Calculation of the reaction field due to off-center point multipoles

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Two general methods for calculating the reaction field generated by a set of off-center point multipoles in a spherical cavity are presented. The methods are a generalization of Kirkwood's original theory for an arbitrary charge distribution. A polytensor formulation, similar to that previously developed for direct multipole interactions, serves to organize the computation and allows straightforward extension to higher derivatives of reaction field energy and gradients of the potential. The computation is reduced to calculation of the Cartesian derivatives of biaxial harmonics. Recursive and explicit formulas are given for the calculation. As an example, the incorporation of reaction field effects in computation of induced dipole moments is discussed. The second procedure, the central multipole method, scales linearly in calculation time with the size of the system. Methods to obtain derivatives analytically based on this method are also described. Our developments allow use of reaction field energy terms with atomic multipole-based empirical potential energy functions. Both methods show particular promise for use in simulation of heterogeneous systems, such as biopolymers, where the remainder of the cavity can be filled explicitly with solvent. © *1997 American Institute of Physics.* [S0021-9606(97)51426-7]

I. INTRODUCTION

Treatment of solvation effects is of major importance in the modeling of molecular structure and energetics. Electrostatic interactions, including long-range electrostatics, are an important component of solvation.[1–8] In the context of classical molecular simulation, the solvation effects due to long-range electrostatic interactions can be viewed as a perturbation to the explicit Coulombic interactions within the system. In this paper we develop two fast analytical methods for including the reaction field (RF) as a correction to explicit simulation results. Both formulations are general and lead to straightforward and systematic implementations for use in computer simulations. In addition to the RF potential, both methods give analytical derivatives of the RF energy. Besides, various degrees of gradients of the RF potential can be calculated in a unified way by the polytensor method, which simplifies application to polarizable systems. Examples are given showing the effect of the RF on the relative orientation of a pair of dipoles in their minimum energy configuration, and the calculation of dipole moments induced by a set of atomic multipoles.

Multicenter multipole expansions are increasingly used in molecular modeling.[9] Our work extends the classical reaction field method of Kirkwood to include multicenter multipoles within a fixed simulation boundary. Multipole representations of electrostatics have four major uses: (1) increased accuracy in detailed representation of a molecular electrostatic potential,[10,11] (2) fast multipole methods to avoid the $O(N^2)$ bottleneck in standard pairwise interaction summations,[12] (3) description of averaged electrostatic effects over a region of space for use in simplified molecular models,[13] and (4) improving convergence relative to single-site models.[14] Multipole parameters have been determined for use in macromolecular simulation[15–17] and a recent paper

has attempted to incorporate multicenter multipole electrostatics into a force field program for flexible molecules.[18]

Long-range electrostatics can be treated either with explicit models or continuum methods. Explicit models treat solvent molecules in a discrete fashion with no distinction between solute and solvent. Lattice sums are usually used to limit the system to a reasonable size.[19,20] In continuum methods, the solute is embedded in a cavity surrounded by structureless continuum solvent. The electric charges of the solute polarize the continuum which in turn affects the electric field inside the cavity. This contribution from the continuum is usually called the reaction field. Some current models include certain explicit solvent molecules within continuum models. As discussed below, such hybrid models can simulate the system more realistically. Particular attention was given to these hybrid models when the formulations in this paper were developed.

The continuum models can be treated by several methods. For simple cavity geometries, analytical solutions exist. Kirkwood derived a general solution for the RF potential for a spherical cavity containing an arbitrary charge distribution.[21] The ion polarization energy (Born charging energy) and the dipole polarization energy (Onsager reaction field) can be derived as special cases of the general result. Beveridge and Schnuelle[22] give a concise review of Kirkwood's work and extended his result to calculation of the RF potential and free energy of an arbitrary charge distribution in a spherical central cavity surrounded by two concentric dielectric continua. Felder and Applequist[23] considered charged and polarizable atoms in a cavity placed in a dielectric continuum. They obtained explicit relationships for the case of a spherical cavity. In order to compute the RF they differentiated the RF potential with respect to the spherical coordinate unit vectors, and then transformed back to Cartesian components. The resulting formula was applied to a

study of the Gibbs energy of proton transfer between carboxylic acids. Felder[24] generalized this method for a charge-dipole system with a cavity in the shape of a prolate or oblate ellipsoid. Other groups have also extended the RF derivation to simple nonspherical cavities.[25–27] For complex molecular surfaces, no analytical solutions exist and numerical methods have to be used. In the spirit of the classical simple RF model, Rivail and co-workers have developed methods to handle cavities of general shape.[28] Their formulation is better able to account for the true molecular surface, but the calculation is performed over a large number of discrete surface points. A correspondingly large system of linear equations must be solved to determine the ''reaction field factors'' used in the energy evaluation. The surface points must be recomputed whenever the molecular geometry changes. First and second derivatives of this method are available.[29] The same method has been applied by these authors to multi-center multipole models of the solute with the expected increase in the number and difficulty of the RF factors to be computed. While very general, the method appears to be too slow for use with macromolecules.

The widely used image charge method[30] is a simple approximation to the full RF term and involves computation of the positions and magnitudes of a set of image charges outside the cavity. The direct interaction of the solute and image charges then gives the RF energy. For homogeneous systems, a moving boundary RF method can be used.[31,32] In this method each site in turn is placed at the center of its own spherical cavity and the corresponding RF term is computed using the classical Kirkwood result. For inhomogeneous systems it is difficult to apply this method since the dielectric constants inside and outside the cavity are no longer well defined.

The ''reaction field'' methods discussed above are all based on solving the Poisson equation (or Poisson–Boltzmann equation when mobile ions are present) using proper boundary conditions. Another widely used procedure for solving the Poisson–Boltzmann equation numerically is the finite difference method. Finite difference Poisson–Boltzmann (FDPB) calculations have long been applied to static conformations of large macromolecules such as proteins.[33] If a fine numerical grid is used, the molecular shape can be accurately represented, but computation time increases with the number of grid points. Several groups have attempted to couple FDPB methods with dynamics simulations.[34] With use of a very coarse 10 Å grid, the method becomes fast enough for use in classical empirical dynamics simulations.[35]

In addition to solving the Poisson or Poisson–Boltzmann equation directly, the continuum model can be handled equivalently by boundary element methods.[1,36–41] These methods treat the continuum electrostatic problem everywhere in space by determining a set of apparent surface charges for each element on the molecular surface. Since only the molecular surface and not the full volume occupied by the molecule is involved, the method is in principle more applicable to macromolecules than the space-oriented methods such as FDPB. However, the method is most widely used at present in tandem with molecular orbital calculations. Usually the surface is partitioned into a large number of elements via a tessellation scheme. In order to determine the induced surface charges on these elements, a large system of equations has to be solved. These equations can be solved either by iteration or matrix inversion. An approximate closure solution was also proposed.[1] Recently, analytical energy derivatives for this method have been described.[42,43] For large molecules, it may be difficult to achieve reasonable accuracy since fine discretization of the molecular surface leads to a large system of equations. Zauhar and Varnek[44] recently implemented a modified algorithm in which only those surface elements close in space are exactly solved, while treating the long-range interactions by a grid-based multipole expansion.

Of the many other continuum solvation methods reported in the literature, two have received particular attention. The Langevin dipole method is an alternative approach that uses point dipole sites on a fixed grid outside the molecular surface. The dipoles are allowed to rotate, thus accommodating the RF effects due to the continuum.[45] Several recent methods based on the generalized Born (GB) equation have shown promise in computation of hydration free energies.[46–49] These GB methods take account of solvent exposure of the solute through parameters related to the burial of charged atoms.

In this paper two general methods are given to calculate the RF due to off-center multipoles. In the following section, we first present a brief outline of the original Kirkwood RF method, then give a general matrix formulation of the RF potential and derivatives for off-center multipoles. Induced dipole polarization is also discussed. A recursive method to calculate the matrix elements then is given. Explicit formulas are provided in Appendix A. Section III describes another method, which we will call the central multipole method. This method scales linearly in calculation time with the size of the system, making it useful for large systems. General methods to calculate derivatives are also given for the central multipole method. Explicit vector formulas for the RF energies through quadrupole–quadrupole interactions are provided as Appendix B.

II. MATRIX FORMULAS FOR REACTION FIELD POTENTIAL AND ENERGY

A. Reaction field energy

Kirkwood's derivation[21] of the RF energy for the general case of an arbitrary charge distribution is based on solving Laplace's equation, $\nabla^2 \Phi = 0$, which is valid for all the sites free of point charges. If we assume the system, which is represented as M discrete point charges q_k, $k = 1 \cdots M$, is buried in a spherical cavity with a radius a surrounded by a dielectric continuum, the relative permittivities inside and outside the cavity being assigned as ϵ_1 and ϵ_2, respectively, then the solution of the RF potential at the position $\mathbf{r} = \{r, \theta, \phi\}$ inside the cavity is

$$\Phi_R(\mathbf{r}) = \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}}$$
$$\times \sum_{k=1}^{M} r_k^n r^n P_n(\cos\gamma_{kr}), \qquad (1)$$

in which $P_n(\cos\theta)$ is a simple Legendre polynomial, γ_{kr} is the angle between $\mathbf{r}_k$ and $\mathbf{r}$, and $\epsilon = \epsilon_2/\epsilon_1$. The RF energy is given by

$$W = \frac{1}{2} \sum_{k=1}^{M} q_k \Phi_R(\mathbf{r}_k)$$
$$= \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \left(\frac{Q_n}{a^{2n+1}}\right) \qquad (2)$$

where

$$Q_n = \sum_{k=1}^{M} \sum_{l=1}^{M} q_k q_l r_k^n r_l^n P_n(\cos\gamma_{lk}). \qquad (3)$$

For $n=0$ and $n=1$, Q_n is equal to the square of the charge and dipole moment, respectively, of the whole system in the cavity. For higher n, it is shown later that Q_n is the complete contraction of two different Cartesian tensors.

We are interested in generalizing Kirkwood's result to point multipoles not located at the origin. One method to do this is to displace point charges slightly away from each other and take the limit as their separation approaches zero while keeping the strength of the multipole constant. Appendix B gives the resulting vector formulas for the RF energy for the first three degrees of multipoles (charge, dipole, and quadrupole) together with sample derivations. The equations become complex for the higher degree multipoles, making generalization difficult. The other disadvantage of this approach is that it is difficult to get derivatives of the RF energy from these formulas, as well as the gradients of the RF potential.

To get a general analytical formula which is convenient to implement in a computer program, we use a polytensor method similar to that used by our group and others for direct multipole interactions.[11,50,51] Assume that there are N multipole sites located at $\mathbf{r}_k$, $k=1\cdots N$, with charges q_{k_i} located around each site in a nonoverlapping fashion at positions $\mathbf{r}_{k_i}$. Each charge is displaced from its own site by a vector $\mathbf{d}_{k_i}$, i.e., $\mathbf{r}_{k_i} = \mathbf{r}_k + \mathbf{d}_{k_i}$, with its three components $d_{k_i}^x$, $d_{k_i}^y$, and $d_{k_i}^z$.

Similar to Eqs. (1) and (2) we write the RF potential at the position $\mathbf{r} = \{r,\theta,\phi\}$ inside the cavity as

$$\Phi_R(\mathbf{r}) = \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}}$$
$$\times \sum_{k=1}^{N} \sum_{i} q_{k_i} r_{k_i}^n r^n P_n(\cos\gamma_{k_i r}), \qquad (4)$$

where $\gamma_{k_i r}$ is the angle between $\mathbf{r}_{k_i}$ and $\mathbf{r}$, and the RF energy

$$W = \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}}$$
$$\times \sum_{k=1}^{M} \sum_{l=1}^{M} \sum_{i} \sum_{j} q_{k_i} q_{l_j} r_{k_i}^n r_{l_j}^n P_n(\cos\gamma_{k_i l_j}), \qquad (5)$$

where $\gamma_{k_i l_j}$ is the angle between $\mathbf{r}_{k_i}$ and $\mathbf{r}_{l_j}$. If we take a Taylor expansion of $\Phi_R(\mathbf{r})$ in Eq. (4) at site k, we get

$$\Phi_R(\mathbf{r}) = \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} \sum_{k=1}^{N} \mathbf{M}_k^t \mathbf{R}_{kr}^{(n)}$$
$$= \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{k=1}^{N} \mathbf{M}_k^t \mathscr{R}_{kr}. \qquad (6)$$

If we make Taylor expansions twice of W in Eq. (5) [or, expand $\Phi_R(\mathbf{r})$ of Eq. (6) at site l], we obtain

$$W = \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} \sum_{k=1}^{N} \sum_{l=1}^{N} \mathbf{M}_k^t \mathbf{R}_{kl}^{(n)} \mathbf{M}_l$$
$$= \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{k=1}^{N} \sum_{l=1}^{N} \mathbf{M}_k^t \mathscr{R}_{kl} \mathbf{M}_l. \qquad (7)$$

In Eqs. (6) and (7) we define the multipole polytensors[50] of site k and l as

$$\mathbf{M}_k = [M_k^{000}, M_k^{100}, M_k^{010}, M_k^{001}, M_k^{200}, M_k^{110}, \ldots]^t,$$
$$\mathbf{M}_l = [M_l^{000}, M_l^{100}, M_l^{010}, M_l^{001}, M_l^{200}, M_l^{110}, \ldots]^t$$

in which the unabridged Cartesian multipoles at site k are defined as $M_k^{000} = \Sigma_i q_{k_i}$, $M_k^{100} = \Sigma_i q_{k_i} d_{k_i}^x$, $M_k^{010} = \Sigma_i q_{k_i} d_{k_i}^y$, $M_k^{001} = \Sigma_i q_{k_i} d_{k_i}^z$, $M_k^{200} = 1/2! \Sigma_i q_{k_i}(d_{k_i}^x)^2$, $M_k^{110} = 1/2! \Sigma_i q_{k_i} d_{k_i}^x d_{k_i}^y, \ldots$. These are the same multipole definitions used in an efficient implementation of the direct multipole interactions.[11,51] The symbol t stands for vector or matrix transposition. The matrix $\mathbf{R}_{kl}^{(n)}$ (or similarly $\mathbf{R}_{kr}^{(n)}$) is defined as

$$\mathbf{R}_{kl}^{(n)} = \left[1, \frac{\partial}{\partial x_k}, \frac{\partial}{\partial y_k}, \frac{\partial}{\partial z_k}, \frac{\partial^2}{\partial x_k^2}, \frac{\partial^2}{\partial x_k \partial y_k}, \ldots\right]^t$$
$$\times \left[1, \frac{\partial}{\partial x_l}, \frac{\partial}{\partial y_l}, \frac{\partial}{\partial z_l}, \frac{\partial^2}{\partial x_l^2}, \frac{\partial^2}{\partial x_l \partial y_l}, \ldots\right] B_n(\mathbf{r}_k, \mathbf{r}_l),$$

where the biaxial harmonic $B_n(\mathbf{r}_k, \mathbf{r}_l)$ between two vectors $\mathbf{r}_k$ and $\mathbf{r}_l$ is defined as $B_n(\mathbf{r}_k, \mathbf{r}_l) = r_k^n r_l^n P_n(\cos\gamma_{kl})$, and the matrix $\mathscr{R}_{kl}$ as

$$\mathscr{R}_{kl} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} \mathbf{R}_{kl}^{(n)}.$$

The matrix $\mathbf{R}_{kl}^{(n)}$ can be written symbolically as

$$\mathbf{R}_{kl}^{(n)} = \begin{bmatrix} \nabla_k^0 \nabla_l^0 & \nabla_k^0 \nabla_l^1 & \nabla_k^0 \nabla_l^2 & \cdots \\ \nabla_k^1 \nabla_l^0 & \nabla_k^1 \nabla_l^1 & \nabla_k^1 \nabla_l^2 & \cdots \\ \nabla_k^2 \nabla_l^0 & \nabla_k^2 \nabla_l^1 & \nabla_k^2 \nabla_l^2 & \cdots \\ \vdots & \vdots & \vdots & \vdots \end{bmatrix} B_n(\mathbf{r}_k, \mathbf{r}_l), \qquad (8)$$

where

$$\nabla_h^p = \frac{\partial^{i+j+k}}{\partial x_h^i \partial y_h^j \partial z_h^k}, \quad p=i+j+k, \quad \text{and} \quad h=k \text{ or } l.$$

From the definition of $\mathbf{R}_{kl}^{(n)}$ we have

$$(\mathbf{R}_{kl}^{(n)})^t = \mathbf{R}_{lk}^{(n)}. \tag{9}$$

From this relation we can write Eq. (7) as

$$W = \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} (2-\delta_{kl})$$

$$\times \sum_{l \geq k} \mathbf{M}_k^t \mathbf{R}_{kl}^{(n)} \mathbf{M}_l$$

$$= \frac{1}{8\pi\epsilon_0\epsilon_1} (2-\delta_{kl}) \sum_{l \geq k} \mathbf{M}_k^t \mathcal{R}_{kl} \mathbf{M}_l, \tag{10}$$

where $\delta_{kl}=1$ if $k=l$, otherwise it is zero.

Since

$$\left(\frac{\partial^2}{\partial x_h^2} + \frac{\partial^2}{\partial y_h^2} + \frac{\partial^2}{\partial z_h^2}\right) B_n = 0, \quad h=k \text{ or } l,$$

the potential [Eq. (6)] or the energy [Eq. (7)] are the same for the unabridged multipoles and for the traceless multipoles, as is the case for direct interaction.[52]

Figure 1 gives a simple example of the use of this method to determine the energetic and structural effects arising from inclusion of the reaction field. Minimum energy configurations were computed for a pair of point dipoles constrained to lie at various positions within a spherical cavity of low dielectric. The figure shows how the RF perturbs the optimal interaction of the two dipoles. In the absence of the reaction field, the minimum energy configuration of the dipoles is to remain exactly in line. Depending on the positions of the dipoles relative to the dielectric boundary, inclusion of the RF term can result in minimum configurations with the dipoles nearly perpendicular. Similarly, as one or both of the dipoles approach the boundary, the RF term makes a large contribution to the total interaction energy.
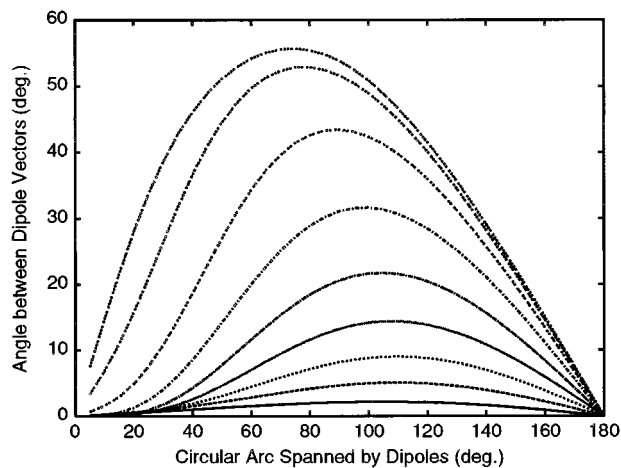
B. Derivatives of reaction field energy

From Eq. (7) and using the symmetrical relation Eq. (9), we can easily write down the equations for the derivatives of the RF energy with respect to the Cartesian coordinates of each atom,
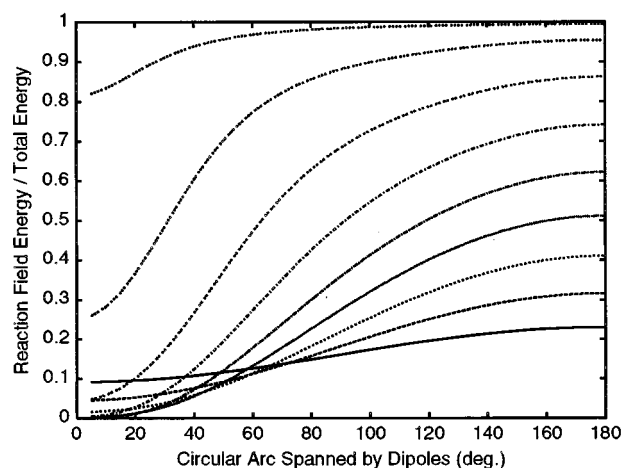
$$\frac{\partial W}{\partial x_k} = \frac{1}{8\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}}$$

$$\times \sum_{l=1}^{N} (2-\delta_{kl}) \mathbf{M}_k^t \mathbf{R}_{(k)kl}^{(n)1x} \mathbf{M}_l$$

$$= \frac{1}{8\pi\epsilon_0\epsilon_1} \mathbf{M}_k^t \sum_{l=1}^{N} \mathcal{R}_{(k)kl}^{1x} \mathbf{M}_l, \tag{11}$$

where the matrices $\mathbf{R}_{(k)kl}^{(n)1x}$ and $\mathcal{R}_{(k)kl}^{1x}$ are defined as

$$\mathbf{R}_{(k)kl}^{(n)1x} = \frac{\partial}{\partial x_k} \mathbf{R}_{kl}^{(n)}$$

(a)

(b)

FIG. 1. Effect of the reaction field term on the interaction between two point dipoles. The dipoles are of equal magnitude and are placed inside a spherical cavity of radius a. The ratio of the dielectric constant outside the cavity to that inside the cavity is taken as 80. The circular arc spanned by the two dipoles is given by an angle θ. One dipole is fixed at a distance $a/2$ from the cavity center. The plotted curves, in order from bottom to top, represent different positions of the second dipole, at distances of $0.1a$, $0.2a$,...,$0.9a$ from the cavity center. For each combination of circular arc spanned and second dipole distance, the minimum energy orientation of the dipoles was determined. In part (a), the y axis shows the angle between the two dipoles in their minimum energy orientation. In part (b), the y axis shows the fraction of the total interaction energy at the minimum energy orientation due to the reaction field term.

and

$$\mathcal{R}_{(k)kl}^{1x} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} (2-\delta_{kl}) \mathbf{R}_{(k)kl}^{(n)1x}.$$

The elements of $\mathbf{R}_{(k)kl}^{(n)1x}$ are taken from $\mathbf{R}_{kl}^{(n)}$. From the structure of $\mathbf{R}_{(k)kl}^{(n)1x}$, we can see $\mathbf{R}_{(k)kl}^{(n)1x}(i,j) = \mathbf{R}_{kl}^{(n)}(3i-1,j)$, $\mathbf{R}_{(k)kl}^{(n)1y}(i,j) = \mathbf{R}_{kl}^{(n)}(3i,j)$, $\mathbf{R}_{(k)kl}^{(n)1z}(i,j) = \mathbf{R}_{kl}^{(n)}(3i+1,j)$. Similar methods can be used to construct the nine matrices for the second derivatives: $\mathbf{R}_{(k)kl}^{(n)2xx}(i,j) = \mathbf{R}_{kl}^{(n)}(9i-4,j)$, $\mathbf{R}_{(k)kl}^{(n)2xy}(i,j) = \mathbf{R}_{kl}^{(n)}(9i-3,j)$, $\mathbf{R}_{(k)kl}^{(n)2xz}(i,j) = \mathbf{R}_{kl}^{(n)}(9i-2,j)$,

$$R^{(n)2yx}_{(k)kl}(i,j) = R^{(n)}_{kl}(9i-1,j), \quad R^{(n)2yy}_{(k)kl}(i,j) = R^{(n)}_{kl}(9i,j),\dots .$$

For the derivatives with respect to $\mathbf{r}_l$, the corresponding columns of $R^{(n)}_{kl}$ will be used to build up the matrices of $R^{(n)1x}_{(l)kl}$, etc. The matrices for higher derivatives can be constructed in a similar way.

C. Reaction field and reaction field gradients

In addition to the RF potential, we can obtain from inspection of Eq. (6) [or Eq. (7)] the field, the gradient of the field, etc., at site k, generated by all sites,

$$[\nabla^0\Phi(\mathbf{r}_k), \nabla^1\Phi(\mathbf{r}_k), \nabla^2\Phi(\mathbf{r}_k),\dots]^t$$

$$= [\Phi(\mathbf{r}_k), -E_x(\mathbf{r}_k), -E_y(\mathbf{r}_k), -E_z(\mathbf{r}_k), \Phi^{2xx}(\mathbf{r}_k),$$

$$\Phi^{2xy}(\mathbf{r}_k),\dots]^t$$

$$= \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} \sum_{l=1}^{N} R^{(n)}_{kl}\mathbf{M}_l$$

$$= \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{l=1}^{N} \mathscr{R}_{kl}\mathbf{M}_l . \tag{12}$$

These quantities can be used in the treatment of polarizability and hyperpolarizabilities, as illustrated in the following section. Unlike the case of direct multipole interactions, the RF interaction includes self-interactions. As a simple example we calculate the field in the center of the cavity due to a dipole. If we write the matrix $\nabla^1_k\nabla^1_l B_n(\mathbf{r}_k,\mathbf{r}_l)$ explicitly and substitute $\mathbf{r}_l=0$, all matrices vanish except for $n=1$, which is an identity matrix. So

$$\mathbf{R}(0) = \frac{1}{4\pi\epsilon_0\epsilon_1} \frac{\boldsymbol{\mu}}{a^3} \frac{2(\epsilon-1)}{2\epsilon+1} .$$

This example is given in Ref. 52 for eccentric dipole directed along the radius direction. Here it is shown that it is true for eccentric dipole of any orientations. As another example, we calculate the various gradients of a *charge* distribution at the center of the cavity. It is easy to verify that

$$\Phi^{(n)}_R(0) = \frac{1}{4\pi\epsilon_0\epsilon_1} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} n!\mathscr{Y}^{(n)},$$

where

$$\mathscr{Y}^{(n)} = (-1)^n \frac{1}{n!} \sum_{i=1}^{N} q_i r_i^{2n+1} \nabla^n \frac{1}{r_i} \tag{13}$$

is the traceless multipole of the charge distribution defined at the center of the cavity.[52] This definition will be used later for the description of another method, the central multipole method, to calculate the RF.

D. Induced dipole moments

Theoretically we can use the results from Sec. II C to study the hyperpolarizability carried out to any desired degree since we can calculate the gradients of the potential to any degree. In this section the formula for calculating induced dipole moments will be presented. The generalization to higher polarizabilities is straightforward.

The induced dipole moments $\boldsymbol{\mu}^{\text{ind}}_k$ are

$$\boldsymbol{\mu}^{\text{ind}}_k = \boldsymbol{\alpha}_k \cdot \mathbf{E}^{\text{tot}}_k = \boldsymbol{\alpha}_k \cdot (\mathbf{E}^d_k + \mathbf{E}_k), \tag{14}$$

where $\boldsymbol{\alpha}_k$ is the polarizability tensor of site k and $\mathbf{E}^{\text{tot}}_k$ is the total field on site k, which includes $\mathbf{E}^d_k$, the field generated directly by all other sites at site k and the RF $\mathbf{E}_k$, generated by all sites. By analogy to Eq. (12), the field as well as various degrees of the gradient of the field, generated directly by all other sites can be written as

$$[\nabla^0\Phi^d(\mathbf{r}_k), \nabla^1\Phi^d(\mathbf{r}_k), \nabla^2\Phi^d(\mathbf{r}_k),\dots]^t$$

$$= [\Phi^d(\mathbf{r}_k), -E^d_x(\mathbf{r}_k), -E^d_y(\mathbf{r}_k), -E^d_z(\mathbf{r}_k),\dots]^t$$

$$= \frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{l=1}^{N}{}' \mathscr{T}_{kl}\mathbf{M}_l ,$$

where the primed sum excludes the term $l=k$. The matrix $\mathscr{T}_{kl}$ is defined as

$$\mathscr{T}_{kl} = \begin{bmatrix} \nabla^0 & \nabla^1 & \nabla^2 & \nabla^3 & \cdots \\ -\nabla^1 & -\nabla^2 & -\nabla^3 & -\nabla^4 & \cdots \\ \nabla^2 & \nabla^3 & \nabla^4 & \nabla^5 & \cdots \\ -\nabla^3 & -\nabla^4 & -\nabla^5 & -\nabla^6 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \end{bmatrix} \left(\frac{1}{r_{kl}}\right), \tag{15}$$

where $\mathbf{r}_{kl} = \mathbf{r}_l - \mathbf{r}_k$ and

$$\nabla^p = \frac{\partial^{i+j+k}}{\partial x_l^i \partial y_l^j \partial z_l^k}, \quad p = i+j+k.$$

$\mathbf{E}^d_k$ arises from two sources, the permanent multipoles $\mathbf{M}_l$ and the induced dipoles $\boldsymbol{\mu}^{\text{ind}}_l$,

$$\mathbf{E}^d_k = -\frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{l=1}^{N}{}' (\mathscr{T}^1_{kl}\mathbf{M}_l + \mathscr{T}^{11}_{kl}\boldsymbol{\mu}^{\text{ind}}_l), \tag{16}$$

where $\mathscr{T}^1_{kl}$ is a submatrix of $\mathscr{T}_{kl}$

$$\mathscr{T}^1_{kl} = [-\nabla^1, -\nabla^2, -\nabla^3, -\nabla^4,\dots]\left(\frac{1}{r_{kl}}\right),$$

and $\mathscr{T}^{11}_{kl}$ is a 3×3 submatrix of $\mathscr{T}^1_{kl}$,

$$\mathscr{T}^{11}_{kl} = -\nabla^2\left(\frac{1}{r_{kl}}\right),$$

which is often called *the dipole field tensor*.

$\mathbf{E}_k$ also arises from the same two sources, the permanent multipoles and the induced dipoles,

$$\mathbf{E}_k = -\frac{1}{4\pi\epsilon_0\epsilon_1} \sum_{l=1}^{N} (\mathscr{R}^1_{kl}\mathbf{M}_l + \mathscr{R}^{11}_{kl}\boldsymbol{\mu}^{\text{ind}}_l), \tag{17}$$

where $\mathscr{R}^1_{kl}$ is a submatrix of $\mathscr{R}_{kl}$

$$\mathscr{R}^1_{kl} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}}$$

$$\times [\nabla^1_k\nabla^0_l, \nabla^1_k\nabla^1_l, \nabla^1_k\nabla^2_l,\dots]B_n(\mathbf{r}_k,\mathbf{r}_l),$$

and $\mathscr{R}^{11}_{kl}$ is a 3×3 submatrix of $\mathscr{R}^1_{kl}$

$$\mathscr{R}_{kl}^{11} = \sum_{n=0}^{\infty} \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n} \frac{1}{a^{2n+1}} \nabla_k^1 \nabla_l^1 B_n(\mathbf{r}_k, \mathbf{r}_l).$$

Substituting Eqs. (16) and (17) into Eq. (14), and collecting the terms containing the induced dipole moments, we get

$$(\mathscr{A}+\mathscr{F})\boldsymbol{\mu} = \mathscr{E}, \tag{18}$$

where $\mathscr{A}$ is the interaction matrix for direct interaction with diagonal blocks $\boldsymbol{\alpha}_k^{-1}$ and off-diagonal blocks $1/4\pi\epsilon_0\epsilon_1$ $\mathscr{T}_{kl}^{11}$; $\mathscr{F}$ is composed of $1/4\pi\epsilon_0\epsilon_1 \mathscr{R}_{kl}^{11}$, which comes from RF; $\mathscr{E}$ is the sum of the field generated by the permanent multipoles directly and through the RF, whose 3×1 blocks are

$$-\frac{1}{4\pi\epsilon_0\epsilon_1} \left(\sum_{l=1}^{N}{}' \mathscr{T}_{kl}^1 + \sum_{l=1}^{N} \mathscr{R}_{kl}^1 \right) \mathbf{M}_l.$$

Usually it is assumed that the polarizability is isotropic, then the diagonal blocks of $\mathscr{A}$ will be α_k^{-1}. Equation (18) is a generalization of the corresponding equation of Felder and Applequist,[23] and leads directly to a set of linear equations whose solution yields the induced dipole moments

$$\boldsymbol{\mu} = (\mathscr{A}+\mathscr{F})^{-1}\mathscr{E}.$$

In practice these equations can be solved iteratively for large systems.

E. Calculation of matrix elements

In this section we give a recursive algorithm to calculate the matrix elements of $\mathbf{R}_{kl}^{(n)}$. This algorithm is much faster than the explicit formula given in Appendix A in a normal simulation. Let the operator $\mathscr{D}_{k_1,k_2,k_3}^{l_1,l_2,l_3}$ denote

$$\mathscr{D}_{k_1,k_2,k_3}^{l_1,l_2,l_3} = \mathscr{D}_K^L = \frac{\partial^{k_1+k_2+k_3+l_1+l_2+l_3}}{\partial x_k^{k_1} \partial y_k^{k_2} \partial z_k^{k_3} \partial x_l^{l_1} \partial y_l^{l_2} \partial z_l^{l_3}}.$$

Suppose that $\mathbf{r}_k = (x_k, y_k, z_k)$ and $\mathbf{r}_l = (x_l, y_l, z_l)$, then $\cos\gamma_{kl} = d/r_k r_l$, where d is the inner product of the two vectors $\mathbf{r}_k$ and $\mathbf{r}_l$, $d = x_k x_l + y_k y_l + z_k z_l$. Furthermore, we make the following definitions: $K_{mi} = \{k_1 - m\delta_{1i}, k_2 - m\delta_{2i}, k_3 - m\delta_{3i}\}$, $L_{mi} = \{l_1 - m\delta_{1i}, l_2 - m\delta_{2i}, l_3 - m\delta_{3i}\}$, where $m = 0$, 1, or 2. For example, $K_{12} = \{k_1, k_2-1, k_3\}$. For $m=0$, we simply denote $K_{0i} = K = \{k_1, k_2, k_3\}$ and $L_{0i} = L = \{l_1, l_2, l_3\}$. Let also denote $x_{h1} = x_h$, $x_{h2} = y_h$, $x_{h3} = z_h$ where $h = k$ or l. From the recursive relation of the Legendre polynomials[53]

$$(n+1)P_{n+1}(z) - (2n+1)zP_n(z) + nP_{n-1}(z) = 0,$$

we have

$$B_n = \frac{1}{n} ((2n-1)d B_{n-1} - (n-1) r_k^2 r_l^2 B_{n-2}).$$

If we define $F = dB_{n-1}$ and $G = r_k^2 r_l^2 B_{n-2}$, we have

$$\mathscr{D}_K^L F = \left(d\mathscr{D}_K^L + \sum_{i=1}^{3} k_i x_{li} \mathscr{D}_{K_{1i}}^L + \sum_{i=1}^{3} l_i x_{ki} \mathscr{D}_K^{L_{1i}} \right.$$
$$\left. + \sum_{i=1}^{3} k_i l_i \mathscr{D}_{K_{1i}}^{L_{1i}} \right) B_{n-1} \tag{19}$$

and

$$\mathscr{D}_K^L G = \left(r_k^2 r_l^2 \mathscr{D}_K^L + 2r_l^2 \sum_i k_i x_{ki} \mathscr{D}_{K_{1i}}^L + 2r_k^2 \sum_i l_i x_{li} \mathscr{D}_K^{L_{1i}} \right.$$
$$+ 4\sum_{i,j} k_i l_j x_{ki} x_{lj} \mathscr{D}_{K_{1i}}^{L_{1j}} + r_l^2 \sum_i k_i(k_i-1) \mathscr{D}_{K_{2i}}^L$$
$$+ r_k^2 \sum_i l_i(l_i-1) \mathscr{D}_K^{L_{2i}} + 2\sum_{i,j} k_i(k_i-1) l_j x_{ki} \mathscr{D}_{K_{2i}}^{L_{1j}}$$
$$+ 2\sum_{i,j} l_i(l_i-1) k_j x_{li} \mathscr{D}_{K_{1i}}^{L_{2j}} + \sum_{i,j} k_i(k_i-1)$$
$$\left. \times l_j(l_j-1) \mathscr{D}_{K_{2i}}^{L_{2j}} \right) B_{n-2}. \tag{20}$$

With $\mathscr{D}_K^L F$ and $\mathscr{D}_K^L G$, we obtain

$$\mathscr{D}_K^L B_n(\mathbf{r}_k, \mathbf{r}_l) = \frac{1}{n} ((2n-1)\mathscr{D}_K^L F - (n-1)\mathscr{D}_K^L G). \tag{21}$$

From the definition of B_n we see that $B_0 = 1$, so the only nonzero element of $\mathscr{D}_{k_1,k_2,k_3}^{l_1,l_2,l_3} B_0$ is $\mathscr{D}_{0,0,0}^{0,0,0} B_0 = B_0 = 1$. When $n=1$, $B_1 = d$, so we have

$$\mathscr{D}_{0,0,0}^{0,0,0} B_1 = d,$$

$$\mathscr{D}_{1,0,0}^{0,0,0} B_1 = x_l, \quad \mathscr{D}_{0,1,0}^{0,0,0} B_1 = y_l, \quad \mathscr{D}_{0,0,1}^{0,0,0} B_1 = z_l,$$

$$\mathscr{D}_{0,0,0}^{1,0,0} B_1 = x_k, \quad \mathscr{D}_{0,0,0}^{0,1,0} B_1 = y_k, \quad \mathscr{D}_{0,0,0}^{0,0,1} B_1 = z_k,$$

$$\mathscr{D}_{1,0,0}^{1,0,0} B_1 = 1, \quad \mathscr{D}_{0,1,0}^{0,1,0} B_1 = 1, \quad \mathscr{D}_{0,0,1}^{0,0,1} B_1 = 1,$$

and all others elements vanish. From Eqs. (19), (20), and (21) and using $\mathscr{D}_K^L B_0$ and $\mathscr{D}_K^L B_1$ as initial values, we can get $\mathscr{D}_K^L B_n$ from $\mathscr{D}_K^L B_{n-1}$ and $\mathscr{D}_K^L B_{n-2}$. It can be seen from Eqs. (19) and (20) that as n goes up, the nonzero terms in these equations depend only on K and L.

III. CENTRAL MULTIPOLE METHOD

The matrix method just discussed fits nicely into the polytensor formalism for direct multipole interactions. As mentioned briefly in the section describing induced dipoles, a main difference between direct interactions and the RF lies in the kernel functions operated on by the Cartesian derivative matrix; $1/r$ for direct interactions vs B_n for RF. In addition, calculation of the RF requires inclusion of self-interaction terms and involves summation of an infinite series. Hence our existing program for direct multipole interactions[51] can be modified with little effort to incorporate the RF calculation. Since large systems usually require as many as 20 terms for the series to converge,[54] and computation of each term is an $O(N^2)$ operation, where N is number of multipole sites, the inclusion of RF effects can make the computation very slow. In this section we present a method to calculate the RF which needs only $O(N)$ time. We call this new linear method the central multipole method, for rea-

sons which will become clear in the following discussion. Since the treatment of multipoles is developed directly from the corresponding method for a charge distribution, we first present the method for charge distributions.

A. Central multipole method for charge distribution

The biaxial harmonic $B_n(\mathbf{r}_k, \mathbf{r}_l) = r_k^n r_l^n P_n(\cos \gamma_{kl})$ can be written as[53]

$$r_k^n r_l^n P_n(\cos \gamma_{kl}) = r_k^{2n+1} \sum_s \sum_t \sum_u \frac{x_l^s y_l^t z_l^u}{s! t! u!} \frac{\partial^{s+t+u}}{\partial x_k^s y_k^t z_k^u} \frac{1}{r_k},$$
(22)

the summation over s, t, and u being taken for all integral values that satisfy $s+t+u=n$. Using Eqs. (3), (13), and (22), and exchanging the order of summation in Q_n, we can see that

$$Q_n = \mathscr{Y}^{(n)} \cdot \mathscr{M}^{(n)}.$$
(23)

The components of $\mathscr{M}^{(n)}$ are defined as

$$\mathscr{M}_{stu}^{(n)} = \sum_{i=1}^N q_i x_i^s y_i^t z_i^u,$$
(24)

which are Cartesian multipoles of the charge distribution with respect to the *center of the cavity*, and $\mathscr{Y}^{(n)}$ are the traceless Cartesian multipoles defined in Eq. (13). Note that in this definition of $\mathscr{M}^{(n)}$ there is no factor of $1/n!$ in contrast to the previous definition used in the matrix method. The symbol $\cdot$ stands for complete contraction. The quantity Q_n is usually referred to in the literature as ''the square of nth moments of the charge distribution.'' It is shown here that expressed in Cartesian multipoles, Q_n is the complete contraction of two multipole tensors, one with trace and one traceless. For $n=0$, $\mathscr{Y}_{000}^{(0)} = \mathscr{M}_{000}^{(0)} = \Sigma_i q_i$ is the total net charge of the system. For $n=1$, $\mathscr{Y}_{100}^{(1)} = \mathscr{M}_{100}^{(1)} = \Sigma_i q_i x_i$, $\mathscr{Y}_{010}(1) = \mathscr{M}_{010}^{(1)} = \Sigma_i q_i y_i$, and $\mathscr{Y}_{001}^{(1)} = \mathscr{M}_{001}^{(1)} = \Sigma_i q_i z_i$, so Q_1 is the square of magnitude of the dipole moment of the system relative to the center of the cavity. For $n>1$ the components of $\mathscr{Y}^{(n)}$ are no longer equal to those of $\mathscr{M}^{(n)}$.

Equation (23) provides an alternative and fast way to calculate the RF energy for an arbitrary charge distribution. Since the calculation of $\mathscr{Y}^{(n)}$ and $\mathscr{M}^{(n)}$ is linear with N, the size of the system, the calculation of RF is reduced to an $O(N)$ operation. Results show that the calculation time is reduced by many orders for large systems. The new method is called the central multipole method since the two different Cartesian tensors involved, $\mathscr{Y}^{(n)}$ and $\mathscr{M}^{(n)}$, are both expanded relative to the center of the cavity.

$\mathscr{Y}^{(n)}$ has $2n+1$ unique terms, while $\mathscr{M}^{(n)}$ has $(n+1) \times (n+2)/2$ unique terms. The degeneracy of $\mathscr{M}_{stu}^{(n)}$ is $n!/(s!t!u!)$. In addition, although the components of $\mathscr{Y}^{(n)}$ and $\mathscr{M}^{(n)}$ are not equal to each other when $n>1$, they are related linearly, such as

$$\mathscr{Y}_{002}^{(2)} = \mathscr{M}_{002}^{(2)} - \tfrac{1}{2}\mathscr{M}_{200}^{(2)} - \tfrac{1}{2}\mathscr{M}_{020}^{(2)},$$

and

$$\mathscr{Y}_{021}^{(3)} = 2\mathscr{M}_{021}^{(3)} - \tfrac{1}{2}\mathscr{M}_{201}^{(3)} - \tfrac{1}{2}\mathscr{M}_{003}^{(3)},$$

so we can in fact only calculate the $(n+1)(n+2)/2$ unique terms of $\mathscr{M}^{(n)}$, and then use these terms to construct the $2n+1$ unique terms of $\mathscr{Y}^{(n)}$ through these linear relations. Details of the calculation will be given elsewhere. Once $\mathscr{M}^{(n)}$ is calculated, $\mathscr{Y}^{(n)}$ can be easily obtained.

B. Central multipole method for multipole distribution

The central multipole method for charge distributions can be generalized to an arbitrary multipole distribution. To do so the $\mathscr{M}^{(n)}$ and $\mathscr{Y}^{(n)}$ should be expanded for these multipoles. This can be easily achieved on $\mathscr{M}^{(n)}$

$$\mathscr{M}_{stu}^{(n)} = \sum_{l=1}^N \sum_m q_{l_m} x_{l_m}^s y_{l_m}^t z_{l_m}^u$$

$$= \sum_{l=1}^N \sum_m q_{l_m}(x_l + d_{l_m}^x)^s (y_l + d_{l_m}^y)^t (z_l + d_{l_m}^z)^u, \quad (25)$$

where $d_{l_m}^x$, $d_{l_m}^y$, and $d_{l_m}^z$ are the x, y, and z components of the displacement of mth partial charge q_{l_m} of site l. Expanding Eq. (25) gives

$$\mathscr{M}_{stu}^{(n)} = \sum_{l=1}^N \sum_{i,j,k} \binom{s}{i}\binom{t}{j}\binom{u}{k} x_l^{s-i} y_l^{t-j} z_l^{u-k} M_l^{ijk},$$
(26)

where M_l^{ijk} is the Cartesian multipoles of site l

$$M_l^{ijk} = \sum_m q_{lm}(d_{l_m}^x)^i (d_{l_m}^y)^j (d_{l_m}^z)^k.$$

Again the factor of $1/n!$ does not appear in this definition, unlike the definition used in the matrix method. For complete convergence the summation over i, j, and k in Eq. (26) is determined by $0 \leq i \leq s$, $0 \leq j \leq t$, and $0 \leq k \leq u$. In actual calculations another condition, $i+j+k \leq p$, where p is the highest order of multipoles for each site, has to be imposed. As explained in the previous section, once $\mathscr{M}^{(n)}$ has been calculated, $\mathscr{Y}^{(n)}$ can be obtained through the same linear transformation.

C. Derivatives using central multipole method

The derivatives can be easily obtained via the central multipole method. From Eq. (23), we get

$$\frac{\partial}{\partial x_l} Q_n = \left(\frac{\partial}{\partial x_l} \mathscr{Y}^{(n)}\right) \cdot \mathscr{M}^{(n)} + \mathscr{Y}^{(n)} \cdot \left(\frac{\partial}{\partial x_l} \mathscr{M}^{(n)}\right).$$
(27)

For a charge distribution, from the definition of $\mathscr{M}^{(n)}$ [Eq. (24)] we see that

$$\frac{\partial}{\partial x_l} \mathscr{M}_{stu}^{(n)} = s q_l x_l^{s-1} y_l^t z_l^u$$
(28)

For a multipole distribution, from the definition of $\mathscr{M}^{(n)}$ [Eq. (26)] we see that

$$\frac{\partial}{\partial x_l}\mathscr{M}_{stu}^{(n)} = \sum_{i,j,k} \binom{s}{i}\binom{t}{j}\binom{u}{k}\left[(s-i)x_l^{s-i-1}y_l^{t-j}z_l^{u-k}M_l^{ijk}\right.$$

$$+ x_l^{s-i}y_l^{t-j}z_l^{u-k}\left(\frac{\partial}{\partial x_l}M_l^{ijk}\right)$$

$$\left.+ \sum_{w\in L_l} x_w^{s-i}y_w^{t-j}z_w^{u-k}\left(\frac{\partial}{\partial x_l}M_w^{ijk}\right)\right]. \quad (29)$$

The last two terms of Eq. (29) come from the local coordinate systems used to define the multipoles at each site.[51] The set L_l includes all other sites the definition of whose multipoles depends on site l. Once we have obtained $\partial/\partial x_l \mathscr{M}^{(n)}$ from either Eq. (28) or Eq. (29), we can get $\partial/\partial x_l \mathscr{Y}^{(n)}$ through the linear transform used above to obtain $\mathscr{Y}^{(n)}$ from $\mathscr{M}^{(n)}$. Then from Eq. (27) we get the derivatives of the RF energy with respect to the coordinates of each site.

IV. DISCUSSION

Methods that directly use the exact molecular surface have clear advantages over the use of a sphere or ellipsoid to describe the molecular shape. However, analytical methods based on simple cavity shapes are more efficient and appropriate when an extended system containing solute and explicit solvent fills an idealized cavity. Molecular simulations using empirical force fields provide many potential uses for this extended system approach. In these cases, the electrostatic solvation effect can be viewed as a long-range correction to the explicit simulation of electrostatics within the extended system itself. Inclusion of such long-range effects is of critical importance to accurate modeling of some properties, such as the dielectric constant of water and solvation of ions. In more recent work inclusion of long-range electrostatics has been proposed to be an important factor in achieving protein simulations that remain close to experimentally determined structures.[55] Multisite multipole potentials can provide accurate models for the local electrostatic interactions in peptides and proteins.[15] The current paper describes a method for incorporating the long-range forces arising from these same multipole-based potentials.

The Cartesian polytensor formulation of Applequist is an efficient method for organizing multipole calculations.[50,56] It has been used by Dykstra[11] for calculation of direct and induced electrostatic interactions in his *ab initio* derived MMC empirical force field.[57] The corresponding spherical polar multipole treatments result in a more compact mathematical formulation,[9] but the redundancy in Cartesian multipole treatments can be easily removed when using the polytensor method. In addition, it provides a compact matrix notation which is readily incorporated into computer programs, and can be easily adapted to higher derivatives of energy and gradients of the potential. In this paper we show that the Cartesian polytensor formulation can be extended to computation of the RF effects by changing the function operated on by the Cartesian derivative matrix from $1/r$ (for explicit interactions) to the biaxial harmonics (for reaction field).

Reaction field methods have numerically unstable asymptotic behavior for charges approaching the dielectric boundary. Such sites generate large apparent surface charges of opposite sign, and are attracted to the interface by a force that becomes infinite at the boundary. In addition, explicit molecules must be restricted to the region inside the cavity itself. Several groups have handled these numerical problems by using constraints to keep atoms from getting too close to the boundary.[58–61] Recently, Wang and Hermans[62] have applied the image charge method to pure water droplets and droplets containing a single cation. They discuss the various problems caused by boundary effects, and suggest an empirical solution that gives the correct cation hydration energy independent of the position of the cation within the cavity. Further studies will be needed to devise general and theoretically justified treatments of effects due to fixed cavity boundaries.

Methods that treat RF effects based on the actual molecular shape do well with regularly shaped small molecules. However these methods may fail near the small cavities, cracks and crevices in large molecules like proteins as discussed by Gilson *et al.*[35] One potential disadvantage is that it may be very difficult to calibrate an isolated molecule method to correctly describe local interactions very close to the solute.

It is well known that tightly bound water molecules play an important structural and dynamic role in many biological macromolecules.[63,64] Tightly bound solvent should be accounted for in molecular surface methods through inclusion of explicit solvent molecules. Supermolecule approaches that use molecular-shaped cavity surrounding the solute and a limited number of explicit solvent molecules have recently been used to model solvation of small systems using both empirical force field[65,66] and quantum mechanical methods.[43] In addition the explicit presence of local solvent provides the space-filling needed to reproduce solute dynamics. These hybrid discrete/continuum approaches correctly account for a limited set of specific local interactions. In our approach, we expand the number of explicit solvent molecules to fill out a spherical system containing at least the first solvation shell, and allowing use of the much simpler analytic formulation available for the spherical cavity.

The methods discussed in this work can incorporate ionic strength with little computational effort, as in Kirkwood's original treatment. If we denote the radii of the original cavity and of the ion-free zone as a and a', respectively, then by solving in different regions Laplace's equation or the linearized Poisson–Boltzmann equation $\nabla^2\Phi(\mathbf{r}) = \kappa^2\Phi(\mathbf{r})$ (where κ is the inverse Debye screening length which is related to the ionic strength), we get

$$W = \frac{1}{8\pi\epsilon_0\epsilon_1}\sum_{n=0}^{\infty}h(n)\frac{1}{a^{2n+1}}\sum_{k=1}^{N}\sum_{l=1}^{N}\mathbf{M}_k^t\mathbf{R}_{kl}^{(n)}\mathbf{M}_l, \quad (30)$$

where

$$h(n) = \frac{(n+1)(1-\epsilon)K_{n+1}(x) - ((n+1)+n\epsilon)(K_{n+1}(x)-K_n(x))(a'/a)^{2n+1}}{((n+1)\epsilon+n)K_{n+1}(x) - n(1-\epsilon)(K_{n+1}(x)-K_n(x))(a'/a)^{2n+1}}. \tag{31}$$

Here the polynomials $K_n(x)$ are defined as

$$K_n(x) = \sum_{s=0}^{n} \frac{2^s n!(2n-s)!}{s!(2n)!(n-s)!} x^s,$$

where $x = \kappa a'$. It can be seen that when $\kappa = 0$, corresponding to zero ionic strength, Eq. (31) reduces to

$$h(n) = \frac{(n+1)(1-\epsilon)}{(n+1)\epsilon+n}$$

since $K_n(0) = 1$. All the equations developed for zero ionic strength hold under Poisson–Boltzmann generalization if the proper $h(n)$ is used.

The total electrostatic force experienced by a system in solution consists of three terms,[67] the first of which is the usual interaction of charges with the electrical field, which includes the Coulomb's law fields and the reaction field. In this paper when we talk about the derivatives of the energy we are discussing this kind of force. However, in addition to this term, there are two other terms that arise from discontinuities in the dielectric constant and ionic strength. These two terms act on the corresponding boundaries. In the case of a spherical cavity containing a solute and filled out with explicit solvent and ions, the boundary pressure due to these discontinuities is only experienced directly by those species close to the boundary. If the solute of interest is near the center of the cavity, the behavior of species near the boundary is not of as much importance as those close to the solute. If the buffer region is thick enough, the boundary pressure for a fixed spherical cavity can be approximated by distributing it over the whole system and should be nearly isotropic. Thus, the boundary pressure plays a less important role in determining the dynamics of the overall system. On the other hand, if a molecular surface is used, it is more likely the anisotropic forces resulting from these last two terms would effect the behavior of the exposed individual atoms. These effects should be taken into account explicitly, adding further computation burden to molecular surface methods. Whether the boundary term can be completely neglected in fixed spherical boundary simulations will require a further set of test simulations.

In this work two general methods are proposed for computation of RF effects. The matrix formulation fits nicely with the existing method for calculating direct multipole interactions. In addition, it can provide various gradients of RF potentials at each site, which will be useful in dealing with the polarizability of the system. However, this method is inherently pairwise, and scales in execution time with the square of the size of the system $[O(N^2)]$. The central multipole method provides an algorithm whose execution time scales linearly with the size of the system $[O(N)]$. This method will be most useful for large systems. As discussed above, larger systems require more terms in the infinite series in order to achieve convergence. However, as the number of series terms, n, rises, the number of components we have to calculate for $\mathscr{M}^{(n)}$ and $\mathscr{Y}^{(n)}$ increases. Thus, the efficiency of the linear central multipole method is degraded when higher orders are used. Even so, the linear nature of the central multipole method makes it vastly superior to the pairwise matrix method for large systems.

At present, the most widely used RF protocol in simulations is the image charge method.[30] Image charges are attractive because of the resulting simple pairwise procedure for calculation of the RF energy. However, the generation of image charge sites entails an additional N^2 calculations between N solute charges and N image charges. A second widely used RF method involves use of only the dipole term ($n=1$) for a system containing neutral molecules.[31,68] Like the image charge procedure, this second method is also pairwise and an approximation to the full RF series summation. Our central multipole method can use any number of series terms to achieved a desired level of convergence and is computationally more efficient than either of these currently used methods.

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APPENDIX A: EXPLICIT FORMULA FOR THE MATRIX ELEMENTS

In this section an explicit formula for the matrix elements is given.

$$\mathscr{D}_{k_1,k_2,k_3}^{l_1,l_2,l_3} B_n(\mathbf{r}_k, \mathbf{r}_l)$$

$$= f_n^0(k_1,k_2,k_3;\mathbf{r}_k) f_n^0(l_1,l_2,l_3;\mathbf{r}_l)$$

$$+ 2\sum_{m=1}^{w} \frac{(n-m)!}{(n+m)!} [f_n^m(k_1,k_2,k_3;\mathbf{r}_k) f_n^m(l_1,l_2,l_3;\mathbf{r}_l)$$

$$+ g_n^m(k_1,k_2,k_3;\mathbf{r}_k) g_n^m(l_1,l_2,l_3;\mathbf{r}_l)],$$

where

$$f_n^m(i,j,k;\mathbf{r}) = \frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k}\, r^n P_n^m(\cos\theta)\cos m\phi$$

$$= \frac{(n+m)!\,i!\,j!}{2^m(n-k)!}\sum_\alpha \frac{(-1)^\alpha}{2^{2\alpha}}\binom{m+2\alpha}{\alpha}$$

$$\times\binom{n-k}{m+2\alpha}z^{n-m-k-2\alpha}\sum_\beta\sum_\gamma(-1)^\gamma\binom{\alpha}{\beta}$$

$$\times\binom{m}{2\gamma}\binom{m+2\beta-2\gamma}{i}\binom{2\alpha-2\beta+2\gamma}{j}$$

$$\times x^{m+2\beta-2\gamma-i}y^{2\alpha-2\beta+2\gamma-j}$$

and

$$g_n^m(i,j,k;\mathbf{r}) = \frac{\partial^{i+j+k}}{\partial x^i \partial y^j \partial z^k}\, r^n P_n^m(\cos\theta)\sin m\phi$$

$$= \frac{(n+m)!\,i!\,j!}{2^m(n-k)!}\sum_\alpha \frac{(-1)^\alpha}{2^{2\alpha}}\binom{m+2\alpha}{\alpha}$$

$$\times\binom{n-k}{m+2\alpha}z^{n-m-k-2\alpha}\sum_\beta\sum_\gamma(-1)^\gamma\binom{\alpha}{\beta}$$

$$\times\binom{m}{2\gamma+1}\binom{m+2\beta-2\gamma-1}{i}$$

$$\times\binom{2\alpha-2\beta+2\gamma+1}{j}$$

$$\times x^{m+2\beta-2\gamma-1-i}y^{2\alpha-2\beta+2\gamma+1-j},$$

from these formulas, we get $n \geq i+j+k$ as the condition for the matrix element to be nonzero.

APPENDIX B: VECTOR FORMULAS FOR POINT MULTIPOLES

In this appendix the formulas for the RF energy expressed in vector notation are given. We use $W_{n_1 n_2}$ to represent the RF energy between n_1th and n_2th degree multipoles at two different sites. $\mathbf{r}_n$ is the vector position of nth degree multipole from the origin of the sphere, and if the energy term involves two multipoles of the same degree, n is omitted. In such cases $\mathbf{r}_i$, $i=1$ or 2 are the position vectors for the two multipoles involved. $\boldsymbol{\mu}$ is the dipole vector and $\mathbf{s}_1$ and $\mathbf{s}_2$ are two vectors that define the quadrupole. In the case of quadrupole–quadrupole interaction, $\mathbf{s}_{i_j}$ stands for the jth vector ($j=1$ or 2) of the ith site ($i=1$ or 2). $\hat{\mathbf{r}}$ stands for the unit vector of $\mathbf{r}$. P_n denotes the nth degree Legendre polynomial $P_n(\cos\gamma_{12})$, where γ_{12} is the angle between two $\mathbf{r}$ vectors. In this Appendix, the ubiquitous factor $1/4\pi\epsilon_0\epsilon_1$ is omitted from all equations

$$W_{00} = \frac{(1-\epsilon)q_1 q_2}{a}\sum_{n=0}^\infty \frac{(n+1)}{(n+1)\epsilon+n}\left(\frac{r_1 r_2}{a^2}\right)^n P_n,$$

$$W_{01} = \frac{(1-\epsilon)q\mu}{a^2}\sum_{n=1}^\infty \frac{(n+1)}{(n+1)\epsilon+n}\frac{r_0^n r_1^{n-1}}{a^{2n-1}}\left[P_n'(\hat{\mathbf{r}}_0\cdot\hat{\boldsymbol{\mu}}) - P_{n-1}'(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})\right],$$

$$W_{11} = \frac{(1-\epsilon)\mu_1\mu_2}{a^3}\sum_{n=1}^\infty \frac{(n+1)}{(n+1)\epsilon+n}\left(\frac{r_1 r_2}{a^2}\right)^{n-1}\{P_n''(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}}_2)(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}_1) - P_{n-1}''[(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}}_1)(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}}_2)+(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}_2)]$$

$$+ P_{n-2}''(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}_2) + P_n'(\hat{\boldsymbol{\mu}}_1\cdot\hat{\boldsymbol{\mu}}_2) - 2P_{n-1}'(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}_2)\},$$

$$W_{02} = \frac{(1-\epsilon)qQ}{a^3}\sum_{n=2}^\infty \frac{(n+1)}{(n+1)\epsilon+n}\frac{r_0^n r_2^{n-2}}{a^{2n-2}}\{P_n''(\hat{\mathbf{r}}_0\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_0\cdot\hat{\mathbf{s}}_2) - P_{n-1}''[(\hat{\mathbf{r}}_0\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_0\cdot\hat{\mathbf{s}}_2)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)] + P_{n-2}''(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2) - P_{n-1}'(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)\},$$

$$W_{12} = \frac{(1-\epsilon)\mu Q}{a^4}\sum_{n=2}^\infty \frac{(n+1)}{(n+1)\epsilon+n}\frac{r_1^{n-1} r_2^{n-2}}{a^{2n-3}}\{P_n'''(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2) - P_{n-1}'''[(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2)$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)+(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2)] + P_{n-2}'''[(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)+(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)]$$

$$- P_{n-3}'''(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2) + P_n''[(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_1)] - P_{n-1}''[(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_1)+(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\boldsymbol{\mu}}) + 2((\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)+(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_2)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)] + P_{n-2}''[(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)+4(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_2)]$$

$$- 2P_{n-1}'(\hat{\mathbf{r}}_1\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)\},$$

$$W_{22}=\frac{(1-\epsilon)Q_1Q_2}{a^5}\sum_{n=2}^{\infty}\frac{(n+1)}{(n+1)\epsilon+n}\left(\frac{r_1r_2}{a^2}\right)^{n-2}\{P_n^{(4)}(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})-P_{n-1}^{(4)}[(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\mathbf{s}_{2_1})]$$

$$+P_{n-2}^{(4)}[(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+A]-P_{n-3}^{(4)}\times B+P_{n-4}^{(4)}(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+P_n'''[(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})$$

$$+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})]-P_{n-1}'''[(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_1})$$

$$+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_1})$$

$$+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})+2A]$$

$$+P_{n-2}'''(C+4B)-P_{n-3}'''[D+8(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})]+P_n''[(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_1})]$$

$$-2P_{n-1}''\times C+P_{n-2}''[(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})+4D+8(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})]-2P_{n-1}'(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})\},$$

$$A=(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})$$

$$+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{s}_{2_1}),$$

$$B=(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})$$

$$\times(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2}),$$

$$C=(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{s}}_{1_2}\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})$$

$$\times(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{1_1})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1}),$$

$$D=(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_1})(\hat{\mathbf{r}}_1\cdot\hat{\mathbf{s}}_{1_2})(\hat{\mathbf{s}}_{2_1}\cdot\hat{\mathbf{s}}_{2_2})+(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_1})(\hat{\mathbf{r}}_2\cdot\hat{\mathbf{s}}_{2_2})(\hat{\mathbf{s}}_{1_1}\cdot\hat{\mathbf{s}}_{1_2}).$$

The multipole of a given site can interact with itself, or with multipoles of different degrees at the same site. We denote by W_{ij}' the RF energy between n_1th and n_2th degree multipoles at the same sites. W_{ij}' can be considered as a special case of W_{ij}. From the generating function of Legendre polynomials,

$$\frac{1}{(1-2xt+t^2)^{1/2}}=\sum_{n=0}P_n(x)t^n,$$

it can be easily derived that

$$P_n^{(m)}(1)=\frac{1}{2^m}\frac{(n+m)!}{(n-m)!m!}.$$

W_{ij}' is then obtained using the expression for $P_n^{(m)}(1)$ and the previously derived W_{ij}. When the degree of the multipoles is the same, a constant factor of 2 is removed. Since only one site is involved, the subscript on $\mathbf{r}$ is omitted.

$$W_{00}'=\frac{(1-\epsilon)q^2}{2a}\sum_{n=0}^{\infty}\frac{(n+1)}{(n+1)\epsilon+n}\left(\frac{r}{a}\right)^{2n},$$

$$W_{01}'=\frac{(1-\epsilon)q\mu}{a^2}\sum_{n=1}^{\infty}\frac{n(n+1)}{(n+1)\epsilon+n}\left(\frac{r}{a}\right)^{2n-1}(\hat{\mathbf{r}}\cdot\hat{\boldsymbol{\mu}}),$$

$$W_{02}'=\frac{(1-\epsilon)qQ}{2a^3}\sum_{n=2}^{\infty}\frac{(n-1)n(n+1)}{(n+1)\epsilon+n}\left(\frac{r}{a}\right)^{2n-2}[3(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)-(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)],$$

$$W_{11}'=\frac{(1-\epsilon)\mu^2}{4a^3}\sum_{n=1}^{\infty}\frac{n(n+1)}{(n+1)\epsilon+n}\left(\frac{r}{a}\right)^{2(n-1)}[(n+1)+(n-1)(\hat{\mathbf{r}}\cdot\hat{\boldsymbol{\mu}})^2],$$

$$W'_{12} = \frac{(1-\epsilon)\mu Q}{2a^4} \sum_{n=2}^{\infty} \frac{(n-1)n(n+1)}{(n+1)\epsilon+n} \left(\frac{r}{a}\right)^{2n-3} \{(n-2)(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)(\hat{\mathbf{r}}\cdot\hat{\boldsymbol{\mu}}) + (n+1)[(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_2) + (\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)(\hat{\boldsymbol{\mu}}\cdot\hat{\mathbf{s}}_1)]$$
$$- n(\hat{\mathbf{r}}\cdot\hat{\boldsymbol{\mu}})(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)\},$$

$$W'_{22} = \frac{(1-\epsilon)Q^2}{16a^5} \sum_{n=2}^{\infty} \frac{(n-1)n(n+1)}{(n+1)\epsilon+n} \left(\frac{r}{a}\right)^{2(n-2)} \{(n+1)(n+2) + 3(n+1)(n-2)[(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)^2 + (\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)^2] + 3(n-2)(n-3)$$
$$\times (\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)^2(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)^2 + 2n(n-1)(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)^2 - 4(n-1)(n-2)(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_1)(\hat{\mathbf{r}}\cdot\hat{\mathbf{s}}_2)(\hat{\mathbf{s}}_1\cdot\hat{\mathbf{s}}_2)\}.$$

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