

Dielectric and thermodynamic response of a generalized reaction field model for liquid state simulations

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A generalized reaction field (GRF) model for simulations of liquid water is presented. The method is based on the solution of the Poisson equation for the reaction field acting on a collection of charges in a spherical cavity which is immersed in a continuum dielectric medium. In this model, the reaction field potential arising from the charges in the spherical cavity can be expressed as an infinite series, each term of which is the reaction field arising from a corresponding multipole in the expansion of the charge distribution. The GRF model is used here in simulations of liquid water and of solutions containing one or two ions in water. The dielectric constant computed for liquid water with the generalized reaction field agrees with previous results obtained using the conventional dipolar reaction field. The water orientational correlation functions converge to within 5% of the correct value when the first three terms are included in the multipolar expansion of the reaction field. Thermodynamic results from simulations of a single ion in water in which the GRF was employed demonstrate that the hydration free energy of the ion agrees with the Born hydration energy when the ion is far from the boundary, but when the ion approaches the boundary, there are significant deviations in the free energy. The results of GRF simulations of two ions in water are also reported.

I. INTRODUCTION

Developing accurate models for simulating the thermodynamic properties of molecular systems with long range electrostatic forces is a difficult problem. When simulating systems with explicit solvent, a key property is the orientational polarization of the solvent. When a spherical cutoff is applied to the Coulomb forces in liquid simulations, there is little effect on radial distribution functions, but there are large perturbations of the orientational correlation functions.¹⁻³ The use of a cutoff in simulations has also been shown to have a large effect on the potentials of mean force of ions in water^{4,5} and on the structures of peptides and proteins in solution.⁶⁻⁸

Two models for the long range interactions which have been employed in liquid simulations are the reaction field⁹ and Ewald sum models.¹⁰ For dipolar fluids and for liquid water, the same dielectric constant has been obtained with the two models.^{11,12} The conventional reaction field model has often been used to simulate pure liquids, but there have been only a few attempts to apply the reaction field method to heterogeneous solutions.¹³ A potential drawback of the Ewald sum method is that it is a model for an infinitely periodic system which is used to simulate an aperiodic system. The effect of unit cell size on thermodynamic functions has not been investigated systematically.

The conventional reaction field model was developed to correct for the perturbations resulting from the use of a cutoff of the Coulomb interactions in simulations of dipolar fluids.⁹ In this model, each dipolar molecule in the liquid is considered in turn to be the center of a sphere of radius R_{cut} ; the sphere is imagined to be surrounded by a continuum solvent with dielectric ϵ_{rf} . The effect of the continuum solvent on the central molecule, which replaces the interactions neglected when the cutoff is introduced, is

to induce a reaction field that is proportional to the total dipole moment within the sphere. The dipole reaction field model would seem to be more appropriate for dipolar liquids than ionic solutions because the use of a shifting origin for the reaction field calculation will lead to large unphysical oscillations in the reaction fields of adjacent molecules when ions are present. The dipole reaction field model has, however, been used in simulations of charged systems.¹³ A question has also been raised as to whether solvent beyond the cutoff is being modeled in a consistent way when a shifting origin is employed in the dipole reaction field model.¹⁴

In this paper, we develop a new reaction field model for approximating long range interactions based on Kirkwood's solution of the electrostatic equations for the reaction field acting on an arbitrary charge distribution in a spherical dielectric cavity immersed in a dielectric fluid.¹⁵ We call this the generalized reaction field (GRF) model. The GRF model and the simulations are described in Sec. II. In Sec. III, we report the orientational correlation functions and dielectric constant computed from liquid water simulations with the GRF model. The charging free energies of one and two ions in water using the GRF model are compared with the results of simulations using a spherical cutoff. In Sec. IV, the conclusions are presented.

II. THE GENERALIZED REACTION FIELD METHOD

Kirkwood solved the linearized Poisson-Boltzmann equation in spherical coordinates to obtain the electrostatic free energy of a set of point charges in a spherical dielectric cavity with interior dielectric D , surrounded by a dielectric continuum characterized by a dielectric constant D_0 .¹⁵ In

the absence of added salt, the reaction field contribution to the free energy of a set of point charges located at the positions $\{r_i\}$ is given by

$$\Delta G = \sum_{k=1}^m \sum_{l=1}^m \frac{Q_k Q_l}{2b} (-B_{kl}), \quad (1)$$

where

$$B_{kl} = \frac{1}{D_i} \sum_{n=0}^{\infty} \frac{(n+1)(D_0 - D_i)}{(n+1)D_0 + nD_i} \left(\frac{r_k}{b}\right)^n \left(\frac{r_l}{b}\right)^n P_n(\cos \theta_{kl}). \quad (2)$$

Q_k and Q_l are the charges at sites with positions r_k and r_l from the origin, b is the radius of the spherical cavity, and θ_{kl} is the angle formed by r_k and r_l . The reaction field free energy terms B_{kl} arise from the modification induced in the Coulombic energy between charges k and l embedded in the cavity with internal dielectric D_i because the cavity is bounded by a medium with a different dielectric constant D_0 . By differentiating the reaction field-free energy with respect to the coordinates of the charges in the central cavity, we can obtain the forces on the charges exerted by the reaction field. The forces are given by

$$F_k^x = \sum_{l=1}^m \frac{Q_k Q_l}{2b} (-B'_{kl}), \quad (3)$$

where

$$\begin{aligned} B'_{kl} = & \frac{1}{D_i} \sum_{n=0}^{\infty} \frac{(n+1)(D_0 - D_i)}{(n+1)D_0 + nD_i} \left[\left(\frac{r_k}{b}\right)^n \left(\frac{r_l}{b}\right)^n \left(\frac{1}{r_k^2}\right) \right. \\ & \times n x_k P_n(\cos \theta_{kl}) \\ & + \left(\frac{r_k}{b}\right)^n \left(\frac{r_l}{b}\right)^n \left[\frac{(n+1)}{(\cos^2 \theta_{kl} - 1)} [P_{n+1}(\cos \theta_{kl}) \right. \\ & \left. \left. - \cos \theta_{kl} P_n(\cos \theta_{kl})] \right] \frac{1}{r_k} \left(\frac{x_l}{r_l} - \frac{x_k}{r_k} \cos \theta_{kl} \right) \right] \end{aligned}$$

if k and l are different, and

$$B'_{kl} = \frac{1}{D_i} \sum_{n=0}^{\infty} \frac{(n+1)(D_0 - D_i)}{(n+1)D_0 + nD_i} \left(\frac{r_k}{b}\right)^n \left(\frac{1}{r_k^2}\right) x_k (-1)^n \quad (4)$$

if $k=l$.

We can use these forces to propagate the equations of motion for systems consisting of collections of molecules with partial atomic charges at sites located within the molecules. The practicality of the method depends on how many terms from Eq. (2) must be retained in order to construct a reasonable approximation to the reaction fields generated by the evolving charge distribution. This in turn will depend on such physical parameters of the problem as the size of the central sphere and the asymmetry of the charge distribution. We call the central sphere the Kirkwood sphere. We must decide how to treat molecules which approach the boundary; molecules can either be reflected or pass through the spherical surface. In the simulations of liquid water and ions in water described below, we allow the solvent to pass through the spherical surface.

This choice avoids the artificial structure that would be induced in the solvent by a reflecting boundary, but it necessitates the introduction of a cutoff, described below, which is applied to the reaction field forces on solvent molecules approaching the surface of the spherical cavity.

A series of molecular dynamics simulations of liquid water, as well as simulations including one or two ions in water, was completed, for which the reaction field forces were calculated using Eqs. (3) and (4). The SPC water model was employed for the direct Coulomb and van der Waals interactions between water molecules.¹⁶ We have previously analyzed the orientational structure (Kirkwood factor G_k) of SPC water using both the conventional dipolar reaction field³ and the Ewald sum¹² methods to treat the long range interactions. The orientational correlation functions provide a sensitive test of the effect of the long range interaction model on the dielectric response of the liquid. All simulations were performed in a cubic box containing 345 water molecules. In a few simulations, the box also contained one or two ions. The ion-water and ion-ion potentials consisted of a 12-6 potential for the van der Waals interactions and a Coulombic term for the electrostatics. The van der Waals parameters corresponding to that of a chloride ion were taken from the work of Jorgensen *et al.*¹⁷ The box length was 21.72 Å in all simulations. The Verlet algorithm was employed to integrate the equations of motion with a 2 fs time step.¹⁸ The SHAKE¹⁹ algorithm was employed to preserve the rigid geometry of the SPC monomers. The average temperature was 300 K and was rescaled periodically to prevent temperature drift.

The nonbonded interactions were calculated in the following way: A sphere of radius 10.85 Å centered at the origin was inscribed inside the cubic box. Water molecules both inside and outside the sphere interacted with each other via the SPC potential with a cutoff $R_c=10.85$ Å. In addition, water molecules inside the sphere experienced a reaction field potential and force computed using Eqs. (3) and (4). The spherical boundary which defines the reaction field cavity is an artificial construct. Because the reaction field contribution to the forces acting on the charges inside the Kirkwood sphere become very large as the charges approach the boundary, a cutoff on the GRF forces acting on molecules was introduced at a distance of 2 Å from the spherical surface. In simulations with 345 water molecules, the time required per iteration of the MD algorithm with a three term expansion of the generalized reaction field applied to the water molecules inside the cavity is about 50% greater than the time per iteration using the conventional dipolar reaction field. For large enough N , the time per iteration will scale with the number of terms included in the GRF expansion of the reaction field force [Eq. (3)].

For the neat water simulations, the dielectric constant ϵ_0 was calculated from the mean square total dipole moment correlation function of the water inside the Kirkwood sphere using the relation²⁰

$$\frac{(2\epsilon_0 + 1)(\epsilon_0 - 1)}{9\epsilon_0} = \frac{4\pi\rho\mu^2}{9kT} G_K, \quad (5)$$

TABLE I. The computed G_k and ϵ_0 for simulations employing increasing numbers of multipoles in the generalized reaction field. N is the number of terms retained in Eqs. (3) and (4), G_k is the orientational structure factor [Eq. (5)], and ϵ_0 is the dielectric constant. The length of the simulation is the number of molecular dynamics steps with step size 0.002 ps.

Simulation	N	Length	G_k	ϵ_0
<i>a</i>	1	29 000	15.6 ± 4.20	398.7
<i>b</i>	2	98 500	3.7 ± 0.19	94.6
<i>c</i>	3	132 000	3.0 ± 0.66	76.7
<i>d</i>	4	138 500	3.2 ± 0.66	81.8
<i>e</i>	6	100 000	2.8 ± 0.79	72.3

where $G_K = \langle M^2 \rangle / (N\mu^2)$ and $\langle M^2 \rangle$ is the mean squared total dipole moment of the molecules inside the Kirkwood sphere. This relation can be used to determine ϵ_0 from G_K if D_0 , the dielectric constant of the continuum is chosen to be close to ϵ_0 . In our simulations, we chose $D_0 = 80$, approximately the dielectric constant of SPC water.³

To investigate the thermodynamics of the generalized reaction field model, a series of simulations of the charging free energy of a single chloride ion in water were carried out at distances $R = 0, 3, 5,$ and 7 \AA from the origin of the Kirkwood sphere. The adiabatic charging method was employed in these free energy simulations.²¹ Simulations were also carried out for the charging free energy of two ions in the Kirkwood sphere separated by 10 \AA in two simulations and by 14 \AA in another. The charging was completed in 40 000 steps in each of the free energy simulations.

As a test of the sensitivity of the reaction field energy to the number of terms retained in the GRF expansion, we have compared the reaction field energies in two simulations in which we have retained the first three and first six terms, respectively (excluding the $n=0$ term), in the expansion of the reaction field forces used in the propagation of the trajectory. The average total reaction field energy in the Kirkwood sphere is -29.1 kcal/mol for the trajectory propagated with the three term expansion and -26.5 kcal/mol for the trajectory propagated with the six term expansion. The average reaction field energy is about 4% of the average total potential energy of the water in the Kirkwood sphere. As an additional test of the sensitivity of the reaction field energy to the number of terms retained in the expansion [Eq. (2)], we have analyzed the configurations generated from a trajectory with $n=6$ terms retained in the GRF forces, including up to $n=20$ terms in the analysis of the reaction field energy. The reaction field energy increases by $\sim 3\%$ when the energy is calculated including the first 20 terms in the expansion compared with the reference energy calculated with the first six terms that were also used to propagate the trajectory.

III. RESULTS AND DISCUSSION

A. Dielectric properties of water with the generalized reaction field

We have completed five simulations of liquid water with the GRF model. The simulations, labeled *a-e*, respectively, in Table I correspond to including the first one, two,

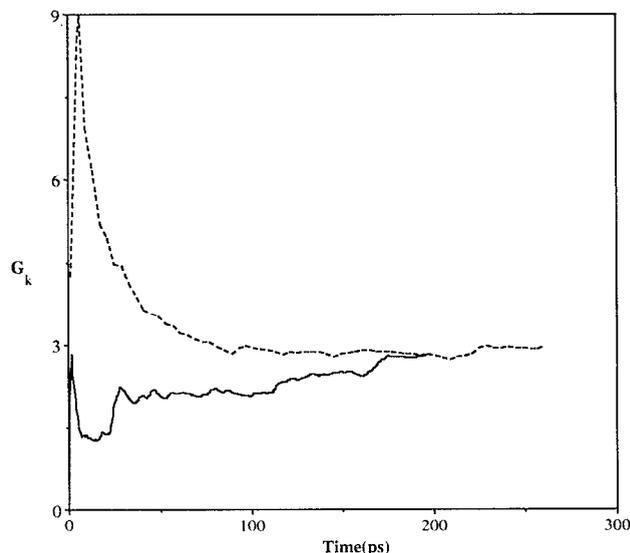


FIG. 1. The cumulative G_k factor for simulations *c* and *e* generated from simulations employing three (dotted line) or six (solid line) terms in the generalized reaction field equations (3) and (4).

three, four, and six terms in the GRF forces [Eqs. (3) and (4)], excluding the $n=0$ term, which is independent of the positions of the charges in the sphere and is zero for neutral systems. For a charged system, the $n=0$ term corresponds to the Born energy [$\Delta G = (Q_{\text{tot}}^2/2b)(1/D_0 - 1)$].²² The buildup with time of the cumulative G_k factor for simulations *c* and *e* are shown in Fig. 1. We note that the convergence of G_K appears to be several times faster with GRF boundary conditions than in simulations where the conventional reaction field is employed.

The G_k factor calculated from the simulation which included only the dipolar contribution ($n=1$) to the GRF force is much too large ($G_k = 15.6$). Too much orientational order is induced when the reaction field is truncated at the dipole term. This result contrasts with that obtained from the conventional reaction field method, which also only includes the dipole reaction field term. Of course, the dipole reaction field is not employed in the same way in the two models. For both models, the force due to the dipolar reaction field is $\mathbf{F}_{\text{RF}} = \{[2(\epsilon_{\text{RF}} - 1)]/[2\epsilon_{\text{RF}} + 1]\} \mathbf{M}/R_C^3$. In the GRF model, however, \mathbf{M} is the total dipole moment of the water molecules in the central sphere, which is fixed in space, while in the conventional reaction field method, a different sphere surrounds each molecule and moves with it. The reaction field acts to increase \mathbf{M} , and \mathbf{M} in turn increases the reaction field forces. In the generalized reaction field model, a feedback is established between \mathbf{M} and \mathbf{F}_{RF} , which results in large values of \mathbf{M} and M^2 . In the conventional reaction field model, however, the different \mathbf{M}_i 's of each sphere vary in magnitude and direction, and therefore cancel each other somewhat, resulting in much smaller $\langle M^2 \rangle$ and a smaller dielectric constant.¹⁴

It is instructive to examine the spatial variation of the reaction field potential energies and forces generated by a point dipole and a point quadrupole located at the origin of

a spherical cavity. This can be accomplished by constructing a system in which a single charge q is located at the position $(0,s,0)$, i.e., removed by a distance s from the origin along the y axis, and enclosed in a sphere of radius a with $\epsilon=1$ inside and $\epsilon=\epsilon_{\text{RF}}$ outside, with azimuthal symmetry about the y axis. It has been shown that the reaction field due to this displaced charge can be represented by an infinite series, each term of which is the reaction field due to a particular multipole located at the origin.²³ For the point dipole, the reaction field energy and force are

$$U_{\text{RF}} = -\frac{2(\epsilon_{\text{RF}}-1)\mu}{2\epsilon_{\text{RF}}+1} \frac{\mu}{a^3} r \cos \theta = -\frac{2(\epsilon_{\text{RF}}-1)\mu}{2\epsilon_{\text{RF}}+1} \frac{\mu}{a^3} y, \quad (6a)$$

$$\mathbf{F}_{\text{RF}}^y = \frac{2(\epsilon_{\text{RF}}-1)\mu}{2\epsilon_{\text{RF}}+1} \frac{\mu}{a^3} \mathbf{j}, \quad \mathbf{F}_{\text{RF}}^x = 0, \quad \mathbf{F}_{\text{RF}}^z = 0. \quad (6b)$$

For the point quadrupole,

$$U_{\text{RF}} = -\frac{3(\epsilon_{\text{RF}}-1)Q_M}{3\epsilon_{\text{RF}}+2} \frac{Q_M}{a^5} r^2 \frac{3\cos^2\theta-1}{2} \\ = -\frac{3(\epsilon_{\text{RF}}-1)Q_M}{3\epsilon_{\text{RF}}+2} \frac{Q_M}{2a^5} (-x^2+2y^2), \quad (7a)$$

$$\mathbf{F}_{\text{RF}}^x = -\frac{3(\epsilon_{\text{RF}}-1)Q_M}{3\epsilon_{\text{RF}}+2} \frac{Q_M}{2a^5} (2x)\mathbf{i}, \quad (7b)$$

$$\mathbf{F}_{\text{RF}}^y = \frac{3(\epsilon_{\text{RF}}-1)Q_M}{3\epsilon_{\text{RF}}+2} \frac{Q_M}{2a^5} (4y)\mathbf{j}, \quad \mathbf{F}_{\text{RF}}^z = 0,$$

where $Q_M = qs^2$.

For the point dipole, the reaction field force is parallel to the direction of the total dipole moment in the sphere and is independent of position. The dipole reaction field force acting on charges within the sphere is therefore the same in magnitude and direction at any point within the Kirkwood sphere. The reaction field forces generated by a point quadrupole, however, increase with distance from the center of the sphere and are positive for $x,y < 0$ and negative for $x,y > 0$. When the quadrupolar reaction field forces are included in the simulation (Table I, simulation d), this produces a significant reduction in the total dipole moment of the system. We now consider the effect on G_K and ϵ_0 as more terms from Eq. (3) are included in the generalized reaction field.

The G_k factor and dielectric constant calculated from simulations including terms up to the dipolar, quadrupolar, octopolar, hexadecapolar, and 64-polar reaction fields, respectively (simulations a – e), are listed in Table I. The G_K factor and ϵ_0 are substantially reduced when the quadrupole term is added, as discussed above. In particular, G_K decreases from 15.6 to 3.7, bringing ϵ_0 into qualitative agreement with the results of previous simulations using the conventional reaction field³ and the Ewald sum methods.¹² When additional reaction field terms are included, there is closer quantitative agreement with previous results and with experiment. Simulations c and d demonstrate that for the sphere size used in these simulations, values of G_K

TABLE II. Ion charging simulations performed with the generalized reaction field. N_{ion} is the number of ions charged up, N is the number of terms retained in the generalized reaction field [Eqs. (3) and (4)], R is the distance of the ions from the origin, and ΔG is the computed charging free energy (in kcal/mol). $N=0$ implies that the GRF was not employed in the simulation (as in simulations k and l).

Simulation	N_{ion}	N	R	ΔG
f	1	3	0	-73.84
g	1	3	3	-74.23
h	1	3	5	-78.81
i	1	3	7	-88.56
j	1	6	7	-87.01
k	1	0	0	-58.75
l	2	0	± 5	-78.86
m	2	3	± 5	-125.56
n	2	3	± 7	-154.61
o	2	6	± 7	-150.00

and ϵ_0 characteristic for SPC water at 300 K are obtained when the first three terms in the reaction field expansion are included. As a check on the convergence of G_k and ϵ_0 , we performed a simulation with six terms in the reaction field expansion. The results are listed in Table I, simulation e . The orientational correlation function and dielectric constant evaluated from simulations including the first three GRF terms agree with those evaluated from a simulation including the first six terms in the GRF expansion to within the standard deviation of these quantities.

B. Thermodynamics with the generalized reaction field

The development of free energy simulation methods has attracted considerable attention in organic and biochemistry.^{24–26} Many chemical problems to which one would like to apply free energy simulations involve changes in the ionization state of one or more groups. One expects that for these problems, the numerical results will be particularly sensitive to the approximations used to treat the long range interactions. To test the behavior of the GRF model in free energy simulations, we have completed a series of free energy simulations corresponding to the charging up of one or two ions in water. The results are summarized in Table II. In simulations f – j , the charging free energy of a single ion was computed at different distances R of the ion from the center of the Kirkwood sphere corresponding to $R=0, 3, 5,$ and 7 \AA . When the ion is placed at the center of the Kirkwood sphere (simulation f), we compute a charging free energy $\Delta G = -73.84 \text{ kcal/mol}$ with the GRF model. This value agrees with the free energy for “growing” a chloride ion computed from simulations with a spherical cutoff if a Born energy correction is also added to account for the free energy of the polarized solvent beyond the cutoff. The Born energy correction is contained naturally in the GRF model; it is simply the $n=0$ term in the reaction field expansion. Note that for a sphere with radius 10.85 \AA , the Born correction corresponds to 20% of the total free energy (compare the ion charging free energy of simulation f using the GRF method to that of simulation k with a spherical cutoff in Table II).

The large correction which must be applied to free energy simulations that use a cutoff illustrates that the long range interactions make a very significant contribution to the charging free energy.

Another test of the GRF model is the sensitivity of the ion charging free energy to the proximity of the ion to the boundary of the Kirkwood sphere. In our model system, the Kirkwood sphere is filled with explicit water surrounded by a dielectric continuum model for the same solvent. Therefore, we would like the charging free energy to be insensitive to the location of the ion within the Kirkwood sphere, since for this problem, the spherical boundary is strictly an artificial device; both the inner and outer solvent regions are supposed to represent the same liquid. We have examined this question in simulations *g-j*. From simulation *g* of Table II, the ion charging free energy is calculated to change by only 0.5% when the ion is moved 3 Å from the origin. However, as the ion approaches the boundary more closely, the charging free energy continues to become more attractive, increasing by 6.7% when the ion is moved 5 Å from the center and 20% when the ion is moved 7 Å from the center. Further studies are needed to distinguish whether the apparent sensitivity of the ion charging free energy to the location of the boundary is the result of the truncation of the reaction field expansion at a small number of terms, or is rather an inherent feature of our model which contains an artificial, sharp dividing surface between explicit and implicit solvent regions. We will report on this in a future communication. We note, however, that there is little change in the solvation free energy of a single ion at 7 Å from the origin when the number of terms retained in the expansion is increased from three to six (compare simulations *i* and *j* in Table II).

There are a few different routes that can be taken to extract a dielectric constant from a liquid simulation. The standard route involves the calculation of orientational correlation functions (G_k factor) of the pure liquid and the use of statistical mechanical connection formulas.²⁰ One can also calculate the dielectric constant from the slope of the ion-ion potentials of mean force. The sensitivity of the slope to the model used for the long range interactions has been noted.^{4,5} A third approach is to compare the charging free energy for one ion with that for the charging free energy of two ions separated by a distance R .²⁷ The dielectric constant is related to the charging free energies by

$$\Delta\Delta G = \Delta G(\text{charging two ions with separation } R) - 2\Delta G(\text{charging one ion}) = C/(\epsilon R), \quad (8)$$

where the constant C is 332 kcal/mol Å. Equation (6) provides a formula for calculating the dielectric constant ϵ which is an extremely sensitive test of the ability of the simulation to reproduce the thermodynamic and dielectric behavior of the infinite system. For a high dielectric liquid, the correct result requires that there be a cancellation between the calculated polarization energies between two simulations whose charge distributions have very different symmetries. It should be noted that for many practical applications of free energy simulations, the symmetry of

the charge distribution is not very different in the initial and final states. We have completed four charging simulations of two ions, labeled *l*, *m*, *n*, and *o* in Table II. In simulation *l*, the two ions are located on the x axis at ± 5 Å and a spherical cutoff $R_{\text{cut}} = 10.85$ Å is used for the ion-water interactions. In simulations *m*, *n*, and *o*, the GRF model is used for the long range interactions. The two ions are separated by 10 and 14 Å in simulations *m* and *n*, *o*, respectively. At an ion separation of 10 Å, the charging free energy is -78.9 kcal/mol with a spherical cutoff and -125.6 kcal/mol using the generalized reaction field model. In a high dielectric liquid, the direct interaction between the ions separated by a distance R is almost exactly cancelled by an "excess" solvent polarization relative to the total solvent polarization of the isolated ions. Comparing twice the charging free energy of one ion with the charging free energy of two ions separated by 10 Å, we do not observe the correct cancellation of the direct Coulomb interaction either in the simulations with a spherical cutoff (simulations *k* and *l*) or with the GRF model (e.g., simulations *h* and *m*). For example, consider the results of the free energy simulations including the generalized reaction field. The polarization energy of the solvent in the presence of two ions separated by 10 Å is obtained by subtracting the direct Coulomb energy of the ions ($+33.2$ kcal/mol) from the charging free energy listed in Table II (-125.6 kcal/mol). The solvent polarization energy for two ions (at $R=10$ Å) is -158.8 kcal/mol, while twice the polarization energy of one ion is $2 \times -78.8 = -157.6$ kcal/mol. The effective dielectric constant calculated using Eq. (8) is very close to 1. This result, which is very similar to the results we obtain in free energy simulations using a simple cutoff, is of course incorrect. The development of a reaction field model (or any explicit solvent model) which can produce the correct cancellation between free energy simulations with such different charge symmetries is a formidable problem. We are currently examining the way in which the cancellation depends on both the system size and the number of terms included in the expansion of the GRF forces.

IV. CONCLUSIONS

The development of models to treat long range interactions in condensed phase simulations is a problem of longstanding interest.²⁸ In contrast to the Ewald sum method for handling the Coulomb potential, reaction field models do not impose an artificial periodicity on systems which are not inherently periodic. Reaction field models do contain an artificial boundary which divides the system into explicit and implicit solvent regions. The use of a spherical boundary as in the GRF model has the advantage that the reaction field forces can be expressed as a series expansion. For an irregular shaped boundary, the reaction field forces would have to be computed numerically.²⁹

Orientalional correlation functions for high dielectric liquids such as water are very sensitive to the way in which the long range Coulomb interactions are treated. We find in simulations of liquid water with the generalized reaction field that the Kirkwood G_k factor and dielectric constant

which depend on the orientational correlations have the correct values for water when we include the first three terms in the multipole expansion of the reaction field in the equations of motion. We have used free energy simulations of one ion and two ions in water as a way to test the thermodynamic response of the GRF model to a charge perturbation. When the ion is close to the center of the sphere, the correct value for the charging free energy is obtained, but the polarization energy becomes too negative when the ion is moved close to the boundary of the Kirkwood sphere. As the ion is moved towards the boundary, higher order multipoles are generated in the expansion of the charge distribution about the origin which need to be retained in the reaction field calculation. We are planning a more systematic study of the relationship among the ion position, the number of terms retained in the GRF expansion, and the charging free energy. In any case, free energy simulations of a single ion in water do not provide a very sensitive test of the long range interaction model. For a single ion in water, the correct charging free energy is obtained even when the Coulomb interactions are subjected to a spherical truncation if a simple Born correction is applied.^{30,31}

The screening of electrostatic interactions between two charged groups in condensed phase simulations provides an important benchmark for any long range interaction model. The usual way to perform this test is to analyze the asymptotic slope of the ion-ion potential of mean force. Spherical truncation clearly leads to bizarre behavior.^{4,5} In contrast, when Ewald sums are used physically reasonable results which agree with the dielectric continuum potential of mean force are obtained.^{5,32} However, this may be a fortuitous result, because for the Ewald sum model, the direct Coulomb force between two ions approaches zero as their separation approaches half the box length. For a physically correct model of an unbounded dielectric medium, the small limiting slope in the ion-ion potential of mean force at ion separations of $\sim 10 \text{ \AA}$ results from the cancellation of a large direct Coulomb interaction by an almost completely compensating excess solvent polarization term. To determine whether the Ewald sum model captures the correct physics of electrostatic screening in high dielectric liquids, additional studies of the effect of the box size on ion-ion potentials of mean force are needed.

We have compared free energy simulations of one ion in water with simulations of two ions in water in order to test the electrostatic screening between charged groups with the GRF model. For the limited set of GRF model parameters studied, we do not observe the correct cancellation between the direct Coulomb energy of the ions and the "extra" solvent polarization. A more systematic study of electrostatic screening with the GRF model is underway.

Much of the present effort in molecular modeling is centered on the description of solvation phenomena; the modeling of solvent effects on electrostatic interactions is of particular importance. Simulations with explicit solvent should provide a powerful tool for developing a deeper

understanding of the connections between the structural and thermodynamic behavior of hydrating solvent as well as developing implicit solvation models which are computationally more efficient. However, it has proven surprisingly difficult to simulate such simple and important phenomena as changing the ionization state of chemical groups in high dielectric media using explicit solvent models.³³ The development of reliable models for treating the long range Coulomb interactions in simulations of electrostatic processes with explicit solvent models remains a challenge.

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- ¹F. H. Stillinger and A. Rahman, *J. Chem. Phys.* **60**, 1545 (1974).
- ²M. R. Pangali, M. Rao, and B. J. Berne, *Mol. Phys.* **40**, 661 (1980).
- ³H. E. Alper and R. M. Levy, *J. Chem. Phys.* **91**, 1242 (1989).
- ⁴S. Huston and P. Rossky, *J. Phys. Chem.* **93**, 7888 (1989).
- ⁵J. S. Bader and D. Chandler, *J. Phys. Chem.* **96**, 6423 (1992).
- ⁶P. E. Smith and B. M. Pettitt, *J. Chem. Phys.* **95**, 8430 (1991).
- ⁷H. Schreiber and O. Steinhauser, *Biochemistry* **31**, 5856 (1992).
- ⁸H. Schreiber and O. Steinhauser, *Chem. Phys.* **168**, 75 (1992).
- ⁹J. A. Barker and R. O. Watts, *Mol. Phys.* **26**, 789 (1973).
- ¹⁰M. P. Allen and D. J. Tildesley, *Computer Simulation of Liquids* (Oxford University, Oxford, 1987), Sec. 5.5.
- ¹¹M. Neumann, O. Steinhauser, and S. Pawley, *Mol. Phys.* **52**, 97 (1984).
- ¹²M. Belhadj, H. E. Alper, and R. M. Levy, *Chem. Phys. Lett.* **179**, 13 (1991).
- ¹³H. Schreiber and O. Steinhauser, *J. Mol. Biol.* **228**, 909 (1992).
- ¹⁴G. King and A. Warshel, *J. Chem. Phys.* **91**, 3647 (1989).
- ¹⁵C. Tanford and J. G. Kirkwood, *J. Am. Chem. Soc.* **79**, 5333 (1957).
- ¹⁶H. J. C. Berendsen, J. P. M. Postma, W. F. Van Gunsteren, and J. Hermans, in *Intermolecular Forces*, edited by B. Pullman (Reidel, Dordrecht, 1981), p. 331.
- ¹⁷W. L. Jorgensen, J. F. Blake, and J. K. Buckner, *Chem. Phys.* **129**, 193 (1989).
- ¹⁸L. Verlet, *Phys. Rev.* **159**, 98 (1967).
- ¹⁹J. Ryckaert, G. Ciccotti, and H. Berendsen, *J. Comp. Phys.* **23**, 327 (1977).
- ²⁰M. Neumann, *Mol. Phys.* **50**, 841 (1983).
- ²¹U. C. Singh, F. K. Brown, P. A. Bash, and P. A. Kollman, *J. Am. Chem. Soc.* **109**, 1607 (1987).
- ²²M. Born, *Z. Phys.* **1**, 45 (1920).
- ²³C. J. F. Bottcher, *Theory of Electric Polarization*, 2nd ed. (Elsevier, Amsterdam, 1973).
- ²⁴W. Jorgensen, *Acc. Chem. Res.* **22**, 184 (1989).
- ²⁵D. L. Beveridge and F. M. DiCapua, *Annu. Rev. Biophys. Biophys. Chem.* **18**, 431 (1989).
- ²⁶T. P. Straatsma and J. A. McCammon, *Annu. Rev. Phys. Chem.* **43**, 407 (1992).
- ²⁷R. M. Levy, M. Belhadj, and D. B. Kitchen, *J. Chem. Phys.* **95**, 3627 (1991).
- ²⁸See NRCC Proceedings No. 9, *The Problem of Long-Range Forces in Computer Simulation of Condensed Media*, edited by D. Ceperley (Lawrence Berkeley Laboratory, Berkeley, 1980).
- ²⁹M. K. Gilson, M. E. Davis, B. A. Luty, and J. A. McCammon, *J. Phys. Chem.* **97**, 3591 (1993).
- ³⁰J. K. Buckner and W. L. Jorgensen, *J. Am. Chem. Soc.* **111**, 2507 (1989).
- ³¹F. Hirata, P. Redfern, and R. M. Levy, *Int. J. Quantum Chem. Biol. Symp.* **15**, 179 (1989).
- ³²E. Guardia, R. Rey, and J. A. Padro, *J. Chem. Phys.* **95**, 2823 (1991).
- ³³F. S. Lee and A. Warshel, *J. Chem. Phys.* **97**, 3100 (1992).

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