Determining polarizable force fields with electrostatic potentials from quantum mechanical linear response theory

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We developed a new method to calculate the atomic polarizabilities by fitting to the electrostatic potentials (ESPs) obtained from quantum mechanical (QM) calculations within the linear response theory. This parallels the conventional approach of fitting atomic charges based on electrostatic potentials from the electron density. Our ESP fitting is combined with the induced dipole model under the perturbation of uniform external electric fields of all orientations. QM calculations for the linear response to the external electric fields are used as input, fully consistent with the induced dipole model, which itself is a linear response model. The orientation of the uniform external electric fields is integrated in all directions. The integration of orientation and QM linear response calculations together makes the fitting results independent of the orientations and magnitudes of the uniform external electric fields applied. Another advantage of our method is that QM calculation is only needed once, in contrast to the conventional approach, where many QM calculations are needed for many different applied electric fields. The molecular polarizabilities obtained from our method show comparable accuracy with those from fitting directly to the experimental or theoretical molecular polarizabilities. Since ESP is directly fitted, atomic polarizabilities obtained from our method are expected to reproduce the electrostatic interactions better. Our method was used to calculate both transferable atomic polarizabilities for polarizable molecular mechanics' force fields and nontransferable molecule-specific atomic polarizabilities. *Published by AIP Publishing*. [<http://dx.doi.org/10.1063/1.4953558>]

I. INTRODUCTION

Molecular dynamics (MD) simulation is an important method for investigating biological systems.^{1,2} The accuracy of MD simulation depends on the force fields. Most empirical force fields use fixed partial charges on molecules (e.g., TIP3P³ and SPC⁴). These force fields are nonpolarizable force fields. Though non-polarizable force fields have achieved much success in the past decades, many challenges still remain. For example, one significant drawback of nonpolarizable force fields is that they cannot respond to the change of dielectric environment. However, due to the conformational changes, dielectric environment in biological systems may change significantly in the process of an MD simulation. The polarization effects are also crucial, for example, for the folding of membrane proteins in the lipid environment or RNA folding in the environment of divalent ions.⁵ In recent years, especially with the increasing power of computers, including polarization effects in MD simulations has been recognized as an effective method to further improve the accuracy of MD simulation results. Reviews accounting for polarization effects in MD simulations have been presented by Yu and van Gunsteren,⁶ Rick and Stuart,⁷ and González.⁸

Three most widely used polarizable models are fluctuating charge model,^{9,10} Drude model,^{11–13} and induced dipole model.^{14,15} The fluctuating charge model uses the chemical potential equalization principle^{16–18} to calculate the flexible atomic partial charges, which vary with the electrostatic environment. Atomic electronegativity (χ^0) and hardness (J), two types of parameters in the fluctuating charge model, can be obtained via quantum mechanical (QM) calculations ($\chi^0 = \frac{1}{2}(IP + EA)$ and $J = IP - EA$, where IP and EA denote the ionization potential and electron affinity).⁹ The disadvantage of this model is that the polarization effects are restricted by the molecular geometry. For example, for a planar molecule, the fluctuating charge model cannot represent the polarization out of the molecular plane, which needs additional fluctuating dipoles. The Drude model and induced dipole model are essentially equivalent.^{6,19,20} Both use dipole moments to represent polarization effects. The difference is in the models of the dipole: the induced dipole model uses atom-centered point dipole moments, while for the Drude model, the Drude particles attached to the atom sites through a spring are used to represent the polarization effects. In practice, the Drude model is easier to implement than the induced dipole model. In the present work, the scheme of the induced dipole model is more convenient and was chosen for our current implementation. However, the parameters obtained in the induced dipole

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model can be easily transformed into those in the Drude model.⁶

Besides these three main polarizable models, many other types of models have been developed. Within the atomic charge framework, Morita and Kato developed the charge response kernel model in which atomic charges linearly respond to the external potential.^{21,22} Piquemal *et al.* developed the SIBFA method which includes non-classical effects such as exchange-polarization.^{23–31}

In the induced dipole model, the induced point dipole at atom site i is proportional to the electric field at the same site ($\mu_i = \alpha_i E_i$, where α_i is the atomic polarizability of atom i). The atomic polarizabilities are the key parameters in the induced dipole model. In previous studies, the atomic polarizabilities were calculated by fitting to the molecular polarizabilities,^{20,32–35} which are obtained either from experimental results or from high-quality QM results. Soteras *et al.* calculated the atomic polarizabilities by fitting the induction energy computed in the perturbation theory.³⁶ Kaminski *et al.* calculated the atomic polarizabilities by fitting to the electrostatic potential (ESP) produced by dipolar probes which are surrounding the molecules.³⁷ Though fitting to molecular polarizabilities can also reproduce electrostatic interaction well, it is in an indirect way. Calculating atomic polarizabilities by direct fitting to electrostatic potential is what we desired in the present study.

However, the definition of atomic polarizabilities is not unique. Besides the “bare” atomic polarizabilities developed by Applequist,³⁸ another type of distributed polarizabilities, which was first developed by Stone,^{54,55} is also widely used. Stone’s method combines the susceptibility function of the charge density⁵⁶ and distributed multipole analysis⁵⁷ to calculate distributed polarizabilities of an isolated molecule under an external perturbation. For practical purpose, Stone *et al.*^{58,59} devised the constrained density-fitting algorithm. Celebi *et al.*⁶⁰ calculated the distributed polarizabilities by induction energy fitting.

In the current work, we developed a new method for the development of polarizable force fields, based on the following rationale. All polarizable force fields describe the linear response of the charge distribution of a molecule to the change in the external electrostatic field. Since this linear response is well described by quantum mechanical theory at many levels, we believe that polarizable force fields should be designed to approximate the QM linear response. Instead of using the linear response electron density, the optimal target of approximation is the electrostatic potential generated from the linear response electron density because the electrostatic potential is what enters into the interaction energy of the molecule with its environment. This is similar to the use of electrostatic potential to fit atomic charges in non-polarizable force fields. Thus our method calculates the atomic polarizabilities by ESP fitting within the quantum mechanical linear response theory. With the linear response function within density functional theory,³⁹ QM calculations are only needed once in the fitting process for each molecule. It also makes our ESP fitting results independent of the orientations and magnitudes of the uniform external electric fields applied. These features lead to more efficient ESP

fitting and accurate atomic polarizabilities. Both transferable atomic polarizabilities for the purpose of force fields and nontransferable atomic polarizabilities for specific molecules are calculated here. Our development of atomic polarizabilities based on linear response parallels the conventional approach of fitting atomic charges based on electrostatic potentials from the electron density. Our method should be useful for building the next generation of polarizable force fields.

II. METHODS

A. Induced dipole model

We first review the induced dipole model here. Consider a molecule of N atoms in a uniform external electric field. The induced dipoles are placed on each atom site and the induced dipole on atom p is given by

$$\mu_p = \alpha_p [E_p - \sum_{q \neq p}^N T_{pq} \mu_q], \quad (1)$$

where α_p is the atomic polarizability of atom p , E_p is the external electric field at atom p , μ_q is the dipole moment at atom q , and T_{pq} is the dipole field tensor,

$$T_{pq} = \frac{f_e}{r_{pq}^3} I - \frac{3f_t}{r_{pq}^5} \begin{bmatrix} x^2 & xy & xz \\ yx & y^2 & yz \\ zx & zy & z^2 \end{bmatrix}, \quad (2)$$

where I is a 3×3 unit matrix, f_e and f_t are screening functions, r_{pq} is the distance between atoms p and q , and x, y , and z are three components of r_{pq} . In Applequist’s model,³⁸ $f_e = 1$ and $f_t = 1$.

It has been noted that Applequist’s model may cause “polarization catastrophe,” which refers to “the infinite polarization by the cooperative interactions between two nearby induced dipoles.”³² To solve this problem, Thole developed two forms of screening functions to damp the short distance inductions.⁴⁰ In the linear form,

$$\begin{aligned} \nu &= r_{pq} / [a(\alpha_p \alpha_q)^{1/6}] \\ \text{if } (\nu \geq 1) & f_e = 1.0, f_t = 1.0, \\ \text{if } (\nu < 1) & f_e = 4\nu^3 - 3\nu^4, f_t = \nu^4. \end{aligned} \quad (3)$$

In the exponential form,

$$\begin{aligned} \nu &= r_{pq} / [a(\alpha_p \alpha_q)^{1/6}], \\ f_e &= 1 - \left(\frac{\nu^2}{2} + \nu + 1\right) \exp(-\nu), \\ f_t &= 1 - \left(\frac{1}{6}\nu^3 + \frac{1}{2}\nu^2 + \nu + 1\right) \exp(-\nu). \end{aligned} \quad (4)$$

Another form was used by Ren and Ponder,^{41–49} which was simplified by Wang *et al.*,³²

$$\begin{aligned} \nu &= r_{pq} / [a(\alpha_p \alpha_q)^{1/6}], \\ f_e &= 1 - \exp(-\nu^3), \\ f_t &= 1 - (\nu^3 + 1) \exp(-\nu^3), \end{aligned} \quad (5)$$

where α_p and α_q are the atomic polarizabilities of atoms p and q , a is the screening factor, and r_{pq} is the distance between atoms p and q .

Rearrange formula (1) to the matrix equation,

$$\begin{bmatrix} \alpha_1^{-1} & \mathbf{T}_{12} & \cdots & \cdots & \mathbf{T}_{1N} \\ \mathbf{T}_{21} & \alpha_2^{-1} & \cdots & \cdots & \mathbf{T}_{2N} \\ \vdots & \vdots & \cdots & \cdots & \vdots \\ \vdots & \vdots & \cdots & \cdots & \vdots \\ \mathbf{T}_{N1} & \mathbf{T}_{N2} & \cdots & \cdots & \alpha_N^{-1} \end{bmatrix} \begin{bmatrix} \mu_1 \\ \mu_2 \\ \vdots \\ \vdots \\ \mu_N \end{bmatrix} = \begin{bmatrix} E_1 \\ E_2 \\ \vdots \\ \vdots \\ E_N \end{bmatrix}, \quad (6)$$

which can be expressed in compact matrix notation as

$$\mathbf{A}\boldsymbol{\mu} = \mathbf{E}. \quad (7)$$

Let $\mathbf{B} = \mathbf{A}^{-1}$,

$$\mathbf{B} = \begin{bmatrix} \mathbf{B}_{11} & \mathbf{B}_{12} & \cdots & \cdots & \mathbf{B}_{1N} \\ \mathbf{B}_{21} & \mathbf{B}_{22} & \cdots & \cdots & \mathbf{B}_{2N} \\ \vdots & \vdots & \cdots & \cdots & \vdots \\ \vdots & \vdots & \cdots & \cdots & \vdots \\ \mathbf{B}_{N1} & \mathbf{B}_{N2} & \cdots & \cdots & \mathbf{B}_{NN} \end{bmatrix}. \quad (8)$$

Note that each $\mathbf{B}_{ij}$ is a three by three matrix, associated with three spacial directions. Define a three by three matrix $\mathbf{C}$ as

$$\mathbf{C} = \sum_{i=1}^N \sum_{j=1}^N \mathbf{B}_{ij}. \quad (9)$$

Then isotropic molecular polarizability is given by

$$\alpha_{mol} = (\mathbf{C}_{11} + \mathbf{C}_{22} + \mathbf{C}_{33})/3. \quad (10)$$

B. Linear response function

The linear response function ($\chi(\mathbf{r}, \mathbf{r}')$), defined as $\chi(\mathbf{r}, \mathbf{r}') = \frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}$, represents the response of the electron density $\rho(\mathbf{r})$ to the change of external electric potential $v(\mathbf{r}')$. Within density functional theory, the analytic expression of $\chi(\mathbf{r}, \mathbf{r}')$ is given as³⁹

$$\chi(\mathbf{r}, \mathbf{r}') = -2 \sum_{ia\sigma, jb\tau} (M^{-1})_{ia\sigma, jb\tau} \phi_{j\tau}^*(\mathbf{r}') \times \phi_{b\tau}(\mathbf{r}') \phi_{i\sigma}(\mathbf{r}) \phi_{a\sigma}^*(\mathbf{r}), \quad (11)$$

where M is a matrix depending on the approximate density functional chosen, which is given by

$$M_{ia\sigma, jb\tau} = \delta_{\sigma\tau} \delta_{ij} \delta_{ab} (\epsilon_{a\sigma} - \epsilon_{i\sigma}) + K_{ia\sigma, jb\tau} + K_{ia\sigma, b\tau}, \quad (12)$$

where

$$K_{st\sigma, uv\tau} = \frac{\partial \langle \phi_{s\sigma} | v_J | \phi_{t\tau} \rangle}{\partial P_{vu}^\tau} + \frac{\partial \langle \phi_{s\sigma} | v_{xc}^\sigma | \phi_{t\tau} \rangle}{\partial P_{vu}^\tau}, \quad (13)$$

$$\frac{\partial \langle \phi_{s\tau} | v_J | \phi_{t\tau} \rangle}{\partial P_{vu}^\tau} = \int \int d\mathbf{r}_1 d\mathbf{r}_2 \phi_{s\sigma}^*(\mathbf{r}_1) \phi_{t\tau}(\mathbf{r}_1) \frac{1}{r_{12}} \phi_{u\tau}^*(\mathbf{r}_2) \times \phi_{v\tau}(\mathbf{r}_2) = (\phi_{s\sigma}^* \phi_{t\tau}, \phi_{u\tau}^* \phi_{v\tau}). \quad (14)$$

For explicit functionals of the electron density,

$$\frac{\partial \langle \phi_{s\sigma} | v_{xc}^\sigma | \phi_{t\sigma} \rangle}{\partial P_{vu}^\tau} = \int \int d\mathbf{r}_1 d\mathbf{r}_2 \phi_{s\sigma}^*(\mathbf{r}_1) \phi_{t\sigma}(\mathbf{r}_1) \times \frac{\delta^2 E_{xc}[\rho^\sigma(\mathbf{r})]}{\delta \rho^\sigma(\mathbf{r}_1) \delta \rho^\tau(\mathbf{r}_2)} \phi_{u\tau}^*(\mathbf{r}_2) \phi_{v\tau}(\mathbf{r}_2). \quad (15)$$

For functionals of the density matrix,

$$\frac{\partial \langle \phi_{s\sigma} | v_{xc}^\sigma | \phi_{t\sigma} \rangle}{\partial P_{vu}^\tau} = \int \int d\mathbf{r}_1 d\mathbf{r}_1' d\mathbf{r}_2 d\mathbf{r}_2' \phi_{s\sigma}^*(\mathbf{r}_1) \phi_{t\sigma}(\mathbf{r}_1') \times \frac{\delta^2 E_{xc}[\rho_s^\sigma(\mathbf{r}_1', \mathbf{r}_1)]}{\delta \rho^\sigma(\mathbf{r}_1', \mathbf{r}_1) \delta \rho^\tau(\mathbf{r}_2', \mathbf{r}_2)} \times \phi_{u\tau}^*(\mathbf{r}_2) \phi_{v\tau}(\mathbf{r}_2'). \quad (16)$$

We use $i, j, k, \dots$ for occupied states, $a, b, c, \dots$ for unoccupied states, s, t, u, v for general states, and Greek letters σ, τ for spin labels. Details of the derivations of the above formula can be found in Yang's paper.³⁹ The linear response function only depends on the ground state properties of the molecules. Under a given perturbation $\delta v(\mathbf{r})$, the change of electron density to first order is then given by

$$\delta\rho(\mathbf{r}) = \int \chi(\mathbf{r}, \mathbf{r}') \delta v(\mathbf{r}') d\mathbf{r}'. \quad (17)$$

C. ESP fitting

In the current work, we performed the ESP fitting in two different ways to obtain atomic polarizabilities for molecular specific force fields and for general force fields. In the first approach, we fit the ESP for specific molecules. The molecule-specific fitting ensures that the atomic polarizabilities obtained are specifically optimized for a particular molecule. In determining atomic polarizabilities $\{\alpha_p\}$, we use the object function L , defined as the weighted squared difference between ϕ_{ESP} , the electrostatic potential from the polarizable force field and ϕ_{QM} , that from QM linear response calculations, namely,

$$L = \int d\Omega \int \omega(\mathbf{r}) [\phi_{ESP} - \phi_{QM}]^2 d\mathbf{r},$$

where $\omega(\mathbf{r})$ is a weight function at grid point $\mathbf{r}$. The details of L are as follows:

$$\begin{aligned} L &= \int d\Omega \int \omega(\mathbf{r}) \left[\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot \boldsymbol{\mu}_a - \int \frac{\delta\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' \right]^2 d\mathbf{r} \\ &= \int d\Omega \int \omega(\mathbf{r}) \left[\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot \boldsymbol{\mu}_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \frac{\delta\rho(\mathbf{r}')}{\delta v(\mathbf{r}'')} \delta v(\mathbf{r}'') d\mathbf{r}'' d\mathbf{r}' \right]^2 d\mathbf{r} \\ &= \int d\Omega \int \omega(\mathbf{r}) \left[\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (\mathbf{A}^{-1} \delta E)_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi(\mathbf{r}', \mathbf{r}'') \mathbf{r}'' \cdot \delta E d\mathbf{r}'' d\mathbf{r}' \right]^2 d\mathbf{r} \\ &= \int d\Omega \int \omega(\mathbf{r}) \left[\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (\mathbf{A}^{-1} \hat{\mathbf{n}})_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi(\mathbf{r}', \mathbf{r}'') \mathbf{r}'' \cdot \hat{\mathbf{n}} d\mathbf{r}'' d\mathbf{r}' \right]^2 d\mathbf{r} dE^2, \end{aligned} \quad (18)$$

where $\mathbf{r}_a$ is the position of atom a , $\boldsymbol{\mu}_a$ is the induced dipole moment on atom a , $\hat{\mathbf{n}}$ is the unit direction vector of the uniform external electric field, A is the matrix defined in Eq. (7), and δE is the magnitude of the uniform external electric field. The integration with respect to the solid angle (Ω) of the external perturbing field allows considering all the orientations of the perturbing field on equal footing.

Since

$$\hat{\mathbf{n}} = \sin \theta \cos \phi \hat{\mathbf{n}}_x + \sin \theta \sin \phi \hat{\mathbf{n}}_y + \cos \theta \hat{\mathbf{n}}_z, \quad (19)$$

where $\hat{\mathbf{n}}_x, \hat{\mathbf{n}}_y, \hat{\mathbf{n}}_z$ are unit vectors in x, y, z directions, separately, we can define the following:

$$\begin{aligned} H_x(\mathbf{r}) &= \sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \hat{\mathbf{n}}_x)_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi(\mathbf{r}', \mathbf{r}'') x'' d\mathbf{r}' d\mathbf{r}'', \\ H_y(\mathbf{r}) &= \sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \hat{\mathbf{n}}_y)_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi(\mathbf{r}', \mathbf{r}'') y'' d\mathbf{r}' d\mathbf{r}'', \\ H_z(\mathbf{r}) &= \sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \hat{\mathbf{n}}_z)_a - \int \int \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi(\mathbf{r}', \mathbf{r}'') z'' d\mathbf{r}' d\mathbf{r}'', \end{aligned} \quad (20)$$

where $x'', y'',$ and z'' are $x, y,$ and z components of $\mathbf{r}''$. Then L can be transformed into

$$\begin{aligned} L &= \int d\Omega \int \omega(\mathbf{r}) [\sin \theta \cos \phi H_x(\mathbf{r}) + \sin \theta \sin \phi H_y(\mathbf{r}) + \cos \theta H_z(\mathbf{r})]^2 d\mathbf{r} \delta E^2 \\ &= \frac{4\pi}{3} \int \omega(\mathbf{r}) [H_x^2(\mathbf{r}) + H_y^2(\mathbf{r}) + H_z^2(\mathbf{r})] d\mathbf{r} \delta E^2. \end{aligned} \quad (21)$$

Since the magnitude of the uniform external electric field, δE , can be taken out of the bracket, the ESP fitting results are independent of the magnitude of the uniform electric fields. The analytic gradient of L with respect to atomic polarizabilities $\{\alpha_p\}$ and screening factor a , used in the optimization process, is given by

$$\begin{aligned} \frac{\partial L}{\partial \alpha_p} &= \frac{8\pi}{3} \int \omega(\mathbf{r}) [H_x(\mathbf{r}) \frac{\partial H_x(\mathbf{r})}{\partial \alpha_p} + H_y(\mathbf{r}) \frac{\partial H_y(\mathbf{r})}{\partial \alpha_p} + H_z(\mathbf{r}) \frac{\partial H_z(\mathbf{r})}{\partial \alpha_p}] d\mathbf{r} \delta E^2 \\ &= -\frac{8\pi}{3} \int \omega(\mathbf{r}) [H_x(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial \alpha_p} A^{-1} \hat{\mathbf{n}}_x)_a \right) + H_y(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial \alpha_p} A^{-1} \hat{\mathbf{n}}_y)_a \right) \\ &\quad + H_z(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial \alpha_p} A^{-1} \hat{\mathbf{n}}_z)_a \right)] d\mathbf{r} \delta E^2, \\ \frac{\partial L}{\partial a} &= \frac{8\pi}{3} \int \omega(\mathbf{r}) [H_x(\mathbf{r}) \frac{\partial H_x(\mathbf{r})}{\partial a} + H_y(\mathbf{r}) \frac{\partial H_y(\mathbf{r})}{\partial a} + H_z(\mathbf{r}) \frac{\partial H_z(\mathbf{r})}{\partial a}] d\mathbf{r} \delta E^2 \\ &= -\frac{8\pi}{3} \int \omega(\mathbf{r}) [H_x(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial a} A^{-1} \hat{\mathbf{n}}_x)_a \right) + H_y(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial a} A^{-1} \hat{\mathbf{n}}_y)_a \right) \\ &\quad + H_z(\mathbf{r}) \cdot \left(\sum_a \nabla \frac{1}{|\mathbf{r}_a - \mathbf{r}|} \cdot (A^{-1} \frac{\partial A}{\partial a} A^{-1} \hat{\mathbf{n}}_z)_a \right)] d\mathbf{r} \delta E^2. \end{aligned} \quad (22)$$

In the second approach, we fit the ESP for general force fields, which means that we aim to obtain atomic polarizabilities that are transferable. In this case, the total object function L is defined as

$$L = \sum_{i=1}^n \frac{1}{\int \omega(\mathbf{r}_i) d\mathbf{r}_i} L_i, \quad (23)$$

where n is the number of molecules in the training set and L_i is the object function for molecule i , as defined in Eq. (21). The denominator of the factor represents the sum of weights of all grid points belonging to molecule i . This factor ensures that each molecule has the same weight in the fitting process.

In the conventional approach for developing force fields, atomic charges are fitted to the electrostatic potential generated from the electron density. In complete parallel, within our approach, atomic polarizabilities are fitted to the linear change

of the electrostatic potential due to the applied external electric field, which is calculated from the linear response theory. This is the key feature of our work. While we focus on polarizable dipole model presently, our idea of fitting to the linear change of the electrostatic potential due to the applied external electric field, which is calculated from the linear response theory, can be applied to other polarizable models.

D. Computation details

We used the weight function developed by Hu *et al.* for electrostatic potential fitting of atomic charges,⁵⁰ which is given by

$$\omega(\mathbf{r}) = \exp[-\sigma(\log \tilde{\rho}(\mathbf{r}) - \log \rho_{ref})^2], \quad (24)$$

where $\tilde{\rho}(\mathbf{r})$ is the predefined electron density that is the sum of atomic electron densities, and ρ_{ref} and σ are two parameters.

TABLE I. Eight induced dipole models studied in the current work. Class 1 contains four models with 1-2 and 1-3 induction included. Class 2 contains four models with 1-2 and 1-3 induction excluded.

Model	Class	Screening function	1-2 (bond)	1-3 (angle)
NTL	1	Thole's linear model	On	On
NTE	1	Thole's exponential model	On	On
NRE	1	Ren and Ponder's exponential model	On	On
NAP	1	Applequist's model	On	On
FTL	2	Thole's linear model	Off	Off
FTE	2	Thole's exponential model	Off	Off
FRE	2	Ren and Ponder's exponential model	Off	Off
FAP	2	Applequist's model	Off	Off

FIG. 1. Dependence of molecular polarizabilities on the basis sets for nine molecules belonging to nine categories in the molecule set we used.

By adjusting ρ_{ref} and σ , a Gaussian-like weight function $\omega(r)$ is generated which weighs heavily on the points in the desired range. We performed a scanning over a large range of σ and ρ_{ref} to look for the suitable parameters for dipole ESP fitting. It turns out that the ESP fitting quality is not significantly affected over a broad range of σ and ρ_{ref} . This conclusion is similar to that in the paper of Hu *et al.*⁵⁰ In our work, we chose $\sigma = 1.0$ and $\ln \rho_{ref} = -11$. In the spirit of Hu's work,⁵⁰ our object function is defined in the entire molecular volume space instead of discretely selected grid points surrounding the target molecule. The object function is thus rotationally invariant the to molecular orientation and continuously change with respect to the molecular geometry.⁵⁰ We constructed an integration grid with standard 3D integration method used in density functional calculations and then computed electrostatic potentials on the grid points with the converged electron density.⁵⁰ In the current work, the standard pruned (75 302) grid implemented in Gaussian was chosen. The small molecule set we used for ESP fitting and testing is the one developed by van Duijnen and Swart,³³ which is a widely used molecule set for atomic polarizability parametrization. However, since the weight function of Hu *et al.*⁵⁰ was only developed for the elements in the first three periods, molecules

TABLE II. Atomic polarizabilities and screening factors for eight models (atomic unit).

Atom type	NTL	NTE	NRE	NAP	FTL	FTE	FRE	FAP
C1 ^a	9.3114	7.4259	7.7525	2.8741	6.2867	6.2827	6.2827	6.2834
C2 ^b	13.4049	10.3546	11.9081	4.5106	7.7322	7.7990	7.7990	7.8004
C3 ^c	9.1352	8.2343	6.8914	5.0019	7.6621	7.7545	7.7599	7.7579
H	2.4456	1.4927	2.0576	1.0257	1.6972	1.6533	1.6547	1.6533
NO	5.7577	6.4642	5.8198	4.8365	4.6469	4.7016	4.7171	4.7049
N	6.9555	5.5249	6.3731	2.9754	5.2880	5.3217	5.3197	5.3217
O2 ^d	5.2833	4.3817	4.7974	2.4841	4.0699	4.0794	4.0740	4.0794
O3 ^e	5.2016	4.5349	4.2825	2.8890	3.7244	3.7548	3.7575	3.7561
F	2.6487	2.1237	1.8571	1.9563	2.3127	2.3005	2.2985	2.2998
Cl	11.8177	12.4075	11.7414	11.3601	11.5208	11.5376	11.5329	11.5356
S4 ^f	15.1662	14.5805	13.7126	10.9094	12.9811	12.9690	12.9797	12.9669
S ^g	16.8438	17.4161	15.2472	12.5357	15.0339	15.0522	15.0589	15.0488
Screening factor	1.7350	0.4130	1.1517	N/A	1.0000	0.1296	0.9959	N/A

^aC1: sp^1 carbon.^bC2: sp^2 carbon.^cC3: sp^3 carbon.^dO2: sp^2 oxygen.^eO3: sp^3 oxygen.^fS4: S in sulfone.^gS: nonsulfone S.

FIG. 2. Scatter plots of QM versus calculated molecular polarizabilities for the training set of all eight models. (a) NTL model. (b) NTE model. (c) NRE model. (d) NAP model. (e) FTL model. (f) FTE model. (g) FRE model. (h) FAP model.

TABLE III. Statistical results of training set for eight models. V_{RRMSD} : relative root mean square deviation. α_{APE} : average percentage error of molecular polarizabilities.

Model	Class 1				Class 2			
	NTL	NTE	NRE	NAP	FTL	FTE	FRE	FAP
V_{RRMSD}	0.2531	0.2334	0.2208	0.2397	0.3657	0.3655	0.3657	0.3656
α_{APE} (%)	7.75	5.43	6.78	12.59	8.08	7.94	8.65	7.93

TABLE IV. Statistical results of testing set for eight models. V_{RRMSD} : relative root mean square deviation. α_{APE} : average percentage error of molecular polarizabilities.

Model	Class 1				Class 2			
	NTL	NTE	NRE	NAP	FTL	FTE	FRE	FAP
V_{RRMSD}	0.1960	0.1813	0.1678	0.1822	0.3859	0.3841	0.3645	0.3856
α_{APE} (%)	4.61	2.93	4.17	8.93	9.87	9.69	8.79	9.74

containing *Br* and *I* in the small molecule set are thus not used for fitting in current work.

Besides introducing the screening functions, excluding 1-2 (bonded) and 1-3 (separated by two bonds) induction can also reduce the risk of “polarization catastrophe.” Thus, we

use eight induced dipole models based on whether 1-2 and 1-3 interactions are excluded and different screening functions are used. Table I summarizes the eight models we studied.

Figure 1 shows that the molecular polarizabilities vary with different basis sets. In the current work, the

TABLE V. Molecular polarizabilities and V_{RRMSD} (relative root mean square deviation) for models in Class 1. α_{Mol} denotes the molecular polarizabilities in atomic unit. Molecules in *italics* are not in the training set.

		QM	NTL		NTE		NRE		NAP	
Molecules		α_{Mol}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}
Alcohols										
2-propanol	CH ₃ CHOHCH ₃	42.08	40.50	0.1085	40.03	0.1192	40.32	0.0977	38.37	0.1070
Ethanol	C ₂ H ₅ OH	29.78	30.02	0.1574	29.59	0.1651	29.92	0.1514	28.70	0.1636
Methanol	CH ₃ OH	17.96	19.05	0.2189	18.57	0.2051	18.80	0.1905	18.08	0.1937
<i>Cyclohexanol</i>	C ₆ H ₁₁ OH	72.47	68.85	0.0897	68.28	0.1022	68.43	0.0812	63.13	0.0957
dev, %			3.91		3.67		3.73		3.73	
Alkanes										
Cyclohexane	C ₆ H ₁₂	67.66	63.98	0.0924	63.79	0.1113	63.84	0.0824	59.52	0.0834
Cyclopentane	C ₅ H ₁₀	56.12	53.51	0.0944	53.42	0.1179	53.17	0.0788	49.98	0.0747
Cyclopropane	C ₃ H ₆	33.58	31.73	0.0959	33.40	0.1551	33.15	0.1123	38.43	0.3192
Ethane	C ₂ H ₆	25.06	25.33	0.1639	25.28	0.1900	25.43	0.1523	25.48	0.1791
Hexane	C ₆ H ₁₄	72.51	70.82	0.1230	70.56	0.1386	71.48	0.1319	68.10	0.1187
Methane	CH ₄	13.39	14.44	0.2604	14.34	0.2669	14.31	0.2146	15.31	0.3019
Propane	C ₃ H ₈	37.0	36.22	0.1323	36.09	0.1518	36.37	0.1260	35.49	0.1275
<i>Dodecane</i>	C ₁₂ H ₂₆	144.57	143.36		142.77		145.27		135.90	
<i>Neopentane</i>	C(CH ₃) ₄	61.51	57.37	0.0824	56.74	0.0914	56.77	0.0626	53.67	0.0723
dev, %			4.06		3.69		3.54		9.15	
Alkenes										
Benzene	C ₆ H ₆	66.08	67.89	0.2159	67.86	0.2110	67.68	0.2012	54.98	0.1973
Chlorobenzene	C ₆ H ₅ Cl	78.79	79.43	0.2042	79.82	0.1929	80.76	0.1888	67.90	0.1799
Ethylene	C ₂ H ₄	24.50	26.62	0.3679	27.36	0.3518	26.80	0.3368	29.27	0.6549
Nitrobenzene	C ₆ H ₅ NO ₂	84.57	82.76	0.1915	82.87	0.1709	84.12	0.1677	71.77	0.1719
<i>Acetylene</i>	C ₂ H ₂	19.19	18.12	0.3288	19.07	0.2334	18.05	0.2106	14.82	0.2832
<i>m</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	92.34	91.17	0.1917	92.00	0.1763	94.23	0.1754	81.09	0.1726
<i>o</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	91.09	90.22	0.1901	91.45	0.1732	93.04	0.1771	80.11	0.1739
dev, %			3.16		2.72		3.57		16.03	
Carbonyls										
N-methylformamide	HCONHCH ₃	36.60	36.59	0.2090	36.75	0.1828	38.24	0.2146	33.17	0.1384
Acetaldehyde	HCOCH ₃	27.79	28.53	0.2484	28.95	0.2412	29.47	0.2677	26.38	0.1698
Acetamide	CH ₃ CONH ₂	36.17	35.81	0.1872	36.01	0.1884	37.43	0.2292	32.11	0.1655
Acetone	CH ₃ COCH ₃	39.25	39.27	0.1865	39.91	0.2012	40.85	0.2344	36.67	0.1097
Formaldehyde	HCOH	15.22	17.90	0.4763	17.80	0.3957	18.11	0.4387	14.67	0.2235
Formamide	HCOH	24.99	25.04	0.2554	25.00	0.2152	26.00	0.2570	21.66	0.2126
<i>N,N</i> -dimethylformamide	HCON(CH ₃) ₂	48.22	47.61	0.1776	47.40	0.1512	49.16	0.1734	42.63	0.1141
<i>N</i> -methylacetamide	CH ₃ CONHCH ₃	47.68	47.65	0.1673	47.74	0.1636	49.93	0.2137	43.04	0.1253
<i>Carbonyl chloride</i>	COCl ₂	39.06	36.91	0.2245	39.12	0.2341	39.60	0.2092	38.34	0.2456
dev, %			3.15		2.85		5.46		8.04	
Cyanides										
Ethyl cyanide	C ₂ H ₅ CN	38.34	36.71	0.1959	37.95	0.1941	37.50	0.1650	35.64	0.1712
Methyl cyanide	CH ₃ CN	26.42	25.60	0.2476	26.83	0.2389	26.19	0.1958	25.59	0.2380
Methyl dicyanide	CH ₂ (CN) ₂	39.73	37.24	0.2374	40.04	0.2469	38.77	0.2023	36.36	0.2364
Tert-butyl cyanide	(CH ₃) ₃ CCN	62.5	58.26	0.1219	59.06	0.1206	58.49	0.0921	54.26	0.1036
<i>Chloromethyl cyanide</i>	CH ₂ ClCN	38.06	36.33	0.2132	37.63	0.2148	37.08	0.1760	35.82	0.2112
<i>Isopropyl cyanide</i>	(CH ₃) ₂ CHCN	50.46	47.63	0.1507	48.72	0.1508	48.29	0.1231	45.26	0.1259
<i>Trichloromethyl cyanide</i>	CCl ₃ CN	64.33	57.05	0.1550	58.81	0.1588	58.49	0.1341	56.92	0.1677
dev, %			5.98		3.14		3.98		8.51	
Diatomics										
Carbon monoxide	CO	11.93	11.92	0.3017	11.30	0.2285	10.86	0.1872	6.68	0.4007
Chlorine	Cl ₂	21.81	25.35	0.3826	24.61	0.4852	24.47	0.3786	25.14	0.3574
Hydrogen	H ₂	2.13	3.81	1.0352	2.85	0.7439	3.36	0.8808	3.65	0.5667
Hydrogen chloride	HCl	10.61	13.52	0.4729	14.02	0.5244	14.07	0.5204	14.29	0.5680
Nitrogen	N ₂	10.5	11.06	0.411	10.48	0.2887	10.58	0.3239	8.71	0.3509
Nitric oxide	NO	10.37	9.32	0.2783	10.44	0.356	9.60	0.2553	10.83	0.5651
Oxygen	O ₂	8.84	9.24	0.3218	8.56	0.2649	9.19	0.2427	5.56	0.3769
dev, %			20.37		12.58		17.67		31.99	

TABLE V. (Continued.)

		QM		NTL		NTE		NRE		NAP	
Molecules		α_{Mol}		α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}
Halogens											
Chloromethane	CH ₃ Cl	23.12	24.92	0.2283	24.86	0.2623	24.84	0.2132	25.06	0.2536	
Fluoromethane	CH ₃ F	14.34	15.71	0.2827	14.91	0.2562	14.64	0.2064	14.9	0.2476	
Tetrachloromethane	CCl ₄	61.2	55.69	0.1206	56.49	0.143	56.87	0.1146	57.14	0.1076	
Tetrafluoromethane	CF ₄	17.66	18.34	0.2398	16.66	0.1885	15.83	0.1458	15.63	0.1112	
Trichloromethane	CHCl ₃	48.33	45.56	0.1406	46.07	0.1825	46.37	0.1407	46.58	0.1407	
Trifluoromethane	CHF ₃	16.81	17.55	0.2431	16.07	0.2088	15.41	0.1666	15.2	0.161	
Dichloromethane	CH ₂ Cl ₂	35.25	35.31	0.187	35.49	0.2375	35.64	0.188	35.72	0.2015	
Difluoromethane	CH ₂ F ₂	15.52	16.71	0.2723	15.49	0.2388	15.02	0.1918	14.94	0.2156	
Trichlorofluoromethane	CFCl ₃	49.68	46.3	0.1281	46.7	0.1573	46.65	0.1298	47.03	0.1234	
dev, %			6.11		4.53		5.53		6.00		
Sulfurs											
Carbon disulfide	CS ₂	47.47	39.23	0.4059	45.23	0.3242	40.97	0.293	44.89	0.2038	
Sulfur dioxide	SO ₂	23.7	22.18	0.1954	23.15	0.1678	23.03	0.122	21.78	0.1464	
Sulfur hexafluoride	SF ₆	29.74	37.95	0.3745	31.19	0.1728	32.2	0.1923	32.45	0.1832	
dev, %			17.13		3.97		8.26		7.55		
Various											
Ammonia	NH ₃	10.71	10.93	0.2755	9.85	0.22	11.08	0.3048	8.51	0.286	
Carbon dioxide	CO ₂	15.01	15.52	0.3683	16.48	0.2562	15.44	0.2271	13.45	0.2214	
Dimethyl ether	CH ₃ OCH ₃	29.93	30.27	0.177	29.78	0.1651	30.22	0.1599	28.91	0.1279	
Ethylene oxide	CH ₂ OCH ₂	25.79	25.61	0.139	26.66	0.1909	26.42	0.1519	29.5	0.4394	
p-dioxane	(CH ₂) ₄ O ₂	53.81	51.82	0.1186	51.48	0.1218	51.58	0.1046	47.85	0.1087	
Water	H ₂ O	6.91	7.98	0.3359	7.35	0.241	7.56	0.2974	7.34	0.4603	
Nitrous oxide	N ₂ O	17.4	15.58	0.3818	15.88	0.2363	15.94	0.2714	17.92	0.4057	
dev, %			5.28		5.88		4.52		9.86		

linear response function was calculated at the level of B3LYP/6-31+G*.^{51,52} All the molecular geometries were optimized at the same level before ESP fitting. Gaussian03⁵³ was used to analytically calculate the molecular polarizabilities at the level of B3LYP/6-31+G* for comparison.^{51,52}

We used the quasi-Newton BFGS algorithm to optimize the object function, with analytic first order derivatives with respect to the parameters (atomic polarizabilities and screening factors). Though this algorithm cannot guarantee global minimal, we find that the convergence is satisfying after trying different initial guesses.

III. RESULTS AND DISCUSSION

The quality of the ESP fitting is assessed by the relative-root-mean-square-deviation (RRMSD), which is defined as

$$V_{RRMSD} = \sqrt{\frac{\sum_{i=1}^{3N} (V_{QM,i} - V_{ESP,i})^2}{\sum_{i=1}^{3N} V_{QM,i}^2}}, \quad (25)$$

where N is the number of grid points, $V_{ESP,i}$ is the electrostatic potential at grid i calculated from the induced dipoles, and $V_{QM,i}$ is the electrostatic potential calculated with the linear response function at grid i . As it is shown in Sec. II, after integrating the orientation in the 3-dimensional physical space, it is equivalent to applying the uniform external electric fields from three different directions. Therefore, summation is over

$3N$. Though we focus on fitting to the ESP, a physically reasonable set of atomic polarizabilities $\{\alpha_p\}$ and screening factor a should also predict molecular polarizabilities well. Thus, we also calculated the average percentage error (APE) of the molecular polarizabilities, defined as

$$\alpha_{APE} = \frac{\sum_{i=1}^n |\alpha_i - \alpha_i^{QM}| / \alpha_i^{QM}}{n}, \quad (26)$$

where α_i is the molecular polarizabilities recovered from the atomic polarizabilities for molecule i , α_i^{QM} is the molecular polarizability for molecule i calculated by QM, and n is the number of molecules.

A. Atomic polarizabilities for force fields

Force fields are usually composed of bonded interaction (such as bond, angle, and dihedral) and nonbonded interaction (electrostatic and van der Waals interaction). In some force fields, contribution to polarization from 1-2 (bond) and 1-3 (separated by two bonds) is absorbed by long-range polarization.³²

When fitting for the purpose of force fields, transferable atomic polarizabilities were generated by fitting small molecules of different categories together as indicated in Eq. (23). The atomic polarizabilities and screening factors obtained for eight induced dipole models are listed in Table II, in which the classification of atom types is the same as that

TABLE VI. Molecular polarizabilities and V_{RRMSD} (relative root mean square deviation) for models in Class 2. α_{Mol} denotes the molecular polarizabilities in atomic unit. Molecules in italics are not in the training set.

		QM	FTL		FTE		FRE		FAP	
Molecules		α_{Mol}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}
Alcohols										
2-propanol	CH ₃ CHOHCH ₃	42.08	40.49	0.1952	40.44	0.1957	40.46	0.1961	40.45	0.1958
Ethanol	C ₂ H ₅ OH	29.78	29.28	0.2453	29.23	0.2451	29.25	0.2456	29.24	0.2453
Methanol	CH ₃ OH	17.96	18.18	0.312	18.13	0.3103	18.14	0.3108	18.13	0.3104
<i>Cyclohexanol</i>	C ₆ H ₁₁ OH	72.47	82.19	0.569	81.19	0.5305	72.8	0.2355	81.8	0.5529
dev, %			5.02		4.68		1.77		4.88	
Alkanes										
Cyclohexane	C ₆ H ₁₂	67.66	67.17	0.1821	67.19	0.184	67.24	0.1846	67.21	0.1842
Cyclopentane	C ₅ H ₁₀	56.12	55.59	0.2169	55.6	0.2197	55.64	0.2203	55.61	0.22
Cyclopropane	C ₃ H ₆	33.58	33.19	0.2814	33.2	0.2834	33.22	0.2839	33.21	0.2836
Ethane	C ₂ H ₆	25.06	25.53	0.3016	25.45	0.301	25.47	0.3016	25.45	0.3012
Hexane	C ₆ H ₁₄	72.51	70.73	0.2078	70.64	0.2094	70.69	0.2099	70.66	0.2096
Methane	CH ₄	13.39	14.45	0.406	14.37	0.4016	14.38	0.4023	14.37	0.4018
Propane	C ₃ H ₈	37	36.7	0.2394	36.62	0.2395	36.64	0.2401	36.63	0.2397
<i>Dodecane</i>	C ₁₂ H ₂₆	144.57	140.34		140.23		140.33		140.27	
<i>Neopentane</i>	C(CH ₃) ₄	61.51	59.23	0.1759	59.15	0.1767	59.19	0.1771	59.16	0.1768
dev, %			2.50		2.45		2.42		2.43	
Alkenes										
Benzene	C ₆ H ₆	66.08	57.07	0.3439	57.21	0.3447	57.22	0.3447	57.22	0.3447
Chlorobenzene	C ₆ H ₅ Cl	78.79	67.04	0.373	67.24	0.3739	67.24	0.3739	67.25	0.3739
Ethylene	C ₂ H ₄	24.5	22.26	0.4298	22.22	0.4299	22.22	0.43	22.22	0.43
Nitrobenzene	C ₆ H ₅ NO ₂	84.57	68.53	0.3823	68.79	0.3825	68.8	0.3825	68.8	0.3825
<i>Acetylene</i>	C ₂ H ₂	19.19	15.97	0.5453	15.87	0.5432	15.88	0.5432	15.87	0.5432
<i>m</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	92.34	77.04	0.3956	77.31	0.3968	77.3	0.3968	77.31	0.3968
<i>o</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	91.09	77.07	0.3896	77.34	0.3905	77.33	0.3905	77.34	0.3905
dev, %			15.06		14.96		14.95		14.95	
Carbonyls										
N-methylformamide	HCONHCH ₃	36.6	33.37	0.3574	33.35	0.3579	33.35	0.358	33.35	0.358
Acetaldehyde	HCOCH ₃	27.79	26.27	0.331	26.27	0.3317	26.27	0.3318	26.27	0.3318
Acetamide	CH ₃ CONH ₂	36.17	33.34	0.2965	33.32	0.2972	33.32	0.2973	33.32	0.2973
Acetone	CH ₃ COCH ₃	39.25	37.44	0.2744	37.43	0.2755	37.44	0.2757	37.44	0.2757
Formaldehyde	HCOH	15.22	15.2	0.4736	15.19	0.473	15.18	0.4729	15.19	0.4731
Formamide	HCOH	24.99	22.2	0.3774	22.17	0.3775	22.17	0.3774	22.18	0.3775
<i>N,N</i> -dimethylformamide	HCON(CH ₃) ₂	48.22	44.64	0.3091	44.62	0.3102	44.63	0.3103	44.63	0.3102
<i>N</i> -methylacetamide	CH ₃ CONHCH ₃	47.68	44.61	0.2878	44.59	0.2886	44.6	0.2888	44.6	0.2887
<i>Carbonyl chloride</i>	COCl ₂	39.06	34.84	0.4338	34.95	0.4356	34.94	0.4354	34.95	0.4356
dev, %			6.97		6.98		6.98		6.97	
Cyanides										
Ethyl cyanide	C ₂ H ₅ CN	38.34	35.47	0.3714	35.46	0.3718	35.47	0.3721	35.47	0.3719
Methyl cyanide	CH ₃ CN	26.42	24.34	0.4703	24.33	0.4702	24.34	0.4705	24.33	0.4703
Methyl dicyanide	CH ₂ (CN) ₂	39.73	34.25	0.4645	34.32	0.4656	34.32	0.4657	34.32	0.4657
Tert-butyl cyanide	(CH ₃) ₃ CCN	62.5	57.94	0.2529	57.94	0.2539	57.97	0.2543	57.95	0.2541
<i>Chloromethyl cyanide</i>	CH ₂ ClCN	38.06	34.18	0.4255	34.23	0.4264	34.23	0.4265	34.23	0.4265
<i>Isopropyl cyanide</i>	(CH ₃) ₂ CHCN	50.46	46.68	0.2979	46.67	0.2987	46.69	0.299	46.68	0.2988
<i>Trichloromethyl cyanide</i>	CCl ₃ CN	64.33	53.87	0.3238	84.05	0.3248	54.04	0.3248	54.05	0.3249
dev, %			10.06		9.98		9.96		9.98	
Diatomics										
Carbon monoxide	CO	11.93	10.36	0.2708	10.36	0.271	10.36	0.2708	10.36	0.271
Chlorine	Cl ₂	21.81	23.04	0.5912	23.08	0.5923	23.07	0.592	23.07	0.5922
Hydrogen	H ₂	2.13	3.39	1.0817	3.31	1.064	3.31	1.0645	3.31	1.0639
Hydrogen chloride	HCl	10.61	13.22	0.5624	13.19	0.5585	13.19	0.5582	13.19	0.5583
Nitrogen	N ₂	10.5	10.58	0.49	10.64	0.4956	10.64	0.4953	10.64	0.4956
Nitric oxide	NO	10.37	8.72	0.4003	8.78	0.4037	8.79	0.4045	8.78	0.4039
Oxygen	O ₂	8.84	8.14	0.4697	8.16	0.47	8.15	0.4698	8.16	0.47
dev, %			18.16		17.58		17.58		17.57	

TABLE VI. (Continued.)

		QM		FTL		FTE		FRE		FAP	
Molecules		α_{Mol}		α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}
Halogens											
Chloromethane	CH ₃ Cl	23.12	24.28	0.3954	24.25	0.3947	24.26	0.395	24.25	0.3948	
Fluoromethane	CH ₃ F	14.34	15.07	0.3865	15.02	0.3841	15.02	0.3846	15.02	0.3843	
Tetrachloromethane	CCl ₄	61.2	53.75	0.2703	53.9	0.2716	53.89	0.2715	53.9	0.2716	
Tetrafluoromethane	CF ₄	17.66	16.91	0.3005	16.96	0.3038	16.95	0.3037	16.96	0.3039	
Trichloromethane	CHCl ₃	48.33	43.92	0.3263	44.02	0.3279	44.01	0.3278	44.02	0.3279	
Trifluoromethane	CHF ₃	16.81	16.3	0.3201	16.31	0.3215	16.31	0.3216	16.31	0.3216	
Dichloromethane	CH ₂ Cl ₂	35.25	34.1	0.3826	34.14	0.3836	34.13	0.3837	34.14	0.3837	
Difluoromethane	CH ₂ F ₂	15.52	15.68	0.3577	15.66	0.3574	15.67	0.3577	15.66	0.3575	
Trichlorofluoromethane	CFCl ₃	49.68	44.54	0.2823	44.67	0.2841	44.66	0.2841	44.67	0.2841	
dev, %			5.93		5.73		5.76		5.73		
Sulfurs											
Carbon disulfide	CS ₂	47.47	36.35	0.6314	36.39	0.6315	36.40	0.6315	36.38	0.6315	
Sulfur dioxide	SO ₂	23.70	21.12	0.3965	21.13	0.3965	21.13	0.3965	21.13	0.3965	
Sulfur hexafluoride	SF ₆	29.74	28.91	0.1825	28.86	0.1816	28.85	0.1815	28.85	0.1814	
dev, %			12.37		12.38		12.39		12.40		
Various											
Ammonia	NH ₃	10.71	10.38	0.3042	10.28	0.2973	10.28	0.2974	10.28	0.2973	
Carbon dioxide	CO ₂	15.01	14.43	0.5783	14.44	0.5786	14.43	0.5783	14.44	0.5787	
Dimethyl ether	CH ₃ OCH ₃	29.93	29.38	0.2601	28.33	0.2595	29.35	0.2599	29.33	0.2596	
Ethylene oxide	CH ₂ OCH ₂	25.79	25.84	0.3183	25.88	0.3198	25.9	0.3203	25.89	0.32	
p-dioxane	(CH ₂) ₄ O ₂	53.81	52.28	0.1832	52.36	0.1846	52.39	0.1851	52.37	0.1848	
Water	H ₂ O	6.91	7.12	0.3171	7.06	0.3094	7.07	0.3098	7.06	0.3094	
Nitrous oxide	N ₂ O	17.4	14.65	0.6124	14.72	0.6141	14.71	0.6139	14.72	0.6141	
dev, %			4.38		4.35		4.38		4.35		

used by Wang *et al.*³² For the convenience of comparison, we divide the eight induced dipole models into two classes based on whether 1-2 and 1-3 interactions are included. In many polarizable force fields, “the short range 1-2 and 1-3 interactions are excluded to reduce the potential of polarization catastrophe.”³² Class 1 contains four models (NTL, NTE, NRE, and NAP) including 1-2 and 1-3 interactions. Class 2 contains the other four models (FTL, FTE, FRE, and FAP) excluding 1-2 and 1-3 interactions. The scatter plots of molecular polarizabilities obtained from QM versus ESP fitting for the training set of eight models are shown in Figure 2. Statistical results of the training set are shown in Table III, and those for the testing set are shown in Table IV.

Since many molecules in our molecule set are simple molecules, which only contain 1-2 and 1-3 interactions, fitting these molecules with models in Class 2 can cause large error, leading to relatively overall large errors, which is reflected in Tables III and IV. However, this phenomenon only means that models in Class 2 are not suitable for simple molecules. Actually, Wang *et al.*³² reported that models in Class 2 show lower α_{APE} when fitted with another molecule set in which molecules are more complex. For this reason, in the following discussion, we will not compare models between Class 1 and Class 2. For Class 1, as we can see from the results of both the training set (Table III) and testing set (Table IV), the three models with screening functions (NTL, NTE, and NRE) have similar α_{APE} , which is smaller than that of NAP. This means that short distance induction without screening can indeed

cause large errors. For Class 2, all four models show similar α_{APE} , which means these four models have similar accuracy in predicting molecular polarizabilities. It was reported by van Duijnen and Swart³³ that when fitting to *ab initio* molecular polarizabilities with NTL and NTE models using the same training set, α_{APE} is about 6%, which is of the same order as our results. V_{RRMSD} is the quantity to assess the quality of ESP fitting. As it is shown in Tables III and IV, $RRMSD$ for all eight models is small and about the same order, which means ESP fittings for eight models are all satisfactory. The errors then could be taken as the intrinsic limitation of polarizable dipole models.

It may be more meaningful to separately consider the α_{APE} for each category of molecules. As it is shown in Tables V and VI, α_{APE} for different categories varies much. Categories of simple molecules (e.g., diatomics and sulfurs) have much larger α_{APE} than other categories. This is because simple molecules, even fitted with models in Class 1, have fewer degrees of freedom to fit the ESP.

B. Molecule specific atomic polarizabilities

For the molecule-specific fitting, atomic polarizabilities and screening factors are optimized for individual molecules. There are nine categories of molecules in the molecule set. In order to compare the results of molecule-specific fitting with force field fitting, we chose nine molecules out, one from each category. Take the NTE model as an example. The

TABLE VII. Comparison between molecule-specific fitting and force field fitting for NTE model. The nine molecules are chosen from nine different categories in the molecule set and are from the training set of the force field fitting. α_{Mol} denotes the molecular polarizabilities in atomic unit. V_{RRMSD} : relative root mean square deviation.

		QM	Molecule-specific fitting		Force field fitting	
		α_{Mol}	α_{Mol}	V_{RRMSD}	α_{Mol}	V_{RRMSD}
Ethanol	C ₂ H ₅ OH	29.78	29.99	0.1373	29.59	0.1651
Ethane	C ₂ H ₆	25.06	24.83	0.1368	25.28	0.1900
Ethylene	C ₂ H ₄	24.50	24.26	0.3064	27.36	0.3518
Acetaldehyde	HCOCH ₃	27.79	27.59	0.1620	28.95	0.2412
Ethyl cyanide	C ₂ H ₅ CN	38.34	37.72	0.1673	37.95	0.1941
Hydrogen	H ₂	2.13	2.94	0.4206	2.85	0.7439
Chloromethane	CH ₃ Cl	23.12	22.46	0.2059	24.86	0.2623
Sulfur dioxide	SO ₂	23.70	23.38	0.1617	23.15	0.1678
Water	H ₂ O	6.91	7.24	0.2185	7.35	0.2410

fitting results are shown in Table VII. The nine molecules we used for comparison are originally in the training set of force field fitting. As it is shown in Table VII, molecule-specific fitting can further improve the accuracy of ESP fitting (i.e., smaller V_{RRMSD}). The relative percentage error of the eight molecules in Table VII (except hydrogen) ranges from 0.7% to 4.8%. This shows comparable accuracy with that obtained in Celebi's work⁶⁰ for distributed polarizabilities, which are also calculated in the molecule-specific way. The large relative percentage error of hydrogen is mainly due to its simple structure. Furthermore, molecular polarizabilities obtained from the molecule-specific fitting are better approximations to the QM results. Molecule-specific fitting is particularly useful when the polarization effects of specific molecules need to be accurately evaluated.

In the electrostatic potential fitting of atomic charge, due to insufficient number of grids on the ESP surface, atoms buried in molecules are usually not well fitted.⁶¹ As our polarizable force field was developed as parallel to the electrostatic potential fitting of atomic charges, it should share this problem. However, the uncertainty of buried charges can be regularized. It was reported that to get around the "buried" atom problem, "the most robust technique consisted of constraining the fitting procedure to reproduce a target charge on non-hydrogen atoms."⁶¹⁻⁶³ The molecule set we used for training and testing in our paper consisted of small molecules, the "buried" atom problem does not affect our results. For large molecules, similar regularization procedure can be adopted to deal with the "buried" atom problem.

In this work, atomic polarizabilities were calculated by ESP fitting after applying uniform external electric fields. In the ideal situation, atomic polarizabilities calculated should not depend on the magnitudes and orientations of the uniform external electric fields. We took two steps to remove the dependence on the orientation of applied electric fields. First, we used the weight function developed by Hu *et al.*⁵⁰ It has been shown that the object function defined in their way shows little molecule orientation dependence.⁵⁰ Second, the orientation of the applied electric fields was integrated in the 3-dimensional physical space. In order to be independent of the magnitude of the applied electric fields (δE), we fit the

ESP within the linear response level. Thus, as indicated by Eq. (21), δE does not affect the optimization of the object function. Actually, there is a deeper reason that the linear response function can be combined with the induced dipole models in the ESP fitting process. The induced dipole model itself is essentially a linear response model ($\mu_i = \alpha_i E_i$), which is consistent with the linear response function. But we need to be aware of the limitation with the ESP fitting method. The fitting quality depends on the choice of the basis sets in the quantum mechanical linear response function calculations, the choice of grid points, and the definition of the object function L itself.

IV. CONCLUSION

In summary, we developed a new method of calculating the atomic polarizabilities by ESP fitting with the linear response theory. The method was used for developing atomic polarizabilities for both force fields and specific molecules using eight induced dipole models. Fitting for force fields can generate transferable atomic polarizabilities, which can be used for the construction of new force fields, while fitting for specific molecules can generate nontransferable atomic polarizabilities specifically optimized for individual molecules. With the introduction of the linear response function, atomic polarizabilities can be calculated accurately and efficiently, in parallel to obtaining atomic charges based on fitting electrostatic potentials.

The present method for calculating atomic polarizabilities parallels the method for fitting atomic charges using ESP, which is widely used in force field development. Atomic polarizabilities obtained here can be directly combined with any existing ESP charges without the need to recalculate the ESP charges. We expect our development will provide a very useful tool for developing polarizable force fields.

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