Efficient treatment of induced dipoles

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Most existing treatments of induced dipoles in polarizable molecular mechanics force field calculations use either the self-consistent variational method, which is solved iteratively, or the “direct” approximation that is non-iterative as a result of neglecting coupling between induced dipoles. The variational method is usually implemented using assumptions that are only strictly valid under tight convergence of the induced dipoles, which can be computationally demanding to enforce. In this work, we discuss the nature of the errors that result from insufficient convergence and suggest a strategy that avoids such problems. Using perturbation theory to reintroduce the mutual coupling into the direct algorithm, we present a computationally efficient method that combines the precision of the direct approach with the accuracy of the variational approach. By analyzing the convergence of this perturbation series, we derive a simple extrapolation formula that delivers a very accurate approximation to the infinite order solution at the cost of only a few iterations. We refer to the new method as extrapolated perturbation theory. Finally, we draw connections to our previously published permanent multipole algorithm to develop an efficient implementation of the electric field and Thole terms and also derive some necessary, but not sufficient, criteria that force field parameters must obey. [<http://dx.doi.org/10.1063/1.4928530>]

I. INTRODUCTION

The push for increasingly accurate classical simulations of large molecules has seen the introduction of more elaborate force field functional forms to describe potential energy surfaces.^{1,2} The electrostatic terms, which typically are the most computationally demanding, can be accurately modeled by extending the fixed point-charge model to include higher order multipole moments^{3–5} and polarization.⁶ While the extra flexibility afforded by these terms allows for accurate descriptions of molecular interactions, the resulting increase in computational cost hinders the ability to properly sample configurational space. Therefore, it is imperative that any augmentation of the functional form of a force field is done in the most computationally efficient manner.

The introduction of polarization terms can prove particularly difficult, since they often deviate from a pairwise additive form and can require a self-consistent solution, *vide infra*. One popular approach is to introduce Drude oscillators,^{7–13} wherein a pair of oppositely charged particles is introduced; the first is placed at its associated polarizable center, while the second is tethered to the polarizable center by a harmonic spring. The magnitude of the spring’s force constant and the particle’s charge is parameterized to reproduce the atomic polarizability. The formal solution for the Drude oscillator energy involves the self-consistent minimization of the energy, with respect to the Drude particles’ positions, for each nuclear configuration. However, this self-consistent procedure is commonly averted

by assigning a small, fictitious mass to each Drude particle and propagating them simultaneously with the atomic motions,^{9–12} this is analogous to the Car-Parinello approach for *ab initio* dynamics.¹⁴ The light mass of the Drude particles requires relatively small time steps to be used to integrate the equations of motion, and dual thermostats are commonly employed to mitigate coupling of the nuclear and electronic degrees of freedom.

Another approach for polarization is to introduce an analytic dipole at each polarizable center, whose magnitudes are determined through linear response theory as the product of the atomic polarizabilities and the local electric fields.^{15–28} Some examples of force fields and fragmentation methods that employ induced dipoles include AMOEBA (atomic multipole optimized energetics for biomolecular applications),^{22,24,25,28} EFP (effective fragment potential),²⁹ the Gaussian Electrostatic Model (GEM),^{30,31} and NEMO (nonempirical molecular orbital).³² When induced dipoles are present, the electric field at each center depends on the magnitudes of all of the other dipoles which, like the Drude model, requires a self-consistent solution.^{22,24,25,27} For the AMOEBA force field, the polarizability of center *A* (α_A) is a scalar, and the induced dipoles on center *A* are determined by α_A , the field at *A* due to the permanent multipole moments on other centers (E_A) and the field at *A* due to the presence of induced dipoles on other centers^{22,24,27,33}

$$\mu_{A,\xi} = \alpha_A \left(E_{A,\xi} + \sum_{\substack{v \\ B \neq A}} \mathcal{T}_{AB,\xi v} \mu_{B,v} \right), \quad (1)$$

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where ξ and ν represent the Cartesian indices $\{x, y, z\}$. The $\mathcal{T}$ term that couples the induced dipoles, and provides damping to avert singularities, will be described in detail below. Numerically solving these linear equations is potentially problematic, as insufficient convergence of the linear equations will lead to artifacts such as phantom heating, while too strict a convergence criterion will be computationally expensive. As in the case of Drude oscillators, an extended Lagrangian approach has also been suggested as a practical means to obtaining the polarizable dipoles.²¹

A “direct” approximation may be made, in which the terms that couple the induced dipoles in Eq. (1) are neglected; by considering only the leading $\mathbf{E}_A$ term on the right hand side of (1), and neglecting $\mathcal{T}$, the linear equations are trivially solved without iteration.^{18–20} This forms the basis of the iAMOEBA (inexpensive AMOEBA)²⁶ method that was recently developed by reparameterizing the AMOEBA water model to account for the incomplete inclusion of polarizable dipoles. The iAMOEBA water model demonstrates excellent performance for many physical properties over a range of conditions. Another promising approximation is the n -body decomposition, wherein the molecular system is treated as a superposition of clusters up to a prescribed size, each of which can be simply evaluated, taking care to avoid multiple counting. The n -body approach is trivially parallelizable and has been shown to yield polarization energy errors of less than 3%, with respect to the variational AMOEBA model, for water clusters, when truncating the expansion at trimers.³⁴

The evaluation of interaction energies and forces between permanent multipoles using the particle mesh Ewald (PME)³⁵ method has been, and remains, an active area of research.^{21,36–46} In 1996, Hättig introduced⁴⁷ a quasi-internal (QI) coordinate system, in which the local z -axis is aligned with the internuclear axis for each pair. The QI coordinate system allows orthogonality to be exploited when spherical harmonic multipole moments are used and vastly simplifies the evaluation of forces and torques.⁴⁸ We recently extended this idea⁴² to include PME treatment of long-range interactions, resulting in an efficient framework for evaluating multipole interactions.

In this work, we demonstrate how knowledge gleaned from the QI coordinate system may be used to speed up the evaluation of permanent field contributions to polarizable dipoles and to derive inequalities that allow us to assess force field parameterization. More importantly, we use perturbation theory (PT) to derive a hierarchy of methods that bridge the gap between the direct approximation and fully variational dipoles; these methods are free from the numerical artifacts that are present in insufficiently converged variational solutions, by construction. While we frame our discussion in the context of the iAMOEBA and AMOEBA force fields hereafter, the results are generalizable to any force field that considers induced dipoles.

II. THEORY

A. Notation

We use tildes to denote quantities that are expressed in the local (QI) frame, which is unique for every pair of atoms.

All quantities without a tilde are assumed to be expressed in the global (laboratory) frame. The unitary matrix $\mathbf{U}_z$ rotates from the QI frame to the laboratory frame; it simultaneously accounts for the orientation of the internuclear vector and the permutation of spherical harmonic functions from $\{\mathcal{R}_{1,0}, \mathcal{R}_{1,1c}, \mathcal{R}_{1,1s}\}$ order, which corresponds to $\{z, x, y\}$ in Cartesians, to $\{x, y, z\}$ order. The relationship between the global and local frame electrostatic field and dipole at center A is therefore

$$\mathbf{E}_A = \mathbf{U}_z \tilde{\mathbf{E}}_A, \quad (2a)$$

$$\boldsymbol{\mu}_A = \mathbf{U}_z \tilde{\boldsymbol{\mu}}_A. \quad (2b)$$

B. Induced dipoles

As in Eq. (1), the polarizability used in the AMOEBA force field is isotropic and rotationally invariant; its inverse takes a simple form

$$\alpha_A^{-1} = \begin{pmatrix} \alpha_A^{-1} & 0 & 0 \\ 0 & \alpha_A^{-1} & 0 \\ 0 & 0 & \alpha_A^{-1} \end{pmatrix}. \quad (3)$$

In the following discussion, we will not limit ourselves to this assumption, and we will cast the equations in terms of a block diagonal generalized atomic polarizability, $\boldsymbol{\alpha}$, whose diagonal entries are the 3×3 atomic polarizability tensors. Recasting (1) in matrix form yields the system of linear equations,

$$\begin{pmatrix} \alpha_1^{-1} & -\mathcal{T}_{12} & \cdots & -\mathcal{T}_{1N} \\ -\mathcal{T}_{12} & \alpha_2^{-1} & \cdots & -\mathcal{T}_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ -\mathcal{T}_{1N} & -\mathcal{T}_{2N} & \cdots & \alpha_N^{-1} \end{pmatrix} \begin{pmatrix} \boldsymbol{\mu}_1 \\ \boldsymbol{\mu}_2 \\ \vdots \\ \boldsymbol{\mu}_N \end{pmatrix} = \begin{pmatrix} \mathbf{E}_1 \\ \mathbf{E}_2 \\ \vdots \\ \mathbf{E}_N \end{pmatrix}. \quad (4)$$

As a more convenient shorthand, we may rewrite (4) as

$$\mathbf{T}\boldsymbol{\mu} = \mathbf{E}, \quad (5)$$

which introduces the coupling tensor $\mathbf{T}$,

$$\mathbf{T} = \boldsymbol{\alpha}^{-1} - \mathcal{T}. \quad (6)$$

The dimensions of $\mathbf{T}$ are $3N \times 3N$, where N is the number of polarizable sites. The off-diagonal blocks of $\mathbf{T}$ are the Thole-damped³³ Cartesian interaction tensors between induced dipoles on two centers A and B , whose internuclear vector $\mathbf{R}_{AB} = \mathbf{R}_B - \mathbf{R}_A$ has norm R and components $\{R_x, R_y, R_z\}$,

$$\mathcal{T}_{AB} = \begin{pmatrix} \frac{3\lambda_5 R_x^2 - \lambda_3 R^2}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_x R_y}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_x R_z}{4\pi\epsilon_0 R^5} \\ \frac{3\lambda_5 R_x R_y}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_y^2 - \lambda_3 R^2}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_y R_z}{4\pi\epsilon_0 R^5} \\ \frac{3\lambda_5 R_x R_z}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_y R_z}{4\pi\epsilon_0 R^5} & \frac{3\lambda_5 R_z^2 - \lambda_3 R^2}{4\pi\epsilon_0 R^5} \end{pmatrix}. \quad (7)$$

The Cartesian Thole damping factors are defined in terms of a dimensionless width parameter, a , by

$$\begin{aligned} \lambda_3 &= 1 - e^{-au^3}, \\ \lambda_5 &= 1 - (1 + au^3)e^{-au^3}, \end{aligned} \quad (8)$$

where the dimensionless, reduced distance is $u = R/(\alpha_A\alpha_B)^{1/6}$, and $\alpha_A = \frac{1}{3}\text{Tr}(\alpha_A)$; the derivation of these expressions has been well described in previous works.^{22,24,27}

Using the notation described above, the polarization energy due to the induced dipoles, μ , is given by the compact expression

$$U = \frac{1}{2}\mu^T \mathbf{T} \mu - \mathbf{E}^T \mu. \quad (9)$$

For a variational method, such as the iterative AMOEBA approach, we obtain μ by requiring a zero residual, $\mathcal{R}$,

$$\mathcal{R} \equiv \left(\frac{dU}{d\mu} \right)^T = \mathbf{T} \mu - \mathbf{E} = \mathbf{0}, \quad (10)$$

which is the origin of Equation (5).

The geometric derivatives, required for dynamics simulations, are

$$\frac{dU}{d\mathbf{r}} = \frac{\partial U}{\partial \mathbf{r}} + \frac{\partial U}{\partial \mu} \frac{\partial \mu}{\partial \mathbf{r}}. \quad (11)$$

The first part of the derivative (the Hellman-Feynman-like term) is simply

$$\begin{aligned} \frac{\partial U}{\partial \mathbf{r}} &= \frac{1}{2}\mu^T \frac{\partial \mathbf{T}}{\partial \mathbf{r}} \mu - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \mu \\ &= -\frac{1}{2}\mu^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \mu - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \mu, \end{aligned} \quad (12)$$

as a consequence of our use of an orientation-independent polarizability tensor α ; an extra term appears for general α tensors, as described in Eq. (15) of Ref. 27. The final term in Eq. (11), due to dipole response, is directly proportional to the residual $\mathcal{R}$ and can therefore only be neglected when the iterative dipole equations are sufficiently tightly converged; insidious errors in the forces may accumulate over long simulations if the induced dipoles are not converged tightly. We will address the form of these dipole response terms and suggest a strategy for approximating them at the end of Section III.

1. Direct polarization: The iAMOEBA model

In the direct polarization approximation, the coupling terms in $\mathbf{T}$ are neglected, and Eq. (6) becomes a diagonal matrix

$$\mathbf{T} = \alpha^{-1}. \quad (13)$$

The dipoles are then defined by analytically solving Eq. (10), yielding

$$\mu_{\text{dir}} = \alpha \mathbf{E}. \quad (14)$$

Inserting Eqs. (13) and (14) into (9), we find the direct polarization energy

$$\begin{aligned} U_{\text{dir}} &= \frac{1}{2}\mu_{\text{dir}}^T \alpha^{-1} \mu_{\text{dir}} - \mathbf{E}^T \mu_{\text{dir}} \\ &= \frac{1}{2}\mathbf{E}^T \mu_{\text{dir}} - \mathbf{E}^T \alpha \mathbf{E} \\ &= -\frac{1}{2}\mathbf{E}^T \mu_{\text{dir}}. \end{aligned} \quad (15)$$

Because the residual $\mathcal{R}$ is zero, only the Hellman-Feynman-like terms contribute to the direct gradient

$$\begin{aligned} \frac{\partial U_{\text{dir}}}{\partial \mathbf{r}} &= \frac{1}{2}\mu_{\text{dir}}^T \frac{\partial \mathbf{T}}{\partial \mathbf{r}} \mu_{\text{dir}} - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \mu_{\text{dir}} \\ &= \frac{1}{2}\mu_{\text{dir}}^T \frac{\partial \alpha^{-1}}{\partial \mathbf{r}} \mu_{\text{dir}} - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \mu_{\text{dir}} \\ &= -\frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \mu_{\text{dir}}. \end{aligned} \quad (16)$$

A key difference between the gradient expressions for iterative, variational model Eq. (12) and direct model's derivative Eq. (16), besides the absence of any $\mathcal{T}$ coupling terms, is that the neglected dipole response term, $\frac{\partial U}{\partial \mu} \frac{\partial \mu}{\partial \mathbf{r}}$, is only approximately zero in the former and is identically so in the latter. Therefore, the direct forces lack the dipole response artifacts that plague an insufficiently converged variational solution.

Given the simplicity of the direct approach, the evaluation of the field due to permanent moments, $\mathbf{E}$, and its derivatives, $\frac{\partial \mathbf{E}^T}{\partial \mathbf{r}}$, will be the computational bottleneck for this method. These quantities are easily evaluated in the QI frame, by repurposing the same intermediates required to evaluate energies and forces involving permanent dipoles interacting with arbitrary order permanent multipole moments. This involves the formation of quasi-internal coordinate multipole moments $\tilde{\mathbf{Q}}$, which are already formed during the evaluation of the permanent multipole interactions and interaction tensor elements $t_{\kappa}^{l_a, l_b}(R)$,^{47,48}

$$t_{\kappa}^{l_a, l_b}(R) = \frac{(-1)^{l_b + \kappa}}{4\pi\epsilon_0 R^{l+1}} \sqrt{\binom{l}{l_a + \kappa} \binom{l}{l_a - \kappa}}. \quad (17)$$

The QI field is easily computed

$$\tilde{\mathbf{E}}_A = \begin{pmatrix} \tilde{E}_{A,0} \\ \tilde{E}_{A,1c} \\ \tilde{E}_{A,1s} \end{pmatrix} = \begin{pmatrix} -\sum_{l_b} \lambda_0^{l_b} t_0^{1, l_b}(R) \tilde{Q}_{l_b 0}^B \\ -\sum_{l_b} \lambda_{1c}^{l_b} t_{1c}^{1, l_b}(R) \tilde{Q}_{l_b 1c}^B \\ -\sum_{l_b} \lambda_{1s}^{l_b} t_{1s}^{1, l_b}(R) \tilde{Q}_{l_b 1s}^B \end{pmatrix} \quad (18)$$

and can be rotated back to the lab frame using Eq. (2a). The λ coefficients are the spherical harmonic Thole damping factors, derived using the procedure outlined in Ref. 42, and are shown in Table I. The derivatives $\frac{\partial \mathbf{E}^T}{\partial \mathbf{r}}$ are processed similarly, after rotating μ to the QI frame, using the procedure outlined by Hättig,⁴⁸ which utilizes the relationship

$$\frac{dt_{\kappa}^{l_a, l_b}(R)}{dR} = -\sqrt{(l_a + 1 + \kappa)(l_a + 1 - \kappa)} t_{\kappa}^{l_a + 1, l_b}(R), \quad (19)$$

and by replacing the λ coefficients with their derivative counterparts, λ' , which are shown in Table II. Ewald summation can be introduced easily: the direct and adjusted terms are obtained by replacing $t_{\kappa}^{l_a, l_b}(R)$ and $\frac{dt_{\kappa}^{l_a, l_b}(R)}{dR}$ with $\tau_{\kappa}^{l_a, l_b}(\beta, R)$ and $\frac{d\tau_{\kappa}^{l_a, l_b}(\beta, R)}{dR}$ from Ref. 42, respectively, while the reciprocal space terms have been discussed in detail by Giese, Panteva, Chen, and York.⁴⁶

Whether or not Ewald summation is used, there are at most three contributions to the field and its gradient from any order of permanent multipole; this is a consequence of orthogonality among spherical harmonics, which is readily exploited in the

TABLE I. The Thole damping factors for quasi-internal spherical harmonic multipole energies.^a

l	λ_0^l	$\lambda_{1c/1s}^l$
0	$1 - e^{-au^3}$	
1	$1 - \left(1 + \frac{3}{2}au^3\right)e^{-au^3}$	$1 - e^{-au^3}$
2	$1 - \left(1 + au^3 + a^2u^6\right)e^{-au^3}$	$1 - (1 + au^3)e^{-au^3}$
3	$1 - \left(1 + au^3 + \frac{9}{20}a^2u^6 + \frac{9}{20}a^3u^9\right)e^{-au^3}$	$1 - \left(1 + au^3 + \frac{3}{5}a^2u^6\right)e^{-au^3}$
4	$1 - \left(1 + au^3 + \frac{87}{175}a^2u^6 + \frac{18}{175}a^3u^9 + \frac{27}{175}a^4u^{12}\right)e^{-au^3}$	$1 - \left(1 + au^3 + \frac{18}{35}a^2u^6 + \frac{9}{35}a^3u^9\right)e^{-au^3}$

^aThe λ coefficients represent the prefactors for Equation (17) in the electric field expression and for evaluating interactions of induced dipoles with permanent multipole moments, using spherical harmonics in the QI frame. See main text and Refs. 22 and 27 for details.

QI frame. Therefore, the QI frame, in conjunction with spherical harmonics, provides an efficient algorithm for obtaining the right hand side of Eq. (4). In a general Cartesian treatment, the six quadrupole components on center B each contribute to the three field components at center A , leading to 18 terms that must be evaluated instead of just three in the approach outlined here. For even higher order expansions, the benefit is greater.

2. Mutual polarization: The AMOEBA model

The dominant cost in the iterative solution of Eq. (10) is the repeated formation of the product $\mathbf{T}\boldsymbol{\mu}$. Unlike the formation of $\mathbf{E}$ in the presence of higher-order multipoles, the QI frame offers no advantage for evaluating the field from dipoles alone. Because of the relative ease of formation of the Cartesian $\mathcal{T}$ tensor, Eq. (7), the use of the QI spherical harmonic approach for this term is not efficient; although the QI basis renders $\mathcal{T}$ diagonal, with only two unique entries, the dipoles would first have to be rotated to the QI basis, and the result rotated back to the lab frame, making this approach relatively expensive.

Efficiency is not the only consideration when designing an induced dipole algorithm, and there is scope for numerical instabilities to impact the variational method. Lipparini and co-workers computed short trajectories²⁷ for ubiquitin using the AMOEBA force field and demonstrated that their stability is dictated not only by the convergence criterion for the induced dipoles but also the guess and the algorithm used to converge the equations. As noted previously, the dipole response contribution to the force is neglected in common implementations of the AMOEBA force field so, unless the dipoles are tightly converged, a small part of the force will be missing. The effect of this force error is dictated in part by the guess used to start the

iterations, as correlation between the velocities and the force errors will lead to instabilities in the trajectory.

In Sec. II C, we focus our efforts on developing an alternative approach that combines the analytic nature of the direct algorithm, with an accuracy close to the variational solution. We will do so by reintroducing the $\mathcal{T}$ coupling into the direct approach via perturbation theory.

C. Perturbation theory

Rather than approximate the $\mathbf{T}$ tensor itself, we can instead find a series of approximations to $\boldsymbol{\mu}$ (or, equivalently, $\mathbf{T}^{-1}$); this leads to a hierarchy of approximations that provide the desired induced dipole couplings and, under the right conditions, will converge to exact result in the high-order limit.

Following the classical derivation of Rayleigh-Schrödinger perturbation theory (RSPT),⁴⁹ we partition Eq. (6) into a model term that can be analytically solved, and the coupling term which is multiplied by an “ordering parameter,” λ ,

$$\mathbf{T} = \boldsymbol{\alpha}^{-1} - \lambda\mathcal{T}. \quad (20)$$

Setting the ordering parameter to 0 yields the direct method, while setting it to 1 gives the full variational approach; we will use λ for bookkeeping purposes before setting it to 1 to recover the full interaction. Because we have expanded the induced dipole field operator in powers of λ , we express the resulting dipoles using a power series in λ ,

$$\boldsymbol{\mu}_n = \boldsymbol{\mu}_{(0)} + \lambda\boldsymbol{\mu}_{(1)} + \lambda^2\boldsymbol{\mu}_{(2)} + \cdots + \lambda^n\boldsymbol{\mu}_{(n)}. \quad (21)$$

Note that the subscripts without parentheses represent total perturbative dipoles, while the subscripts in parentheses are

TABLE II. The Thole damping factors for quasi-internal spherical harmonic multipole energy first derivatives.^a

l	$\lambda_0'^l$	$\lambda_{1c/1s}'^l$
0	$1 - \left(1 + \frac{3}{2}au^3\right)e^{-au^3}$	
1	$1 - \left(1 + au^3 + \frac{3}{2}a^2u^6\right)e^{-au^3}$	$1 - (1 + au^3)e^{-au^3}$
2	$1 - \left(1 + au^3 + \frac{1}{4}a^2u^6 + \frac{3}{4}a^3u^9\right)e^{-au^3}$	$1 - \left(1 + au^3 + \frac{3}{4}a^2u^6\right)e^{-au^3}$
3	$1 - \left(1 + au^3 + \frac{51}{100}a^2u^6 - \frac{9}{100}a^3u^9 + \frac{27}{100}a^4u^{12}\right)e^{-au^3}$	$1 - \left(1 + au^3 + \frac{12}{25}a^2u^6 + \frac{9}{25}a^3u^9\right)e^{-au^3}$
4	$1 - \left(1 + au^3 + \frac{1}{2}a^2u^6 + \frac{69}{350}a^3u^9 - \frac{18}{175}a^4u^{12} + \frac{27}{350}a^5u^{15}\right)e^{-au^3}$	$1 - \left(1 + au^3 + \frac{1}{2}a^2u^6 + \frac{9}{70}a^3u^9 + \frac{9}{70}a^4u^{12}\right)e^{-au^3}$

^aThe λ' coefficients represent the prefactors for Equation (19) in the electric field gradient expression and the gradient expression for induced dipoles interacting with permanent multipole moments, using spherical harmonics in the QI frame. See main text and Refs. 22 and 27 for details.

reserved for the individual components. To proceed, we substitute Eqs. (20) and (21) into Eq. (10), and multiply through by α , giving

$$(\boldsymbol{\mu}_{(0)} + \lambda \boldsymbol{\mu}_{(1)} + \lambda^2 \boldsymbol{\mu}_{(2)} + \cdots) = \alpha \mathbf{E} + \lambda \alpha \mathcal{T}(\boldsymbol{\mu}_{(0)} + \lambda \boldsymbol{\mu}_{(1)} + \lambda^2 \boldsymbol{\mu}_{(2)} + \cdots). \quad (22)$$

Collecting like powers of λ , order-by-order, yields

$$\begin{aligned} \boldsymbol{\mu}_{(0)} &= \alpha \mathbf{E}, \\ \lambda \boldsymbol{\mu}_{(1)} &= \lambda \alpha \mathcal{T} \boldsymbol{\mu}_{(0)}, \\ \lambda^2 \boldsymbol{\mu}_{(2)} &= \lambda^2 \alpha \mathcal{T} \boldsymbol{\mu}_{(1)}, \\ &\vdots \\ \lambda^n \boldsymbol{\mu}_{(n)} &= \lambda^n \alpha \mathcal{T} \boldsymbol{\mu}_{(n-1)}. \end{aligned} \quad (23)$$

Finally, expanding out the expressions for lower-order $\boldsymbol{\mu}_{(n)}$ components, we find

$$\begin{aligned} \boldsymbol{\mu}_{(0)} &= \alpha \mathbf{E}, \\ \boldsymbol{\mu}_{(1)} &= \alpha \mathcal{T} \alpha \mathbf{E}, \\ \boldsymbol{\mu}_{(2)} &= \alpha \mathcal{T} \alpha \mathcal{T} \alpha \mathbf{E}, \\ &\vdots \\ \boldsymbol{\mu}_{(n)} &= \alpha (\mathcal{T} \alpha)^n \mathbf{E}. \end{aligned} \quad (24)$$

This result is the Neumann series

$$\mathbf{T}^{-1} = (\alpha^{-1} - \mathcal{T})^{-1} = \alpha \sum_{n=0}^{\infty} (\mathcal{T} \alpha)^n \quad (25)$$

that Wang and Skeel used⁵⁰ to form an approximate preconditioner that accelerates the iterative variational dipole equations. The PT series converges if $\rho(\mathcal{T} \alpha) < 1$, where ρ is the spectral radius. Truncation of the same series has been proposed by Kaminski, Friesner, and Zhou as an approximate polarization method, albeit not within the context of perturbation theory.²³ We will expand on these ideas further by using the analytic nature of the dipoles to derive the dipole response terms needed to exactly evaluate the induced dipole forces. We will also exploit the systematic nature of Eq. (24) to inform extrapolations to the infinite order PT result which, under reasonable conditions, coincides with the variational solution.

1. Contributions from the residual

The stationary nature of both the direct and variational polarization models permits the use of Eq. (12) to evaluate forces, as long as the residual is converged sufficiently closely to zero. In the n th order perturbation (PT_n) series, however, the residual defined by Eq. (10) is not necessarily zero,

$$\begin{aligned} \frac{\partial U_{\text{PTn}}}{\partial \boldsymbol{\mu}_n} &= \mathcal{R}_{\text{PTn}}^T = \boldsymbol{\mu}_n^T \mathbf{T} - \mathbf{E}^T \\ &= \mathbf{E}^T (\alpha + \alpha \mathcal{T} \alpha + \cdots + \alpha (\mathcal{T} \alpha)^n) \mathbf{T} - \mathbf{E}^T \\ &= \mathbf{E}^T (\alpha + \alpha \mathcal{T} \alpha + \cdots + \alpha (\mathcal{T} \alpha)^n) (\alpha^{-1} - \mathcal{T}) - \mathbf{E}^T \\ &= -\mathbf{E}^T (\alpha \mathcal{T})^{n+1} \\ &= -\boldsymbol{\mu}_{(n+1)}^T \alpha^{-1}. \end{aligned} \quad (26)$$

If the series is convergent, then $\lim_{n \rightarrow \infty} \boldsymbol{\mu}_n = 0$; in this case, the residual disappears, and we are back in the variational regime at infinite order.

The nonzero residual manifests itself in higher-order contributions to the energy, as well as in the dipole response term for the forces. Rewriting Eq. (9),

$$\begin{aligned} U &= \frac{1}{2} \boldsymbol{\mu}^T \mathbf{T} \boldsymbol{\mu} - \mathbf{E}^T \boldsymbol{\mu} \\ &= \frac{1}{2} (\boldsymbol{\mu}^T \mathbf{T} - \mathbf{E}^T) \boldsymbol{\mu} - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu} \\ &= \frac{1}{2} \mathcal{R}^T \boldsymbol{\mu} - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}, \end{aligned} \quad (27)$$

we find that the polarization energy for a converged variational method is simply $-\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}$. For the perturbative approach, we use Eq. (26) to find the energetic effect of the non-zero residual for n th-order perturbation theory,

$$\begin{aligned} U_{\text{PTn}} &= \frac{1}{2} \mathcal{R}_{\text{PTn}}^T \boldsymbol{\mu}_n - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_n \\ &= -\frac{1}{2} \boldsymbol{\mu}_{(n+1)}^T \alpha^{-1} \boldsymbol{\mu}_n - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_n \\ &= -\frac{1}{2} \mathbf{E}^T (\alpha \mathcal{T})^{n+1} (\alpha + \cdots + \alpha (\mathcal{T} \alpha)^n) \mathbf{E} - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_n \\ &= -\frac{1}{2} \mathbf{E}^T (\boldsymbol{\mu}_{2n+1} - \boldsymbol{\mu}_n) - \frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_n \\ &= -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_{2n+1}. \end{aligned} \quad (28)$$

Therefore, if we define a different perturbation energy functional

$$U_n = -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_n, \quad (29)$$

which has the same infinite order value as U_{PTn} , Eq. (28) shows that the n th order dipole is sufficient to determine U_{2n+1} , which is reminiscent of Wigner's $(2n + 1)$ rule.⁵¹ According to Eq. (15), the direct model's energy corresponds to U_0 . We will investigate U_{PTn} hereafter, as it is based on (9) and we want to elucidate the connections between perturbation theory and the variational approach.

2. Zeroth order: PT0

The zeroth-order dipole is equivalent to the direct model's dipole,

$$\boldsymbol{\mu} = \boldsymbol{\mu}_0 = \alpha \mathbf{E}. \quad (30)$$

In the direct approach, neglect of the $-\mathcal{T}$ contribution to $\mathbf{T}$ yields $U = -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_0$. Although the same dipoles enter the PT0 expression, the coupling terms in $\mathbf{T}$ are retained so we use (28) to evaluate the PT0 energy,

$$U_{\text{PT0}} = -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_1. \quad (31)$$

The dipole derivative, with respect to geometric distortions, is

$$\frac{\partial \boldsymbol{\mu}_0}{\partial \mathbf{r}} = \alpha \frac{\partial \mathbf{E}}{\partial \mathbf{r}}, \quad (32)$$

which combines with Eq. (26) to give the dipole response terms in Eq. (11),

$$\begin{aligned}\frac{\partial U_{\text{PT0}}}{\partial \mu_0} \frac{\partial \mu_0}{\partial \mathbf{r}} &= -\boldsymbol{\mu}_{(1)}^T \alpha^{-1} \alpha \frac{\partial \mathbf{E}}{\partial \mathbf{r}} \\ &= -\boldsymbol{\mu}_{(1)}^T \frac{\partial \mathbf{E}}{\partial \mathbf{r}}.\end{aligned}\quad (33)$$

Adding these to Eq. (12) gives the total gradient of the PT0 polarization energy,

$$\frac{\partial U_{\text{PT0}}}{\partial \mathbf{r}} = -\frac{1}{2} \boldsymbol{\mu}_0^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_0 - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \boldsymbol{\mu}_1. \quad (34)$$

3. First order: PT1

The next method in the series, PT1, is derived similarly using the first order dipoles

$$\boldsymbol{\mu} = \boldsymbol{\mu}_1 = \alpha \mathbf{E} + \alpha \mathcal{T} \alpha \mathbf{E}, \quad (35)$$

resulting in the energy expression

$$U_{\text{PT1}} = -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_3. \quad (36)$$

The PT1 gradient is obtained by using the relationship

$$\frac{\partial \boldsymbol{\mu}_1}{\partial \mathbf{r}} = \alpha \frac{\partial \mathbf{E}}{\partial \mathbf{r}} + \alpha \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \alpha \mathbf{E} + \alpha \mathcal{T} \alpha \frac{\partial \mathbf{E}}{\partial \mathbf{r}} \quad (37)$$

and symmetrizing the result to ensure that it conforms to Newton's third law,

$$\begin{aligned}\frac{\partial U_{\text{PT1}}}{\partial \mathbf{r}} &= -\frac{1}{2} (\boldsymbol{\mu}_1^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_1 + \boldsymbol{\mu}_0^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_{(2)} + \boldsymbol{\mu}_{(2)}^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_0) \\ &\quad - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \boldsymbol{\mu}_3.\end{aligned}\quad (38)$$

D. Extrapolated perturbation theory: ExPT

According to Eq. (28), the PT series converges very systematically towards the iterative result, when in the convergent regime. We can write the infinite order energy as

$$\begin{aligned}U_{\text{PT}\infty} &= U_{\text{PT}n} + (U_{\text{PT}\infty} - U_{\text{PT}n}) \\ &= -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_{2n+1} - O(\boldsymbol{\mu}_{(2n+2)}).\end{aligned}\quad (39)$$

Because the error term decays as $(\alpha \mathcal{T})^{2n}$, the PT series can be modeled as

$$U_{\text{PT}\infty} = U_{\text{PT}n} - b \exp(-cn) \quad (40)$$

which involves three unknowns: $U_{\text{PT}\infty}$, b , and c . Taking the lowest three terms in PT series, it is easy to show that the exponent c is given by the expression

$$c = \frac{U_{\text{PT0}} - U_{\text{PT1}}}{U_{\text{PT2}} - 2U_{\text{PT1}} + U_{\text{PT0}}}, \quad (41)$$

which requires knowledge of the second order PT energy, U_{PT2} . Therefore, to simplify the extrapolation, we assume that c is constant; a similar approach has been used to determine a two-point exponential fit in the context of basis set error extrapolation in quantum chemistry.⁵² By considering the series $n = 0, 1$ and solving for the two remaining unknowns, $U_{\text{PT}\infty}$ and b , we find

$$U_{\text{PT}\infty} \approx c_0 U_{\text{PT0}} + c_1 U_{\text{PT1}}, \quad (42)$$

where $c_0 = \frac{\exp(-c)}{\exp(-c)-1}$ and $c_1 = \frac{-1}{\exp(-c)-1}$, and only the zeroth- and first-order energies are required. Recognizing that these definitions yield the constraint $c_0 + c_1 = 1$, the problem of determining the optimal exponent c in Eq. (40) is equivalently cast as determining the optimal c_1 coefficient, from which c_0 is trivially determined. Equation (42) defines the ExPT energy, with the c_1 coefficient to be determined. One possibility is to determine a global parameter from a wide variety of test systems, as in the basis set error extrapolation of Karton and Martin.⁵² Another approach is to perform a short "training" trajectory for each system of interest; this approach has been suggested for the recently proposed multiple environment single system approach to mixed quantum mechanical / molecular mechanical calculations.⁵³

Defining the induced dipole as $\boldsymbol{\mu}_{\text{ExPT}} = c_0 \boldsymbol{\mu}_1 + c_1 \boldsymbol{\mu}_3$, we can write the ExPT energy in a more familiar form as

$$U_{\text{ExPT}} = -\frac{1}{2} \mathbf{E}^T \boldsymbol{\mu}_{\text{ExPT}}. \quad (43)$$

Similarly, the gradient becomes

$$\begin{aligned}\frac{\partial U_{\text{ExPT}}}{\partial \mathbf{r}} &= -\frac{1}{2} c_1 (\boldsymbol{\mu}_1^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_1 + \boldsymbol{\mu}_0^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_{(2)} + \boldsymbol{\mu}_{(2)}^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_0) \\ &\quad - \frac{1}{2} c_0 \boldsymbol{\mu}_0^T \frac{\partial \mathcal{T}}{\partial \mathbf{r}} \boldsymbol{\mu}_0 - \frac{\partial \mathbf{E}^T}{\partial \mathbf{r}} \boldsymbol{\mu}_{\text{ExPT}}.\end{aligned}\quad (44)$$

Cursory testing revealed that the coefficients $c_0 = -0.3$ and $c_1 = 1.3$, which correspond to an exponent of 1.47, provide reasonable values and these will be assumed hereafter. We will demonstrate the sensitivity of the final result to the choice of fitting parameters in Sec. III. Our test data are too limited in scope to make concrete recommendations for extrapolation coefficients, but we will use these values to show that the method can deliver accurate results in some tough model systems.

III. RESULTS

All methods described herein have been implemented in the CHARMM simulation package.^{54,55} As a preliminary test of the PT methods, we computed short trajectories for a few simple systems. The first is a 125 molecule water cluster at 300 K, using the AMOEBA 2003 water parameters;²² this system is small enough to permit easy numerical inversion of $\mathbf{T}$ and represents a fairly difficult test due to the inherent inhomogeneity at the liquid-air interface. The starting geometry for this water box's $\mathbf{T}$ tensor has extremal eigenvalues of (0.46, -0.89) and the perturbation series is guaranteed to be convergent. The convergence of the PT series is contingent upon the condition $\rho(\mathcal{T} \alpha) < 1$, but the singularity in the $\mathcal{T}$ coupling term, as the interaction distance tends to zero, is tempered by the presence of Thole damping terms. For this reason, we also tested the same system with the polarizabilities of both O and H doubled; this is referred to as "modified water" hereafter. The extremal $\mathbf{T}$ eigenvalues for the starting geometry of this modified water test case are (0.49, -1.45) and the PT series is divergent, making this an even more stringent test of the PT methods. Finally to test the performance of the theory in bulk solution with periodic boundary conditions, we employ two MgCl_2 molecules, solvated in a 27.77 Å cube containing

FIG. 1. Errors, with respect to the fully converged variational approach (AMOEBA), in the polarization energy along a short trajectory for (a) a cluster of 125 AMOEBA water molecules, (b) the 125 AMOEBA water cluster with all polarizabilities doubled, (c) two MgCl_2 molecules solvated in a periodic box containing 729 water molecules, with AMOEBA parameters. The approximate methods tested are the direct approach and zeroth-order, first-order, and extrapolated perturbation theories.

729 water molecules; this test case uses the PME method to evaluate long-range electrostatics. The reference AMOEBA values were generated by converging induced dipoles to a RMS error of 10^{-6} D, using the Always Stable Predictor Corrector (ASPC) guess and the diagonal preconditioner.^{27,56} In all cases, a 2 fs integration time step was used, and the SHAKE restraint algorithm was applied to the motions of the hydrogen atoms.

Figure 1 depicts the error in the polarization energy for the three test cases, with respect to the full variational AMOEBA energy, along short trajectories. In all cases, the trajectories were generated using the full iterative AMOEBA method, with single-point calculations performed to assess the approximate methods—namely, direct polarization, PT0, PT1, and ExPT. The direct algorithm is that used in iAMOEBA; here, we distinguish between the two because iAMOEBA is reparameterized to account for the absence of induced dipole mutual coupling terms, while the direct approach demonstrated herein uses the original AMOEBA parameters.

The errors in the polarization energies provided by the direct approach are -35% in the water tests and around -10% for the MgCl_2 case. However, the standard deviations of these errors are only 0.29% and 0.33% for water and MgCl_2 , respectively, which shows that the potential energy surface is shifted with respect to the variational method but the shape is mostly retained. This shift in the surface is accounted for in the iAMOEBA reparameterization and the small fluctuations in the error explain why this method is able to deliver accurate results. The errors for PT0 are around -15% for the water test cases and -8% for the MgCl_2 test, which fall to -2.8% and 1.9% at the PT1 level. Using the coefficient $c_1 = 1.3$, the largest error for the ExPT method is observed for the AMOEBA water test case. The errors for the water, modified water, and MgCl_2 tests using the ExPT method are just 0.9%, -0.1% , and -0.1% , respectively; the standard deviations in these tests are just

0.03%, 0.22%, and 0.09%, demonstrating an excellent consistency along the trajectory. This is very encouraging, given that the computational cost of obtaining the induced dipoles is similar to that for the PT1 method and is roughly equivalent to three iterations of the variational approach; the average number of iterations required to converge the AMOEBA reference values was 7.1, 8.0, and 8.1 for the water, modified water, and MgCl_2 tests, respectively.

Figure 2 shows the errors in the polarization energies for the approximate methods discussed herein, averaged over the trajectories, along with extrapolation formula (40), fit using the PT0 and PT1 series as in the derivation of Eq. (42). While the water and MgCl_2 tests converge smoothly toward the varia-

FIG. 2. Errors for the first terms in the perturbation series in the polarization energy, with respect to the variational approach, along the short trajectories depicted in Fig. 1 for (a) a cluster of 125 AMOEBA water molecules, (b) the 125 AMOEBA water cluster with polarizabilities doubled, (c) two MgCl_2 solvated in a periodic box containing 729 water molecules, using AMOEBA parameters. The mean error is depicted by a black dot, while the blue error bars depict standard deviations of the error. Also shown is fit function (40), fit to the PT0 and PT1 energies.

tional result, the modified water test offers a glimpse of how the PT series behaves outside the convergent regime. By fifth order, the magnitude of the error in the PT series increases to 7.6%, from just 2.0% at second order. Despite this divergence, the extrapolation from the PT0/PT1 pair delivers an error of only -0.1% , with respect to the variational approach. The ability to sum divergence series using only a few terms is commonly observed in rational function approximations, such as Padé approximants.

To demonstrate the sensitivity of the ExPT method's result to the choice of extrapolation parameters, we varied them, under the constraint $c_0 + c_1 = 1$ and plotted the corresponding errors along the trajectories shown in Fig. 1, with the results shown in Fig. 3. For the water test case, the error would be reduced to zero by reducing the c_1 coefficient to around 1.23, while a larger value of around 1.32 is optimal for the MgCl_2 test. The optimum values for c_1 span a range of about 0.09 for the limited tests presented in this work, and any attempts to improve simple approximation (42) should be based on a diverse test set. The errors in the energies with respect to the full AMOEBA method are quite insensitive to the variations in c_1 , which encourages the possibility of choosing a global exponent in Eq. (40). For example, varying the c_1 coefficient from 1.2 to 1.4 results in mean polarization energy errors for the MgCl_2 test that vary from -0.72% to 0.5% . Absolute energies are less important than relative energies, so in Fig. 4, we repeat the sweep over c_1 values, plotting the slope and correlation coefficient of the linear fit of ExPT energies to their corresponding variational values along the trajectories. The fits for the water and MgCl_2 tests reach the optimal slope of 1 at $c_1 = 1.3$ and $c_1 = 1.36$, respectively. The difficulty of the modified water test is highlighted here, as its optimal slope is achieved at $c_1 = 1.16$, much lower than the other tests, but the correlation coefficient does not exceed 0.95 for any value of c_1 . In all cases the correlation coefficient is very insensitive to the choice of c_1 , so the slope of the fit should be given more consideration in determining a good choice for c_1 .

FIG. 3. Errors, with respect to the variational approach, in the ExPT polarization energy along the short trajectories depicted in Fig. 1 for (a) a cluster of 125 AMOEBA water molecules, (b) the 125 AMOEBA water cluster with polarizabilities doubled, (c) two MgCl_2 solvated in a periodic box containing 729 water molecules, using AMOEBA parameters. The errors are plotted as a function of the mixing coefficient c_1 , with $c_0 = 1 - c_1$. The mean error is depicted by a black dot, while the blue error bars depict standard deviations of the error. The black vertical lines in each plot represent the optimal c_1 value, while the orange lines show the $c_1 = 1.3$ assumed for these tests.

FIG. 4. Slope (blue line) and correlation coefficients (black line) for the linear fit of the ExPT polarization energies to the corresponding variational energies, along the short trajectories depicted in Fig. 1 for (a) a cluster of 125 AMOEBA water molecules, (b) the 125 AMOEBA water cluster with polarizabilities doubled, (c) two MgCl_2 solvated in a periodic box containing 729 water molecules, using AMOEBA parameters. The errors are plotted as a function of the mixing coefficient c_1 , with $c_0 = 1 - c_1$. The vertical orange lines show the $c_1 = 1.3$ assumed for these tests.

A more fine-grained analysis of the polarization energy errors is presented in Figs. 5–7, which show scatter graph analyses for the water, modified water, and MgCl_2 tests, respectively; these tests all employ our tentative c_1 value of 1.3. In all cases we observe the expected narrowing of the distribution moving from the direct algorithm to the more accurate ExPT, with a concomitant convergence of the linear fit function's slope towards unity. Our preliminary test data demonstrate that a c_1 value around 1.3 is a reasonable choice, with the energies relatively insensitive to this parameter; ongoing testing, considering the effects of forces, is being performed to refine the c_1 value and to assess the resulting errors with respect to the variational approach.

The above analysis has focussed on single point energy errors, along pre-recorded AMOEBA trajectories. To demonstrate the stability of the trajectories generated by ExPT, we performed NVE simulations on a periodic box of 38 MgCl_2 molecules solvated in 4096 waters. Trajectories from the iterative algorithm, using the ASPC guess and diagonal preconditioner and a range of convergence criteria, were generated for comparison; identical initial conditions and truncation parameters were used for all simulations. The resulting high frequency corrected energies, derived from the expectation value of the shadow Hamiltonian,⁵⁷ are plotted in Fig. 8. While the iterative algorithm with dipoles converged to a RMS error of 10^{-2} D or 10^{-3} D generates catastrophic failures, due to the neglected dipole response terms, both the ExPT algorithm and the more tightly converged iterative approach produce cooling effects amounting to just $-0.58 \text{ kcal mol}^{-1}/\text{ns}$ and $-0.07 \text{ kcal mol}^{-1}/\text{ns}$, respectively. For reference, the high frequency corrected energy in the absence of polarization is $-34810 \text{ kcal mol}^{-1}$.

The expressions for the forces, Equations (34), (38), and (44), have been verified by close comparison to finite difference results for a number of small systems. Given the analytic nature of the dipole response terms resulting from perturbation theory, we can use them to estimate the magnitude of the corresponding terms in the variational approach. In light of Eqs. (10) and

FIG. 5. Scatter plot showing the correlation between polarization energies (in kcal mol⁻¹) from the fully iterative model (y axis) and the approximate perturbative treatments (x axis) for the 125 molecule AMOEBA water cluster test case, computed along the trajectories in Fig. 1.

(32), appending a force correction such as

$$\frac{\partial U}{\partial \mu} \frac{\partial \mu}{\partial \mathbf{r}} \approx \mathcal{R}^T \alpha \frac{\partial \mathbf{E}}{\partial \mathbf{r}} \quad (45)$$

to the variational forces provided by Eq. (12) may ameliorate any instabilities in the trajectory caused by neglect of dipole response forces and may allow more permissive convergence criteria to be used. The residual is already available from the iterations, so such a term would be trivial to compute. In the limit of tightly converged dipoles, the correction would have no

effect, due to the presence of the residual as a factor. Finally, we note that the formulation of the virial follows the standard techniques that are common to other induced dipole methods, so the details are omitted here.

IV. INEQUALITIES FOR FORCE FIELD PARAMETERS

While we did not exploit the QI coordinate system for the field terms resulting from induced dipoles, we can use it to extract some useful information. The important issue

FIG. 6. Scatter plot showing the correlation between polarization energies (in kcal mol⁻¹) from the fully iterative model (y axis) and the approximate perturbative treatments (x axis) for the 125 molecule AMOEBA water cluster with doubled polarizabilities test case, computed along the trajectories in Fig. 1.

FIG. 7. Scatter plot showing the correlation between polarization energies (in kcal mol⁻¹) from the fully iterative model (y axis) and the approximate perturbative treatments (x axis) for the two MgCl₂ molecules solvated in 729 waters (with periodic boundary conditions, using AMOEBA parameters) test case, computed along the trajectories in Fig. 1.

of whether force field parameterizations provide physically reasonable models was discussed by Lipparini and co-workers²⁷ who stated that, “the careful study of the matrix $\mathbf{T}$ also should motivate chemists to derive new force fields with parameters that ensure the proper variational behavior of the polarization energy (resulting in no negative eigenvalue in the matrix $\mathbf{T}$!).” Here, we briefly outline a method that uses the sparsity provided by the QI basis to provide such an analysis. Focusing on a diatomic system, we can write Eq. (10) in the QI basis

$$\tilde{\mathbf{E}} = \tilde{\mathbf{T}}\tilde{\boldsymbol{\mu}}. \quad (46)$$

Using Eq. (2b), we form a composite rotation matrix for this pair of atoms

$$\mathbf{U} = \begin{pmatrix} \mathbf{U}_z & \mathbf{0} \\ \mathbf{0} & \mathbf{U}_z \end{pmatrix} \quad (47)$$

FIG. 8. Trajectories in the microcanonical ensemble for a periodic system of 38 MgCl₂ molecules, solvated in 4096 water molecules, obtained using the ExPT method as well as the variational method with a range of convergence criteria. The high frequency corrected energy is plotted as a function of time, with a linear fit for each simulation depicted in the legend.

and use it to rotate the result of Eq. (46) back into the lab frame,

$$\mathbf{E} = \mathbf{U}\tilde{\mathbf{T}}\tilde{\boldsymbol{\mu}}. \quad (48)$$

Finally, inserting the identity $\mathbf{U}^T\mathbf{U} = \mathbf{I}$ into Eq. (48), we find the relationships between the lab and QI frame $\mathbf{T}$ tensor

$$\mathbf{E} = \underbrace{\mathbf{U}\tilde{\mathbf{T}}\mathbf{U}^T}_{\mathbf{T}} \underbrace{\mathbf{U}\tilde{\boldsymbol{\mu}}}_{\boldsymbol{\mu}}, \quad (49)$$

which is the well-known similarity transformation used to effect a change of basis. The similarity transformation preserves eigenvalues, so $\mathbf{T}$ and $\tilde{\mathbf{T}}$ have the same spectrum. The $\tilde{\mathbf{T}}$ tensor for a diatomic with isotropic atomic polarizabilities, and internuclear distance R , is provided by Table I and Equation (17),

$$\tilde{\mathbf{T}} = \begin{pmatrix} \frac{1}{\alpha_1} & 0 & 0 & t_0 & 0 & 0 \\ 0 & \frac{1}{\alpha_1} & 0 & 0 & t_1 & 0 \\ 0 & 0 & \frac{1}{\alpha_1} & 0 & 0 & t_1 \\ t_0 & 0 & 0 & \frac{1}{\alpha_2} & 0 & 0 \\ 0 & t_1 & 0 & 0 & \frac{1}{\alpha_2} & 0 \\ 0 & 0 & t_1 & 0 & 0 & \frac{1}{\alpha_2} \end{pmatrix}, \quad (50)$$

where $t_0 = \frac{2(1-e^{-au^3}(1+\frac{3}{2}au^3))}{4\pi\epsilon_0 R^3}$ and $t_1 = \frac{-(1-e^{-au^3})}{4\pi\epsilon_0 R^3}$. The sparsity pattern in the QI basis, resulting from orthogonality, affords an analytic expression for $\tilde{\mathbf{T}}$'s four unique

eigenvalues ϵ ,

$$\epsilon = \left(\frac{\alpha_1 + \alpha_2 \pm \sqrt{(\alpha_1 - \alpha_2)^2 + (4\alpha_1\alpha_2 t_0)^2}}{2\alpha_1\alpha_2} \right). \quad (51)$$

For the homonuclear case, $\alpha_1 = \alpha_2$ and Eq. (51) reduces down to

$$\epsilon = \left(\frac{\frac{1}{\alpha} \pm 2t_0}{\frac{1}{\alpha} \pm t_1} \right). \quad (52)$$

Positivity of ϵ for the dimer case is a necessary, but not sufficient, condition for the parameterization to be valid.

V. CONCLUSIONS

We have demonstrated that the quasi-internal coordinate system, paired with spherical harmonic multipoles, may be used to efficiently evaluate the electric field required in polarization computations and have provided the Thole damping factors needed to implement these techniques for modern force fields. We deemed the QI coordinate system inappropriate for imposing the variational conditions for the induced dipoles and instead resorted to perturbation theory to obtain an accurate, non-iterative polarization energy functional that can deliver performance similar to the iterative, variational approach. We demonstrated that perturbation theory yields a hierarchy of analytic methods that, under reasonable conditions, will converge to the variational solution. Preliminary testing showed that the lowest order PT methods deliver results close to the iterative method, but perhaps not close enough to avoid reparameterization.

To improve the accuracy of the PT method, we explored the idea of combining lower order terms in the series to approximate the infinite order solution. One possible approach we outlined is to determine the convergence of the series *a priori* from the energy expressions and use this to motivate an exponential fit of the PT series. By introducing a single empirical parameter, we were able to obtain an approximate extrapolated result from a two point fit to the two lowest terms in the PT hierarchy. Preliminary testing demonstrated that this is a viable strategy and we showed that the extrapolation can perform well in cases where the PT series is divergent. We refer to this extrapolated perturbation theory as the ExPT method. Because of its close adherence to the variational result, the ExPT method will hopefully be compatible with existing AMOEBA force field parameters; however, careful testing of this is warranted, as is careful optimization of the extrapolation parameter c_1 . We are continuing to investigate methods for combining the low-order dipoles and will perform thorough benchmarking for biologically relevant systems. The PT family of methods can be easily implemented into any existing variational code, given that the crux of implementing all of these methods is the evaluation of sparse matrix-vector multiplications involving the action of $\mathcal{T}$ on a generic, dense vector.

The most efficient and stable guesses currently available for the variational method use information from previous steps

in the trajectory; for this reason, they degrade in quality as the time step used in the simulation becomes larger. The time step restrictions are even more severe for the extended Lagrangian implementation of the Drude oscillator approach, where a short time step is required in the integration to correctly account for the motions of the light Drude particles. Furthermore, long time scale variational simulations could be impacted by the neglect of dipole response contributions to the forces, if the dipoles are insufficiently converged. These factors may be an impediment to using the variational induced dipole approach for long time scale simulations, as they introduce the need to find a compromise between tight converge of the dipoles, whose computational cost limits the time scales accessible, and accumulating errors in the forces, whose impact may grow in severity at longer time scales. Because the PT methods need no guess and include the dipole response contributions analytically, they offer a solution to these problems and are a good candidate for probing long time scale phenomena using large time steps in the integrator.

Finally, we demonstrated how the sparsity of the $\mathbf{T}$ tensor for a dimer, in the QI coordinate system, may be exploited to derive criteria to judge the validity of force field parameters; this should serve as a useful aid for the development of these next-generation methods.

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