to be expected because the
net dipole of the channel water should attract cations at the left end and anions at the right
end. This could in part explain the higher excess charges observed here.

In Figure 10.7, the density of the SPC/E water near the two boundaries of the
system \((z = 0 \text{ and } 55 \text{ Å})\) is 56.4 M, approximately that of bulk water. Although there is
no reason to expect the SPC/E model of water to give reasonable pressures in this NVT simulation, mobility of the ions and water were reasonable, with the average water diffusion coefficient in the bulk compartment (0 < z < 5 Å and 50 < z < 55 Å) being computed as 2.3×10^{-5} \text{cm}^2/\text{s}, that of Na\(^+\) as 1.3×10^{-5} \text{cm}^2/\text{s}, and that of Cl\(^-\) as 1.1×10^{-5} \text{cm}^2/\text{s}. The computed diffusion coefficients compare well with the experimental values. Three layers of water ordering can be observed with increasing structure near the membrane surface, seen as peaks in oxygen density at 5, 9, and 12 Å on the left. Similar peaks occur on the right. The water structure may be important in the overall potential profile for this system, but may not be significant to biological systems where the lipid head group structure is much more complex and the head groups are mobile.

The water oxygen atoms in the channel have an average density near that in the bulk. They are clearly structured in 10 layers, corresponding to the eleven rings of atoms forming the channel wall, and oriented by the applied potential. The Na\(^+\) density in the channel also shows peaks. These are located at the oxygen minima and suggest a steric preference for more vacant locations. As will be shown below, strong interactions between water and the channel walls are only modestly disrupted by Na\(^+\) in the channel.

### 10.3.3 Electrostatic Potential Decomposition

The contributions of the particles of the system and the applied potential to the net electrical potential along the axis of the channel was computed from the ensemble average charge distribution. In doing this, we took care to avoid delta function contributions to the potential due to close proximity of charged particles to the test point by performing the calculation strictly in reciprocal space, setting \(r_{\text{cut}}\) to 2 Å, re-adjusting the tuning parameter, \(\alpha\), and excluding the real-space contributions. In Figure 10.8 the
Figure 10.8. Decomposition of the electrostatic potential along the channel axis for the 0.5 M and 1.1 V applied potential case. Potentials were probed by test particle insertion at positions along the $z$ axis. The total potential (—) is given by the sum of the potential due to the ions (·····), the potential due to the water molecules (- - - - -), and the applied potential (– · – · – ·). The electrostatic potentials were taken as averages over the entire duration of the simulations.

contributions of the ions, water molecules, the applied potential, and their sum are plotted for the same 100 ns simulation used for Figure 10.7. As can be seen, there is very little potential drop in the bath and the total voltage drop of 1.1 V occurs across the membrane.

To help understand the origin of this electrostatic potential decomposition, it is useful to examine how the applied potential orients the water molecules in the system. This is shown in Table 10.3, which gives the total ensemble average cosine of the angle between the water dipole and the $z$ axis for each of four different regions. Column I is the central region of the bath near the periodic boundaries ($z<5$ or $z>50 \text{ Å}$), column II is near the left wall ($5<z<15 \text{ Å}$), column III is in the channel ($15<z<40 \text{ Å}$), and column IV is near the right wall ($40<z<50 \text{ Å}$). This statistic would be zero for fully randomized water orientations. It should be noted that the orientation increases with applied potential.
near the walls and in the channel, and is negligible everywhere when no potential is applied and at all voltages in the central region. The slight reductions in channel water orientation at higher bath ion concentrations may reflect increased disruption of the channel waters by passing ions.

The decomposition of the electrostatic potential into water and ion contributions can be understood in terms of two major dipoles: the channel water dipole and the capacitative charge dipole. The waters in the channel are oriented by the applied potential (Figure 10.8, Table 10.3) with the negative end of the dipole towards the channel entry at $z = 15$ Å. The ion distribution at the membrane water interface forms the capacitative charge, which constitutes a macroscopic dipole oriented in the opposite direction. In the bulk region of the bath, orientation and accumulation effects are small.

Table 10.3. Ensemble average water orientation for regions (I) near boundaries, (II) near the left wall, (III) in the channel, and (IV) near the right wall. See text for details.

<table>
<thead>
<tr>
<th>Conc. (mol/L)</th>
<th>V (volts)</th>
<th>$\langle \cos(\theta) \rangle$</th>
</tr>
</thead>
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<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.55</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
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<td>0.02</td>
</tr>
<tr>
<td></td>
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<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>0.55</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
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<tr>
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<tr>
<td></td>
<td>2.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>
such that the effects of the two components on the potential should be small. A positively-charged test particle placed inside the channel is driven from right to left by the channel water dipole, in opposition to the applied potential and the capacitively charged dipole. The latter left-to-right driving force dominates. In contrast, a positively-charged test particle placed in the bath is driven from left to right by the channel water dipole and the applied potential, in opposition to the capacitatively charged dipole. In this case, opposite driving forces cancel, leaving very little potential drop in the bath.

The total potential drop across the membrane has an approximately linear profile except at the ends of the channel, where large swings in the water potential (dashed line), presumably due to oriented water dipoles in the structured layers near the interface, contribute a significant biphasic potential. This has the shape of the potential expected from a combination an infinite sheet of surface charge and an infinite sheet of dipoles. In the present case, the potential is due strictly to the waters and ions because the membrane atoms are all neutral. The total potential drop occurs primarily in the channel region at the four applied potentials of 0.0, 0.55, 1.1, and 2.2 V as shown in Figure 10.9. The drop is not quite linear in any case, being somewhat steeper on the left hand side.

10.3.4 Ion Potential Energy Decomposition

There is enough sampling with these long trajectories that the average ion-environment interaction energy can be used directly as a rough gauge of the free-energy barriers for ion passage, without resorting to specialized sampling techniques such as umbrella sampling. In Figure 10.10, we present one of the major components of the total system potential energy, the ion-environment interaction energy, as a function of the ion $z$ position for the case of 2 M, 0.55 V. Here the environment is defined as all water
Figure 10.9. Comparison of the total electrostatic potential as a function of \( z \) for the 0.5 M systems with 0.0 V (solid line), 0.55 V (dotted line), 1.1 V (dashed line), and 2.2 V (dot and dash line) applied potential. Potentials were calculated in the same fashion as described in the Figure 10.8 caption.

molecules, all other ions, and all membrane and channel wall atoms, as well as their long-range images, including both local and inverse space components. Excluded from the sum are the water-water, water-channel, and water-membrane interaction energies and the applied potential. Because we used the SPC/E model for water and there are no other bonded atoms in the system, only nonbonded interaction energies play a role in the interaction energy. The \( \text{Na}^+ \)-environment interactions in the bulk average between \(-385\) and \(-390\) kJ/mol, roughly consistent with the enthalpy of hydration for \( \text{Na}^+ \) at infinite dilution (\(-438\) kJ/mol, as cited in Hille,\textsuperscript{47} pg. 276). For ions in the channel, this favorable interaction energy is less negative, corresponding to an energy barrier of about 15 kJ/mol. The barrier peaks to the right of the channel center at \( \sim30 \) Å and declines quite sharply towards the exit at 40 Å. The fact that the interaction energy remains favorable
Figure 10.10. Individual ion potential energy (due interactions with the whole system, excluding the applied potential) as a function of $z$ for the 2 M and 0.55 V applied potential case. The (circle) symbol represents Na$^+$ ion energies and the (triangle) symbol represents Cl$^-$ ion energies. This figure differs from Figures 10.8 and 10.9 in that the simulated ions themselves were used to compute the potentials (no test particle insertions were used) and LJ interactions were included. Only ions within 2 Å of a line drawn through the center of the channel and parallel to the $z$ axis were included in the averaging. Water-channel and water-water interaction energies are not included.

throughout the channel suggests that the polar channel walls can almost fully compensate for the second shell and more distant electrostatic coordination of the ion, and is consistent with MD simulations performed by Roux and Karplus$^1$ for Na$^+$ entry into the gramicidin channel. In contrast, the average Cl$^-$-environment interaction energy is ~-482 kJ/mol in the bulk, which is considerably more negative than the enthalpy of hydration (-342 kJ/mol as cited in Hille,$^{47}$ pg. 276) and may suggest that the Spohr$^{53}$ Cl$^-$-water interaction potential used here is too strong. Nevertheless, the energetic basis for the channel selectivity is clearly revealed by the height of the peak in the interaction barrier, ~30 kJ/mol. We suspect that the channel water energy would also contribute further to
this peak based on geometric considerations shown below. Again, the barrier tends to be highest towards the channel exit, which, for Cl\(^-\), is on the left.

The increased energy barrier to Cl\(^-\) passage can be partly ascribed to the channel waters and their interactions with the channel wall. Figure 10.11 shows the average H, O, Na\(^+\), and Cl\(^-\) densities as a function of distance from the center of the channel for one of the trajectories. Oxygen density is seen to peak near 3 Å from the channel center with H peaks on either side. Thus, the channel walls strongly attract the channel water molecules. Both Na\(^+\) and Cl\(^-\), when present, stay nearer the axis than most of the channel waters, which is more problematic for Cl\(^-\) than for Na\(^+\) because the proximity of the water oxygens would be repulsive for Cl\(^-\) but attractive for Na\(^+\). The interposed H peak would partly ameliorate this selectivity, but the protons each only bear half the magnitude of the

![Figure 10.11. Average density of the various species inside the channel (15<z<40 Å) for the 2 M, 0.55 V case. Density is given as a function of r, the distance from the center of the channel, where r = 5.3125 Å corresponds to the center of the spheres that make up the channel walls (marked by the arrow). For plotting convenience ion densities were multiplied by 100 and hydrogen densities were divided by 2. Traces for the various species are: O (solid line), H (dotted line), Na\(^+\) (dash and dot line), Cl\(^-\) (dashed line).](image-url)
partial charge on the oxygen. Channel water and Na\textsuperscript{+} momentum computations show that the direction of water movements correlate with the Na\textsuperscript{+} movements in the channel, but visual inspection of the trajectories indicates that permeating ions do not sweep all of the waters ahead of them, as is the case in the narrower gramicidin channel, but rather they tend to pass among the waters, which mostly remain in contact with the channel wall (data not shown).

10.4 Discussion

It has been shown that the process of ion transport through a model biological channel can be simulated with molecular-level detail covering the entry, passage, and exit events, while covering enough time to predict the ionic current as a function of ionic concentration and applied potential. A sufficient number of complete passages were obtained to provide reasonable estimates of the current for membrane potentials as low as 0.5 V with permeant ion concentrations as low as 0.5 M. Although both values are above those seen \textit{in vivo} in land organisms, such values have been attained in lipid bilayer experiments.\textsuperscript{66} This represents considerable progress toward effective modeling of ion transport through channels under realistic conditions.

The use of a small, periodic system with a fast and efficient long-range force calculation scheme has made this calculation possible. A reasonable electrostatic potential profile as a function of position relative to the membrane has been shown to exist for the model system, at least as an ensemble average (Figure 10.9). It has also been shown that the molecular nature of the solvent is indispensable to the exploration of the selectivity issues, as well as channel entry, passage, and exit dynamics. These various
stages of ion transport across the membrane are clearly very distinct, yet would have been altogether ignored if the large reservoir region had been excluded.

Here, we will first compare our apparent channel conductance and current voltage relationship shapes to those measured for biological channels (specifically the NACHR channel and gramicidin A channel). We will then compare these findings to those of recent BD simulations. Finally, we evaluate the electrical characteristics of our system and consider the statistical uncertainties and conceptual inadequacies of our approach.

Our model channel is not intended to represent any specific biological protein, but has an internal diameter (8.125 Å) similar to that of the NACHR, porins, voltage-gated calcium channels, and others.\textsuperscript{47,67} The wall polarity, due to the partial charges on the atoms lining the wall, was designed through the use of standard peptide unit atomic charges to be similar to that of a gramicidin channel or the P region of a potassium channel, and is probably higher than that of other channels, except where they have charged side chains. If the channel conductance is computed in the usual fashion as the current divided by the total applied potential, a value of 32.9 pS is obtained for the 2M NaCl at 0.55 V, slightly higher than the conductance of a gramicidin A channel in 2 M NaCl, 30.4 pS at 0.2 V,\textsuperscript{68} and lower than that of a NACHR channel, 44 and 49 pS in chromaffin cells and myotubes respectively under physiological conditions (as cited in Hille,\textsuperscript{47} pg. 332). Thus, the model channel has lower conductance than expected for its diameter. This is probably due to the restriction of the Na\textsuperscript{+} ions to the neighborhood of the channel axis by the channel waters, as well as the immobile channel walls.

The current voltage relations of gramicidin channels in phosphocholine bilayers shift from sublinear in 0.1 M NaCl to slightly superlinear in 1 M NaCl.\textsuperscript{68-69} This is
consistent with the superlinearity in the model channel current-voltage relationships for moderate to high concentrations. The superlinearity is interesting, because at such high voltages one might expect the currents to saturate because the average field should only extend slightly into the bath. However, Figure 10.9 shows that for our model the applied field has considerable effect on the average electrostatic potential between \( z = 11 \) and 15 Å. Also, there is evidence that ion movements are affected by the applied field just outside of the channel in Figure 10.5, where the average ion velocity in the region \( z = 12-15 \) Å clearly rises above zero. Presumably, the high voltage dependence of entry implied by the occupancy data in Table 10.2 combines with the high voltage dependence of translocation to prevent saturation.

The selectivity for cations observed here may be a general property of channels of the diameter used here. Water hydrogen atoms can achieve close proximity to negatively-polarized channel atoms, such as carbonyl or hydroxyl oxygen and amide nitrogen, whereas water oxygens are at greater separations from related positively-polarized channel atoms. In our channel, waters were generally adsorbed on the wall surface and rotated with many of the protons pointing toward the wall and oxygen atoms near the center (Figure 10.11), a favorable orientation for coordination of cations but not for anions. This is reminiscent of the water structure observed for smooth-walled nonpolar 3-Å radius cylinders, which also showed partitioning of \( \text{Na}^+ \) towards the center of the cylinder, suggesting that the channel water structure (and channel selectivity) may be yet a more general property of the channel wall curvature. The channel water structure is probably the origin of the difference in the interaction energy profiles for the two species in Figure 10.10.
The extent and findings of our applied-field MD simulations can be compared to recent BD simulations of ion channel behavior. Using BD simulations with explicit ions and smooth-walled channels with reflective boundaries surrounding the system volume, an applied field, and induced charge at the dielectric interface boundaries, Chung and colleagues have performed extensive simulations of model NACHR\textsuperscript{42} and potassium\textsuperscript{41} channels. Their simulations are typically 0.5-1.0 µs long for each state point, and they covered many more state points than we considered. It appears that their production speed is still roughly 50 times faster than ours. They use a long time step of 100 fs (with a short one of 2 fs for steep regions on the energy surface) but don’t include waters; we use a uniform time step of 2.5 fs and explicit water.

They found that the currents in these two types of channels could be well predicted provided the correct magnitude and distribution of radial dipoles is introduced along the channel walls to ameliorate the ion passage energy barrier due to the membrane dielectric. For instance, currents for the potassium channel model were similar in magnitude and I-V shape to those shown here provided they used a reasonable set of radial and SS1-helix dipoles. For one set of data analyzed carefully, the rate of ion entries into the channel increased in proportion to \(c^{1/3}\) instead of to \(c\), the permeant ion concentration. This was explained by saying that the entry process may just depend on a small cylindrical antechamber occupancy, rather than the ion concentration in the bulk as is usually predicted.\textsuperscript{31,48} Examination of the mean empty channel time in our results seem consistent with a linear concentration dependence of entry, although statistics do not allow discernment between a linear and a lower power concentration dependence.
It is interesting that Chung et al.\textsuperscript{41} observed a high drift velocity for an ion reaching the top of the principal energy barrier. Perhaps our observation of a high average velocity during ion exit (Figure 10.5) is similar. Both thermodynamic and kinetic factors may play a role in the high velocity in the exit region. The potential energy drop seen in Figure 10.10 should accelerate the ion out of the channel. At 1.1 and 2.2 V, the velocity is seen to rise steadily along the length of the channel due to acceleration by the net electric field in the channel (Figure 10.9). However, this kinetic effect is not prominent for the 0.55 V case, and would probably be minor at physiological membrane potentials.

Finally, it is interesting to relate the electrical parameters of our system to those of a macroscopic system. The effects of periodic boundaries and a small unit cell can be dramatic and need to be carefully considered to determine the legitimacy of comparisons with experimental results. In the central cell, the bilayer has an area of $625 \, \text{Å}^2$, a predicted capacitance based on membrane area, thickness and the permittivity of free space of $0.30 \, \mu\text{F/cm}^2$, and an apparent capacitance, based on the observed excess charge in the double layer, of $2.74 \, \mu\text{F/cm}^2$. This corresponds to a net capacitative charge of $1.46 \times 10^{-19} \, \text{C}$ in the central cell at the 1.1 V applied potential, or 0.59 e. The excess observed membrane capacitance may be due to the channel water, which raises the effective dielectric constant of the membrane. This effect might be exaggerated here by the presence of lateral images of the channel and its contents.

Clearly, our simplified model also lacks other electrostatic features considered germane to control of ion channel conductance. Atomic polarizability of alkane chain atoms (which yields a typical dielectric constant of $\sim 2$) would somewhat reduce the
electrostatic barrier to translocation, and the interfacial dipole layer, known to affect gramicidin channel conductance is not properly represented by the water-membrane interface in the model. However, judging from the Na\(^+\)-environment interaction energy (Figure 10.10), the so-called “image barrier” is quite low in our system (~15 kJ/mol), probably due to the moderately large diameter of the channel and continued solvation of the ion in the channel. (We note here that, because of the explicit water, it is not necessary to implement image charges to represent the dielectric interfaces, as is required with BD). The interfacial dipole potential in our system is ~0.3 V (Figure 10.9), similar to that measured for phospholipid bilayers.

Electrophysiologists would be concerned about a possible series resistance artifact in our system. Using a conductivity meter, we measure the specific conductivity of 1M NaCl to be 12.9 Ω\(-\)cm. From this macroscopic measurement and an estimate of the accessible volume of the two baths of 25 Å length (total) and 625 Å\(^2\), we expect the resistance of the two baths in our central cell to total 51.6 MΩ. Compared to the channel resistance, which, using the conductance for 1 M NaCl at 1.1 V in Table 10.2, is 44.5 GΩ, this is a negligible series resistance. We note, in this context, that the observed conductance of the channel is lower than expected for a volume conductor with bulk conductivity and the dimensions of the channel, which, from the channel's ion accessible radius (~2 Å), the channel length, and the bulk solution resistivity, would be ~390 pS in 1 M NaCl. This can be attributed to immobilization of the channel water molecules by the polar, rigid channel walls reducing ion mobility in the pore and to the potential energy barrier for ion crossing, as well as other atomistic factors.
In summary, multiple ion passages can be simulated in a model channel if sufficient concentration and voltage are utilized. The use of periodic boundary conditions prevents artificial charge buildup and yields closed circuit conditions. A uniform applied field results in appropriate compensations by SPC/E water molecules and explicit Na\(^+\) and Cl\(^-\) ions. The results demonstrate the importance of including explicit solvent in the simulation. Cation selectivity is strong due to water structure in the channel. Channel water is strongly oriented by the applied field, enhancing the capacitative charge and probably the electric field near the channel entry and exit, possibly adding a voltage-dependence to the entry rate constant and possibly stimulating expulsion of the ion at the exit. We feel that this type of modeling should be applied to simple biological channels to explore more carefully the factors affecting ion entry, throughput, exit, and multiple occupancy.
References

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11 CONCLUSION

We have developed slab-geometry molecular dynamics methodology that is applicable to a wide variety of interfacial chemistry problems, and have applied this methodology to the prediction of activity coefficients, electrochemical interface characterization, and ion transport through a model biological membrane. Slab-geometry MD is a valuable tool for the examination of molecular level events and characterization for a wide range of problems, and is limited primarily by molecular model adequacy and computational resources availability. Research in this field will continue to intensify as molecular models improve, computational power grows, and algorithms become better in terms of efficiency and applicability to real-world problems.

Although traditional MD approaches are not directly applicable to slab-geometry systems because of the difficulties associated with the interface boundaries, modification makes application possible. Periodic boundary conditions may or may not still be used in the z direction, long-range forces must be treated differently, and system homogeneity assumptions must be reconsidered. Although modifications must be considered on a case-by-case basis, we have shown that $P^3M$ is an efficient and reliable way to calculate long-range forces that can be applied to most slab-geometry systems. With the addition of a correction term (as in $P^3MC$), an isolated slab-geometry system can be simulated.

In Chapters 3-5, we have demonstrated the application of slab-geometry MD to the prediction of activity coefficients for six representative binary mixtures of
industrially-important compounds. Osmotic molecular dynamics enables us to predict activity coefficients from first principles and is mostly limited by the cross-interaction parameters of the molecular models. Future improvement of molecular models will make OMD an invaluable tool to chemical engineers for the non-empirical prediction of activity coefficients and excess properties.

Interfacial electrochemical properties were examined by slab-geometry MD in Chapters 6-9. Ion density distribution profiles and double-layer capacitance were calculated as a function of temperature for the low effective temperature region, and MC CS results were cross-examined using MD EW3DC for the RPM (Chapter 7). In Chapters 8 and 9, we applied the P³MC methodology to the calculation of the double layer potential drop as a function of electrode charge, ion concentration, and ion size for model electrolyte systems with molecular solvent. Molecular solvent proved to be a costly, yet essential, improvement over previous work. Future work must continue to improve electrode and molecular models while keeping computational costs down in order to better understand interfacial electrochemistry characteristics.

Chapter 10 described the first attempt to predict I-V curves for a model channel/membrane system that included both discrete solvent molecules and a bulk fluid reservoir region. The efficient P³M methodology along with judicious choices for the system parameters enabled 100 ns worth of simulation each at 10 state points for a total of an entire microsecond’s worth of simulation. Channel selectivity of Na⁺ ions over Cl⁻ ions would have been missed had the water molecules been excluded. Future work should also include a flexible, more realistic channel structure.
Slab-geometry problems represent a very important class of problems that can be examined using appropriate MD methodology. This work has demonstrated the feasibility of studying a variety of scientific questions using slab-geometry MD. We recommend application of this methodology to other slab-geometry problems of interest such as liquid-liquid equilibrium and heterogeneous catalysis. We also recommend further model improvements for the problems studied here, including improved cross-parameter interactions for multi-component mixtures, better electrode representations, and better ion channel representations.