CHAPTER 9

FORMALISMS FOR THE EXPLICIT INCLUSION OF ELECTRONIC POLARIZABILITY IN MOLECULAR MODELING AND DYNAMICS STUDIES

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Abstract: Current methodologies for modelling electronic polarization effects in empirical force fields are presented. Emphasis is placed on the mathematical details of the methods used to introduce polarizability, namely induced dipoles, Drude oscillators or fluctuating charge. Overviews are presented on approaches used to damp short range electrostatic interactions and on Extended Langrangian methods used to perform Molecular Dynamics simulations. The final section introduces the polarizable methods under development in the context of the program CHARMM

Keywords: Empirical force field, Electronic polarization, Polarizability, Force field, Inducible dipoles, Drude oscillators, Fluctuating charge, Molecular dynamics, CHARMM

9.1.   INTRODUCTION

Molecular mechanical (MM) force fields (FF) are widely used in molecular modeling studies of systems with thousands on up to millions of atoms. To date they have proved to be surprisingly accurate in many applications despite their simplified functional forms. This accuracy is, to some extent surprising, due to the number of approximations in FFs, the biggest of which is typically the method by which the charge distribution of the molecules is treated. In additive force fields, which represents the bulk of current FFs [1, 2] this is done by assigning partial fixed charges to the atoms, thus creating a force field whose electrostatic properties are not capable of reacting to changes in the environment. Additive force fields common for biomolecular simulations [3–6] share the same general functional form:

$$U = U_{bond} + U_{LJ} + U_{elect} \tag{9-1a}$$

$$U_{elect} = \sum_{i=1}^{N} \sum_{j \neq i} \frac{q_i q_j}{r_{ij}} \tag{9-1b}$$

where U_{bond} (**r**) represents the bonded terms (bonds, angles, dihedrals, etc), U_{LJ} (**r**) represents the van der Waals (vdW) interactions and is typically treated as a 6–12 Lennard-Jones (LJ) term and U_{elect} (**r**) is the electrostatic term of the Coulomb form (Eq. 9-1b). In recent years it has became that the additive treatment of electrostatic interactions is limiting and that electronic polarization will play a central role in the next generation of force fields for molecular simulations, including both molecular dynamics (MD) and Monte Carlo (MC) methods [7–9]. Accordingly, much effort is being devoted to the development of methods and parameters required for the implementation of polarizable force fields.

In nature, the charge distribution of a molecule can be significantly influenced or 'polarized' by its surroundings, a phenomenon that may be included in FFs via the explicit inclusion of electronic polarizability. A large motivating factor towards polarizable force fields is the fact that it is increasingly important to simulate heterogeneous environments, which requires that a given model is able to provide an environment-dependent response. For example, it is commonly accepted that modeling a water molecule with fixed point charges is not adequate to simultaneously describe bulk water molecules as well as water in highly hydrophobic environments [10, 11]. This is more critical if it is considered that a given molecule may visit these environments within the course of a single simulation. Therefore, the inclusion of molecular polarizability seems a basic requirement in order to develop force fields suitable for a wide range of hetergeneous environments.

Electronic polarizability is often included in force fields via the use of induced dipoles. Assuming that hyperpolarization effects are absent, the induced dipoles respond linearly relative to the electric field. In this case, the induced dipole **μ** on an atom is the product of the total electric field **E** and the atomic polarizability tensor **α**.

$$\boldsymbol{\mu} = \boldsymbol{\alpha} \cdot \mathbf{E} \tag{9-2}$$

The total electric field, **E**, is composed of the external electric field from the permanent charges $\mathbf{E}^0$ and the contribution from other induced dipoles. This is the basis of most polarizable force fields currently being developed for biomolecular simulations. In the present chapter an overview of the formalisms most commonly used for MM force fields will be presented. It should be emphasized that this chapter is not meant to provide a broad overview of the field but rather focuses on the formalisms of the induced dipole, classical Drude oscillator and fluctuating charge models and their development in the context of providing a practical polarization model for molecular simulations of biological macromolecules [12–21]. While references to works in which the different methods have been developed and applied are included throughout the text, the major discussion of the implementation of these models focuses

on efforts in the context of the program CHARMM. For additional information the reader is referred to issue 6 of volume 3 of the Journal of Chemical Theory and Computation which was a "Special Issue on Polarization."

9.2. METHODS TO INCLUDE POLARIZATION IN CLASSICAL FORCE FIELDS

9.2.1. Induced Dipoles

One method for treating polarizability is the assignment of both partial atomic charges and induced dipoles on the atoms in a molecule. In its most common implementation in biomolecular simulations, inducible point dipoles are added to some or all atomic sites in the molecule [22–25]. An alternative methodology proposed by Allinger and co-workers is the use of bond dipoles [26].

The dipole moment, $\boldsymbol{\mu}_i$, induced on a site i is proportional to the electric field at that site, $\mathbf{E}_i$. The proportionality constant is the polarizability tensor, $\boldsymbol{\alpha}_i$. The dipole feels an electric field both from the permanent charges of the system and from the other induced dipoles. The expression for $\boldsymbol{\mu}_i$ is

$$\boldsymbol{\mu}_i = \boldsymbol{\alpha}_i \cdot \mathbf{E}_i = \boldsymbol{\alpha}_i \cdot \left[\mathbf{E}_i^0 - \sum_{j \neq i} \mathbf{T}_{ij} \boldsymbol{\mu}_j \right] \tag{9-3}$$

where $\mathbf{E}_i^0$ is the field from the permanent charges. (Note that permanent dipoles or higher multipoles, when present, contribute to $\mathbf{E}^0$.) The induced dipoles interact through the dipole field tensor, $\mathbf{T}_{ij}$

$$\mathbf{T}_{ij} = \frac{1}{r_{ij}^3} \left[\mathbf{I} - 3\frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2} \right] \tag{9-4}$$

where $\mathbf{I}$ is the identity matrix, $\mathbf{r}$ is the distance between i and j, and x, y, and z are the Cartesian components of the vector between i and j.

The inducing field responsible for the energy of the induced dipoles, U_{ind}, has contributions from three terms: the permanent or static field, U_{stat}, the induced dipole–induced dipole interaction, U_{dip}, and the polarization energy, U_{pol},

$$U_{ind} = U_{stat} - U_{dip} - U_{pol} \tag{9-5}$$

The energy U_{stat} is the interaction energy of the N induced dipoles with the static electric field,

$$U_{stat} = -\sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \mathbf{E}_i^0, \tag{9-6}$$

the energy U_{dip} represents the induced dipole–induced dipole interaction via the dipole field tensor, $\mathbf{T}_{ij}$

$$U_{elect} = \frac{1}{2} \sum_{i=1}^{N} \sum_{j \neq i} \boldsymbol{\mu}_i \cdot \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j \tag{9-7}$$

and the polarization energy, U_{pol},

$$U_{pol} = \frac{1}{2} \sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \mathbf{E}_i \tag{9-8}$$

is defined as the energy cost needed to induce the dipoles [22, 27]. By using Eq. (9-3) the electric field can be replaced by $\boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i$, and U_{pol} becomes

$$U_{pol} = \frac{1}{2} \sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i \tag{9-9}$$

where $\boldsymbol{\alpha}_i^{-1}$ is the inverse of the polarization tensor. All polarizable models in which dipole moments, charges, or other multipoles can be modified by their environment will have a polarization term corresponding to U_{pol}. Inserting the expressions for U_{stat}, U_{elect} and U_{pol} into Eq. (9-5) yields

$$U_{ind} = \sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \left[-\mathbf{E}_i^0 + \frac{1}{2} \sum_{j=i} \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j + \frac{1}{2} \mathbf{E}_i \right] \tag{9-10}$$

and using the relationship of Eq. (9-3) ($\mathbf{E}_i = \mathbf{E}_i^0 - \sum \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j$), reduces the dependence of U_{ind} to a function of the static field, $\mathbf{E}^0$,

$$U_{ind} = -\frac{1}{2} \sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \mathbf{E}_i^0 \tag{9-11}$$

It is noteworthy that the induced energy is the dot product of the induced dipole and the static field and not the total field. The interpretation of Eq. (9-11) is that a static field is required to originate induced dipoles.

Interesting properties of the induced dipole polarizable model can be derived by simple mathematical manipulation. A particularly important one relates the minimum of the energy with converged values of the induced dipole. By combining Eqs. (9-9) and (9-10), the induction energy can be rewritten as

$$U_{ind} = -\sum_{i=1}^{N} \boldsymbol{\mu}_i \cdot \mathbf{E}_i^0 + \frac{1}{2} \sum_{i=1}^{N} \sum_{j \neq i} \boldsymbol{\mu}_j \cdot \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j + \frac{1}{2} \sum_{i=1}^{N} \boldsymbol{\mu}_j \cdot \boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i \qquad (9\text{-}12)$$

and the derivative of U_{ind} with respect to the induced dipoles is

$$\nabla_{\boldsymbol{\mu}_i} U_{ind} = -\mathbf{E}_i^0 + \sum_{j \neq i} \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j + \boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i = 0 \qquad (9\text{-}13)$$

Taking into consideration Eq. (9-3), makes the derivative in Eq. (9-13) zero because $\boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i = \mathbf{E}_i^0 - \sum \mathbf{T}_{ij} \cdot \boldsymbol{\mu}_j$. The converged values of the induced dipoles are those that minimize the energy. Consecutive (iterative) adjustments of $\boldsymbol{\mu}_i$ are referred to as self-consistent field (SCF) calculations and represent a systematic optimization of the polarization degrees of freedom to attain values of those degrees of freedom that minimize the energy. More details are presented in Section 9.4. Other polarizable models also have auxiliary variables, analogous to $\boldsymbol{\mu}$, which are adjusted to minimize the energy in similar ways.

An approximation to the induced point dipole model that uses induced charges was proposed by Ferenczy and Reynolds [28–36]. This induced charge method involves point charges only and those depend on the environment. In this sense the method is related to the fluctuating charge model (see below). It is based on the idea of representing a series of multipole moments by several lower rank multipole moments on neighboring sites (e.g. representing a dipole by two individual monopoles) [29, 30, 37, 38]. Such a model was shown to be efficient in accounting for electrostatic interactions, and preliminary extensions to polarization using point charges have been described [32, 34]. The method shares similarities with the approaches of Zhu et al. [39] and Sprik [15] but without the requirements for a regular geometry or a molecular dynamics implementation, respectively. The method was systematically extended so that both the polarization energy and its derivatives can be determined.

More recently, Ponder and co-workers [40–48] developed the AMOEBA force field based on a modification of the formulation of Applequist [49] and Thole [50]. It is based on a modification of Eq. (9-3) with the static electric field due to permanent charges replaced by permanent multipoles:

$$\boldsymbol{\mu}_i = \boldsymbol{\alpha}_i \cdot \mathbf{E}_i = \boldsymbol{\alpha}_i \cdot \left[\sum_{j \neq i} \mathbf{T}_{ij}^{\alpha} \mathbf{M}_j + \sum_{k \neq i} \mathbf{T}_{ik}^{\alpha\beta} \boldsymbol{\mu}_k \right] \qquad (9\text{-}14)$$

where $\mathbf{M}(M_i = (q_i, \mu_{i,x}, \mu_{i,y}, \mu_{i,z}, Q_{i,xx}, Q_{i,xy}, Q_{,xz} \cdots Q_{i,zz})^T)$ is the vector of permanent atomic multipole components, up to quadrupole, and $\mathbf{T}$ is the interaction matrix, defined previously.

In the AMOEBA force field the "permanent" atomic multipoles are determined from QM calculations [40]. The prescription considers that the resulting multipoles on the atoms result from two components, the "permanent" and the "induced" moments:

$$\mathbf{M}_i = \mathbf{M}_i^{perm} + \mathbf{M}_i^{ind} \tag{9-15}$$

$\mathbf{M}_i^{ind}$ results from induction from all sites in the absence of an external field and is defined by an expression similar to Eq. (9-3)

$$\mathbf{M}_{i,\alpha}^{ind} = \alpha_i \cdot \left[\sum_{j \neq i} \mathbf{T}_{ij}^\alpha \mathbf{M}_j^{perm} + \sum_{k \neq i} \mathbf{T}_{ik}^\alpha \mathbf{M}_k^{ind} \right] \tag{9-16}$$

Substituting Eq. (9-15) into Eq. (9-16) results in

$$\mathbf{M}_{i,\alpha}^{ind} = \alpha_i \cdot \left[\sum_{j \neq i} \mathbf{T}_{ij}^\alpha \left(\mathbf{M}_j - \mathbf{M}_j^{ind} \right) + \sum_{k \neq i} \mathbf{T}_{ik}^\alpha \mathbf{M}_k^{ind} \right]. \tag{9-17}$$

In the case $j = k$, Eq. (9-17) simplifies greatly and becomes

$$\mathbf{M}_{i,\alpha}^{ind} = \alpha_i \sum_{j \neq i} \mathbf{T}_{ij}^\alpha \mathbf{M}_j \tag{9-18}$$

Otherwise, if $j \neq k$ and after rearrangement and introduction of different fractional scaling factors the following equation results:

$$
\begin{aligned}
\mathbf{M}_{i,\alpha}^{ind} &= \alpha_i \cdot \left[\sum_{Allsites} s_j^p \mathbf{T}_{ij}^\alpha \left(\mathbf{M}_j - \mathbf{M}_j^{ind} \right) + \sum_{Allsites} s_j^m \mathbf{T}_{ik}^\alpha \mathbf{M}_k^{ind} \right] \\
&= \alpha_i \cdot \left[\sum_{Allsites} s_j^p \mathbf{T}_{ij}^\alpha \mathbf{M}_j + \sum_{Allsites} \left(s_j^m - s_j^p \right) \mathbf{T}_{ij}^\alpha \mathbf{M}_j^{ind} \right]
\end{aligned} \tag{9-19}
$$

The scaling factor s_j can take any value between 0 and 1 and is applied to site j. The superscripts p and m indicate permanent and mutual induction, respectively. Equation (9-19) can be solved iteratively using similar procedures to those used to solve Eq. (9-3). The formal "permanent" moments can be calculated by subtracting induced moments from moments from ab initio calculations. For any conformation of a given compound the atomic multipoles can be determined from Distributed Multipole Analysis (DMA) [51].

Calculation of the energy and forces acting on a molecular system requires knowledge of the magnitude of the inducible dipoles. The forces associated with the dipoles (spatial derivatives of the potential) [13], can be computed from Eq. (9-12), and on atomic site k are

$$F_k = -\nabla U_{ind} = \sum_{i=1}^N \mu_i \nabla_k E_i^0 + \frac{1}{2} \sum_{i=1}^N \mu_i \cdot \sum_{j=1}^N \left(\nabla_k T_{ij} \right) \cdot \mu_j \tag{9-20}$$

All contributions to the forces from terms involving derivatives with respect to the dipoles are zero because of the condition in Eq. (9-13) [13, 52]. Attaining this condition is a necessary prerequisite for using induced dipoles, or any electronic polarization, in force field calculations.

The electric field that each dipole feels depends on all other induced dipoles requiring the use of a self-consistent method as mentioned above. To achieve this, Eq. (9-13) can be rearranged and written in matrix form considering that $\mathbf{A} = \boldsymbol{\alpha}^{-1} (\mathbf{I} - \boldsymbol{\alpha} \mathbf{T})$,

$$\mathbf{A} \cdot \boldsymbol{\mu} = \mathbf{E}^0 \tag{9-21}$$

The diagonal elements of the matrix $\mathbf{A}_{ii}$ are $\boldsymbol{\alpha}_i^{-1}$ and the off-diagonal elements of $\mathbf{A}_{ij}$ are $\mathbf{T}_{ij}$. Equation (9-21) determines how the dipoles are coupled to the static electric field. There are three major methods to determine the dipoles: matrix inversion, iterative methods and predictive methods.

The system in Eq. (9-21) can be solved with direct matrix inversion. Bernardo et al. [53] found the method more robust but significantly slower than the iterative procedure. For a system with N dipoles, solving for each of them involves inverting the $N \times N$ matrix, A – an $O(N^3)$ operation that is typically much more computationally expensive to perform at each step of a $O(N)$ or $O(N^2)$ molecular dynamics simulation and this method has been used very rarely [53]. In the iterative method, the left-hand side of the Eq. (9-3) is calculated by substituting an initial guess for $\boldsymbol{\mu}$ into the right-hand side, and then the cycle is repeated until the desired level of self-consistency is achieved [52, 54, 55]. Both matrix inversion and iterative methods may be used in the SCF calculation to determine the induced dipoles following which the energies, forces as well as second and higher order derivatives acting on the molecular system may be determined. Such information is necessary for energy minimizations and molecular dynamics (MD) simulations. However, the requirement of computational accessibility allowing for MD simulations of large molecular systems requires special considerations when electronic polarizability is included in the model. These will be discussed below in Section 9.4.

9.2.2.   Classical Drude Oscillator Model

The models discussed in the previous section treat the polarization on each polarizable center using point dipoles. An alternative approach is to model the polarizable centers using dipoles of finite length, represented by an explicit pair of point charges. A variety of different models of polarizability have used this approach, but especially noteworthy are the Drude models (also known as "shell" or "charge on spring" models) frequently used in simulations of solid state ionic materials and recently extended to water and organic compounds [10, 11, 56–65]. Efforts in our laboratory are aimed at developing a classical Drude model based polarizable force field for biological macromolecules (see Section 9.5).

The Drude model can trace its origins to the work of Paul Drude in 1902 and was developed as a simple way to describe the dispersive properties of materials [66]. In the classical formalism, it represents electronic polarization by introducing a massless charged particle attached to each polarizable atom by a harmonic spring. The positions of these "auxiliary" particles are then adjusted self-consistently to their local energy minima for any given configuration of the atoms in the system. A quantum version of the model has been used in early applications to describe the dipole–dipole dispersion interactions [67–70]. A semiclassical version of the model was used more recently to describe molecular interactions [71], and electron binding [72]. The classical version of the model has been quite useful in statistical mechanical studies of dense systems and in recent decades has seen widespread use in MD and MC simulations. Examples of applications include ionic crystals [73–78], simple liquids of polarizable particles [63, 64, 79–83], liquid water [10, 11, 56, 84–87], and the hydration of small ions [61, 88]. In recent years, the Drude model was extended to interface with QM approaches for use in QM/MM methods [89].

A particularly attractive aspect of the Drude oscillator model is that it preserves the simple charge–charge Coulomb electrostatic interactions to treat polarizability and, therefore, may be implemented in standard biomolecular simulation programs in a relatively straightforward way. Despite this technical advantage, Drude oscillators have not been as widely used as the point dipole or charge transfer models, probably because of the difficulties designing efficient computational schemes to solve the fast motion of the auxiliary particles in MD simulations [56]. In contrast with the point dipole [90] and fluctuating charge models [17, 91], extended Lagrangian algorithms have only recently been implemented [12], as discussed below in Section 9.4. Prior to this applications of the Drude model to liquids usually used computationally costly direct SCF iterative schemes.

In the classical Drude polarizable model polarization is determined by a pair of point charges separated by a variable distance $\mathbf{d}$. For a given atom with charge q a mobile Drude particle (also referred to as a Drude oscillator in the text) carrying a charge q_D is introduced. The charge on the parent atom is replaced by $q - q_D$ in order to preserve the net charge of the atom–Drude oscillator pair. The Drude particle is harmonically bound to the atomic particle with a force constant k_D. Thus, the Drude model can be described as consisting of an effective nuclear charge and a charge in the valence shell responsible for most of the polarization of the atom. The mathematical formulation of the Drude model is in fact an empirical method of representing the dipolar polarization of the site when $\|\mathbf{d}\| \to 0$.

In the absence of an electric field, the Drude particle coincides with the position of the atom, $\mathbf{r}$, and the atom appears as a point charge of magnitude q. In the presence of a uniform electric field $\mathbf{E}$, the Drude particle assumes a displaced position $\mathbf{r} + \mathbf{d}$. The Drude separation $\mathbf{d}$ is related to k_D, $\mathbf{E}$ and q_D:

$$\mathbf{d} = \frac{q_D \mathbf{E}}{k_D} \tag{9-22}$$

The formula for the induced atomic dipole, $\mathbf{\mu}$ as a function of $\mathbf{d}$ is

$$\mathbf{\mu} = \frac{q_D^2 \mathbf{E}}{k_D} \tag{9-23}$$

From which results a simple expression for the isotropic atomic polarizability:

$$\alpha = \frac{q_D^2}{k_D} \tag{9-24}$$

As with any model involving inducible dipoles, the potential energy of the system contains terms representing the interaction with the static field, the interaction with other dipoles and the polarization energy (self energy), in addition to the standard representation of the bonding terms (bonds, angles, dihedrals, etc.) and intermolecular interactions, typically represented by a Lennard-Jones term in biological force fields.

$$U(\mathbf{r}, \mathbf{d}) = U_{bond}(\mathbf{r}) - U_{LJ}(\mathbf{r}) - U_{elect}(\mathbf{r}, \mathbf{d}) - U_{self}(\mathbf{d}) \tag{9-25}$$

The dependence on the nuclear positions is indicated by $\mathbf{r}$ and the dependence on the Drude positions is indicated by $\mathbf{d}$. In Eq. (9-25) $U_{bond}(\mathbf{r})$ is the intramolecular energy contribution from, typically, the bond lengths, valence angles, and dihedral angles, $U_{LJ}(\mathbf{r})$ is a Lennard-Jones "6–12" nonpolar contribution, $U_{elect}(\mathbf{r}, \mathbf{d})$ represents all Coulombic interactions, atom–atom, atom–Drude, and Drude–Drude, and $U_{self}(\mathbf{d})$ represents the atom–Drude harmonic bonds. The term $U_{self}(\mathbf{d})$ arises from the harmonic spring separating the two charges and has the simple expression

$$U_{self}(\mathbf{d}) = \frac{1}{2} \sum_{i=1}^{N} k_i d_i^2 \tag{9-26}$$

The electrostatic interaction between independent polarizable atoms is simply the sum of the charge–charge interactions between the four charge sites (i.e. two atoms and their respective Drude particles):

$$U_{elect}(\mathbf{r}, \mathbf{d}) = \frac{1}{2} \sum_{i=1}^{N} \sum_{j \neq i} q_i q_j \left[\frac{1}{|\mathbf{r}_{ij}|} - \frac{1}{|\mathbf{r}_{ij} - \mathbf{d}_j|} + \frac{1}{|\mathbf{r}_{ij} + \mathbf{d}_i|} + \frac{1}{|\mathbf{r}_{ij} - \mathbf{d}_j + \mathbf{d}_i|} \right] \tag{9-27}$$

For a given $\mathbf{\alpha}$ the force constant k_D can be chosen in a way that the displacement $\mathbf{d}$ of the Drude particle remains much smaller than the interatomic distance. This guarantees that the resulting induced dipole $\mathbf{\mu}$, is almost equivalent to a point dipole. In the Drude polarizable model the only relevant parameter is the combination q_D^2/k_D which defines the atomic polarizability, α. It is

noteworthy that the electrostatic interaction in the Drude model requires only the charge–charge terms already present in MD and Monte-Carlo simulation codes. No new interaction types, such as the dipole field tensor $\mathbf{T}_{ij}$ of Eq. (9-3) are required. The computational advantage of not having to compute the dipole–dipole interactions is balanced by the extra charge–charge calculations. In the case of the CHARMM implementation [10, 11, 58, 60, 63–65] the computational impact of the Drude model is minimized by hydrogen atoms not carrying Drude particles thereby diminishing number charge–charge interactions that need to be calculated.

The Drude oscillators are typically treated as isotropic on the atomic level. However, it is possible to extend the model to include atom-based anisotropic polarizability. When anisotropy is included, the harmonic self-energy of the Drude oscillators becomes

$$
\begin{aligned}
U_{\text{self}} &= \frac{1}{2} \mathbf{d} \cdot \left[K^D \right] \cdot \mathbf{d} \\
&= \frac{1}{2} \left(\left[K_{11}^D \right] d_1^2 + \left[K_{22}^D \right] d_2^2 + \left[K_{33}^D \right] d_3^2 \right)
\end{aligned}
\tag{9-28}
$$

Where the quantities d_1^2, d_2^2 and d_3^2 are the projections of the Drude displacement vector $\mathbf{d}$ on orthogonal axis defined on a local intramolecular reference frame. The intramolecular reference frame may be defined, for example, by the C$=$O vector and the N—C$=$O plane of an amide bond [65].

The term U_{elec} of Eq. (9-27) corresponds to the sum over all Coulombic interactions between the core charges q_i, located at $\mathbf{r}_i$, and the Drude charges q_i^D, located at $\mathbf{r}_i^D = \mathbf{r}_i + \mathbf{d}$. The interactions of the various pairs of charges are treated according to the topological bonding order determined from the atoms in the molecule. As in standard fixed charge force fields, the interactions between core charges corresponding to 1–2 (neighbor) and 1–3 (next-neighbor) pairs are accounted by explicit bonding terms in the potential energy, U_{internal}, and necessarily excluded from the electrostatic energy. Similarly, the interactions of the Drude oscillators with core charges are excluded for 1–2 and 1–3 pairs. The Coulomb interactions between Drude oscillators corresponding to 1–2 and 1–3 atom pairs are present and screened by the function $f_1(r_{ij})$ [50]. The form of the screening function used in the Drude model of CHARMM is

$$
f_1(r_{ij}) = 1 - \left(1 + \frac{(\alpha_i + \alpha_j) r_{ij}}{2 \left(\alpha_i \alpha_j \right)^{1/6}} e^{-(a_i + a_j) r_{ij} / (\alpha_i \alpha_j)^{1/6}} \right)
\tag{9-29}
$$

where r_{ij} is the distance between Drude charges, α_i is the trace of the atomic polarizability tensor, and the Thole damping parameters, a_i, modulate the screening strength of $f_1(r_{ij})$. The interactions involving all core charges and all Drude oscillators are included for all 1–4 pairs and beyond without screening. Additional details of the damping function are presented in Section 9.3.

9.2.3. Fluctuating Charges Model

Polarizability can also be introduced into standard potentials (Eq. 9-1) by allowing the values of the partial charges to respond to the electric field of their environment. This may be achieved by coupling the charges to their environment using electronegativity equalization (EE) or chemical potential equalization (CPE). This method for treating polarizability has been called the "fluctuating charge" method [17, 92], the "chemical potential (electronegativity) equalization" method [93–108], or "charge equilibration" method [109–115] and has been applied to a variety of systems [17, 116–126]. A practical advantage of this approach is that it introduces polarizability without introducing new interactions. Compared to the Drude model, this can be done using the same number of charge–charge interactions as would be present in a nonpolarizable simulation.

   In the fluctuating charge method [109] variable discrete charges are located on atomic sites within the molecule. Their value is computed, for a given molecular geometry, by minimization of the electrostatic energy. The energy of a molecule, as well as a system comprised of a collection of molecules, can be described hierarchically starting from the energy of an isolated atom. Using a neutral atom as a reference point, the energy of an isolated atom can be expanded as second-order Taylor series of the charge [127]:

$$U^{atom}(q_\alpha) = U_\alpha(0) + \chi_\alpha^0 q_\alpha + \frac{1}{2} J_{\alpha\alpha}^0 q_\alpha^2 \tag{9-30}$$

The coefficients χ_α^0 and $J_{\alpha\alpha}^0$ have a clear physical interpretation. χ_α^0 is the "Mulliken electronegativity", namely one-half of the ionization energy and the electron affinity [128].

$$\chi_\alpha^0 = \frac{IP_\alpha + EA_\alpha}{2} \tag{9-31}$$

The value $\frac{1}{2} J_{\alpha\alpha}^0$ is called the "absolute hardness" and can be obtained as half of the difference between the ionization potential and the electron affinity [129].

$$\frac{1}{2} J_{\alpha\alpha}^0 = \frac{IP_\alpha - EA_\alpha}{2} \tag{9-32}$$

   When atoms are brought together to form an isolated molecule, the molecular energy consist of contributions from the individual atoms plus intra-atomic interactions, and thus is a function of both charges and coordinates, $U^{molec}(\mathbf{r}_{\mu\nu}, q)$. In the following equations indices α and β run over charged sites on a given molecule and μ and ν indicate atoms that comprise the molecule. The distinction is relevant since in many models (ex. TIP4P-FQ water model) charged and atomic sites are not coincident. Typically, when there is no external electrostatic field the potential can be partitioned into Coulombic and nonelectrostatic $V^{nonelec}(\mathbf{r}_{\mu\nu})$ types of interactions:

$$U^{molec}(\mathbf{r}, q) = \sum_{\alpha=1}^{N_{site}} \left[\chi_\alpha^0 q_\alpha + \frac{1}{2} J_{\alpha\alpha}^0 q_\alpha^2 \right]$$

$$+ \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{\alpha\beta}(\mathbf{r}_{\alpha\beta}) q_\alpha q_\beta \tag{9-33}$$

$$+ V^{nonelec}(\mathbf{r}_{\mu\nu})$$

In a multi-molecular system with N_{molec} molecules and each molecule consisting of N_{atom} atoms and N_{site} charged sites, the total energy becomes

$$U^{system}(\mathbf{r}, q) = \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \left[\chi_{i\alpha}^0 q_{i\alpha} + \frac{1}{2} J_{i\alpha i\alpha}^0 q_{i\alpha}^2 \right]$$

$$+ \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha i\beta}(\mathbf{r}_{i\alpha i\beta}) q_{i\alpha} q_{i\beta} \tag{9-34}$$

$$+ \sum_{i=1}^{N_{molec}} \sum_{j>1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha j\beta}(\mathbf{r}_{i\alpha j\beta}) q_{i\alpha} q_{j\beta}$$

$$+ V^{nonelec}(\mathbf{r}_{i\mu j\nu})$$

Equation (9-34) without the $V^{nonelec}(\mathbf{r}_{i\mu j\nu})$ term is denoted as $U^{elec}(\mathbf{r}, q)$:

$$U^{elect}(\mathbf{r}, q) = \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \left[\chi_{i\alpha}^0 q_{i\alpha} + \frac{1}{2} J_{i\alpha i\alpha}^0 q_{i\alpha}^2 \right]$$

$$+ \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha i\beta}(\mathbf{r}_{i\alpha i\beta}) q_{i\alpha} q_{i\beta} \tag{9-35}$$

$$+ \sum_{i=1}^{N_{molec}} \sum_{j>1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha j\beta}(\mathbf{r}_{i\alpha j\beta}) q_{i\alpha} q_{j\beta}$$

The energy given by Eq. (9-35) replaces the Coulomb energy $q_i q_j / \mathbf{r}_{ij}$ in Eq. (9-1). The charges q_i are now treated as independent variables, and the polarization response is determined by variations in the charge values. These charges depend on the interactions with other molecules as well as other charge sites on the same molecule, and will change for every time step or configuration sampled during a simulation. The charge values used for each configuration are, in principle, those that minimize the energy given by Eq. (9-35).

Charge conservation can be imposed in two ways. A charge neutrality constraint can be applied to the entire system, thus allowing charge to move from one atomic site to another until the electronegativities are equal on all the atoms of the system.

Alternatively, charge can be constrained independently on each molecule (or other subgroup), so that charge flows only between atoms on the same molecule until the electronegativities are equalized within each molecule, but not between distinct molecules [17]. At each molecular configuration $\mathbf{r}$, the charges are redistributed among the atoms so as to equalize the instantaneous electronegativities. In other words, the ground-state charge distribution $q^{eq}(\mathbf{r})$ satisfies the following equations

$$\left(\frac{\partial U^{system}}{\partial q_{i\alpha}}\right)_{q=q^{eq}} = \left(\frac{\partial U^{system}}{\partial q_{i\beta}}\right)_{q=q^{eq}} \tag{9-36}$$

or equivalently

$$\left(\frac{\partial U^{elect}}{\partial q_{i\alpha}}\right)_{q=q^{eq}} = \left(\frac{\partial U^{elect}}{\partial q_{i\beta}}\right)_{q=q^{eq}} \tag{9-37}$$

and the ground-state energy $U_g(\mathbf{r}) = U^{system}(q^{eq}, \mathbf{r})$. The same set of coupled linear equations can be obtained by variationally minimizing the total energy $U^{system}(q, \mathbf{r})$ with respect to the charge distribution, subject to the constraints of molecular charge conservation,

$$\sum_{\alpha} q_{i\alpha} = 0 \tag{9-38}$$

or the constraint of overall charge conservation,

$$\sum_{i}\sum_{\alpha} q_{i\alpha} = 0 \tag{9-39}$$

An analogy may be drawn between the ground state Born-Oppenheimer potential energy and $U_g(\mathbf{r})$. The charges, q, in this case play a role similar to the electronic wave functions, and they represent the electronic degrees of freedom. In fact, Eq. (9-37) is the principle of chemical potential equalization [130] in density functional electronic structure theory [131] reformulated for the point-charge representation. In the adiabatic limit, the nuclei evolve dynamically on the Born-Oppenheimer potential energy surface. In the same fashion, the principle of electronegativity equalization requires the charge density to fluctuate adiabatically as the nuclear coordinates evolve in time.

In most cases, charge is conserved for each molecule, so there is no charge transfer between molecules. In quantum mechanics, charge transfer is an important part of the interaction energy, so there are reasons to remove this constraint [132–136]. Unfortunately, many fluctuating charge methods are known to suffer from a superlinear scaling of the polarizability with increasing molecular size that penalizes model transferability and prevents application of these methods to large molecules of biological importance [107, 137]. The principal cause of this failure is the fact that in the traditional fluctuating charge models, charge can flow between covalent bonds at small energetic cost, thus covering large portions of the molecule. This method may

be suited for small molecules, highly conjugated large size π systems like polyenes, but is in general not accurate for bigger systems, as charge will be able to flow to far regions of the extended molecules.

One solution was developed based on the concept of atom–atom charge transfer (AACT) [137]. In this approach the energy is Taylor expanded in terms of charges transferred between atomic pairs within the molecule, rather than in terms of the atomic charges themselves. Similar in spirit is the bond-charge increment (BCI) [120, 138] model, which only allows for charge to flow between two atoms that are directly bonded to each other, guaranteeing that the total charge of each set of bonded atoms is conserved. In a related effort the Atom-Bond Electronegativity Equalization Method (ABEEM) [139–143] has been developed based in concepts from density functional theory. In this model, the total electronic energy of a molecule in the ground state is a complex function of different quantities: (a) valence-state chemical potential of atom a, bond $a - b$ and lone-pairs, (b) valence-state hardness of atom a, bond $a - b$, and lone-pairs, (c) partial charges of atom a, bond $a - b$, and lone-pairs, (d) distances between the different components, atoms, bonds and lone-pairs. The combination of ABEEM and molecular mechanics was performed bringing ABEEM charges of atoms, bonds, and lone-pair electrons into the intermolecular electrostatic interaction term in molecular mechanics [144, 145].

9.3.   DAMPING FUNCTIONS IN POLARIZABLE FORCE FIELDS

The development of the methods described in Section 9.2 was an important step in modeling polarization because it led to accurate calculations of molecular polarizability tensors. The most serious issue with those methods is known as the "polarization catastrophe" since they are unable to reproduce the substantial decrease of the total dipole moment at distances close to contact as obtained from ab initio calculations. As noted by Applequist et al. [49], and Thole [50], a property of the unmodified point dipole is that it may originate infinite polarization by the cooperative interaction of the two induced dipoles in the direction of the line connecting the two. The mathematical origins of such singularities are made more evident by considering a simple system consisting of two atoms (A and B) with isotropic polarizabilities, α_A and α_B. The molecular polarizability, has two components, one parallel and one perpendicular to the bond axis between A and B,

$$\alpha_{||} = (\alpha_A + \alpha_B + 4\alpha_A\alpha_B/r^3)/(1 - 4\alpha_A\alpha_B/r^6) \qquad (9\text{-}40a)$$

$$\alpha_{\perp} = (\alpha_A + \alpha_B - 2\alpha_A\alpha_B/r^3)/(1 - \alpha_A\alpha_B/r^6) \qquad (9\text{-}40b)$$

When the distance r between the two points approaches $4(\alpha_A\alpha_B)^{1/6}$, the parallel component $\alpha_{||}$ goes to infinity and will be negative for shorter distances.

The singularities can be avoided by making the polarizabilities sufficiently small so that at the typical distances between the atoms (> 1 Å) the factor $4\alpha_A\alpha_B/r^6$ is always less than one. The Applequist polarizabilities are in fact small compared to ab

initio values [50] Applequist's atomic polarizabilities were selected to optimize the molecular polarizabilities for a set of 41 molecules. Careful choice of polarizabilities can move the singularities in Eqs. (9-40a) and (9-40b) to small distances, but not eliminate them altogether, thus causing problems for simulation techniques such as MC, which tend to sample these nonphysical regions of configuration space.

While nonbonded atom pairs will typically not come within 1 Å of each other, it is possible for covalently bound pairs, either directly bounds, as in 1–2 pairs, or at the vertices of an angle, as in 1–3 pairs. Accordingly it may be considered desirable to omit the 1–2 and 1–3 dipole–dipole interactions as is commonly performed on additive force fields for the Coulombic and van der Waals terms. However, it has been shown that inclusion of the 1–2 and 1–3 dipole–dipole interactions is required to achieve anistropic molecular polarizabilites when using isotropic atomic polariz-abilites [50]. For example, in a Drude model of benzene in which isotropic polariza-tion was included on the carbons only inclusion of the 1–2 and 1–3 dipole–dipole interactions along with the appropriate damping of those interactions allowed for reproduction of the anisotropic molecular polarizability of the molecule [64]. Thus, it may be considered desirable to include these short range interactions in a polarizable force field.

Another way to deal with this limitation is the inclusion of electrostatic damp-ing, which can be achieved through the method outlined by Thole [50, 146], that uses charge distributions instead of point charges. The screening (attenuation) of the dipole–dipole interaction can be physically interpreted as correcting for the fact that the electronic distribution is not well represented by point charges and point dipoles at small distances [49, 50, 147]. Mathematically, screening avoids the singularities such as those in Eqs. (9-40a) and (9-40b). Basically, Eqs. (9-2), (9-3) and (9-4) retain their significance with the only change being that both the electric field created by fixed charges is damped by the function $f_1(r)$, that effectively changes the contri-bution to **E** from the charge at j [53, 148–151], and, when created by point dipoles, by $f_2(r)$.

$$\mathbf{E} = f_1(\mathbf{r})q\frac{\mathbf{r}}{r^3} \tag{9-41}$$

$$\mathbf{T} = f_2(\mathbf{r})3\frac{\mathbf{r}\cdot\mathbf{r}}{r^5} - f_1(\mathbf{r})\frac{\mathbf{I}}{r^3} \tag{9-42}$$

The method of Thole was developed with the help of the induced dipole formu-lation, when all dipoles interact through the dipole field tensor. The modification introduced by Thole consisted in changing the dipole field tensor:

$$
\begin{aligned}
\left(T_{pq}\right)_{ij} &= \delta_{ij}r^{-3} - 3x_ix_jr^{-5} \\
&= \left(\alpha_p\alpha_q\right)^{-1/2}\left(\delta_{ij}\mu^{-3} - 3u_iu_ju^{-5}\right) \\
&= \left(\alpha_p\alpha_q\right)^{-1/2}t_{ij}\left(\mathbf{u}\right)
\end{aligned}
\tag{9-43}
$$

where $\mathbf{u} = \mathbf{x}/(\alpha_p\alpha_q)^{-1/6}$ and δ_{ij} is the Kronecker delta. T is a shape function that does not depend on p or q, but is related to a model charge distribution $\rho(u)$. Thole originally investigated various forms for the charge distribution and two were considered:

$$\rho(u) = \begin{cases} \dfrac{3}{\pi}\dfrac{(a-u)}{a^4} & u < a \\ 0 & u \geq a \end{cases} \quad \text{(linear)} \qquad (9\text{-}44a)$$

$$\rho(u) = \left(\dfrac{a^3}{8\pi}e^{-au}\right) \text{(exponential)} \qquad (9\text{-}44b)$$

with associated dipole–dipole tensors:

$$\begin{array}{ll} T_{ij} = (4v^3 - 3v^4)\,\delta_{ij}/r^3 - 3v^4\,(r_ir_j/r^5) & r < s \\ T_{ij} = \delta_{ij}/r^3 - 3r_ir_j/r^5 & r \geq s \\ s = a(\alpha_p\alpha_q)^{1/6} & v = r/s \end{array} \quad \text{(linear)} \qquad (9\text{-}45a)$$

and

$$T_{ij} = \left[1 - \left(a^2r^2/2 + ar + 1\right)e^{-ar}\right]\delta_{ij}/r^3 - 3\left[1 - \left(a^3r^3/6 + a^2r^2/2 + ar + 1\right)\right.$$
$$\left. e^{-ar}\right]r_ir_j/r^5 \quad \text{(exponential)} \qquad (9\text{-}45b)$$

Thole's polarizability parameters were selected to optimize the molecular polarizabilities for a set of 16 molecules. The method was later expanded to fit 52 molecules [146]. It must be emphasized that this electric-field damping method is totally independent of the polarization scheme used. For the Drude and fluctuating charge methods only $f_1(r)$ is required, whereas for methods based on induced dipoles both $f_1(r)$ and $f_2(r)$ are necessary. In the context of the induced dipole model other models were proposed since the formula of Thole does not provide enough attenuation. For example, in Ref. [152] the field is evaluated using

$$S(r_{ij}) = 1 - \exp\left[-\gamma\left(\frac{r_{ij}}{s_{ij}}\right)^n\right] \qquad (9\text{-}46)$$

for all values of r_{ij} and the constants γ and n determine the extent of attenuation.

9.4.   MOLECULAR DYNAMICS WITH POLARIZABLE FORCE FIELDS

In general MD simulations are performed via integrating Newton's equations of motion using a variety of integrators as previously described [153–155]. The concepts for MD simulations are similar to all methods of describing polarization discussed

in Section 9.2. In the following sections details of the implementations for different methodologies will be addressed.

9.4.1.   Molecular Dynamics Using Induced Dipoles

In the case of the induced dipole methods, computation of the forces acting on the particles of the system requires self consistent determination of the inducible dipoles. A mathematically elegant way of doing it is by performing a SCF calculation to obtain the polarization contribution to the energy and forces from which the new atomic positions are determined. The computational requirement of this step can be greatly decreased by using a good initial guess for the SCF calculation and an initial guess for the electric field is typically obtained from the static field, $\mathbf{E}^0$ and the dipoles from the previous time step of the MD simulation [52, 156]. The iterative SCF calculation is then performed. Convergence limits on the dipoles reported in the literature range from 1×10^{-2} D to 1×10^{-6} D and have been made more strict over time [14, 157–161]. This is necessary as MD simulations require very strict convergence limits due to poor energy conservation [162]. While iterative methods can achieve the required level of convergence, the procedure is still CPU time intensive in cases that the system is large. (For example, in a simulation of 4000 polarizable sites the matrix $\mathbf{A}$ in Eq. (9-21) will have dimensions of 12,000 * 12,000 = 144,000,000 elements and the CPU time needed to achieve convergence will be quite significant.

Predictive methods that calculate $\mathbf{u}$ for the next time step of a MD simulation based on information from previous timesteps have been developed to minimize the computational cost. Ahlström et al. [13] used a first-order predictor algorithm, in which values of $\mathbf{u}$ from the two previous times steps are used to determine $\mathbf{u}$ at the next time step. A very serious drawback of this method is that it is not stable for long simulation times. However, it has been combined with iterative solutions, either by providing the initial iteration of the electric field values [163, 164], or by performing an iterative SCF step less frequently than every step [13, 165]. Higher-order predictor algorithms have also been described in the literature [13, 163, 166].

Another approach to minimize computational costs was a simplification of the iterative method proposed by Kaminski et al. [167]. The method consists in truncating the iterative SCF process after the second iteration. Equation (9-47) shows the process which is actually the initial iterations of the full iterative process.

$$\boldsymbol{\mu}_i^{1st} = \alpha_i \mathbf{E}_i^0 \tag{9-47a}$$

$$\boldsymbol{\mu}_i^{2nd} = \alpha_i \mathbf{E}_i^0 + \alpha_i \sum_{j \neq i} \mathbf{T}_{ij} \boldsymbol{\mu}_i^{1st} \tag{9-47b}$$

In the first-order approximation (Eq. 9-47a) the magnitude of the inducible dipoles is determined based on the assumption that they cannot interact with each other at all. The second-order approximation from Eq. (9-47b) is able to retain a greater part

of the dipole–dipole interactions than the first-order approximation while providing the benefits of reduced computational cost compared to the full iterative method. It should be noted that the second-order approximation in Eq. (9-47b) does not have a direct physical meaning and can be viewed as introducing a set of induced dipoles with magnitudes calculated on the assumption that each of them perceive all the other dipoles as if those other dipoles were induced by the electrostatic field of the permanent charges only.

An important advance in making explicit polarizable force fields computationally feasible for MD simulation was the development of the extended Lagrangian methods. This extended dynamics approach was first proposed by Sprik and Klein [91], in the sipirit of the work of Car and Parrinello for ab initio MD dynamics [168]. A similar extended system was proposed by van Belle et al. for inducible point dipoles [90, 169]. In this approach each dipole is treated as a dynamical variable in the MD simulation and given a mass, M_μ, and velocity, $\dot{\boldsymbol{\mu}}$. The dipoles thus have a kinetic energy, $\sum_i M_\mu (\dot{\mu})^2/2$, and are propagated using the equations of motion just like the atomic coordinates [90, 91, 170, 171]. The equation of motion for the dipoles is

$$M_\mu \ddot{\boldsymbol{\mu}} = -\nabla \boldsymbol{\mu}_i = \mathbf{E}_i - \boldsymbol{\alpha}_i^{-1} \cdot \boldsymbol{\mu}_i. \tag{9-48}$$

The dipole mass does not correspond to any physical mass and is chosen based on the requirement of having approximately adiabatic fictitious dynamics for the duration of the MD simulation. This is satisfied with small values of M_μ. The timestep of the simulation is chosen such that the frequency of the fictitious modes is much larger than the fastest nuclear frequency in order to keep the coupling between fictitious and real dynamics low, which is achieved by using small integration timesteps [172]. It is desirable to keep the kinetic energy of the dipoles small so that the dipole degrees-of-freedom are cold and near the potential energy minimum (corresponding to the exact solution of Eq. 9-3) such that it approximates the SCF condition.

Because this method avoids iterative calculations to attain the SCF condition, the extended Lagrangian method is a more efficient way of calculating the dipoles at every time step. However, polarizable point dipole methods are still more computationally intensive than nonpolarizable simulations. Evaluating the dipole–dipole interactions in Eqs. (9-7) and (9-20) is several times more expensive than evaluating the Coulombic interactions between point charges in Eq. (9-1). In addition, the requirement for a shorter integration timestep as compared to an additive model increases the computational cost.

Most liquid phase molecular simulations with explicit atomic polarizabilities are performed with MD rather than MC techniques. This is due to the fact that, despite its general computational simplicity, MC with explicit polarization [173, 174] requires that Eq. (9-21) be solved every MC step, when even one molecule in the system is moved, and the number of configurations in an average Monte Carlo computation is orders of magnitude greater than in a MD simulation. For nonpolarizable, pairwise-additive models, MC methods can be efficient because only the

interactions involving the moved particle need to be recalculated (while the other $(N-1) \times (N-1)$ interactions are unchanged). For polarizable models, all $N \times N$ interactions must be calculated, in principle, when one particle moves. Consequently, exact polarizable MC calculations can be two to three orders of magnitude slower than comparable nonpolarizable calculations [175]. This is true for all models that account for explicit polarization. Thus, employing MC becomes much less practical for polarizable systems, even though it might be otherwise preferable. The induced dipole polarizable model has, nevertheless, been used in MC simulations with single particle moves [158, 159, 167, 176–181]. To make the update of the induced dipoles at each step more efficient the distances between all the particles may be stored, since most of them are unchanged. However, the memory usage is high. Alternatively, various approximate methods, involving incomplete convergence or updating only a subset of the dipoles, have been suggested [176]. Unfortunately, these methods result in significant errors in computed physical properties [175, 178].

One final point concerns the long-ranged nature of the interactions in induced dipole based models. Dipole–dipole and dipole–charge interactions are termed long-ranged because they do not decrease faster than volume grows – i.e., as r^3. If periodic boundary conditions are used, which is common on MD simulations of biomolecular systems, some treatment of the long-ranged interactions is needed. All models, whether polarizable or not, face this problem, but for polarizable models this is a more significant issue. The use of cut-offs or other truncation schemes will change both the static field and the dipole field tensor. These changes to the electric field will modify the value of the induced dipoles, which in turn will change the field at other sites. Accordingly, the treatment of long-ranged forces feeds back on itself in a way that does not occur with nonpolarizable models. Nymand and Linse [182] showed that different boundary conditions (including Ewald sums, spherical cut-off and reaction field methods) lead to more significant differences in equilibrium, dynamical and structural properties for polarizable water models than for nonpolarizable models. It is thus crucial to treat the long-ranged interactions as accurately as possible in polarizable simulations. The most complete treatment of the long-ranged forces is the Ewald summation technique [161, 162, 183, 184]. Faster-scaling methods, such as the fast multipole and particle mesh algorithms, have also been extended to the treatment of point dipoles [161, 185–188].

9.4.2. Molecular Dynamics Using the Classical Drude Oscillator

Several different methods exist for treating the motion of the polarizable degrees of freedom in dynamic simulations with the Drude model. Similarly to models based on induced dipoles, there are iterative adiabatic techniques and fully dynamic methods based on extended Lagrangians. In the adiabatic methods, it is assumed that a correspondence between the Drude charge and the electronic degrees of freedom obeying the Born-Oppenheimer approximation exists. The heavier and slowly-moving nuclei and atomic core charges are considered to move adiabatically in the field generated

by the Drude charges. The positions of the Drude particles are assumed to react instantaneously in response to the motion of the nuclei, and thus always remain in positions in which they experience no net force. Those are the positions that minimize the total energy of the system attained via an SCF calculation as discussed above. The forces on the atomic charges are then used to propagate the dynamics, using standard numerical integration methods. The other alternative is to treat the charges dynamically, allowing them to occupy positions away from the minimum-energy position dictated by the nuclei, and thus experience non-zero forces.

When the Drude particles are treated adiabatically, a SCF method must be used to solve for the displacements of the Drude particle, $\mathbf{d}$, similarly to the dipoles $\boldsymbol{\mu}_i$ in the induced dipole model. The implementation of the SCF condition corresponding to the Born-Oppenheimer approximation is straightforward and the real forces acting on the nuclei must be determined after the Drude particles have attained the energy minimum for a particular nuclear configuration. In the case of N polarizable atoms with positions $\mathbf{r}$, the relaxed Drude particle positions $\mathbf{r} + \mathbf{d}^{SCF}$ are found by solving

$$\frac{\partial U}{\partial \mathbf{d}_i} = 0 \tag{9-49}$$

where index i runs from 1 to N. U_{bond} and U_{LJ} are independent of $\mathbf{d}$, and

$$\frac{\partial U_{self}}{\partial \mathbf{d}_i} + \frac{\partial U_{elec}}{\partial \mathbf{d}_i} = 0. \tag{9-50}$$

These equations define the force equilibria on the Drude particles

$$k_D \mathbf{d}_i - q_D \mathbf{E}_i = 0 \tag{9-51}$$

where $\mathbf{E}_i$ is the total electric field in $\mathbf{r} - \mathbf{d}$, arising from the fixed charges as well as all the induced dipoles (modeled with Drude oscillators). For atomic positions $\mathbf{r}$, the relaxed displacements produce the potential

$$U^{SCF}(\mathbf{r}) = U(\mathbf{r}, \mathbf{d}) \tag{9-52}$$

and the atomic motions in the SCF regime are described by

$$m_i \ddot{\mathbf{r}}_i = -\frac{\partial U\left(\mathbf{r}, \mathbf{d}^{SCF}\right)}{\partial \mathbf{r}_i} \tag{9-53}$$

Integrating Eq. (9-53) in MD simulations requires that the positions of the Drude particles be set at their energy minimum at every integration time step, by solving Eq. (9-51). This simple simulation method has been widely used in MD [75, 76, 87, 189] and to a lesser extent in MC simulations, although examples of application exist [171]. Nonetheless, the SCF procedure is limited and computationally expensive, because any nonconverged SCF calculation introduces systematic drag

forces on the physical atoms that considerably affect energy conservation and the stability of the temperature [56, 76, 190]. Depending on the convergence criterion used, these iterative methods typically require between three and ten iterations [56, 57, 76, 87, 190, 191]. It is interesting to compare the Drude model with models based on induced dipoles. The induced energy of the Drude model system can be written as

$$U_{ind}\left(\mathbf{r}_i, \mathbf{d}\right) = \sum_{i=1}^{N} \left\{ \frac{1}{2} k_i d_i^2 + q_i \left[\mathbf{r}_{ii} \cdot \mathbf{E}_i^0 - (\mathbf{r}_{ii} + \mathbf{d}_i) \cdot \mathbf{E}_i^0 \right] + \left[\frac{1}{2} \sum_{i=1}^{n} \sum_{j \neq i} \right. \right.$$

$$\left. \left. \times \left(\frac{1}{\mathbf{r}_{ij}} - \frac{1}{\left| \mathbf{r}_{ij} - \mathbf{d}_j \right|} + \frac{1}{\left| \mathbf{r}_{ij} + \mathbf{d}_i \right|} + \frac{1}{\left| \mathbf{r}_{ij} - \mathbf{d}_j + \mathbf{d}_i \right|} \right) \right] \right\} \quad (9\text{-}54)$$

This equation is the equivalent of Eq. (9-12) for the induced dipole model but has one important difference. Equation (9-13), the derivative of Eq. (9-12), is linear and standard matrix methods can be used to solve for the $\boldsymbol{\mu}_i$ because Eq. (9-12) is a quadratic function of $\boldsymbol{\mu}_i$, while Eq. (9-54) is not a quadratic function of $\mathbf{d}$ and thus matrix methods are usually not used to find the Drude particle displacements that minimize the energy.

An important alternative to SCF is to extend the Lagrangian of the system to consider dipoles as additional dynamical degrees of freedom as discussed above for the induced dipole model. In the Drude model the additional degrees of freedom are the positions of the moving Drude particles. All Drude particles are assigned a small mass $m_{D,i}$, taken from the atomic masses, m_i, of their parent atoms and both the motions of atoms and Drude particles (at positions $\mathbf{r}_i$ and $\mathbf{r}_{D,i} \equiv \mathbf{r}_i + \mathbf{d}_i$) are propagated

$$\left(m_i - m_{D,i}\right) \ddot{\mathbf{r}}_i = -\frac{\partial U}{\partial \mathbf{r}_i} \quad (9\text{-}55)$$

$$m_{D,i} \ddot{\mathbf{r}}_{D,i} = -\frac{\partial U}{\partial \mathbf{r}_{D,i}} \quad (9\text{-}56)$$

The motion of Drude particles is expected to be decoupled from the atomic motion if m_D is sufficiently small. The obvious drawback is that a small m_D requires a small integration time step [77, 85]. For a single Drude oscillator, a significant speedup can be attained by using a multi-timestep integration approach [118, 119], but this advantage is lost for a dense system of polarizable atoms, because the long-range $1/r^3$ dipole–dipole interactions include high-frequency oscillations and have to be integrated using very short time steps. However, even if m_D is very small, the Drude particles will eventually reach a thermal equilibrium with the rest of the system. Therefore, simulation approaches relying solely on the kinetic decoupling of the Drude oscillators to maintain a Born-Oppenheimer regimen are inappropriate for long simulation runs. To overcome this the long thermalization time can be exploited to remain close to the SCF energy surface by periodically resetting the positions

of the Drude oscillators to their energy minimum [118], but doing so makes the simulation irreversible.

From this point of view it is of interest to examine the consequences of full thermalization of the classical Drude oscillators on the properties of the system. This is particularly important given the fact that any classical fluctuations of the Drude oscillators are *a priori* unphysical according to the Born-Oppenheimer approximation upon which electronic induction models are based. It has been shown [12] that under the influence of thermalized (hot) fluctuating Drude oscillators the corrected effective energy of the system, truncated to two-body interactions is

$$U^{eff}(\mathbf{r}) = U^{SCF}(\mathbf{r}) - \frac{3}{2} k_B T \sum_{i=1}^{N} \sum_{j \neq i} \frac{\alpha_i \alpha_j}{r_{ij}^6} + \cdots. \tag{9-57}$$

In addition to the static induction effects included in U_{SCF}, the hot Drude oscillators give rise to a $1/r^6$, temperature-dependent, attractive term. This $\frac{3}{2} k_B T \alpha^2 / r^6$ term is the classical thermodynamic equivalent of the London quantum dispersive attraction $IE\alpha^2/r^6$. It corresponds to a small perturbation to the London forces, because $k_B T$ is at least two orders of magnitude smaller than the typical ionization energy IE. The smaller the temperature of the Drude motion, the closer the effective potential is to the SCF potential, making Eq. (9-57) independent of m_D, the mass of the oscillators.

To approximately reproduce the dynamics equivalent to the SCF regimen of Eq. (9-51) a scheme involving low-temperature Drude particles was devised. It involves the use of two Nose'–Hoover thermostats [192]: one to keep the atoms at room temperature T and the second to reduce the thermal fluctuations of the Drude oscillators by imposing a temperature T_* on the Drudes such that $T_* << T$. The idea of cooling the polarization degrees of freedom with a separate thermostat was carefully studied by Sprik [15], who showed that, for cold dipoles, both the equilibrium and diffusion properties are independent of the value of the dipole inertia parameter (the analog of m_D), as long as it is sufficiently small. For Drude oscillators, the temperature T_* should be small enough to leave almost no kinetic energy in the atom–Drude vibrations, yet large enough to allow the Drude particles to readjust to the room-temperature motion of the atoms. This is attained with the second thermostat by coupling the motion of the Drude particles relative to their nuclei, $\mathbf{d}$ (not to their absolute motion $\dot{\mathbf{r}}_D$). Denoting $\mathbf{R}_i$ the center of mass of each $(\mathbf{r}_i, \mathbf{r}_{D,i})$ pair, m_i the total mass of the pair (as before), and $m_i' = m_D(1 - m_D/m_i)$ the reduced mass, the equations of motion are

$$m_i \ddot{\mathbf{R}}_i = \mathbf{F}_{R,i} - m_i \dot{\mathbf{R}}_i \dot{\eta} \tag{9-58}$$

$$m_i' \ddot{\mathbf{d}}_i = \mathbf{F}_{d,i} - m_i' \dot{\mathbf{d}}_i \dot{\eta}_* \tag{9-59}$$

$$Q\ddot{\eta} = \sum m_j \dot{R}_j^2 - N_f k_B T \tag{9-60}$$

$$Q_* \ddot{\eta}_* = \sum m_j' \dot{d}_j^2 - N_{f*} k_B T_* \tag{9-61}$$

Indices i and j run from 1 to N, the total number of atoms. Because not all atoms have to be polarizable, the total number of Drude particles, N_D, may be less than N. If a given atom i bears no Drude oscillator, $\mathbf{R}_i$ corresponds to $\mathbf{r}_i$, m'_i is zero, and the corresponding Eqs. (9-59) and (9-61) are ignored. N_f is the number of degrees of freedom associated with the atomic motion, accounting for distance constraints imposed by SHAKE [193], and $N_f \equiv 3N_D$ is the number of degrees of freedom associated with the motion of the Drude oscillators. Q and Q_* are the inertia factors of the Nosé–Hoover thermostats. The "velocities" $\dot{\eta}$ and $\dot{\eta}_*$ are acting as friction coefficients, that is, as scaling exponents on the velocities $\dot{\mathbf{r}}$ and $\dot{\mathbf{d}}$, respectively.

9.4.3. Molecular Dynamics Using Fluctuating Charges

In most fluctuating charge models, if the energy is quadratic in the charges (as in Eq. 9-35), the minimization condition (Eq. 9-37) leads to a coupled set of linear equations for the charges. As with the polarizable induced dipole and Drude models, solving for the charges can be done by matrix inversion, iteration, or extended Lagrangian methods. And similarly to the other polarizable models, the matrix methods tend to be avoided because of their computational cost, and when they are used, the matrix inversion is typically not performed at every step [194, 195].

Applications of the fluctuating charge model have relied on iterative methods to determine the converged charges [52, 159, 164, 196] and for very large-scale systems, multilevel methods have also been developed [197, 198]. MC methods have also been used with fluctuating-charge models [116, 194].

As with the other polarizable models, proper treatment of long-range electrostatic interactions is essential as found by English [199]. In a comparison of the Lekner [200–202], Ewald [162, 183] and reaction field [203–205] methods to handle the long range electrostatics of several water models, including the additive flexible SPC, rigid SPC, SPC/E, TIP4P and TIP4P-Ew, and the polarizable TIP4P-FQ, English [199] found that the Lekner method gave the best results, while the reaction field method produced the worst agreement with the experimental data. Another interesting conclusion was that the Ewald method was 3.5–5 times faster than the Lekner technique. Despite this variety of available techniques, the most common approach is to use a matrix inversion or iterative method only to obtain the initial energy-minimized charge distribution and then use an extended Lagrangian method to propagate the charges dynamically in order to take advantage of its computational efficiency.

As discussed for the induced dipole and Drude polarizable models the extended Lagrangian method [168, 206, 207] is the most efficient strategy to perform MD simulations. In the extended Lagrangian applied to a fluctuating charge system [17, 92], the charges are given a fictitious mass, m_q, and evolved in time according to Newton's equation of motion. The extended Lagrangian corresponding to the energy defined in Eq. (9-34) is

$$L = \frac{1}{2} \sum_{i=1}^{N_{molec}} \left(\sum_{\mu=1}^{N_{atom}} M_\mu \dot{r}_{i\mu}^2 + \sum_{\alpha=1}^{N_{site}} m_q q_{i\alpha}^2 \right) - U^{system}(\mathbf{r}, \mathbf{q}) - \sum_{i=1}^{N_{molec}} \lambda_i \sum_{\alpha=1}^{N_{site}} q_{i\alpha} \quad (9\text{-}62)$$

In Eq. (9-62) M_μ is the mass of atom μ. The mass m_q does not correspond to any physical mass and is simply set to a value small enough such that the charges follow the atomic coordinates adiabatically. The Lagrangian also includes an N_{molec} number of constraints to ensure that each molecule remains electrostatically neutral.

Based on the Lagrangian of Eq. (9-62), the equations of motion for the positions and charges are

$$M_\mu \ddot{\mathbf{r}}_{i\mu} = -\frac{\partial}{\partial \mathbf{r}_{i\mu}} \left[U^{system}(\mathbf{r}, \mathbf{q}) \right] \quad (9\text{-}63)$$

and

$$m_q \ddot{\mathbf{q}}_{i\alpha} = -\frac{\partial U^{system}(\mathbf{r}, \mathbf{q})}{\partial \mathbf{r}_{i\mu}} - \lambda_i \quad (9\text{-}64)$$

These equations of motion can be integrated by many standard ensembles: constant energy, constant volume, constant temperature and constant pressure. More complex forms of the extended Lagrangian are possible and readers are referred to Ref. [17] for a Lagrangian that allows intermolecular charge transfer.

Although a direct comparison between the iterative and the extended Lagrangian methods has not been published, the two methods are inferred to have comparable computational speeds based on indirect evidence. The extended Lagrangian method was found to be approximately 20 times faster than the standard matrix inversion procedure [117] and according to the calculation of Bernardo et al. [208] using different polarizable water potentials, the iterative method is roughly 17 times faster than direct matrix inversion to achieve a convergence of 1.0×10^{-8} D in the induced dipole.

9.5.   POLARIZABLE FORCE FIELDS IN CHARMM

9.5.1.   Classical Drude Oscillatory

The polarizable Drude model in CHARMM results from the work of MacKerell, Roux and co-workers [10, 11] and it is geared at developing polarizable force fields for biological macromolcules. Significant progress on the model has been made to date. The algorithm for extended Lagrangian MD has been generically described in Ref. [12] and a water model that is a generalization of the TIP4P model and has been described in Refs. [10] and [11]. The second water model, termed SWM4-NDP, uses a negative charge on the Drude particle (e.g. NDP) and represents the model that acts as the baiss for the rest of the force field. The protocols to determine fixed charges, polarizabilities and Thole factors are published in Refs. [58] and [60].

Results of parameter optimization and MD simulations of small model compounds have been published, including alcohols [63], alkanes [63], aromatic [64] and heteroaromatic [209] compounds and liquid amides [65]. Studies of ions in aqueous solution were also performed [61, 88] and results from an MD simulation on a DPPC lipid monolayer have been reported (Harder, MacKerell, Roux, submitted). Notable from the monolayer study was the reproduction of the dipole potential across the monolayer, a value that cannot be reproduced using non-polarizable models. This exciting, unforeseen observation points to the types of results that may be obtained from polarizable macromolecular force fields that are not accessible to the present additive models.

Details of the implementation of the Drude model in CHARMM follow. The potential energy function is the same of Eq. (9-25). The interactions of the various pairs of charges are treated according to the connectivity of the atoms in the molecule. As in standard additive force fields, the interactions between core charges corresponding to 1–2 (neighbor) and 1–3 (next-neighbor) covalently bound atom pairs are accounted by explicit bonding terms in the potential energy, $U_{internal}$, and excluded from the electrostatic and LJ energy calculations. Similarly, the interactions of the Drude oscillators with core charges are excluded for 1–2 and 1–3 pairs; however, the 1–2 and 1–3 dipole–dipole interactions are included in the model. The Coulomb interactions between Drude oscillators corresponding to 1–2 and 1–3 atom pairs are damped by a Thole like function S_{ij} [50, 146]. An important extension of the damping function was the inclusion of atom-specific damping parameters, α in Eq. (9-27), allowing for improved reproduction of the molecular polarizability tensor in polar neutral species [65, 209]. The interactions involving all core charges and all Drude oscillators are included for all 1–4 pairs and beyond without screening.

An important addition to the model was the inclusion of virtual particles representative of lone pairs on hydrogen bond acceptors [60]. Their inclusion was motivated by the inability of the atom-based electrostatic model to treat interactions with water as a function of orientation. By distributing the atomic charges on to lone pairs it was possible to reproduce QM interaction energies as a function of orientation. The addition of lone pairs may be considered analogous to the use of atomic dipoles on such atoms. In the model, the polarizability is still maintained on the parent atom. In addition, anisotropic atomic polarizability, as described in Eq. (9-28), is included on hydrogen bond acceptors [65]. Its inclusion allows for reproduction of QM polarization response as a function of orientation around S, O and N atoms and it facilitates reproduction of QM interaction energies with ions as a function of orientation.

The parametrization protocol developed for the polarizable Drude model of CHARMM is well defined. A procedure for determining core and Drude charges [58, 60] and Thole damping parameters [65] has been developed and is analogous to work by Friesner and co-workers [117, 120, 138, 210, 211]. A map of the electrostatic potential (ESP) that surrounds the model compound monomer is evaluated on a set of specified grid points using density functional theory computations at the B3LYP/aug-cc-pVDZ level. To measure the electronic response of the molecule, a series of perturbed ESP maps is computed by placing a single $+0.5e$ test charge

at chemically relevant positions around the molecule. The same calculations are repeated using the Drude model, restricting the force constant tensor of each oscillator to be isotropic. Optimal parameters are chosen to minimize the difference between the QM and Drude ESP maps [58, 60]. On atoms bearing lone pairs the atomic charge is moved to the lone pair. It must be emphasized that the lone pair geometry and the force constant tensor are not part of the automated fitting procedure described above. The force constant tensor of atoms with lone pairs required for the anisotropic polarizability is determined by comparing to the local QM polarization response in the vicinity of the oxygen atom. Perturbation charges are placed around the lone pair and the QM and Drude polarization responses are computed. The components of the force constants are then manually adjusted to reproduce the QM polarization responses. Optimization of the components of the potential energy equation (Eq. 9-25) not dependent of the Drude oscillator positions, namely the bonding and Lennard-Jones terms, are adjusted as described previously for the additive CHARMM force field [2, 212, 213].

9.5.2.   Fluctuating Charge Model

The polarizable fluctuating charge model in CHARMM results from the work of Patel, Brooks and co-workers [92, 214]. The water model is based on the TIP4P-FQ model of Rick, Stuart and Berne [17]. In the development of the force field the electronegativities and hardnesses were treated as empirical parameters and do not have any association with experimental or QM values, for example, from ionization energies and electron affinities of single atoms.

The fitting of electronegativities and hardnesses is done independently of each other with the help of a reformulation of the fluctuating charge model in terms of a linear response model [117, 120, 210]. In the presence of an external potential $\vec{\Phi}$ the electrostatic energy defined in Eq. (9-35) is:

$$
\begin{aligned}
U_{pert}^{ee}\left(\mathbf{r},\mathbf{q}\right) = & \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \left[\chi_{i\alpha}^{0} q_{i\alpha}^{pert} + \frac{1}{2} J_{i\alpha i\alpha}^{0} \left(q_{i\alpha}^{pert} \right)^{2} \right] \\
& + \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha i\beta}\left(\mathbf{r}_{i\alpha i\beta}\right) q_{i\alpha}^{pert} q_{i\beta}^{pert} \\
& + \sum_{i=1}^{N_{molec}} \sum_{j>1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \sum_{\beta>\alpha}^{N_{site}} J_{i\alpha j\beta}\left(\mathbf{r}_{i\alpha j\beta}\right) q_{i\alpha}^{pert} q_{j\beta}^{pert} \\
& + \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{site}} \Phi_{i\alpha} q_{i\alpha}^{pert}
\end{aligned}
\tag{9-65}
$$

where q^{pert} is a charge in the presence of the external field. At equilibrium, the conditions

$$\frac{\partial U^{ee}}{\partial q_i} = 0, \qquad i = 1, N_{site} \tag{9-66}$$

and

$$\frac{\partial U^{ee}_{pert}}{\partial q^{pert}_i} = 0, \qquad i = 1, N_{site} \tag{9-67}$$

lead to the following equations:

$$\mathbf{J} \cdot \mathbf{q} = -\chi \tag{9-68}$$

and

$$\mathbf{J} \cdot \mathbf{q}^{pert} = -\left(\chi + \mathbf{\Phi}\right) \tag{9-69}$$

Taking the difference of Eqs. (9-68) and (9-69) yields an expression for the response of the molecular charge distribution to the external field

$$\mathbf{J} \cdot \left(\mathbf{q}^{pert} - \mathbf{q}\right) = \mathbf{J} \cdot \Delta\mathbf{q} = -\mathbf{\Phi} \Rightarrow \Delta\mathbf{q} = -\left(\mathbf{J}\right)^{-1}\mathbf{\Phi} \tag{9-70}$$

An objective function measuring the deviation from the parameterized model and the target response, determined, for example, from density functional theory based methods can be defined as

$$\varepsilon = \left\|\left(\Delta q^{DFT} - \Delta q^{FQ}\right)\right\| \tag{9-71}$$

Minimization of Eq. (9-71) or other related expression of Δq^{DFT} and Δq^{FQ} yields optimal model parameters. Details of the choice of model compounds and placement of probes is given in reference [92]. Parameterization of the atom electronegativities is performed next by fitting to charge distributions of the optimized model compounds in the gas phase. Dipole moments are included in the fitting procedure as this was found necessary to accurately reproduce gas-phase moments, since those are very sensitive to small changes in the charge distributions [92]. MD is performed within an extended Lagrangian formalism and optimization of the LJ parameters has been based on the reproduction of small molecular pure solvent properties [92]. Application of the model have been performed on interfaces [215–217], ions in aqueous solution [218, 219] and a simulation study of DMPC have been reported [220]. Recently, the implementation of the fluctuating charge model in CHARMM was extended to allow for calculation of free energies of salvation [221], an important tool for future force field.

9.5.3.   Induced Dipole Model

An implementation of the induced dipole method in CHARMM has been reported [25], based on the polarizable intermolecular potential functions (PIPF) model of Gao and co-workers [23, 24]. The PIPF potential combined with the CHARMM22 force field as been designed PIPF-CHARMM. The implementation closely follows the description of the induced dipole model in Section 9.2. The induced dipole at the ith interaction site due to the homogeneous external electric field $\mathbf{E}_i$ is given by Eq. (9-3) and the dipole field tensor is defined by Eq. (9-4). Infinite polarization[1] is avoided by using Thole's damping scheme [50, 146]. The damping scheme implemented is equivalent to considering a smeared charge distribution between two interacting sites with a charge distribution of the exponential form, similar to Eq. (9-44b). The three standard methods to solve Eq. (9-3) discussed in Section 9.2.1, namely the self-consistent approach (iterative procedure), the direct solution via matrix algebra and the extended Lagrangian method have been implemented. Application of the PIPF-CHARMM method to liquid amides and alkanes have been reported [25]. When used in conjunction with the CHARMM22 force field the method required only minor modifications of several torsional parameters, yielding adequate structural and thermodynamic properties.

9.6.   CONCLUSION

In this chapter we have presented an overview of the formalisms used for the inclusion of inducible electronic polarizability into empirical forces. All methods are based on the polarizability relaxing in a self consistent fashion in the electric field of the static charges and multipoles and in the field of the inducible dipoles. Introduction of dipoles may be based on the explicit introduction of inducible dipoles on atomic centers or along bonds, introduction of dipoles via the inclusion of additional charge sites attached directly to polarizable atoms, termed the Drude model, or by allowing charges to fluctuate in the surrounding electric field. All three approaches have been implemented and are currently undergoing development, though at the time of the writing of this chapter, a broad polarizable force field for biological macromolecules was not yet available. In one limit, the three methods are similar, yielding molecular polarizabilities as a function of environment; however, differences do exist. For example, in the fluctuating charge model out of plane polarization does not occur in planar molecular unless off-atomic sites are included in the model whereas the Drude model, via the explicit inclusion of different particles allows for the inclusion of mechanical polarizabilities by including LJ parameters on the Drude particles [8]. While such aspects could be the subject of additional discussions, in the end it is the proper implementation of a polarizable model in combination with an accurate optimization of the parameters in that model that will lead to the

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[1] See Section 9.5 for a detailed discussion.

ultimate utility of polarizable force fields to the scientific community. We look forward to these future developments in the laboratories of others as well as in our own laboratories.

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