# Polarizable Force Fields for Biomolecular Modeling

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# 1. Introduction

Molecular mechanics based modeling has been widely used in the study of chemical and biological systems. The classical potential energy functions and their parameters are referred to as force fields. Empirical force fields for biomolecules emerged in the early 1970's,[1] followed by the first molecular dynamics simulations of the bovine pancreatic trypsin inhibitors (BPTI).[2-4] Over the past 30 years, a great number of empirical molecular mechanics force fields, including AMBER,[5] CHARMM,[6] GROMOS,[7] OPLS,[8] and many others, have been developed. These force fields share similar functional forms, including valence interactions represented by harmonic oscillators, point dispersion-repulsion for van der Waals (vdW) interactions, and an electrostatic contribution based on fixed atomic partial charges. This generation of molecular mechanics force fields has been widely used in the study of molecular structures, dynamics, interactions, design and engineering. We refer interested readers to some recent reviews for detailed discussions.[9, 10]

Although the fixed charge force fields enjoyed great success in many areas, there remains much room for improvement. In fixed charge based electrostatic models, the atomic partial charges are meant to be ñpre-polarizedò for condensed phases in an averaged fashion, typically achieved by the fortuitous overestimation of electrostatic charges by low-level *ab initio* quantum mechanics. Such models thus lack the ability to describe the variation in electrostatics due to many-body polarization effects, which have been shown to be a significant component of intermolecular forces.[10-12] With the rapid growth of computational resources, there has been increasing effort to explicitly incorporate many-body induction into molecular mechanics to improve the accuracy of molecular modeling.

Classical electrostatics models that take into account polarization appeared as early as the 1950s. Barker in his 1953 paper ñStatistical Mechanics of Interacting Dipolesò discussed the electrostatic energy of molecules in terms of ñpermanent and induced dipolesò.[13] Currently, polarizable models generally fall into three categories: those based on induced point dipoles,[9, 14-23] the classical Drude oscillators,[24-26] and fluctuating charges.[27-30] More sophisticated force fields that are ñelectronic structure-basedò[31, 32] or use ñmachine learning methodsò[33] also exist, but incur higher computational costs. Discussions of the advantages and disadvantages of each model and their applications will be presented in the following sections.

Compared to fixed charge models, the polarizable models are still in a relatively early stage. Only in the past decade or so has there been a systematic effort to develop general polarizable force fields for molecular modeling. A number of reviews have been published to discuss various aspects of polarizable force fields and their development.[9, 34-40] Here, we focus on the recent development and applications of different polarizable force fields. We begin with a brief introduction to the basic principles and formulae underlying alternative models. Next, the recent progress of several well-developed polarizable force fields is reviewed. Finally, applications of polarizable models to a range of molecular systems, including water and other small molecules, ion solvation, peptides, proteins and lipid systems are presented.

# 1. Modeling Polarization Effects

## 1.1. Induced Dipole Models

To describe electrostatic interactions involving polarization, we consider a system consisting of a collection of charge distribution sites located at lone-pair positions, atomic centers and/or molecular centers, depending on the resolution of the model. The total charge distribution at site *i* is the sum of permanent and induced charge

$$\mathbf{M_i} = \mathbf{M_i^0} + \mathbf{M_i^{ind}} \quad [1]$$

where ***M*** represents the charge distribution. This distribution can be a simple point charge, a point multipole expansion with charge, dipole, quadrupole and/or higher order moments, or a continuous charge distribution. While the principles described below are not limited to any particular representation of charge distribution, we will use point multipoles for convenience.

The electrostatic interaction energy between two charge sites *i* and *j* is given by

$$\mathbf{U_{ele}} = \frac{1}{2}\sum_i \sum_{j\neq i} \mathbf{M_i^t T_{ij} M_j} \quad [2]$$

where ***T*** is the interaction operator and is a function of the distance between *i* and *j*. In the case of point charge interactions, ***T*** is simply 1/r. The work (positive energy) needed to polarize a charge distribution also has a quadratic dependence on the induced charge distribution:

$$\mathbf{U_{work}} = \frac{1}{2}\sum_i \left(\mathbf{M_i^{ind}}\right)^t \alpha_i^{-1} \mathbf{M_i^{ind}} \quad [3]$$

where $\breve{\boldsymbol{U}}$ is the polarizability of site *i* that includes all orders of polarizability including dipole polarizability.[41] Although $\breve{\boldsymbol{U}}$ is generally treated as an isotropic quantity, as in the

Applequist scheme [41], *ab initio* anisotropic polarizability tensors can be derived from quantum mechanical calculations.[42, 43]

The total electrostatic energy is

$$U_{ele} = \frac{1}{2}\sum_i \sum_{j\neq i} M_i^t T_{ij} M_j + \frac{1}{2}\sum_i \left(M_i^{ind}\right)^t \alpha_i^{-1} M_i^{ind} \quad [4]$$

The values of the induced moments minimize the total energy, by satisfying

$$\frac{\partial U_{ele}}{\partial M_i^{ind}} = \sum_{j\neq i} T_{ij} M_j + \alpha_i^{-1} M_i^{ind} = 0 \quad [5]$$

As a result

$$M_i^{ind} = \alpha_i^{-1} \sum_{j\neq i} T_{ij}\left(M_j^0 + M_j^{ind}\right) \quad [6]$$

Equation [6] can be solved iteratively to obtain the induced dipoles. The self-consistent calculation is computationally expensive; however it can be accelerated with predictors and non-stationary iterative methods.[44]

Substituting $\alpha_i^{-1} M_i^{ind}$ from Eq [5] into Eq [6], the final electrostatic energy becomes

$$U_{ele} = \frac{1}{2}\sum_i \sum_{j\neq i} \left(M_j^0\right)^t T_{ij} M_j^0 + \frac{1}{2}\sum_i \sum_{j\neq i} \left(M_i^{ind}\right)^t T_{ij} M_j^0 \quad [7]$$

where the first term is the permanent electrostatic energy and the second term is the polarization energy.

## 1.2. Classic Drude Oscillators

In the Drude oscillator model, the polarization effect is described by a point charge (the Drude oscillator) attached to each non-hydrogen atom via a harmonic spring. The point

charge can move relative to the attachment site in response to the electrostatic environment. The electrostatic energy is the sum of the pairwise interactions between atomic charges and the partial charge of the Drude particles

$$E_{ele} = \sum_{A<B}^{N} \frac{q_C(A)q_C(B)}{r_C(A)-r_C(B)} + \sum_{A<B}^{N,N_D} \frac{q_D(A)q_C(B)}{|r_D(A)-r_C(B)|} + \sum_{A<B}^{N_D} \frac{q_D(A)q_D(B)}{|r_D(A)-r_D(B)|} + \frac{1}{2}\sum_{A}^{N_D} k_D(r_D(A)-r_C(B))^2 \quad [8]$$

where $N_D$ and $N$ are the number of Drude particles and non-hydrogen atoms, $q_D$ and $q_C$ are the charges on the Drude particle and its parent atom, respectively, $r_D$ and $r_C$ are their respective positions, and $k_D$ is the force constant of the harmonic spring between the Drude oscillator and its parent atom. The last term in Equation [8] accounts for the cost of polarizing the Drude particles.

The atomic polarizability ($\alpha$) is a function of both the partial charge on the Drude particle and the force constant of the spring

$$\alpha = \frac{q_D^2(A)}{k_D} \quad [9]$$

Both the induced-dipole and Drude oscillator approaches benefit from short-range Thole damping to avoid a polarization catastrophe and to produce an anisotropic molecular polarization response.[45]

## 1.3. Fluctuating Charges

The formalism of the fluctuating charge model is based on the charge equilibration (CHEQ) method,[46] in which the chemical potential is equilibrated via the redistribution of charge density. The charge-dependent energy for a system of $M$ molecules containing $N_i$ atoms per molecule is expressed as

$$\mathbf{E_{CHEQ}}(R,Q) = \sum_{i=1}^{M}\sum_{\alpha=1}^{N} \chi_{i\alpha}Q_{i\alpha} + \frac{1}{2}\sum_{i=1}^{M}\sum_{j=1}^{M}\sum_{\alpha=1}^{N_i}\sum_{\beta=1}^{N_j} J_{i\alpha i\beta}\,Q_{i\alpha}Q_{j\beta} + \frac{1}{2}\sum_{i=1}^{MN'}\sum_{j=1}^{MN'} \frac{Q_iQ_j}{4\pi\epsilon_0 r_{ij}}$$

$$+\sum_{j=1}^{M}\lambda_i\left(\sum_{i=1}^{N} Q_{ij} - Q_j^{Total}\right) \qquad (10)$$

where $Q_i$ is the partial charge on atomic site $i$. The $\boldsymbol{\chi}$ describes the atomic electronegativity controlling the directionality of electron flow, and $J$ is the atomic hardness that represents the resistance to electron flow to or from the atom. These parameters are optimized to reproduce molecular dipoles and the molecular polarization response. The charge degrees of freedom are typically propagated via an extended Lagrangian formulation:[47]

$$\mathbf{L} = \sum_{i=1}^{M}\sum_{\alpha=1}^{N}\frac{1}{2}\mathbf{m}_{i\alpha}\left(\frac{\mathrm{d}\mathbf{r}_{i\alpha}}{\mathrm{dt}}\right)^2 + \sum_{i=1}^{M}\sum_{\alpha=1}^{N}\frac{1}{2}\mathbf{m}_{Q,i\alpha}\left(\frac{\mathrm{dQ}_{i\alpha}}{\mathrm{dt}}\right)^2 - \mathrm{E}(\mathrm{Q},\mathbf{r}) - \sum_{i=1}^{M}\lambda_i\sum_{\alpha=1}^{N}\mathrm{Q}_{i\alpha} \quad [11]$$

where the first two terms represent the nuclear and charge kinetic energies, the third term is the potential energy, and the fourth term is the molecular charge neutrality constraint enforced on each molecule $i$ via a Lagrange multiplier $\boldsymbol{\lambda}_i$. The extended Lagrangian approach can also be applied to the induced dipole and Drude oscillator models described earlier. While the extended Lagrangian seems to be more efficient than the iterative method, fictitious masses and smaller time-steps are required to minimize the coupling

between the polarization and atomic degrees of freedom, which can never be completely eliminated.[44]

A few general force fields have been developed based on these formulas to explicitly treat the polarization effect. We now discuss development highlights for some of the representative force fields.

# 2. Recent Developments

## 2.1. AMOEBA

The AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) force field, developed by Ponder, Ren and co-workers,[15, 18, 37] utilizes atomic multipoles to represent permanent electrostatics and induced atomic dipoles for many-body polarization. The valence interactions include bond, angle, torsion and out-of-plane contributions using typical molecular mechanics functional forms. The van der Waals interaction is described by a buffered-14-7 function. The atomic multipole moments consist of charge, dipole and quadrupole moments, which are derived from *ab initio* quantum mechanical calculations using procedures such as Stoneôs Distributed Multipole Analysis (DMA).[48-50] The higher order moments make possible anisotropic representations of the electrostatic potential outside atoms and molecules. The polarization effect is explicitly taken into account via atomic dipole induction. The combination of permanent atomic multipoles and induced dipoles enables AMOEBA to capture electrostatic interactions in both gas and condensed phase accurately. The vdW parameters of AMOEBA are optimized simultaneously against both *ab initio* gas-phase data and condensed-phase experimental properties.

In the past decade, AMOEBA has been applied to the study of water,[15] monovalent and divalent ions,[51-53] small molecules,[54, 55] peptides[18, 56] and proteins.[57-59] AMOEBA demonstrated that a polarizable force field is able to perform well in both gas and solution phases with a single set of parameters. In addition, AMOEBA is the first general-purpose polarizable force field utilized in molecular dynamics simulations of protein-ligand binding and calculation of absolute and relative binding free energies.[58-62] The computed binding free energies between trypsin and benzamidine derivatives suggests significant non-additive electrostatic interactions as the ligand desolvates from water and enters the protein pocket (see Section 4.4 for further discussion). AMOEBA has recently been extended to biomolecular X-ray crystallography refinement[63, 64], and consistently successful prediction of the structure, thermodynamic stability and solubility of organic crystals[65] are encouraging.

AMOEBA has been implemented in several widely used software packages including TINKER,[66] OpenMM,[67] Amber,[68] and Force Field X.[69] The AMOEBA polarizable force field was first implemented within the FORTRAN-based TINKER software package[70] using Particle Mesh Ewald (PME) for long-range electrostatics. Implementation of the polarizable-multipole Poisson-Boltzmann,[71] which depends on the Adaptive Poisson-Boltzmann Solver (APBS),[72] and generalized Kirkwood[73] continuum electrostatics models also exist in TINKER, which is now being parallelized using OpenMP. The algorithms in TINKER are also available from within CHARMM using the MSCALE interface.[74, 75] Alternative FORTRAN implementations of AMOEBA using PME are available in the Sander and PMEMD molecular dynamics engines of AMBER,[68] with the latter parallelized using MPI. The PME treatment of AMOEBA electrostatics has recently

been extended within the Java Runtime Environment (JRE) program *Force Field X* by incorporating explicit support for crystal space group symmetry,[63] parallelizing for heterogeneous computer hardware environments[63] and supporting advanced free energy methods such as the Orthogonal Space Random Walk (OSRW) strategy.[65, 76] These advancements are critical for applications such as AMOEBA-assisted biomolecular X-ray refinement,[63, 77] efficient computation of protein-ligand binding affinity,[57, 61] and prediction of the structure, stability and solubility of organic crystals.[65] Finally, the OpenMM software is working toward a general implementation of AMOEBA using the CUDA GPU programming language.[78]

## 2.2. SIBFA

The SIBFA (Sum of Interactions Between Fragments *Ab initio* computed) force field for small molecules and flexible proteins, developed by Gresh, Piquemal *et. al*,[79-83] is one of the most sophisticated polarizable force fields because it incorporates polarization, electrostatic penetration [84] and charge-transfer effects.[85]

The polarization is treated with an induced dipole model, in which the distributed anisotropic polarizability tensors[43] are placed on the bond centers and on the heteroatom lone pairs. Quadrupolar polarizabilities are used to treat metal centers. The force field is designed to enable the simultaneous and reliable computation of both intermolecular and conformational energies governing the binding specificities of biologically and pharmacologically relevant molecules. Similar to AMOEBA, permanent multipoles are used for permanent electrostatics in SIBFA. Flexible molecules are modeled by combining the constitutive rigid fragments. SIBFA is formulated on the basis of quantum

chemistry and calibrated on energy decomposition analysis, as oppose to AMOEBA which relies more on condensed-phase experimental data. It aims to produce accurate interaction energy comparable with *ab initio* results. The development of SIBFA emphasizes separability, anisotropy, nonadditivity and transferability. The analytical gradients for charge-transfer energy and solvation contribution are not yet available in SIBFA although molecular dynamics simulations with a simplified potential have been attempted and will be reported in the near future.

SIBFA has been validated on a wide range of molecular systems from water clusters[86] to large complexes like metalloenzymes encompassing Zn(II).[87-92] It has been used to investigate molecular recognition problems including the binding of nucleic acids to metal ions,[93-95] the prediction of oligopeptide conformations,[86, 96] and for ligand-protein binding.[97] Most of the SIBFA calculations reproduced closely the quantum chemistry results, including both the interaction energy and the decomposed energy terms. At the same time, electrostatic parameters are demonstrated to be transferable between similar molecules.

,A Gaussian based electrostatic model (GEM) has been explored as an alternative to distributed point multipole electrostatic representation.[98] GEM computes the molecular interaction energies using an approach similar to SIBFA but replacing distributed multipoles by electron densities.[99] GEM better captures the short-range effects on intermolecular interaction energies, and it naturally includes the penetration effect. Calculations on a few simple systems like water clusters[99] have demonstrated GEMôs capability to reproduce quantum chemistry results. Furthermore, implementating PME for GEM in a PBC showed reasonable computational efficiency thanks to the use of

231 Hermite Gaussian functions.[100] Therefore, replacing SIBFAôs distributed multipoles with
232 the GEM continuous electrostatic model will be a future direction of methodology
233 development.[98]

## 234 2.3. NEMO

235 NEMO (Non-Empirical Molecular Orbital) is a polarizable potential developed by
236 Karlström and co-workers.[101-103] The NEMO potential energy function is composed of
237 electrostatics, induction, dispersion and repulsion terms. The induction component is
238 modeled using induced pointï dipole moments with recent addition of induced pointï
239 quadrupole moments.[22] The electrostatics, previously represented by atomic charges and
240 dipoles, has also been extended to include atomic quadrupole moments leading to notable
241 improvement on formaldehyde. The atomic multipole moments are now obtained from ab
242 *initio* calculation using a LoProp procedure.[104] The LoProp is claimed to provide atomic
243 multipoles and atomic polarizabilities that are less sensitive to basis sets than are other
244 methods such as Distributed Multipole Analysis (DMA). Also, NEMO is the only force
245 field that explores the possibility of including interactions between permanent multipoles
246 and higher-order induced multipoles involving higher-order hyperpolarizabilities.[22]

247 NEMO has demonstrated its ability to describe accurately both inter and intramolecular
248 interactions in small systems, including: glycine dipeptide conformation profiles,[105] ion-
249 water droplets,[106] and urea transition from nonplanar to planar conformation in water.[107]
250 Its applicability to biomacromolecules is not yet known.

## 251 2.4. CHARMM-Drude

In addition to the induced dipole model, the classical Drude oscillator model is another popular approach for modeling polarization effects.[39, 108] Roux, MacKerell and their colleagues have been developing a polarizable CHARMM force field based on this approach. [25, 26, 109, 117] Unlike the induced dipole model, which treats the polarization response using point dipoles, the Drude model represents the polarizable centers by a pair of point charges. A point partial charge is tethered via a harmonic spring for each non-hydrogen atom. This point charge (the Drude oscillator) can react to the electrostatic environment and cause the displacement of the local electron density. The atomic polarizability depends on both the Drude particle charge and the harmonic force constant. In MD simulations, the extended Lagrangian is used to evaluate the polarization response, by allowing the Drude particles to move dynamically and experience nonzero forces. Small fictitious masses are assigned to each Drude particle and independent low temperature thermostats are applied to the Drude particle degrees of freedom.[118] In case of energy minimization, self-consistent iteration will be required to solve for the polarization.

Determining electrostatic parameters for the Drude oscillator is not as straightforward as for induced dipole models. Masses assigned to the Drude particles are chosen empirically. The values for atomic charges and polarizabilities requires a series of calculations of perturbed ESP maps. This force field has been parameterized for water[25, 26], and for a series of organic molecules including: alkanes,[110] alcohols,[111] aromatics,[112] ethers,[113, 114] amides,[109] sulfurs,[115] and ions.[119, 120] An attempt has also been made to combine the Drude-based polarizable force field with quantum mechanics in QM/MM methods.[121] It was noted that pair-specific vdW parameters are needed to obtain accurate hydration free

energies of small molecules using the polarizable force field. This is likely due to the problematic combining rules used to compute the vdW interactions between unlike atoms.

The Drude model has been implemented in CHARMM[74, 122] and in the NAMD package,[123] in which the computational cost is about 1.2 to 1.8 times greater than that of fixed-charge CHARMM.[124]

## 2.5. CHARMM-FQ

The fluctuating charge model (FQ), also known as charge equilibration or electronegativity equalization model, is an empirical approach for calculating charge distributions in molecules. In this formalism, the partial charge on each atom is allowed to change to adapt to different electrostatic environments. The variable partial charges are computed by minimizing the electrostatic energy for a given molecular geometry. Compared with the induced dipole and Drude models, the fluctuating charge models are minimally parameterized and easier to implement because the polarizability is induced without introducing new interactions beyond the point charges. Either extended Lagrangian or self-consistent iteration can be used to compute the fluctuating charges in MD simulations, with similar advantages and disadvantages as discussed above.

The CHARMM-FQ force field,[125, 126] developed by Patel, Brooks, and their coworkers, has been parameterized for small molecules,[28] proteins,[28, 127] lipids, lipid bilayers,[113, 128] and carbohydrates.[125] The force field has been applied to investigate liquidï vapor interfaces in addition to biophysical studies.[129] There are some known limitations for fluctuating charge models, however, such models allow artificial charge transfer between widely separated atoms but that can be controlled with additional constraints. Also the

297 intramolecular charge-flow is limited by the chemical connectivity. It is thus difficult to
298 capture the out-of-plane polarization in molecules such as aromatic benzenes with
299 additional charge sites. The CHARMM-FQ force field has been implemented in the
300 CHARMM software package.[74]

301 ## 2.6. X-Pol

302 Gao and coworkers proposed the X-Pol framework by combining the fragment-based
303 electronic structure theory with a molecular mechanical force field.[31, 32, 130] Unlike the
304 traditional force fields, X-Pol does not require bond stretching, angle, and torsion terms
305 because they are represented explicitly by quantum mechanics. The polarization and
306 charge transfer between fragments are also evaluated quantum mechanically.[130]
307 Furthermore, X-Pol can be used to model chemical reactions.

308 In X-Pol, large molecular systems are divided into small fragments. Electrostatic
309 interactions within the fragments are treated using the electronic structure theory. The
310 electrostatic interactions between fragments are described by the combined quantum
311 mechanical and molecular mechanical (QM/MM) approach. Also, a vdW term is added to
312 the interfragment interaction as a consequence of omitting electron correlation and
313 exchange repulsion. A double self-consistent-field (DSCF) procedure is used to converge
314 the total electronic energy of the system as well as the energy within the fragments (this
315 includes the mutual polarization effect).

316 The X-Pol potential has been applied to MD simulations of liquid water,[131] liquid
317 hydrogen fluoride,[132] and covalently bonded fragments.[133, 134] This model was recently
318 used in a molecular dynamics simulation of a solvated protein.[135] As expected the

computational efficiency of the X-Pol is in between that of a simple classical force field and a full *ab initio* method. The solvated trypsin required 62.6 h to run a 5 ps simulation on a single 1.5 GHz IBM Power4 processor. A parallel version of X-Pol is being developed.

## 2.7. PFF

Kaminski *et al.* developed a polarizable protein force field (PFF) based on *ab initio* quantum theory.[136, 137] The electrostatic interaction is modeled with induced dipoles and permanent point charges. With the exception of a dispersion parameter, all other parameters, including the electrostatic charges and polarizabilities, are obtained by fitting to quantum chemical binding energy calculations for homodimers. The dispersion parameters are later refined by fitting to the experimental densities of organic liquids.[16] Gas-phase many-body effects, as well as conformational energies, are well reproduced,[137] and MD simulations for real proteins are reasonably accurate at modest computational costs.[16, 138]

To reduce the computational cost, a POSSIM (Polarizable Simulations with Second-order Interaction Model) force field was later proposed, in which the calculation of induced dipoles stops after one iteration.[139, 140] The computational efficiency can be improved by almost an order of magnitude by using this formalism. Because the analytical gradients (forces) are unavailable, a Monte-Carlo technique is used in condensed-phase simulations. POSSIM has been validated on selected small model systems, showing good agreement with *ab initio* quantum mechanical and experimental data. Parameters for alanine and protein backbone have been reported.[141]

Polarizable force fields for non-biological systems also exist. A many-body polarizable force field by Smith and coworkers was developed and applied to the simulations of ion conduction in polyethylene oxide (PEO).[142-144] Cummings and coworkers developed an interesting Gaussian charge polarizable force field for ions and in polyethylene oxide (PEO).[145-147] A polarizable force field for ionic liquids was also reported to provide accurate thermodynamics and transport properties.[148]

# 3. Applications

## 3.1. Water Simulations

Due to its important role in life, water is a natural choice for polarizable force field development. After the polarizable (and dissociable) water model of Stillinger and David,[149] more than a dozen polarizable water models have been reported.[150]

Similar to how the polarization models discussed previously, the polarizable water models likewise fall into three major categories. Most belong to the first category, including the Stillinger and Davidôs water model, SPCP,[151] PTIP4P, [152] CKL,[153] NCC,[154] PROL,[155] Dang-Chang[156] and others. These models all adopted the induced dipole framework to treat polarization, typically using a single polarizable site on water. TTM models[157-160] and the AMOEBA water model[15] utilize an interactive, distributed atomic polarizability with Tholeôs damping scheme[45] to treat electrostatics and polarization. The Drude Oscillator-based water models include SWM4-DP,[26] and SWM4-NDP,[25] as well as the Charge-On-Spring (COS) model,[161] and its improved variation.[162] The third group includes the SPC-FQ and TIP4P-FQ[163] water models that utilize the fluctuating charge scheme to model polarization. The partial charges flow from one atom to another, and the

363 total charge of a water molecule need not be zero. Stern *et al.* proposed a unique water
364 model (POL5) by combining the fluctuating charge with the point induced dipole
365 scheme.[164] Several more sophisticated polarizable water models based on quantum
366 mechanics were developed based on quantum mechanics, including QMPFF,[165] DPP2,[166]
367 and Polarflex.[167] For example, the charge penetration, induction, and charge transfer
368 effects have been incorporated into the DPP2 (Distributed Point Polarizable Model)
369 model which reproduces well the high-level *ab initio* energetics and structures for large
370 water clusters.

371 An advantage of a polarizable water model over most non-polarizable models is the
372 ability to describe the structure and energetics of water in both gas and condensed phases.
373 Water dimer interaction energies, the geometry of water clusters and the heat of
374 vaporization of neat water can be reproduced well by most polarizable models. Some
375 highly parameterized nonpolarizable force fields such as TIP5P, TIP4P-EW and
376 TIP4P/2005 actually perform as well or better than some polarizable force fields over a
377 range of liquid properties, including the density-temperature profile, radial distribution
378 function, and diffusion coefficient. However, for water molecules experiencing
379 significant changes in environment, e.g., from bulk water to the vicinity of ions or
380 nonpolar molecules, only the polarizable models can capture the change of water dipole,
381 structure and energetics.[168]

382 Polarization water models are being extended and applied to other phases as well as to
383 the interface between different phases. Rick *et al* recently incorporated charge transfer
384 into their polarizable water model that was then used to study ice/water coexistence
385 properties and properties of the ice Ih phase.[169] The POL3 water model[14, 170] was used to

study the ice-vapor interface, and to calculate the melting point of ice Ih. Bauer and Patel used the TIP4P-QP model to study the liquid-vapor coexistence.[171]

## 3.2. Ion Solvation

Ions are an important component in many chemical and biological systems. Nearly half of all proteins contain metal ions, and they play essential roles in many fundamental biological functions. Some metal ions are critical for both protein structure and function. In enzymes, ions can bind and orient the substrates through electrostatic interactions at the active sites, thus controlling catalytic reaction. Divalent ions are vital in nucleic acid structures. Modeling ion-water and ion-biomolecule interactions accurately is very important.

Due to the high electron density and small sizes of ions, the non-polarizable models fail to capture the structural details adequately and do not or to reproduce the atomic dipole of water around the ions.[172-176] Several studies of ion solvation have been reported using different polarizable models[51-53, 116, 120, 177-187] with analyses focused on solvation structures, charge distribution, and binding energies. Noted that no straightforward experimental measurement of hydration free energy data exist because the macroscopic system must be neutral. Different assumptions are used to decompose the experimental hydration free energy into single ion contributions. The hydration free energy of some monovalent ions such as $Na^+$ and $K^+$ from different sources can vary by as much as 10 kcal/mol. It is more reliable to compare the hydration free energy of the whole salt and the relative energy between cations or anions.

The AMOEBA polarizable force field has been used to model a number of anions and cations, including $Na^+$, $K^+$, $Mg^{++}$, $Ca^{++}$, $Zn^{++}$, $Cl^-$, $Br^-$, and $I^-$.[51-53, 188] Parameters for these ions, including the vdW parameters and polarization damping coefficients (for divalent ions only), were obtained by fitting to the *ab initio* QM interaction energy profiles of ion-water pairs. Molecular dynamics simulations were then performed to evaluate the ion-cluster solvation enthalpies and solvation free energies.[51-53, 188] The excellent agreement between calculated and experimental hydration free energy, often within 1%, demonstrate that polarizable force fields are transferable between phases. *Ab initio* energy decomposition using, e.g., the Constrained Space Orbital Variations (CSOV) method,[99, 189] have also been applied to examine the polarization component of the ion-water interaction energy and to guide the force field parameterization.[53, 190] More recently, the AMOEBA force field was used to model the hydration of high valent Th(IV)[94] and studies on open-shell actinides are underway.

The SIBFA model was used to examine Pb(II),[191] lanthanides (La(III) and Lu(III)) and actinides (Th(IV)) in water.[94] SIBFA-predicted interaction energies generally matched well with the *ab initio* results, including the energy decompositions. Lamoureux and Roux developed the CHARMM polarizable force field for alkali and halide ions based on the Drude Oscillator.[177] Hydration free energies, calculated via thermodynamic integration,[192] showed an encouraging agreement with experiment.

## 3.3. Small Molecules

Small molecules are building blocks of biomolecules and serve as substrates and inhibitors. Abundant experimental measurements on various physical and chemical

properties exist for common organic molecules which in turn are used in the parameterization of the force fields. Polarizable and non-polarizable force fields can usually produce reasonable estimations of physical properties of neat liquids.[193-196] Extensive studies using polarizable force fields, covering major functional group, including alkanes, alcohols, aldehydes, ketones, ethers, acids, aromatic compounds, amines, amides, and some halogen compounds have been reported.[28, 36, 55, 110, 112, 126, 197-199] Calculations of structure, dipole moment, heterodimer binding energy, liquid diffusion constant, density, heat of vaporization, and hydration free energy are usually performed to assess the quality of force field parameters.

The electrostatic multipole parameters in AMOEBA were derived using the DMA procedure. They can be further optimized to the electrostatic potentials of chosen *ab initio* theory and basis sets. The AMOEBA valence parameters were derived from *ab initio* data such as molecular geometries and vibrational frequencies of the gas-phase monomer. The vdW parameters are estimated from gas-phase cluster calculations, and subsequently refined in liquid simulations using experimental data (e.g., densities and heats of vaporization). The torsional parameters the last obtained during the parameterization scheme are derived by fitting to *ab initio* QM conformational energy profiles. An automated protocol (PolType) that can generate AMOEBA parameters for small molecules is under development.[200] Because force field parameterization is a tedious process, such an automated tool is convenient and reduces the likelihood of human error.

The CHARMM-Drude force field developers devoted much of their efforts on organic compounds. Their parameterization scheme starts from an initial guess of charge (based

452 on the CHARMM22 force field), and invokes changes at some lone pair sites. Those
453 parameters are then fit to a series of ñperturbedò ESP maps. The vdW parameters are then
454 optimized to match neat liquid properties as is done many other force fields.[115] Overall, a
455 systematic improvement over the CHARMM22 additive force field has been observed for
456 both gas-phase and condensed-phase properties. These studies on small molecules lay the
457 groundwork for developing a Drude-based polarizable force field for proteins and nucleic
458 acids.

459 ## 3.4. Proteins

460 One of the goals for polarizable force fields is to model accurately protein structures,
461 dynamics, and interactions. Proteins are a ubiquitous class of biopolymers whose
462 functionalities depend on the details of their 3D structures, which, in turn, are largely
463 determined by their amino acid sequences. Fixed-charge force fields for proteins, like
464 AMBER, CHARMM, and OPLS-AA, have been developed and for years subjected to
465 various tests and validations. The development of polarizable protein force fields is still
466 in its infancy. Although the importance of including polarization effects was recognized
467 long ago, polarizable protein force fields emerged only in the past decade.[9, 21, 28, 29, 37, 138,
468 201-205]

469 The use of polarizable electrostatics in protein simulations dates back to 1976,[1] when
470 Warshel and Levitt simulated lysozyme via single point calculations. Kaminski et al.
471 reported in 2002 an *ab initio* polarizable protein force field (PFF) based on inducible
472 dipoles and point charges.[16,137] Simulations on bovine pancreatic trypsin inhibitor using
473 PDFF showed a satisfactory root mean square displacement (RMSD) compared to the

experimental crystal structure and polarization was found to affect the solvation dynamics.[138] The fluctuating-charge based ABEEM/MM force field was used to examine protein systems like trypsin inhibitors[206] and the heme prosthetic group.[207] The SIBFA force field has been used to study the interaction between focal adhesion kinase (FAK) and five pyrrolopyrimidine inhibitors.[208] The energy balances accounting for the solvation/desolvation effects calculated by SIBFA agree with experimental ordering. Water networks in the binding pocket were shown to be critical in terms of binding affinity. Moreover, the polarization contribution was considered as an indispensable component during the molecular recognition. In comparison, the continuum reaction field procedure fails to reproduce these properties. In addition kinases, the SIBFA protein force field has been used to study a variety of metalloproteins encompassing cations such as $Cu^{+}$, $Zn^{++}$, $Ca^{++}$ or $Mg^{++}$, as well as enabling inhibition studies.[91, 209-211] Future molecular dynamics simulations should extend the applicability of SIBFA to protein-ligand binding.

Ren and coworkers have been systematically developing the AMOEBA protein force field, and using it to study to several protein systems to understand protein-ligand binding.[57-59, 61] More recently an X-Pol force field for proteins has been developed and demonstrated in a simulation of solvated trypsin.[32]

The first attempt to compute the protein-ligand binding free energy using a polarizable force field was made on the trypsin-benzamidine systems using AMOEBA.[57, 61, 62] The absolute binding free energy of benzamidine to trypsin, and the relative binding free energies for a series of benzamidine analogs, were computed using a rigorous alchemical transformation. AMOEBA was successful in evaluating the binding free energies

497 accurately with an average error well within 1.0 kcal/mol. A similar study on trypsin,
498 thrombin and urokinase was reported using another *ab initio* QM-based polarizable force
499 field.[212] A thermodynamic integration scheme was used to compute the relative binding
500 free energies, which were in excellent agreement with experimental data (root mean
501 squre error (RMSE)=1.0 kcal/mol).

502 AMOEBA was later used to examine an ñentropic paradoxò associated with ligand
503 preorganization discovered in a previous study of conformationally constrained
504 phosphorylated-peptide analogs that bind to the SH2 domain of the growth receptor
505 binding protein 2 (Grb2).[59] The paradox refers to the unusual trend in which the binding
506 of unconstrained peptides (assumed to lose more entropy upon binding) is actually more
507 favorable entropically than are the constrained counterparts. AMOEBA correctly
508 reproduced the experimental trend and at the same time repeated a mechanism in which
509 the unconstrained peptide ligands were ñlockedò by intramolecular nonbonded
510 interactions. The simulations uncovered a crucial caveat that had not been previously
511 acknowledged regarding the general design principle of ligand preorganization, which is
512 presumed by many to have a favorable effect on binding entropy.

513 More recently, Zhang *et al.* demonstrated the ability of AMOEBA in dealing with
514 systems with a metal ion.[58] Those authors studied the Zinc-containing matrix
515 metalloproteinases (MMPs) in a complex with an inhibitor where the coordination of
516 $Zn^{++}$ was with organic compounds and protein side chains. Polarization was found to play
517 a key role in $Zn^{++}$ coordination geometry in MMP. In addition, the relative binding free
518 energies of selected inhibitors binding with MMP13 were found to be in excellent
519 agreement with experimental results. As with the previous trypsin study, it was found that

binding affinities are likely to be overestimated when the polarization between ligands and environments is ignored.

Having a more rigorous physical model for treating polarization, the ability to model protein-ligand interactions has been improved significantly. Systems involving highly charged species, like metal ions, can now be treated with confidence. This in turn, provides tremendous opportunities for investifating important proteins for drug discovery and for protein engineering.

## 3.5. Lipids

With the rapid development of computational resources, simulations of large systems like lipid bilayers with membrane proteins is feasible.[126, 213] Patel and coworkers have been developing a polarizable force field for biomembranes to study the structure and dynamics of ion channel systems.[40, 113, 128, 214] Simulations of solvated DMPC (dimyristoyl phosphatidylcholine) and dipalmitoylphosphatidylcholine (DPPC) bilayers were reported.[113, 214] The distribution of the membrane components along the lipid bilayer is similar to that from a fixed charge model. The water dipole moment was found to increase from about 1.9 Debye in the middle of the membrane plane to the average bulk value of 2.5~2.6 Debye. The lipid surface computed with the polarizable force field was not improved from those of non-polarizable ones however. In addition, ion permeation in a gramicidin A channel embedded in a DMPC bilayer was investigated.[113] Davis and Patel concluded that including the electronic polarization lowered the ion permeation free energy barrier significantly, from 12 kcal/mol to 6 kcal/mol.

## 3.6. Continuum Solvents for Polarizable Biomolecular Solutes

A continuum solvent replaces explicit atomic details with a bulk, mean-field response. It is possible to demonstrate from statistical mechanics that an implicit solvent potential of mean force (PMF) exists, wihch preserves exactly the solute thermodynamic properties obtained from explicit solvent.[215] It is possible to formulate a *perfect* implicit solvent in principle, but in practice approximations are necessary to achieve efficiency. This remains an active area of research.[216] An implicit solvent PMF can be formulated via a thermodynamic cycle that discharges the solute in vapor, grows the uncharged (apolar) solute into a solvent $W_{apolar}(\mathbf{X})$ and finally recharges the solute within a continuum dielectric $W_{elec}(\mathbf{X})$

$$W_{PMF}(\mathbf{X}) = W_{apolar}(\mathbf{X}) + W_{elec}(\mathbf{X}) \quad [12]$$

The continuum electrostatic energy, including mobile electrolytes, can be described by either the nonlinear Poisson-Boltzmann Equation (NPBE) or the simplified linearized Poisson-Boltzmann Equation (LPBE)

$$\nabla \cdot [\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] - \bar{\kappa}^2(\mathbf{r})\phi(\mathbf{r}) = -4\pi\rho(\mathbf{r}) \quad [13]$$

where the coefficients are a function of position $\mathbf{r}$, $\phi$ is the potential, $\varepsilon$ is the pemittivity, $\bar{\kappa}$ is the modified Debye-Hückel screening factor, and $\rho$ is the solute charge density.[217, 218] Implementations of a Poisson-Boltzmann continuum for many-body quantum mechanical potentials have been applied to small molecules for decades. Examples include the Polarizable Continuum Model (PCM) [219, 220], COSMO [221] and the Solvent Model series (SM*x*).[222] In contrast, applications of biomolecular continuum electrostatics have been limited mainly to fixed partial charge solute descriptions for reasons of computing efficiency force field availability. However, as a result of increasing

564 computational power and the completion of the polarizable force fields for biomolecules
565 described above, the coupling of classical many-body potentials to continuum
566 electrostatics is now possible.

567 An important initial demonstration of polarizable biomolecules within a Poisson-
568 Boltzmann continuum used the Polarizable Force Field (PFF) of Maple *et al.* to model
569 protein-ligand interactions.[223] A second demonstration used the Electronic Polarization
570 from Internal Continuum (EPIC), which accounts for intramolecular polarization using a
571 continuum dielectric.[224, 225] Finally, the polarizable multipole Poisson-Boltzmann (PMPB)
572 model based on the AMOEBA force field demonstrated that the self-consistent reaction
573 field (SCRF) of proteins within a continuum solvent is consonant with the ensemble
574 average response of explicit solvent.[71] Contrarily, end-state calculations of protein-ligand
575 binding affinity using the PMPB model were shown to not recapitulate explicit solvent
576 alchemical free energies to chemical accuracy.[61] This motivates development of analytic
577 continuum electrostatics (discussed next), which are fast enough to allow binding
578 affinities to be computed using alchemical sampling, rather than merely relying on end-
579 states. A key advantage of EPIC is that the biomolecular self-consistent field (SCF) is
580 determined by a single numerical finite-difference (FD) solution of the PBE, unlike the
581 aforementioned atom-centered PFF and PMPB models that require a new solution for
582 each SCF iteration. However, a tradeoff of EPICôs efficiency gain is a reduction in model
583 flexibility because electrostatic masking rules cannot be incorporated into the FD solver
584 (i.e., the permanent field due to 1-2 or 1-3 interactions cannot be neglected). Although
585 masking of short-range bonded interactions is the standard approach used by essentially
586 all biomolecular force fields, this is not possible for an EPIC style energy model.

The first example of an analytic continuum electrostatic model for polarizable biomolecules is the generalized Kirkwood (GK) model for the AMOEBA force field.[73] The AMOEBA/GK approach has been combined with alchemical sampling to predict trypsin-ligand binding affinity with a correlation coefficient of 0.93. This is a significant improvement over the PMPB end-state approach.[226] A second example, based on the ABEEM$\sigma\pi$ fluctuating charge force field combined with a generalized Born (GB) continuum electrostatic model, showed promising results for the computation of solvation free energies for small organic molecules and peptide fragments.[227]

## 3.7. **Macromolecular X-ray Crystallography Refinement**

X-ray crystallography is the dominant experimental method for determining the 3-dimensional coordinates of macromolecules. Collected diffraction data is the Fourier transform of the ensemble average electron density of the macromolecular crystal. While reciprocal space amplitudes of Bragg diffraction peaks are measured, their phases are not. Instead, phase information is derived from the Fourier transform of a model structure that is sufficiently close to the actual experimental ensemble. This is known as molecular replacement (MR). After an initial model has been built into the electron density, further refinement is based optimizating a target function $E_{\text{target}}$ of the form

$$E_{\text{target}} = w_A E_{\text{X-ray}} + E_{\text{Force Field}} \qquad [14]$$

where $E_{\text{X-ray}}$ evaluates the agreement between measured and calculated diffraction amplitudes, $E_{\text{Force Field}}$ restrains the model using prior knowledge of intra- and intermolecular chemical forces and $w_A$ weights the relative strength of the two terms.[77,

608 [228] We now focus on the evolution of the prior chemical knowledge used during the X-
609 ray refinement process, and we culminate in ongoing work using polarizable force fields
610 in combination with PME electrostatics algorithms to obtain the most accurate,
611 informative biomolecular models possible.

612 The first application of molecular mechanics to macromolecular X-ray crystallography
613 refinement (based on fixed partial charge electrostatics evaluated using a spherical cutoff)
614 was on influenza-virus hemagglutinin by Weis *et al.* in 1990.[229] This work demonstrated
615 that electrostatics maintained chemically reasonable hydrogen-bonding, although charged
616 surface residues were sometimes observed to form incorrect salt bridges.[229] The latter
617 observation highlights the importance of accounting for dielectric screening arising from
618 the heterogeneous distribution of solvent within a macromolecular crystal, by using one
619 of the above described continuum electrostatics models. For example, the generalized
620 Born (GB) model for fixed charge electrostatics has been described, albeit with a
621 spherical cutoff approximation.[230] Comparing refinements with and without GB
622 screening showed that roughly 10% of the amino acid side-chain conformations were
623 altered, with 75% of these side-chain differences due to residues at the macromolecular
624 surface.[230] Although these first applications of fixed charge force field electrostatics were
625 encouraging, the use of spherical cutoffs to approximate crystal lattice sums is now
626 known to be only conditionally convergent and therefore prone to a variety of artifacts.[231]

627 In 1921, Ewald introduced an absolutely convergent solution to the problem of evaluating
628 electrostatic lattice summations in crystals. He did this by separating the problem into a
629 short-ranged real space sum and a periodic, smoothly varying, long-range sum that can be
630 evaluated efficiently in reciprocal space.[232] This approach, now known as Ewald

631 summation, has been described for both fixed partial charges and atomic multipoles.[233,
632 234] More recently, the efficiency of Ewald summation was improved via the particle-mesh
633 Ewald (PME) algorithm, wherein the reciprocal space summation leverages the fast
634 Fourier transforms (FFT)[235] via b-Spline interpolation[236] for both fixed partial charge and
635 atomic multipole descriptions.[237]

636 The speed of the PME algorithm has been further improved for crystals by incorporating
637 explicit support for space group symmetry and by parallelization for heterogeneous
638 computer architectures.[63] Combining the polarizable AMOEBA force field with
639 electrostatics evaluated using PME has been shown to improve macromolecular models
640 from X-ray crystallography refinement in a variety of contexts.[64, 77, 238-240] At high
641 resolution (~1 Å or lower**)**, the information contained within a polarizable atomic
642 multipole force field can be used to formulate the electron density of the scattering model
643 ($E_{\text{X-ray}}$), in addition to contributing chemical restraints ($E_{\text{Force Field}}$).[64, 238] The importance
644 of the prior chemical information contained in a polarizable force field is most significant
645 when positioning parts of the model that are not discernable from the experimental
646 electron density, as in the orientation of water hydrogen atoms[239] or secondary structure
647 elements for mid-to-low resolution data sets (~3-4 Å).[63]

648 Let use consider an example, the AMOEBA-assisted biomolecular X-ray refinement with
649 electrostatics evaluated via PME in the program *Force Field X*. This program was used to
650 re-refine nine mouse and human DNA methyltransferase 1 (Dnmt1) data sets deposited in
651 the Protein databank (PDB). Significant improvements in model quality (presented in
652 Table 1) were achieved as assayed by the MolProbity [241] structure validation tool. The
653 MolProbity score is calibrated to reflect the expected resolution of the X-ray data. After

re-refinement, the average MolProbity score was reduced to 2.14, indicating a level of model improvement consistent with collecting data to 0.67 Å higher resolution. For example, the pose of *S*-adenosyl-L-homocysteine **(**SAH) from mouse (3PT6) and human (3PTA) structures differed by an RMSD of 1.6 Å before re-refinement, but only 0.9 Å afterwards.

**Table 1.** DNA Methyltransferase 1 (Dnmt1) Models Before and After Polarizable X-Ray Refinement with the Program *Force Field X*.

| | | **Protein Databank** | | | | **Re-Refined with *Force Field X*** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Statistics | | MolProbity | | Statistics | | MolProbity | |
| PDB | Res. (Å) | R | $R_{free}$ | Score | (%) | R | $R_{free}$ | Score | (%) |
| 3AV4 | 2.8 | 0.232 | 0.267 | 2.87 | 68.0 | 0.238 | 0.282 | 2.25 | 95.0 |
| 3AV5 | 3.3 | 0.188 | 0.264 | 3.09 | 79.0 | 0.216 | 0.275 | 2.44 | 97.0 |
| 3AV6 | 3.1 | 0.195 | 0.255 | 2.99 | 81.0 | 0.213 | 0.265 | 2.37 | 97.0 |
| 3EPZ | 2.3 | 0.213 | 0.264 | 2.27 | 78.0 | 0.254 | 0.292 | 2.09 | 87.0 |
| 3OS5 | 1.7 | 0.211 | 0.238 | 2.01 | 54.0 | 0.182 | 0.213 | 1.77 | 74.0 |
| 3PT6 | 3.0 | 0.211 | 0.266 | 2.95 | 78.0 | 0.207 | 0.268 | 1.97 | 99.0 |
| 3PT9 | 2.5 | 0.196 | 0.256 | 2.72 | 60.0 | 0.181 | 0.248 | 1.90 | 97.0 |
| 3PTA | 3.6 | 0.257 | 0.291 | 3.65 | 57.0 | 0.211 | 0.271 | 2.41 | 99.0 |
| 3SWR | 2.5 | 0.220 | 0.272 | 2.69 | 62.0 | 0.204 | 0.264 | 2.03 | 95.0 |
| Mean | 2.7 | 0.214 | 0.264 | 2.80 | 68.6 | 0.212 | 0.264 | 2.14 | 93.3 |
| Mean Improvement | | | | | | | | **0.67** | **24.8** |

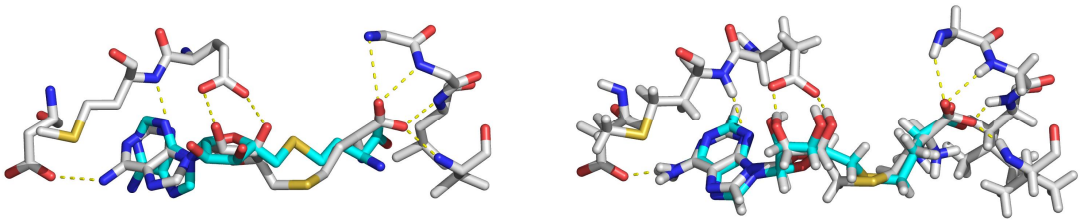

**Figure 1.** Polarizable biomolecular X-ray refinement on two Dnmt1 data sets. The left panel shows the deposited pose of SAH from data sets 3PT6 (mouse, grey) and 3PTA (human, cyan) do not agree (coord. RMSD 1.6 Å). In the right panel, the poses of SAH from mouse and human structures are more consistent (coord. RMSD 0.9 Å) after *Force*

*Field X* refinement.

## 3.8. Prediction of Organic Crystal Structure, Thermodynamics and Solubility

It was emphasized in 1998 that predicting crystal structures from chemical composition remained a major unsolved challenge.[242] Significant progress has been made since then to address this challenge, as evidenced by successes of the 4th and 5th blind tests of crystal structure prediction (CSP) organized by the Cambridge Crystallographic Data Center (CCDC).[243, 244] Prediction of crystal structures is important in the pharmaceutical industry, where extensive experimental screens are necessary to explore the range of stable polymorphs a molecule may form. The unique three-dimensional molecular packing of each polymorph determines its physical properties such as stability and bioavailability. For this reason, both FDA approval and patent protection are awarded to a specific crystal polymorph, rather than to the molecule itself. To illustrate this point, eight companies have filed eleven patents on five possible crystal forms of the molecule cefdinir.[245]

Prediction of thermodynamically stable crystal structures from chemical composition requires a potential energy function capable of distinguishing between large numbers of structures that are closely spaced in thermodynamic stability.[246, 247] In this section, we restrict our focus to energy models that explicitly account for electronic polarization classically[65, 248, 249] and neglect the more expensive electronic structure methods sometimes used to (re)score favorable structures.[250]

The vast majority of CSP has been limited to using intermolecular potentials that lack explicit inclusion of polarization,[249, 251] although its importance has become a topic of

689 interest[35, 252-254]. Non-polarizable force fields, based on fixed partial charges or fixed
690 atomic multipoles, must implicitly account for the 20% to 40% of the lattice energy
691 attributable induction.[249] On the other hand, polarizable models such as the AMOEBA
692 force field for organic molecules [54, 255] based on the Thole damping scheme[45] and the
693 Williams-Stone-Misquitta (WSM) method[256, 257] for obtaining distributed polarizabilities
694 allow one to include polarization during CSP explicitly.

695 Beyond polarization, modeling the conformational flexibility and corresponding
696 intermolecular energetics of organic molecules via sampling methods such as molecular
697 dynamics is essential to predicting the thermodynamic properties of crystals.[258] For
698 example, the structure, stability and solubility of *n*-alkylamide crystals, from acetamide
699 through octanamide, can be predicted by an alchemical sampling method to compute the
700 sublimation/deposition phase transition free energy.[65]

701 # 4. Summary

702 Significant progress has been made in the past decade in developing general-purpose
703 polarizable force fields. Polarizable force fields have exhibited success in disparate
704 research areas including ion solvation, protein-ligand interactions, ion channels and lipids,
705 macromolecular structural refinement and so on. There remain plenty of challenges ahead.
706 The importance of polarization still needs to be established systematically for a wide
707 range of biological systems. While polarizable force fields in principle have better
708 transferability than do non-polarizable force fields, they are also expected to also perform
709 better in a broader range of systems, making parameterization a more elaborate process.
710 In addition to polarization, treatment of other physical effects, including high-order

711 permanent charge distributions interactions, short-range electrostatic penetration and
712 charge-transfer effects need further improvement to advance the overall quality of
713 classical electrostatic models. Because computational efficiency (including the need for
714 parallelization) has been a major barrier to the adoption of polarizable force fields, better
715 and more efficient algorithms are also required to advance the application of polarizable
716 force fields. A future area for advancement is to combine the polarizable force fields with
717 fixed-charge force fields in a multiscale fashion, as is done with QM/MM. Technically
718 this can be achieved straightforwardly but caution is needed to ensure the interactions
719 across the two resolutions are balanced.

720 **Acknowledgement.** The authors are grateful to the support provided by Robert A. Welch
721 Foundation (F-1691).

722

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