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MULTIPLE ELECTROSTATIC METHODS
FOR PROTEIN MODELING WITH REACTION FIELD TREATMENT

by

Yong Kong

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ABSTRACT OF THE DISSERTATION

Multipole Electrostatic Methods
for Protein Modeling with Reaction Field Treatment

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Yong Kong

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Professor David J. States, Chairperson

This dissertation focuses on electrostatics in the computer modeling of biomacromolecules. The commonly used partial charge model is replaced with an atom-centered multipole model, which provides a more accurate description of electrostatic interactions. A Cartesian polytensor method is adopted which simplifies the organization of the computation. To treat the solvent effects, general methods for calculating the reaction field generated by off-center point multipoles in a spherical cavity are developed, which are the generalization of Kirkwood’s original theory for an arbitrary charge distribution. This reaction field method scales linearly with the size of the system, allowing long-range electrostatic effects to be considered with little computational expense. Computer programs for the multipole electrostatics and reaction field have been incorporated into the TINKER molecular modeling package developed in the Ponder lab.

As an application of the methodology, polarizable multipole water models were
developed. The parameters for water model were obtained from high level ab initio calculations and adjusted to reproduce the water dimer energy and structure, as well as the bulk structure properties. Energy minimization of small clusters and molecular dynamic simulations of bulk properties of water were carried out and results were compared with experiments and high level ab initio calculations. The models give accurate predictions for small water clusters and the structure and energetics of bulk water.
In memory of my father,

Kong Xiang Lian
Dedicated to my mother,

Jiang Ying Zun
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Chapter 1

A Polarizable Multipole

Electrostatics Force Field for

Flexible Biological Macromolecules

1.1 Introduction

The functions and relative stabilities of proteins and other macromolecules are determined by the balance between a variety of forces. These forces arise not only from the interactions between the atoms within the molecules, but also from the interactions between the molecules and their environments. Among these forces, electrostatic interactions are the most important factor in determining the structure and function of biomolecules (Warshel & Russell, 1984; Rogers, 1986; Harvey, 1989; Davis & McCammon, 1990; Sharp & Honig, 1990; Warshel & Aqvist, 1991; Rashin, 1993; Smith
van Gunsteren, 1993; Tomasi & Persico, 1994; Cramer & Truhlar, 1995; Honig & Nicholls, 1995; Nakamura, 1996). A back-of-the-envelope calculation shows that the electrostatic energy for a charged amino acid in a polar solvent is about two orders of magnitude larger than its van der Waals interactions (Warshel & Russell, 1984). Therefore, in order to get a detailed understanding of the behavior of macromolecules in solution from computer simulations, it is important to describe as accurately as possible the electrostatic interactions within the macromolecules themselves and between the macromolecules and their environments.

In the current generation of empirical force fields for biomolecular simulations, the electrostatic interactions are approximated by atomic partial charge models, in which the electron structure of an atom is represented by a partial charge located at atomic nucleus. These models are easy to implement and fast to calculate. However, it has been recognized that simple partial charge representations are intrinsically unable to accurately model the electrostatic potential around polar molecules. The partial charge model can be regarded as only the first term in an infinite multipole expansion of the electrostatic potential. To model the electrostatic potential correctly, higher order terms are needed. For small-molecule dimers, Buckingham et al. have shown that reliable prediction of experimentally observed geometries requires multipole expansion through quadrupoles (Buckingham & Fowler, 1985; Hurst et al., 1986). Williams showed that optimally fit partial charges produce a potential with a 10-15% root-mean-square (RMS) difference from the target \textit{ab initio} potential, while the average RMS error in an optimal multipole-based potential is usually less than
0.1% relative to the *ab initio* potential (Williams, 1988). For HF dimers, Spackman showed that the partial charge models can not even predict qualitatively the geometry (Spackman, 1986). Using formamide as an example, Colonna *et al.* analyzed *ab initio* derived electric field and multipole modeling and demonstrated that the atom-centered partial charge models have significant errors (Colonna *et al.*, 1992). Sokalski *et al.* showed that the angular characteristics of the electrostatic potential around functional groups capable of forming hydrogen bonds can be considerably distorted within the partial charge model (Sokalski *et al.*, 1993). The inaccuracy of the partial charge models was also discussed by Dykstra (Dykstra, 1993).

Another limitation of the current generation of empirical force fields is that they use a pairwise additive potential to model electrostatic interactions. It has long been recognized that nonadditive interactions due to electric polarization and many-body effects play an important role in both homogeneous systems such as liquid water (Elrod & Saykally, 1994) and inhomogeneous systems such as proteins (van Belle *et al.*, 1987). An often cited example is the total dipole moment of a water molecule which changes from 1.855 D in the gas phase to approximately 2.6 D in condensed phase (Coulson & Eisenberg, 1966). For a bulk system such as liquid water, the nonadditive effects can be incorporated into a pairwise additive potential in an average way by carefully parameterizing the potential against the thermodynamic properties of the bulk (Section 2.2). In fact, the popular pairwise water models in current use, such as SPC (SPC/E) (Berendsen *et al.*, 1981; Berendsen *et al.*, 1987) and TIP3P (Jorgensen, 1981; Jorgensen *et al.*, 1983) are parameterized in this
way. For isotropic, homogeneous systems this kind of effective potential can give some correct average properties, but for anisotropic, inhomogeneous systems such as proteins, as well as water molecules around surfaces, this approach will break down. Several groups have tried to take the nonadditive many-body interactions explicitly into additional special potential functions for small molecules in homogeneous systems such as ions in water (Wojcik & Clementi, 1986; Caldwell et al., 1990). For large molecules, it would be cumbersome to implement this approach. For an empirical force field aiming for general-propose biomolecular simulations, a common approach is to incorporate polarizability into the existing molecular mechanics force field. For the sake of simplicity, only dipole polarizability is usually considered. For some models of small molecules such as water, higher order polarizabilities are also incorporated (Millot & Stone, 1992).

A related problem arises when the polarizability is incorporated into the potential function. In the effective pairwise potentials, the polarization effects are included \textit{implicitly} in the parameterization procedure so that the final permanent charges, and dipoles if any, are artificially larger than the gas phase values. When the polarizability is incorporated, the gas phase values are usually used, and the decrease in these values makes it harder to maintain the correct short-range structural features of liquid water using simple potentials with just three interaction sites per water molecules (King & Warshel, 1989). For example, the inclusion of the polarizability term together with the decrease in the permanent dipole tends to delocalize the attractive solvent-solvent interactions, leading to a higher diffusion constant (King & Warshel, 1989). This may
be one of the reasons why some previous polarizable water models are less successful than those carefully parameterized effective pairwise interaction models (Barnes et al., 1979; Rullmann & van Duijnen, 1988). Multipole expansion can provide a much more detailed description of short-range interactions (Dykstra, 1993). Together with inclusion of polarizability, a multipole model will give a more accurate representation of the electrostatic interactions.

One of the goals of this dissertation is to extend the approximation of electrostatic interactions in empirical force fields for macromolecule modeling from the partial charge models to higher order of multipoles. The multipole interactions have been implemented in a force field that is suitable for simulations of flexible biomolecules by using a polytensor formalism. The formulas can be readily extended to any desired order of multipoles. In addition, the analytical derivatives can be obtained in a systematic way. When cast in the matrix formula, the field and gradient of field can be easily obtained, which makes it handy to incorporate the polarizability into the force field.

In this Chapter the polytensor formulation for direct multipole interactions will be described as well as the formulas for derivatives and the field. Since the representation of multipoles depends on coordinate systems, this Chapter will also describe how the multipoles are represented in the force field. Directionality of the dipole and higher multipoles in flexible molecules is addressed. The final sections contain a discussion of induced dipoles and the related problem of calculation of derivatives when the induced dipoles are taken into account.
1.2 Polytensor formulas for multipole interaction

For the partial charge models, the electrostatic interactions are simply given by Coulomb’s law. The potential at point $P$ given by a partial charge $q_k$ at site $k$ is given by

$$\phi_k(P) = \frac{1}{4 \pi \varepsilon_0 \varepsilon_1} \frac{q_k}{|r_P - r_k|},$$  \hspace{1cm} (1.1)

and the interaction energy between two charges $q_k$ and $q_l$ is given by

$$W_{kl} = q_l \phi_k(P_l) = q_k \phi_l(P_k) = \frac{1}{4 \pi \varepsilon_0 \varepsilon_1} \frac{q_k q_l}{|r_l - r_k|},$$  \hspace{1cm} (1.2)

if the reference energy is chosen at infinite separation. Here $\varepsilon_0$ is the permittivity of free space (absolute permittivity), and $\varepsilon_1$ is the permittivity of the dielectrics (relative permittivity) where the charges reside. The other term for $\varepsilon_1$ is dielectric constant, but this term is now in the trend of being abandoned (Scaife, 1989). The former term will be used in this dissertation.

Since the electrostatic potentials are additive (Jackson, 1975), the potential at point $P$ given by a collection of charges $\{q_k\}$ is given by

$$\phi_k(P) = \frac{1}{4 \pi \varepsilon_0 \varepsilon_1} \sum_k \frac{q_k}{|r_P - r_k|},$$  \hspace{1cm} (1.3)
and the interaction energy of the charge collection is given by

\[ W = \frac{1}{2} \sum_l q_l \phi(P_l) = \frac{1}{2} \sum_k q_k \phi(P_k) \]

\[ = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{k,l \neq l} \frac{q_k q_l}{|r_l - k_P|} = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{l>k} \frac{q_k q_l}{|r_l - k_P|}. \quad (1.4) \]

The simplicity of Eqs. 1.3 and 1.4 makes it easy to implement the partial charge models in empirical force fields.

For higher multipoles, the formulas become increasingly complicated. Standard textbooks on electrostatics usually cover the dipole-dipole interaction, which is given in vector form as

\[ W = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{\mu_k \cdot \mu_l}{r_{kl}} - 3(\mu_k \cdot r_{kl})(\mu_l \cdot r_{kl}) \frac{r_{kl}^5}{r_{kl}^4}. \quad (1.5) \]

where \( r_{kl} = r_l - r_k \). The formulas involving quadrupoles or higher multipoles are cumbersome if written out explicitly. Some formulas are compiled by several authors (Hirschfelder et al., 1954; Jansen, 1957; Jansen, 1958; Buckingham, 1967; Rein, 1973; Burley & Petsko, 1988; Stone, 1996). Two different routes are usually taken to obtain compact, general formulas for multipole potentials or energy. Both routes are based on expansion of \( 1/r_{kl} \). If we expand \( 1/r_{kl} \) in terms of spherical harmonics, we end up with the spherical tensor formulation (Stone, 1996). If we expand in terms of Taylor series, we end up with the Cartesian multipole formulation. The following development is based on Cartesian multipole formulation.
In this section we derive the matrix formulas for the electrostatic interaction energy between two sites \( k \) and \( l \). The ubiquitous factor \( 1/4\pi\varepsilon_0\varepsilon_1 \) will be omitted in the following discussion. Assume that there are \( n \) multipole sites located at \( \mathbf{r}_k \), \( k = 1\ldots n \), with partial charges \( q_{ki} \) located around site \( k \) in a nonoverlapping fashion at positions \( \mathbf{r}_{ki} \). Each charge is displaced from its own multipole center by a vector \( \mathbf{d}_{ki} \), i.e., \( \mathbf{r}_{ki} = \mathbf{r}_k + \mathbf{d}_{ki} \), with its three components \( d_{ki}^x, d_{ki}^y, \) and \( d_{ki}^z \) (Figure 1.1).

![Figure 1.1: Partial charges around a multipole center.](image)

The potential generated by the charges distribution \( \{q_{ki}\} \) around site \( k \) at the point \( P \) outside the charge distribution is given by, based on Eq. 1.3,

\[
\phi_k(P) = \sum_i \frac{q_{ki}}{|\mathbf{r}_{kP} - \mathbf{d}_{ki}|}
\]

(1.6)

where \( \mathbf{r}_{kP} = \mathbf{r}_P - \mathbf{r}_k \) and \( i \) sums over all the charges around site \( k \). If we take the
Taylor series expansion of the Eq. 1.6, we obtain

\[ \phi_k(P) = \left[ \sum_i q_{ki}, \sum_i q_{ki} d_{ki}^x, \sum_i q_{ki} d_{ki}^y, \sum_i q_{ki} d_{ki}^y, \sum_i q_{ki} (d_{ki}^x)^2, \sum_i q_{ki} d_{ki}^x d_{ki}^y, \cdots \right] \begin{bmatrix} 1 \\ \frac{\partial}{\partial x_k} \\ \frac{\partial}{\partial y_k} \\ \frac{\partial}{\partial z_k} \\ \frac{\partial^2}{\partial x_k^2} \\ \frac{\partial^2}{\partial x_k \partial y_k} \\ \vdots \end{bmatrix} \frac{1}{r_{kP}}. \] (1.7)

If we define the unabridged Cartesian multipoles at site \( k \) as (Böttcher et al., 1973; Applequist, 1984)

\[ M_k^{000} = \sum_i q_{ki}, \quad M_k^{100} = \sum_i q_{ki} d_{ki}^x, \quad M_k^{010} = \sum_i q_{ki} d_{ki}^y, \quad M_k^{001} = \sum_i q_{ki} d_{ki}^z, \]
\[ M_k^{200} = \frac{1}{2!} \sum_i q_{ki} (d_{ki}^x)^2, \quad M_k^{110} = \frac{1}{2!} \sum_i q_{ki} d_{ki}^x d_{ki}^y, \quad \cdots, \] (1.8)

which have the general form of

\[ M_k^{\lambda \mu \nu} = \frac{1}{n!} \sum_i q_{ki} (d_{ki}^x)^\lambda (d_{ki}^y)^\mu (d_{ki}^z)^\nu, \] (1.9)
with \( n = \lambda + \mu + \nu \), and the unabridged Cartesian polytensor at site \( k \) as (Applequist, 1985; Applequist, 1989)

\[
\mathbf{M}_k = \left[ M_k^{000}, M_k^{100}, M_k^{010}, M_k^{001}, M_k^{200}, M_k^{110}, \cdots \right]^t,
\]

(1.10)

where \( t \) stands for matrix transposition, and similarly at site \( l \) as

\[
\mathbf{M}_l = \left[ M_l^{000}, M_l^{100}, M_l^{010}, M_l^{001}, M_l^{200}, M_l^{110}, \cdots \right]^t,
\]

(1.11)

then we can rewrite Eq. 1.7

\[
\phi_k(P) = \mathbf{M}_k^t \left[ 1, \frac{\partial}{\partial x_k}, \frac{\partial}{\partial y_k}, \frac{\partial}{\partial z_k}, \frac{\partial^2}{\partial x_k^2}, \frac{\partial^2}{\partial x_k \partial y_k}, \cdots \right]^t \frac{1}{r_{kp}}.
\]

(1.12)

Based on Eq. 1.4, the interaction energy of site \( k \) and \( l \) is

\[
W_{kl} = \sum_j q_{lj} \phi(P_{lj}) = \mathbf{M}_k^t \left[ 1, \frac{\partial}{\partial x_k}, \frac{\partial}{\partial y_k}, \frac{\partial}{\partial z_k}, \frac{\partial^2}{\partial x_k^2}, \frac{\partial^2}{\partial x_k \partial y_k}, \cdots \right]^t \sum_j q_{lj} \frac{1}{r_{klj}},
\]

(1.13)

in which \( j \) sums over all the charges around site \( l \). If we express \( 1/r_{klj} \) at site \( l \) in the Taylor series (Figure 1.2), we have

\[
W_{kl} = \mathbf{M}_k^t \left[ 1, \frac{\partial}{\partial x_k}, \frac{\partial}{\partial y_k}, \frac{\partial}{\partial z_k}, \frac{\partial^2}{\partial x_k^2}, \frac{\partial^2}{\partial x_k \partial y_k}, \cdots \right]^t \times \left[ 1, \frac{\partial}{\partial x_l}, \frac{\partial}{\partial y_l}, \frac{\partial}{\partial z_l}, \frac{\partial^2}{\partial x_l^2}, \frac{\partial^2}{\partial x_l \partial y_l}, \cdots \right] \left( \frac{1}{r_{kl}} \right) \mathbf{M}_l,
\]

(1.14)
where \( r_{kl} = r_l - r_k \).

Figure 1.2: Interaction between two multipole sites.

If we write out the second and third terms of Eq. 1.14 and denote it as \( T_{kl} \), we have

\[
T_{kl} = \begin{bmatrix}
1 & \frac{\partial}{\partial x_l} & \frac{\partial}{\partial y_l} & \frac{\partial}{\partial z_l} & \cdots \\
\frac{\partial}{\partial x_k} & \frac{\partial^2}{\partial x_k \partial x_l} & \frac{\partial^2}{\partial x_k \partial y_l} & \frac{\partial^2}{\partial x_k \partial z_l} & \cdots \\
\frac{\partial}{\partial y_k} & \frac{\partial^2}{\partial y_k \partial x_l} & \frac{\partial^2}{\partial y_k \partial y_l} & \frac{\partial^2}{\partial y_k \partial z_l} & \cdots \\
\frac{\partial}{\partial z_k} & \frac{\partial^2}{\partial z_k \partial x_l} & \frac{\partial^2}{\partial z_k \partial y_l} & \frac{\partial^2}{\partial z_k \partial z_l} & \cdots \\
\frac{\partial^2}{\partial x_k^2} & \frac{\partial^3}{\partial x_k^2 \partial x_l} & \frac{\partial^3}{\partial x_k^2 \partial y_l} & \frac{\partial^3}{\partial x_k^2 \partial z_l} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \ddots
\end{bmatrix} \left( \frac{1}{r_{kl}} \right), \quad (1.15)
\]
then $W_{kl}$ can be written in a compact form

$$W_{kl} = M_k^l T_{kl} M_l.$$  \hfill (1.16)

The matrix $T_{kl}$ takes care of the geometry of the two sites involved. It should be pointed out that if we express the interaction energy in terms of spherical harmonics, a similar form like Eq. 1.16 will be obtained (Stone, 1996). $T_{kl}$ can be written symbolically as

$$T_{kl} = \begin{bmatrix}
\nabla_0 \nabla_0 & \nabla_0 \nabla_1 & \nabla_0 \nabla_2 & \cdots \\
\nabla_1 \nabla_0 & \nabla_1 \nabla_1 & \nabla_1 \nabla_2 & \cdots \\
\nabla_2 \nabla_0 & \nabla_2 \nabla_1 & \nabla_2 \nabla_2 & \cdots \\
\vdots & \vdots & \vdots & \ddots \\
\end{bmatrix} \left( \frac{1}{r_{kl}} \right). \hfill (1.17)
$$

Since $(\partial/\partial x_k)(1/r_{kl}) = -(\partial/\partial x_l)(1/r_{kl})$, etc., we have

$$T_{kl} = \begin{bmatrix}
\nabla^0 & \nabla^1 & \nabla^2 & \nabla^3 & \cdots \\
-\nabla^1 & -\nabla^2 & -\nabla^3 & -\nabla^4 & \cdots \\
\nabla^2 & \nabla^3 & \nabla^4 & \nabla^5 & \cdots \\
-\nabla^3 & -\nabla^4 & -\nabla^5 & -\nabla^6 & \cdots \\
\vdots & \vdots & \vdots & \vdots & \ddots \\
\end{bmatrix} \left( \frac{1}{r_{kl}} \right) \hfill (1.18)
$$

where

$$\nabla^p \equiv \frac{\partial^{i+j+k}}{\partial x_i^j y_l^j z_k^k}, \quad p = i + j + k.$$
From Eq. 1.18 we can see that the matrix \( T_{kl} \) is not symmetrical. This reflects the fact that if we exchange the multipoles of site \( k \) and \( l \), the interaction energy will change sign if the sum of the orders of the two multipoles involved is odd.

If we assign the point charge as 0\(^{th}\) order multipole, the dipole as 1\(^{st}\) order multipole, and so on, then \( m^{th} \) Cartesian multipole has \( 3^m \) components, so if the site \( k \) has a multipole expansion up to \( p^{th} \) order and the site \( l \) up to \( q^{th} \) order, then \( T_{kl} \) will have \( [(3^{p+1} - 1)/2] \times [(3^{q+1} - 1)/2] \) elements\(^1\). Since this number increases exponentially with the highest order of multipole expansion, the size of the matrix \( T_{kl} \) will be huge for large \( m \). However, as will be discussed later (Section 1.10), the matrix formulation only serves as a conceptual framework for the final code implementation, and the number of the unique elements which are actually used in the program increases only linearly with \( p \).

The matrix \( T_{kl} \) can also be written as

\[
T_{kl} = \begin{bmatrix}
\nabla^0 & \nabla^1 & \nabla^2 & \nabla^3 & \ldots \\
-\nabla^1 & -\nabla^2 & -\nabla^3 & -\nabla^4 & \ldots \\
\nabla^2 & \nabla^3 & \nabla^4 & \nabla^5 & \ldots \\
-\nabla^3 & -\nabla^4 & -\nabla^5 & -\nabla^6 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \vdots
\end{bmatrix}

\left( \frac{1}{r_{kl}} \right) = \begin{bmatrix}
T_{00}^{kl} & T_{01}^{kl} & T_{02}^{kl} & T_{03}^{kl} & \ldots \\
T_{10}^{kl} & T_{11}^{kl} & T_{12}^{kl} & T_{13}^{kl} & \ldots \\
T_{20}^{kl} & T_{21}^{kl} & T_{22}^{kl} & T_{23}^{kl} & \ldots \\
T_{30}^{kl} & T_{31}^{kl} & T_{32}^{kl} & T_{33}^{kl} & \ldots
\end{bmatrix}
\tag{1.19}
\]

where \( T_{pq}^{kl} \) is the multipole interaction matrix between \( p^{th} \) order multipole of site \( k \)

\(^1\)Expansion to \( p^{th} \) order multipole requires \( \sum_{m=0}^{p} 3^m = (3^{p+1} - 1)/2 \) components.
and \( q^{th} \) order multipole of site \( l \),

\[
W_{kl}^{pq} = (M_{k}^{p})^{t} T_{kl}^{pq} M_{l}^{q} = (-1)^{p} \nabla^{p+q} \frac{1}{r_{kl}}.
\]  

(1.20)

For example, \( T_{kl}^{11} = -\nabla^{2}(1/r_{kl}) \) is the well-known dipole field tensor (Böttcher et al., 1973). The matrix formula provides a systematic way to calculate the interaction of multipoles up to any desired order. In order to do so we simply expand the matrix \( T_{kl} \) to the appropriate dimensions. The elements of \( T_{kl} \) can be calculated using the method discussed in later sections (Section 1.10, Appendix A). For example, if we can represent each site with dipole and quadrupole without the partial charge, as in some of the polarizable multipole water models we developed (Chapter 2), we have

\[
T_{kl} = \begin{bmatrix}
T_{kl}^{11} & T_{kl}^{12} \\
T_{kl}^{21} & T_{kl}^{22}
\end{bmatrix} = \begin{bmatrix}
-\nabla^{2} & -\nabla^{3} \\
\nabla^{3} & \nabla^{4}
\end{bmatrix} \left( \frac{1}{r_{kl}} \right),
\]  

(1.21)

so it is easy to change the formulas for special need.

### 1.3 Derivatives of energy with respect to position for fixed multipoles

For computer simulation the first and second derivatives are usually needed (Allen & Tildesley, 1987; Leach, 1996). In this and the following sections we use the matrix formula developed in the previous section to provide a systematic way to calculate
these derivatives. In fact, the method can be extended to any order of derivatives.

In this section we for the time being ignore the dependence of the multipoles themselves on the coordinates and consider only the dependence of the matrix $T_{kl}$ on the coordinates. In this case from Eq. 1.16 we get the derivatives in the form of

$$\frac{\partial W_{kl}}{\partial x_k} = M'_k \left[ \frac{\partial}{\partial x_k} T_{kl} \right] M_l,$$

$$\frac{\partial^2 W_{kl}}{\partial x_k \partial y_k} = M'_k \left[ \frac{\partial^2}{\partial x_k \partial y_k} T_{kl} \right] M_l,$$

etc.

$$\frac{\partial W_{kl}}{\partial x_l} = M'_k \left[ \frac{\partial}{\partial x_l} T_{kl} \right] M_l,$$

$$\frac{\partial^2 W_{kl}}{\partial x_l \partial y_l} = M'_k \left[ \frac{\partial^2}{\partial x_l \partial y_l} T_{kl} \right] M_l,$$

etc.

If we denote $T^{lx}_{(k)kl} = \partial T_{kl} / \partial x_k$, $T^{lx}_{(l)kl} = \partial T_{kl} / \partial x_l$, $T^{2xy}_{(k)kl} = \partial^2 T_{kl} / \partial x_k \partial y_k$, $T^{2xy}_{(l)kl} = \partial^2 T_{kl} / \partial x_l \partial y_l$, and so on, from the structure of the matrix $T_{kl}$ we can see that matrices $T^{lx}_{(k)kl}$, $T^{lx}_{(l)kl}$, $T^{2xy}_{(k)kl}$, $T^{2xy}_{(l)kl}$, etc. can be simply constructed from matrix $T_{kl}$. For the first derivatives we have

$$T^{lx}_{(k)kl}(i, j) = T_{kl}(3i - 1, j), \quad T^{lx}_{(l)kl}(i, j) = T_{kl}(3i, j), \quad T^{lz}_{(k)kl}(i, j) = T_{kl}(3i + 1, j)$$

$$T^{lx}_{(l)kl}(i, j) = T_{kl}(i, 3j - 1), \quad T^{ly}_{(l)kl}(i, j) = T_{kl}(i, 3j), \quad T^{lz}_{(l)kl}(i, j) = T_{kl}(i, 3j + 1),$$

and for the second derivatives we have

$$T^{2xx}_{(k)kl}(i, j) = T_{kl}(9i - 4, j), \quad T^{2xy}_{(k)kl}(i, j) = T_{kl}(9i - 3, j), \quad T^{2xy}_{(l)kl}(i, j) = T_{kl}(9i - 2, j), \quad \ldots$$

$$T^{2xx}_{(l)kl}(i, j) = T_{kl}(i, 9j - 4), \quad T^{2xy}_{(l)kl}(i, j) = T_{kl}(i, 9j - 3), \quad T^{2xz}_{(l)kl}(i, j) = T_{kl}(i, 9j - 2), \quad \ldots$$

From the structure of these matrices, it can be seen that for the multipoles up to $p^{\text{th}}$ order, we need a $[(3p+1)-1]/2 \times [(3p+1)-1]/2$ matrix $T_{kl}$ for the interaction energy. For the first derivatives we need to expand this matrix to $[(3p+1)-1]/2 \times [(3p+2)-1]/2$.
so as to construct matrices $T_{(l)kl}(i,j)$, $T_{(l)kl}^{1y}(i,j)$, and $T_{(l)kl}^{1z}(i,j)$. For the second derivatives we need to expand the matrix to $[(3p+1) - 1]/2 \times [(3p+3) - 1]/2$ to construct the 9 matrices of $T_{(l)kl}^{2xx}(i,j)$, $T_{(l)kl}^{2yy}(i,j)$, $T_{(l)kl}^{2zz}(i,j)$, etc. For the multipoles up to quadrupoles, all we need is

$$T_{kl} = \begin{bmatrix}
\nabla^0 & \nabla^1 & \nabla^2 & \nabla^3 & \nabla^4 \\
-\nabla^1 & -\nabla^2 & -\nabla^3 & -\nabla^4 & -\nabla^5 \\
\nabla^2 & \nabla^3 & \nabla^4 & \nabla^5 & \nabla^6 \\
\end{bmatrix}_{13 \times 121} \left( \frac{1}{r_{kl}} \right) \quad (1.22)$$

from which we use the left part of the matrix to calculate energy,

$$T_{kl} = \begin{bmatrix}
\nabla^0 & \nabla^1 & \nabla^2 \\
-\nabla^1 & -\nabla^2 & -\nabla^3 \\
\nabla^2 & \nabla^3 & \nabla^4 \\
\end{bmatrix}_{13 \times 13} \left( \frac{1}{r_{kl}} \right), \quad (1.23)$$

the middle part to calculate the first derivatives,

$$T'_{kl} = \begin{bmatrix}
\nabla^1 & \nabla^2 & \nabla^3 \\
-\nabla^2 & -\nabla^3 & -\nabla^4 \\
\nabla^3 & \nabla^4 & \nabla^5 \\
\end{bmatrix}_{13 \times 13} \left( \frac{1}{r_{kl}} \right), \quad (1.24)$$
and the right part to calculate the second derivatives.

\[
\mathbf{T}_{kl}'' = \begin{bmatrix}
\nabla^2 & \nabla^3 & \nabla^4 \\
-\nabla^3 & -\nabla^4 & -\nabla^5 \\
\nabla^4 & \nabla^5 & \nabla^6 \\
\end{bmatrix}_{13 \times 117} \left( \frac{1}{r_{kl}} \right).
\quad (1.25)
\]

As can be seen from these three matrices, many blocks in the matrix for the lower derivative are reused in the matrix for the higher derivative. For the first derivatives, only the block \(\nabla^5(1/r_{kl})\) of \(\mathbf{T}_{kl}'\) is new from \(\mathbf{T}_{kl}\). For the second derivatives, only the block \(\nabla^6(1/r_{kl})\) of \(\mathbf{T}_{kl}''\) is new from \(\mathbf{T}_{kl}'\).

### 1.4 Gradients of the potential

To deal with the polarizability we have to calculate the various degree of gradients of the potential at a given site (Section 1.8). From Eq. 1.16 we can see that the electric field, the gradient of the field, etc., at site \(l\), generated by site \(k\), are given by

\[
\left[ \nabla^0\phi_k(P_l), \nabla^1\phi_k(P_l), \nabla^2\phi_k(P_l), \cdots \right] = \mathbf{M}_k' \mathbf{T}_{kl}
\]

\[
= \left[ \phi_k(P_l), -E_x(P_l), -E_y(P_l), -E_z(P_l), \phi^{2xx}(\mathbf{r}_l), \phi^{2xy}(\mathbf{r}_l), \cdots \right] \quad (1.26)
\]
and similarly at site \( k \) by site \( l \)

\[
\begin{bmatrix}
\nabla^0 \phi_l(P_k), \nabla^1 \phi_l(P_k), \nabla^2 \phi_l(P_k), \ldots
\end{bmatrix}^t = T_{kl} M_l
\]

\[
= \begin{bmatrix}
\phi_l(P_k), -E_x(P_k), -E_y(P_k), -E_z(P_k), \phi^{2xx}(P_k), \phi^{2xy}(P_k), \ldots
\end{bmatrix}^t
\tag{1.27}
\]

From Eqs. 1.26 and 1.27 we see that the three components of the field at site \( l \) generated by site \( k \) is

\[
[E_x(P_l), E_y(P_l), E_z(P_l)] = M_l^t \left[ -\nabla^1, -\nabla^2, -\nabla^3, \ldots \right]^t \left( \frac{1}{r_{kl}} \right),
\tag{1.28}
\]

and similarly, the three components of the field at site \( k \) generated by site \( l \) is

\[
[E_x(P_k), E_y(P_k), E_z(P_k)]^t = \left[ \nabla^1, \nabla^2, \nabla^3, \ldots \right] \left( \frac{1}{r_{kl}} \right) M_l.
\tag{1.29}
\]

These quantities are needed to calculate the induced dipoles, which will be discussed in Section 1.7.

\section{1.5 Representation of flexible multipoles}

In molecular dynamics simulations we have to deal with flexible molecules. The representation of point charges in a flexible molecule is trivial since point charges do not depend on coordinate systems. However, higher order Cartesian multipoles have dependence on coordinate systems, i.e., they have to be represented in a given
coordinate system. As the atom in which the multipoles are located moves, or the nearby atoms change their positions, the multipoles will change correspondingly. The multipoles in \( \mathbf{M}_k \) and \( \mathbf{M}_l \) in Eq. 1.16 are referred to the same coordinate system. In order to handle this dependence on coordinate system, we define Cartesian multipoles at each site in a local coordinate system. We choose the site where the multipoles are located (site 1) as the origin of the local coordinate system (Figure 1.3), and two other non-collinear nearby sites (sites 2 and 3) to determine the directions of each axes. We have two representations implemented right now. In one implementation (Figure 1.3a), We use sites 2 and 3 to determine the \( z-x \) plane, and use the bisector of vectors \( \mathbf{r}_{12} \) and \( \mathbf{r}_{13} \) as the \( z \)-axis. The \( x \)-axis is chosen to form an acute angle with \( \mathbf{r}_{12} \). In the other implementation (Figure 1.3b), we determine the \( z-x \) plane as before but simply use \( \mathbf{r}_{12} \) as the \( z \)-axis. The \( x \)-axis is chosen to have an acute angle with \( \mathbf{r}_{13} \).

Once the \( z \)-axis and the \( x \)-axis are determined, the \( y \)-axis can be determined. The advantage of the bisector local coordinate system (Figure 1.3a) is that it makes sites 2 and 3 symmetrical with respect to the \( z \)-axis, which is appropriate when dealing with symmetrical molecules, such as water.

Before we use the matrix formula Eq. 1.16, we have to convert the Cartesian multipoles represented in the local coordinate systems into the global coordinate system. If we denote \( \mathcal{M}_k \) as the Cartesian multipole polytensor of site \( k \) in the local coordinate system, and \( \mathbf{M}_k \) as the corresponding polytensor in the global coordinate
Figure 1.3: Two representations of multipoles in local coordinate system

system, then

\[ M_k = A_k \mathcal{M}_k, \quad (1.30) \]

where

\[
A_k = \begin{bmatrix}
A^{(0)}_k \\
A^{(1)}_k \\
\vdots \\
A^{(m)}_k \\
\vdots
\end{bmatrix}.
\]

The \( A^{(m)}_k \) is defined as \( \underbrace{A_k \otimes A_k \cdots \otimes A_k}_m \) and \( \otimes \) stands for direct matrix product.
operation. We define $A^{(0)}_k = 1$. The matrix $A_k$ is defined as the rotation matrix to transform a vector from the local coordinate system of multipoles at site $k$ to the global coordinate system, i.e., $A_{ij} = (\hat{i} \cdot \hat{j})$, where $\hat{i}$ and $\hat{j}$ stand for the unit vectors of the global and local axis directions, respectively.

If we denote $r_{12} = r_2 - r_1$ and $r_{13} = r_3 - r_1$, and $\hat{r}_{12}$ and $\hat{r}_{13}$ as the corresponding unit vectors, then for the bisector local coordinate system (Figure 1.3a),

$$\hat{i}' = \frac{r_{13} - (r_{13} \cdot \hat{k}')}{|r_{13} - (r_{13} \cdot \hat{r}_{13})|}$$

$$\hat{j}' = \hat{k}' \times \hat{i}'$$

$$\hat{k}' = \frac{\hat{r}_{12} + \hat{r}_{13}}{|\hat{r}_{12} + \hat{r}_{13}|}, \quad (1.32)$$

and for the second coordinate system (Figure 1.3b),

$$\hat{i}' = \frac{r_{13} - (r_{13} \cdot \hat{k}')}{|r_{13} - (r_{13} \cdot \hat{r}_{13})|}$$

$$\hat{j}' = \hat{k}' \times \hat{i}'$$

$$\hat{k}' = \hat{r}_{12}. \quad (1.33)$$

---

2The matrix direct product $A_{m \times n} \otimes B_{m' \times n'}$ is defined as

$$A_{m \times n} \otimes B_{m' \times n'} = \begin{bmatrix} a_{11}B & a_{12}B & \ldots & a_{1n}B \\ a_{21}B & a_{22}B & \ldots & a_{2n}B \\ \vdots & \vdots & \ddots & \vdots \\ a_{m1}B & a_{m2}B & \ldots & a_{mn}B \end{bmatrix}_{mm' \times nn'} \quad (1.31)$$
1.6 Derivatives with flexible multipoles

From Eqs. 1.16 and 1.30 we see that

\[ W_{kl} = M_k^t A^t_k T_{kl} A_l M_l, \quad (1.34) \]

so for the flexible multipoles, the derivatives have to be obtained by using chain rules,

\[ \frac{\partial W_{kl}}{\partial x_k} = M_k^t \left[ (\frac{\partial}{\partial x_k} A^t_k) T_{kl} A_l + A^t_k (\frac{\partial}{\partial x_k} T_{kl}) A_l + A_k^t T_{kl} \left( \frac{\partial}{\partial x_k} A_l \right) \right] M_l \]

\[ \frac{\partial^2 W_{kl}}{\partial x_k \partial y_k} = M_k^t \left[ \frac{\partial^2 A^t_k}{\partial x_k \partial y_k} T_{kl} A_l + \frac{\partial A^t_k}{\partial x_k} \frac{\partial T_{kl}}{\partial y_k} A_l + \frac{\partial A^t_k}{\partial x_k} T_{kl} \frac{\partial A_l}{\partial y_k} \right. \]

\[ + \frac{\partial^2 T_{kl}}{\partial x_k \partial y_k} A_l + A_k^t \frac{\partial^2 A^t_k}{\partial x_k \partial y_k} A_l + \frac{\partial^2 A^t_k}{\partial x_k \partial y_k} T_{kl} \frac{\partial A_l}{\partial y_k} \]

\[ + \frac{\partial A^t_k}{\partial y_k} \frac{\partial T_{kl}}{\partial x_k} A_l + A_k^t \frac{\partial T_{kl}}{\partial y_k} \frac{\partial A_l}{\partial x_k} + \frac{\partial A^t_k}{\partial y_k} T_{kl} \frac{\partial^2 A_l}{\partial x_k \partial y_k} \left] M_l \right. \]

The terms like \((\partial/\partial x_k)T_{kl}\) and \((\partial^2/\partial x_k \partial y_k)T_{kl}\) in these expressions can be calculated using the methods described in section 1.3. The other terms, like \((\partial/\partial x_k)A_k\) and \((\partial^2/\partial x_k \partial y_k)A_k\), can be obtained from the definitions of the local coordinate systems (Eqs. 1.5 and 1.5). These terms can be obtained by using symbolic mathematic packages, such as MAPLE (Char et al., 1992). Some simple relations exist among
these terms, such as

\[
\left( \frac{\partial}{\partial \xi_1} + \frac{\partial}{\partial \xi_2} + \frac{\partial}{\partial \xi_3} \right) A_k = 0, \quad \xi = x, y, \text{ or } z.
\]

for the bisector representation.

## 1.7 Induced dipole

Since the current commonly used empirical force fields only implement partial charge models for the electrostatics, the published formulations for incorporating polarizability do not apply to multipole electrostatic models. In this section methods will be developed for incorporating polarization effects into the force field with the multipole electrostatics developed in the previous sections.

Theoretically we can use the matrix formula to study the hyperpolarizability carried out to any desired degree since we can calculate the gradients of the potential to any degree in a systematic way (see Section 1.4). We present here the formula for calculating induced dipole moments, which are usually used in simulation. The generalization to higher polarizabilities is straightforward. The induced dipole moments \( \mu_{k}^{\text{ind}} \) can be calculated as

\[
\mu_{k}^{\text{ind}} = \alpha_k \cdot f_k
\]  

(1.35)

where \( \alpha_k \) is the polarizability tensor of site \( k \) and \( f_k \) is the total electric field on site
generated by all other sites (Böttcher et al., 1973). From Eq. 1.28 we have

\[ f_k = \sum_{l=1}^{n'} \left\{ \left[ \nabla^1, \nabla^2, \nabla^3, \cdots \right] \left( \frac{1}{r_{kl}} \right) M_l + \nabla^2 \left( \frac{1}{r_{kl}} \right) \mu^\text{ind}_l \right\} \]  \hspace{1cm} \text{(1.36)}

where \( \mu^\text{ind}_l \) is the induced dipole at site \( l \) and the primed sum excludes the term \( l = k \).

If we put Eq. 1.36 into Eq. 1.35 and rearrange, we obtain

\[ C \mu^\text{ind} = T^1 M = E, \]  \hspace{1cm} \text{(1.37)}

where \( C \) is a \( 3n \times 3n \) interaction matrix with diagonal blocks \( \alpha_k^{-1} \) and off-diagonal blocks \( -\nabla^2 (1/r_{kl}) \); \( E \) is a \( 3n \) vector representing the sum of the fields generated by the permanent multipoles in all the other sites, which comes from the first term of Eq. 1.36.

\[ E = [E_1, E_2, \cdots, E_n]^t \]  \hspace{1cm} \text{(1.38)}

\[ E_k = \sum_{l=1}^{n'} \left\{ \left[ \nabla^1, \nabla^2, \nabla^3, \cdots \right] \left( \frac{1}{r_{kl}} \right) M_l \right\} \]  \hspace{1cm} \text{(1.39)}

Eq. 1.37 can be written explicitly as

\[
\begin{bmatrix}
\alpha_1^{-1} & -\nabla_2^1 & -\nabla_3^1 & \cdots & -\nabla_n^1 \\
-\nabla_2^2 & \alpha_2^{-1} & -\nabla_3^2 & \cdots & -\nabla_n^2 \\
-\nabla_3^3 & -\nabla_2^3 & \alpha_3^{-1} & \cdots & -\nabla_n^3 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
-\nabla_n^1 & -\nabla_n^2 & -\nabla_n^3 & \cdots & \alpha_n^{-1}
\end{bmatrix}_{3n \times 3n}
\begin{bmatrix}
\mu^\text{ind}_1 \\
\mu^\text{ind}_2 \\
\mu^\text{ind}_3 \\
\vdots \\
\mu^\text{ind}_n
\end{bmatrix}_{3n \times 1}
= \begin{bmatrix}
0 & T_{12} & T_{13} & \cdots & T_{1n} \\
T_{21} & 0 & T_{13} & \cdots & T_{2n} \\
T_{31} & T_{32} & 0 & \cdots & T_{3n} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
T_{n1} & T_{n2} & T_{n3} & \cdots & 0
\end{bmatrix}_{3n \times wn} \begin{bmatrix}
M_1 \\
M_2 \\
M_3 \\
\vdots \\
M_n
\end{bmatrix}_{wn \times 1}
\]  \hspace{1cm} \text{(1.40)}
where we use $\nabla^2_{kl}$ to stand for $\nabla^2(1/r_{kl})$ and $T^i_{kl}$ for $[\nabla^1, \nabla^2, \nabla^3, \ldots ](1/r_{kl})$. Here $w = (3^{p+1} - 1)/2$, where $p$ is the highest multipole order. Formally we can get $\mu$ by inverting the matrix $C$ as

$$\mu^{ind} = C^{-1}E,$$  \hspace{1cm} (1.41)

but for large system, $C$ is so big ($3n \times 3n$) that we can not afford to calculate its inverse. In practice, we have to approximate $C^{-1}$. We can write $C$ as

$$C = P^{-1} - T^{11} = P^{-1}(I - PT^{11})$$ \hspace{1cm} (1.42)

where

$$P = \begin{bmatrix}
\alpha_1 \\
\alpha_2 \\
\alpha_3 \\
\vdots \\
\alpha_n
\end{bmatrix}_{3n \times 3n} \hspace{1cm} (1.43)$$

and

$$T^{11} = \begin{bmatrix}
0 & \nabla^2_{12} & \nabla^2_{13} & \cdots & \nabla^2_{1n} \\
\nabla^2_{21} & 0 & \nabla^2_{23} & \cdots & \nabla^2_{2n} \\
\nabla^2_{31} & \nabla^2_{32} & 0 & \cdots & \nabla^2_{3n} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
\nabla^2_{n1} & \nabla^2_{n2} & \nabla^2_{n3} & \cdots & 0
\end{bmatrix}_{3n \times 3n} \hspace{1cm} (1.44)$$
so

\[ C^{-1} = (I - PT)^{-1}P \]

\[ = [I + PT + (PT)^2 + (PT)^3 + \ldots] P, \]  \hspace{1cm} (1.45)

hence

\[ \mu^{\text{ind}} = [I + PT + (PT)^2 + (PT)^3 + \ldots] P\mathcal{E}. \] \hspace{1cm} (1.46)

Since \( P\mathcal{E} \) is the dipole moments induced by the field generated by permanent multipoles, it is usually called direct induced dipoles. For any dipole polytensor \( \mu, T^{11}\mu \) is the corresponding field polytensor, we see that \( PT^{11}\mu \) is the induced dipole polytensor generated by \( \mu \). Hence

\[ \mu^{\text{ind}} = \mu^{(1)} + \mu^{(2)} + \mu^{(3)} + \ldots \] \hspace{1cm} (1.47)

where \( \mu^{(1)} = P\mathcal{E} \) is the direct induced dipoles and \( \mu^{(n+1)} = PT^{11}\mu^{(n)}, n = 1, 2, 3, \ldots \). This provides an iterative algorithm to calculate \( \mu^{\text{ind}} \) for large systems. In practice, we can facilitate the iteration by using the new \( \mu^{\text{ind}}_k \) as soon as they have been calculated.
1.8 Potential energy with polarizability

When the polarizability is considered, the electrostatics energy of the system is more complicated than that described in Section 1.2 and sometimes cause confusion. The following is in the line of Applequist’s presentation (Applequist, 1985; Applequist, 1984), but we will decompose the energy in a different way which is more suitable for computer simulations. Applequist’s results are very general in that they include all orders of multipoles and all orders of polarizabilities. In addition, a static external field is included. We present the general formulas first, and later simplify them for the situation where there is no external field, which is usually the case in molecular simulations.

First, a second degree polarizability polytensor of component $i$ of the system is defined as

$$ P_i = \begin{bmatrix} p_i^{(0,0)} & p_i^{(0,1)} & p_i^{(0,2)} & \ldots \\ p_i^{(1,0)} & p_i^{(1,1)} & \ldots \\ p_i^{(2,0)} & \ldots \\ \vdots & & & & & \end{bmatrix}, \quad (1.48) $$

where

$$ p_{i,\alpha_1\alpha_2\ldots\alpha_n,\beta_1\ldots\beta_m}^{(n,m)} = \left[ \frac{\partial M_{i,\alpha_1\alpha_2\ldots\alpha_n}^{(n)}}{\partial F_{i,\beta_1\ldots\beta_m}^{(m)}} \right]_0. $$

The subscript 0 indicates that the partial derivative is evaluated when all the field gradients are zero. The $n^{th}$ order gradient at $r_i$ is defined as

$$ F_i^{(n)} = -\nabla_i^n \phi_i, $$

27
and \( F_i \) is the polytensor of \( F_i^{(n)} \), \( n = 0, 1, 2, \cdots \). The multipole moments of all orders depend on \( F_i \) and the polarizability polytensor \( P_i \) as

\[
M_i = M_{00i} + P_i \cdot F_i,
\]

\( M_{00i} \) is the \textit{intrinsic} multipole polytensor of component \( i \), the multipoles that the component \( i \) has in absence of all other components and the external field. This is the Taylor expansion of the multipoles of component \( i \).

Then consider a system of \( n \) components, and define the following matrices

\[
\mathcal{M} = \begin{bmatrix} M_1 \\ \vdots \\ M_n \end{bmatrix}, \quad \mathcal{E} = \begin{bmatrix} E_1 \\ \vdots \\ E_n \end{bmatrix},
\]

\[
\mathcal{P} = \begin{bmatrix} P_1 & 0 & \cdots \\ 0 & P_2 & \cdots \\ \vdots & \vdots & \ddots \\ \vdots & \vdots & \ddots & P_n \end{bmatrix}, \quad \mathcal{T} = \begin{bmatrix} 0 & T_{12} & \cdots & T_{1n} \\ T_{21} & 0 & \cdots \\ \vdots & \vdots & \ddots \\ T_{n1} & T_{n2} & \cdots & 0 \end{bmatrix}.
\]

Here \( E_i \) is the \textit{external} field at site \( i \), so the definition of \( \mathcal{E} \) here is different from that in Section 1.7. \( T_{kl} \) is defined in the same sense as in Eq. 1.40, with a sign difference. With the help of these matrices, the multipole matrix \( \mathcal{M} \) can be written as (Applequist, 1985)

\[
\mathcal{M} = \mathcal{M}_{00} + \mathcal{B}(\mathcal{E} - \mathcal{T}\mathcal{M}_{00})
\]

(1.49)
where

\[ B = (I + PT)^{-1}P. \]

When there is no external field \((E = 0)\), the multipole is simplified to

\[ M = (I - BT)M_{00} = M_{00} - BTM_{00} = M_{00} - (P^{-1} + T)^{-1}TM_{00}, \quad (1.50) \]

hence the induced multipoles are

\[ M^{ind} = -BTM_{00} = -(P^{-1} + T)^{-1}TM_{00}, \quad (1.51) \]

which is a more general expression for Eq. 1.40.

The energy \(W\) of an assembly in a static external field is the sum of two terms, the work \(V\) required to polarize each components of the system to their final states, and the work \(U\) required to transfer the components so polarized to their final positions.

The polarization work \(V_i\) for component \(i\) is (Applequist, 1985)

\[ V_i = \frac{1}{2}F_i \cdot P_i \cdot F_i, \quad (1.52) \]

and in polytensor form

\[ V = \frac{1}{2}(\mathcal{E} - TM)^{t}(M - M_{00}). \quad (1.53) \]
\[ U \text{ is given by} \]
\[ U = -\sum_{i=1}^{n} (E_i + \frac{1}{2} f_i) \cdot M_i. \]

and in polytensor form

\[ U = -(\mathcal{E} - \frac{1}{2} \mathcal{T} \mathcal{M})^t \mathcal{M}. \] \hspace{1cm} (1.54)

The \( f_i \) is, as in Section 1.7, the total field on site \( i \) generated by all other sites. When \( \mathcal{E} = 0 \), \( U \) and \( V \) are given by

\[ U = \frac{1}{2} \mathcal{M}^t \mathcal{T} \mathcal{M} \] \hspace{1cm} (1.55)

and

\[ V = -\frac{1}{2} \mathcal{M}^t \mathcal{T} \mathcal{M}^{\text{ind}}. \] \hspace{1cm} (1.56)

Berendsen et al. call \( U \) in Eq. 1.55 as the full electrostatic interaction energy and \( V \) in Eq. 1.56 as the self-energy (Berendsen et al., 1987). Notice that \( V \) is always positive, which represents the cost to distort the system to its final polarized state.
From Eqs. 1.53 and 1.54 the interaction energy\(^3\)

\[
W = U + V \tag{1.59}
\]

\[
= \frac{1}{2} \mathcal{M}^t \mathcal{T} \mathcal{M} - \frac{1}{2} \mathcal{M}^t \mathcal{T} \mathcal{M}^{ind} \tag{1.60}
\]

\[
= \frac{1}{2} \mathcal{M}^t \mathcal{T} \mathcal{M}_{00} \tag{1.61}
\]

\[
= \frac{1}{2} \mathcal{M}_{00}^t \mathcal{T} \mathcal{M}_{00} + \frac{1}{2} \mathcal{M}_{00}^t \mathcal{T} \mathcal{M}^{ind} \tag{1.62}
\]

Eq 1.62 can be easily interpreted in the following way. The first term is the interaction energy when the polarization is not taken into account, and the second term is the extra energy when the polarization is considered. When the energy is decomposed in this way, it is easy to distinguish the effects the polarization is taken into account in a simulation. It is clear, however, that these two terms are not equal to \(U\) and \(V\), respectively. In the following sections we will still call the second term polarization energy, but the difference between the definitions should be kept in mind. Two earlier papers dealing with polarization made a mistake in decomposing the polarization energy (Lybrand & Kollman, 1985; Cieplak et al., 1987), and the mistake was later

\(^3\)Using Eqs. 1.53 and 1.54, the energy of the system is obtained as

\[
W = -\frac{1}{2} \{ \mathcal{E}^t \mathcal{M}_{00} + (\mathcal{E} - \mathcal{T} \mathcal{M}_{00})^t [\mathcal{M}_{00} + \mathcal{B}(\mathcal{E} - \mathcal{T} \mathcal{M}_{00})] \}
\]

\[
= -\frac{1}{2} [\mathcal{E}^t \mathcal{M}_{00} + (\mathcal{E} - \mathcal{T} \mathcal{M}_{00})^t \mathcal{M}] \tag{1.57}
\]

In the absence of an external field, Eq. 1.57 reduces to

\[
W = \frac{1}{2} \mathcal{M}_{00}^t \mathcal{T} (\mathcal{I} - \mathcal{B} \mathcal{T}) \mathcal{M}_{00}, \tag{1.58}
\]

Using Eq. 1.51, Eq. 1.58 can be again written as Eq. 1.62.
pointed out by other authors (Berne & Wallqvist, 1988; Rullmann & van Duijnen, 1988).

1.9 Derivatives when polarizability is considered

For the derivatives when polarizability is considered, special treatment is needed. Suppose that we have finished the calculation of induced dipoles $\mu^{ind}$, using either matrix inversion or iteration method. The energy from the induced dipoles can be written in the polytensor form as

$$W^{ind} = -\frac{1}{2} (\mu^{ind})^t \mathcal{E}, \quad (1.63)$$

which is the direct application of Eq. 1.62 when only dipole polarization is considered. Here the definition of $\mathcal{E}$ is switched back to the definition in Section 1.7, which is the sum of the fields generated by the permanent multipoles in all the other sites. Using Eq. 1.41 and noticing that $\mathcal{C}^t = \mathcal{C}$, we have

$$W^{ind} = -\frac{1}{2} \mathcal{E}^t \mathcal{C}^{-1} \mathcal{E}, \quad (1.64)$$

so

$$\frac{\partial W^{ind}}{\partial x_k} = -\frac{1}{2} \left[ \frac{\partial \mathcal{E}^t}{\partial x_k} \mathcal{C}^{-1} \mathcal{E} + \mathcal{E}^t \frac{\partial \mathcal{C}^{-1}}{\partial x_k} \mathcal{E} + \mathcal{E}^t \mathcal{C}^{-1} \frac{\partial \mathcal{E}}{\partial x_k} \right],$$
which simplifies to

\[
\frac{\partial W^{\text{ind}}}{\partial x_k} = -\frac{1}{2} \left[ 2(\mu^{\text{ind}})^t \frac{\partial \mathcal{E}}{\partial x_k} + \mathcal{E}^t \frac{\partial C^{-1}}{\partial x_k} \mathcal{E} \right].
\]  

(1.65)

Using the identity \( C^{-1}C = \mathcal{I} \), we have

\[
\frac{\partial C^{-1}}{\partial x_k} C + C^{-1} \frac{\partial C}{\partial x_k} = 0,
\]

so

\[
\frac{\partial C^{-1}}{\partial x_k} = -C^{-1} \frac{\partial C}{\partial x_k} C^{-1}.
\]

Substituting this expression into Eq. 1.65, we obtain

\[
\frac{\partial W^{\text{ind}}}{\partial x_k} = -(\mu^{\text{ind}})^t \frac{\partial \mathcal{E}}{\partial x_k} - \frac{1}{2} (\mu^{\text{ind}})^t \frac{\partial T^{11}}{\partial x_k} \mu^{\text{ind}}
\]

\[
= -(\mu^{\text{ind}})^t \frac{\partial \mathcal{T}^1}{\partial x_k} M - (\mu^{\text{ind}})^t \mathcal{T}^1 \frac{\partial A}{\partial x_k} M - \frac{1}{2} (\mu^{\text{ind}})^t \frac{\partial T^{11}}{\partial x_k} \mu^{\text{ind}}
\]

(1.66)

Each term in Eq. 1.9 can be calculated using the methods discussed in above sections.

Eq. 1.9 is a generalization of the formula for partial charge models (Kuwajima & Warshel, 1990). From the derivation it can be seen that for the derivative formula to work correctly, we have to use the same \( \mathcal{E} \) to calculate both induced dipoles (Eq. 1.41) and the polarization energy (Eq. 1.63), otherwise Eq. 1.64 would look like

\[
W^{\text{ind}} = -\frac{1}{2} \mathcal{E}^t C^{-1} \mathcal{E}_2.
\]
and if we want to get a formula like Eq. 1.9, we have to calculate two set of induced dipoles for each of $\mathcal{E}$. So when using various cutoff schemes commonly used in simulations, caution should be excised to use the same $\mathcal{E}$ to calculate induced dipoles and the induced energy, otherwise the derivatives will be broken.

### 1.10 The elements of the interaction matrix

All the components of the polarizable multipole electrostatic model outlined in above sections depend on the calculation of the elements of the interaction matrix, i.e., the Cartesian derivatives of $1/r_{kl}$. Before going to the details of the calculation, let first check the number of elements that we need.

The dimensions of interaction matrices $T_{kl}$, $T'_{kl}$, and $T''_{kl}$ increase exponentially with the highest order of multipoles. However, since we have relation

\[
\left( \frac{\partial^2}{\partial x_h^2} + \frac{\partial^2}{\partial y_h^2} + \frac{\partial^2}{\partial z_h^2} \right) \left( \frac{1}{r_{kl}} \right) = 0, \quad h = k \text{ or } l, \quad (1.67)
\]

and relations like

\[
\frac{\partial^2}{\partial x_l \partial y_l} \left( \frac{1}{r_{kl}} \right) = \frac{\partial^2}{\partial y_l \partial x_l} \left( \frac{1}{r_{kl}} \right), \quad (1.68)
\]

the number of unique elements does not increase exponentially. In fact, for the block $\nabla^m(1/r_{kl})$ in the matrix (Eq. 1.18), only $2m + 1$ elements are unique. This can be proved as the following.
For the element $\partial^m / (\partial x^\lambda_l \partial y^\mu_l \partial z^\nu_l) (1/r_{kl})$ in the block of $\nabla^m (1/r_{kl})$, if we choose $\lambda$ first, we have $m + 1$ choices: $0, 1, \ldots, m$; Once $\lambda$ has been fixed as $\lambda_0$, $\mu$ has a range of $0 \leq \mu \leq m - \lambda_0$ to choose from, so there are $m - \lambda_0 + 1$ possibilities for $\mu$. Once $\lambda$ and $\mu$ are chosen, $\nu$ has no other choice but $m - \lambda - \mu$. So from Eq. 1.68 the number of unique terms is $\sum_{\lambda_0=0}^{m} (m - \lambda_0 + 1) = (m + 1)(m + 2)/2$. Of these $(m + 1)(m + 2)/2$ terms, there are $(m - 1)m/2$ terms (substituting $m - 2$ for $m$) that are related by Eq. 1.67. So we only need to calculate $(m + 1)(m + 2)/2 - (m - 1)m/2 = 2m + 1$ terms.

If the highest multipole is of order $p$, then from the Eq. 1.18 we can see that we need to calculate up to $\nabla^{2p} (1/r_{kl})$, so $(2p + 1)^2$ unique elements are needed. For interactions up to quadrupole, we need to calculate 25 matrix elements. For the first derivatives, from Eq. 1.24 we see that only the block $\nabla^{2p+1} (1/r_{kl})$ is new, which has $2(2p + 1) + 1$ unique elements. For the second derivatives, we need in addition the block $\nabla^{2p+2} (1/r_{kl})$, so additionally $2(2p + 2) + 1$ unique elements. The total unique elements that are needed for the first and second derivatives are $(2p+2)^2$ and $(2p+3)^2$, respectively. If the highest order of multipole is quadrupole, there are 36 and 49 unique elements for the first and second derivatives, respectively. The details of calculation for the matrix elements are given in Appendix A.

\footnote{From $\sum_{m=0}^{2p} (2m + 1) = (2p + 1)^2$.}
Chapter 2

Polarizable Multipole Water Models

2.1 Introduction

In this Chapter polarizable multipole water models will be introduced. As will be discussed in the next section, water models of various function forms and complexities have been developed. Some of these models can be easily incorporated into the existing force fields for biomolecular simulations, and some are tailored specially for water molecules. Because of the ubiquitous presence of water in biological system, a high quality water model is indispensable in computer simulations of biomacromolecules. In this Chapter the formalism developed in Chapter 1 will be applied to water molecules. Following a brief and selective survey of the history of water model development, the parameters used in the TINKER water models will be presented.
Then the properties of the TINKER water models will be studied. Since in biological systems water usually presents and functions in the forms of both small clusters and bulk (Levitt & Park, 1993), the properties of small water clusters will be investigated, together with bulk properties.

2.2 Computer simulation of water

Water is the most important liquid system on earth and has received more extensive investigations than any other liquids, yet its microscopic properties still remain poorly understood (Stillinger, 1980). Usually liquids are loosely divided into two classes. One class is so called “regular” or unstructured liquids. These liquids are held together by relatively weak, nondirectional van der Waals forces. These liquids can be described fairly accurately by simple empirical rules. The other class is structured liquids which are held together by much stronger, directed forces, such as hydrogen bonds. These structured liquids have properties that are significantly different from those of regular liquids, and can not be described by simple empirical rules. Of the structured liquids, water has more unusual properties than others. Among these unusual properties are: high relative permittivity (dielectric constant), high melting, boiling, and critical temperatures, negative volume of melting, numerous crystalline polymorphs, existence of a density maximum at 4 °C, very high heat capacity, etc (Stillinger, 1980). The combination of these complications makes it difficulty, if not impossible, to study water by using analytical methods. Direct computer simulations of water
provide a promising alternative approach which draws attentions of many researchers.

Modeling of water can be traced back to the pioneering work of Bernal and Fowler (Bernal & Fowler, 1933). With the advent of computer, the simulation of water became and still is an active research area. As discussed below, although many water models have been proposed, none of them can reproduce all the properties of water. Because it is difficult to extract many-body effects in the intermolecular interactions experimentally (Elrod & Saykally, 1994), the most common way to build a water model is to use effective pair potentials to describe bulk water properties. The BNS model introduced by Ben-Naim and Stillinger in 1972 is among the first such effective pair potential models (Ben-Naim & Stillinger, 1972). The model includes four point-charges in addition to a Lennard-Jones term. The model was fit to the second virial coefficients and ice data; Later the model was modified to fit liquid water properties (Stillinger & Rahman, 1974). The modified model is referred to as ST2 model. The model is a 5-site model with charges on hydrogens and on two lone pair positions oriented tetrahedrally around the oxygen. The Lennard-Jones term was calculated only for oxygen-oxygen interactions. Afterwards, two series of effective pair potential models, TIP and SPC models, become popular, especially in biological system simulations. TIP (Transferable Intermolecular Potential) models were developed by Jorgensen et al. (Jorgensen, 1981; Jorgensen et al., 1983). TIP3P and TIP4P are the more popular ones among this series of water models. The rigid water molecule takes the experimental geometry. In contrast to experimental data (Section 2.5.2), the oxygen-oxygen radial distribution curve of the original model
is flat beyond the first peak. The oxygen-hydrogen and hydrogen-hydrogen radial distribution functions are also not well structured. TIP4P is a four-site model in which the negative charge is moved off the oxygen towards the hydrogens at a point on the bisector of the HOH angle. The properties of TIP4P are improved compared with the TIP3P model (Jorgensen et al., 1983). The SPC (Simple Point Charge) model was developed by Berendsen’s group (Berendsen et al., 1981). The model is a three-site model with a Lennard-Jones term for oxygen-oxygen interactions. The model was fit to liquid data. For geometry the model uses a bond length of 1 Å and a tetrahedral model for the bond angle. Later the authors found that an energy term is missing in the model (as well as all other effective pair potentials), i.e., the positive self-energy term (see section 1.8 for a more detailed discussion). The SPC model gives the potential energy as -41.7 kJ/mol, which is close to the experimental value -41.5 kJ/mol. However, if the self-energy term is taken into account, which is about 3.74 kJ/mol calculated using the molecular polarizability and the difference between the effective and gas phase dipole moments, the corrected potential energy is only about -38.0 kJ/mol, so the charge on the model has to be enhanced. The model was modified by reparameterizing the charge and the coefficient of the $r^{-12}$ term in the Lennard-Jones potential by including the self-energy term into the energy (Berendsen et al., 1987). The modified model is named as SPC/E for extended simple point charge model. It has found that the modified model gives better radial distribution curves, especially for the second neighbor peaks. Also the model improves in other properties, in particular the density and the diffusion constant. Besides the models mentioned
above, some other effective pair potentials of water have been developed. Among
them the RWK model (Reimers et al., 1982) is notable.

As discussed in Section 1.1, the polarization effects play an important role in polar
systems such as water. The effective pair potentials try to incorporate the effects
indirectly through the parameterization procedure. In contrast, some water models
incorporate polarization directly (Barnes et al., 1979; Rullmann & van Duijnen, 1988;
Ahlström et al., 1989; Kuwajima & Warshel, 1990; Caldwell et al., 1990; Caldwell &
Kollman, 1995; Dang & Chang, 1997). Usually the polarization effects are treated
in the traditional way as discussed in Section 1.7, but alternative methods have been
proposed, such as the Drude oscillator method (Sprik & Klein, 1988; van Belle et al.,
1992), which treats polarization as an explicit degree of freedom. In the dynamical
fluctuating charge model (Rick et al., 1994) the point charges on the atomic sites
are treated as dynamical variables and thus allowed to fluctuate in response to the
environment. Since no new intermolecular interactions are introduced, the method
only increases the computer time slightly compared to the fixed charge models. The
drawback of the model is that since the charges are in fixed positions which lie in the
water molecule plane, the effective induced dipole is constricted in the same plane
and no induction out of the molecule plane is possible, whereas from experiment it
is known that polarizability is almost isotropic ($\alpha_{xx} = 1.468\text{Å}^3$, $\alpha_{yy} = 1.415\text{Å}^3$, $\alpha_{zz} =
1.528\text{Å}^3$) (Murphy, 1977).

In contrast to use effective pair potential, another line of modeling water is to
construct “true” pair potentials, which try to describe the interactions between two
water molecules as accurately as possible (Matsuoka et al., 1976; Wallqvist et al., 1990; Millot & Stone, 1992; Åstrand et al., 1995). While the effective pair potential models are usually parameterized using experimental bulk properties, “true” pair potential models are based on ab initio calculations. The ab initio calculation of intermolecular interactions uses either the supermolecule method or the perturbation method, and each method has its advantages and disadvantages. The supermolecule method is simple to use but is subject to the basis set superposition error (BSSE), and the current methods to correct the errors are controversial, especially at the correlated level (Scheiner, 1991; Scheiner, 1994). The perturbation method gives insight into the nature of bonding since it computes the energy components corresponding to different physical effects separately, such as electrostatics, short range repulsion, dispersion, induction and charge transfer, but it suffers a number of drawbacks. Usually the models based on ab initio calculations are very complicated. The ASP (Anisotropic Site Potential) model (Millot & Stone, 1992) includes charge, dipole, and quadrupole on oxygen, and charge and dipole on hydrogen. Besides, it has polarizabilities up to quadrupole on oxygen. The NEMO water model (Wallqvist et al., 1990; Åstrand et al., 1995) fits the analytical potential functions to ab initio SCF potentials. Two virtual charge sites were used in the original model in order to fit the multicenter multipole expansion of the interaction energy (Wallqvist et al., 1990). Later a model using atomic dipole moments and anisotropic polarizabilities was introduced (Åstrand et al., 1995). Since the prime objective of the “true” potential models is accuracy, the computing efficiency is usually overlooked or ignored. The methods of development
of these models lead naturally to good representation of small water clusters, but the bulk properties are usually either not satisfactorily reproduced, or not simulated at all because of the expense of computation. Furthermore, the specially tailored potential function forms also prevent their use in the conventional force fields for biomolecular simulations.

Some models used water molecules as basic units. The pioneering work of Barnes et al. used multipole expansion for the water molecule up to quadrupoles as well as a spherically symmetric Lennard-Jones function (Barnes et al., 1979). The non-pair additivity is handled using the classical polarization tensor. Their polarizable electropole (PE) water models give excellent reproduction of water dimer, but for other clusters the agreement with quantum mechanical calculation and experiments is poor. For example, it gives the sequential configuration as the most stable structure for water trimer, instead of the ring structure. It also gives a poor internal energy (-6.8 kcal/mol) for liquid water (experimental value is about -9.9 kcal/mol). The soft sticky dipole (SSD) potential model (Liu & Ichiye, 1996) is another one-site model. It has a single interaction site at the molecular center of mass with a spherical repulsive potential, a dipole potential, and a short-range tetrahedral “sticky” potential. The major merit of the model is its efficiency. It is several times faster than the TIP3P model. For the model to be used in molecular dynamic simulations, however, the special quaternion algorithm has to be incorporated.

Another variation of water models is the central force models (Lemberg & Stillinger, 1975), which model the liquid water as a 1:2 mixture of oxygen and hydrogen.
These models are seldom used in simulation of complex systems.

2.3 Parameterization procedures for TINKER water models

As mentioned in Section 2.2, different models use different procedures for parameterization. For the “true” potential models, the parameters usually come from high level \textit{ab initio} calculations. For the effective potential models, experimental thermodynamic properties are usually used. Currently there seems no water model which can reproduce thermodynamic properties close to experimental values purely by fitting the \textit{ab initio} data on water water dimer potentials (Matsuoka \textit{et al.}, 1976; Millot \\& Stone, 1992), while the effective pair potentials are not satisfactory for small water clusters (Section 2.4). We choose a middle road to parameterize the TINKER polarizable multipole water models. The parameters were obtained through \textit{ab initio} calculations, but their final values are adjusted based on the simulation results against experimental values. More specifically, the dimer structure and energy, the bulk density/pressure, the bulk internal energy, and the radial distribution functions are used in the adjustments.

2.3.1 Rigid water molecules

First, we should decide whether the water molecules in the models should be rigid or flexible. Like other polyatomic molecules, water molecules are flexible in nature.
The bond angle can bend and the bond length can stretch. It is likely that for an accurate treatment the flexibility of monomer has to be taken into account. The same argument has been made for quantum mechanical calculations on small water clusters (Xantheas, 1996), though the effect may be small for water dimers. The structure of flexible water molecules is a complex superposition of all the different motions. Since the time step of a molecular dynamic simulation is dictated by the highest frequency motion in the system, which is usually determined by bond stretching, flexible water molecules will require shorter time step than the rigid molecules. It is also controversial whether introduction of flexibility directly into the current classical force field will improve the accuracy (Wallqvist & Teleman, 1991; Dang & Pettitt, 1987; Anderson et al., 1987; Tironi et al., 1996). Tironi et al. reparameterized the SPC water model to introduce the flexibility and compared the results with those from the rigid model. Their results seem to indicate that introduction of flexibility does not increase the accuracy over the rigid model (Tironi et al., 1996).

In this first version of TINKER water models, we assume rigid water monomers. Since some of the current popular water models use the experimental geometry (such as TIP3P model) and some use the tetrahedral geometry (such as SPC model), for the reason of comparison we developed two TINKER water models, one uses the the experimental geometry, and the other uses the tetrahedral geometry. For the TINKER1 water model we choose the experimental geometry (Benedict et al., 1956), i.e., bond length of 0.9572 Å and bond angle 104.52°. For the TINKER2 water model, SPC geometry is used, i.e., bond length of 1.0 Å and bond angle equal to the
Table 2.1: Geometry parameters of TINKER water models

<table>
<thead>
<tr>
<th>model</th>
<th>( r_{OO} ) (Å)</th>
<th>( \angle \text{HOH} ) (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TINKER1</td>
<td>0.9572</td>
<td>104.52</td>
</tr>
<tr>
<td>TINKER2</td>
<td>1.0000</td>
<td>109.47</td>
</tr>
</tbody>
</table>

The tetrahedral angle, 109.47°. The geometry parameters of TINKER water model are summarized in Table 2.1.

### 2.3.2 van der Waals potentials

Most of the effective pair potential water models, like most of the widely used force fields such as AMBER (Cornell et al., 1995) and CHARMM (Brooks et al., 1983), use the conventional Lennard-Jones 12-6 function for van der Waals potentials (Burkert & Allinger, 1982). The “true” potential water models usually use more complicated forms (Millot & Stone, 1992). For van der Waals potentials, it has been noticed that Lennard-Jones 12-6 potential is not the right form (Rullmann & van Duijnen, 1988). An improved van der Waals potential has to be used in order to have compatible accuracy with the multipole electrostatics (Dudek & Ponder, 1995). We use the buffered 14-7 potentials (Halgren, 1992) for the van der Waals potentials in the TINKER multipole water models, since it has been shown by early work (Dudek & Ponder, 1995) that this potential together with multipoles up to quadrupole gives the least deviation from the \textit{ab initio} potential surface. The Lennard-Jones 12-6 function seems too hard, i.e., the repulsion force increases too steeply with decreasing distance.
### Table 2.2: van der Waals parameters of TINKER water models

<table>
<thead>
<tr>
<th>atom</th>
<th>TINKER1</th>
<th></th>
<th></th>
<th>TINKER2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\epsilon$(kcal/mol)</td>
<td>$r^<em>$</em>(Å)</td>
<td>$d$</td>
<td>$\epsilon$(kcal/mol)</td>
<td>$r^<em>$</em>(Å)</td>
<td>$d$</td>
</tr>
<tr>
<td>O</td>
<td>3.490</td>
<td>0.0760</td>
<td>1.000</td>
<td>3.490</td>
<td>0.0760</td>
<td>1.000</td>
</tr>
<tr>
<td>H</td>
<td>3.010</td>
<td>0.0160</td>
<td>0.850</td>
<td>3.040</td>
<td>0.0130</td>
<td>0.810</td>
</tr>
</tbody>
</table>

between two interacting sites, and the exponential function used in MM2 (Allinger, 1977) and MM3 (Allinger et al., 1989) force fields seems too soft.

The buffered $n$-$m$ potential between atoms $i$ and $j$ has the general form of

\[
E_{vdW(buf-n-m)}^{ij} = \epsilon_{ij} \left( \frac{1 + \delta}{\rho_{ij} + \delta} \right)^{n-m} \left( \frac{1 + \gamma}{\rho_{ij}^m + \gamma} - 2 \right),
\]

where $\delta$ and $\gamma$ are buffering constants and $\rho_{ij} = r_{ij}/r_{ij}^*$. We used the suggested parameters $n = 14$, $m = 7$, $\delta = 0.07$ and $\gamma = 0.12$. Other parameters are listed in Table 2.2.

Usually the geometric-mean rule ($\sqrt{r_{ii}^*r_{jj}^*}$) or arithmetic-mean rule ($(r_{ii}^* + r_{jj}^*)/2$) is used in traditional force field. These rules tend to produce too small a minimum-energy distance when the two atoms’ $r^*$ differ significantly (Halgren, 1992). To improve the accuracy of the combination rule, The cubic-mean rule for $r_{ij}^*$ (Halgren, 1992) is used in TINKER water models

\[
r_{ij}^* = \frac{r_{ii}^{*3} + r_{jj}^{*3}}{r_{ii}^{*2} + r_{jj}^{*2}}.
\]

For the well depth parameter $\epsilon$, the usually used geometric-mean rule ($\sqrt{\epsilon_{ii}\epsilon_{jj}}$)
overestimates the well depths while the harmonic-mean rule \((2\epsilon_i\epsilon_j/(\epsilon_i + \epsilon_j))\) underestimates the well depths. Combining these two rules, i.e., making a harmonic-mean of \(\sqrt{\epsilon_i\epsilon_j}\) and \(2\epsilon_i\epsilon_j/(\epsilon_i + \epsilon_j)\), a new rule labeled as HHG is obtained (Halgren, 1992)

\[
\epsilon_{ij} = \frac{2\sqrt{\epsilon_i\epsilon_j} \times 2\epsilon_i\epsilon_j / (\epsilon_i + \epsilon_j)}{\sqrt{\epsilon_i\epsilon_j} + 2\epsilon_i\epsilon_j / (\epsilon_i + \epsilon_j)} = \frac{4\epsilon_i\epsilon_j}{(\sqrt{\epsilon_i} + \sqrt{\epsilon_j})^2}.
\] (2.3)

TINKER models used HHG rule for the combination of the well depths.

The parameter \(d\) in Table 2.2 is a scale factor which scales the distance between the atom and other atoms.

### 2.3.3 Multipoles and polarizabilities

There are few experimental values for atomic multipoles of water atoms, so the atomic multipoles will be derived directly from high level \(ab\ initio\) calculations. Basis set quality is very important in extracting electric properties from \(ab\ initio\) calculations. We used the ELP (Electrical Properties) basis sets (Liu & Dykstra, 1987). The basis sets are based on the triple-\(\zeta\) core-valence sets (Dunning, 1971) which are augmented with diffuse valence function. In addition, the hydrogen is doubly polarized and the oxygen is triply polarized. Second-order Møller-Plesset perturbation (MP2) was used to incorporate electron correlation.

Atomic charge is not a quantum mechanical observable since there is no atomic charge operator (Bachrach, 1994). However, several methods exist to obtain distributed multipoles from quantum mechanical calculations. For the partial charges,
the classical Mulliken population analysis can be used (Mulliken, 1955). Alternatively, the spatially based method of topological electron density analysis developed by Bader (Bader, 1991) divides the molecular space based on the electron density and can be used to obtain atomic multipoles. Another often used method is to fit the charges and multipoles to the electrostatic potential which can be generated exactly from molecular wavefunctions (Breneman & Wiberg, 1990; Bayly et al., 1993). What we used to get the atomic multipoles for the TINKER water models is the distributed multipole analysis (DMA) method developed by Stone (Stone, 1981; Stone & Alderton, 1985; Stone, 1996). For small molecule dimers, Buckingham and Fowler have shown that by using the multipoles up to quadrupoles derived from DMA to represent the intermolecular electrostatic interactions, they can reliably predict the experimentally observed geometries (Buckingham & Fowler, 1983; Buckingham & Fowler, 1985). A similar but slightly more complicated model was proposed by Spackman (Spackman, 1986) for studying hydrogen-bonded dimers. It is found that as long as quadrupoles are included, different multipole partitioning schemes have little effect on the results. There is another comparison study on the effects of different charge partitioning schemes on water models (Soetens & Millot, 1995), although the inclusion of multipoles only to dipole level makes the comparison less conclusive.

The *ab initio* calculation was carried out with the program GAMESS (Schmidt *et al.*, 1993) and multipoles are extracted using the built-in DMA. The multipoles and polarizabilities of TINKER water models are listed in Table 2.3 and Table 2.4. The quadrupoles of TINKER2 model are scaled by a factor of 0.6 of the DMA results.
Table 2.3: Electrostatic parameters of TINKER1 models

<table>
<thead>
<tr>
<th>atom</th>
<th>dipole (eÅ)</th>
<th>quadrupole (eÅ²)</th>
<th>polarizability α(Å³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µx  µy  µz</td>
<td>Qxx  Qyy  Qzz  Qxz  Qyz</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>0.0  0.0  0.17698</td>
<td>0.07094 0.07663 0.00569 0.0 0.0 0.0</td>
<td>0.541</td>
</tr>
<tr>
<td>H</td>
<td>0.05017 0.0 -0.18416</td>
<td>0.00609 0.00455 -0.01064 0.0 0.00487 0.0</td>
<td>0.329</td>
</tr>
</tbody>
</table>

Table 2.4: Electrostatic parameters of TINKER2 models

<table>
<thead>
<tr>
<th>atom</th>
<th>dipole (eÅ)</th>
<th>quadrupole (eÅ²)</th>
<th>polarizability α(Å³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µx  µy  µz</td>
<td>Qxx  Qyy  Qzz  Qxz  Qyz</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>0.0  0.0  0.18451</td>
<td>0.04438 -0.04794 0.00356 0.0 0.0 0.0</td>
<td>0.446</td>
</tr>
<tr>
<td>H</td>
<td>0.05230 0.0 -0.19200</td>
<td>0.00381 0.00285 -0.00666 0.0 0.00305 0.0</td>
<td>0.271</td>
</tr>
</tbody>
</table>

The atomic polarizabilities is usually fit empirically to experimental molecular polarizabilities, although methods exist for using quantum mechanical calculations (Stone & Alderton, 1985). We used the values given by Miller (Miller, 1990a; Miller, 1990b) and scaled them by different factors in the parameterization process. The final values are list in Table 2.3 and Table 2.4. Since electron clouds are modeled as point multipoles in the TINKER water models, as two atoms approach each other, the induced dipoles on each atoms will become unphysically large, a phenomenon that has already been observed in partial charge models. A damping procedure has to be used in order to prevent such a “polarization catastrophe” (Stillinger & David, 1978; Thole, 1981; Kuwajima & Warshel, 1990; Bernardo et al., 1994). We applied the following damping function (Thole, 1981; Bernardo et al., 1994) to the electric...
where \( r_{ij}^* = 1.662(\alpha_i\alpha_j)^{1/6} \). The function \( f(r_{ij}) \) behaves as \( r_{ij}^3 \) as \( r_{ij} \) approach zero, which attenuates the increase of the electric field, which behaves as \( r_{ij}^{-2} \). As the distance between two atoms becomes large, \( f(r_{ij}) \) approaches identity.

### 2.4 Small cluster of water molecules

#### 2.4.1 Introduction

The advance in both laser spectroscopy technology and theoretical methods has stimulated a wave of studies on water clusters in recent years (Wales, 1996; Liu et al., 1996b). As the nanotechnology comes more and more closer to reality, it is natural that the properties of nanoclusters attract increasing attentions. Furthermore, theories have been proposed which linked the bulk properties of water to those of the discrete clusters (Benson & Siebert, 1992). The motivation also comes from the desire to develop more realistic water models that are more accurate in widely varying situations (Elrod & Saykally, 1994). It is also hoped that the study of water clusters of various size will help one to understand how the bulk properties are approached as the cluster size increases (Lee et al., 1995). Since in biological systems a small number of water molecules usually occupy strategic positions and interact with the
rest of the system distinctively, it is important to model correctly the interaction of small water clusters (Section 1.1).

From detailed studies of the water dimer, it is known that flexible basis sets and inclusion of electron correlation effects are necessary to obtain an accurate description of hydrogen bonding in water clusters by \textit{ab initio} methods (Scheiner, 1991; Xantheas & Dunning, 1993; Scheiner, 1994; Estrin \textit{et al.}, 1996). Because of this stringent requirement of computing power, it is difficult to get high quality \textit{ab initio} results with complete geometry optimization for larger water clusters. Since the TINKER water models are developed in such a way that on the one hand they are efficient enough compared with the high level quantum mechanical calculations to easily carry out the dynamic simulations, and on the other hand they have the subtlety to model the directionality and polarization of the intermolecular interactions, it is our hope that they can serve as a bridge between the gap of the two extremes of modeling complexity. In the following sections the properties of small water clusters up to ten molecules will be studied using the TINKER multipole water models, and the results will be compared with other simpler water models. Four such models will be compared. SPC (Berendsen \textit{et al.}, 1981), SPC/E (Berendsen \textit{et al.}, 1987) and TIP3P (Jorgensen \textit{et al.}, 1983) are all three-site, effective pair potential models, and POL3 (Caldwell & Kollman, 1995) is a three-site partial charge model with dipole polarizability on three atoms. SPC, SPC/E and POL3 have the same geometry as the TINKER2 model, i.e., the tetrahedral bond angle and bond length of 1 Å, and TIP3P uses the experimental geometry, like the TINKER1 model.
In the following sections, the optimal and low energy structures from TINKER and other models will be studied. To find the global and local minima random searches were carried out. Each monomer in the clusters is translated with a random distance and the energy was minimized by using the optrigid program in the TINKER molecular modeling package with the water monomers kept as rigid bodies. optrigid optimizes energy using an optimally conditioned variable metric method without line searches (Davidon, 1975). For water clusters up to hexamer, this method easily finds the local minima reported in literature. For example, using an eigenmode following algorithm which was developed to effectively locate local minima on complex potential energy surface (Hildrebrandt, 1977), Tsai and Jordan found 22 local minima for the TIP4P water pentamer (Tsai & Jordan, 1993b), and 137 for the TIP4P water hexamer (Tsai & Jordan, 1993a). The random search method used in this work found 37 and 165 local minima for the TIP4P water pentamer and hexamer, respectively. The 37 local minima found for the TIP4P pentamer in this work include all the 22 reported structures (Tsai & Jordan, 1993b), and the 45 lowest energy structures of the 165 local minima found for TIP4P hexamer in this work include the 44 reported lowest energy structures (Tsai & Jordan, 1993a). For water clusters smaller than pentamer, the random search and the eigenmode following algorithm found the exact same local minima for both the TIP3P and TIP4P models.
2.4.2 Monomer

As discussed in Section 2.2, the effective pair potential models have the dipole moment enhanced in order to take into the polarization effects for bulk simulations. On the other hand, the dipoles in TINKER models are not deliberately enhanced. From Table 2.5 it can be seen that the dipoles of the water monomer in TINKER models are quite close to the experimental gas phase dipole value.

The dipole and quadrupole moments from various models are listed in Table 2.5 together with the experimental values of dipole (Lovas, 1978) and quadrupole moments (Verhoeven & Dymanus, 1970; Flygare, 1974). Since the dipole moment of water molecule does not vanish, the values of quadrupole moments depend on the coordinate system (Böttcher et al., 1973). The system defined by Verhoeven and Dymanus is used here (Verhoeven & Dymanus, 1970). In this definition, the center of mass is used as the origin (Figure 2.1). The z-axis is defined as the dipole direction and y-axis is perpendicular to the molecule plane.

Since there are only few parameters that can be adjusted, atom-centered three-site partial charge models cannot reproduce both the dipole and quadrupole moments.
Table 2.5: Monomer properties

<table>
<thead>
<tr>
<th>Model</th>
<th>dipole (Debye)</th>
<th>$Q_{xx}$</th>
<th>$Q_{yy}$</th>
<th>$Q_{zz}$</th>
<th>$Q_{xy}$</th>
<th>$Q_{xz}$</th>
<th>$Q_{yz}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TINKER1</td>
<td>1.878</td>
<td>2.671</td>
<td>-2.602</td>
<td>-0.069</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TINKER2</td>
<td>1.924</td>
<td>2.673</td>
<td>-2.394</td>
<td>-0.279</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>POL3</td>
<td>2.024</td>
<td>1.884</td>
<td>-1.622</td>
<td>-0.262</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>SPC</td>
<td>2.274</td>
<td>2.116</td>
<td>-1.822</td>
<td>-0.294</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>SPC/E</td>
<td>2.351</td>
<td>2.187</td>
<td>-1.884</td>
<td>-0.304</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TIP3P</td>
<td>2.347</td>
<td>1.762</td>
<td>-1.681</td>
<td>-0.080</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Exp.</td>
<td>1.855&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-2.50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reference (Lovas, 1978).

<sup>b</sup>Reference (Verhoeven & Dymanus, 1970; Flygare, 1974)

of the water monomer. If a partial charge model reproduces correctly the gas phase dipole moment, then the quadrupole moments will be about 40% less than experimental value. POL3 model, which has a permanent dipole of 2.024 D, has a quadrupole moment about 30% less than experimental values. Other effective pair potential models give slightly bigger quadrupole moments because of their enhanced dipole moments (Table 2.5), but the values are still much less than the experimental values. From Table 2.5 we see that both of the TINKER models give reasonable representations of the molecular quadrupole moments of the water molecules. It has been
argued that quadrupole moments should be an important constraint in building a water model (Carnie & Patey, 1982; Watanabe & Klein, 1989). It should be noted that in the parameterization process of developing TINKER water models, the dipole and quadrupole moments are not the targets for adjusting the parameters. One of the effective pair potential models, the WK model (Watanabe & Klein, 1989), fits the charges so that the experimental values of quadrupole moments are reproduced. The dipole moment of model is thus even bigger than the effective pair potential models listed in Table 2.5 with a value of 2.6 D. The model is reported to give good relative permittivity, but the diffusion constant is too low. The properties of small clusters are not reported. Although the small clusters are not studied by this model, it is our experience that a model with such a big dipole moment will give poor performance for small clusters.

2.4.3 Dimer

The dimer of water molecules has received extensive experimental (Odutola & Dyke, 1980) and theoretical studies (Scheiner, 1991; Scheiner, 1994). It is studied as one of the prototype of hydrogen bonds. Although a lot of studies have been done on this system, there still remain many uncertainties (Scheiner, 1994). Some of the reported experimental values and high level ab initio results are listed in Table 2.6. As mentioned in Section 2.3, the properties of dimer are used in adjusting the parameters of the TINKER models. Figure 2.2 shows the lowest energy structure of the water dimer. Besides the binding energy, other structure features of the water dimer that
are used in the parameterization process are depicted in Figure 2.2. These include the oxygen-oxygen distance $r_{OO}$, the donor angle $\theta_d$, and the acceptor angle $\theta_a$.

![Figure 2.2: The lowest energy structure of the water dimer.](image)

The dimer properties of TINKER models, as well as those from other models, are listed in Table 2.6. The lowest energy structures of TINKER models are shown in Figure 2.3 and 2.4, respectively.

From Table 2.6 we can see that the partial charge models produce too low a binding energy. Although there is still disagreement among quantum mechanical calculations, it seems that the results are converging to about -5.0 kcal/mol (Feyereisen et al., 1996). For the experimental value of binding energy, the often quoted value of $-5.40\pm0.70$ was obtained by measurement of thermal conductivity (Curtiss et al., 1979). The enthalpy $\Delta H = -3.59$ kcal/mol was extracted from the measured thermal conductivity data at different temperatures by a fitting procedure. By correcting with vibrational energy, rotational energy, and translational energy, which adds up to about -1.85 kcal/mol, the binding energy was obtained. The other two methods that have been used to measure the binding energy involved measurement and analysis of second virial coefficient data and variation of infrared absorption intensity with
temperature. Since the simple partial charge models use enhanced dipole moments, the wells of their binding energy are too deep. Both the TINKER models reproduce the binding energy quite well.

Another discrepancy of the simple partial charge models is that they give the $r_{oo}$ distance too short. The anisotropic polarizable SPC models also give too short a $r_{oo}$
Table 2.6: Dimer properties

<table>
<thead>
<tr>
<th>Method</th>
<th>$U_{pot}$ (kcal/mol)</th>
<th>$r_{OO}$ (Å)</th>
<th>$\theta_d$ (°)</th>
<th>$\theta_a$ (°)</th>
<th>$\mu_{ave}$ (Debye)</th>
<th>$\mu_{tot}$ (Debye)</th>
<th>$\mu_{\parallel}$ (Debye)</th>
<th>$\mu_{\perp}$ (Debye)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TINKER1</td>
<td>-5.010</td>
<td>2.924</td>
<td>58.36</td>
<td>71.06</td>
<td>2.053</td>
<td>2.112</td>
<td>2.100</td>
<td>0.227</td>
</tr>
<tr>
<td>TINKER2</td>
<td>-5.114</td>
<td>2.898</td>
<td>57.64</td>
<td>59.12</td>
<td>2.082</td>
<td>2.449</td>
<td>2.448</td>
<td>0.059</td>
</tr>
<tr>
<td>POL3</td>
<td>-5.442</td>
<td>2.789</td>
<td>52.11</td>
<td>19.71</td>
<td>2.199</td>
<td>3.676</td>
<td>3.565</td>
<td>0.897</td>
</tr>
<tr>
<td>SPC</td>
<td>-6.610</td>
<td>2.752</td>
<td>52.27</td>
<td>22.15</td>
<td>2.274</td>
<td>3.622</td>
<td>3.498</td>
<td>0.941</td>
</tr>
<tr>
<td>SPC/E</td>
<td>-7.200</td>
<td>2.733</td>
<td>52.37</td>
<td>22.29</td>
<td>2.351</td>
<td>3.738</td>
<td>3.610</td>
<td>0.970</td>
</tr>
<tr>
<td>TIP3P</td>
<td>-6.540</td>
<td>2.747</td>
<td>48.35</td>
<td>21.55</td>
<td>2.347</td>
<td>3.847</td>
<td>3.743</td>
<td>0.892</td>
</tr>
<tr>
<td>ab initio</td>
<td>-5.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>2.10&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5.0±0.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exp.</td>
<td>-5.40±0.70&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.976&lt;sup&gt;f&lt;/sup&gt;</td>
<td>51±10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>57±10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.643&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.64&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.38&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.952&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference (Saebø et al., 1993)
<sup>b</sup> Reference (Mas & Szalewicz, 1996)
<sup>c</sup> Reference (Feyereisen et al., 1996)
<sup>d</sup> Reference (Gregory et al., 1997)
<sup>e</sup> Reference (Curtiss et al., 1979).
<sup>f</sup> Reference (Odutola & Dyke, 1980). Average structure including zero point vibrational oscillations of water molecules in the dimer.
<sup>g</sup> Reference (Odutola & Dyke, 1980). Estimated equilibrium distance.
distance, around 2.78-2.80 Å (Rullmann & van Duijnen, 1988; Bernardo et al., 1994). TINKER models give longer \( r_{oo} \) distances which are closer to the experimental and \textit{ab initio} values. Confusions sometimes arise in the interpretation of the experimental geometry values (Burkert & Allinger, 1982). The experimental structure of the water dimer was deduced by Dyke and coworkers (Odutola & Dyke, 1980) by using molecular beam electric resonance spectroscopy. The radio frequency and microwave spectra for various isotopically substituted water dimers were analyzed by an iterative least-square fitting procedure. The rigid-rotor model was used to determine the dimer geometry, with the monomer geometries fixed at the experimental equilibrium values of bond length 0.9572 Å and bond angle 104.52° (Benedict et al., 1956). The often cited value of 2.976 Å for \( r_{oo} \) describes the average oxygen-oxygen distances when the water monomers are vibrating around the zero point equilibrium position. The potential well of the dimer interaction is not perfect harmonic: at shorter distances the energy rises more steeply, and at longer distances more slowly. The effects of the anharmonicity thus tend to increase the vibrationally averaged distance compared with the equilibrium distance. To estimate the equilibrium geometry, intermolecular vibrational frequencies have to be used to assess the effect of anharmonicity, usually taken from \textit{ab initio} calculations. Thus uncertainties exist in the correction of the anharmonicity. Dyke and coworkers gave a correction of 0.024 Å, leading to an equilibrium distance of 2.952 Å. Other corrections have been reported, for example, a value of 0.131 Å is given (Åstrand et al., 1995), resulting in an equilibrium distance of 2.845 Å.
The $r_{OO}$ distance is closely related to the binding energy $U_{pot}$. If we adjust the parameters to keep $r_{OO}$ longer, the well of the binding energy will become too shallow. In Figure 2.5 and Figure 2.6 the minimum-energy surfaces of the TINKER water dimer as a function of the oxygen-oxygen distance are shown together with the polarization energy. The oxygen-oxygen distance is fixed at each separation and each water molecule of the dimer is optimized as a rigid body. From Figure 2.5 and Figure 2.6 we can see that the polarization energy takes quite a proportion of the potential energy. The wells of the polarization energy of TINKER models are deeper than other polarizable models, such as the anisotropic polarizable SPC model (Bernardo et al., 1994). In the lowest energy configuration, the polarization energy makes about 21% and 18% contribution to the total energy of the water dimer for the TINKER1 and TINKER2 models, respectively.

Most of the water models reproduce the donor angle $\theta_d$ correctly (Figure 2.2), but give the acceptor angle $\theta_d$ too small. This has been attributed to the lack of directionality on the oxygen (Rullmann & van Duijnen, 1988). TINKER models give the acceptor angle $\theta_d$ much closer to the experimental value. It has been found that the quadrupole moments play an important role in determining this angle.
Figure 2.5: Minimum-energy surface of the water dimer of TINKER1 model as a function of the oxygen-oxygen distance. The energy is in the unit of kcal/mol, and the distance in angstroms (Å). Also shown is the polarization energy.

Figure 2.6: Minimum-energy surface of the water dimer of TINKER2 model as a function of the oxygen-oxygen distance. The energy is in the unit of kcal/mol, and the distance in angstroms (Å). Also shown is the polarization energy.
2.4.4 Trimer

Like the water dimer, the water trimer also received extensive theoretical investigations (Wales, 1993; Xantheas & Dunning, 1993; Fowler & Schaefer III, 1995; Estrin et al., 1996; Walsh & Wales, 1996). It serves as a prototype to study the three-body contributions to the interaction energy in bulk water. There exist some experimental results (Pugliano & Saykally, 1992), but an accurate experimental geometry is not available. From quantum mechanical calculations, it is now agreed that the lowest energy configuration is a cyclic structure, with all three water molecules acting as both hydrogen donors and acceptors. Two of the free hydrogen atoms lie in one side of the plane of the three oxygens, the third on the other side. The global minimum structure of TINKER1 trimer is shown in Figure 2.7. The global minimum of TINKER2 trimer has the similar structure. The various properties of TINKER water trimers in the optimal structures as well as the trimers from other models are listed in Table 2.7. From the table we can see that binding energy of TINKER trimers is very close to the result obtained at high level \textit{ab initio} calculation [ triple-$\zeta$ plus double polarization plus diffuse functions (TZ2P+diff) CCSD (single and double excitation coupled cluster) ] (Fowler & Schaefer III, 1995), while other models give the binding energy too low. The structures of minimum energy configuration of TINKER models also agree well with the quantum mechanical calculations. The distances between three oxygen atoms are not equal, as predicted by \textit{ab initio} calculations. In addition, the order of $r_{OO}$ is also in accord with \textit{ab initio} calculations, with the oxygen-oxygen distance between the water molecules whose free hydrogens on the same side of the
oxygen plane being the longest, and the oxygen-oxygen distance involving the hy-
drogen donor whose free hydrogen on the other side of the oxygen ring being the
shortest. The trimers from both TINKER models show this trend. On the other
hand, the other models predict a symmetrical structure. All the oxygen-oxygen dis-
tances are identical. Besides, the structures are planar: the free hydrogens also lie in
the same oxygen plane. From the the quantum mechanical calculation, this structure
lies about 1.67 kcal/mol above the global minimum (Fowler & Schaefer III, 1995).
For TINKER models randomized research does not find this planar structure as a
local minimum.

There is another local minimum predicted by \textit{ab initio} calculations which has a
lower energy than the planar structure, in which all the three free hydrogen atoms lie
in the same side of the oxygen plane. Both TINKER models correctly predict this
local minimum (Figure 2.8). In addition, the energy gap between this minimum and
the global minimum is close to that predicted by the quantum mechanical calculation:
TINKER1 gives a gap of 1.10 kcal/mol for three water molecules and TINKER2 gives
a gap of 0.83 kcal/mol, while the high level theory gives a gap of 0.85 kcal/mol (Fowler
& Schaefer III, 1995).

2.4.5 Tetramer

For the water tetramer the experimental (Cruzan \textit{et al.}, 1996) or theoretical (Xantheas
& Dunning, 1993; Schütz \textit{et al.}, 1995; Estrin \textit{et al.}, 1996; Wales & Walsh, 1997)
information is not as abundant as that for the water dimer or trimer. For the global
Figure 2.7: The lowest energy structure of the water trimer.

Figure 2.8: The second lowest energy structure of the water trimer from TINKER1 model.
Table 2.7: Trimer properties

<table>
<thead>
<tr>
<th></th>
<th>$U_{pot}^a$ (kcal/mol)</th>
<th>$r_{OO}$ (Å)</th>
<th>$r_{OO}$ (Å)</th>
<th>$\angle(O \cdots H-O)$ (°)</th>
<th>$\mu_{ave}$ (Debye)</th>
<th>$\mu_{tot}$ (Debye)</th>
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<td>2.883</td>
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<td>CCSD$^d$</td>
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<td>2.825</td>
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<td>exp.$^e$</td>
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$^a$Potential energy per monomer.

$^b$Reference (Xantheas & Dunning, 1993).

$^c$Reference (Gregory et al., 1997).

$^d$Reference (Fowler & Schaefer III, 1995).

$^e$Reference (Pugliano & Saykally, 1992; Liu et al., 1996a).

minimum structure, it is generally agreed that a cyclic ring structure, with the free hydrogens pointing alternatively up and down relative to the oxygen ring (\{udud\}, u=up, d=down), has the lowest energy. The TINKER water models correctly predict this global minimum structure. Figure 2.9 shows the structure from TINKER1 model. It should be pointed out that although the four oxygens are almost in the same plane,
they are not exactly planar. Instead they are out of plane about 4°. Other properties, as well as a comparison among models, are listed in Table 2.8. The global minimum structures of TINKER tetramers are symmetrical, so are those from the other models. However, all the other models predict a global minimum structure in which all the free hydrogens lie in the same plane as the oxygens.

Besides the $S_4$ symmetry ($\{udud\}$), the quantum mechanical calculations also predict several other low energy structures (Schütz et al., 1995; Wales & Walsh, 1997). The second lowest energy structure is also predicted to be a ring, with two neighboring free hydrogens pointing up relative to the ring plane and the other two pointing down ($\{uudd\}$). This structure is predicted to lie 0.93 kcal/mol above the global minimum (Schütz et al., 1995). Both TINKER models correctly predict this
structure to have the second lowest energy, with an energy gap of 1.09 kcal/mol for TINKER1 model and 0.87 kcal/mol for TINKER2 model. The second lowest energy structure is shown in Figure 2.10. Both TINKER models predict a third lowest energy structure, with three hydrogen atoms pointing up and the remaining one pointing down (\{uuud\}). The energy of this local minimum is very close to the second local minimum, with an energy gap of 0.20 kcal/mol for TINKER1 model and 0.15 kcal/mol for TINKER2 model. The energetics of this minimum agrees with the calculation of Schütz et al., though their results indicate that this structure is not a stationary point on the potential surface. The structure from TINKER1 model of this minimum is shown in Figure 2.11. The binding energy of water tetramer is very sensitive to the level of theory used if calculated quantum mechanically (Estrin et al., 1996), and currently its value can not be settled from high level calculations.

2.4.6 Pentamer

There are few high level ab initio calculations for the water pentamer. Some empirical force fields have been used to study the water pentamer (Kim et al., 1986; Tsai & Jordan, 1993b). The consensus optimal equilibrium structure of pentamer is a cyclic ring structure, following the pattern of tetramer and trimer. The free hydrogens point out of the oxygen ring plane with alternate directions, three up and two down, so there are two neighboring free hydrogens pointing into the same direction. The TINKER models correctly predict this global minimum, which is shown in Figure 2.12. Other properties of the optimal structure are listed in Table 2.9. Since there are odd
Table 2.8: Tetramer properties

<table>
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<tr>
<th></th>
<th>$U_{\text{pot}}$</th>
<th>$r_{\text{OO}}$</th>
<th>$\angle(\text{O} \cdot \cdot \text{H} \cdot \text{O})$</th>
<th>$\mu_{\text{ave}}$</th>
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<td>(kcal/mol)</td>
<td>(Å)</td>
<td>(°)</td>
<td>(Debye)</td>
<td>(Debye)</td>
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<td>TINKER1</td>
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<td>TINKER2</td>
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<td>175.7</td>
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</tr>
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</tr>
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<td>173.9</td>
<td>2.351</td>
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</tr>
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<td>166.1</td>
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<tr>
<td>MP2$^b$</td>
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<tr>
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<td>exp.$^d$</td>
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</tbody>
</table>

*a* Potential energy per monomer.

*b* Reference (Xantheas & Dunning, 1993).

*c* Reference (Gregory et al., 1997).

*d* Reference (Cruzan et al., 1996; Liu et al., 1996a).
Figure 2.10: The second lowest energy structure of the water tetramer from TINKER1 model.

Figure 2.11: The third lowest energy structure of the water tetramer from TINKER1 model.
number of free hydrogens, the structure is no longer symmetrical. The five oxygen-oxygen distances are 2.7389, 2.7401, 2.7414, 2.7457, and 2.7628 for TINKER1 model, and 2.7371, 2.7379, 2.7380, 2.7406, and 2.7585 for TINKER2 model. As can be seen from the table, the geometry and dipole moment of the TINKER pentamers are much closer to the quantum mechanical calculations than those from other models. For other local minima, two TINKER models predicts slightly different orders. The second lowest energy structure for the TINKER1 model is shown in Figure 2.13, while this structure was predicted to be the fourth lowest energy structure by TINKER2 model. TINKER2 predicts as the second lowest energy structure a ring with free hydrogens in \{uudpd\} configuration relative to the ring, where p indicates that the hydrogen is in the oxygen plane. The energy orders are also slightly different from the prediction by \textit{ab initio} calculation using DZP/BLYP level theory (double-\(\zeta\) plus polarization with the use of density functional theory to consider the correlation effects) (Wales & Walsh, 1996). It seems that potential surface of the water pentamer is more complicated than expected before and higher level theory is needed to settle the problem.
Figure 2.12: The lowest energy structure of the water pentamer from TINKER1 model.

Figure 2.13: The local minimum of the water pentamer. TINKER1 model predicts this structure to be the second lowest energy structure, while TINKER2 predicts it the fourth lowest in energy.
Table 2.9: Pentamer properties

<table>
<thead>
<tr>
<th></th>
<th>$U_{\text{pot}}^a$ (kcal/mol)</th>
<th>$r_{\text{OO}}$ (Å) (ave)</th>
<th>$\angle(O \cdots H\cdots O)$ (°) (ave)</th>
<th>$\mu_{\text{ave}}$ (Debye)</th>
<th>$\mu_{\text{tot}}$ (Debye)</th>
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<td>TINKER2</td>
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<td>2.742</td>
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<td>1.165</td>
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<td>2.75</td>
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</table>

$^a$Potential energy per monomer.

$^b$Reference (Xantheas & Dunning, 1993).

$^c$Reference (Gregory et al., 1997).

$^d$Reference (Liu et al., 1996a).

### 2.4.7 Hexamer

Consensus seems to be reached that for the water trimer, tetramer and pentamer, the optimal structures are cyclic, and for heptamer and larger clusters three-dimensional structures are global minima. The water hexamer receives considerable attention because of its intermediate position (Franken et al., 1992; Tsai & Jordan, 1993a; Kim
It seems clear that for the water hexamer there are several different stable structures which are very close in energy. The “prism” structure is usually regarded as the global minimum on the potential surface (Tsai & Jordan, 1993a; Liu et al., 1996c), while the “cage” structure is slightly more stable when quantum vibrational zero-point energy corrections are taken into account. The ring structure is a local minimum, but is generally not considered as the lowest energy structure. TINKER1 model predicts the prism structure as the lowest energy structure (Figure 2.14), the cage (Figure 2.15) and the “book” (Figure 2.16) structures as the second and third classes of low energy structures (each class has many closely related, but not the same, structures). TINKER2 model predicts the cage as the lowest energy structure, the book (Figure 2.18) and the prism as the second and third classes of low energy structures. Both models predicts ring structure as a local minimum, but the energies of the ring structures are much higher than the prism, cage or book structures. The properties of these structures from TINKER models as well as other models are listed in Table 2.10, Table 2.11, Table 2.12, and Table 2.13. From these tables it is clear that TINKER models predict the structure, energy gap, and dipole moments quite close to the available quantum mechanical calculations. On the other hand, the other models cannot predict the cage or prism structures as the low energy structures. None of these models can predict the nine-hydrogen-bonded prism structure; Instead, one of the hydrogen bond is broken (Figure 2.19).
Figure 2.14: The lowest energy structure of TINKER1 hexamer: prism.

Figure 2.15: The second lowest energy structure of TINKER1 hexamer: cage.
Figure 2.16: The third lowest energy structure of TINKER1 hexamer: book

Figure 2.17: The ring structure of TINKER1 hexamer.
Table 2.10: Hexamer properties: ring structure

<table>
<thead>
<tr>
<th>Model</th>
<th>$U_{\text{pot}}$</th>
<th>$\Delta U_{\text{pot}}$</th>
<th>$r_{\text{OO}}$</th>
<th>$\angle(O\cdots H-O)$</th>
<th>$\mu_{\text{ave}}$</th>
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</thead>
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<tr>
<td></td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td>(Å)</td>
<td>(°)</td>
<td>(Debye)</td>
<td>(Debye)</td>
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\(^a\)Potential energy per monomer.
\(^b\)Relative to the lowest energy for six water molecules.
\(^c\)Reference (Xantheas & Dunning, 1993).
\(^d\)Reference (Tsai & Jordan, 1993a), MP2/aug-ccpVDZ\(^*\) without BSSE correction.
\(^e\)Reference (Gregory \textit{et al.}, 1997).
Table 2.11: Hexamer properties: prism structure

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<tr>
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<th>$U_{pot}^a$ (kcal/mol)</th>
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</table>

$^a$Potential energy per monomer.
$^b$Relative to the lowest energy for six water molecules.
$^c$Reference (Tsai & Jordan, 1993a), MP2/aug-ccpVDZ* without BSSE correction.
$^d$Reference (Gregory et al., 1997).
$^e$The distance between the two oxygens which actually do not form a hydrogen bond is included. See text for details.
<table>
<thead>
<tr>
<th></th>
<th>$U_{pot}^a$</th>
<th>$\Delta U_{pot}^b$</th>
<th>$r_{oo}$</th>
<th>$\mu_{ave}$</th>
<th>$\mu_{tot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td>(Å)</td>
<td>(Debye)</td>
<td>(Debye)</td>
</tr>
<tr>
<td>TINKER1</td>
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<td>0.3516</td>
<td>2.753</td>
<td>2.463</td>
<td>2.457</td>
</tr>
<tr>
<td>TINKER2</td>
<td>-7.271</td>
<td>0</td>
<td>2.845</td>
<td>2.397</td>
<td>2.241</td>
</tr>
<tr>
<td>POL3</td>
<td>-7.192</td>
<td>3.125</td>
<td>2.883</td>
<td>2.479</td>
<td>3.188</td>
</tr>
<tr>
<td>SPC</td>
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<td>0.849</td>
<td>2.780</td>
<td>2.274</td>
<td>2.153</td>
</tr>
<tr>
<td>SPC/E</td>
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<td>0.967</td>
<td>2.762</td>
<td>2.351</td>
<td>2.226</td>
</tr>
<tr>
<td>TIP3P</td>
<td>-7.779</td>
<td>1.115</td>
<td>2.776</td>
<td>2.347</td>
<td>2.169</td>
</tr>
<tr>
<td>MP2$^c$</td>
<td>0.22</td>
<td></td>
<td>2.882</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP2$^d$</td>
<td></td>
<td>2.64</td>
<td></td>
<td>1.904</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Potential energy per monomer.

$^b$Relative to the lowest energy for six water molecules.

$^c$Reference (Tsai & Jordan, 1993a), MP2/aug-ccpVDZ* without BSSE correction.

$^d$Reference (Gregory et al., 1997).
Table 2.13: Hexamer properties: book structure

<table>
<thead>
<tr>
<th></th>
<th>$U_{\text{pot}}^a$</th>
<th>$\Delta U_{\text{pot}}^b$</th>
<th>$r_{\text{OO}}$</th>
<th>$\mu_{\text{ave}}$</th>
<th>$\mu_{\text{tot}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td>(Å)</td>
<td>(Debye)</td>
<td>(Debye)</td>
</tr>
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<td>TINKER1</td>
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<td>2.798</td>
<td>2.453</td>
<td>1.881</td>
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<tr>
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<td>2.532</td>
</tr>
<tr>
<td>POL3</td>
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<td>2.714</td>
<td>2.552</td>
<td>2.256</td>
</tr>
<tr>
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<td>2.274</td>
<td>2.347</td>
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<td>2.722</td>
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<tr>
<td>TIP3P</td>
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<td>0</td>
<td>2.736</td>
<td>2.347</td>
<td>2.207</td>
</tr>
<tr>
<td>MP2$^c$</td>
<td></td>
<td>0.32</td>
<td>2.782</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Potential energy per monomer.

$^b$Relative to the lowest energy for six water molecules.

$^c$Reference (Tsai & Jordan, 1993a), MP2/aug-ccpVDZ* without BSSE correction.
Figure 2.18: The book structure predicted by TINKER2 model.

Figure 2.19: The prism structure from TIP3P water model. One hydrogen bond is broken.
The lowest energy structure of the book class predicted by TINKER1 model is slightly different from that reported earlier (Tsai & Jordan, 1993a; Liu et al., 1996c) (Figure 2.16). One of the two water molecules in the middle receives two hydrogens from its two neighbor water molecules, and the other middle water molecule donates two hydrogens to two neighbors. On the other hand, TINKER2 model predicts a lowest energy structure of the book class which is the same as that reported before (Figure 2.18). From the nonexhaustive random search we did not find the “boat” structure described in one of the work (Liu et al., 1996c) by using modified ASP model (Millot & Stone, 1992). A newly proposed model did not find this structure either (Dang & Chang, 1997). Whether this “boat” structure represents a local minimum is still an open question.

Nonexhaustive random searches show that the TINKER models have at least 400 local minima for the water hexamer. On the contrary, the simple partial charge models we tested give about 60 minima. If the TINKER minimum structures are used as the starting structure for minimization in these models, several TINKER minima will collapse into the same local minimum in these models, and the correlation is not linear. These correlations are shown in Figures 2.20, 2.21, 2.22 and 2.23. The potential surface of TINKER model will be discussed in a following section (Section 2.7).

2.4.8 Heptamer

Little information is known about the structure and energetics of the water heptamer, but the consensus is that the optimal structure of the water heptamer should be three-
Figure 2.20: The local minima of TINKER1 hexamer and the corresponding minima of TIP3P model. Both axes are in the unit of kcal/mol.

Figure 2.21: The local minima of TINKER2 hexamer and the corresponding minima of POL3 model. Both axes are in the unit of kcal/mol.
Figure 2.22: The local minima of TINKER2 hexamer and the corresponding minima of SPC model. Both axes are in the unit of kcal/mol.

Figure 2.23: The local minima of TINKER2 hexamer and the corresponding minima of SPC/E model. Both axes are in the unit of kcal/mol.
Figure 2.24: The lowest energy structure of the water heptamer from TINKER1 model. One hydrogen bond is broken in the base triangle.

Figure 2.25: The local minimum of the water heptamer from TINKER1 model. The base triangle forms a hydrogen bond ring.
dimensional. The lowest energy structure of TINKER1 model is shown in Figure 2.24. If the criterion of 2.3 Å is used for the oxygen-oxygen distance between hydrogen bond forming water molecules (Wawak et al., 1992; Wales & Walsh, 1996), the three molecules in the base of the structure (Figure 2.24) do not from a closed ring: one of the oxygen-oxygen distance is just over 2.3 Å. On the other hand, structures that form hydrogen bond between these two molecules have slightly higher energy (Figure 2.25). This happens to both of TINKER models. The structures predicted by TINKER models agree with the prediction from density functional theory (Lee et al., 1995).

2.4.9 Octamer

Like the water heptamer, the water octamer receives little experimental or high level theoretical studies. Most of the low energy structures predicted by TINKER models are cubic, in agreement with the MCY model predictions (Kim et al., 1986) and density functional theory predictions (Lee et al., 1995; Estrin et al., 1996). The most stable structure of the water octamer from TINKER1 model is shown in Figure 2.26.

2.4.10 Nonamer and Decamer

The lowest energy structures for the water nonamer and decamer of TINKER1 model are shown in Figure 2.27 and Figure 2.28, respectively. These structures come from nonexhaustive random search. The structures are closely related to those predicted by density functional theory (Lee et al., 1995).
Figure 2.26: The most stable structure of the water octamer from TINKER1 model.

Figure 2.27: The most stable structure of the water nonamer from TINKER1 model.
2.4.11 Summary of water clusters

From previous sections it is clear that both TINKER models can be used to predict the energetics and structures of small water clusters reliably. Furthermore, unlike the simple charge models, TINKER water models retain the richness of the potential surfaces of water clusters. As the size of the cluster increases, it is expected that the properties of the cluster will resemble those of the bulk water. In Figures 2.29, 2.30, and 2.31, the oxygen-oxygen distance, average dipole moment, and the binding energy per water molecule are shown.
Figure 2.29: The $r_{OO}$ distances of different water clusters in unit of angstrom (Å). The HF and MP2 results are from reference (Xantheas & Dunning, 1993) for self-consistence. The calibrated experimental data are from (Liu et al., 1996b).

Figure 2.30: The average dipole moment of different water clusters in unit of Debye (D). The MP2 results are from reference (Gregory et al., 1997). Data from ring structures are used for hexamer.
Figure 2.31: The binding energy of different water clusters in unit of kcal/mol/monomer.

From Figures 2.29 it can be seen that the average oxygen-oxygen distance decreases as the size of the water clusters increases. This trend has been observed from \textit{ab initio} calculation (Xantheas & Dunning, 1993; Xantheas, 1994) and experiments (Cruzan \textit{et al.}, 1996). Exponential functions have been used to fit the trend. TINKER models predict this trend correctly, and the predicted oxygen-oxygen distances are quite close to the MP2 \textit{ab initio} results, and even closer to the calibrated experimental results (Liu \textit{et al.}, 1996b). The oxygen-oxygen distances for the cyclic hexamer predicted by TINKER models are very close to the oxygen-oxygen separation in the ordered phase of water such as ice (2.759 Å) (Kuhs & Lehmann, 1983). The cyclic water ring is usually used in modeling the hydrogen bonding in ice. On the other hand, the oxygen-oxygen distance in liquid water is measured as 2.84 Å (Narten
et al., 1982). Simple charge models tend to estimate the oxygen-oxygen distance too short, and do not show as much a change in $r_{OO}$ as the size of the cluster increases. The reason for the relative longer distance for TINKER trimers is not clear at this moment.

From Figure 2.30 we can see that the dipole moment of TINKER models increases from a value close to the gas phase value to a value around 2.6 D, which is the value in condensed phase (Coulson & Eisenberg, 1966). The dipole moment of liquid water is not known, but is estimated to be around 2.6 D or higher.

The binding energy per water monomer is shown in Figure 2.31. The magnitude of binding energy clearly shows a trend to first increase monotonically with the size of the cluster, and then saturate when the size becomes bigger. The same trend has also been predicted by ab initio calculations (Lee et al., 1995). Moreover, the TINKER models also predict the so called “magic numbers”, i.e., water clusters of 4, 8, 12, etc., have larger binding energy per monomer, predicted by density functional theory (Lee et al., 1995). It is speculated that more stable water system are formed by maximizing the number of planar shaped four member rings (Figure 2.9 and Figure 2.26) (Lee et al., 1995).

From these three figures, it can be concluded that the simple charge models cannot handle the transition from small clusters to bulk water properly. The $r_{OO}$ distances are too short for small clusters and do not change much with the size of the clusters (Figure 2.29), and the binding energy per monomer increases too steeply with size of the clusters (Figure 2.31). These trends are obviously the results of the
parameterization procedures which rely heavily on the thermodynamic properties. On the other hand, the TINKER models give more accurate representations of water clusters in the transition region. The cooperative effects are evident from these three figures: All the three quantities increase distinctly as the size of the cluster increases, showing the importance of three-body or even four-body interactions. As the size becomes bigger, these quantities approach the bulk limit in an exponential like manner, indicating that the role of many-body effects decreases for larger clusters. As discussed before, the properties of small water clusters are important in understanding the structures and functions of biological molecules. For a water model to be useful in this sense, the transition region from the monomer to bulk water has to be reproduced authentically. The TINKER models to some extent satisfactorily simulate the structure and energetics of water molecules in this transition region.

Some comments are relevant here on the comparison of the quality of the models. Throughout previous sections the properties of various models are compared with experimental data and \textit{ab initio} results. As is evident from the discussions, caution should be excised not to take a particular given value as the “final” truth. In fact, the \textit{ab initio} calculations have their limitations, and the results are not always closer to the true values than those from empirical potentials. The interpretation of the experimental data usually depends on certain assumptions from theoretical calculations. While computationists are usually seeking support from experimental data, experimentalists are using the computational results to rationalize their results. The “experiment” and “theory” are always intertwined together. Therefore, to judge a
model the overall performance, not the ability to give a particular value, should be evaluated.

## 2.5 Bulk properties of the water model

### 2.5.1 Introduction

The bulk properties of TINKER water models as well as other models will be assessed in this Section. The simulations were carried out with the dynamic program in TINKER molecular modeling package. Except for the calculation of relative permittivity, which will be discussed in details in section 2.6, usually 216 water molecules in a cubic box of length 18.6216 Å are used in simulation. Periodical boundary conditions are applied together with a spherical cut-off of 9 Å. To keep the bond length and angle constant, the rattle algorithm is used (Andersen, 1983). The simulations were carried out in the canonical (NVT) or isothermal-isobaric (NPT) ensembles. The temperature was kept at 300 K by scaling the velocities (Berendsen et al., 1984). The equations of motion were integrated with the Beeman multistep recursion formula (Beeman, 1976). The time step was 2 fs and configurations were saved every 0.1 ps for analysis. The convergence criterion for the induced dipole is usually set to $10^{-6}$ (Debye/atom). The Table 2.14 lists some of the bulk properties from the simulations. In the following sections, the simulation of the radial distribution functions (Section 2.5.2), relative permittivity (Section 2.6), and self diffusion constant (Section 2.5.3) will be discussed.
Table 2.14: Bulk properties

<table>
<thead>
<tr>
<th>Model</th>
<th>$U_{pot}$ (kcal/mol)</th>
<th>$P$ (atm)</th>
<th>$r_{OO}$ Å</th>
<th>$g_{OO}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TINKER1</td>
<td>-10.22</td>
<td>732</td>
<td>2.82</td>
<td>2.81</td>
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<tr>
<td>TINKER2</td>
<td>-10.02</td>
<td>884</td>
<td>2.80</td>
<td>2.66</td>
</tr>
<tr>
<td>POL3</td>
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<td>220</td>
<td>2.73</td>
<td>2.93</td>
</tr>
<tr>
<td>SPC</td>
<td>-10.15</td>
<td>293</td>
<td>2.77</td>
<td>2.82</td>
</tr>
<tr>
<td>TIP3P</td>
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<td>86</td>
<td>2.77</td>
<td>2.69</td>
</tr>
<tr>
<td>exp.</td>
<td>-9.92$^c$</td>
<td>1</td>
<td>2.87$^d$</td>
<td>3.09$^d$</td>
</tr>
</tbody>
</table>

$^a$The position of the first peak of the radial distribution $g_{OO}$.

$^b$The first peak of the radial distribution $g_{OO}$.

$^c$Reference (Jorgensen et al., 1983).

$^d$Reference (Soper & Phillips, 1986).

2.5.2 Radial distribution functions

The structure of simple liquids can be characterized by a set of distribution functions, of which the pair distribution function is the simplest and is particularly important. Generally, for a $N$ molecule system, the probability that molecule 1 is in $d\mathbf{r}_1$ at $\mathbf{r}_1$, molecule 2 is in $d\mathbf{r}_2$ at $\mathbf{r}_2$, \ldots, and molecule $n$ is in $d\mathbf{r}_n$ at $\mathbf{r}_n$, irrespective of the other remaining $N-n$ molecules, is given by (McQuarrie, 1976; Hansen & McDonald, 1986)

$$P^{(n)}(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_n) = \frac{\int \cdots \int e^{-\beta U_N} d\mathbf{r}_{n+1} \cdots d\mathbf{r}_N}{Z_N}$$  \hspace{1cm} (2.5)
where $Z_N$ is the configuration integral. If the order of the molecules is not considered, the probability that any molecule is in $dr_1$ at $r_1$, ..., and any molecule is in $dr_n$ at $r_n$, is given by

$$
\rho^{(n)}(r_1, r_2, \ldots, r_n) = \frac{N!}{(N-n)!} P^{(n)}(r_1, r_2, \ldots, r_n). \tag{2.6}
$$

The correlation function $g^{(n)}(r_1, r_2, \ldots, r_n)$ is defined as

$$
\rho^{(n)}(r_1, r_2, \ldots, r_n) = \rho^n g^{(n)}(r_1, r_2, \ldots, r_n), \tag{2.7}
$$

where $\rho = N/V$ is the density of the system.

Of these distribution functions, $g^{(2)}(r_1, r_2)$ plays a central role in determining the properties of the liquid. In a homogeneous and isotropic system, $g^{(2)}(r_1, r_2)$ is only a function of the relative distance between molecule 1 and 2, i.e., $r_{12}$. For simplicity $r_{12}$ is denoted as $r$. $g(r) = g^{(2)}(r_1, r_2)$ is usually called the radial distribution function. $\rho g(r) dr$ gives the unnormalized probability of observing a second molecule in $dr$ if a molecule is at the origin of $r$. It gives a local density around a fixed molecule. For a system with pair-wise additive potentials, it can be shown that all the thermodynamic functions of the system can be written in terms of $g(r)$. In addition, the radial distribution functions can be measured from x-ray diffraction (Narten & Levy, 1971) and neutron scattering experiments (Soper & Phillips, 1986; Soper et al., 1997). Some research has been carried out to use reverse Monte Carlo simulation to derive an empirical water potential to reproduce the experimental radial distribution functions.
(Pusztai & McGreevy, 1988; Jedlovszky et al., 1996). A related distribution function, the spatial distribution function (SDF), which includes an angular term as well as the radial term, was also proposed (Kusalik & Svishchev, 1994).

The radial distribution functions can be easily generated from computer simulations (Allen & Tildesley, 1987). Since $g(r)$ is a good indication of the structure of the system, it is now customary to compare the radial distribution functions from simulations of a water model to the experimental curves, although it should be kept in mind that the experimental data are not without ambiguity, especially with respect to the height of the peaks (Soper et al., 1997). The radial distribution functions between oxygen and oxygen ($g_{OO}(r)$), oxygen and hydrogen ($g_{OH}(r)$), and hydrogen and hydrogen ($g_{HH}(r)$) from TINKER models as well as from other models are shown in Figures 2.32, 2.33, 2.34, 2.35, 2.36, 2.37.

From these distribution functions, we can see that for the oxygen-oxygen distribution function $g_{OO}(r)$, the TINKER models give a quite good reproductions of the experimental data. The positions of the first peaks are more accurate than other models, so are the slopes the first peaks. In addition, the first troughs and the second peaks are also in good agreement with the experimental data, while the other simple charge models usually give a flat distribution after the first peak. It is likely that the detailed descriptions of the local electrostatic interactions in TINKER model make the water system more structured. The oxygen-hydrogen distribution function $g_{OH}(r)$, which through its first peak describes the hydrogen binding of the water system, is also reproduced quite satisfactorily by the TINKER models. For the hydrogen-hydrogen
Figure 2.32: Oxygen-oxygen radial distribution function for TINKER models compared with neutron scattering experimental data (Soper & Phillips, 1986).

Figure 2.33: Oxygen-oxygen radial distribution function for other models compared with neutron scattering experimental data (Soper & Phillips, 1986).
Figure 2.34: Oxygen-hydrogen radial distribution function for TINKER models compared with neutron scattering experimental data (Soper & Phillips, 1986).

Figure 2.35: Oxygen-hydrogen radial distribution function for other models compared with neutron scattering experimental data (Soper & Phillips, 1986).
Figure 2.36: Hydrogen-hydrogen radial distribution function for TINKER models compared with neutron scattering experimental data (Soper & Phillips, 1986).

Figure 2.37: Hydrogen-hydrogen radial distribution function for other models compared with neutron scattering experimental data (Soper & Phillips, 1986).
distribution function $g_{HH}(r)$, TINKER models give an accurate position of the peaks, but overestimate the height of the first peak.

2.5.3 Self diffusion coefficient

Transport coefficients are used to describe phenomenologically the response of a system to a perturbation (Allen & Tildesley, 1987; Haile, 1992). One of the important transport coefficients is the self diffusion coefficient, $D$, which appears in Fick’s first and second law as

$$\mathbf{J} = -D \nabla C, \quad \frac{\partial C}{\partial t} = D \nabla^2 C$$

where the flux $\mathbf{J}$ measures the transfer of material per unit area in unit time, and $C$ is the concentration of the material (Cantor & Schimmel, 1980). The two laws are related by the mass-conservation law

$$\frac{\partial C}{\partial t} = -\nabla \cdot \mathbf{J}.$$ 

From Fick’s law the Einstein relation can be obtained

$$D = \lim_{t \to \infty} \frac{\langle [r(t) - r(0)]^2 \rangle}{6t}.$$
From the Green-Kubo formula (Allen & Tildesley, 1987; Haile, 1992; Hansen & McDonald, 1986; McQuarrie, 1976; Zwanzig, 1965)

\[
\langle [A(t) - A(0)]^2 \rangle = \frac{1}{2t} \int_0^t d\tau \langle \dot{A}(\tau) \dot{A}(\tau) \rangle \left(1 - \frac{\tau}{t}\right),
\]

the diffusion constant can be expressed in another way

\[
D = \frac{1}{3} \int_0^\infty dt \langle \mathbf{v}(t) \cdot \mathbf{v}(0) \rangle.
\]

In computer simulation of a system with \( N \) particles, the diffusion constant is usually calculated from (Haile, 1992)

\[
D = \frac{1}{6N} \lim_{t \to \infty} \frac{d}{dt} \left\langle \sum_{i=1}^N [\mathbf{r}_i(t) - \mathbf{r}_i(0)]^2 \right\rangle.
\]

The mean square displacement of TINKER1 model at 298 K is shown in Figure 2.38. The calculated diffusion constants of both TINKER models are around \( 1.0 \times 10^{-5} \) cm\(^2\)/sec, which is lower than the experimental value \( 2.3 \times 10^{-5} \) cm\(^2\)/sec (Krynicki et al., 1978). The POL3 model gives a diffusion constant around \( 2.1 \times 10^{-5} \) cm\(^2\)/sec, which is different from the previous published value of \( 3.1 \times 10^{-5} \) cm\(^2\)/sec obtained by the authors of this model (Caldwell & Kollman, 1995). It should be noticed that the authors of the POL3 model also gave a value of \( 3.1 \times 10^{-5} \) cm\(^2\)/sec for SPC/E model, which is different from value of \( 2.5 \times 10^{-5} \) cm\(^2\)/sec given by the original paper on SPC/E model (Berendsen et al., 1987). For SPC/E, we get a value
around $2.1 \times 10^{-5}$ cm$^2$/sec, which is slightly lower than the originally reported value, but is closer to the more recently reported value of $2.2 \times 10^{-5}$ cm$^2$/sec (Kusalik & Svishchev, 1994). The diffusion constant of SPC model is about $3.3 \times 10^{-5}$ cm$^2$/sec, and TIP3P model gives the highest diffusion constant among the models, about $4.2 \times 10^{-5}$ cm$^2$/sec.

Although the values of diffusion constant for the same model varies in the literature, it seems that the simple charge models are too “mobile”, while the more complicated models are too “rigid”. The five-site NEMO model, whose charges are fit to multsite multipole expansions from \textit{ab initio} potentials, gives a diffusion constant $1.3 \times 10^{-5}$ cm$^2$/sec (Wallqvist \textit{et al.}, 1990). In the later version of the model, in
which atomic dipole and anisotropic polarizabilities are used (Åstrand et al., 1995),
the diffusion constant drops to $1.0 \times 10^{-5}$ cm$^2$/sec. The WK model, which fits the
charges to the experimental molecular quadrupole values, yields a diffusion constant
of $1.1 \times 10^{-5}$ cm$^2$/sec (Watanabe & Klein, 1989). As pointed out by these authors
(Wallqvist et al., 1990), the strong electrostatic forces may sever to damp the dynam-
ics of the system. Adding polarization to the nonpolarizable models also slows down
the dynamics (Ahlström et al., 1989; Bernardo et al., 1994). It has been pointed
out (Bernardo et al., 1994) that molecular diffusion and rotation are activated pro-
cesses which depend on the height of the energy barriers. On the other hand, the
average equilibrium internal energy and structures are determined by the fluctuations
around the configurations with the highest probabilities. Both the polarizable and
nonpolarizable models are parameterized based on the equilibrium properties. If the
polarization in the transition states is smaller than in the ground states compared
with the nonpolarizable models, the height of the barriers will increase, slowing down
the dynamics. In the next generation of the TINKER water model, it may be proven
to be useful if dynamic properties are used in the parameterization process.

The typical trajectories of a molecule from TINKER1 and TIP3P are shown in
Figure 2.39. Further research is necessary to get a clear answer to the questions
whether the detailed electrostatic potential surface slows down the system.
Figure 2.39: Typical trajectories from TINKER1 and TIP3P water models. The y-axis is the one component of the coordinate (in angstroms) of a water molecule at a given time. The x-axis is the time in unit of picosecond.

2.6 Dielectric properties

2.6.1 Introduction

For several reasons, the calculation of dielectric properties of polar liquid from computer simulations attracts intense research interests. First, the behavior of aqueous solutions of charged or polar solute is, to a large extent, determined by the bulk dielectric properties of the solvent. Second, as discussed below, the relative permittivity (dielectric constant) is one of the properties which include the collective orientational correlations between molecules and thus is influenced by long-range interactions. Its convergence also requires long simulations. Thus the simulation of dielectric prop-
erties imposes a stringent test of the model and computation methodology used. Finally, the high value of dielectric constant is one of unusual properties of water. A water model should reproduce the relative permittivity of the water and thus give a microscopic explanation of its dielectric properties.

Extensive literatures exist for the theory of dielectrics, following the pioneering work of Maxwell, Lorentz, Debye, Onsager, and Kirkwood. The advent of computer stimulates another surge of investigation on the theory of dielectrics. The explicit simulation of interactions between relatively large number of particles removes some of the difficulties in the previous analytical theories. On the other hand, the limitation of the current computing power introduces some new constraints on the implementation. Some of these, such as the boundary conditions used in order to simulate systems larger than the computer can explicitly handle, caused some confusions in the earlier study of dielectrics by computer simulations, which was later clarified (Neumann, 1983).

While the techniques such as the boundary condition and cut-off which are usually used in computer simulation are found to have small or negligible effect on the structure of systems involving short-range interactions (Allen & Tildesley, 1987), when the long-range interactions are involved, the boundary condition and cut-off do affect the properties of the system (Alper & Levy, 1989; Schreiber & Steinhauser, 1992; Smith & van Gunsteren, 1993; Steinbach & Brooks, 1994). Since the dielectric properties involve dipole-dipole interactions, which scale as $1/r^3$, the long-range interactions have a large influence on the dielectric properties of the system. This can be demonstrated
by the following equations (Fröhlich, 1958)

\[
\frac{4\pi \langle M^2 \rangle_v}{9 \ V kT} = \frac{\varepsilon - 1}{\varepsilon + 2} 
\]

(2.8)

\[
\frac{4\pi \langle M^2 \rangle_{\infty}}{9 \ V kT} = \frac{(2\varepsilon + 1)(\varepsilon - 1)}{9 \varepsilon} 
\]

(2.9)

where \( \langle M^2 \rangle \) is the mean square dipole moment of a spherical volume \( V \) at the temperature \( T \), and \( k \) is Boltzmann’s constant. Eq 2.8 is a Clausius-Mossotti type of equation and applies to an isolated sphere in vacuum. Eq 2.9 is known as Kirkwood-Fröhlich equation and applies to the sample of \( V \) embedded in an infinite dielectric continuum having the same dielectric constant \( \varepsilon \) as the sample in \( V \). It is clear from these two equations that different boundary conditions give rise to quite different behaviors of the dipole fluctuations inside \( V \): in the right-hand side of Eq. 2.8, the same power of \( \varepsilon \) appears in both numerator and denominator, while in Eq. 2.9 the power of \( \varepsilon \) in the numerator is higher by one than that in the denominator.

Several methods have been developed to handle the long-range interactions. One of the methods is Ewald sum (De Leeuw et al., 1980; Allen & Tildesley, 1987). In this method, the central box containing the system of interest is surrounded by its infinite crystal-like image boxes. Each site inside the central box interacts with all the sites inside the central box and all their images. By using the periodicity of the system, the total interaction energy can be calculated. This method has been used to study the relative permittivity by computer simulations (Anderson et al., 1987; Sprik, 1991; Rick et al., 1994).
The other commonly used method is the reaction field method (Barker & Watts, 1973). In this method the molecules beyond a certain distance are treated as continuum and the long-range interactions are taken into account, either by adding a correction term corresponding to the first term of an infinite series which arise from the interaction with the continuum (Neumann, 1985; Neumann, 1986; Alper & Levy, 1989; Smith & van Gunsteren, 1994), or by using an image method which is an alternative development of the same infinite series (Friedman, 1975; Wallquist, 1993; Wang & Hermans, 1995). The first method is usually used together with the periodic boundary conditions. This method, which was originally developed for point dipole interactions (Barker & Watts, 1973), however, was criticized recently when it is applied to interaction site models (Omelyan, 1996a). Omelyan showed that the traditional molecular center of mass cut-off method used for molecular dipole model cannot be applied directly to partial charge interaction site models. Instead, individual site cut-off should be used. Correction terms was proposed for the molecular center of mass cut-off method based on the image charge method (Friedman, 1975), and the effects of the different truncations have been shown to be significant (Omelyan, 1996a).

The second reaction field method, the image method, is usually applied to a fixed spherical cavity. A fast implementation of the full reaction field terms will be given in the following Chapter (Kong & Ponder, 1997b).

Ideally, the Ewald sum method should be more suitable for studying systems which have intrinsic periodicity such as crystals. Application of the method for liquids
and solutions has been compared with other methods for handling the long-range interactions, such as reaction field method. These studies show that both methods give consistent results for relative permittivities under certain conditions (Neumann et al., 1984).

Since both methods have intrinsic limitations, some authors use alternative methods to investigate the dielectric properties. One of the strategies is to simulate a microscopic droplet in vacuum. This method will be discussed in the next section.

2.6.2 Simulation of a droplet in vacuum: dipole moment fluctuations

Both Ewald sum and reaction field methods are in effect based on simulation of bulk properties. In fact, they are engineered to tackle the long-range interactions in the bulk simulations which can not be treated explicitly. In contrast, simulations of a microscopic droplet in vacuum offer several advantages. By the nature of the simulation, there is no long-range interactions beyond the droplet. Every interaction can be treated explicitly, so there is no need to rely on assumptions used in continuum model methods, such as the assumption that the bulk water responses instantaneously to the local fluctuation. Also there is no periodic boundary conditions involved, thus avoiding the artificial periodicity introduced in Ewald sum. Simulation of a droplet is also suitable for simulation of inhomogeneous biological macromolecules.

The difficulties for droplet simulation to obtain the relative permittivity arise from the fact that the surrounding vacuum inhibits the fluctuations of the polarizations of
the droplet. In other words, the depolarizing field arising from the apparent charges on the surface of the system makes the fluctuations quite insensitive to the value of \( \varepsilon \). This is reflected in Eq. 2.8, from which it is clear that for a reasonable large \( \varepsilon \), the right side of the equation is very close to unity and nearly independent of \( \varepsilon \). In order to overcome these difficulties, several authors proposed to use the fluctuation of the dipole moment of a inner spherical region (Scaife, 1962; Scaife, 1989; Berendsen, 1972). The early applications of the method were for the simulation of Stockmayer liquid (Bossis, 1979; Bossis et al., 1980; Hesse-Bezot et al., 1984; Powles et al., 1984), recently the method has been used for water and proteins (Simonson & Perahia, 1995a; Simonson & Perahia, 1995b; Simonson, 1996).

In the following we outline the derivation of the formulas used in the droplet simulation. Since our water models have atomic quadrupoles, which is not included in any other water models whose dielectric properties have been characterized, relevant comments will be made for the formulas.

To develop a formula to calculate the relative permittivity, consider a system made of \( n \) concentric spheres. The innermost region is labeled as 1, the next shell 2, ..., and the outmost region \( n \) goes to infinity. Each region \( i \) has a relative permittivity of \( \varepsilon_i \) and a radius of \( r_i \) (Simonson & Perahia, 1995a). If we introduce an applied field \( \mathbf{E} = E \mathbf{k} \), uniform far from the system, then a uniform cavity field \( \mathbf{F} \) will be generated in region 1.

Since \( \mathbf{E} \) is only an artificial device to get the fluctuation formulas, we can make it small enough so that the dielectric response is within the linear range. Hence in the
\[ \mathcal{P} = \varepsilon_0 (\varepsilon_1 - 1) \mathbf{F}, \quad (2.10) \]

here \( \mathcal{P} \) is the macroscopic polarization (de Groot, 1969; Russakoff, 1970; Scaife, 1989). \( \mathcal{P} \) is related to the microscopic polarization \( \wp \) (atomic electric polarization in de Groot’s term (de Groot, 1969)) by

\[ \mathcal{P}(\mathbf{r}) = \langle \wp(\mathbf{r}) \rangle \]

where \( \langle \rangle \) stands for averaging. Different authors, when tried to derive Maxwell’s macroscopic equations from Lorentz’s microscopic equations, used different averaging methods, such as spatial averaging or phase space averaging, but always obtained the same results (de Groot, 1969; Russakoff, 1970; Scaife, 1989). \( \wp \) is given by

\[ \wp(\mathbf{r}) = \sum_k \wp_k = \sum_{n=1}^{\infty} (-1)^{n-1} \nabla^{n-1} \cdot \sum_k M_k^{(n)} \delta(\mathbf{r}_k - \mathbf{r}) \]

\[ = \sum_k m_k \delta(\mathbf{r}_k - \mathbf{r}) - \nabla \cdot \sum_k Q_k \delta(\mathbf{r}_k - \mathbf{r}) + \cdots, \quad (2.11) \]

where \( m_k \), \( Q_k \) and \( M_k^{(n)} \) are the dipole, quadrupole and \( n \)th-pole moment of the \( k \)th atom.

Taking the average of \( \wp \), and using the property that spatial differentiation com-
mutes with averaging (de Groot, 1969; Scaife, 1989), we have

\[ \mathcal{P}(r) = \langle \varphi(r) \rangle = \sum_{n=1}^{\infty} (-1)^{n-1} \nabla^{n-1} \cdot \left\langle \sum_k M_k^{(n)} \right\rangle \]

\[ = \left\langle \sum_k m_k \delta(r_k - r) \right\rangle - \nabla \cdot \left\langle \sum_k Q_k \delta(r_k - r) \right\rangle + \cdots. \]

(2.12)

Since in computer simulation the system which is studied explicitly usually consists of a few hundreds or thousands of molecules, we are dealing with mass elements in the sense that the systems are macroscopically infinitesimal. If we take the spatial average of Eq. 2.12 over such a cell of a volume of \( V \), we get the average polarization of the cell

\[ \mathcal{P} = \overline{\mathcal{P}(r)} \approx \frac{1}{V} \left\{ \left\langle \int_V \sum_k m_k \delta(r_k - r) \right\rangle \right. \]

\[ - \left. \left\langle \int_V \nabla \cdot \sum_k Q_k \delta(r_k - r) \right\rangle + \cdots \right\} \]

\[ = \frac{1}{V} \left\{ \left\langle \sum_k m_k \right\rangle \right. \]

\[ - \left. \left\langle \sum_k \int_V \nabla \cdot Q_k \delta(r_k - r) \right\rangle + \cdots \right\}, \]

(2.13)

the second and the following terms vanish because of the properties of Dirac \( \delta \)-function (Lighthill, 1958)

\[ \int \delta'(x) F(x) dx = - \int \delta(x) F'(x) dx = - F'(0). \]
Hence,

\[ P \approx \frac{\langle \sum_k m_k \rangle}{V} = \frac{\langle M \rangle}{V} \quad (2.14) \]

even when there are higher multipole moments. Here \( M = \sum_k m_k \) is the total dipole moment of the system. To reiterate, since we are dealing with a *macroscopically infinitesimal* cell, and the densities of quadrupole or higher multipole moments contribute to the polarization only through spatial gradients, which almost vanish inside the cell, the average polarization of the cell is still mainly determined by the dipole moments.

\( F \) can be determined by the standard electrostatic methods and is a function of \( \varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n \) and \( r_1, r_2, \cdots, r_n \). If we only write out the dependence on permittivities explicitly and leave out the \( r \)'s, \( F \) has the form

\[ F = f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n) E. \quad (2.15) \]

Similarly, if the applied field \( E \) oscillates with a high frequency, only part of the freedoms of the dielectrics can respond, so in this case

\[ F^{hi} = f(\varepsilon_1^{hi}, \varepsilon_2^{hi}, \cdots, \varepsilon_n^{hi}) E. \quad (2.16) \]
From Eq. 2.10 and Eq. 2.14, we have

\[ \langle M_{\text{tot}} \rangle = \varepsilon_0 (\varepsilon_1 - 1) V F = \varepsilon_0 (\varepsilon_1 - 1) V f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n) E. \]  

(2.17)

Similarly, we have for the high frequency part of the dipole moment

\[ \langle M_{\text{hi}} \rangle = \varepsilon_0 (\varepsilon_{1}^{\text{hi}} - 1) V F^{\text{hi}} = \varepsilon_0 (\varepsilon_{1}^{\text{hi}} - 1) V f(\varepsilon_{1}^{\text{hi}}, \varepsilon_{2}^{\text{hi}}, \cdots, \varepsilon_{n}^{\text{hi}}) E. \]  

(2.18)

Now we need to derive a microscopic relation between \( \langle M \rangle \) and \( E \) using statistical mechanics. Suppose that we only simulate the low frequency freedom of region 1 explicitly. Using Boltzmann distribution, we have

\[ \langle M_{\text{lo}} \rangle = \int_0^\pi \sin \theta d\theta \int \mathbf{M}_{\text{lo}}(\mathbf{X}) \cdot \mathbf{k} e^{-\beta U(\mathbf{X}, \mathbf{E})} d\mathbf{X} \]

\[ \int_0^\pi \sin \theta d\theta \int e^{-\beta U(\mathbf{X}, \mathbf{E})} d\mathbf{X}, \]  

(2.19)

here

\[ \mathbf{X} = (\mathbf{r}_1, \mathbf{r}_2, \cdots, \mathbf{r}_n) \]

is the configuration of the system, \( U(\mathbf{X}, \mathbf{E}) \) is the potential energy of the system in the configuration \( \mathbf{X} \) and in the presence of the the field \( \mathbf{E} \), \( \theta \) is the angle between \( \mathbf{E} \) and \( \mathbf{M}_{\text{lo}}(\mathbf{X}) \), and \( \beta = 1/kT \). Since the field inside region 1 is uniform, only the instantaneous dipole moment \( \mathbf{M}_{\text{lo}}(\mathbf{X}) \) interacts with the field to contribute an
additional term to the potential energy \(-M_{lo}(X) \cdot F^{(1)}\), so

\[ U(X, E) = U(X) - M_{lo}(X) \cdot F^{(1)}, \]

where \(U(X) = U(X, 0)\) is the potential energy of the system in the absence of the applied macroscopic field \(E\). The field \(F^{(1)}\), like the field \(F\), is a function of the permittivities of the \(n\) regions. But in this case the relative permittivity of region 1 is no longer equal to \(\varepsilon_1\). The low frequency freedoms of region 1 are being simulated explicitly and are taken into account microscopically, and the remaining parts of high frequency freedoms form a continuum with a relative permittivity of \(\varepsilon_{hi}^1\), so

\[ F^{(1)} = f(\varepsilon_{hi}^1, \varepsilon_2, \cdots, \varepsilon_n)E. \] (2.20)

Developing the series of \(\exp(U(X) - M_{lo}(X) \cdot F^{(1)})\) in Eq. 2.19, and using \(M_{lo}(X) \cdot F^{(1)} = MF^{(1)} \cos \theta\) and

\[ \int_0^\pi \sin \theta \cos^n \theta d\theta = \frac{1 + (-1)^n}{n + 1}, \]

Eq. 2.19 becomes, by abbreviating \(\langle M \rangle\) for \(\langle M_{lo} \rangle\) and \(F\) for \(F^{(1)}\),

\[ \langle M \rangle = \frac{1}{1!} \frac{1}{3!} \frac{1}{5!} \frac{1}{7!} \frac{\beta F \langle M^2 \rangle}{1 + \frac{1}{3!} \beta^2 F^2 \langle M^2 \rangle + \frac{1}{5!} \beta^4 F^4 \langle M^4 \rangle + \cdots}, \]

(2.21)
which expands to

$$\langle M \rangle = \frac{1}{3} \langle M^2 \rangle \beta F + \left[ \frac{1}{30} \langle M^4 \rangle - \frac{1}{18} \langle M^2 \rangle^2 \right] \beta^3 F^3$$

$$+ \left[ \frac{1}{840} \langle M^6 \rangle - \frac{1}{120} \langle M^2 \rangle \langle M^4 \rangle + \frac{1}{108} \langle M^2 \rangle^3 \right] \beta^5 F^5 + \cdots \quad (2.22)$$

If we take the first term of Eq. 2.22, which is justified with small $E$ and hence small $F$, we have

$$\langle M_{lo} \rangle \approx \frac{1}{3} \langle M^2_{lo} \rangle \beta F^{(1)} = \frac{1}{3} \langle M^2_{lo} \rangle \beta f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n)E. \quad (2.23)$$

Since

$$\langle M_{tot} \rangle = \langle M_{hi} \rangle + \langle M_{lo} \rangle,$$

by using Eqs. 2.17, 2.18 and 2.23, we have the desired dipole fluctuation formula

$$\frac{1}{4\pi \varepsilon_0 r_1^3} \beta \langle M^2_{lo} \rangle = \frac{(\varepsilon_1 - 1)f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n) - (\varepsilon_{hi} - 1)f(\varepsilon_{hi}, \varepsilon_{hi}, \cdots, \varepsilon_{hi})}{f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n)}. \quad (2.24)$$

Kirkwood's original theory applies to non-polarizable polar molecules (Kirkwood, 1939). Attempts to extend the theory to polarizable molecules resulted in many confusions (Neumann & Steinhauser, 1984). Only recently has the issue been clarified from a unified point of view (Felderhof, 1979). It turns out that Kirkwood's original equations apply to polarizable systems too, as long as the dipole moment includes contributions from the electronic degrees of freedom. As for Eq. 2.24, if the polar-
ization is simulated explicitly, we can put $\varepsilon_1^{hi} = 1$, and let $\langle M_0 \rangle = \langle M_{tot} \rangle$, so we have

$$\frac{1}{4\pi\varepsilon_0 r_1^3} \beta \langle M_{tot}^2 \rangle = \frac{(\varepsilon_1 - 1)f(\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n)}{f(1, \varepsilon_2, \cdots, \varepsilon_n)}. \quad (2.25)$$

The function $f$ depends on $\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_n$ and $r_1, r_2, \cdots, r_n$. It can be obtained by using standard electrostatic methods with proper boundary conditions (Smythe, 1968; Böttcher et al., 1973; Jackson, 1975; Scaife, 1989). For $n = 3$, we can write it out explicitly as

$$f(\varepsilon_1, \varepsilon_2, \varepsilon_3) = \frac{9 \varepsilon_2 \varepsilon_3}{(\varepsilon_1 + 2\varepsilon_2)(\varepsilon_2 + 2\varepsilon_3) - 2(r_1/r_2)^3(\varepsilon_3 - \varepsilon_2)(\varepsilon_1 - \varepsilon_2)}. \quad (2.26)$$

If we put $\varepsilon_2 = \varepsilon_3$, Eq. 2.26 reduces to the familiar formula (Böttcher et al., 1973)

$$f(\varepsilon_1, \varepsilon_2) = \frac{3 \varepsilon_2}{\varepsilon_1 + 2\varepsilon_2}.$$  

### 2.6.3 Simulation of a droplet in vacuum: multipole moment fluctuations

The dipole moment fluctuation formula is widely used in computer simulations for calculation of relative permittivity, and different formulas have been derived for simulations in different boundary conditions (Neumann, 1983). As far as we know, the dipole moment fluctuation formula Eq. 2.24 and its variants are the only fluctua-
tion formulas that have been used to obtain relative permittivity from simulations. However, other formulas for higher multipole fluctuations exist in literature (Scaife, 1989). Since our water model includes atomic quadrupole explicitly, we want to try these formulas to see what effects these quadrupoles have on the calculated relative permittivity and whether we can get a consistent result from different formulas. The derivation of the formulas is in the same line as used in the previous section, only in this case the applied external potential is arbitrary. To facilitate the derivation, spherical multipoles are used so as to use the orthogonal properties of the Legendre functions (Hobson, 1931). The details of the derivation can be found in Scaife’s monographs (Scaife, 1989). Here the main results are listed. Scaife defines the spherical multipoles as

\[ m^{(c)}_{n,m} = \sum_k q_k r_k^n P_n^m (\cos \theta) \cos m\phi \]
\[ m^{(s)}_{n,m} = \sum_k q_k r_k^n P_n^m (\cos \theta) \sin m\phi, \quad (2.27) \]

which is slightly different from the definitions of Jackson (Jackson, 1975) or Stone (Stone, 1996). Here \( n \) is the order of multipoles.

We now focus on the \( n = 3 \) case, with \( \varepsilon_3 = 1 \), i.e., the system consists of an inner sphere of a radius \( r_1 \) and a permittivity \( \varepsilon_1 \) surrounded by a dielectric shell of a radius \( r_2 \) and a permittivity \( \varepsilon_2 \). The whole system is immersed in vacuum. With the definition of Eq. 2.27, the mean square multipole fluctuations in the inner sphere
surrounded by a dielectric shell are given by

\[
\frac{1}{4\pi\varepsilon_0} \beta \langle (m^{(1)})^2 \rangle = \frac{r_1^{2n+1}n(\varepsilon_1 - 1)((n + 1)\varepsilon_2 + n)[1 - \eta^{2n+1}f_n(1, \varepsilon_2)]}{z_{n,m}(2n + 1)[(n + 1)\varepsilon_2 + n\varepsilon_1][1 - f_n(\varepsilon_1, \varepsilon_2)]},
\]

(2.28)

where \(m^{(1)} = m^{(c)}_{n,m}\) or \(m^{(s)}_{n,m}\) is the total multipole moments of the inner sphere, \(\eta = r_1/r_2\),

\[z_{n,m} = (2 - \delta_{0,m}) \frac{(n - m)!}{(n + m)!}\]

and

\[f_n(\varepsilon_1, \varepsilon_2) = \frac{n(n + 1)(\varepsilon_2 - 1)(\varepsilon_2 - \varepsilon_1)}{[n(n + 1)\varepsilon_2 + n\varepsilon_1][n\varepsilon_2 + (n + 1)]}.\]

We can write out explicitly the formulas for dipole and quadrupole moment fluctuations. Assume the \(k^{th}\) atom is at the position \(r_k = \{x_k, y_k, z_k\}\) with respect to the center of the cavity. When \(n = 1\),

\[m^{(c)}_{1,0} = \sum_k q_k z_k = M_z\]

\[m^{(c)}_{1,1} = \sum_k q_k x_k = M_x\]

\[m^{(s)}_{1,1} = \sum_k q_k y_k = M_y,\]

the formulas for fluctuations reduces to the ones derived in the previous section; When
\( n = 2, \)

\[
m^{(c)}_{2,0} = \sum_k \frac{1}{2} q_k (3z_k^2 - r_k^2)
\]

\[
m^{(c)}_{2,1} = \sum_k 3q_k x_k z_k
\]

\[
m^{(s)}_{2,1} = \sum_k 3q_k y_k z_k
\]

\[
m^{(c)}_{2,2} = \sum_k 3q_k (x_k^2 - y_k^2)
\]

\[
m^{(s)}_{2,2} = \sum_k 6x_k y_k,
\]

and if we have \textit{atomic} multipoles, they become for \( n = 1 \)

\[
m^{(c)}_{1,0} = \sum_k [q_k z_k + m_{z,k}]
\]

\[
m^{(c)}_{1,1} = \sum_k [q_k x_k + m_{x,k}]
\]

\[
m^{(s)}_{1,1} = \sum_k [q_k y_k + m_{y,k}],
\]

and for \( n = 2 \)

\[
m^{(c)}_{2,0} = \sum_k \frac{1}{2} \left[ 2(q_k z_k^2 + 2z_k m_{z,k} + 2Q_{zz,k}) - (q_k x_k^2 + 2x_k m_{x,k} + 2Q_{xx,k}) - (q_k y_k^2 + 2y_k m_{y,k} + 2Q_{yy,k}) \right]
\]

\[
m^{(c)}_{2,1} = \sum_k 3[q_k x_k z_k + z_k m_{x,k} + x_k m_{z,k} + 2Q_{xz,k}]
\]

\[
m^{(s)}_{2,1} = \sum_k 3[q_k y_k z_k + z_k m_{y,k} + y_k m_{z,k} + 2Q_{yz,k}]
\]

\[
m^{(c)}_{2,2} = \sum_k 3 \left[ (q_k x_k^2 + 2x_k m_{x,k} + 2Q_{xx,k}) - (q_k y_k^2 + 2y_k m_{y,k} + 2Q_{yy,k}) \right]
\]
\[ m_{2,2}^{(a)} = \sum_k 6 [q_k x_k y_k + x_k m_{y,k} + y_k m_{x,k} + 2Q_{xy,k}], \]

where \( \{m_{x,k}, m_{y,k}, m_{z,k}\} \) and \( \{Q_{xx,k}, Q_{xy,k}, Q_{xz,k}, Q_{yz,k}, Q_{zz,k}\} \) are the three components of the atomic dipole and the five components of the atomic quadrupole of the \( k^{th} \) atom, respectively, defined in the previous chapter.

The fluctuation formulas are, for \( n = 1 \),

\[
\langle (m_{1,0}^{(c)})^2 \rangle = \langle (m_{1,1}^{(c)})^2 \rangle = \langle (m_{1,1}^{(s)})^2 \rangle = \frac{(4\pi \varepsilon_0)kT_1^3}{3} h_1
\]

\[
h_1 = \frac{(\varepsilon_1 - 1)[(2\varepsilon_2 + 1)(\varepsilon_2 + 2) - 2\eta^3(\varepsilon_2 - 1)^2]}{(2\varepsilon_2 + \varepsilon_1)(\varepsilon_2 + 2) - 2\eta^3(1 - \varepsilon_2)(\varepsilon_1 - \varepsilon_2)}, \tag{2.29}
\]

and for \( n = 2 \)

\[
\langle (m_{2,0}^{(c)})^2 \rangle = \frac{2}{5} (4\pi \varepsilon_0)kT_1^5 h_2
\]

\[
\langle (m_{2,1}^{(c)})^2 \rangle = \langle (m_{2,1}^{(s)})^2 \rangle = \frac{6}{5} (4\pi \varepsilon_0)kT_1^5 h_2
\]

\[
\langle (m_{2,2}^{(c)})^2 \rangle = \langle (m_{2,2}^{(s)})^2 \rangle = \frac{24}{5} (4\pi \varepsilon_0)kT_1^7 h_2
\]

\[
h_2 = \frac{(\varepsilon_1 - 1)[(3\varepsilon_2 + 2)(2\varepsilon_2 + 3) - 6\eta^5(\varepsilon_2 - 1)^2]}{(3\varepsilon_2 + 2\varepsilon_1)(2\varepsilon_2 + 3) - 6\eta^5(1 - \varepsilon_2)(\varepsilon_1 - \varepsilon_2)}, \tag{2.30}
\]

From Eqs. 2.29 and 2.30 we can see why they can give more accurate estimation of \( \varepsilon_1 \) than Eq. 2.8. Suppose that the droplet is homogeneous, we can assign \( \varepsilon_2 = \varepsilon_1 \). Then if we make asymptotic expansions of \( h_1 \) and \( h_2 \), we have

\[
h_1 \approx \frac{2}{3} (1 - \eta^3) \varepsilon_1 + \frac{1}{3} (10 \eta^3 - 1) - \frac{1}{3} (26 \eta^3 + 1) \varepsilon_1^{-1} + 18 \eta^3 \varepsilon_1^{-2} + O(\varepsilon_1^{-3})
\]
\[ h_2 \approx \frac{3}{5} (1 - \eta^5) \varepsilon_1 + \frac{1}{5} \left( \frac{27}{2} \eta^5 - 1 \right) - \frac{1}{5} \left( \frac{117}{4} \eta^5 + 2 \right) \varepsilon_1^{-1} + \frac{75}{8} \eta^5 \varepsilon_1^{-2} + O(\varepsilon_1^{-3}) , \]

(2.31)

while the asymptotic expansion of the right hand side of Eq. 2.8 gives

\[ \frac{\varepsilon_1 - 1}{\varepsilon_2 + 2} \approx 1 - 3\varepsilon_1^{-1} + 6\varepsilon_1^{-2} + O(\varepsilon_1^{-3}) . \]

(2.32)

It is clear that the linear term in Eq. 2.31 gives much better estimations of \( \varepsilon_1 \) than Eq. 2.32, where the constant term dominates for large \( \varepsilon_1 \).

Before leaving this section, we mention briefly another method that has been used to evaluate permittivity from computer simulation, i.e., by using a homogeneous applied field (Watts, 1981; Alper & Levy, 1989). Although this method seems more straightforward, simulation works seem to indicate that this technique is not any more efficient than the fluctuation method (Pollock & Alder, 1980; Petersen et al., 1989). The non-linear effects become important at even small values of the polarization.

Another point that is worth mentioning is the size of the system. The above formulation is based on Boltzmann distribution (Eq. 2.19), which is only valid for large system. A correction term, which includes explicitly the size of the system, has recently been derived (Omelyan, 1996b). It was shown that for a Stockmayer system of hundreds of particles, the correction term is sufficiently small. It has also been noticed from simulations on other systems that a system of a few hundred molecules can faithfully represent the macroscopic properties of the bulk system. As will be discussed in the next section, our own work confirm this point.
2.6.4 Simulation methods and results

In order to keep molecules from escaping from the droplet, a “wall” potential is usually used. A soft spherical wall potential was used by Simonson and coworkers (Simonson & Perahia, 1995a; Simonson, 1996), which was developed a decade ago (Brooks III & Karplus, 1983) For TINKER models we adopted a simpler wall potential, which was used by other groups for droplet simulations (Bossis, 1979; Bossis et al., 1980; Hesse-Bezot et al., 1984; Wang & Hermans, 1995). The wall potential has the form

\[ U_{\text{wall}} = \frac{A}{(r_{\text{wall}} - r)^{12}} - \frac{B}{(r_{\text{wall}} - r)^6}, \]  

(2.33)

where \( r_{\text{wall}} - r \) is the distance between the center of the mass of a water molecule and the wall. The \( r_{\text{wall}} \) was chosen to be 2.5 Å larger than the radius of the droplet. We used the values \( A = 2048 \text{ kcal/(mol Å}^{12} \text{)} \) and \( B = 64 \text{ kcal/(mol Å}^{6} \text{)} \) in the literature (Wang & Hermans, 1995). As discussed below, the choice of the wall potential does not seem to have much effect on calculated relative permittivity. As in the bulk simulation, the time step is 2 fs and the configuration was saved every 0.1 ps for analysis. RATTLE was used to keep the constrain on the geometry of water molecules. For the calculation of permittivities the first 300 ps simulations were not used. For the simulations in this section the temperature is kept at 300 K. The permittivities are calculated by putting \( \varepsilon_2 = \varepsilon_1 \) in Eq. 2.29 for dipole fluctuation formula or in Eq. 2.30 for quadrupole fluctuation formula and the resulting cubic equations are solved.

To test the methodology, simulations were first run with SPC and TIP3P models.
Two droplets were used for TIP3P model, one with 14 Å radius (380 water molecules) and one with 11 Å (184 water molecules). A droplet with 12 Å radius was also simulated but since the properties are similar, the results from the 12 Å droplet will not be shown here. For SPC model a droplet with 12 Å radius (237 water molecules) was simulated. The densities of 1 Å thick shells are shown in Figure 2.40 for TIP3P and SPC models. From the figure it is evident that except for the outmost 2 Å region, the density in the inner part of the droplets is not perturbed by the wall potential. The running averages of relative permittivities of SPC model calculated with the dipole fluctuation formula are shown in Figure 2.41 for \( r_1 = 6, 7, 8, \) and 9 Å. It is clear that as long as that \( r_1 \) is not too short and not too close to \( r_2 \), the calculated permittivities do not depend on the choice of \( r_1 \). Similar conclusion can be drawn from the simulations on two TIP3P droplets, which are shown in Figure 2.42 and Figure 2.43, respectively. The results from these three simulations calculated with the dipole fluctuation formula are summarized in Figure 2.44. Clearly from these results we can get the conclusions that the results have little dependence on the radius of the droplet \( r_2 \), as long as \( r_2 \geq 11\text{Å} \), which corresponds to about 180 water molecules.

From these results the relative permittivity of SPC model at 300 K is estimated at about 53.3, which is in agreement with the reported value of 54.0 (Smith & van Gunsteren, 1994). The calculated relative permittivity of TIP3P model is around 68 at 300 K, while the reported result for TIP3P model, by using the similar method of simulating a droplet in the vacuum, is about 82 at 294 K (Simonson, 1996). The radii
Figure 2.40: Densities of 1 Å thick shells as the function of the distance (in Å) away from the droplet center for a SPC droplet (12 Å) and two TIP3P droplets (11 Å and 14 Å).

Figure 2.41: Running averages of the relative permittivity of the SPC droplet with a 12 Å radius calculated with the dipole fluctuation formula for $r_1 = 6, 7, 8,$ and $9$ Å. The time is in picosecond.
Figure 2.42: Running averages of the relative permittivity of the TIP3P droplet with a 11 Å radius calculated with the dipole fluctuation formula for $r_1 = 5.85, 6.85, 7.2, 7.857, 8.0,$ and $8.5$ Å. The time is in picosecond.

Figure 2.43: Running averages of relative permittivity of TIP3P droplet with a 14 Å radius calculated with the dipole fluctuation formula for $r_1 = 5.85, 8.0, 10.0,$ and $12.0$ Å. The time is in picosecond.
of the droplets used in this report are 14 Å and 24 Å, respectively. As mentioned above, the difference in the size of the droplets should not lead to different results. The discrepancy between the results can be explained by the following facts. First, in Simonson simulations the densities are about 8% higher, while in our simulations the densities are close to the experimental value (Figure 2.40). Second, the dipole value of 2.32 D was used for TIP3P model in Simonson simulations, which is smaller than the 2.347 D value we used. Third, he assigned $\varepsilon_2 = 80$ to calculate $\varepsilon_1$, while we assume $\varepsilon_2 = \varepsilon_1$. The temperature is another factor for his higher results. We come to the conclusion that the two simulations would give much closer results if all these factors are taken into account. We do not believe that the different “wall” potential used is the major factor for the discrepancy.
Based on these results on simple charge models, we use 11 Å droplets for the TINKER model simulations. Each droplet consists of 186 water molecules. The densities of TINKER models are shown in Figure 2.45. Like the simple partial charge models (Figure 2.40), the TINKER models give reasonable densities, except for the outmost 2 Å regions. The running averages of relative permittivities at 300 K calculated with the dipole fluctuation formula from two TINKER models are shown in Figure 2.46 and Figure 2.47. The converged results are summarized in Figure 2.48. From these results the permittivity of TINKER1 model is calculated to be 55, and for TINKER2 model, the permittivity is estimated to be 54. The results are comparable with the simple partial charge models, and higher than the result of 37 reported for the MCY model (Neumann, 1985). Sprik has speculated that there is relation between the average dipole moment and the permittivity (Sprik, 1991). In bulk simulations both TINKER water models give an average dipole moment around 2.6 D, the best estimate of the true value and the criterion used by Sprik to build models to obtain the correct permittivity, but the permittivities are still lower than the experimental value. The relation between the average dipole moment and the permittivity may be more complicated than expected.

The results of the simple partial charge models calculated with the quadrupole fluctuation formula (Eq. 2.30) are shown in Figures 2.49, 2.50, and 2.51. The results calculated from different \( r_1 \) are summarized in Figure 2.52. From these results some tentative conclusions can be made. First, for these partial charge models, the permittivities calculated by using the quadrupole fluctuation formula are systematically
Figure 2.45: Densities of 1 Å thick shells as the function of the distance (in Å) away from the droplet center for TINKER water models. The radii of the droplets are 11 Å.

Figure 2.46: Running averages of the relative permittivity of the TINKER1 droplet with a 11 Å radius calculated with the dipole fluctuation formula for $r_1 = 4, 5, 6, 7, 8,$ and 9 Å. The time is in picosecond.
Figure 2.47: Running averages of the relative permittivity of the TINKER2 droplet with a 11 Å radius calculated with the dipole fluctuation formula for $r_1 = 4$, 5, 6, 7, 8, and 9 Å. The time is in picosecond.

Figure 2.48: Relative permittivities of TINKER models calculated with different $r_1$ using the dipole fluctuation formula and the quadrupole formula.
lower than those calculated by using the dipole fluctuation formula. The difference is about 4. Second, from the TIP3P data it seems that the 11 Å droplet may be too small to apply the quadrupole formula: while the permittivity of the 14 Å droplet drops from 68 to about 64, that of the 11 Å droplet drops from 68 to about 54. On the other hand, the permittivity of the 12 Å SPC droplet drop from 53.3 to around 49. Since we do not have data on a 11 Å SPC droplet, it is difficult to say whether this decrease is model specific, or related to the quadrupole formula itself. We put the corresponding results for the 11 Å TINKER droplets in Figure 2.53 and Figure 2.54, and summary of the results at different $r_1$ using the quadrupole formula in Figure 2.48. For the 11 Å TINKER droplets, the quadrupole formula gives slightly lower values for the permittivities, like the 14 Å TIP3P droplet and the 12 Å SPC droplet. However, it does not give a big drop like the 11 Å TIP3P droplet. It seems that the dipole and quadrupole moments not only behave differently on the sizes of the droplets, but also have a complicated dependence on the models themselves. To elucidate the relationship will require further investigation.

### 2.6.5 Temperature derivative of Kirkwood’s g-factor

A sensitive test of a water model is the temperature dependence of Kirkwood’s g-factor, $g_k$, which can be expressed in the equation

$$yg_k = \frac{(\epsilon - 1)(2\epsilon + 1)}{9\epsilon}$$

$$y = \frac{4\pi N \langle \mu^2 \rangle}{9(4\pi\varepsilon_0)VT}.$$  \hspace{1cm} (2.34)
Figure 2.49: Running averages of the permittivity of the 12 Å SPC droplet calculated with quadrupole fluctuation formula at different $r_1$.

Figure 2.50: Running averages of the permittivity of the 11 Å TIP3P droplet calculated with quadrupole fluctuation formula at different $r_1$. 
Figure 2.51: Running averages of the permittivity of the 14 Å TIP3P droplet calculated with quadrupole fluctuation formula at different $r_1$.

Figure 2.52: Relative permittivities of simple charge models calculated with different $r_1$ using the quadrupole fluctuation formula.
Figure 2.53: Running averages of the permittivity of the TINKER1 model calculated with quadrupole fluctuation formula at different $r_1$.

Figure 2.54: Running averages of the permittivity of the TINKER2 model calculated with quadrupole fluctuation formula at different $r_1$. 

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Experimental data indicate that $g_k$ decreases with increase in temperature. The relative permittivity of water can be expressed as a function of temperature and density by using the formula recommended by the International Association for the Properties of Steam (IAPS) (Uematsu & Franck, 1980)\(^1\).

The dependence of $\varepsilon$ for water on temperature is shown in Figure 2.55 by using Eq. 2.35, and keeping the density $\rho = 1000 \text{ kg/m}^3$.

Using the Kirkwood-Fröhlich equation (Böttcher et al., 1973)

$$g_k\mu^2 = \left(4\pi\varepsilon_0\right)\frac{9kT\varepsilon}{4\pi N}\frac{(\varepsilon - \varepsilon_\infty)(2\varepsilon + \varepsilon_\infty)}{\varepsilon(\varepsilon_\infty + 2)}$$  \((2.36)\)

where $\varepsilon_\infty$ is the high frequency permittivity of water, which has a value of 1.79

\(^1\)The formula is given as

$$\varepsilon = 1 + \frac{a_1}{T^*}\rho^* + \left(\frac{a_2}{T^*} + a_3 + a_4T^*\right)\rho^{*2} + \left(\frac{a_5}{T^*} + a_6T^* + a_7T^*\right)\rho^{*3} + \left(\frac{a_8}{T^*} + a_9 + a_{10}\right)\rho^{*4},$$

where

$$\rho^* = \frac{\rho}{\rho_0}, \quad T^* = \frac{T}{T_0},$$

$\rho$ is the density in kg/m\(^3\), $T$ is the temperature in K, and the numerical constants $a_i$’s are given by

- $a_1 = 7.62571 \times 10^6$, $a_2 = 2.44003 \times 10^2$, $a_3 = -1.40569 \times 10^2$, $a_4 = 2.77841 \times 10^1$, $a_5 = -9.62805 \times 10^1$, $a_6 = 4.17909 \times 10^1$, $a_7 = -1.02099 \times 10^1$, $a_8 = -4.52059 \times 10^1$, $a_9 = 8.46395 \times 10^1$, $a_{10} = -3.58644 \times 10^1$,
- $T_0 = 298.15 \text{ K}$, $\rho_0 = 1000 \text{ kg/m}^3$.

Eq 2.35 is valid in the range

$$273.15 \text{ K} \leq T \leq 823.15 \text{ K} \quad \text{and} \quad 0 \leq \rho \leq 1150 \text{ kg/m}^3,$$

the later condition corresponding to an approximate pressure range

$$0 \leq P \leq 500 \text{ Mpa}.$$
Figure 2.55: Dependence of $\varepsilon$ for water on temperature.

(Buckingham, 1956), and using the gas phase dipole moment $\mu = 1.85$ D and density $\rho = 1000$ kg/m$^3$, the dependence of Kirkwood’s g-factor on temperature is plotted in Figure 2.56.

Clearly, just as the permittivity, the Kirkwood’s g-factor is also a decreasing function of temperature. However, these two quantities have different dependences on $T$. It seems that it is easier for most water models to get smaller values of permittivity at higher temperature, but more difficult to get the correct trend for Kirkwood’s
Figure 2.56: Dependence of Kirkwood’s g-factor for water on temperature.

g-factor (Neumann, 1985; Neumann, 1986; Smith & van Gunsteren, 1994). For example, the permittivity of SPC water model decreases as temperature increases from 277 K to 300 K, but $g_k$ increases (Smith & van Gunsteren, 1994). The same event also happens to TIP4P water model as temperature increases from 293 K to 373 K (Neumann, 1986). As pointed out by Neumann, the “experimental” $g_k$ values is actually calculated from Kirkwood-Fröhlich equation (Eq. 2.36), which is only an approximate relation for polar system, so how reliable these values are is also debatable. However,
it is believed that the true value of $g_k$ will not inverse the temperature dependence.

To evaluate the temperature dependence of $g_k$, the usual practice is to run simulations at different temperatures and calculate $g_k$ separately. However, $\partial g_k / \partial T$ can be calculated directly from a single run of the simulation. Suppose we are using the dipole fluctuation formula, such as eq 2.29. First we shall evaluate $\partial \langle M^2 \rangle / \partial T$. From

$$\langle M^2 \rangle = \frac{\int M^2(X) e^{-\beta U(X)} dX}{\int e^{-\beta U(X)} dX}, \quad (2.37)$$

take derivative with respect to temperature $T$, we get

$$\frac{\partial \langle M^2 \rangle}{\partial T} = \frac{1}{kT^2} \left[ \langle UM^2 \rangle - \langle U \rangle \langle M^2 \rangle \right]. \quad (2.38)$$

Both terms on the right side of Eq. 2.38 can be easily evaluated in a single run of the simulation. Since Kirkwood’s g-factor is a function of $\varepsilon$ (Eq. 2.34), and $\varepsilon$ is a function of $\langle M^2 \rangle$, it is easy to calculate $\partial g_k / \partial T$ once $\partial \langle M^2 \rangle / \partial T$ is known. Similar formulas for wave-vector-dependent dielectric tensor have been derived (Omelyan, 1995). For multipole fluctuations, the same procedures also apply.

In Figure 2.57 the calculated Kirkwood’s g-factors for TINKER1 model at $T = 277$ K and $T = 300$ K are shown. From the figure we can see that the $g_k$ of TINKER1 model seems insensitive to the temperature changes, though the permittivity increases a little bit to 57.2 at $T = 277$ K.
Figure 2.57: Kirkwood’s g-factors of TINKER1 model at $T = 277\,\text{K}$ and $T = 300\,\text{K}$. $r_1 = 7\text{Å}$.

2.7 Summary of TINKER water models

In this section we give a summary of the properties of TINKER water models. As stated before, the objective for developing the TINKER water models is two-fold. The first motivation comes from the desire to develop a water model that will be more accurate in a wide range of situations that arise in simulations of biological systems, from small clusters to bulk system. The other aim is to use water as a testing case to verify the polarizable multipole force field developed in Chapter 1. In contrast to some water models which are developed specially for water molecules and incorporate some special functions, our force field has a more general potential functions that are suitable for large, flexible biomacromolecules. From the results
presented in the previous sections, it can be seen that the TINKER water models perform quite satisfactorily in some aspects, such as the prediction of small water clusters and energetics (Section 2.4), as well as the bulk structures (Section 2.5.2). For the dielectric properties, the TINKER models are comparable to the simple partial charge models (Section 2.6). One drawback of the models is their dynamic properties (Section 2.5.3). The TINKER water models have lower diffusion constants than the experimental value, while the simple charge models tend to overestimate the diffusion constants. By judging the radial distribution functions the bulk structure predicted by TINKER models is quite close to that determined experimentally. It seems that in the bulk systems, the TINKER models also predict the major minima correctly, but the potential surfaces of TINKER models overestimate the barriers between the local minima. Our results seem to give an indirect support for the hypothesis that in liquid water, small clusters like tetramer and octamer appear to be the principal species (Benson & Siebert, 1992).

Since the bulk properties of water models with the detailed descriptions of electrostatic interactions like the TINKER model have not been studied very thoroughly before, other conditions used in the simulations, such as the cut-off distance, may also affect the results. Hence in the future development not only the parameters used in the models should be fine-tuned, but also the various methodologies used should be carefully studied.

The accuracy of the multipole models comes with the increase in the computation time. Although efforts have been made to speed up the implementation, there is still
room for further improvement. For example, currently the full interaction matrix
(Section 1.10) is used for the interaction energy and derivatives. Some of the elements
of the matrix may be negligibly small. Method may be developed which will not use
these elements at all and in the same time avoid the discontinuities thus introduced.
Chapter 3

Reaction Field from Off-Center Point Multipoles

3.1 Introduction

Treatment of solvation effects is of major importance in the modeling of molecular structure and energetics. Electrostatic interactions, including long range electrostatics, are an important component of solvation (Rogers, 1986; Harvey, 1989; Davis & McCammon, 1990; Sharp & Honig, 1990; Warshel & Aqvist, 1991; Rashin, 1993; Smith & van Gunsteren, 1993; Tomasi & Persico, 1994; Cramer & Truhlar, 1995; Nakamura, 1996). In the context of classical molecular simulation, the solvation effects due to long range electrostatic interactions can be viewed as a perturbation to the explicit Coulombic interactions within the system. In this Chapter we develop two fast analytical methods for including the reaction field (RF) as a correction to
explicit simulation results. Both formulations are general and lead to straightforward and systematic implementations for use in computer simulations. In addition to the RF potential, both methods give analytical derivatives of the RF energy. Besides, various degrees of gradients of the RF potential can be calculated in a unified way by the polytensor method, which simplifies application to polarizable systems. Examples are given showing the effect of the RF on the relative orientation of a pair of dipoles in their minimum energy configuration, and the calculation of dipole moments induced by a set of atomic multipoles.

Multi-center multipole expansions are increasingly used in molecular modeling (Stone, 1996). Our work extends the classical reaction field method of Kirkwood to include multi-center multipoles within a fixed simulation boundary. Multipole representations of electrostatics have four major uses: (1) increased accuracy in detailed representation of a molecular electrostatic potential (Williams, 1991; Dykstra, 1993), (2) fast multipole methods to avoid the $O(N^2)$ bottleneck in standard pairwise interaction summations (Greengard, 1994), (3) description of averaged electrostatic effects over a region of space for use in simplified molecular models (Pappu et al., 1996), and (4) improving convergence relative to single-site models (Fowler & Buckingham, 1991). Multipole parameters have been determined for use in macromolecular simulation (Dudek & Ponder, 1995; Price et al., 1991; Sokalski et al., 1993) and a recent paper has attempted to incorporate multi-center multipole electrostatics into a force field program for flexible molecules (Koch & Egert, 1995).

Long range electrostatics can be treated either with explicit models or continuum
methods. Explicit models treat solvent molecules in a discrete fashion with no distinction between solute and solvent. Lattice sums are usually used to limit the system to a reasonable size (De Leeuw et al., 1980; Darden et al., 1993). In continuum methods, the solute is embedded in a cavity surrounded by structureless continuum solvent. The electric charges of the solute polarize the continuum which in turn affects the electric field inside the cavity. This contribution from the continuum is usually called the reaction field. Some current models include certain explicit solvent molecules within continuum models. As discussed below, such hybrid models can simulate the system more realistically. Particular attention was given to these hybrid models when the formulations in this paper were developed.

The continuum models can be treated by several methods. For simple cavity geometries, analytical solutions exist. Kirkwood derived a general solution for the RF potential for a spherical cavity containing an arbitrary charge distribution (Kirkwood, 1934). The ion polarization energy (Born charging energy) and the dipole polarization energy (Onsager reaction field) can be derived as special cases of the general result. Beveridge and Schnuelle (Beveridge & Schnuelle, 1975) give a concise review of Kirkwood’s work and extended his result to calculation of the RF potential and free energy of an arbitrary charge distribution in a spherical central cavity surrounded by two concentric dielectric continua. Felder and Applequist (Felder & Applequist, 1981) considered charged and polarizable atoms in a cavity placed in a dielectric continuum. They obtained explicit relationships for the case of a spherical cavity. In order to compute the RF they differentiated the RF potential with respect to the
spherical coordinate unit vectors, and then transformed back to Cartesian components. The resulting formula was applied to a study of the Gibbs energy of proton transfer between carboxylic acids. Felder (Felder, 1981) generalized this method for a charge-dipole system with a cavity in the shape of a prolate or oblate ellipsoid. Other groups have also extended the RF derivation to simple nonspherical cavities (Harrison et al., 1976; Rivial & Rinaldi, 1976; Rivial & Terryn, 1982). For complex molecular surfaces, no analytical solutions exist and numerical methods have to be used. In the spirit of the classical simple RF model, Rivail and coworkers have developed methods to handle cavities of general shape (Dillet et al., 1993). Their formulation is better able to account for the true molecular surface, but the calculation is performed over a large number of discrete surface points. A correspondingly large system of linear equations must be solved to determine the “reaction field factors” used in the energy evaluation. The surface points must be recomputed whenever the molecular geometry changes. First and second derivatives of this method are available (Dillet et al., 1996). The same method has been applied by these authors to multi-center multipole models of the solute with the expected increase in the number and difficulty of the RF factors to be computed. While very general, the method appears to be too slow for use with macromolecules.

The widely used image charge method (Friedman, 1975) is a simple approximation to the full RF term and involves computation of the positions and magnitudes of a set of image charges outside the cavity. The direct interaction of the solute and image charges then gives the RF energy. A recently proposed correction term
increases the accuracy of the approximation (Abagyan & Totrov, 1994). A more detailed discussion will be found in Appendix B. For homogeneous systems, a moving boundary RF method can be used (Essex & Jorgensen, 1995; Tironi et al., 1995). In this method each site in turn is placed at the center of its own spherical cavity and the corresponding RF term is computed using the classical Kirkwood result. For inhomogeneous systems it is difficult to apply this method since the dielectric constants inside and outside the cavity are no longer well defined.

The “reaction field” methods discussed above are all based on solving the Poisson equation (or Poisson-Boltzmann equation when mobile ions are present) using proper boundary conditions. Another widely used procedure for solving the Poisson-Boltzmann equation numerically is the finite difference method. Finite difference Poisson-Boltzmann (FDPB) calculations have long been applied to static conformations of large macromolecules such as proteins (Warwicker & Watson, 1982). If a fine numerical grid is used, the molecular shape can be accurately represented, but computation time increases with the number of grid points. Several groups have attempted to couple FDPB methods with dynamics simulations (Sharp, 1991). With use of a very coarse 10 Å grid, the method becomes fast enough for use in classical empirical dynamics simulations (Gilson et al., 1995).

In addition to solving the Poisson or Poisson-Boltzmann equation directly, the continuum model can be handled equivalently by boundary element methods (Tomasi & Persico, 1994; Miertus et al., 1981; Miertus & Tomasi, 1982; Zauhar & Morgan, 1985; Coitino et al., 1995; Cammi et al., 1995; Cossi et al., 1995). These methods
treat the continuum electrostatic problem everywhere in space by determining a set of apparent surface charges for each element on the molecular surface. Since only the molecular surface and not the full volume occupied by the molecule is involved, the method is in principle more applicable to macromolecules than the space-oriented methods such as FDPB. However, the method is most widely used at present in tandem with molecular orbital calculations. Usually the surface is partitioned into a large number of elements via a tessellation scheme. In order to determine the induced surface charges on these elements, a large system of equations has to be solved. These equations can be solved either by iteration or matrix inversion. An approximate closure solution was also proposed (Tomasi & Persico, 1994). Recently, analytical energy derivatives for this method have been described (Cammi & Tomasi, 1994; Coitino & Tomasi, 1996). For large molecules, it may be difficult to achieve reasonable accuracy since fine discretization of the molecular surface leads to a large system of equations. Zauhar and Varnek (Zauhar & Varnek, 1996) recently implemented a modified algorithm in which only those surface elements close in space are exactly solved, while treating the long-range interactions by a grid-based multipole expansion.

Of the many other continuum solvation methods reported in the literature, two have received particular attention. The Langevin dipole method is an alternative approach that uses point dipole sites on a fixed grid outside the molecular surface. The dipoles are allowed to rotate, thus accommodating the RF effects due to the continuum (Warshel & Russell, 1984). Several recent methods based on the generalized Born (GB) equation have shown promise in computation of hydration free energies.
These GB methods take account of solvent exposure of the solute through parameters related to the burial of charged atoms.

In this Chapter two general methods are given to calculate the RF due to off-center multipoles. In the following section, we first present a brief outline of the original Kirkwood RF method, then give a general matrix formulation of the RF potential and derivatives for off-center multipoles. Induced dipole polarization is also discussed. A recursive method to calculate the matrix elements then is given. Explicit formulas are provided in Appendix C. Section 3.3 describes another method, which we will call the central multipole method. This method scales linearly in calculation time with the size of the system, making it useful for large systems. General methods to calculate derivatives are also given for the central multipole method. Explicit vector formulas for the RF energies through quadrupole-quadrupole interactions are provided as Appendix D.

3.2 Matrix formulas for reaction field potential and energy

3.2.1 Reaction field energy

Kirkwood’s derivation (Kirkwood, 1934) of the RF energy for the general case of an arbitrary charge distribution is based on solving Laplace’s equation, $\nabla^2 \Phi = 0$, (Still et al., 1990; Davis, 1994; Bliznyuk & Greedy, 1995; Schaefer & Karplus, 1996).
which is valid for all the sites free of point charges. If we assume the system, which is represented as $M$ discrete point charges $q_k$, $k = 1 \ldots M$, is buried in a spherical cavity with a radius $a$ surrounded by a dielectric continuum, the relative permittivities inside and outside the cavity being assigned as $\varepsilon_1$ and $\varepsilon_2$ respectively, then the solution of the RF potential at the position $\mathbf{r} = \{r, \theta, \phi\}$ inside the cavity is

$$\Phi_R(\mathbf{r}) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{k=1}^{M} q_k r_k^n r^n P_n(\cos \gamma_{kr})$$ (3.1)

in which $P_n(\cos \theta)$ is a simple Legendre polynomial, $\gamma_{kr}$ is the angle between $\mathbf{r}_k$ and $\mathbf{r}$, and $\varepsilon = \varepsilon_2/\varepsilon_1$. The RF energy is given by (Böttcher et al., 1973)

$$W = \frac{1}{2} \sum_{k=1}^{M} q_k \Phi_R(\mathbf{r}_k) = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \left( \frac{Q_n}{a^{2n+1}} \right)$$ (3.2)

where

$$Q_n = \sum_{k=1}^{M} \sum_{l=1}^{M} q_k q_l r_k^n r_l^n P_n(\cos \gamma_{lk}).$$ (3.3)

For $n = 0$ and $n = 1$, $Q_n$ is equal to the square of the charge and dipole moment, respectively, of the whole system in the cavity. For higher $n$, it is shown later that $Q_n$ is the complete contraction of two different Cartesian tensors.

We are interested in generalizing Kirkwood’s result to point multipoles not located at the origin. One method to do this is to displace point charges slightly away from each other and take the limit as their separation approached zero while keeping the
strength of the multipole constant. Appendix D gives the resulting vector formulas for
the RF energy for the first three degrees of multipoles (charge, dipole, and quadrupole)
together with sample derivations. The equations become complex for the higher
degree multipoles, making generalization difficult. The other disadvantage of this
approach is that it is difficult to get derivatives of the RF energy from these formulas,
as well as the gradients of the RF potential.

To get a general analytical formula which is convenient to implement in a computer
program, we use a polytensor method similar to that used by our group and others
for direct multipole interactions (Applequist, 1985; Dykstra, 1993; Kong & Ponder,
1997a). Assume that there are \( N \) multipole sites located at \( r_k, k = 1 \ldots N \), with
charges \( q_k \) located around each site in a nonoverlapping fashion at positions \( r_{ki} \).
Each charge is displaced from its own site by a vector \( d_{ki} \), i.e., \( r_{ki} = r_k + d_{ki} \), with
its three components \( d_{xki}, d_{yki} \) and \( d_{zki} \).

Similar to Eqs. 3.1 and 3.2 we write the RF potential at the position \( r = \{r, \theta, \phi\} \)
inside the cavity as

\[
\Phi_R(r) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{k=1}^{N} \sum_{i} q_k r_{ki} r^n P_n(\cos \gamma_{ki,r})
\]

(3.4)

where \( \gamma_{ki,r} \) is the angle between \( r_{ki} \) and \( r \), and the RF energy

\[
W = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{k=1}^{M} \sum_{l=1}^{M} \sum_{i} \sum_{j} q_k q_l r_{ki} r_{lj} r^n P_n(\cos \gamma_{ki,lj}),
\]

(3.5)
where \( \gamma_{ki} \) is the angle between \( r_{ki} \) and \( r_{lj} \). If we take a Taylor expansion of \( \Phi_R(r) \) in Eq. 3.4 at site \( k \), we get

\[
\Phi_R(r) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{k=1}^{N} M_{kR}^{(n)} \frac{R_{kr}}{r_{kr}}
\]

\[
= \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{k=1}^{N} M_kR_{kr}. \tag{3.6}
\]

If we make Taylor expansions twice of \( W \) in Eq. 3.5 (or, expand \( \Phi_R(r) \) of Eq. 3.6 at site \( l \)), we obtain

\[
W = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{k=1}^{N} \sum_{l=1}^{N} M_k^{(n)} R_{kl} M_l
\]

\[
= \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{k=1}^{N} \sum_{l=1}^{N} M_k R_{kl} M_l. \tag{3.7}
\]

In Eqs. 3.6 and 3.7 we define the multipole polytensors (Applequist, 1985) of site \( k \) and \( l \) as

\[
M_k = [M_k^{000}, M_k^{100}, M_k^{010}, M_k^{001}, M_k^{200}, M_k^{110}, \ldots]^t
\]

\[
M_l = [M_l^{000}, M_l^{100}, M_l^{010}, M_l^{001}, M_l^{200}, M_l^{110}, \ldots]^t
\]

in which the *unabridged Cartesian multipoles* at site \( k \) are defined as

\[
M_{k000} = \sum_i q_{ki},
\]

\[
M_{k100} = \sum_i q_{ki}d_{ki}^x,
\]

\[
M_{k010} = \sum_i q_{ki}d_{ki}^y,
\]

\[
M_{k001} = \sum_i q_{ki}d_{ki}^z,
\]

\[
M_{k200} = 1/2! \sum_i q_{ki}(d_{ki}^x)^2,
\]

\[
M_{k110} = 1/2! \sum_i q_{ki}(d_{ki}^x d_{ki}^y), \ldots
\]

These are the same multipole definitions used in an efficient implementation of the direct multipole interactions (Dykstra, 1993; Kong &
Ponder, 1997a). The symbol $t$ stands for vector or matrix transposition. The matrix $\mathbf{R}_{kl}^{(n)}$ (or similarly $\mathbf{R}_{kr}^{(n)}$) is defined as

\[
\mathbf{R}_{kl}^{(n)} = \left[ 1, \frac{\partial}{\partial x_k}, \frac{\partial}{\partial y_k}, \frac{\partial}{\partial z_k}, \frac{\partial^2}{\partial x_k \partial y_k}, \cdots \right]^t \left[ 1, \frac{\partial}{\partial x_l}, \frac{\partial}{\partial y_l}, \frac{\partial}{\partial z_l}, \frac{\partial^2}{\partial x_l \partial y_l}, \cdots \right] B_n(\mathbf{r}_k, \mathbf{r}_l),
\]

where the biaxial harmonic $B_n(\mathbf{r}_k, \mathbf{r}_l)$ between two vectors $\mathbf{r}_k$ and $\mathbf{r}_l$ is defined as $B_n(\mathbf{r}_k, \mathbf{r}_l) = r_k^n r_l^n P_n(\cos \gamma_{kl})$, and the matrix $\mathcal{R}_{kl}$ as

\[
\mathcal{R}_{kl} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \mathbf{R}_{kl}^{(n)}.
\]

The matrix $\mathbf{R}_{kl}^{(n)}$ can be written symbolically as

\[
\mathbf{R}_{kl}^{(n)} = \begin{bmatrix}
\nabla_k^0 \nabla_l^0 & \nabla_k^0 \nabla_l^1 & \nabla_k^0 \nabla_l^2 & \cdots \\
\nabla_k^1 \nabla_l^0 & \nabla_k^1 \nabla_l^1 & \nabla_k^1 \nabla_l^2 & \cdots \\
\nabla_k^2 \nabla_l^0 & \nabla_k^2 \nabla_l^1 & \nabla_k^2 \nabla_l^2 & \cdots \\
\vdots & \vdots & \vdots & \ddots 
\end{bmatrix} B_n(\mathbf{r}_k, \mathbf{r}_l) \quad (3.8)
\]

where

\[
\nabla_h^p = \frac{\partial^{i+j+k}}{\partial x_i \partial y_j \partial z_k}, \quad p = i+j+k \quad \text{and} \quad h = k \text{ or } l.
\]

From the definition of $\mathbf{R}_{kl}^{(n)}$ we have

\[
(\mathbf{R}_{kl}^{(n)})^t = \mathbf{R}_{ik}^{(n)}. \quad (3.9)
\]
From this relation we can write Eq. 3.7 as

\[ W = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} (2 - \delta_{kl}) \sum_{l \geq k} M_k^n R_{kl}^{(n)} M_l \]

\[ = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} (2 - \delta_{kl}) \sum_{l \geq k} M_k^n R_{kl} M_l, \quad (3.10) \]

where \( \delta_{kl} = 1 \) if \( k = l \), otherwise it is zero.

Since

\[ \left( \frac{\partial^2}{\partial x_h^2} + \frac{\partial^2}{\partial y_h^2} + \frac{\partial^2}{\partial z_h^2} \right) B_n = 0, \quad h = k \text{ or } l, \]

the potential (Eq. 3.6) or the energy (Eq. 3.7) are the same for the unabridged multipoles and for the traceless multipoles, as is the case for direct interaction (Böttcher et al., 1973).

Figure 3.1 gives a simple example of the use of this method to determine the energetic and structural effects arising from inclusion of the reaction field. Minimum energy configurations were computed for a pair of point dipoles constrained to lie at various positions within a spherical cavity of low dielectric. The figure shows how the RF perturbs the optimal interaction of the two dipoles. In the absence of the reaction field, the minimum energy configuration of the dipoles is to remain exactly in line. Depending on the positions of the dipoles relative to the dielectric boundary, inclusion of the RF term can result in minimum configurations with the dipoles nearly perpendicular. Similarly, as one or both of the dipoles approach the boundary, the RF term makes a large contribution to the total interaction energy.
Figure 3.1: Effect of the reaction field term on the interaction between two point dipoles. The dipoles are of equal magnitude and are placed inside a spherical cavity of radius $a$. The ratio of the dielectric constant outside the cavity to that inside the cavity is taken as 80. The circular arc spanned by the two dipoles is given by an angle $\theta$. One dipole is fixed at a distance $a/2$ from the cavity center. The plotted curves, in order from bottom to top, represent different positions of the second dipole, at distances of $0.1a, 0.2a, \ldots, 0.9a$ from the cavity center. For each combination of circular arc spanned and second dipole distance, the minimum energy orientation of the dipoles was determined. In part (a), the $y$-axis shows the angle between the two dipoles in their minimum energy orientation. In part (b), the $y$-axis shows the fraction of the total interaction energy at the minimum energy orientation due to the reaction field term.
3.2.2 Derivatives of reaction field energy

From Eq. 3.7 and using the symmetrical relation Eq. 3.9, we can easily write down the equations for the derivatives of the RF energy with respect to the Cartesian coordinates of each atom,

\[
\frac{\partial W}{\partial x_k} = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{l=1}^{N} (2 - \delta_{kl}) M_k^l R_{(k)kl}^{(n)ix} M_l
\]

\[
= \frac{1}{8\pi\varepsilon_0\varepsilon_1} M_k^l \sum_{l=1}^{N} R_{(k)kl}^{(n)ix} M_l,
\]

where the matrices \( R_{(k)kl}^{(n)ix} \) and \( R_{(k)kl}^{(n)iy} \) are defined as

\[
R_{(k)kl}^{(n)ix} = \frac{\partial}{\partial x_k} R_{kl}^{(n)}
\]

and

\[
R_{(k)kl}^{(n)ix} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} (2 - \delta_{kl}) R_{(k)kl}^{(n)ix}.
\]

The elements of \( R_{(k)kl}^{(n)ix} \) are taken from \( R_{kl}^{(n)} \). From the structure of \( R_{(k)kl}^{(n)ix} \), we can see

\[
R_{(k)kl}^{(n)ix}(i,j) = R_{kl}^{(n)}(3i - 1, j), R_{(k)kl}^{(n)iy}(i,j) = R_{kl}^{(n)}(3i, j), R_{(k)kl}^{(n)iz}(i,j) = R_{kl}^{(n)}(3i + 1, j).
\]

Similar methods can be used to construct the nine matrices for the second derivatives:

\[
R_{(k)kl}^{(n)2xx}(i,j) = R_{kl}^{(n)}(9i - 4, j), R_{(k)kl}^{(n)2xy}(i,j) = R_{kl}^{(n)}(9i - 3, j), R_{(k)kl}^{(n)2xz}(i,j) = R_{kl}^{(n)}(9i - 2, j),
\]

\[
R_{(k)kl}^{(n)2yx}(i,j) = R_{kl}^{(n)}(9i - 1, j), R_{(k)kl}^{(n)2yy}(i,j) = R_{kl}^{(n)}(9i, j), \ldots
\]

For the derivatives with respect to \( r_l \), the corresponding columns of \( R_{kl}^{(n)} \) will be used to build up the matrices of \( R_{(l)kl}^{(n)ix} \), etc. The matrices for higher derivatives can be constructed in a
In addition to the RF potential, we can obtain from inspection of Eq. 3.6 (or Eq. 3.7) the field, the gradient of the field, etc., at site \( k \), generated by all sites,

\[
\begin{bmatrix}
\nabla^0 \Phi(r_k), \nabla^1 \Phi(r_k), \nabla^2 \Phi(r_k), \ldots
\end{bmatrix}^t
\]

\[
= \begin{bmatrix}
\Phi(r_k), -E_x(r_k), -E_y(r_k), -E_z(r_k), \Phi^{2xx}(r_k), \Phi^{2xy}(r_k), \ldots
\end{bmatrix}^t
\]

\[
= \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \sum_{l=1}^{N} R_{kl}^{(n)} M_l = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{l=1}^{N} R_{kl} M_l.
\]

(3.12)

These quantities can be used in the treatment of polarizability and hyperpolarizabilities, as illustrated in the following section. Unlike the case of direct multipole interactions, the RF interaction includes self-interactions. As a simple example we calculate the field in the center of the cavity due to a dipole. If we write the matrix \( \nabla^1_k \nabla^1_l B_n(r_k, r_l) \) explicitly and substitute \( r_l = 0 \), all matrices vanish except for \( n = 1 \), which is an identity matrix. So

\[
R(0) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{\mu}{a^3} \frac{2(\varepsilon - 1)}{2\varepsilon + 1}.
\]

This example is given in (Böttcher et al., 1973) for eccentric dipole directed along the radius direction. Here it is shown that it is true for eccentric dipole of any orientations.

As another example, we calculate the various gradients of a charge distribution at the
center of the cavity. It is easy to verify that

\[
\Phi_R^{(n)}(0) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} n! \mathcal{Y}^{(n)},
\]

where

\[
\mathcal{Y}^{(n)} = (-1)^n \frac{1}{n!} \sum_{i=1}^{N} q_i r_i^{2n+1} \nabla^n \frac{1}{r_i}
\]

is the traceless multipole of the charge distribution defined at the center of the cavity (Böttcher et al., 1973). This definition will be used later for the description of another method, the central multipole method, to calculate RF.

### 3.2.4 Induced dipole moments

Theoretically we can use the results from section 3.2.3 to study the hyperpolarizability carried out to any desired degree since we can calculate the gradients of the potential to any degree. In this section the formula for calculating induced dipole moments will be presented. The generalization to higher polarizabilities is straightforward.

The induced dipole moments \( \mu_k^{\text{ind}} \) are

\[
\mu_k^{\text{ind}} = \alpha_k \cdot E_k^{\text{tot}} = \alpha_k \cdot (E_k^d + E_k)
\]

where \( \alpha_k \) is the polarizability tensor of site \( k \) and \( E_k^{\text{tot}} \) is the total field on site \( k \), which includes \( E_k^d \), the field generated directly by all other sites at site \( k \) and the RF
\( \mathbf{E}_k \), generated by all sites. By analogy to Eq. 3.12, the field as well as various degrees of the gradient of the field, generated directly by all other sites can be written as

\[
\begin{bmatrix}
\nabla^0 \Phi^d(r_k), \nabla^1 \Phi^d(r_k), \nabla^2 \Phi^d(r_k), \cdots \\
-\nabla^1 \Phi^d(r_k), -\nabla^2 \Phi^d(r_k), -\nabla^3 \Phi^d(r_k), \cdots \\
\nabla^2 \Phi^d(r_k), \nabla^3 \Phi^d(r_k), \nabla^4 \Phi^d(r_k), \cdots \\
-\nabla^3 \Phi^d(r_k), -\nabla^4 \Phi^d(r_k), -\nabla^5 \Phi^d(r_k), \cdots \\
\vdots & \vdots & \vdots & \vdots
\end{bmatrix}^t = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{l=1}^{N} T_{kl} \mathbf{M}_l,
\]

where the primed sum excludes the term \( l = k \). The matrix \( T_{kl} \) is defined as

\[
T_{kl} = \begin{bmatrix}
\nabla^0 & \nabla^1 & \nabla^2 & \nabla^3 & \cdots \\
-\nabla^1 & -\nabla^2 & -\nabla^3 & -\nabla^4 & \cdots \\
\nabla^2 & \nabla^3 & \nabla^4 & \nabla^5 & \cdots \\
-\nabla^3 & -\nabla^4 & -\nabla^5 & -\nabla^6 & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots
\end{bmatrix} \left( \frac{1}{r_{kl}} \right)
\]

(3.15)

where \( r_{kl} = r_l - r_k \) and

\[
\nabla^p = \frac{\partial^i j^k}{\partial x^i \partial y^j \partial z^k}, \quad p = i + j + k.
\]

\( \mathbf{E}_k^d \) arises from two sources, the permanent multipoles \( \mathbf{M}_l \) and the induced dipoles \( \mathbf{\mu}_l^{ind} \),

\[
\mathbf{E}_k^d = -\frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{l=1}^{N} \left( T_{kl}^{11} \mathbf{M}_l + T_{kl}^{11} \mathbf{\mu}_l^{ind} \right),
\]

(3.16)
where $T_{kl}^1$ is a submatrix of $T_{kl}$

$$T_{kl}^1 = [-\nabla^1, -\nabla^2, -\nabla^3, -\nabla^4, \ldots ](\frac{1}{r_{kl}}),$$

and $T_{kl}^{11}$ is a $3 \times 3$ submatrix of $T_{kl}^1$

$$T_{kl}^{11} = -\nabla^2(\frac{1}{r_{kl}}),$$

which is often called the dipole field tensor.

$E_k$ also arises from the same two sources, the permanent multipoles and the induced dipoles,

$$E_k = -\frac{1}{4\pi\varepsilon_0\varepsilon_1} \sum_{l=1}^{N} (\mathcal{R}_{kl}^1 M_l + \mathcal{R}_{kl}^{11} \mu_{l}^{ind}), \quad (3.17)$$

where $\mathcal{R}_{kl}^1$ is a submatrix of $\mathcal{R}_{kl}$

$$\mathcal{R}_{kl}^1 = \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \nabla_k^1 \nabla_l^0 \nabla_k^1 \nabla_l^1 \nabla_k^1 \nabla_l^2 \cdots B_n(r_k, r_l),$$

and $\mathcal{R}_{kl}^{11}$ is a $3 \times 3$ submatrix of $\mathcal{R}_{kl}^1$

$$\mathcal{R}_{kl}^{11} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\varepsilon)}{(n+1)\varepsilon + n} \frac{1}{a^{2n+1}} \nabla_k^1 \nabla_l^1 B_n(r_k, r_l).$$

Substituting Eqs. 3.16 and 3.17 into Eq. 3.14, and collecting the terms containing the
induced dipole moments, we get

\[(\mathcal{A} + \mathcal{F})\mu = \mathcal{E},\]  

(3.18)

where \(\mathcal{A}\) is the interaction matrix for direct interaction with diagonal blocks \(\alpha_k^{-1}\) and off-diagonal blocks \(1/4\pi\varepsilon_0\varepsilon_1 T^{11}_{kl}\); \(\mathcal{F}\) is composed of \(1/4\pi\varepsilon_0\varepsilon_1 R^{11}_{kl}\), which comes from RF; \(\mathcal{E}\) is the sum of the field generated by the permanent multipoles directly and through the RF, whose \(3 \times 1\) blocks are

\[-\frac{1}{4\pi\varepsilon_0\varepsilon_1}\left(\sum_{l=1}^{N} T^{l}_{kl} + \sum_{l=1}^{N} R^{1}_{kl}\right)M_i.\]

Usually it is assumed that the polarizability is isotropic, then the diagonal blocks of \(\mathcal{A}\) will be \(\alpha_k^{-1}\). Eq 3.18 is a generalization of the corresponding equation of Felder and Applequist (Felder & Applequist, 1981), and leads directly to a set of linear equations whose solution yields the induced dipole moments

\[\mu = (\mathcal{A} + \mathcal{F})^{-1}\mathcal{E}.\]

In practice these equations can be solved iteratively for large systems.

### 3.2.5 Calculation of matrix elements

In this section we give a recursive algorithm to calculate the matrix elements of \(\mathbf{R}^{(n)}_{kl}\).

This algorithm is much faster than the explicit formula given in Appendix C in a
normal simulation. Let the operator \( \mathcal{D}^{l_1,l_2,l_3}_{k_1,k_2,k_3} \) denote

\[
\mathcal{D}^{l_1,l_2,l_3}_{k_1,k_2,k_3} = \mathcal{D}^L_K = \frac{\partial^{k_1+k_2+k_3+l_1+l_2+l_3}z^{k_3} x^{l_1} y^{l_2} z^{l_3}}{\partial x^{k_1} \partial y^{k_2} \partial z^{k_3} \partial x^{l_1} \partial y^{l_2} \partial z^{l_3}}.
\]

Suppose that \( r_k = (x_k, y_k, z_k) \) and \( r_l = (x_l, y_l, z_l) \), then \( \cos \gamma_{kl} = d / (r_k r_l) \), where \( d \) is the inner product of the two vectors \( r_k \) and \( r_l \), \( d = x_k x_l + y_k y_l + z_k z_l \). Furthermore, we make the following definitions: \( K_{mi} = \{k_1 - m\delta_1i, k_2 - m\delta_2i, k_3 - m\delta_3i\} \), \( L_{mi} = \{l_1 - m\delta_1i, l_2 - m\delta_2i, l_3 - m\delta_3i\} \), where \( m = 0, 1, \) or \( 2 \). For example, \( K_{12} = \{k_1, k_2 - 1, k_3\} \).

For \( m = 0 \), we simply denote \( K_{0i} = K = \{k_1, k_2, k_3\} \) and \( L_{0i} = L = \{l_1, l_2, l_3\} \). Let’s also denote \( x_{h1} = x_h, x_{h2} = y_h, x_{h3} = z_h \) where \( h = k \) or \( l \). From the recursive relation of the Legendre polynomials (Hobson, 1931)

\[
(n + 1)P_{n+1}(z) - (2n + 1)zP_n(z) + nP_{n-1}(z) = 0,
\]

we have

\[
B_n = \frac{1}{n} \left((2n - 1)d B_{n-1} - (n - 1)r^2_k r^2_l B_{n-2}\right).
\]

If we define \( F = d B_{n-1} \) and \( G = r^2_k r^2_l B_{n-2} \), we have

\[
\mathcal{D}^L_K F = (d \mathcal{D}^L_K + \sum_{i=1}^{3} k_i x_{ki} \mathcal{D}^L_{K_{1i}} + \sum_{i=1}^{3} l_i x_{ki} \mathcal{D}^L_{L_{1i}} + \sum_{i=1}^{3} k_i l_i \mathcal{D}^L_{K_{1i}}) B_{n-1}
\]

(3.19)
and

\[
\mathcal{D}_{K}^{L}G = \left( r_k^2 \mathcal{D}_{K}^{L} + 2 r_k^2 \sum_{i} k_i x_{ki} \mathcal{D}_{K_{1i}}^{L} + 2 r_k^2 \sum_{i} l_i x_{li} \mathcal{D}_{K}^{L_{1i}} + 4 \sum_{i,j} k_i l_j x_{ki} x_{lj} \mathcal{D}_{K_{1i}}^{L_{1j}} \right)
\]

\[+ r_k^2 \sum_{i} k_i (k_i - 1) \mathcal{D}_{K_{2i}}^{L} + r_k^2 \sum_{i} l_i (l_i - 1) \mathcal{D}_{K}^{L_{2i}} + 2 \sum_{i,j} k_i (k_i - 1) l_j x_{ki} \mathcal{D}_{K_{2i}}^{L_{1j}} \]

\[+ 2 \sum_{i,j} l_i (l_i - 1) k_j x_{li} \mathcal{D}_{K_{1i}}^{L_{2j}} + \sum_{i,j} k_i (k_i - 1) l_j (l_j - 1) \mathcal{D}_{K_{2i}}^{L_{2j}} \] \(B_{n-2}\) \(3.20\)

With \(\mathcal{D}_{K}^{L}F\) and \(\mathcal{D}_{K}^{L}G\), we obtain

\[
\mathcal{D}_{K}^{L}B_{n}(r_k, r_l) = \frac{1}{n} ((2n - 1) \mathcal{D}_{K}^{L}F - (n - 1) \mathcal{D}_{K}^{L}G). \tag{3.21}
\]

From the definition of \(B_{n}\) we see that \(B_{0} = 1\), so the only non-zero element of \(\mathcal{D}_{k_1,k_2,k_3}^{L_1,l_2,l_3} B_{0}\) is \(\mathcal{D}_{0,0,0}^{0,0,0} B_{0} = B_{0} = 1\). When \(n = 1\), \(B_{1} = d\), so we have

\[
\mathcal{D}_{0,0,0}^{0,0,0} B_{1} = d,
\]

\[
\mathcal{D}_{1,0,0}^{0,0,0} B_{1} = x_l, \quad \mathcal{D}_{0,1,0}^{0,0,0} B_{1} = y_l, \quad \mathcal{D}_{0,0,1}^{0,0,0} B_{1} = z_l,
\]

\[
\mathcal{D}_{0,0,0}^{1,0,0} B_{1} = x_k, \quad \mathcal{D}_{0,0,0}^{0,1,0} B_{1} = y_k, \quad \mathcal{D}_{0,0,0}^{0,0,1} B_{1} = z_k,
\]

\[
\mathcal{D}_{1,0,0}^{1,0,0} B_{1} = 1, \quad \mathcal{D}_{0,1,0}^{1,0,0} B_{1} = 1, \quad \mathcal{D}_{0,0,1}^{1,0,0} B_{1} = 1,
\]

and all others elements vanish. From Eqs. 3.19, 3.20 and 3.21 and using \(\mathcal{D}_{K}^{L}B_{0}\) and \(\mathcal{D}_{K}^{L}B_{1}\) as initial values, we can get \(\mathcal{D}_{K}^{L}B_{n}\) from \(\mathcal{D}_{K}^{L}B_{n-1}\) and \(\mathcal{D}_{K}^{L}B_{n-2}\). It can be seen from Eqs. 3.19 and 3.20 that as \(n\) goes up, the non-zero terms in these equations depend only on \(K\) and \(L\).
### 3.3 Central multipole method

The matrix method just discussed fits nicely into the polytensor formalism for direct multipole interactions. As mentioned briefly in the section describing induced dipoles, a main difference between direct interactions and the RF lies in the kernel functions operated on by the Cartesian derivative matrix; $1/r$ for direct interactions vs. $B_n$ for RF. In addition, calculation of the RF requires inclusion of self-interaction terms and involves summation of an infinite series. Hence our existing program for direct multipole interactions (Kong & Ponder, 1997a) can be modified with little effort to incorporate the RF calculation. Since large systems usually require as many as 20 terms for the series to converge (States & Karplus, 1987), and computation of each term is an $O(N^2)$ operation, where $N$ is number of multipole sites, the inclusion of RF effects can make the computation very slow. In this section we present a method to calculate the RF which needs only $O(N)$ time. We call this new linear method the central multipole method, for reasons which will become clear in the following discussion. Since the treatment of multipoles is developed directly from the corresponding method for a charge distribution, we first present the method for charge distributions.
3.3.1 Central multipole method for charge distribution

The biaxial harmonic $B_n(r_k, r_l) = r_k^n r_l^n P_n(\cos \gamma_{kl})$ can be written as (Hobson, 1931)

$$r_k^n r_l^n P_n(\cos \gamma_{kl}) = r^{2n+1}_k \sum_s \sum_t \sum_u \frac{x^s y^t z^u}{s! t! u!} \frac{\partial^{s+t+u}}{\partial x^s_k y^t_k z^u_k} \frac{1}{r_k},$$

(3.22)

the summation over $s$, $t$, and $u$ being taken for all integral values that satisfy $s+t+u = n$. Using Eqs. 3.3, 3.13, and 3.22, and exchanging the order of summation in $Q_n$, we can see that

$$Q_n = \mathcal{Y}^{(n)} \cdot \mathcal{M}^{(n)}. \quad (3.23)$$

The components of $\mathcal{M}^{(n)}$ are defined as

$$\mathcal{M}^{(n)}_{stu} = \sum_{i=1}^{N} q_i x^s_i y^t_i z^u_i \quad (3.24)$$

which are Cartesian multipoles of the charge distribution with respect to the center of the cavity, and $\mathcal{Y}^{(n)}$ are the traceless Cartesian multipoles defined in Eq. 3.13. Note that in this definition of $\mathcal{M}^{(n)}$ there is no factor of $1/n!$ in contrast to the previous definition used in the matrix method (Eq. 1.8). The symbol $\cdot$ stands for complete contraction. The quantity $Q_n$ is usually referred to in the literature as “the square of $n$th moments of the charge distribution”. It is shown here that expressed in Cartesian multipoles, $Q_n$ is the complete contraction of two multipole tensors, one with trace and one traceless. For $n = 0$, $\mathcal{Y}^{(0)}_{000} = \mathcal{M}^{(0)}_{000} = \sum_i q_i$ is the total net charge.
of the system. For \( n = 1 \), \( Y^{(1)}_{100} = M^{(1)}_{100} = \sum_i q_i x_i \), \( Y^{(1)}_{010} = M^{(1)}_{010} = \sum_i q_i y_i \), and \( Y^{(1)}_{001} = M^{(1)}_{001} = \sum_i q_i z_i \), so \( Q_1 \) is the square of magnitude of the dipole moment of the system relative to the center of the cavity. For \( n > 1 \) the components of \( Y^{(n)} \) are no longer equal to those of \( M^{(n)} \).

Eq 3.23 provides an alternative and fast way to calculate the RF energy for an arbitrary charge distribution. Since the calculation of \( Y^{(n)} \) and \( M^{(n)} \) is linear with \( N \), the size of the system, the calculation of RF is reduced to an \( O(N) \) operation. Results show that the calculation time is reduced by many orders for large systems (Appendix E). The new method is called the central multipole method since the two different Cartesian tensors involved, \( Y^{(n)} \) and \( M^{(n)} \), are both expanded relative to the center of the cavity.

\( Y^{(n)} \) has \( 2n + 1 \) unique terms, while \( M^{(n)} \) has \( (n + 1)(n + 2)/2 \) unique terms. The degeneracy of \( M^{(n)}_{stu} \) is \( n!/(s!t!u!) \). In addition, although the components of \( Y^{(n)} \) and \( M^{(n)} \) are not equal to each other when \( n > 1 \), they are related linearly, such as

\[
Y^{(2)}_{002} = M^{(2)}_{002} - \frac{1}{2} M^{(2)}_{200} - \frac{1}{2} M^{(2)}_{020},
\]

and

\[
Y^{(3)}_{021} = 2M^{(3)}_{021} - \frac{1}{2} M^{(3)}_{201} - \frac{1}{2} M^{(3)}_{003},
\]

so we can in fact only calculate the \( (n + 1)(n + 2)/2 \) unique terms of \( M^{(n)} \), and then use these terms to construct the \( 2n + 1 \) unique terms of \( Y^{(n)} \) through these linear relations. Details of the calculation will be given in Appendix F. Once \( M^{(n)} \)
is calculated, \( Y^{(n)} \) can be easily obtained.

### 3.3.2 Central multipole method for multipole distribution

The central multipole method for charge distributions can be generalized to an arbitrary multipole distribution. To do so the \( M^{(n)} \) and \( Y^{(n)} \) should be expanded for these multipoles. This can be easily achieved on \( M^{(n)} \)

\[
M_{stu}^{(n)} = \frac{1}{n!} \sum_{l=1}^{N} \sum_{m} q_{lm} x_{lm}^{s} y_{lm}^{t} z_{lm}^{u} = \sum_{l=1}^{N} \sum_{m} q_{lm} (x_{l} + d_{lm}^{x})^{s} (y_{l} + d_{lm}^{y})^{t} (z_{l} + d_{lm}^{z})^{u},
\]

(3.25)

where \( d_{lm}^{x}, d_{lm}^{y}, \) and \( d_{lm}^{z} \) are the \( x, y, \) and \( z \) components of the displacement of \( m \)-th partial charge \( q_{lm} \) of site \( l \). Expanding Eq. 3.25 gives

\[
M_{stu}^{(n)} = \sum_{l=1}^{N} \sum_{i,j,k} \left( \begin{array}{c} s \\ i \\ j \\ k \end{array} \right) x_{l}^{s-i} y_{l}^{t-j} z_{l}^{u-k} M_{ijkl}^{ij},
\]

(3.26)

where \( M_{ijkl}^{ij} \) is the Cartesian multipoles of site \( l \)

\[
M_{ijkl}^{ij} = \sum_{m} q_{lm} (d_{lm}^{x})^{i} (d_{lm}^{y})^{j} (d_{lm}^{z})^{k}.
\]

Again the factor of \( 1/n! \) does not appear in this definition, unlike the definition used in the matrix method (Eq. 1.8). For complete convergence the summation over \( i, j, \) and \( k \) in Eq. 3.26 is determined by \( 0 \leq i \leq s, 0 \leq j \leq t, \) and \( 0 \leq k \leq u. \) In actual calculations another condition, \( i+j+k \leq p, \) where \( p \) is the highest order of multipoles
for each site, has to be imposed. As explained in the previous section, once $M^{(n)}$ has been calculated, $Y^{(n)}$ can be obtained through the same linear transformation (Appendix F).

### 3.3.3 Derivatives using central multipole method

The derivatives can be easily obtained via the central multipole method. From Eq. 3.23, we get

$$
\frac{\partial}{\partial x_l} Q_{n} = \left( \frac{\partial}{\partial x_l} Y^{(n)} \right) \cdot M^{(n)} + Y^{(n)} \cdot \left( \frac{\partial}{\partial x_l} M^{(n)} \right). \tag{3.27}
$$

For a charge distribution, from the definition of $M^{(n)}$ (Eq. 3.24) we see that

$$
\frac{\partial}{\partial x_l} M^{(n)}_{stu} = s_{l} x_{l}^{s-1} y_{l}^{t} z_{l}^{u}. \tag{3.28}
$$

For a multipole distribution, from the definition of $M^{(n)}$ (Eq. 3.26) we see that

$$
\frac{\partial}{\partial x_l} M^{(n)}_{stu} = \sum_{i,j,k} \left( s_{i} \right) \left( t_{j} \right) \left( u_{k} \right) \left( s^{i-1} y_{i}^{t-j} z_{i}^{u-k} M^{ij k}_{l} \right.
+ x_{l}^{s-i} y_{l}^{t-j} z_{l}^{u-k} \left( \frac{\partial}{\partial x_l} M^{ij k}_{l} \right)
+ \sum_{w \in L_{l}} x_{w}^{s-i} y_{w}^{t-j} z_{w}^{u-k} \left( \frac{\partial}{\partial x_l} M^{ij k}_{w} \right) \right]. \tag{3.29}
$$

The last two terms of Eq. 3.29 come from the local coordinate systems used to define the multipoles at each site (Kong & Ponder, 1997a) (see Section 1.5). The set $L_{l}$ includes all other sites the definition of whose multipoles depends on site $l$. Once we
have obtained $\partial/\partial x_i M^{(n)}$ from either Eq. 3.28 or 3.29, we can get $\partial/\partial x_i Y^{(n)}$ through the linear transform used above to obtain $Y^{(n)}$ from $M^{(n)}$. Then from Eq. 3.27 we get the derivatives of the RF energy with respect to the coordinates of each site.

3.4 Discussion

Methods that directly use the exact molecular surface have clear advantages over the use of a sphere or ellipsoid to describe the molecular shape. However, analytical methods based on simple cavity shapes are more efficient and appropriate when an extended system containing solute and explicit solvent fills an idealized cavity. Molecular simulations using empirical force fields provide many potential uses for this extended system approach. In these cases, the electrostatic solvation effect can be viewed as a long range correction to the explicit simulation of electrostatics within the extended system itself. Inclusion of such long range effects is of critical importance to accurate modeling of some properties, such as the dielectric constant of water and solvation of ions. In more recent work inclusion of long range electrostatics has been proposed to be an important factor in achieving protein simulations that remain close to experimentally determined structures (York et al., 1994). Multi-site multipole potentials can provide accurate models for the local electrostatic interactions in peptides and proteins (Dudek & Ponder, 1995). The current Chapter describes a method for incorporating the long range forces arising from these same multipole-based potentials.
The Cartesian polytensor formulation of Applequist is an efficient method for organizing multipole calculations (Applequist, 1985; Applequist, 1989). It has been used by Dykstra (Dykstra, 1993) for calculation of direct and induced electrostatic interactions in his ab initio derived MMC empirical force field (Dykstra, 1989). The corresponding spherical polar multipole treatments result in a more compact mathematical formulation (Stone, 1996), but the redundancy in Cartesian multipole treatments can be easily removed when using the polytensor method. In addition, it provides a compact matrix notation which is readily incorporated into computer programs, and can be easily adapted to higher derivatives of energy and gradients of the potential. In this Chapter we show that the Cartesian polytensor formulation can be extended to computation of the RF effects by changing the function operated on by the Cartesian derivative matrix from 1/r (for explicit interactions) to the biaxial harmonics (for reaction field).

Reaction field methods have numerically unstable asymptotic behavior for charges approaching the dielectric boundary. Such sites generate large apparent surface charges of opposite sign, and are attracted to the interface by a force that becomes infinite at the boundary. In addition, explicit molecules must be restricted to the region inside the cavity itself. Several groups have handled these numerical problems by using constraints to keep atoms from getting too close to the boundary (King & Warshel, 1989; Alper & Levy, 1993; Juffer & Berendsen, 1993; Wallquist, 1993). Recently, Wang and Hermans (Wang & Hermans, 1995) have applied the image charge method to pure water droplets and droplets containing a single cation. They discuss
the various problems caused by boundary effects, and suggest an empirical solution that gives the correct cation hydration energy independent of the position of the cation within the cavity. Further studies will be needed to devise general and theoretically justified treatments of effects due to fixed cavity boundaries.

Methods that treat RF effects based on the actual molecular shape do well with regularly shaped small molecules. However these methods may fail near the small cavities, cracks and crevices in large molecules like proteins as discussed by Gilson, et al. (Gilson et al., 1995) One potential disadvantage is that it may be very difficult to calibrate an isolated molecule method to correctly describe local interactions very close to the solute (Rick & Berne, 1994; Bader et al., 1997).

It is well known that tightly bound water molecules play an important structural and dynamic role in many biological macromolecules (Levitt & Park, 1993; Ladbury, 1996). Tightly bound solvent should be accounted for in molecular surface methods through inclusion of explicit solvent molecules. Supermolecule approaches that use molecular-shaped cavity surrounding the solute and a limited number of explicit solvent molecules have recently been used to model solvation of small systems using both empirical force field (Varnek et al., 1995; Rick & Berne, 1994) and quantum mechanical methods (Coitino & Tomasi, 1996). In addition the explicit presence of local solvent provides the space-filling needed to reproduce solute dynamics. These hybrid discrete/continuum approaches correctly account for a limited set of specific local interactions. In our approach, we simply expand the number of explicit solvent molecules to fill out a spherical system containing at least the first solvation shell.
and allowing use of the much simpler analytic formulation available for the spherical cavity.

The methods discussed in this work can incorporate ionic strength with little computational effort, as in Kirkwood’s original treatment. If we denote the radii of the original cavity and of the ion-free zone as \( a \) and \( a' \), respectively, then by solving in different regions Laplace’s equation or the linearized Poisson-Boltzmann equation \( \nabla^2 \Phi_3(r) = \kappa^2 \Phi_3(r) \) (where \( \kappa \) is the inverse Debye screening length which is related to the ionic strength), we get

\[
W = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} \sum_{n=0}^{\infty} \frac{h(n)}{a^{2n+1}} \sum_{k=1}^{N} \sum_{l=1}^{N} M_k^l R_{kl}^{(n)} M_l,
\]

(3.30)

where

\[
h(n) = \frac{(n + 1)(1 - \varepsilon)K_{n+1}(x) - ((n + 1) + n\varepsilon)(K_{n+1}(x) - K_n(x))(a'/a)^{2n+1}}{((n + 1)\varepsilon + n)K_{n+1}(x) - n(1 - \varepsilon)(K_{n+1}(x) - K_n(x))(a'/a)^{2n+1}}.
\]

(3.31)

Here the polynomials \( K_n(x) \) are defined as

\[
K_n(x) = \sum_{s=0}^{n} \frac{2^s n!(2n-s)!}{s!(2n)!(n-s)!} x^s,
\]

where \( x = \kappa a' \). It can be seen that when \( \kappa = 0 \), corresponding to zero ionic strength, Eq. 3.31 reduces to

\[
h(n) = \frac{(n + 1)(1 - \varepsilon)}{(n + 1)\varepsilon + n}
\]

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since $K_n(0) = 1$. All the equations developed for zero ionic strength hold under Poisson-Boltzmann generalization if the proper $h(n)$ is used.

The total electrostatic force experienced by a system in solution consists of three terms (Gilson et al., 1993), the first of which is the usual interaction of charges with the electrical field, which includes the Coulomb’s law fields and the reaction field. In this Chapter when we talk about the derivatives of the energy we are discussing this kind of force. However, in addition to this term, there are two other terms that arise from discontinuities in the dielectric constant and ionic strength. These two terms act on the corresponding boundaries. In the case of a spherical cavity containing a solute and filled out with explicit solvent and ions, the boundary pressure due to these discontinuities is only experienced directly by those species close to the boundary. If the solute of interest is near the center of the cavity, the behavior of species near the boundary is not of as much importance as those close to the solute. If the buffer region is thick enough, the boundary pressure for a fixed spherical cavity can be approximated by distributing it over the whole system and should be nearly isotropic. Thus, the boundary pressure plays a less important role in determining the dynamics of the overall system. On the other hand, if a molecular surface is used, it is more likely the anisotropic forces resulting from these last two terms would effect the behavior of the exposed individual atoms. These effects should be taken into account explicitly, adding further computation burden to molecular surface methods. Whether the boundary term can be completely neglected in fixed spherical boundary simulations will require a further set of test simulations.
In this work two general methods are proposed for computation of RF effects. The matrix formulation fits nicely with the existing method for calculating direct multipole interactions. In addition, it can provide various gradients of RF potentials at each site, which will be useful in dealing with the polarizability of the system. However, this method is inherently pairwise, and scales in execution time with the square of the size of the system \(O(N^2)\). The central multipole method provides an algorithm whose execution time scales linearly with the size of the system \(O(N)\). This method will be most useful for large systems. As discussed above, larger systems require more terms in the infinite series in order to achieve convergence. However, as the number of series terms, \(n\), rises, the number of components we have to calculate for \(\mathcal{M}^{(n)}\) and \(\mathcal{Y}^{(n)}\) increases. Thus, the efficiency of the linear central multipole method is degraded when higher orders are used. Even so, the linear nature of the central multipole method makes it vastly superior to the pairwise matrix method for large systems.

At present, the most widely used RF protocol in simulations is the image charge method (Friedman, 1975). Image charges are attractive because of the resulting simple pairwise procedure for calculation of the RF energy. However, the generation of image charge sites entails an additional \(N^2\) calculations between \(N\) solute charges and \(N\) image charges. A second widely used RF method involves use of only the dipole term \((n = 1)\) for a system containing neutral molecules (Neumann, 1985; Essex & Jorgensen, 1995). Like the image charge procedure, this second method is also pairwise and an approximation to the full RF series summation. Our central
multipole method can use any number of series terms to achieved a desired level of convergence and is computationally more efficient than either of these currently used methods.
Appendix A

Calculation of matrix elements

To obtain a general scheme to calculate the Cartesian derivatives of $1/r$, it is easier to get the derivatives of $1/r^{2\alpha}$ first, then put $\alpha$ to $1/2$. From the generating function of ultraspherical (Gegenbauer) polynomials (Abramowitz & Stegun, 1964) we have, by denoting $r = \sqrt{x^2 + y^2 + z^2}$,

$$\frac{1}{[(z-h)^2 + x^2 + y^2]^{\alpha}} = \frac{1}{r^{2\alpha}} \left\{ \frac{1}{1 - 2 \frac{hz}{r^2} + \left[ \frac{h}{r} \right]^2} \right\}^\alpha = \frac{1}{r^{2\alpha}} \sum_{n=0}^{\infty} C_n^{(\alpha)}(t) \left[ \frac{h}{r} \right]^n, \quad (A.1)$$

where $t = z/r$ and $C_n^{(\alpha)}(t)$ is the ultraspherical (Gegenbauer) polynomial

$$C_n^{(\alpha)}(t) = \frac{1}{\Gamma(\alpha)} \sum_{m=0}^{\left\lfloor n/2 \right\rfloor} \frac{(-1)^m \Gamma(\alpha + n - m)}{m! (n - 2m)!} (2t)^{n-2m}. \quad (A.2)$$

Here $\Gamma(\alpha)$ is the Gamma (Factorial) function.
On the other hand, the left side of Eq. A.1 can be developed in a Taylor series

\[
\frac{1}{[(z - h)^2 + x^2 + y^2]^\alpha} = \sum_{n=0}^{\infty} \frac{(-1)^n h^n}{n!} \frac{\partial^n}{\partial z^n} \frac{1}{r^{2\alpha}}. \tag{A.3}
\]

From Eqs. A.1 and A.3 we see that

\[
\frac{\partial^n}{\partial z^n} \frac{1}{r^{2\alpha}} = (-1)^n \frac{n!}{r^{2\alpha+n}} C_n^{(\alpha)} (t) = \sum_{m=0}^{[n/2]} \frac{(-1)^{n+m} 2^{n-2m} n! \Gamma(\alpha + n - m)}{m!(n-2m)! \Gamma(\alpha)} z^{n-2m} \frac{1}{r^{2(\alpha+n-m)}}. \tag{A.4}
\]

Similar formulas can be applied to \(x\) and \(y\) components, so the general formula for the Cartesian derivatives of \(1/r^{2\alpha}\) is given by

\[
\frac{\partial^{\lambda+\mu+\nu}}{\partial x^\lambda \partial y^\mu \partial z^\nu} \left( \frac{1}{r^{2\alpha}} \right) = \sum_{s=0}^{[\lambda/2]} \sum_{t=0}^{[\mu/2]} \sum_{u=0}^{[\nu/2]} a_s^\lambda(a) a_t^\mu(\lambda + \alpha - s) a_u^\nu(\lambda + \mu + \alpha - s - t)
\]

\[
\times x^{\lambda-2s} y^{\mu-2t} z^{\nu-2u} r^{-2(p+\alpha-s-t-u)} \tag{A.5}
\]

where \(p = \lambda + \mu + \nu\) and \(a_s^i(\alpha)\) is defined as

\[
a_s^i(\alpha) = \frac{(-1)^{i+s} 2^{i-2s} i! \Gamma(\alpha + i - s)}{s!(i-2s)! \Gamma(\alpha)},
\]

which does not depend on geometry of the two vectors (Cipriani & Silvi, 1982).

These values can be calculated before the simulation and stored for later use. For the electrostatic interaction, we only need the special case of Eq. A.5 for \(\alpha = 1/2\). In this

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case, by using

\[ \Gamma(n + \frac{1}{2}) = \frac{1 \cdot 3 \cdot 5 \cdot 7 \cdots (2n - 1)}{2^n} \Gamma\left(\frac{1}{2}\right), \]

Eq. A.5 becomes

\[
\frac{\partial^{\lambda+\mu+\nu}}{\partial x^\lambda \partial y^\mu \partial z^\nu} \left( \frac{1}{r} \right) = \frac{(-1)^p \lambda! \mu! \nu!}{2^{p+1} r^{p+1}} \\
\times \sum_{s=0}^{[\lambda/2]} \sum_{t=0}^{[\mu/2]} \sum_{u=0}^{[\nu/2]} \frac{(-1)^{s+t+u} (2p-2s-2t-2u)!}{s!t!u!(\lambda-2s)!(\mu-2t)!(\nu-2u)!(p-s-t-u)!} \\
\times \left( \frac{x}{r} \right)^{\lambda-2s} \left( \frac{y}{r} \right)^{\mu-2t} \left( \frac{z}{r} \right)^{\nu-2u}
\]

(A.6)

We need \( r^{p+1} \), and various powers of \( x/r, y/r, \) and \( z/r \).

Eq A.6 is quite general for the matrix elements up to any order of multipoles. Currently in the TINKER modeling package we use quadrupole as the highest order multipoles. In order to speed the calculation we calculate the matrix elements explicitly. The 36 elements (Section 1.10) that are needed to calculate energy and first derivatives are given below.

The zeroth order block \( \nabla^0(1/r_{kl}) \) has only one element, \( 1/r_{kl} \). This block is used for the monopole-monopole (partial charge) interactions.

The first order block \( \nabla^1(1/r_{kl}) \) has three unique elements.

\[
\frac{\partial}{\partial x} \frac{1}{r} = \frac{x}{r^3} \\
\frac{\partial}{\partial y} \frac{1}{r} = \frac{y}{r^3} \\
\frac{\partial}{\partial z} \frac{1}{r} = \frac{z}{r^3}
\]
The second order block $\nabla^2(1/r_{kl})$ has five unique elements.

\[
\frac{\partial^2 1}{\partial x^2 r} = \frac{3x^2 - r^2}{r^5} \\
\frac{\partial^2 1}{\partial y^2 r} = \frac{3y^2 - r^2}{r^5} \\
\frac{\partial^2 1}{\partial x \partial z r} = \frac{3xz}{r^5} \\
\frac{\partial^2 1}{\partial x \partial y r} = \frac{3xy}{r^5} \\
\frac{\partial^2 1}{\partial y \partial z r} = \frac{3yz}{r^5}
\]

The third order block $\nabla^3(1/r_{kl})$ has seven unique elements.

\[
\frac{\partial^3 1}{\partial x^3 r} = \frac{3x(3r^2 - 5x^2)}{r^7} \\
\frac{\partial^3 1}{\partial y^3 r} = \frac{3y(3r^2 - 5y^2)}{r^7} \\
\frac{\partial^3 1}{\partial x^2 y r} = \frac{3y(r^2 - 5x^2)}{r^7} \\
\frac{\partial^3 1}{\partial x^2 z r} = \frac{3z(r^2 - 5x^2)}{r^7} \\
\frac{\partial^3 1}{\partial y^2 z r} = \frac{3z(r^2 - 5y^2)}{r^7} \\
\frac{\partial^3 1}{\partial x y^2 r} = \frac{3x(r^2 - 5y^2)}{r^7} \\
\frac{\partial^3 1}{\partial x y z r} = -\frac{15xyz}{r^7}
\]
The fourth order block $\nabla^4 (1/r_{kl})$ has nine unique elements.

\[
\begin{align*}
\frac{\partial^4 1}{\partial x^4 r} &= \frac{105 x^4 - 90 x^2 r^2 + 9 r^4}{r^9} \\
\frac{\partial^4 1}{\partial y^4 r} &= \frac{105 y^4 - 90 r^2 y^2 + 9 r^4}{r^9} \\
\frac{\partial^4 1}{\partial x^3 \partial y r} &= \frac{15 xy (7 x^2 - 3 r^2)}{r^9} \\
\frac{\partial^4 1}{\partial x^3 \partial z r} &= \frac{15 xz (7 x^2 - 3 r^2)}{r^9} \\
\frac{\partial^4 1}{\partial x \partial y^3 r} &= \frac{15 xy (7 y^2 - 3 r^2)}{r^9} \\
\frac{\partial^4 1}{\partial y^3 \partial z r} &= \frac{15 yz (7 y^2 - 3 r^2)}{r^9} \\
\frac{\partial^4 1}{\partial x^2 \partial y \partial z r} &= \frac{15 yz (7 x^2 - r^2)}{r^9} \\
\frac{\partial^4 1}{\partial x^2 \partial y^2 r} &= \frac{15 xz (7 y^2 - r^2)}{r^9} \\
\frac{\partial^4 1}{\partial x^4 \partial y r} &= \frac{105 x^2 y^2 + 15 z^2 r^2 - 12 r^4}{r^9}
\end{align*}
\]

The fifth order block $\nabla^5 (1/r_{kl})$ has eleven unique elements.

\[
\begin{align*}
\frac{\partial^5 1}{\partial x^5 r} &= -\frac{15 x (63 x^4 - 70 x^2 r^2 + 15 r^4)}{r^{11}} \\
\frac{\partial^5 1}{\partial y^5 r} &= -\frac{15 y (63 y^4 - 70 y^2 r^2 + 15 r^4)}{r^{11}} \\
\frac{\partial^5 1}{\partial x^3 \partial y^2 r} &= -\frac{15 x (63 x^2 y^2 - 7 x^2 r^2 - 21 y^2 r^2 + 3 r^4)}{r^{11}} \\
\frac{\partial^5 1}{\partial x^2 \partial y^3 r} &= -\frac{15 y (63 x^2 y^2 - 21 x^2 r^2 - 7 y^2 r^2 + 3 r^4)}{r^{11}} \\
\frac{\partial^5 1}{\partial x^4 \partial y r} &= -\frac{45 y (21 x^4 - 14 x^2 r^2 + r^4)}{r^{11}}
\end{align*}
\]
\[
\frac{\partial^5}{\partial x \partial y^4} \frac{1}{r} = -\frac{45 x (21 y^4 - 14 y^2 r^2 + r^4)}{r^{11}}
\]
\[
\frac{\partial^5}{\partial y^4 \partial z} \frac{1}{r} = -\frac{45 z (21 y^4 - 14 y^2 r^2 + r^4)}{r^{11}}
\]
\[
\frac{\partial^5}{\partial x^4 \partial z} \frac{1}{r} = -\frac{45 z (21 x^4 - 14 x^2 r^2 + r^4)}{r^{11}}
\]
\[
\frac{\partial^5}{\partial x^3 \partial y \partial z} \frac{1}{r} = -\frac{315 xyz (3 x^2 - r^2)}{r^{11}}
\]
\[
\frac{\partial^5}{\partial x \partial y^2 \partial z} \frac{1}{r} = -\frac{315 xyz (3 y^2 - r^2)}{r^{11}}
\]
\[
\frac{\partial^5}{\partial x^2 \partial y^2 \partial z} \frac{1}{r} = -\frac{15 z (63 x^2 y^2 + 7 z^2 r^2 - 6 r^4)}{r^{11}}
\]
Appendix B

Approximations to Kirkwood’s result

B.1 Introduction

The original Kirkwood’s result (Eq. 3.1) for the RF potential at the position \( r = \{r, \theta, \phi\} \) generated by site \( k \) can be written in a general form as

\[
\Phi_R(r) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{q_k}{a} \sum_{n=0}^{\infty} h(n) t^n P_n(\alpha) \tag{B.1}
\]

where \( t = rr_k/a^2 \), \( \alpha = \cos \gamma_{kr} \) (\( \gamma_{kr} \) is the angle suspended by the vector \( r \) and \( r_k \)), and \( h(n) \) is determined by whether there is an ionic strength. When the ionic strength is
zero,

\[ h(n) = \frac{(n + 1)(1 - \varepsilon)}{(n + 1)\varepsilon + n}, \quad (B.2) \]

and when the ionic strength is not zero,

\[ h(n) = \frac{(n + 1)(1 - \varepsilon)K_{n+1}(x) - (n + 1 + n\varepsilon)(K_{n+1}(x) - K_n(x))(a'/a)^{2n+1}}{((n + 1)\varepsilon + n)K_{n+1}(x) - n(1 - \varepsilon)(K_{n+1}(x) - K_n(x))(a'/a)^{2n+1}}, \quad (B.3) \]

where \( x = \kappa a' \) and the polynomials \( K_n(x) \) are defined as

\[ K_n(x) = \sum_{s=0}^{n} \frac{2^n!(2n - s)!}{s!(2n)!(n - s)!} x^s. \]

It can be seen that when \( \kappa = 0 \), Eq. B.3 reduces to Eq. B.2 since \( K_n(0) = 1 \).

In this Appendix, series approximation of \( h(n) \) will be examined and three image methods (\( q_{im}^B \), \( q_{im}^R \), and \( q_{im}^{B01} \)) will be developed. Some of the results, such as Friedman’s image charge method (Friedman, 1975), are used by various authors (Abagyan & Totrov, 1994; Wang & Hermans, 1995). Other methods are only alluded in literature or are not mentioned at all.

### B.2 Series expansion of \( h(n) \)

In practice, Eq. B.1 is too complicated to calculate for a large system. Methods exist which expand \( h(n) \) to approximate the infinite series when there is no ionic strength...
Eq. B.2). Eq B.2 can be expanded in a Taylor series in two ways. Either

\[
h(n) = \frac{1 - \varepsilon}{\varepsilon} \frac{1}{1 + \frac{1}{\varepsilon(n+1)}} = \frac{1 - \varepsilon}{\varepsilon} \sum_{m=0}^{\infty} (-1)^m \left[ \frac{n}{\varepsilon(n+1)} \right]^m, \quad (B.4)
\]

or

\[
h(n) = \frac{1 - \varepsilon}{1 + \varepsilon} \frac{1}{\frac{1}{1 + \frac{1}{\varepsilon(n+1)}}} = \frac{1 - \varepsilon}{1 + \varepsilon} \sum_{m=0}^{\infty} \left[ \frac{1}{(1 + \varepsilon)(n+1)} \right]^m.
\]

(B.5)

In the first expansion, \(h(n)\) is expressed in the power of \(1/\varepsilon\), whereas in the second \(h(n)\) is expressed in the power of \(1/(1 + \varepsilon)\). Kirkwood and Westheimer equivalently used the first expansion (Kirkwood & Westheimer, 1938). Friedman used the second expansion to derive the image charge method (Eq. B.5). Substituting Eq. B.4 into Eq. B.1, we get

\[
\Phi_R(r) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon}{\varepsilon} \frac{q_k}{a} \sum_{m=0}^{\infty} \left( -\frac{1}{\varepsilon} \right)^m \sum_{n=0}^{\infty} \left[ \frac{n}{n+1} \right]^m \int \Phi_P(\alpha)
\]

\[
= \sum_{m=0}^{\infty} B_m(r, t), \quad (B.6)
\]

where

\[
B_m(r, t) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon}{\varepsilon} \frac{q_k}{a} \left( -\frac{1}{\varepsilon} \right)^m \sum_{n=0}^{\infty} \left[ \frac{n}{n+1} \right]^m t^n P_n(\alpha). \quad (B.7)
\]
Substituting Eq. B.5 into Eq. B.1, we get

\[
\Phi_R(r) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon}{1 + \varepsilon} \frac{q_k}{a} \sum_{m=0}^{\infty} \frac{1}{(1 + \varepsilon)^m} \sum_{n=0}^{\infty} \frac{1}{(n + 1)^m} t^n P_n(\alpha)
\]

\[
= \sum_{m=0}^{\infty} R_m(r, t)
\]  \hspace{1cm} (B.8)

where

\[
R_m(r, t) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon}{1 + \varepsilon} \frac{q_k}{a} \sum_{n=0}^{\infty} \frac{1}{(n + 1)^m} t^n P_n(\alpha).
\]  \hspace{1cm} (B.9)

These expressions can be used to get \( B_m(r, t) \) and \( R_m(r, t) \) from \( B_{m-1}(r, t) \) and \( R_{m-1}(r, t) \). First, from these expressions we get the following relations

\[
\frac{\partial}{\partial t} \left[ t \int_0^t B_m(r, s) \frac{1}{s} ds \right] = \int_0^t \frac{1}{s} \left[ \frac{\partial}{\partial s} s B_m(r, s) \right] ds = -\frac{1}{\varepsilon} B_{m-1}(r, t),
\]  \hspace{1cm} (B.10)

and

\[
\frac{\partial}{\partial t} tR_m(r, t) = \frac{1}{1 + \varepsilon} R_{m-1}(r, t).
\]  \hspace{1cm} (B.11)

From these relations, we can get

\[
B_m(r, t) = -\frac{t}{\varepsilon} \frac{\partial}{\partial t} \left[ \frac{1}{t} \int_0^t B_{m-1}(r, s) ds \right] = \frac{1}{\varepsilon t} \int_0^t s \frac{\partial}{\partial s} B_{m-1}(r, s) ds,
\]  \hspace{1cm} (B.12)
and

\[ R_m(r, t) = \frac{1}{(1 + \varepsilon)t} \int_0^t R_{m-1}(r, s) ds. \] (B.13)

Using the generating function of Legendre polynomials,

\[ g(t, \alpha) = \frac{1}{\sqrt{1 - 2\alpha t + t^2}} = \sum_{n=0}^{\infty} t^n P_n(\alpha), \] (B.14)

the explicit expressions for \( B_0(r, t) \) and \( R_0(r, t) \) can be obtained as

\[ B_0(r, t) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon q_k}{\varepsilon} \frac{1}{\alpha \sqrt{1 - 2\alpha t + t^2}}, \] (B.15)

and

\[ R_0(r, t) = \frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon q_k}{1 + \varepsilon} \frac{1}{\alpha \sqrt{1 - 2\alpha t + t^2}}. \] (B.16)

Using the relations B.12 and B.13, we can get \( B_1(r, t) \) and \( R_1(r, t) \)\(^1\) from \( B_0(r, t) \) and \( R_0(r, t) \) as

\[ B_1(r, t) = -\frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon q_k}{\varepsilon^2} a \left[ \frac{1}{\sqrt{1 - 2\alpha t + t^2}} - \frac{1}{t} \ln\left( \frac{\sqrt{1 + t^2 - 2\alpha t + t - \alpha}}{1 - \alpha} \right) \right] \text{ if } \alpha \neq 1, \]

\[ = -\frac{1}{4\pi \varepsilon_0 \varepsilon_1} \frac{1 - \varepsilon q_k}{\varepsilon^2} a \left[ \frac{1}{1 - t} + \frac{\ln(1 - t)}{t} \right] \text{ if } \alpha = 1. \]

\(^1\)The factor 1 + \( \varepsilon \) is not squared in the original paper (Friedman, 1975). In addition, the sign is wrong for \( \alpha = 1 \).
and

\[
R_1(r, t) = \begin{cases} 
\frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{1 - \varepsilon}{(1 + \varepsilon)^2} \frac{q_k}{a} t \ln(\frac{\sqrt{1 + t^2 - 2\alpha t} + t - \alpha}{1 - \alpha}) & \text{if } \alpha \neq 1, \\
-\frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{1 - \varepsilon}{(1 + \varepsilon)^2} \frac{q_k}{a} \ln(1 - t) & \text{if } \alpha = 1.
\end{cases}
\]

If \(B_0(r, t)\) and \(B_1(r, t)\) are combined together with the neglect of terms in \(1/\varepsilon^2\), we obtain

\[
B_{01}(r, t) = B_0(r, t) + B_1(r, t) \simeq \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{q_k}{a} \left\{ \frac{1}{\varepsilon} \left[ \frac{2}{\sqrt{1 - 2\alpha t + t^2}} - \frac{1}{t} \ln(\frac{\sqrt{1 + t^2 - 2\alpha t} + t - \alpha}{1 - \alpha}) \right] - \frac{1}{\sqrt{1 - 2\alpha t + t^2}} \right\},
\]

(B.17)

which is the same result obtained by Kirkwood and Westheimer (Kirkwood & Westheimer, 1938) through a different method\(^2\). For higher order terms, there does not exist a closed form.

\(^2\)Denoting \(\omega = 1/\varepsilon\), Kirkwood and Westheimer (Kirkwood & Westheimer, 1938) expressed

\[
S(t, \alpha) = \sum_{n=0}^{\infty} \frac{(n+1)}{(n+1)\varepsilon + n} t^n P_n(\alpha) = \omega \sum_{n=0}^{\infty} \frac{(n+1)}{(n+1)\omega + 1} t^n P_n(\alpha)
\]

as

\[
S(t, \alpha) = \omega \frac{\partial}{\partial t} \left[ t^{\omega/(\omega+1)} \int_0^{t^{1/(\omega+1)}} g(s^{1/\omega}, \alpha) \, ds \right].
\]

(B.18)

Series expansion in powers of \(\omega\) of Eq. B.18 gives the same result as Eq. B.17.
B.3 Image methods

The $B_0(r,t)$, $B_{01}(r,t)$ and $R_0(r,t)$ can be casted in terms of the image charge $q_{im}$ of the true charge $q_k$, a method that is widely used in electrostatic studies. Substituting $t$ into Eqs. B.15 and B.16, the $B_0(r,t)$ and $R_0(r,t)$ can be written as

$$B_0(r,t) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{1 - \varepsilon}{\varepsilon} \frac{a q_k}{r_k} \frac{1}{\sqrt{r^2 - 2ar(a^2/r_k) + (a^2/r_k)^2}} = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{q_{im}^B}{|r - r_{im}^B|},$$

(B.19)

and

$$R_0(r,t) = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{1 - \varepsilon}{1 + \varepsilon} \frac{a q_k}{r_k} \frac{1}{\sqrt{r^2 - 2ar(a^2/r_k) + (a^2/r_k)^2}} = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{q_{im}^R}{|r - r_{im}^R|}.$$

(B.20)

Substituting $t$ into Eq. B.17 and neglecting the logarithm part, we obtain

$$B_{01}(r,t) \simeq \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{2 - \varepsilon}{\varepsilon} \frac{a q_k}{r_k} \frac{1}{\sqrt{r^2 - 2ar(a^2/r_k) + (a^2/r_k)^2}} = \frac{1}{4\pi\varepsilon_0\varepsilon_1} \frac{q_{im}^{B_{01}}}{|r - r_{im}^{B_{01}}|}.$$

(B.21)

Simple interpretations exist for these expressions. The potential can be considered to be generated from an image charge located at $(a^2/r_k)\hat{r}$. The magnitude of these
image charges are

\[
q^B_{im} = \frac{1 - \varepsilon}{\varepsilon} \frac{a}{r_k} q_k \quad \text{for } B_0(r, t)
\]

\[
q^R_{im} = \frac{1 - \varepsilon}{1 + \varepsilon} \frac{a}{r_k} q_k \quad \text{for } R_0(r, t)
\]

\[
q^{B_{01}}_{im} = \frac{2 - \varepsilon}{\varepsilon} \frac{a}{r_k} q_k \quad \text{for } B_{01}(r, t)
\]

Of these image methods, it seems that only the \( q^R_{im} \), which is developed by Friedman (Friedman, 1975), is widely used. The reason for these may be due to the fact that series B.5 converges faster than series B.4. This is a little misleading since eventually only the first one or two terms are used. So the quality of approximation of the first two terms are more important than the convergence properties. It is also noted that \( q^R_{im} \) and \( q^{B_{01}}_{im} \) do not give the correct answer when the charge is located in the center of the cavity (Friedman, 1975; Abagyan & Totrov, 1994). In this case the exact solution has a closed form given by the Born formula

\[
W_0 = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} \frac{q_k^2 (1 - \varepsilon)}{a \varepsilon},
\]  

(B.22)

while the image methods \( q^R_{im} \) and \( q^{B_{01}}_{im} \) give

\[
W_0^R = \frac{1}{8\pi \varepsilon_0 \varepsilon_1} \frac{q_k^2 (1 - \varepsilon)}{a \left(1 + \varepsilon\right)},
\]  

(B.23)
and

\begin{equation}
W_{0}^{B_{01}} = \frac{1}{8\pi\varepsilon\varepsilon_{1}} \frac{q_{k}^{2}(2 - \varepsilon)}{a \varepsilon},
\end{equation}

respectively. This is due to the exclusion of the higher order terms. An correction scheme was proposed (Abagyan & Totrov, 1994) which utilizes the fact that the higher order terms have little dependence on the position of the charge. The position independent part of the higher terms, which consists of most of the higher order terms, can be obtained from the difference between the RF energy of the first term and the Born energy. For the image charge method \(q_{im}^{R}\), the correction term is

\begin{equation}
R_{c} = \frac{2(W_{0} - W_{0}^{R})}{q_{k}} = \frac{1}{4\pi\varepsilon\varepsilon_{1}} \frac{q_{k}(1 - \varepsilon)}{a(1 + \varepsilon)},
\end{equation}

and for image charge method \(q_{im}^{B_{01}}\), the correction term is

\begin{equation}
B_{c} = \frac{2(W_{0} - W_{0}^{B_{01}})}{q_{k}} = \frac{1}{4\pi\varepsilon\varepsilon_{1}} \frac{q_{k}}{\varepsilon a}.
\end{equation}

For a system of \(N\) charges, the approximate RF energy is given by

\begin{equation}
W_{im} = \frac{1}{2} \sum_{k} \sum_{l} q_{k} (A_{kl} + A_{c}),
\end{equation}

where \(k\) sums over the \(N\) true charges and \(l\) sums over the \(N\) image charges. \(A_{kl}\) stands for \(B_{0}(r_{k}, t), B_{01}(r_{k}, t)\) or \(R_{0}(r_{k}, t)\), which is the potential generated by the
image charge \( l \). \( A_c \) is the correction term. There is no need for correction for \( B_0(r, t) \).

Since

\[
\sum_k \sum_l q_k q_l = q_t^2,
\]

where \( q_t \) is sum of all true charges, the approximate RF energy can be written as

\[
W_{im} = \frac{1}{2} \sum_{k,l} q_k A_{kl} + F_c q_t^2,
\]

where the correction factor \( F_c \)

\[
F_c = \frac{1}{8 \pi \varepsilon_0 \varepsilon_1 \varepsilon a (1 + \varepsilon)},
\]

for \( q_{im}^R \) image charge method, and

\[
F_c = \frac{1}{8 \pi \varepsilon_0 \varepsilon_1 \varepsilon a},
\]

for \( q_{im}^{Bo} \) image charge method. The correction term is a very effective method to remedy the inaccuracy of the original method. The cost of computation is minimal, since only the total charge of the system is needed. On the other hand, the uncorrected term remains the same, which requires pairwise calculations.
B.4 Limitations of image methods

The image methods provide a conceptually simple device to approximate Kirkwood’s infinite series. But the methods suffer several limitations. Before the use of the correction term, the accuracy is one of the concerns. The accuracy has been improved significantly with the correction term (Abagyan & Totrov, 1994). Besides the inherent limitation of the pairwise nature of these image methods, the other limitation is that they only apply to zero ionic strength, i.e., Eq. B.2. The central multipole method, however, does not focus on $h(n)$. Instead, any $h(n)$ that is physically correct can be used without affecting the formulas

$$W = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{h(n)}{a^{2n+1}} Q_n = \frac{1}{8\pi\varepsilon_0\varepsilon_1} \sum_{n=0}^{\infty} \frac{h(n)}{a^{2n+1}} M^{(n)} \cdot \gamma^{(n)}.$$

The extension to multipole distributions imposes another obstacle for the image charge methods. The image of multipole itself can be obtained by a proper limiting process. Friedman gave the image of a dipole (Friedman, 1975). The image of a dipole consists of one charge and one dipole located at the same position $(a^2/r_k)\hat{r}$. The magnitude of the image charge is given

$$q_{lim}^R = \frac{\varepsilon - 1}{\varepsilon + 1} a(\hat{\mu}_k \cdot \hat{r}_k) r_k^2,$$

3Hill gave an approximation of the effective dielectric constant when the ions are present in the case of $\varepsilon_1 \ll \varepsilon_2$ (Hill, 1956).
the magnitude of the image dipole is given

$$\mu^R_{\text{im}} = \frac{\varepsilon - 1}{\varepsilon + 1} \left( \frac{a}{r_k} \right)^3 \mu_k.$$

The image dipole is coplanar with $\mu_k$ and $r_k$, with $r_k$ bisecting the angle formed by $\mu^R_{\text{im}}$ and $\mu_k$. For a distribution of $N$ dipoles, the image charge methods require $N^2$ calculations of dipole-dipole interactions and $N^2$ calculations of charge-dipole interactions. Including quadrupoles will entail further complexity. Compared to the image methods, the central multipole method provides an efficient and systematic method to calculate the RF energy and derivatives for the multipole distributions.
Appendix C

Explicit formulas for matrix elements

In this appendix an explicit formula is given for the calculation of the elements of $R_{kl}^{(n)}$ (Section 3.2.5), i.e., $D_{k_1,k_2,k_3}^{l_1,l_2,l_3} B_n(r_k,r_l)$, where the operator $D_{k_1,k_2,k_3}^{l_1,l_2,l_3}$ stands for

$$D_{k_1,k_2,k_3}^{l_1,l_2,l_3} = D_k = \frac{\partial^{k_1+k_2+k_3+l_1+l_2+l_3}}{\partial x^{k_1} \partial y^{k_2} \partial z^{k_3} \partial x^{l_1} \partial y^{l_2} \partial z^{l_3}}$$

and the biaxial harmonic $B_n(r_k,r_l)$ between two vectors $r_k$ and $r_l$ is defined as $B_n(r_k,r_l) = r_k^n r_l^n P_n(\cos \gamma_{kl})$. Since the compact form $r_k^n r_l^n P_n(\cos \gamma_{kl})$ is dependent on both $r_k$ and $r_l$, we can use the addition theorem of Legendre polynomials (Hobson, 1931) to expand $r_k^n r_l^n P_n(\cos \gamma_{kl})$ into

$$r_k^n r_l^n P_n(\cos \gamma_{kl}) = r_k^n r_l^n \left( P_n(\cos \theta_k) P_n(\cos \theta_l) \right)$$
\[
+ 2 \sum_{m=1}^{+n} \left( \frac{(n-m)!}{(n+m)!} P_n^m(\cos \theta_k) P_n^m(\cos \theta_l) \right) \cos(\phi_k - \phi_l)
\]

\[
= r_k r_l \left( (P_n^m(\cos \theta_k) P_n^m(\cos \theta_l)
+ 2 \sum_{m=1}^{+n} \left( \frac{(n-m)!}{(n+m)!} P_n^m(\cos \theta_k) P_n^m(\cos \theta_l)(\cos \phi_k \cos \phi_l + \sin \phi_k \sin \phi_l) \right),
\]

where \( P_n^m(\cos \theta) \) is the associated Legendre polynomials. Our task is thus reduced to the calculation of

\[
\frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k} r^n P_n^m(\cos \theta) \cos \phi \quad \text{and} \quad \frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k} r^n P_n^m(\cos \theta) \sin \phi.
\]

From the relations (Hobson, 1931)

\[
r^n P_n^m(\cos \theta) \cos m \phi = \frac{(n+m)!}{2^n m!} \sum_{\alpha=0}^{\left\lfloor \frac{n-m}{2} \right\rfloor} \left( -1 \right)^{\alpha} \frac{n}{2^{2\alpha}} \binom{m}{\alpha} \binom{m+2\alpha}{\alpha} z^{n-m-2\alpha}
\]

\[
\sum_{\beta=0}^{\alpha} \sum_{\gamma=0}^{\left\lfloor \frac{m}{2} \right\rfloor} (-1)^{\gamma} \binom{\alpha}{\beta} \binom{m}{2\gamma} x^{m+2\beta-2\gamma} y^{2\alpha-2\beta+2\gamma},
\]

\[
r^n P_n^m(\cos \theta) \sin m \phi = \frac{(n+m)!}{2^n m!} \sum_{\alpha=0}^{\left\lfloor \frac{n-m}{2} \right\rfloor} \left( -1 \right)^{\alpha} \frac{n}{2^{2\alpha}} \binom{m}{\alpha} \binom{m+2\alpha}{\alpha} z^{n-m-2\alpha}
\]

\[
\sum_{\beta=0}^{\alpha} \sum_{\gamma=0}^{\left\lfloor \frac{m}{2} \right\rfloor} (-1)^{\gamma} \binom{\alpha}{\beta} \binom{m}{2\gamma+1} x^{m+2\beta-2\gamma-1} y^{2\alpha-2\beta+2\gamma+1}.
\]

(C.1)
From Eq. C.1 it can be seen that for $k \leq n-m$

\[
\frac{\partial^k}{\partial z^k} (r^n P^m_n (\cos \theta) \cos m\phi) = \frac{(n+m)!}{(n+m-k)!} r^{n-k} P^m_{n-k} (\cos \theta) \cos m\phi
\]

\[
\frac{\partial^k}{\partial z^k} (r^n P^m_n (\cos \theta) \sin m\phi) = \frac{(n+m)!}{(n+m-k)!} r^{n-k} P^m_{n-k} (\cos \theta) \sin m\phi
\]

\[(C.2)\]

otherwise the derivatives are zero. Thus from Eqs. C.1 and C.2, we have

\[
f^m_n (i, j, k; r) \equiv \frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k} r^n P^m_n (\cos \theta) \cos m\phi
\]

\[= \frac{(n+m)!}{2^m(n-k)!} \sum_{\alpha=0}^{\lfloor \frac{n-m}{2} \rfloor} \frac{(-1)^\alpha}{2^{2\alpha}} \binom{m+2\alpha}{\alpha} \binom{n-k}{m+2\alpha} z^{n-m-k-2\alpha}
\]

\[
\sum_{\beta=0}^\alpha \sum_{\gamma=0}^\beta (-1)^\gamma \binom{\alpha}{\beta} \binom{m+2\beta-2\gamma}{i} \binom{2\alpha-2\beta+2\gamma}{j}
\]

\[\times x^{m+2\beta-2\gamma-i} y^{2\alpha-2\beta+2\gamma-j}\]

\[(C.3)\]

\[
g^m_n (i, j, k; r) \equiv \frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k} r^n P^m_n (\cos \theta) \sin m\phi
\]

\[= \frac{(n+m)!}{2^m(n-k)!} \sum_{\alpha=0}^{\lfloor \frac{m-1}{2} \rfloor} \frac{(-1)^\alpha}{2^{2\alpha}} \binom{m+2\alpha}{\alpha} \binom{n-k}{m+2\alpha} z^{n-m-k-2\alpha}
\]

\[
\sum_{\beta=0}^\alpha \sum_{\gamma=0}^\beta (-1)^\gamma \binom{\alpha}{\beta} \binom{m}{2\gamma+1} \binom{m+2\beta-2\gamma-1}{i} \binom{2\alpha-2\beta+2\gamma+1}{j}
\]

\[\times x^{m+2\beta-2\gamma-1-i} y^{2\alpha-2\beta+2\gamma+1-j}. \]
From these relations we finally get the expression of the matrix elements

\[ D^L_k B_n(r_k, r_l) = f_0^0(\lambda, \mu, \nu; r_k) f_0^0(s, t, u; r_l) \]

\[ + 2 \sum_{m=1}^{w} \frac{(n-m)!}{(n+m)!} [f_m^m(\lambda, \mu, \nu; r_k) f_m^m(s, t, u; r_l) + g_m^m(\lambda, \mu, \nu; r_k) g_m^m(s, t, u; r_l)]. \]
Appendix D

Vector formulas for multipole reaction field

In this Appendix the formulas for the reaction field energy expressed in vector notation are given. We use $W_{n_1 n_2}$ to represent the reaction field energy between $n_1^{th}$ and $n_2^{th}$ degree multipoles at two different sites. $\mathbf{r}_n$ is the vector position of $n^{th}$ degree multipole from the origin of the sphere, and if the energy term involves two multipoles of the same degree, $n$ is omitted. In such cases $\mathbf{r}_i$, $i = 1 \text{ or } 2$ are the position vectors for the two multipoles involved. $\mathbf{\mu}$ is the dipole vector and $\mathbf{s}_1$ and $\mathbf{s}_2$ are two vectors that define the quadrupole. In the case of quadrupole-quadrupole interaction, $s_{ij}$ stands for the $j^{th}$ vector ($j = 1 \text{ or } 2$) of the $i^{th}$ site ($i = 1 \text{ or } 2$). $\hat{\mathbf{r}}$ stands for the unit vector of $\mathbf{r}$. $P_n$ denotes the $n^{th}$ degree Legendre polynomial $P_n(\cos \gamma_{12})$, where $\gamma_{12}$ is the angle between two $\mathbf{r}$ vectors. For the purpose of this Appendix, the ubiquitous factor $1/4\pi\varepsilon_0\varepsilon_1$ is omitted from all equations.
\[ W_{00} = \frac{(1 - \varepsilon)q_1 q_2}{a} \sum_{n=0}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \left(\frac{r_1 r_2}{a^2}\right)^n \]
\[ W_{01} = \frac{(1 - \varepsilon)q \mu}{a^2} \sum_{n=1}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \left[ P'_n(\hat{r}_0 \cdot \hat{\mu}) - P'_{n-1}(\hat{r}_1 \cdot \hat{\mu}) \right] \]
\[ W_{11} = \frac{(1 - \varepsilon)\mu_1 \mu_2}{a^3} \sum_{n=1}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \left(\frac{r_1 r_2}{a^2}\right)^{n-1} \]
\[ \{ P''_n(\hat{r}_1 \cdot \hat{\mu}_2)(\hat{r}_2 \cdot \hat{\mu}_1) - P''_{n-1}[\hat{r}_1 \cdot \hat{\mu}_1](\hat{r}_1 \cdot \hat{\mu}_2) + (\hat{r}_2 \cdot \hat{\mu}_1)(\hat{r}_2 \cdot \hat{\mu}_2) \}
\]
\[ + P''_{n-2}(\hat{r}_1 \cdot \hat{\mu}_1)(\hat{r}_2 \cdot \hat{\mu}_2) + P''_n(\hat{\mu}_1 \cdot \hat{\mu}_2) - 2P''_{n-1}(\hat{r}_1 \cdot \hat{\mu}_1)(\hat{r}_2 \cdot \hat{\mu}_2) \}
\]
\[ W_{02} = \frac{(1 - \varepsilon)q Q}{a^3} \sum_{n=2}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \frac{r_0^{n-2}r_2^{n-2}}{a^{2n-2}} \]
\[ \{ P''_n(\hat{r}_0 \cdot \hat{s}_1)(\hat{r}_0 \cdot \hat{s}_2) - P''_{n-1}(\hat{r}_0 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) + (\hat{r}_0 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_1) \}
\]
\[ + P''_{n-2}(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) - P''_{n-1}(\hat{s}_1 \cdot \hat{s}_2) \}
\]
\[ W_{12} = \frac{(1 - \varepsilon)\mu Q}{a^4} \sum_{n=2}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \frac{r_1^{n-3}r_2^{n-2}}{a^{2n-3}} \]
\[ \{ P'''_n(\hat{r}_2 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2) \]
\[ - P'''_{n-1}[\hat{r}_2 \cdot \hat{\mu}](\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) + (\hat{r}_2 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_1 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2) \]
\[ + P'''_{n-2}[\hat{r}_1 \cdot \hat{\mu}](\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) + (\hat{r}_1 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_2 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) \]
\[ - P'''_{n-3}(\hat{r}_1 \cdot \hat{\mu})(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) \]
\[ + P'''_{n}[(\hat{r}_1 \cdot \hat{s}_1)(\hat{\mu} \cdot \hat{s}_2) + (\hat{r}_1 \cdot \hat{s}_2)(\hat{\mu} \cdot \hat{s}_1)] \]
\[ - P'''_{n-1}[(\hat{r}_2 \cdot \hat{s}_1)(\hat{\mu} \cdot \hat{s}_2) + (\hat{r}_2 \cdot \hat{s}_2)(\hat{\mu} \cdot \hat{s}_1)] + (\hat{s}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{\mu}) \]
\[ + 2((\hat{r}_1 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) + (\hat{r}_1 \cdot \hat{\mu})(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_1)) \]
\[ + P'''_{n-2}[(\hat{r}_1 \cdot \hat{\mu})(\hat{s}_1 \cdot \hat{s}_2) + 4(\hat{r}_1 \cdot \hat{\mu})(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2)] \]
\[ W_{22} = \frac{(1 - \varepsilon) Q_1 Q_2}{a^5} \sum_{n=2}^{\infty} \frac{(n + 1)}{(n + 1) \varepsilon + n} \left( \frac{r_1 r_2}{a^2} \right)^{n-2} \]

\[ \{ P_n^4(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) \]

\[ - P_{n-1}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2))(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2)(\hat{r}_1 \cdot \hat{s}_1)] \]

\[ + P_{n-2}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2) + (\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_2) + A] \]

\[ - P_{n-3}^4 \times B \]

\[ + P_{n-4}^4(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2)(\hat{r}_2 \cdot \hat{s}_2) \]

\[ + P_{n-4}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ - P_{n-5}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ - P_{n-6}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ + P_{n-5}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ + P_{n-6}^4[(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1) + (\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ + (\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ + P_{n-6}^4(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1) + 2A] \]

\[ + P_{n-2}^4(C + 4B) \]

\[ - P_{n-3}^4[D + 8(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]

\[ + P_{n}^4[(\hat{s}_1 \cdot \hat{s}_2)(\hat{s}_1 \cdot \hat{s}_2) + (\hat{s}_1 \cdot \hat{s}_2)(\hat{s}_1 \cdot \hat{s}_2)] \]

\[ - 2P_{n-1}^4 \times C \]

\[ + P_{n-2}^4[(\hat{s}_1 \cdot \hat{s}_1)(\hat{s}_1 \cdot \hat{s}_1) + 4D + 8(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_1 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)(\hat{r}_2 \cdot \hat{s}_1)] \]
\[-2P_{n-1}'(\hat{s}_{11} \cdot \hat{s}_{12})(\hat{s}_{21} \cdot \hat{s}_{22})\] 

\[A = (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_1 \cdot \hat{s}_{21})(\hat{r}_2 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_2 \cdot \hat{s}_{12})(\hat{r}_1 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_1 \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{21})
\]

\[B = (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_2 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_1 \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{12}) + (\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_1 \cdot \hat{s}_{22})(\hat{r}_1 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_2 \cdot \hat{s}_{22})(\hat{r}_1 \cdot \hat{s}_{21})
\]

\[C = (\hat{r}_1 \cdot \hat{s}_{11})(\hat{s}_{12} \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{s}_{12} \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{21}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{s}_{12} \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{s}_{12} \cdot \hat{s}_{22})(\hat{r}_2 \cdot \hat{s}_{21})
\]

\[D = (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_2 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{11})(\hat{r}_1 \cdot \hat{s}_{22})(\hat{r}_1 \cdot \hat{s}_{22}) + (\hat{r}_1 \cdot \hat{s}_{12})(\hat{r}_1 \cdot \hat{s}_{22})(\hat{r}_1 \cdot \hat{s}_{22})
\]

In the following an outline of the derivation for the energy \(W_{01}\) is presented. From Figure D.1 we have \(r'_1 = r_1 + d\), so

\[r'_1 = [r_1^2 + d^2 + 2(r_1 \cdot d)]^{\frac{1}{2}}\]

and

\[\left(\hat{r}_0 \cdot \hat{r}'_1\right) = \frac{(\hat{r}_0 \cdot r'_1)}{r'_1} = \frac{\hat{r}_0 \cdot (r_1 + d)}{r'_1} = \frac{r_1(\hat{r}_0 \cdot \hat{r}_1) + d(\hat{r}_0 \cdot \hat{m})}{r'_1}\]

Combining eqs 3.2 and 3.3 and substituting \(q = \mu/d\), then using L’Hospital’s rule to take the limit as \(d\) goes to zero while keeping \(\mu\) constant, we get \(W_{01}\). Other \(W_{ij}\) can be derived in a similar way.
The multipole of a given site can interact with itself, or with multipoles of different degrees at the same site. We denote by $W'_{ij}$ the reaction field energy between $n_1^{th}$ and $n_2^{th}$ degree multipoles at the same sites. $W'_{ij}$ can be considered as a special case of $W_{ij}$. From the generating function of Legendre polynomials,

$$
\frac{1}{(1 - 2xt + t^2)^2} = \sum_{n=0}^{\infty} P_n(x)t^n
$$

it can be easily derived that

$$P_n^{(m)}(1) = \frac{1}{2^m} \frac{(n + m)!}{(n - m)!m!}$$

$W'_{ij}$ is then obtained using the expression for $P_n^{(m)}(1)$ and the previously derived $W_{ij}$. When the degree of the multipoles is the same, a constant factor of 2 is removed. Since only one site is involved, the subscript on $r$ is omitted.

$$W'_{00} = \frac{1 - \varepsilon}{2a} \sum_{n=0}^{\infty} \frac{(n + 1)}{(n + 1)\varepsilon + n} \left( \frac{r_1}{a} \right)^{2n}$$
\[ W'_{01} = \frac{(1 - \varepsilon)q\mu}{a^2} \sum_{n=1}^{\infty} \frac{n(n+1)}{(n+1)\varepsilon + n \left( \frac{r}{a} \right)^2} \left( \hat{r} \cdot \hat{\mu} \right) \]

\[ W'_{02} = \frac{(1 - \varepsilon)qQ}{2a^3} \sum_{n=2}^{\infty} \frac{(n-1)n(n+1)}{(n+1)\varepsilon + n \left( \frac{r}{a} \right)^2} \left[ 3(\hat{r} \cdot \hat{s}_1)(\hat{r} \cdot \hat{s}_2) - (\hat{s}_1 \cdot \hat{s}_2) \right] \]

\[ W'_{11} = \frac{(1 - \varepsilon)\mu^2}{4a^3} \sum_{n=1}^{\infty} \frac{n(n+1)}{(n+1)\varepsilon + n \left( \frac{r}{a} \right)^2} \left[ (n+1) + (n-1)(\hat{r} \cdot \hat{\mu})^2 \right] \]

\[ W'_{12} = \frac{(1 - \varepsilon)\mu Q}{2a^4} \sum_{n=2}^{\infty} \frac{(n-1)n(n+1)}{(n+1)\varepsilon + n \left( \frac{r}{a} \right)^2} \{ (n+1)(n+2) \} \]

\[ W'_{22} = \frac{(1 - \varepsilon)Q^2}{16a^5} \sum_{n=2}^{\infty} \frac{(n-1)n(n+1)}{(n+1)\varepsilon + n \left( \frac{r}{a} \right)^2} \{ (n+1)(n+2) \} \]

\[ + 3(n+1)(n-2)[(\hat{r} \cdot \hat{s}_1)^2 + (\hat{r} \cdot \hat{s}_2)^2] + 3(n-2)(n-3)(\hat{r} \cdot \hat{s}_1)^2(\hat{r} \cdot \hat{s}_2)^2 \]

\[ + 2n(n-1)(\hat{s}_1 \cdot \hat{s}_2)^2 - 4(n-1)(n-2)(\hat{r} \cdot \hat{s}_1)(\hat{r} \cdot \hat{s}_2)(\hat{s}_1 \cdot \hat{s}_2) \]
Appendix E

Preliminary results of the central multipole method

In this Appendix some preliminary results will be given for the timing of the central multipole method (Chapter 3). In Figure E.1 the timing for the calculation of energy and energy plus first derivative of four systems consisting of 1000, 2000, 10000, and 20000 random interaction sites are shown. In each calculation up to $n = 20$ is used in the infinite series (Eq. 3.2). It is clear that in both situations the time increases linearly with the size of the system. In Figure E.2 the timing as a function of $n$ (the running index of the infinite series), for two systems (10000 sites and 20000 sites, respectively) is given. The time for energy calculations are scaled by a factor of 25 for the system of 10000 sites and 26 for the system of 20000 sites to make them in the same scale as the time for energy plus first derivative calculations. As discussed in the Section 3.4, the time does not scale linearly with $n$ for a given system. The
timing for energy plus derivative deviates more discernibly from linearity than that for energy. The reason for this is that more time will be spent on the transformation of the two central multipoles (Appendix F).

Figure E.1: Timing for the central multipole method. Up to $n = 20$ is calculated in the infinite series (Eq. 3.2). Four systems consisting of 1000, 2000, 10000, and 20000 interaction sites are used. The time is in the unit of second.
Figure E.2: Timing as a function of \( n \), the calculated terms in the infinite series (Eq. 3.2), for two systems of 10000 and 20000 sites. The time for energy calculations are scaled by a factor of 25 for the system of 10000 sites and 26 for the system of 20000 sites to make them in the same scale as the time for energy plus first derivative calculations. The time is in the unit of second.
Appendix F

Transformation from $M^{(n)}$ to $Y^{(n)}$

In this Appendix a detailed scheme is given for transformation from $M^{(n)}$ to $Y^{(n)}$ (Chapter 3, Section 3.3). This transformation applies not only to arbitrary charge distributions, it also applies to multipole distributions as well as the derivatives, as indicated in Chapter 3. As discussed in Section 3.3, there are $(m+1)(m+2)/2$ unique components for $M^{(n)}$, and for each $M^{(n)}_{stu}$ the degeneracy is $n!/(s!t!u!), s + t + u = n$. To get a general transformation from $M^{(n)}$ to $Y^{(n)}$, we have to have a system to label these $(m+1)(m+2)/2$ components. In the next section a method that has been implemented will be described.

F.1 A system to label $M^{(n)}$ and $Y^{(n)}$

For $n$th order multipole there are $3^n$ components. Since we use sometimes up to $n = 20$ or more terms (States & Karplus, 1987) for large systems to achieve convergence,
we need a method to label these components systematically. The system to label
the multipole components is not unique. In the following the method that has been
implemented in TINKER modeling package will be described. In this system the
index $j$ of the $y$ component of the multipole changes first, followed by $x$ component
index $i$. The $i$ goes from 0 to $n$, and $j$ goes from 0 to $n-i$. The $z$ component index $k$
is determined by $i + j + k = n$. For example, for $n = 3$ the components will arrange
in an array like

<table>
<thead>
<tr>
<th>component index</th>
<th>i</th>
<th>j</th>
<th>k</th>
<th>degeneracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

If we denote $p = \text{the position of the multipole specified by } \{i, j, k\}$ in the array
beginning from 1, it is easy to verify that

$$p = \sum_{q=0}^{i-1} (n + 1 - q) + j + 1 = \frac{1}{2} (2n + 3 - i)i + j + 1,$$

(F.1)
so for a given multipole \{i, j, k\} its position can be easily found in the array. On the other hand, from the multipole component’s position in the array we can also get the exponents i, j, and k uniquely. Given any p, the exponent i is the smallest integer that makes

\[ p - \sum_{q=0}^{i} (n+1-q) = \frac{1}{2}i^2 - (n + \frac{1}{2})i + p - n - 1 \leq 0, \quad (F.2) \]

which gives

\[ i = \left\lceil n + \frac{1}{2} - \sqrt{\frac{(2n+3)^2 - 8p}{2}} \right\rceil. \quad (F.3) \]

The function \(\lceil x \rceil\) is the ceiling function of \(x\), which gives the smallest integer greater than or equal to \(x\). The value of \(j\) can be obtained from

\[ j = p - 1 - \sum_{q=0}^{i-1} (n+1-q) = \frac{1}{2}i^2 - (n + \frac{3}{2})i + p - 1 \quad (F.4) \]

once the value of \(i\) is determined.

**F.2 Transformation from \(\mathcal{M}^{(n)}\) to \(\mathcal{Y}^{(n)}\)**

From the definition of \(\mathcal{M}^{(n)}\) and \(\mathcal{Y}^{(n)}\), we can transform \(\mathcal{M}^{(n)}\) to \(\mathcal{Y}^{(n)}\) either analytically or explicitly. If we denote \(A^{(n)}\) as the \([ (n+1)(n+2)/2 \times (n+1)(n+2)/2 ]\) matrix,
that transforms $\mathcal{M}^{(n)}$ to $\mathcal{Y}^{(n)}$,

$$\mathcal{Y}^{(n)} = A^{(n)} \mathcal{M}^{(n)},$$

where we write $\mathcal{M}^{(n)}$ and $\mathcal{Y}^{(n)}$ as vectors in the order described in Section F.1, then for $n = 0$, $A^{(0)}$ is a scalar 1. For $n = 1$, $A^{(1)}$ is a $3 \times 3$ identity matrix. For $n = 2$,

$$A^{(2)} = \begin{bmatrix}
1 & 0 & -1/2 & 0 & 0 & -1/2 \\
0 & 3/2 & 0 & 0 & 0 & 0 \\
-1/2 & 0 & 1 & 0 & 0 & -1/2 \\
0 & 0 & 0 & 3/2 & 0 & 0 \\
0 & 0 & 0 & 0 & 3/2 & 0 \\
-1/2 & 0 & -1/2 & 0 & 0 & 1
\end{bmatrix}.$$  

It has been noticed that for $n > 1$, $A^{(n)}$ is singular, i.e., its determinant vanishes.

We can try to calculate the elements of $A_n(i,j)$ in closed forms. The matrix $A^{(n)}$ has a general form of

$$A^{(n)} = \begin{bmatrix}
A^{(n)}_{n+1} & 0 & B^{(n)}_{(n+1) \times (n-1)} & 0 & B^{(n)}_{(n+1) \times (n-3)} & \cdots \\
0 & A^{(n)}_n & 0 & B^{(n)}_{n \times (n-2)} & 0 & \cdots \\
B^{(n)}_{(n-1) \times (n+1)} & 0 & A^{(n)}_{n-1} & 0 & B^{(n)}_{(n-1) \times (n-3)} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots
\end{bmatrix}.$$
The main diagonal is partitioned into \( n + 1 \) square matrices with dimensions \((n+1) \times (n+1), n \times n, \ldots, 1\), which we can denote as \( A_{n+1}^{(n)}, A_{n+1}^{(n)}, \ldots, A_1^{(n)} \). The matrix \( A^{(n)} \) is a sparse matrix. The diagonal elements of the top-left \((n+1) \times (n+1)\) block \( A_{n+1}^{(n)} \) can be written as

\[
\begin{align*}
A_{n+1}^{(n)}(1,1) &= 1 \\
A_{n+1}^{(n)}(2,2) &= \frac{n + 1}{2} \\
A_{n+1}^{(n)}(3,3) &= \frac{3n^2 + n + 2}{16} \\
A_{n+1}^{(n)}(4,4) &= \frac{5n^3 - 6n^2 + n + 12}{96} \\
A_{n+1}^{(n)}(5,5) &= \frac{35n^4 - 130n^3 + 121n^2 + 70n + 216}{3072} \\
A_{n+1}^{(n)}(6,6) &= \frac{63n^5 - 455n^4 + 1055n^3 - 625n^2 - 38n + 2160}{30720} \\
\end{align*}
\]

\( \cdots \) \quad \text{(F.5)}

then comes next \( n \times n \) diagonal block \( A_n^{(n)} \), etc., until it reaches the bottom-right corner \( A_1^{(n)} \), which has a single element 1. The elements of all other off-diagonal blocks can be generated by a similar way. The matrices \( A_i^{(n)} \) and \( B_{i \times j}^{(n)} \) themselves are in turn sparse matrices, with at most\(^1\) \([a \, b/2]\) nonzero elements, where \( a \) and \( b \) are the dimensions of the block. In fact the upper limit for the number of nonzero

\(^1\text{It occurs to some of the matrix elements of a given } A^{(n)} \text{ to be cancelled in the positions where the corresponding elements in other matrices do not vanish, such as } A^{(7)}(4,17) \text{ and } A^{(12)}(4,80), \text{ so the actual number of the nonzero elements for a given } A^{(n)} \text{ is sometimes smaller than the upper limit given by Eqs. F.7 or F.8. For } n \text{ from 0 to 20, this happens only when } n = 7, 12, 17.\)
elements is given by

\[ u(A^{(n)}) = \sum_{i=0}^{n} \sum_{j=0}^{n} \left( \frac{(2i + 1)(2j + 1)}{2} \right) + 2 \sum_{i=1}^{n+1} \sum_{j=1}^{n+1} ij, \quad (F.6) \]

which gives to

\[ u(A^{(n)}) = \frac{1}{16} (n + 2)^2 (n^2 + 2n + 4) \quad (F.7) \]

for even \( n \) and

\[ u(A^{(n)}) = \frac{1}{16} (n + 1)^2 (n^2 + 4n + 7) \quad (F.8) \]

for odd \( n \). Eqs F.7 and F.8 can be easily verified by induction from Eq. F.6.

As discussed in Chapter 3, the number of unique components of \( Y^{(n)} \) is \( 2n + 1 \), so we do not need the whole square matrix \( A^{(n)} \) to get \( Y^{(n)} \) from \( M^{(n)} \). What we actually need is the upper \((2n + 1) \times (n+1)(n+2)/2\) submatrix of \( A^{(n)} \), i.e.

\[
A_s^{(n)} = \begin{bmatrix}
A^{(n)}_{n+1} & 0 & B^{(n)}_{(n+1)\times(n-1)} & 0 & B^{(n)}_{(n+1)\times(n-3)} & \cdots \\
0 & A^{(n)}_n & 0 & B^{(n)}_{n\times(n-2)} & 0 & \cdots 
\end{bmatrix}.
\]

The number of nonzero elements of \( A_s^{(n)} \) is given by

\[ u(A_s^{(n)}) = \frac{1}{8} (n + 2)(2n^2 + 3n + 4) \quad (F.9) \]
for even $n$ and

$$u(A^{(n)}) = \frac{1}{8}(n + 1)(2n^2 + 5n + 5)$$ (F.10)

for odd $n$.

Since approximately one-fourth of the matrix elements are nonzero, in actual implementation we used separate codes for different $A^{(n)}$ instead of using a general formula that fits for any $n$. A MAPLE (Char et al., 1992) program was written to generate $A^{(n)}$ for each $\mathcal{M}^{(n)}$ up to $n = 30$. 
Bibliography


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