

Polarizable Force Fields Based on Physical Models and Quantum Chemical Calculations

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This perspective gives a brief overview of recent developments of the polarizable force fields (FFs)—a kind of specific FF method that includes polarization effect into conventional molecular mechanics. The commonly adopted polarizable models, that is, the fluctuating charge model, Drude model, and the inducible dipole model are expatiated. Taking advantage of the recent development of computational techniques and fragment-based low-scaling quantum

mechanics (QM) methods, QM-based polarizable FFs appeared and particularly aroused great interest in biological systems. Current applications and limitations of several models are discussed. Opportunities and challenges for future development are also addressed. © 2014 Wiley Periodicals, Inc.

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Why Polarizable?

Molecular dynamics (MD) simulations, as a reliable investigation of the real systems comparable to experiments, have been conducted for 50 years. The merit of MD simulation vitally depends on the accuracy of the potential energy surface (PES), on which the simulated molecular system evolves, and the structural and dynamical properties are obtained from the phase space trajectory. Early MD simulations relied on classical force fields (FFs), also called molecular mechanics (MM), due to their much less computational costs than that of quantum mechanics (QM).

The atoms and molecules consist of nuclei and electrons. Classical FFs treat the electronic responses in a mean field manner, with PES represented by analytical functions with empirical parameters and/or numerical tables. As shown in Scheme 1, most FFs have a common form which contains bonded and nonbonded terms, sometimes plus terms that describe external stimuli (e.g., electric field). Though the intramolecular interactions are often well described by bonded terms, the temporal and spatial properties, which are of primary interest in condensed phase simulations, are often governed by the nonbonded terms with van der Waals and electrostatic interactions.

The electrostatic interactions depend on charge distributions. In traditional MD simulation with the nonpolarizable FF, the charge distribution is mimicked by the fixed partial charges, with the nuclei and electrons interpolated on the atomic sites and, sometimes, fictitious sites. Thus, the electronic degrees of freedom are implicitly included in the nonpolarizable FF. Such treatment closely resembles Born–Oppenheimer principle, which requests the electrons to follow the nuclear motion instantaneously on the adiabatic PES. By such treatment, the static dielectric constant of water, that is, 78 at room temperature, is often well reproduced by a variety of water models. For example, the static dielectric constant is 82 for the TIP3P water model. However, the optical dielectric constant is 1 for all the nonpolarizable FFs, which fails on

reproducing the experimental value of 1.78 for water. In fact, the nonpolarizable FF is destined to fail in reproducing any optical dielectric constant, not just that of water.

The reason for the failure of the FF with fixed partial charges on the optical dielectric constant is attributed to the lack of the explicit electronic degrees of freedom. At the high optical frequency limit, the response of the molecule is solely electronic, because the nuclear motion cannot follow the ultrafast oscillating electric field anymore. Such redistribution of the electron density in response to a fast oscillating electric field, either externally applied or from other molecules in the system, is known as the polarization effect. Even for the static electric field, the electron distribution of a rigid molecule is distorted if the local electric field is strong in the condensed phase, and polarization effect is even more important if the solvation structure of a solute is anisotropic. Thus, for a system consisting of polarizable molecules in an anisotropic environment, a polarizable FF, with explicit electronic degrees of freedom, is highly desired.

Recently, increasing examples have shown that nonpolarizable FFs are incapable in dealing with certain situations.^[1,2] When put under electric fields, polarizable systems, especially those with ions, are expected to bear non-negligible polarizations. For example, the nonpolarizable FF treatment is ineffective to reproduce experimental observations of an electroswitchable biological system, but utilization of a QM-

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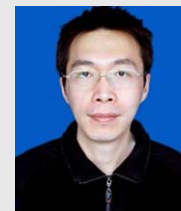
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based charge polarization model works well in modeling the switching process under external electric fields.^[2]

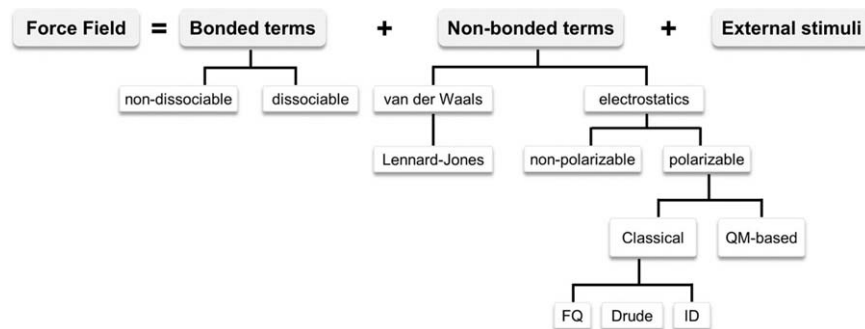
Classical Polarizable Electrostatic Models

To take into account the polarization effects within FFs, several polarization models have been developed on basis of the physical pictures of polarization, which can be classified into three categories for the different treatments, that is, the fluctuating charge (FQ) model, Drude model, which is also known as Shell model, and the inducible dipole (ID) model (Scheme 1). As shown in Scheme 2a, in the FQ model,^[3] partial charges are generally assigned on the atomic sites in a molecule, and the charge redistribution in response to the external electric field or conformational change is governed by electronegativity equilibration method (EEM). Drude model is a charge-on-spring model, in which a Drude charge is attached to the atomic site with a spring, which mimics nuclear-electron motion.^[4] The ID model is inherent from the classical electrodynamics for the molecular polarizability, and the implementation of the ID model in the MD simulation is stemmed from multiple expansion of a charge distribution, which is often truncated at the dipole term in the ID model.

The solution of the above polarizable FFs is driven by the optimization of the charge distribution, Drude particle position, or the induced dipole moments, toward the minimum energy configuration, for the system evolution on the adia-

batic PES. Such optimization scheme is analogue to the mean field treatment of the Schrödinger equation with variational method in *ab initio* calculations. In fact, polarizable FFs were developed on the very early stage, accompanied with the development of the MD simulations. Early MD simulations with polarizable FF of dipolar liquids often utilized ID model, such as polarizable Stockmayer fluid^[5] and polarizable water model,^[6] while Drude model is extensively adopted in the MD simulations of inorganic salts.^[7]

For the three categories of the polarizable FFs, the ID model seems to be the most natural way to introduce the electronic polarization effect. Through incorporating the polarization effect by the ID model, Liu and coworkers implemented a polarizable ellipsoidal force field model for halogen bonds^[8] to reproduce a wider range of PES. However, the additional dipole degree of freedom in the ID model needs special care, especially for the electrostatic interactions, that is, the charge-charge, charge-dipole, and dipole-dipole interactions. For Drude model, there are additional Drude charges, and thus the total number of particles effectively increases. For FQ model, there are in principle no additional charges and no induced dipoles. However, it fails on the single atomic molecules (rare gas) or ions (chloride). Also, there is no out-of-plane polarization for the flat molecules such as water and benzene, because the charges have nowhere to go on the plane normal direction. To remedy this shortcoming, additional fictitious sites are often introduced in FQ model. For example, a seven-

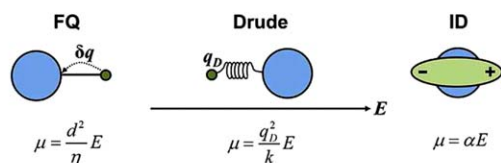


Scheme 1. Energy expressions of FFs.

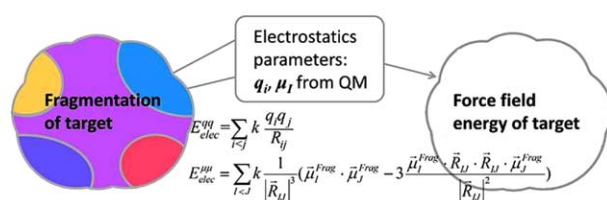
site ABEEM-7P FQ model was developed for water, in which the charges are distributed on the atomic sites, bond, and lone electron pairs.^[9]

Like the QM counterpart, the formulism and the technique of the polarizable FF are complete, and the only shorthand that hinders its massive applications is the additional computational cost. For the optimization scheme, the polarizable FF increases the cost by a factor of at least 2,^[10] due to the time consuming electrostatic interactions in the iterative scheme toward the self-consistent solution. In terms of the three polarizable models, FQ model is expected to run faster than the other two, due to the additional degrees of freedom of the Drude charges or induced dipoles in Drude or ID models. Alternatively, the extended-Lagrangian method for the electronic degree of freedom can be implemented without iteration,^[11] which is a classical analogue to the Car–Parrinello approach. However, the MD integration time step is reduced because the electronic degree of freedom is essentially massless. Thus, a small enough fictitious mass needs to be assigned to the charge or induced dipole, which is often coupled to a low temperature thermostat to ensure that the system evolves on the adiabatic PES.^[12]

(a) Classical polarizable electrostatic models:



(b) Fragmentation QM-based polarizable models:



Scheme 2. a) Classical polarizable electrostatic models, with the induced dipole μ by an external electric field E . For FQ model, d denotes the separation between two atomic sites, and η is the hardness of charge flow between them; For Drude model, q_D represents Drude charge which is attached to an atomic site via a spring of force constant k ; For ID model, a polarizable center of polarizability α is assigned on atomic site. b) Fragmentation QM-based polarizable models.

The implementation of the above polarizable FF in the generalized FF greatly facilitates its usage. Recent development of CHARMM adopts Drude model, while the ID model has been used in AMBER for a long time. FQ model was implemented in the reactive FF,^[13] with the atomic partial charges determined by EEM. It should be mentioned that FQ model also finds special usage in the constant electric potential simulation of the ideal polarizable electrode, with the electrode fixed on the imposed electric potential.^[14]

Transferability is the key to all FFs. Thus, it is the ultimate target to develop a universal polarizable FF. The parameterization in FFs is a challenging task. For the above-mentioned polarizable FFs, atomic electronegativity and hardness are needed for the FQ model, Drude charge and spring force constant are needed for the Drude model, and atomic polarizability is needed for the ID model. For the latter two models, Thole smearing factor^[15] is often adopted to avoid the so-called “polarization catastrophe.” Thus, additional parameters are needed in the polarizable FF for the electronic degrees of freedom. Moreover, once polarizable FFs are used, all the bonded and nonbonded parameters (bond, angle, dihedral, Lennard-Jones, and partial charge, etc.) adopted in the nonpolarizable FFs need refitting. This requires huge experimental data and QM calculations, which will be accomplished in a long time with great efforts.

QM-Based Polarizable FFs

QM, such as high level *ab initio* method or density functional theory, provides precise molecular interactions, but the computational burden limits its applications in large and complex systems involving thousands to millions of atoms. Thus, the combination of QM with FF, that is, QM/MM method, provides practical solution. Indeed, the tremendous success of MD simulations at the multiscaled level has become evident for the past decades, and Nobel Prize in Chemistry in 2013 was dedicated to Karplus, Levitt, and Warshel. Actually, in the milestone work of Warshel and Levitt of the QM/MM treatment of the enzymic reactions, the MM part was treated by the ID model.^[16]

Due to the difficulty of getting empirical parameters from experiments, QM calculations have been widely applied in the parameterization stage for the MM models. The polarization effect manifests in QM with wave function optimization of the

Schrödinger equation. Therefore, several flavors of QM-based polarization models appeared recently.^[17–21] The key of direct fusing QM into FFs relies on the reduction of the high computational costs of the QM calculation, $O(N_{\text{basis}}^2)$, where N_{basis} is the number of basis sets and $\alpha \geq 3$, toward nearly linear scaling (i.e., $\alpha = 1$). Taking benefit of the locality and transferability of subsystems in a large-sized system, the fragment-based QM calculations, in which the entire system is divided into molecular fragments (Scheme 2b), have been proposed during the past several years. For large and complex systems, the QM/MM approach can be applied with fragment-based treatment for the electronic polarization, with the wave function represented by Hartree product.^[17] Gao has developed a fragment-based QM method, explicit polarization (X-Pol),^[17,18] to construct the PES and wave functions on the basis of QM. The intrafragment polarization and the mutual polarization between different fragments are treated explicitly using self-consistent QM calculations.

Different from other electrostatics models that are based on interactions between atomic centers, the fragment-centered dipoles^[19] and even coarse-grained (CG)^[20] treatment have been introduced by Jiang and Ma.^[22] The generalized energy-based fragmentation approach^[23] has been applied to get the charges and fragment-based dipoles on-the-fly with high computational efficiency. The molecular fragments can be set as a secondary structure (α -helix, β -turn, coil) or a residue for peptides. The fragment-centered dipoles were used to reduce the computational costs in the long-range electrostatic interactions from $O(N_{\text{atom}}^2)$ to $O(N_{\text{frag}}^2)$, where N_{atom} and N_{frag} are numbers of atoms and fragments, respectively, and N_{frag} is much smaller than N_{atom} .

Nevertheless, the above QM description of the polarization effect is still computationally expensive, considering millions to billions integration time steps are needed to propagate the system toward nanosecond to microsecond time scale. To further reduce the computational cost of QM-based polarization model, a multilayered coarse-grained model was proposed to bridge the QM-based nonparameterization electrostatic energy with the parameterized electrostatics terms. A hybrid set of fragments can be chosen as a secondary structure, a residue, or even an atom, according to the variation of atomic charges and fragment-centered dipoles in response to the surrounding electrostatic environment. For the polarization “inert” fragments, the parameter-fitted fragment dipole moments were used to represent the charge distribution of individual fragments, while for the electrostatically “sensitive” atoms exhibit large fluctuations of charges with the varied environments, the variable charges are updated in each QM calculation along MD time evolution. With the help of QM calculations, the development of a classically parameterized FF that takes into account the electronic polarization remains a hot topic.

Conclusions and Perspective

Due to the importance of the polarization effect in MD simulations, a special issue in Journal of Chemical Theory and Computation was devoted to this topic in 2007.^[24] However, wide

applications of the polarizable FFs have not emerged. The reasons are twofolds. Apart from the aforementioned dirty work of reparameterization, there was also lack of a general purpose MD package for long term. Such situation effectively prevents the wide applications of polarizable FF, and makes it a black-box.

The situation has been changed! There was recently a systematic development of the polarizable FF of organic and biomolecular systems with FQ^[25] and Drude model.^[11] Moreover, the Drude-2013 FF has been implemented in the general purpose MD packages, such as CHARMM and NAMD.^[11] Besides, the newly released AMBER has been continuously adding ID model into the package with systematic polarizable FF of proteins, as the late Peter Kollman’s long-term goal. All the above efforts fill the gap between methods and applications, and will ultimately make a polarizable MD simulation as easy as performing a nonpolarizable counterpart nowadays.

The development of computational methodologies never stops. There were attempts to combine FQ and ID models for the polarizable OPLS-AA FF.^[26] Such combination of the different polarizable models effectively takes advantage of the merit of individual ones. The recent development of the QM/MM method implemented explicit polarization in the MM part with analytical derivatives.^[27,28] We are also expecting the multi-scaled scheme with QM/MM/CG for the Onion method in biological simulations. As pointed out in a recent review on classical electrostatics models,^[29] the combination of recent advancements in developing powerful techniques for MD simulations of larger systems with longer time scales is highly desired to further improve the applicability of polarization models. Indeed, with recent development of parameterization procedure for the polarizable FF, QM/MM methodology, and the generalized MD simulation package, a massive usage of the polarizable FF, as the next generation of the standard FF, is now booming.

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