

Polarizable Force Fields for Biomolecular Modeling

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¹ Polarizable Force Fields for Biomolecular Modeling

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24 **1. Introduction**

Molecular mechanics based modeling has been widely used in the study of chemical and 25 26 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 27 1970's,¹ followed by the first molecular dynamics simulations of the bovine pancreatic 28 trypsin inhibitors (BPTI).²⁻⁴ Over the past 30 years, a great number of empirical 29 molecular mechanics force fields, including AMBER,⁵ CHARMM,⁶ GROMOS,⁷ OPLS,⁸ 30 31 and many others, have been developed. These force fields share similar functional forms, including valence interactions represented by harmonic oscillators, point dispersion-32 repulsion for van der Waals (vdW) interactions, and an electrostatic contribution based 33 on fixed atomic partial charges. This generation of molecular mechanics force fields has 34 been widely used in the study of molecular structures, dynamics, interactions, design and 35 engineering. We refer interested readers to some recent reviews for detailed discussions.⁹ 36 10 37

Although the fixed charge force fields enjoyed great success in many areas, there remains 38 39 much room for improvement. In fixed charge based electrostatic models, the atomic 40 partial charges are meant to be opre-polarizedo for condensed phases in an averaged fashion, typically achieved by the fortuitous overestimation of electrostatic charges by 41 low-level *ab initio* quantum mechanics. Such models thus lack the ability to describe the 42 variation in electrostatics due to many-body polarization effects, which have been shown 43 to be a significant component of intermolecular forces.¹⁰⁻¹² With the rapid growth of 44 computational resources, there has been increasing effort to explicitly incorporate many-45 46 body induction into molecular mechanics to improve the accuracy of molecular modeling. 47 Classical electrostatics models that take into account polarization appeared as early as the 1950s. Barker in his 1953 paper õStatistical Mechanics of Interacting Dipolesö discussed 48 the electrostatic energy of molecules in terms of õpermanent and induced dipolesö.¹³ 49 Currently, polarizable models generally fall into three categories: those based on induced 50 point dipoles,^{9, 14-23} the classical Drude oscillators,²⁴⁻²⁶ and fluctuating charges.²⁷⁻³⁰ More 51 sophisticated force fields that are õelectronic structure-basedö^{31, 32} or use õmachine 52 learning methodsö³³ also exist, but incur higher computational costs. Discussions of the 53 54 advantages and disadvantages of each model and their applications will be presented in the following sections. 55

Compared to fixed charge models, the polarizable models are still in a relatively early 56 stage. Only in the past decade or so has there been a systematic effort to develop general 57 polarizable force fields for molecular modeling. A number of reviews have been 58 published to discuss various aspects of polarizable force fields and their development.^{9, 34-} 59 ⁴⁰ Here, we focus on the recent development and applications of different polarizable 60 force fields. We begin with a brief introduction to the basic principles and formulae 61 62 underlying alternative models. Next, the recent progress of several well-developed polarizable force fields is reviewed. Finally, applications of polarizable models to a 63 range of molecular systems, including water and other small molecules, ion solvation, 64 65 peptides, proteins and lipid systems are presented.

66 1. Modeling Polarization Effects

67 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

$$M_i = M_i^0 + M_i^{ind}$$
 [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.

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

79
$$\mathbf{U}_{ele} = \frac{1}{2} \sum_{i} \sum_{j \neq i} \mathbf{M}_{i}^{t} \mathbf{T}_{tj} \mathbf{M}_{j}$$
 [2]

80 where T is the interaction operator and is a function of the distance between i and j. In the 81 case of point charge interactions, T is simply 1/r. The work (positive energy) needed to 82 polarize a charge distribution also has a quadratic dependence on the induced charge 83 distribution:

84
$$\mathbf{U}_{\text{work}} = \frac{1}{2} \sum_{i} \left(\mathbf{M}_{i}^{\text{ind}} \right)^{t} \alpha_{i}^{-1} \mathbf{M}_{i}^{\text{ind}}$$
[3]

85 where is the polarizability of site *i* that includes all orders of polarizability including 86 dipole polarizability.⁴¹ Although 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}

89 The total electrostatic energy is

90
$$\mathbf{U}_{\text{ele}} = \frac{1}{2} \sum_{i} \sum_{j \neq i} \mathbf{M}_{i}^{\text{t}} \mathbf{T}_{ij} \mathbf{M}_{j} + \frac{1}{2} \sum_{i} \left(\mathbf{M}_{i}^{\text{ind}} \right)^{\text{t}} \alpha_{i}^{-1} \mathbf{M}_{i}^{\text{ind}}$$
 [4]

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

92
$$\frac{\partial \mathbf{U}_{ele}}{\partial \mathbf{M}_{i}^{ind}} = \sum_{j \neq i} \mathbf{T}_{ij} \mathbf{M}_{j} + \alpha_{i}^{-1} \mathbf{M}_{i}^{ind} = \mathbf{0}$$
 [5]

93 As a result

94
$$\mathbf{M}_{i}^{\text{ind}} = \alpha_{i}^{-1} \sum_{j \neq i} \mathbf{T}_{ij} \left(\mathbf{M}_{j}^{0} + \mathbf{M}_{j}^{\text{ind}} \right)$$
[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

99
$$U_{ele} = \frac{1}{2} \sum_{i} \sum_{j \neq i} \left(\mathbf{M}_{i}^{0} \right)^{t} \mathbf{T}_{ij} \mathbf{M}_{j}^{0} + \frac{1}{2} \sum_{i} \sum_{j \neq i} \left(\mathbf{M}_{i}^{ind} \right)^{t} \mathbf{T}_{ij} \mathbf{M}_{j}^{0}$$
[7]

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

102 **1.2.** Classic Drude Oscillators

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

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

108

$$\sum_{A < B} E_{ele} = \sum_{A < B}^{N} \frac{q_{\mathcal{C}}(A)q_{e}(B)}{r_{\mathcal{C}}(A) - r_{\mathcal{C}}(B)|} + \sum_{A < B}^{N,N_{D}} \frac{q_{D}(A)q_{C}(B)}{|r_{D}(A) - r_{\mathcal{C}}(B)|} + \sum_{A < B}^{N_{D}} \frac{q_{D}(A)q_{D}(B)}{|r_{D}(A) - r_{D}(B)|} + \frac{1}{2} \sum_{A}^{N_{D}} k_{D}(r_{D}(A) - r_{\mathcal{C}}(B))^{2}$$
109
109
(8]

110 where N_D and N are the number of Drude particles and non-hydrogen atoms, q_D and q_C 111 are the charges on the Drude particle and its parent atom, respectively, r_D and r_C are their 112 respective positions, and k_D is the force constant of the harmonic spring between the 113 Drude oscillator and its parent atom. The last term in Equation [8] accounts for the cost 114 of polarizing the Drude particles.

The atomic polarizability () is a function of both the partial charge on the Drude particleand the force constant of the spring

117
$$\alpha = \frac{q_D^2(A)}{k_D}$$
[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

121 **1.3.** Fluctuating Charges

122 The formalism of the fluctuating charge model is based on the charge equilibration 123 (CHEQ) method,⁴⁶ in which the chemical potential is equilibrated via the redistribution of 124 charge density. The charge-dependent energy for a system of M molecules containing N_i 125 atoms per molecule is expressed as

126
$$E_{CHEQ}(R,Q) = \sum_{i=1}^{M} \sum_{\alpha=1}^{N} \chi_{i\alpha} Q_{i\alpha} + \frac{1}{2} \sum_{i=1}^{M} \sum_{\beta=1}^{M} \sum_{\alpha=1}^{N_{i}} \sum_{\beta=1}^{N_{j}} J_{i\alpha i\beta} Q_{i\alpha} Q_{j\beta} + \frac{1}{2} \sum_{i=1}^{MN'} \sum_{j=1}^{MN'} \frac{Q_{i} Q_{j}}{4\pi\epsilon_{0} r_{ij}}$$

127
$$+ \sum_{j=1}^{M} \lambda_{l} \left(\sum_{l=1}^{N} Q_{lj} - Q_{j}^{Total} \right)$$
(10)

where Q_i is the partial charge on atomic site *i*. The 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

134
$$\mathbf{L} = \sum_{i=1}^{M} \sum_{\alpha=1}^{N} \frac{1}{2} m_{i\alpha} (\frac{\mathrm{d}r_{i\alpha}}{\mathrm{d}t})^{2} + \sum_{i=1}^{M} \sum_{\alpha=1}^{N} \frac{1}{2} m_{\mathbf{Q},i\alpha} (\frac{\mathrm{d}Q_{i\alpha}}{\mathrm{d}t})^{2} - \mathbf{E}(\mathbf{Q},\mathbf{r}) - \sum_{i=1}^{M} \lambda_{i} \sum_{\alpha=1}^{N} Q_{i\alpha} [11]$$

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 $_i$. 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

143 A few general force fields have been developed based on these formulas to explicitly 144 treat the polarization effect. We now discuss development highlights for some of the 145 representative force fields.

146 **2. Recent Developments**

147 **2.1. AMOEBA**

The AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) 148 force field, developed by Ponder, Ren and co-workers,^{15, 18, 37} utilizes atomic multipoles 149 to represent permanent electrostatics and induced atomic dipoles for many-body 150 polarization. The valence interactions include bond, angle, torsion and out-of-plane 151 152 contributions using typical molecular mechanics functional forms. The van der Waals interaction is described by a buffered-14-7 function. The atomic multipole moments 153 consist of charge, dipole and quadrupole moments, which are derived from ab initio 154 quantum mechanical calculations using procedures such as Stone Distributed Multipole 155 Analysis (DMA).⁴⁸⁻⁵⁰ The higher order moments make possible anisotropic 156 representations of the electrostatic potential outside atoms and molecules. The 157 polarization effect is explicitly taken into account via atomic dipole induction. The 158 159 combination of permanent atomic multipoles and induced dipoles enables AMOEBA to 160 capture electrostatic interactions in both gas and condensed phase accurately. The vdW parameters of AMOEBA are optimized simultaneously against both *ab initio* gas-phase 161 data and condensed-phase experimental properties. 162

In the past decade, AMOEBA has been applied to the study of water,¹⁵ monovalent and 163 divalent ions,⁵¹⁻⁵³ small molecules,^{54, 55} peptides^{18, 56} and proteins.⁵⁷⁻⁵⁹ AMOEBA 164 demonstrated that a polarizable force field is able to perform well in both gas and 165 solution phases with a single set of parameters. In addition, AMOEBA is the first 166 general-purpose polarizable force field utilized in molecular dynamics simulations of 167 protein-ligand binding and calculation of absolute and relative binding free energies.⁵⁸⁻⁶² 168 The computed binding free energies between trypsin and benzamidine derivatives 169 170 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 171 has recently been extended to biomolecular X-ray crystallography refinement^{63, 64}, and 172 consistently successful prediction of the structure, thermodynamic stability and solubility 173 of organic crystals⁶⁵ are encouraging. 174

AMOEBA has been implemented in several widely used software packages including 175 TINKER,⁶⁶ OpenMM,⁶⁷ Amber,⁶⁸ and Force Field X.⁶⁹ The AMOEBA polarizable force 176 field was first implemented within the FORTRAN-based TINKER software package⁷⁰ 177 178 using Particle Mesh Ewald (PME) for long-range electrostatics. Implementation of the polarizable-multipole Poisson-Boltzmann,⁷¹ which depends on the Adaptive Poisson-179 Boltzmann Solver (APBS),⁷² and generalized Kirkwood⁷³ continuum electrostatics 180 models also exist in TINKER, which is now being parallelized using OpenMP. The 181 algorithms in TINKER are also available from within CHARMM using the MSCALE 182 interface.^{74, 75} Alternative FORTRAN implementations of AMOEBA using PME are 183 available in the Sander and PMEMD molecular dynamics engines of AMBER,⁶⁸ with the 184 latter parallelized using MPI. The PME treatment of AMOEBA electrostatics has recently 185

been extended within the Java Runtime Environment (JRE) program Force Field X by 186 incorporating explicit support for crystal space group symmetry,⁶³ parallelizing for 187 heterogeneous computer hardware environments⁶³ and supporting advanced free energy 188 methods such as the Orthogonal Space Random Walk (OSRW) strategy.^{65, 76} These 189 advancements are critical for applications such as AMOEBA-assisted biomolecular X-ray 190 refinement,^{63, 77} efficient computation of protein-ligand binding affinity,^{57, 61} and 191 prediction of the structure, stability and solubility of organic crystals.⁶⁵ Finally, the 192 193 OpenMM software is working toward a general implementation of AMOEBA using the CUDA GPU programming language.⁷⁸ 194

195 **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 200 anisotropic polarizability tensors⁴³ are placed on the bond centers and on the heteroatom 201 lone pairs. Quadrupolar polarizabilities are used to treat metal centers. The force field is 202 designed to enable the simultaneous and reliable computation of both intermolecular and 203 conformational energies governing the binding specificities of biologically and 204 205 pharmacologically relevant molecules. Similar to AMOEBA, permanent multipoles are 206 used for permanent electrostatics in SIBFA. Flexible molecules are modeled by combining the constitutive rigid fragments. SIBFA is formulated on the basis of quantum 207

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 clusters⁸⁶ to 215 large complexes like metalloenzymes encompassing Zn(II).⁸⁷⁻⁹² It has been used to 216 investigate molecular recognition problems including the binding of nucleic acids to 217 metal ions,⁹³⁻⁹⁵ the prediction of oligopeptide conformations,^{86, 96} and for ligand-protein 218 binding.⁹⁷ Most of the SIBFA calculations reproduced closely the quantum chemistry 219 results, including both the interaction energy and the decomposed energy terms. At the 220 same time, electrostatic parameters are demonstrated to be transferable between similar 221 222 molecules.

,A Gaussian based electrostatic model (GEM) has been explored as an alternative to 223 distributed point multipole electrostatic representation.⁹⁸ GEM computes the molecular 224 interaction energies using an approach similar to SIBFA but replacing distributed 225 multipoles by electron densities.⁹⁹ GEM better captures the short-range effects on 226 intermolecular interaction energies, and it naturally includes the penetration effect. 227 Calculations on a few simple systems like water clusters⁹⁹ have demonstrated GEMøs 228 capability to reproduce quantum chemistry results. Furthermore, implementating PME 229 for GEM in a PBC showed reasonable computational efficiency thanks to the use of 230

Hermite Gaussian functions.¹⁰⁰ Therefore, replacing SIBFAøs distributed multipoles with the GEM continuous electrostatic model will be a future direction of methodology development.⁹⁸

234 **2.3. NEMO**

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

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

251 2.4. CHARMM-Drude

252 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 253 colleagues have been developing a polarizable CHARMM force field based on this 254 approach.^{25, 26, 109, 117} Unlike the induced dipole model, which treats the polarization 255 response using point dipoles, the Drude model represents the polarizable centers by a pair 256 of point charges. A point partial charge is tethered via a harmonic spring for each non-257 hydrogen atom. This point charge (the Drude oscillator) can react to the electrostatic 258 259 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. 260 261 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. 262 Small fictitious masses are assigned to each Drude particle and independent low 263 temperature thermostats are applied to the Drude particle degrees of freedom.¹¹⁸ In case 264 265 of energy minimization, self-consistent iteration will be required to solve for the polarization. 266

267 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. 268 The values for atomic charges and polarizabilities requires a series of calculations of 269 perturbed ESP maps. This force field has been parameterized for water^{25, 26}, and for a 270 series of organic molecules including: alkanes,¹¹⁰ alcohols,¹¹¹ aromatics,¹¹² ethers,^{113, 114} 271 amides,¹⁰⁹ sulfurs,¹¹⁵ and ions.^{119, 120} An attempt has also been made to combine the 272 Drude-based polarizable force field with quantum mechanics in QM/MM methods.¹²¹ It 273 was noted that pair-specific vdW parameters are needed to obtain accurate hydration free 274

energies of small molecules using the polarizable force field. This is likely due to theproblematic 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

280 **2.5. CHARMM-FQ**

The fluctuating charge model (FQ), also known as charge equilibration or 281 282 electronegativity equalization model, is an empirical approach for calculating charge distributions in molecules. In this formalism, the partial charge on each atom is allowed 283 284 to change to adapt to different electrostatic environments. The variable partial charges are computed by minimizing the electrostatic energy for a given molecular geometry. 285 Compared with the induced dipole and Drude models, the fluctuating charge models are 286 minimally parameterized and easier to implement because the polarizability is induced 287 without introducing new interactions beyond the point charges. Either extended 288 Lagrangian or self-consistent iteration can be used to compute the fluctuating charges in 289 MD simulations, with similar advantages and disadvantages as discussed above. 290

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

301 **2.6. X-Pol**

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

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

The X-Pol potential has been applied to MD simulations of liquid water,¹³¹ liquid hydrogen fluoride,¹³² and covalently bonded fragments.^{133, 134} This model was recently 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.

323 **2.7. PFF**

324 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 325 permanent point charges. With the exception of a dispersion parameter, all other 326 parameters, including the electrostatic charges and polarizabilities, are obtained by fitting 327 to quantum chemical binding energy calculations for homodimers. The dispersion 328 parameters are later refined by fitting to the experimental densities of organic liquids.¹⁶ 329 Gas-phase many-body effects, as well as conformational energies, are well reproduced,¹³⁷ 330 and MD simulations for real proteins are reasonably accurate at modest computational 331 costs.^{16, 138} 332

To reduce the computational cost, a POSSIM (Polarizable Simulations with Second-order 333 Interaction Model) force field was later proposed, in which the calculation of induced 334 dipoles stops after one iteration.^{139, 140} The computational efficiency can be improved by 335 almost an order of magnitude by using this formalism. Because the analytical gradients 336 (forces) are unavailable, a Monte-Carlo technique is used in condensed-phase simulations. 337 POSSIM has been validated on selected small model systems, showing good agreement 338 with ab initio quantum mechanical and experimental data. Parameters for alanine and 339 protein backbone have been reported.¹⁴¹ 340

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

347 **3. Applications**

348 **3.1. Water Simulations**

349 Due to its important role in life, water is a natural choice for polarizable force field 350 development. After the polarizable (and dissociable) water model of Stillinger and 351 David,¹⁴⁹ more than a dozen polarizable water models have been reported.¹⁵⁰

352 Similar to how the polarization models discussed previously, the polarizable water models likewise fall into three major categories. Most belong to the first category, 353 including the Stillinger and Davidøs water model, SPCP,¹⁵¹ PTIP4P,¹⁵² CKL,¹⁵³ NCC,¹⁵⁴ 354 PROL,¹⁵⁵ Dang-Chang¹⁵⁶ and others. These models all adopted the induced dipole 355 framework to treat polarization, typically using a single polarizable site on water. TTM 356 models¹⁵⁷⁻¹⁶⁰ and the AMOEBA water model¹⁵ utilize an interactive, distributed atomic 357 polarizability with Tholess damping scheme⁴⁵ to treat electrostatics and polarization. The 358 Drude Oscillator-based water models include SWM4-DP,²⁶ and SWM4-NDP,²⁵ as well as 359 the Charge-On-Spring (COS) model,¹⁶¹ and its improved variation.¹⁶² The third group 360 includes the SPC-FQ and TIP4P-FQ¹⁶³ water models that utilize the fluctuating charge 361 scheme to model polarization. The partial charges flow from one atom to another, and the 362

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 scheme.¹⁶⁴ Several more sophisticated polarizable water models based on quantum 365 mechanics were developed based on quantum mechanics, including OMPFF,¹⁶⁵ DPP2,¹⁶⁶ 366 and Polarflex.¹⁶⁷ For example, the charge penetration, induction, and charge transfer 367 effects have been incorporated into the DPP2 (Distributed Point Polarizable Model) 368 model which reproduces well the high-level *ab initio* energetics and structures for large 369 370 water clusters.

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

Polarization water models are being extended and applied to other phases as well as to the interface between different phases. Rick *et al* recently incorporated charge transfer into their polarizable water model that was then used to study ice/water coexistence 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

388 **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 396 to capture the structural details adequately and do not or to reproduce the atomic dipole 397 of water around the ions.¹⁷²⁻¹⁷⁶ Several studies of ion solvation have been reported using 398 different polarizable models^{51-53, 116, 120, 177-187} with analyses focused on solvation 399 structures, charge distribution, and binding energies. Noted that no straightforward 400 experimental measurement of hydration free energy data exist because the macroscopic 401 402 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 403 monovalent ions such as Na^+ and K^+ from different sources can vary by as much as 10 404 405 kcal/mol. It is more reliable to compare the hydration free energy of the whole salt and the relative energy between cations or anions. 406

The AMOEBA polarizable force field has been used to model a number of anions and 407 cations, including Na⁺, K⁺, Mg⁺⁺, Ca⁺⁺, Zn⁺⁺, Cl⁻, Br⁻, and I^{-, 51-53, 188} Parameters for these 408 ions, including the vdW parameters and polarization damping coefficients (for divalent 409 ions only), were obtained by fitting to the *ab initio* OM interaction energy profiles of ion-410 water pairs. Molecular dynamics simulations were then performed to evaluate the ion-411 cluster solvation enthalpies and solvation free energies.^{51-53, 188} The excellent agreement 412 between calculated and experimental hydration free energy, often within 1%, demonstrate 413 414 that polarizable force fields are transferable between phases. Ab initio energy decomposition using, e.g., the Constrained Space Orbital Variations (CSOV) method,^{99,} 415 ¹⁸⁹ have also been applied to examine the polarization component of the ion-water 416 interaction energy and to guide the force field parameterization.^{53, 190} More recently, the 417 AMOEBA force field was used to model the hydration of high valent Th(IV)⁹⁴ and 418 419 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.

426 **3.3. Small Molecules**

427 Small molecules are building blocks of biomolecules and serve as substrates and428 inhibitors. Abundant experimental measurements on various physical and chemical

429 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 430 usually produce reasonable estimations of physical properties of neat liquids.¹⁹³⁻¹⁹⁶ 431 Extensive studies using polarizable force fields, covering major functional group, 432 including alkanes, alcohols, aldehydes, ketones, ethers, acids, aromatic compounds, 433 amines, amides, and some halogen compounds have been reported.^{28, 36, 55, 110, 112, 126, 197-} 434 ¹⁹⁹ Calculations of structure, dipole moment, heterodimer binding energy, liquid diffusion 435 436 constant, density, heat of vaporization, and hydration free energy are usually performed to assess the quality of force field parameters. 437

The electrostatic multipole parameters in AMOEBA were derived using the DMA 438 procedure. They can be further optimized to the electrostatic potentials of chosen ab 439 initio theory and basis sets. The AMOEBA valence parameters were derived from ab 440 initio data such as molecular geometries and vibrational frequencies of the gas-phase 441 monomer. The vdW parameters are estimated from gas-phase cluster calculations, and 442 subsequently refined in liquid simulations using experimental data (e.g., densities and 443 444 heats of vaporization). The torsional parameters the last obtained during the parameterization scheme are derived by fitting to *ab initio* QM conformational energy 445 profiles. An automated protocol (PolType) that can generate AMOEBA parameters for 446 small molecules is under development.²⁰⁰ Because force field parameterization is a 447 tedious process, such an automated tool is convenient and reduces the likelihood of 448 449 human error.

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

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

459 **3.4. Proteins**

460 One of the goals for polarizable force fields is to model accurately protein structures, dynamics, and interactions. Proteins are a ubiquitous class of biopolymers whose 461 462 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 AMBER, CHARMM, and OPLS-AA, have been developed and for years subjected to 464 465 various tests and validations. The development of polarizable protein force fields is still in its infancy. Although the importance of including polarization effects was recognized 466 long ago, polarizable protein force fields emerged only in the past decade.^{9, 21, 28, 29, 37, 138,} 467 201-205 468

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

experimental crystal structure and polarization was found to affect the solvation 474 dynamics.¹³⁸ The fluctuating-charge based ABEEM/MM force field was used to examine 475 protein systems like trypsin inhibitors²⁰⁶ and the heme prosthetic group.²⁰⁷ The SIBFA 476 force field has been used to study the interaction between focal adhesion kinase (FAK) 477 and five pyrrolopyrimidine inhibitors.²⁰⁸ The energy balances accounting for the 478 solvation/desolvation effects calculated by SIBFA agree with experimental ordering. 479 Water networks in the binding pocket were shown to be critical in terms of binding 480 481 affinity. Moreover, the polarization contribution was considered as an indispensable component during the molecular recognition. In comparison, the continuum reaction field 482 483 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 484 as Cu⁺, Zn⁺⁺, Ca⁺⁺ or Mg⁺⁺, as well as enabling inhibition studies.^{91, 209-211} Future 485 486 molecular dynamics simulations should extend the applicability of SIBFA to proteinligand binding. 487

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

More recently, Zhang *et al.* demonstrated the ability of AMOEBA in dealing with systems with a metal ion.⁵⁸ Those authors studied the Zinc-containing matrix metalloproteinases (MMPs) in a complex with an inhibitor where the coordination of Zn^{++} was with organic compounds and protein side chains. Polarization was found to play a key role in Zn^{++} coordination geometry in MMP. In addition, the relative binding free energies of selected inhibitors binding with MMP13 were found to be in excellent 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 ligandsand 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.

527 **3.5.** Lipids

With the rapid development of computational resources, simulations of large systems like 528 lipid bilayers with membrane proteins is feasible.^{126, 213} Patel and coworkers have been 529 developing a polarizable force field for biomembranes to study the structure and 530 dynamics of ion channel systems.40, 113, 128, 214 Simulations of solvated DMPC 531 (dimyristoyl phosphatidylcholine) and dipalmitoylphosphatidylcholine (DPPC) bilayers 532 were reported.^{113, 214} The distribution of the membrane components along the lipid bilayer 533 is similar to that from a fixed charge model. The water dipole moment was found to 534 increase from about 1.9 Debye in the middle of the membrane plane to the average bulk 535 value of 2.5~2.6 Debye. The lipid surface computed with the polarizable force field was 536 not improved from those of non-polarizable ones however. In addition, ion permeation in 537 a gramicidin A channel embedded in a DMPC bilayer was investigated.¹¹³ Davis and 538 Patel concluded that including the electronic polarization lowered the ion permeation free 539 energy barrier significantly, from 12 kcal/mol to 6 kcal/mol. 540

3.6. Continuum Solvents for Polarizable Biomolecular Solutes

542 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 543 mean force (PMF) exists, which preserves exactly the solute thermodynamic properties 544 obtained from explicit solvent.²¹⁵ It is possible to formulate a *perfect* implicit solvent in 545 principle, but in practice approximations are necessary to achieve efficiency. This 546 remains an active area of research.²¹⁶ An implicit solvent PMF can be formulated via a 547 thermodynamic cycle that discharges the solute in vapor, grows the uncharged (apolar) 548 solute into a solvent $W_{apolar}(\mathbf{X})$ and finally recharges the solute within a continuum 549 dielectric $W_{elec}(\mathbf{X})$ 550

551
$$W_{PMF}(X) = W_{apolar}(X) + W_{elec}(X)$$
[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)

555
$$\nabla \cdot [\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] - \bar{\kappa}^2(\mathbf{r})\phi(\mathbf{r}) = -4\pi\rho(\mathbf{r})$$
[13]

where the coefficients are a function of position $\mathbf{r}, \boldsymbol{\phi}$ is the potential, $\boldsymbol{\varepsilon}$ is the pemittivity, 556 $\bar{\kappa}$ is the modified Debye-Hückel screening factor, and p is the solute charge density.^{217,} 557 ²¹⁸ Implementations of a Poisson-Boltzmann continuum for many-body quantum 558 mechanical potentials have been applied to small molecules for decades. Examples 559 include the Polarizable Continuum Model (PCM)^{219, 220}, COSMO²²¹ and the Solvent 560 Model series (SMx).²²² In contrast, applications of biomolecular continuum electrostatics 561 562 have been limited mainly to fixed partial charge solute descriptions for reasons of computing efficiency force field availability. However, as a result of increasing 563

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

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

The first example of an analytic continuum electrostatic model for polarizable 587 biomolecules is the generalized Kirkwood (GK) model for the AMOEBA force field.⁷³ 588 The AMOEBA/GK approach has been combined with alchemical sampling to predict 589 trypsin-ligand binding affinity with a correlation coefficient of 0.93. This is a significant 590 improvement over the PMPB end-state approach.²²⁶ A second example, based on the 591 ABEEM $\sigma\pi$ fluctuating charge force field combined with a generalized Born (GB) 592 continuum electrostatic model, showed promising results for the computation of solvation 593 free energies for small organic molecules and peptide fragments.²²⁷ 594

595 3.7. Macromolecular X-ray Crystallography Refinement

596 X-ray crystallography is the dominant experimental method for determining the 3dimensional coordinates of macromolecules. Collected diffraction data is the Fourier 597 transform of the ensemble average electron density of the macromolecular crystal. While 598 reciprocal space amplitudes of Bragg diffraction peaks are measured, their phases are not. 599 Instead, phase information is derived from the Fourier transform of a model structure that 600 601 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 602 refinement is based optimizating a target function E_{target} of the form 603

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

where E_{X-ray} evaluates the agreement between measured and calculated diffraction amplitudes, $E_{Force Field}$ restrains the model using prior knowledge of intra- and intermolecular chemical forces and w_A weights the relative strength of the two terms.^{77,} ²²⁸ We now focus on the evolution of the prior chemical knowledge used during the Xray refinement process, and we culminate in ongoing work using polarizable force fields
in combination with PME electrostatics algorithms to obtain the most accurate,
informative biomolecular models possible.

The first application of molecular mechanics to macromolecular X-ray crystallography 612 613 refinement (based on fixed partial charge electrostatics evaluated using a spherical cutoff) was on influenza-virus hemagglutinin by Weis et al. in 1990.²²⁹ This work demonstrated 614 that electrostatics maintained chemically reasonable hydrogen-bonding, although charged 615 surface residues were sometimes observed to form incorrect salt bridges.²²⁹ The latter 616 617 observation highlights the importance of accounting for dielectric screening arising from the heterogeneous distribution of solvent within a macromolecular crystal, by using one 618 of the above described continuum electrostatics models. For example, the generalized 619 Born (GB) model for fixed charge electrostatics has been described, albeit with a 620 spherical cutoff approximation.²³⁰ Comparing refinements with and without GB 621 screening showed that roughly 10% of the amino acid side-chain conformations were 622 623 altered, with 75% of these side-chain differences due to residues at the macromolecular surface.²³⁰ Although these first applications of fixed charge force field electrostatics were 624 encouraging, the use of spherical cutoffs to approximate crystal lattice sums is now 625 known to be only conditionally convergent and therefore prone to a variety of artifacts.²³¹ 626

In 1921, Ewald introduced an absolutely convergent solution to the problem of evaluating electrostatic lattice summations in crystals. He did this by separating the problem into a short-ranged real space sum and a periodic, smoothly varying, long-range sum that can be evaluated efficiently in reciprocal space.²³² This approach, now known as Ewald summation, has been described for both fixed partial charges and atomic multipoles.²³³,
²³⁴ More recently, the efficiency of Ewald summation was improved via the particle-mesh
Ewald (PME) algorithm, wherein the reciprocal space summation leverages the fast
Fourier transforms (FFT)²³⁵ via b-Spline interpolation²³⁶ for both fixed partial charge and
atomic multipole descriptions.²³⁷

The speed of the PME algorithm has been further improved for crystals by incorporating 636 explicit support for space group symmetry and by parallelization for heterogeneous 637 computer architectures.⁶³ Combining the polarizable AMOEBA force field with 638 electrostatics evaluated using PME has been shown to improve macromolecular models 639 from X-ray crystallography refinement in a variety of contexts.^{64, 77, 238-240} At high 640 resolution (~1 Å or lower), the information contained within a polarizable atomic 641 multipole force field can be used to formulate the electron density of the scattering model 642 $(E_{\text{X-ray}})$, in addition to contributing chemical restraints $(E_{\text{Force Field}})^{64, 238}$ The importance 643 644 of the prior chemical information contained in a polarizable force field is most significant when positioning parts of the model that are not discernable from the experimental 645 electron density, as in the orientation of water hydrogen atoms²³⁹ or secondary structure 646 elements for mid-to-low resolution data sets (\sim 3-4 Å).⁶³ 647

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

654	re-refinement, the average MolProbity score was reduced to 2.14, indicating a level of
655	model improvement consistent with collecting data to 0.67 Å higher resolution. For
656	example, the pose of S-adenosyl-L-homocysteine (SAH) from mouse (3PT6) and human
657	(3PTA) structures differed by an RMSD of 1.6 Å before re-refinement, but only 0.9 Å
658	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 <i>Force Field X</i>					
		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*

3.8. Prediction of Organic Crystal Structure, Thermodynamics and Solubility

It was emphasized in 1998 that predicting crystal structures from chemical composition 669 remained a major unsolved challenge.²⁴² Significant progress has been made since then to 670 address this challenge, as evidenced by successes of the 4th and 5th blind tests of crystal 671 structure prediction (CSP) organized by the Cambridge Crystallographic Data Center 672 (CCDC).^{243, 244} Prediction of crystal structures is important in the pharmaceutical industry. 673 where extensive experimental screens are necessary to explore the range of stable 674 polymorphs a molecule may form. The unique three-dimensional molecular packing of 675 each polymorph determines its physical properties such as stability and bioavailability. 676 For this reason, both FDA approval and patent protection are awarded to a specific 677 crystal polymorph, rather than to the molecule itself. To illustrate this point, eight 678 companies have filed eleven patents on five possible crystal forms of the molecule 679 cefdinir.245 680

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

interest^{35, 252-254}. Non-polarizable force fields, based on fixed partial charges or fixed atomic multipoles, must implicitly account for the 20% to 40% of the lattice energy attributable induction.²⁴⁹ On the other hand, polarizable models such as the AMOEBA force field for organic molecules ^{54, 255} based on the Thole damping scheme⁴⁵ and the Williams-Stone-Misquitta (WSM) method^{256, 257} for obtaining distributed polarizabilities allow one to include polarization during CSP explicitly.

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

701 **4. Summary**

Significant progress has been made in the past decade in developing general-purpose 702 polarizable force fields. Polarizable force fields have exhibited success in disparate 703 704 research areas including ion solvation, protein-ligand interactions, ion channels and lipids, macromolecular structural refinement and so on. There remain plenty of challenges ahead. 705 706 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 better in a broader range of systems, making parameterization a more elaborate process. 709 In addition to polarization, treatment of other physical effects, including high-order 710

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

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