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Yue Shi, Pengyu Ren, Michael Schnieders, Jean-Philip Piquemal

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1 Polarizable Force Fields for Biomolecular Modeling

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Yue Shi, Pengyu Ren^a

5

a. Department of Biomedical Engineering

6

The University of Texas at Austin

7

1 University Station, C0800

8

Austin, TX 78712

9

10

11

Michael Schnieders^b

12

b. Department of Biomedical Engineering, College of Engineering and

13

Department of Biochemistry, Carver College of Medicine

14

The University of Iowa

15

Iowa City, Iowa, 52242

16

17

18

Jean-Philip Piquemal^c

19

c. Laboratoire de Chimie Théorique (UMR 7616),

20

UPMC, Sorbonne Universités,

21

CC 137, 4 place Jussieu,

22

75252 Paris Cedex 05, France

23

24 **1. Introduction**

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

37 ¹⁰

38 Although the fixed charge force fields enjoyed great success in many areas, there remains
39 much room for improvement. In fixed charge based electrostatic models, the atomic
40 partial charges are meant to be "pre-polarized" for condensed phases in an averaged
41 fashion, typically achieved by the fortuitous overestimation of electrostatic charges by
42 low-level *ab initio* quantum mechanics. Such models thus lack the ability to describe the
43 variation in electrostatics due to many-body polarization effects, which have been shown
44 to be a significant component of intermolecular forces.¹⁰⁻¹² With the rapid growth of
45 computational resources, there has been increasing effort to explicitly incorporate many-
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
48 1950s. Barker in his 1953 paper “Statistical Mechanics of Interacting Dipoles” discussed
49 the electrostatic energy of molecules in terms of “permanent and induced dipoles”.¹³
50 Currently, polarizable models generally fall into three categories: those based on induced
51 point dipoles,^{9, 14-23} the classical Drude oscillators,²⁴⁻²⁶ and fluctuating charges.²⁷⁻³⁰ More
52 sophisticated force fields that are “electronic structure-based”^{31, 32} or use “machine
53 learning methods”³³ also exist, but incur higher computational costs. Discussions of the
54 advantages and disadvantages of each model and their applications will be presented in
55 the following sections.

56 Compared to fixed charge models, the polarizable models are still in a relatively early
57 stage. Only in the past decade or so has there been a systematic effort to develop general
58 polarizable force fields for molecular modeling. A number of reviews have been
59 published to discuss various aspects of polarizable force fields and their development.^{9, 34-}

60 ⁴⁰ Here, we focus on the recent development and applications of different polarizable
61 force fields. We begin with a brief introduction to the basic principles and formulae
62 underlying alternative models. Next, the recent progress of several well-developed
63 polarizable force fields is reviewed. Finally, applications of polarizable models to a
64 range of molecular systems, including water and other small molecules, ion solvation,
65 peptides, proteins and lipid systems are presented.

66 **1. Modeling Polarization Effects**

67 **1.1. Induced Dipole Models**

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

$$72 \quad \mathbf{M}_i = \mathbf{M}_i^0 + \mathbf{M}_i^{\text{ind}} \quad [1]$$

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

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

$$79 \quad U_{\text{ele}} = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{M}_i^T \mathbf{T}_{ij} \mathbf{M}_j \quad [2]$$

80 where \mathbf{T} is the interaction operator and is a function of the distance between i and j . In the
 81 case of point charge interactions, \mathbf{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:

$$84 \quad U_{\text{work}} = \frac{1}{2} \sum_i (\mathbf{M}_i^{\text{ind}})^T \alpha_i^{-1} \mathbf{M}_i^{\text{ind}} \quad [3]$$

85 where α_i is the polarizability of site i that includes all orders of polarizability including
 86 dipole polarizability.⁴¹ Although α_i is generally treated as an isotropic quantity, as in the

87 Applequist scheme ⁴¹, *ab initio* anisotropic polarizability tensors can be derived from
 88 quantum mechanical calculations.^{42, 43}

89 The total electrostatic energy is

$$90 \quad U_{\text{ele}} = \frac{1}{2} \sum_i \sum_{j \neq i} \mathbf{M}_i^t \mathbf{T}_{ij} \mathbf{M}_j + \frac{1}{2} \sum_i (\mathbf{M}_i^{\text{ind}})^t \alpha_i^{-1} \mathbf{M}_i^{\text{ind}} \quad [4]$$

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

$$92 \quad \frac{\partial U_{\text{ele}}}{\partial \mathbf{M}_i^{\text{ind}}} = \sum_{j \neq i} \mathbf{T}_{ij} \mathbf{M}_j + \alpha_i^{-1} \mathbf{M}_i^{\text{ind}} = 0 \quad [5]$$

93 As a result

$$94 \quad \mathbf{M}_i^{\text{ind}} = \alpha_i^{-1} \sum_{j \neq i} \mathbf{T}_{ij} (\mathbf{M}_j^0 + \mathbf{M}_j^{\text{ind}}) \quad [6]$$

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

98 Substituting $\alpha_i^{-1} \mathbf{M}_i^{\text{ind}}$ from Eq [5] into Eq [6], the final electrostatic energy becomes

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

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

102 **1.2. Classic Drude Oscillators**

103 In the Drude oscillator model, the polarization effect is described by a point charge (the
 104 Drude 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

$$\begin{aligned}
 108 \quad E_{\text{ele}} = & \sum_{\mathbf{A} < \mathbf{B}}^N \frac{q_C(\mathbf{A})q_C(\mathbf{B})}{|r_C(\mathbf{A}) - r_C(\mathbf{B})|} + \sum_{\mathbf{A} < \mathbf{B}}^{N, N_D} \frac{q_D(\mathbf{A})q_C(\mathbf{B})}{|r_D(\mathbf{A}) - r_C(\mathbf{B})|} + \sum_{\mathbf{A} < \mathbf{B}}^{N_D} \frac{q_D(\mathbf{A})q_D(\mathbf{B})}{|r_D(\mathbf{A}) - r_D(\mathbf{B})|} + \\
 & \frac{1}{2} \sum_{\mathbf{A}}^{N_D} k_D (r_D(\mathbf{A}) - r_C(\mathbf{B}))^2
 \end{aligned} \tag{8}$$

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.

115 The atomic polarizability (α) is a function of both the partial charge on the Drude particle
 116 and the force constant of the spring

$$117 \quad \alpha = \frac{q_D^2(\mathbf{A})}{k_D} \tag{9}$$

118 Both the induced-dipole and Drude oscillator approaches benefit from short-range Thole
 119 damping to avoid a polarization catastrophe and to produce an anisotropic molecular
 120 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

$$\begin{aligned}
 \mathbf{E}_{\text{CHEQ}}(\mathbf{R}, \mathbf{Q}) = & \sum_{i=1}^M \sum_{\alpha=1}^N \chi_{i\alpha} Q_{i\alpha} + \frac{1}{2} \sum_{i=1}^M \sum_{j=1}^M \sum_{\alpha=1}^{N_i} \sum_{\beta=1}^{N_j} J_{i\alpha j\beta} Q_{i\alpha} Q_{j\beta} + \frac{1}{2} \sum_{i=1}^{MN'} \sum_{j=1}^{MN'} \frac{Q_i Q_j}{4\pi\epsilon_0 r_{ij}} \\
 & + \sum_{j=1}^M \lambda_j (\sum_{i=1}^N Q_{ij} - Q_j^{\text{Total}}) \quad (10)
 \end{aligned}$$

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

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

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

141 between the polarization and atomic degrees of freedom, which can never be completely
142 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**

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

163 In the past decade, AMOEBA has been applied to the study of water,¹⁵ monovalent and
164 divalent ions,⁵¹⁻⁵³ small molecules,^{54, 55} peptides^{18, 56} and proteins.⁵⁷⁻⁵⁹ AMOEBA
165 demonstrated that a polarizable force field is able to perform well in both gas and
166 solution phases with a single set of parameters. In addition, AMOEBA is the first
167 general-purpose polarizable force field utilized in molecular dynamics simulations of
168 protein-ligand binding and calculation of absolute and relative binding free energies.⁵⁸⁻⁶²
169 The computed binding free energies between trypsin and benzamidine derivatives
170 suggests significant non-additive electrostatic interactions as the ligand desolvates from
171 water and enters the protein pocket (see Section 4.4 for further discussion). AMOEBA
172 has recently been extended to biomolecular X-ray crystallography refinement^{63, 64}, and
173 consistently successful prediction of the structure, thermodynamic stability and solubility
174 of organic crystals⁶⁵ are encouraging.

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

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

195 **2.2. SIBFA**

196 The SIBFA (Sum of Interactions Between Fragments *Ab initio* computed) force field for
197 small molecules and flexible proteins, developed by Gresh, Piquemal *et. al.*,⁷⁹⁻⁸³ is one of
198 the most sophisticated polarizable force fields because it incorporates polarization,
199 electrostatic penetration⁸⁴ and charge-transfer effects.⁸⁵

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

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

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

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

231 Hermite Gaussian functions.¹⁰⁰ Therefore, replacing SIBFA's 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 point-dipole moments with recent addition of induced point
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**

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

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

275 energies of small molecules using the polarizable force field. This is likely due to the
276 problematic combining rules used to compute the vdW interactions between unlike atoms.
277 The Drude model has been implemented in CHARMM^{74, 122} and in the NAMD
278 package,¹²³ in which the computational cost is about 1.2 to 1.8 times greater than that of
279 fixed-charge CHARMM.¹²⁴

280 **2.5. CHARMM-FQ**

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

291 The CHARMM-FQ force field,^{125, 126} developed by Patel, Brooks, and their coworkers,
292 has been parameterized for small molecules,²⁸ proteins,^{28, 127} lipids, lipid bilayers,^{113, 128}
293 and carbohydrates.¹²⁵ The force field has been applied to investigate liquid-vapor
294 interfaces in addition to biophysical studies.¹²⁹ There are some known limitations for
295 fluctuating charge models, however, such models allow artificial charge transfer between
296 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

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

323 **2.7. PFF**

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

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

341 Polarizable force fields for non-biological systems also exist. A many-body polarizable
342 force field by Smith and coworkers was developed and applied to the simulations of ion
343 conduction in polyethylene oxide (PEO).¹⁴²⁻¹⁴⁴ Cummings and coworkers developed an
344 interesting Gaussian charge polarizable force field for ions and in polyethylene oxide
345 (PEO).¹⁴⁵⁻¹⁴⁷ A polarizable force field for ionic liquids was also reported to provide
346 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
353 models likewise fall into three major categories. Most belong to the first category,
354 including the Stillinger and David's water model, SPCP,¹⁵¹ PTIP4P,¹⁵² CKL,¹⁵³ NCC,¹⁵⁴
355 PROL,¹⁵⁵ Dang-Chang¹⁵⁶ and others. These models all adopted the induced dipole
356 framework to treat polarization, typically using a single polarizable site on water. TTM
357 models¹⁵⁷⁻¹⁶⁰ and the AMOEBA water model¹⁵ utilize an interactive, distributed atomic
358 polarizability with Thole's damping scheme⁴⁵ to treat electrostatics and polarization. The
359 Drude Oscillator-based water models include SWM4-DP,²⁶ and SWM4-NDP,²⁵ as well as
360 the Charge-On-Spring (COS) model,¹⁶¹ and its improved variation.¹⁶² The third group
361 includes the SPC-FQ and TIP4P-FQ¹⁶³ water models that utilize the fluctuating charge
362 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

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

388 **3.2. Ion Solvation**

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

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

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

420 The SIBFA model was used to examine Pb(II) ,¹⁹¹ lanthanides (La(III) and Lu(III)) and
421 actinides (Th(IV)) in water.⁹⁴ SIBFA-predicted interaction energies generally matched
422 well with the *ab initio* results, including the energy decompositions. Lamoureux and
423 Roux developed the CHARMM polarizable force field for alkali and halide ions based on
424 the Drude Oscillator.¹⁷⁷ Hydration free energies, calculated via thermodynamic
425 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 and
428 inhibitors. Abundant experimental measurements on various physical and chemical

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

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

450 The CHARMM-Drude force field developers devoted much of their efforts on organic
451 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 unperturbed 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 PDFFF showed a satisfactory root mean square displacement (RMSD) compared to the

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

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

492 The first attempt to compute the protein-ligand binding free energy using a polarizable
493 force field was made on the trypsin-benzamidine systems using AMOEBA.^{57, 61, 62} The
494 absolute binding free energy of benzamidine to trypsin, and the relative binding free
495 energies for a series of benzamidine analogs, were computed using a rigorous alchemical
496 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 square error (RMSE)=1.0 kcal/mol).

502 AMOEBA was later used to examine an entropic paradox 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 locked 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

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

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

527 **3.5. Lipids**

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

541 **3.6. Continuum Solvents for Polarizable Biomolecular Solutes**

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

$$551 \quad W_{\text{PMF}}(\mathbf{X}) = W_{\text{apolar}}(\mathbf{X}) + W_{\text{elec}}(\mathbf{X}) \quad [12]$$

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

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

556 where the coefficients are a function of position \mathbf{r} , ϕ is the potential, $\boldsymbol{\epsilon}$ is the permittivity,
 557 $\bar{\kappa}$ is the modified Debye-Hückel screening factor, and ρ is the solute charge density.^{217,}

558 ²¹⁸ Implementations of a Poisson-Boltzmann continuum for many-body quantum
 559 mechanical potentials have been applied to small molecules for decades. Examples
 560 include the Polarizable Continuum Model (PCM)^{219, 220}, COSMO²²¹ and the Solvent
 561 Model series (SMx).²²² In contrast, applications of biomolecular continuum electrostatics
 562 have been limited mainly to fixed partial charge solute descriptions for reasons of
 563 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 EPIC's 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.

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

595 3.7. Macromolecular X-ray Crystallography Refinement

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

$$604 \quad E_{\text{target}} = w_A E_{\text{X-ray}} + E_{\text{Force Field}} \quad [14]$$

605 where $E_{\text{X-ray}}$ evaluates the agreement between measured and calculated diffraction
606 amplitudes, $E_{\text{Force Field}}$ restrains the model using prior knowledge of intra- and
607 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 interpolation²³⁶ 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 ($E_{X\text{-ray}}$), 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 atoms²³⁹ or secondary structure
647 elements for mid-to-low resolution data sets ($\sim 3-4$ Å).⁶³

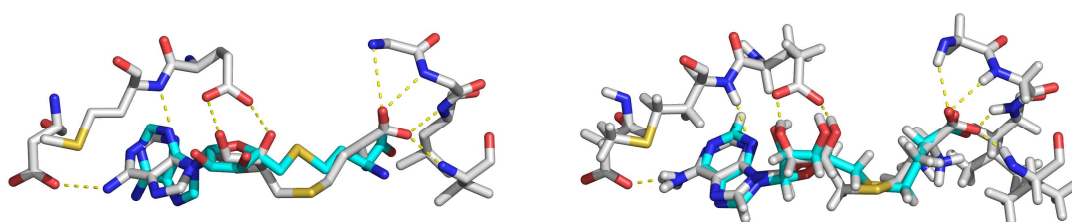
648 Let us consider an example, the AMOEBA-assisted biomolecular X-ray refinement with
649 electrostatics evaluated via PME in the program *Force Field X*. This program was used to
650 re-refine nine mouse and human DNA methyltransferase 1 (Dnmt1) data sets deposited in
651 the Protein databank (PDB). Significant improvements in model quality (presented in
652 Table 1) were achieved as assayed by the MolProbity²⁴¹ structure validation tool. The
653 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.

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

PDB	Res. (Å)	Protein Databank		MolProbity		Re-Refined with <i>Force Field X</i>		MolProbity	
		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

661



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

666 *Field X* refinement.

667 **3.8. Prediction of Organic Crystal Structure, Thermodynamics and** 668 **Solubility**

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

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

687 The vast majority of CSP has been limited to using intermolecular potentials that lack
688 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 scheme⁴⁵ 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.

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722

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