Self-consistent treatment of the local dielectric permittivity and electrostatic potential in solution for polarizable macromolecular force fields

Sergio A. Hassan^{a)}

Center for Molecular Modeling, DCB/CIT, National Institutes of Health, U.S. DHHS, Bethesda, Maryland 20892, USA

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A self-consistent method is presented for the calculation of the local dielectric permittivity and electrostatic potential generated by a solute of arbitrary shape and charge distribution in a polar and polarizable liquid. The structure and dynamics behavior of the liquid at the solute/liquid interface determine the spatial variations of the density and the dielectric response. Emphasis here is on the treatment of the interface. The method is an extension of conventional methods used in continuum protein electrostatics, and can be used to estimate changes in the static dielectric response of the liquid as it adapts to charge redistribution within the solute. This is most relevant in the context of polarizable force fields, during electron structure optimization in quantum chemical calculations, or upon charge transfer. The method is computationally efficient and well suited for code parallelization, and can be used for on-the-fly calculations of the local permittivity in dynamics simulations of systems with large and heterogeneous charge distributions, such as proteins, nucleic acids, and polyelectrolytes. Numerical calculation of the system free energy is discussed for the general case of a liquid with field-dependent dielectric response. [<http://dx.doi.org/10.1063/1.4742910>]

I. INTRODUCTION

Accurate modeling of liquid interfaces is important in many areas of science and technology, e.g., in the study of biological membranes, aqueous electrolyte films, electrical double layers, polyelectrolytes, and colloidal suspensions. The predicted behavior of proteins and nucleic acids is particularly sensitive to the treatment of the liquid interface, and inaccurate modeling can lead to large errors in the calculation of energies and forces. Prediction of biophysical properties, such as redox potentials, pKa shifts, dissociation rates, and binding modes and energies, can thus be compromised. Electrostatic interactions are one of the forces that determine biological function at the molecular scale, so interfacial properties that control electrostatic effects must be correctly described. In aqueous solutions the spatial variations of the structure and dynamics of water molecules at the solute/liquid interfaces are partially determined by the water–water and solute–water hydrogen-bond network, which lead to spatial variations of the density, ρ , and the dielectric permittivity, ϵ . Since the solute can affect the behavior of one or more layers of water at the interface,^{1–4} bulk-liquid properties are recovered at a certain distance from the surface, depending on its size, shape, topography, and charge distribution. Consequently, the macroscopic functions ρ and ϵ are highly system-dependent and difficult to characterize theoretically. Since the electrostatic potential ϕ generated by a solute is determined by ϵ , which is in turn determined by the field, solution of the electrostatic problem requires self-consistent determination of ϵ

and ϕ . This problem is usually avoided in biomolecular electrostatics, where the form of ϵ is assumed and the Poisson equation (PE) is then solved numerically. The most common approach imposes a sharp dielectric boundary between the solute and the liquid. This simplification is known to be inadequate at the nanometer scale as it introduces spurious forces in dynamics simulations⁵ and other artifacts.⁶ To overcome some of these problems a variety of smoothing dielectric functions have been proposed,^{5,7,8} usually based on geometric considerations. Efforts to incorporate some physical rationale in the determination of these functions have more recently been reported.⁹ However, the fact remains that the physics of aqueous interfaces is rather complicated, and has not yet been properly represented in biomolecular electrostatics. Similar simplifications are also common in quantum mechanical continuum solvent models¹⁰ despite that solutes of interest are usually comparable in size to those of the liquid molecules and their spatial correlations lengths. The relation between electron structure and liquid structure has nonetheless been discussed by several authors.^{11,12}

The simplified models discussed above have been the standard in bio-macromolecular electrostatics, and have been applied to systems with large surface charges, including nucleic acids and lipid membranes. Since the earliest attempts at solving the PE for solutes of arbitrary shape and charge distributions,^{13,14} increasingly sophisticated algorithms have been developed to improve accuracy and computational efficiency.^{15–17} Comparatively little effort has been devoted to improving the physical description of the system, especially in cases where large charges are present at the molecular interface. Recent developments have suggested possible directions for improvements.^{18–20} In the approach

^{a)} Author to whom correspondence should be addressed. Electronic mail: hassan@mail.nih.gov.

used here¹⁸ the liquid is assumed to be composed of polar and polarizable molecules that react to the field created by the solute. This treatment is based on the classical theory of dielectrics, which despite its well-established foundations, simplicity, and potential for unlimited improvability, has traditionally been ignored in biomolecular electrostatics, presumably due to computational cost. The method presented here is an improvement upon conventional continuum applications, and is particularly useful for systems with large and heterogeneous surface charges, or when charge redistribution occurs. This latter feature is important in quantum chemical structure optimization, and in light of recent development in biomolecular polarizable force fields (e.g., see Ref. 21).

II. DIELECTRIC MODEL OF THE LIQUID

Several effects at the interface contribute to the local dielectric response of the liquid. The density determines the average amount of polar/polarizable material that can locally respond to the field, while dielectric saturation, short-range water–water and solute–water orientational correlations, non-local correlations, and the anisotropy of the reaction field due to the exclusion of liquid by the solute, further modulate the local dielectric response.^{22,23} The coexistence of these effects results in a complicated structure/dynamic behavior, which is reflected in the functional form of the static and dynamic dielectric permittivity of the liquid. Statistical mechanics naturally describes these (coupled) effects based on the fundamental molecular interactions, as represented in the Hamiltonian of the system. In contrast, a phenomenological continuum model requires that these effects be incorporated. An approximation based on local properties of the liquid has been reported previously,¹⁸ which is valid for any polar/polarizable medium. The liquid is composed of molecules with isotropic polarizability α and permanent dipole moments of magnitude μ . The polarization field $\mathbf{P}$ at a position $\mathbf{r}$ in the liquid is separated into two local contributions, $\mathbf{P}(\mathbf{r}) = \rho(\mathbf{r})\alpha\mathbf{E}_i(\mathbf{r}) + \rho(\mathbf{r})\langle\boldsymbol{\mu}\rangle$, where $\langle\boldsymbol{\mu}\rangle$ is the Boltzmann average of the dipole moment orientations at position $\mathbf{r}$, and $\mathbf{E}_i$ is the microscopic field acting on a liquid molecule at $\mathbf{r}$. The local static permittivity $\varepsilon(\mathbf{r})$ is obtained by solving numerically the equation¹⁸

$$\frac{[\varepsilon(\mathbf{r}) - 1][1 - \alpha f(\mathbf{r})]}{4\pi\rho(\mathbf{r})} = \frac{3\alpha\varepsilon(\mathbf{r})}{[2\varepsilon(\mathbf{r}) + 1]} + \frac{\mu}{E(\mathbf{r})} L \left\{ \frac{3\varepsilon(\mathbf{r})\mu}{kT[1 - \alpha f(\mathbf{r})][2\varepsilon(\mathbf{r}) + 1]} E(\mathbf{r}) \right\} \quad (1)$$

at each point in space, where $L(x)$ is the Langevin function; k is the Boltzmann constant; and T is the absolute temperature. The function f is related to the magnitude of the local reaction field, which is assumed to be isotropic everywhere in the liquid (cf. Sec. VI), and is given by $3f(\mathbf{r})/8\pi = \rho(\mathbf{r})[\varepsilon(\mathbf{r}) - 1]/[2\varepsilon(\mathbf{r}) + 1]$; $E(\mathbf{r})$ is the magnitude of the macroscopic (Maxwell) field at position $\mathbf{r}$. The local density $\rho(\mathbf{r})$ in Eq. (1) can be obtained from the classical theory of non-uniform fluids.²³ In particular, the integral equation form of ρ obtained from density functional theory is given by²³

$$\rho(\mathbf{r}) = \eta \exp[-\beta U(\mathbf{r}) + c[\rho(\mathbf{r}); \mathbf{r}]], \quad (2)$$

where η depends on the temperature and the mass of the liquid molecules; U is the interaction potential energy between the solute and the liquid molecules at position $\mathbf{r}$; and c is the single-particle direct correlation function, related to the Ornstein–Zernike two-particle direct correlation function $c^{(2)}$ through $c[\rho(\mathbf{r}); \mathbf{r}] = \int \rho(\mathbf{r}')c^{(2)}(\mathbf{r}, \mathbf{r}')d\mathbf{r}'$. Because direct numerical solutions can be obtained only in limited cases, efforts have been directed at calculating ρ through suitable analytical approximations of c or $c^{(2)}$. These include hypernetted chain, Percus–Yevick, and mean-spherical approximation; and also the reference interaction site model (RISM) and its three-dimensional extension (3D-RISM), among others. Alternative solutions can be obtained through a combination of theory and simulations;²⁴ this method provides an explicit representation of short-range correlations, which may lead to more realistic density profiles at the critical interfacial region. A more recent approach to incorporate short-range correlations in ρ in the context of the PE models water–water interactions through isotropic Yukawa potentials.¹⁹

Conceptually, the method described in this paper does not depend on the particular functional form of ρ , so the simplest approximation is used to illustrate. In this case liquid–liquid pair correlations are described by a local mean field,²³ thus

$$\rho(\mathbf{r}) = \rho_0 \exp[-\beta V_{eff}(\mathbf{r})], \quad (3)$$

where V_{eff} is the effective solute–liquid interaction potential energy, modeled here as a Lennard–Jones type function,¹⁸ i.e.,

$$V_{eff}(\mathbf{r}) = \sum_{I=1}^N \xi_I [(\sigma_I/r_I)^{12} - 2(\sigma_I/r_I)^6], \quad (4)$$

where N is the number of atoms in the solute, and $r_I = |\mathbf{r} - \mathbf{r}_I|$, with $\mathbf{r}_I$ being the nuclei coordinates; ξ and σ are parameters that determine the heights and positions of the density peaks. Upon careful parameterization, this barometric-law approximation provides a crude but reasonable representation of the spatial density distributions of water in the vicinity of amphiphilic molecules obtained from dynamics simulations.¹⁸

Equation (1) converges to known limits:¹⁸ setting $\mu = 0$, it yields the dielectric permittivity of a non-polar, polarizable liquid, which is equal to the optical permittivity ε_∞ of a polar and polarizable liquid. For a spatially uniform liquid with density $\rho_0 = 1/\nu$ (ν is the molecular volume) the Lorentz–Lorenz relation, $\alpha/\nu = 3(\varepsilon_\infty - 1)/4\pi(\varepsilon_\infty + 2)$, is obtained. Finally, the Onsager equation, $4\pi\mu^2/9kTv = (\varepsilon_0 - \varepsilon_\infty)(2\varepsilon_0 + \varepsilon_\infty)/\varepsilon_0(\varepsilon_\infty + 2)^2$, is recovered in the limit of weak fields, or far from the solute where the liquid is not perturbed. Electrostriction can be represented^{25,26} by local changes in ν , but its dependence on the field strength is not modeled here. Although electrostriction does not play a major role in the dielectric response of the liquid, it has a measurable effect in the thermodynamics of solvation.²⁶ Additional improvements of Eq. (1) are discussed in Sec. VI, but two important corrections can be mentioned here: short-range liquid–liquid orientational correlations could be introduced *ad hoc* by changing μ^2 to $\mu^2 g_K$ in Eq. (1), where g_K is the Kirkwood factor.²⁷ With this modification Eq. (1) converges to the Kirkwood–Fröhlich equation. More generally, g_K depends on E , which is an important correction in the vicinity of charges or in regions

of high electric fields, in general.²⁸ This dependence of g_K on E is one manifestation of the short-range *solute–liquid* orientational correlation that controls the behavior of the liquid molecules at the interface; effects of solute-water hydrogen bonds should also be included in g_K to properly model the dielectric response of the first hydration shell (cf. Sec. VI).

III. SELF-CONSISTENT CALCULATION OF ϵ AND ϕ

To solve Eq. (1) for ϵ the magnitude E of the electric field is needed, which is calculated from the potential ϕ as a solution of the Poisson equation, $-\nabla[\epsilon(\mathbf{r})\nabla\phi(\mathbf{r})] = \rho_q(\mathbf{r})$, where ρ_q is the solute charge distribution. The two unknown functions $\epsilon(\mathbf{r})$ and $\phi(\mathbf{r})$ must then be calculated self-consistently at each point in space. This is done as follows: the first iteration starts with the vacuum field $\mathbf{E}_0(\mathbf{r})$, and the first-order permittivity function $\epsilon^{(1)}(\mathbf{r})$ is calculated numerically from Eq. (1), as discussed in Ref. 18. This first iteration already contains information on the dielectric saturation and the spatial variations of the liquid density, but saturation effects are overesti-

ated at this stage. Using $\epsilon^{(1)}(\mathbf{r})$ a first-order electrostatic potential $\phi^{(1)}(\mathbf{r})$ is obtained by solving the PE, as described below. The corresponding field $\mathbf{E}^{(1)}(\mathbf{r})$ is then calculated numerically from $\mathbf{E}^{(1)}(\mathbf{r}) = -\nabla\phi^{(1)}(\mathbf{r})$ and its magnitude $E^{(1)}(\mathbf{r})$ introduced back into Eq. (1) to obtain a second-order correction $\epsilon^{(2)}(\mathbf{r})$ of the liquid permittivity. The procedure is repeated λ times to convergence, which leads to the final solution in the form $\epsilon(\mathbf{r}) \approx \epsilon^{(\lambda)}(\mathbf{r})$ and $\phi(\mathbf{r}) \approx \phi^{(\lambda)}(\mathbf{r})$. A flow chart is shown in Fig. 1.

The electrostatic problem is solved on a non-uniform grid with cubic cells of volumes v_{ijk} centered at points (i, j, k) . Integrating both sides of the PE within a cell yields

$$-\int_{v_{ijk}} \nabla[\epsilon(\mathbf{r})\nabla\phi(\mathbf{r})]dv = 4\pi \int_{v_{ijk}} \rho_q(\mathbf{r})dv = 4\pi q_{ijk}, \quad (5)$$

and after recasting the first integral into the corresponding surface integral an equation is obtained for the potential ϕ_{ijk} in terms of the potentials in neighboring cells in the known form²⁹

$$\phi_{ijk} = \frac{4\pi q_{ijk}/h_{ijk}^2 + (\phi_{i-1jk}\epsilon_{ijk}^e/h_{ijk}^e + \phi_{i+1jk}\epsilon_{ijk}^w/h_{ijk}^w + \phi_{ij-1k}\epsilon_{ijk}^s/h_{ijk}^s + \phi_{ij+1k}\epsilon_{ijk}^n/h_{ijk}^n + \phi_{ijk-1}\epsilon_{ijk}^b/h_{ijk}^b + \phi_{ijk+1}\epsilon_{ijk}^f/h_{ijk}^f)}{(\epsilon_{ijk}^e/h_{ijk}^e + \epsilon_{ijk}^w/h_{ijk}^w + \epsilon_{ijk}^s/h_{ijk}^s + \epsilon_{ijk}^n/h_{ijk}^n + \epsilon_{ijk}^b/h_{ijk}^b + \epsilon_{ijk}^f/h_{ijk}^f)} \quad (6)$$

with the usual upper-index notation ($d = e, w, n, s, b, f$) to indicate directions (cf. Fig. 2, left panel); ϵ_{ijk}^d is the permittivity at the center of the cell wall in the direction d , and h_{ijk}^d is the distance between the grid point and the neighboring point in the same direction. The total charge enclosed by the cell is q_{ijk} , and h_{ijk} is the cell side length. Derivation of Eq. (6) assumes that ϕ varies linearly between (i, j, k) and neighboring points $(i \pm 1, j \pm 1, k \pm 1)$.

Applications of PE methods to protein electrostatics usually require making assumptions about the permittivity of the protein in addition to that of the solvent. In general, the dielectric response of a protein to an external field varies from site to site, and is anisotropic due to the constraints imposed by the covalent bonds. The protein interior is thus spatially heterogeneous, and experiments have been designed to probe local permittivity values.³⁰ Proteins should then be characterized by a position-dependent static dielectric tensor, or modeled as a position-dependent function $\epsilon_p(\mathbf{r})$ if isotropic behavior is assumed. For small molecules the permittivity can be approximated by a constant $\epsilon_p \sim 1$ –4 throughout the volume of the solute, which reflects only electronic polarizability. For macromolecules, however, reliable prediction of $\epsilon_p(\mathbf{r})$ from a rigid structure (e.g., crystal coordinates) is not yet possible, although models have been developed^{31,32} and empirical approaches used successfully to predict anomalous pKa shifts.³³ Moreover, the dielectric response of a protein and the liquid

are coupled, and nonlocal effects also play a role.³⁴ Molecular dynamics simulations can be used to estimate local values of ϵ_p from time averages,^{35,36} but this is computationally demanding, hence not common in protein-electrostatics. Since the focus of this paper is on the liquid, no attempt is made to model the permittivity of the solute. The solute is assumed to simply displace the liquid, which is represented by ρ vanishing in the solute interior, and has no internal relaxation mechanisms, thus $\epsilon_p(\mathbf{r}) = 1$. This assumption has no effects on the performance of the method. Once $\epsilon_p(\mathbf{r})$ is available, either from theory, simulations, or experiments, it can then be combined with $\epsilon(\mathbf{r})$ to assign permittivity values to the grid points. Otherwise, electronic and conformational relaxations could be introduced explicitly through dynamics, as shown in Fig. 1, thus avoiding the need to model ϵ_p *a priori* from a static structure.

A. Grid configuration and resolution

The system is initially divided in a homogeneous grid of cubic cells with sides of length h . These cells are subsequently divided uniformly into n^3 sub-cells or joined together into cubic cells of side length $2h$. The larger the local variations in the liquid density, the more refined the grid should be to increase accuracy. Therefore, n is made proportional to the magnitude of the local density gradient, i.e., $n \propto |\nabla\rho|$,

FIG. 1. Flowchart of the algorithm (upper panel). Block A represents the self-consistent iterative method for ϵ and ϕ described in Sec. III (lower panel). Loops 1 and 2 are proposed (but not analyzed herein) to allow solute-conformation/liquid-density relaxations, and charge relaxation, respectively.

resulting in sub-cells with sides of length h/n . The constant of proportionality defines the local resolution of the grid, and is estimated from the error in the calculation of the amount of liquid in a cell obtained by integration of the density. In one dimension (same for 3D), assuming $\rho(x) = \nabla \rho x$ in the interval $0 \leq x \leq h$, with $\nabla \rho$ a constant, the mass of liquid in the cell is $M = h^2 \nabla \rho / 2$, while a simple rectangular integration yields $M' = (h^2 \nabla \rho / 2)(n - 1)/n$. A dimensionless quantity can be defined as $\zeta = |M' - M|/M_0$, where $M_0 = \rho_0 h$ is the mass of the bulk liquid in a cell of the same volume. ζ is a measure of absolute error, a more convenient quantity than the relative error. For a given error ζ the minimum value of n is estimated as

$$n = \text{int} \left[\frac{|\Delta \rho|}{2\rho_0 \zeta} + \frac{3}{2} \right], \quad (7)$$

where $\Delta \rho = h \nabla \rho$ is the difference in density between the opposite sides of the initial cell. The procedure just outlined leads to a non-uniform, composite grid on which the self-consistent calculations are performed. If $n = 1$ (far from interfaces) the cell is a candidate for coalescence with neighboring cells; if $n > 1$ for a coalesced cell, it is then divided according to Eq. (7).

B. Charge distribution

Grid-based methods require charges to be assigned to the grid points [cf. Eq. (6)], and the way this is done affects the results. In classical force fields, point charges are typically assigned to the nearest nodes based on some distance criterion.^{7,37,38} An approach suitable for continuum charge distribution is used here, which is more appropriate for non-classical applications, especially in the context of atoms-in-molecules theory in quantum chemistry.³⁹ An atom I with charge q_I centered at $\mathbf{r}_I$ is assigned a charge distribution $\rho_q(\mathbf{r}) = q_I A_I \exp(-|\mathbf{r} - \mathbf{r}_I|^2 / 2a^2)$, where A_I is a constant; the smaller the value of a , the more localized the charge is; in the limit $a \rightarrow 0$, with $A_I = (2\pi)^{-3/2} a^{-3}$, the point-charge distribution $\rho_q(\mathbf{r}) = q_I \delta(\mathbf{r} - \mathbf{r}_I)$ is recovered. Since the continuum distribution is mapped onto a grid, charge conservation is enforced by the condition $q_I = \int_{\mathbb{R}^3} \rho_q(\mathbf{r}) d\mathbf{v}$, so $A_I^{-1} = \sum_{ijk} \exp(-|\mathbf{r}_{ijk} - \mathbf{r}_I| / 2a^2) v_{ijk}$, where the summation runs over all the cells. The assignment $q_{I,ijk}$ of a single charge q_I to the grid point at $\mathbf{r}_{ijk}$ is then $q_{I,ijk} = \rho_q(\mathbf{r}_{ijk}) v_{ijk}$, while the total charge on the same point is

$$q_{ijk} = \sum_{I=1}^N q_{I,ijk} = v_{ijk} \sum_{I=1}^N q_I A_I \exp(-|\mathbf{r}_{ijk} - \mathbf{r}_I| / 2a^2), \quad (8)$$

which are the values used in Eq. (6).

C. Numerical solutions

Efficient algorithms to solve partial differential equation by finite differences in non-uniform grids are based on multi-grid methods.⁴⁰ For highly heterogeneous systems containing disjoint regions of varying grid resolutions a multi-level multi-patch adaptive method for composite grids⁴¹ is most appropriate. In these methods the non-uniform grid is decomposed into a set of uniform grids on which finite-difference solutions are easily obtained; residuals and errors are then transferred up and down between the levels to achieve convergence in the original non-uniform grid. A more direct method is used here in which the elliptical problem is solved directly on the non-uniform grid structure. Figure 2 (right panel) shows a two-dimensional cell divided into sub-cells belonging to three classes: interior (light grey), sides (dark grey), and vertices (white). The treatment of each of these sub-cells is slightly different, and the extension to higher dimensions is straightforward. Interior sub-cells belong to a local uniform grid. Side and vertex sub-cells generally involve different distances h^d , as illustrated for the sub-cell at the upper-right corner. West and south derivatives are straightforward, requiring equal distances h^w and h^s and the potentials at grid points $(i-1, j)$

FIG. 2. Left panel: Quantities defined in Eq. (6) to solve the Poisson equation in a two-dimensional non-uniform grid. Right panel: Representation of the three classes of sub-cells obtained upon cell refinement according to Eq. (7): interior (light grey), side (dark grey), and vertex (white) sub-cells require different treatment in the context of non-uniform grids. Extension to three-dimensions is straightforward.

and $(i, j-1)$. North and east derivatives involve different distances h^e and h^n , and the potentials $\phi_{i+1,j}$ and $\phi_{i,j+1}$ are not necessarily on grid points. These potentials are calculated by linear interpolation of the potentials on adjacent cells, i.e., $\phi = (a\phi_a + b\phi_b)/(a + b)$ in this two-dimensional example. The potential ϕ_b may require additional interpolation from adjacent cells, one of which may need further interpolation still, and so forth; these higher corrections are neglected. In three dimensions a Renka–Cline triangular interpolation is used to calculate ϕ from the potentials ϕ_a , ϕ_b , and ϕ_c on the three adjacent coplanar points.

IV. COMPUTATIONAL PERFORMANCE

Hydration of $\text{NH}_3^+ - \text{Arg}^+ - \text{CO}_2^-$ is used here to illustrate the method and evaluate its computational performance. This molecule is chosen because interfacial water density was calculated in a previous study⁴² using molecular dynamics simulations, and the parameters ξ and σ in Eq. (4) were optimized¹⁸ to reproduce the density peaks from Eq. (3). The geometric center of the molecule is positioned at the origin of the coordinate system, and the electrostatic problem is solved within a centered cuboid of volume $V \sim (48 \times 52 \times 56) \text{ \AA}^3$. Figure 3(a) shows the charge distribution $\rho_q(\mathbf{r})$ on the plane containing the guanidinium cation, calculated from Eq. (8) using $a = 0.1 \text{ \AA}$ and partial charges taken from the CHARMM protein force field. The charge distribution on the arginine side chain can be clearly recognized at the right, while the charges on the $-\text{NH}_3^+$ and $-\text{CO}_2^-$ termini groups are on the left, on both sides of the plane. Figure 3(b) shows the liquid density $\rho(\mathbf{r})$ on the same plane, as calculated from Eq. (3). Local variations in liquid density up to $\rho/\rho_0 \sim 3.6$ are observed in the first hydration shell of the H atoms on the guanidinium group, as obtained from simulations.¹⁸ This density profile determines the grid resolution according to Eq. (7), and the grid is shown in Fig. 3(c).

Dirichlet boundary conditions are imposed by fixing the values of ϕ_0/ϵ_w on the grid points at the walls of the system, where ϕ_0 is the vacuum potential. The self-consistent dielectric permittivity and electrostatic potential

are plotted in Figs. 4(a) and 4(b), respectively. The permittivity shows a smooth transition from the empty interior ($\epsilon = 1$) to the bulk ($\epsilon_w \approx 78.4$; at ambient conditions), with a heterogeneous interface $\sim 2\text{--}3 \text{ \AA}$ wide extending outwardly from the first hydration shell. The form of $\epsilon(\mathbf{r})$ is determined by the competing effects of the density, dielectric saturation, and reaction fields, as discussed in Ref. 18. This particular form of ϵ will change if water–water and solute–water short-range orientational correlations are introduced in Eq. (1), as discussed in Sec. II. These effects are expected to broaden and further distort the interfacial region, especially around large charges,²⁷ since Eq. (1) underestimates dielectric saturation; the extent of these modifications remains to be studied (cf. Sec. VI). The electrostatic potential (Fig. 4(b)) shows the regions of positive field (black) generated by the charged side chain and N-terminus, and the region of negative field (white) surrounding the negatively charged C-terminus. The outermost contour lines indicate regions beyond which the potential is negligible.

Convergence of iterative methods is a well-established topic in numerical analysis, treated formally in terms of the spectral radius of the iteration matrix.²⁹ Physics-based criteria have often been used in protein electrostatics³⁷ and are also common in applications of the Schrödinger–Poisson equation in solids;⁴³ this is the choice here. Convergence of the potential for a given $\epsilon^{(\eta)}$ ($1 \leq \eta \leq \lambda$) is achieved in the k th relaxation cycle once $|\phi_{ijk}^{(k)} - \phi_{ijk}^{(k-1)}| < 10^{-4} \text{ V}$ for all grid points in the system. This threshold is based on the expected strength of electric fields near ions in aqueous solutions ($\sim 10 \text{ V}$), and was shown to be adequate in practice. Likewise, convergence of the dielectric is reached in the λ th iteration once $|\epsilon_{ijk}^{(\lambda)} - \epsilon_{ijk}^{(\lambda-1)}| < 0.1$ for all the grid points. Figure 4(c) (upper panel) displays the convergence of the self-consistent calculation for two standard relaxation methods:²⁹ weighted Jacobi (WJ) and Gauss–Seidel (GS). Different weighting factors ω were considered in the WJ method, and two cases are shown, for $\omega = 1$ (strict Jacobi) and $\omega = 2/3$. WJ leads to practically identical values of ϵ and ϕ for all the grid points regardless of the value of ω , but differences are observed in performance,

FIG. 3. Grey scale representation of (a) molecular charge density (white: negative charge, black; positive charge), and (b) liquid density (white: larger density, black: $\rho = 0$; heights and locations of the water density peaks were calculated in Ref. [18]). (c) Non-uniform grid with local resolution determined by the liquid density; the highest resolution is at the solute/liquid interface. The cells have sides of length $h = 1$ Å, and using $\zeta \sim 0.1$ yields $n = 2$ –13 [cf. Eq. (7)]. Coordinates x and y are in Å. For visualization purpose all quantities defined on the non-uniform grid are interpolated onto a high-resolution uniform grid using random Renka–Cline interpolation with the OriginLab software.

FIG. 4. Grey-scale representation of (a) dielectric $\epsilon(\mathbf{r})$ (white: larger values, peaks of up to $\epsilon \sim 150$ are observed; black: $\epsilon = 1$), and (b) potential $\phi(\mathbf{r})$ (white: negative field; black: positive) obtained self-consistently as illustrated in Fig. 1 (cf. Sec. III). Coordinates x and y are in Å. (c) Convergence of the calculation (upper panel) for two relaxation methods used to solve Eq. (6): weighted Jacobi with $\omega = 1$ (strict Jacobi, solid circles) and $\omega = 2/3$ (open circles), and Gauss-Seidel (squares; red-black GS yields identical results). Convergence of the calculation for the $\text{Na}^+ - \text{Cl}^-$ ion pair at a fixed separation of 2.6 Å is also shown for comparison (lower panel).

with Jacobi converging faster. If $\tau^{(\eta)}$ denotes the time for convergence of the potential for a given permittivity $\varepsilon^{(\eta)}$, the total CPU time of the calculation is $\tau_T = \sum_{\eta=1}^{\lambda} \tau^{(\eta)}$. For Jacobi relaxation, $\tau^{(1)}$ accounts for $\sim 75\%$ of τ_T , while $\tau_T - \tau^{(1)}$ is $\sim 25\%$. This allocation of CPU times between the first cycle and the remaining cycles is independent of ω , and similar to that observed in other test molecules of varying size and charge distributions (not shown). The total CPU time of the calculation depends on several factors, but solving the PE appears to be the most time-consuming portion, particularly for $\varepsilon^{(1)}$. In contrast, solving Eq. (1) is comparatively fast. These observations indicate that the performance of the method is acceptable and efforts in this direction are justified.

Several GS relaxation schemes were considered, including the more efficiently parallelizable red-black GS, which was applied here to the cells, and to the cells and sub-cells combined. None of these GS variants proved superior to others, or showed major differences in convergence and performance, but this may not be so in more complicated systems. Moreover, the self-consistent solutions obtained with GS were identical with those obtained with WJ, but GS reached convergence in fewer relaxation steps. This improved efficiency in solving the PE may lead to fewer dielectric cycles as well, especially in systems with large local variations in density and charge (not shown). Overall, GS is at least $\sim 35\%$ faster than WJ methods. Successive over-relaxation could improve the performance,⁴⁴ but this GS extension is not analyzed here. For comparison, Fig. 4(c) (lower panel) shows the convergence in the case of $\text{Na}^+ - \text{Cl}^-$ ion pair separated 2.6 Å. A series of alkali and halide ions pairs were studied previously¹⁸ using the first-order permittivity $\varepsilon(\mathbf{r}) \approx \varepsilon^{(1)}(\mathbf{r})$ and the approximation $E(\mathbf{r}) \approx E_0(\mathbf{r})/\varepsilon^{(1)}(\mathbf{r})$ for the magnitude of the field in Eq. (1). The analysis illustrated the effects of saturation, spatial density variations, and reaction fields on the liquid environment. The qualitative behavior is reproduced with the more advanced self-consistent treatment described here, although quantitative differences are apparent.

V. THERMODYNAMICS

In an isochoric-isothermal charging process, each volume element dv of the liquid at position $\mathbf{r}$ is subject to an electric field of magnitude $E'(\mathbf{r})$, which grows from zero to its final value $E(\mathbf{r})$. The internal energy of the liquid within dv is given by $U(E') = u(E')dv$, where u is the local internal energy density, given by⁴⁵

$$u(E) = u_0 + \frac{1}{4\pi} \int_0^E \varepsilon(E') E' dE' + \frac{1}{4\pi} \int_0^E E'^2 \frac{\partial \varepsilon(E')}{\partial E'} dE' + \frac{T}{4\pi} \int_0^E E' \frac{\partial \varepsilon(E')}{\partial T} dE', \quad (9)$$

where ε is a solution of Eq. (1) for a fields of magnitude E' , and u_0 is the internal energy density of the liquid in absence of the field at the same temperature and pressure. The electrostatic contribution to the entropy of the liquid in dv is given by $S(E') = s(E')dv$, where s is the local entropy density given

by

$$s(E) = s_0 + \frac{1}{4\pi} \int_0^E E' \frac{\partial \varepsilon(E')}{\partial T} dE', \quad (10)$$

where s_0 is the corresponding entropy in absence of the field. The local Helmholtz free energy density f is $f = u - Ts$, so the electrostatic contribution to the total free energy of hydration, ΔF_e , is obtained by integrating $f(E)$ over the three-dimensional space, i.e.,

$$\Delta F_e = \int_{\mathbb{R}^3} \{f(E) - f_0\} dv - \frac{1}{8\pi} \int_{\mathbb{R}^3} E_0^2 dv, \quad (11)$$

where $f_0 = u_0 - Ts_0$. E_0 is the vacuum field, so the second integral in Eq. (11) is the electrostatic free energy of the solute at infinite distance from the liquid. Equation (11) can be rearranged as

$$\Delta F_e = \frac{1}{8\pi} \int_{\mathbb{R}^3} \left\{ 2 \int_0^E \varepsilon_r(E') E' dE' - E_0^2 \right\} dv, \quad (12)$$

where $\varepsilon_r = dD'/dE'$ is the *differential relative permittivity*, a common experimental measure of the nonlinear effects of the field; D' is the magnitude of the electric displacement $\mathbf{D}' = \varepsilon \mathbf{E}'$. The term $\varepsilon_r E'$ in Eq. (12) can be computed rapidly from Eq. (1) at each point $\mathbf{r}$, and Eq. (12) is itself well suited for code parallelization. Equation (12) quantifies not only the reversible work needed to polarize a spatially non-uniform dielectric of permittivity $\varepsilon(\mathbf{r})$, but also the work needed to form the dielectric during the charging process. If $\varepsilon(\mathbf{r})$ were independent of E' , i.e., if the dielectric medium is created by an external source [e.g., an external field $E(\mathbf{r})$] prior to the charging process, and the solute is then charged in the presence of this already-formed dielectric, Eq. (12) takes the more familiar form

$$\Delta F_e = \frac{1}{8\pi} \int_{\mathbb{R}^3} [\mathbf{D} \cdot \mathbf{E} - E_0^2] dv. \quad (13)$$

This is the expression used to derive pairwise screening functions in the SCP continuum solvent model,⁴⁶ although in that case $\varepsilon(\mathbf{r})$ depends on $\mathbf{r}$ implicitly through the field $E(\mathbf{r})$ created by the solute.

VI. DISCUSSION AND CONCLUSION

Reliable prediction of electrostatic effects in solution, such as pKa shifts, redox potentials, dissociation rates, and hydration energies depends on the accurate description of the dielectric behavior of the system, especially at the solute/liquid interface. Recent developments in polarizable force fields require that conventional continuum electrostatic methods be modified to allow adaptation of the static dielectric permittivity to variable charge distributions. This is desirable also in the context of traditional non-polarizable force fields whenever changes in protonation states, or charge transfer in general, occur; and in simulations of systems with large and heterogeneous charge distributions, such as nucleic acids, polyelectrolytes, and most biologically active protein. Conformational changes in these macromolecules generate local electrostatic fields of varying strength that affect the local dielectric permittivity and thermodynamics through saturation,

electrostriction, density changes, etc. To deal with these problems in proteins, semi-microscopic models of the liquid have been proposed in which water molecules are modeled as dipoles fixed on a lattice surrounding the protein.⁴⁷ These dipoles interact with each other and with the protein, thus allowing the required adaptation of the medium to changes in charge distributions. These models are naturally more practical than fully atomistic water models, and do not require dealing with the concepts arising in the continuum. The main limitations of these semi-microscopic models are that the dipoles are fixed in space, which emphasizes the solid-like nature of the fluid and complicates dealing with protein conformational changes; the liquid density tends to be homogeneous; details of the interfacial region are poorly described; and the computational cost can be prohibitive in large-scale computations. A continuum solvent model based on this semi-microscopic notion that alleviates some of these problems was reported earlier,¹⁸ and summarized in Eq. (1). It is obtained from local statistical averages of the microscopic dipoles, as in the classical theory of dielectrics.²² The model incorporates both ρ and ϵ in a phenomenological framework, and provides the basis for a computationally efficient method that allows ϵ to adjust to the field generated by the solute. The method involves two iterative procedures, one over ϵ , which is calculated from Eq. (1), and a conventional relaxation of Eq. (6) to obtain ϕ . The performance and robustness of the algorithm was assessed in Sec. IV, where numerical convergence and stability were analyzed with different relaxation schemes. Application of the method was illustrated for $\text{NH}_3^+ - \text{Arg}^+ - \text{CO}_2^-$, but similar performance was obtained for other single and paired $\text{NH}_3^+ - \text{X} - \text{CO}_2^-$ species (where X denotes a polar or a charged amino acid) for which water densities were calculated in previous studies.^{18,42} Equation (1) shows that charge redistribution within the solute affects ϵ not only directly through the field created by the new charges, but also indirectly through the changes that these charges induce in ρ . Formally, then, the three quantities ϵ , ϕ , and ρ should be calculated self-consistently, and ρ_q must also be included in the self-consistent treatment in quantum chemical optimization (cf. Fig. 1). The method is well suited for code parallelization, and can be adapted for molecular dynamics in the context of conventional PE-based approaches (cf. Fig. 1).

Although interfacial effects and molecular interactions at interfaces have been a traditional area of study in established areas of physics and chemistry,⁴⁸ the study of biomolecular interfaces is comparatively new. As a result, the structural and dynamic behavior of water at the surface of biomolecules is not yet well understood. Few general observations, however, can be made that are relevant to the development of the model. Water density at hydrophilic interfaces has been studied experimentally and by computer simulations. Neutron scattering and x-ray diffraction methods⁴⁹ as well as simulations^{50,51} suggest that, on average, the density of water in the first hydration shells of globular proteins tend to be higher than that of the bulk. However, the density changes locally over the protein surface, increasing in the vicinity of charged groups and decreasing in the vicinity of non-polar groups.⁵² Hydration of non-polar surfaces has also been the focus of extensive studies; in particular, the ef-

fects of short-range surface–liquid interactions (e.g., dispersion forces).^{53,54} Non-polar hydration appears to be characterized by mild density depletion (partial dewetting), a phenomenon long predicted theoretically but detected experimentally only recently.^{4,55} Water density at non-polar surfaces, however, is very sensitive to small changes in surface polarity, and dewetting appears to vanish when polar groups are attached to the surface.⁴ A computationally efficient model of ρ capable of representing this variety of effects induced by heterogeneous surfaces would be desirable. From a computational-efficiency perspective, gradual improvements of (zero-order) Eq. (3) based on short-range and long-range correlations, as discussed in Sec. II, is probably most convenient.

Although the local density determines the amount of polar/polarizable material that responds locally to the field, other microscopic effects are present that contribute to the local dielectric response of interfacial water (cf. Introduction). Traditional dielectric spectroscopy of protein solutions^{56,57} shows that protein/water interfaces have unique dielectric behaviors, different from that of bulk water. Simulations have also shown that the average dielectric permittivity of interfaces tends to be lower than that of the bulk solution.³⁴ Dynamics simulations and terahertz spectroscopy have shown that the dynamics of water can be affected beyond the second hydration shells of proteins.^{58,59}

The dielectric model used here captures some of the interfacial effects in polar/polarizable liquids, such as saturation and reaction field, as well as spatial variations of density. The model is clearly incomplete and some level of empiricism is needed in practice, but this can be minimized by gradual improvements of Eqs. (1) and (3). A number of physical effects still needs to be incorporated, most importantly short-range water–water orientational correlations, which are expected to change the width of the interface.²⁷ For this, the Kirkwood–Fröhlich model^{45,60} is a natural extension of the Onsager model⁶¹ on which Eq. (1) is based. An empirical correction for orientational correlations in the presence of large electric fields can be readily implemented through a field-dependent Kirkwood factor g_K (cf. Sec. II). Other short-range solute–liquid interactions, such as van der Waals and hydrogen bonds (if present) are not explicitly accounted for, but they clearly affect the orientational correlation of liquid molecules closest to the solute surfaces, hence their response to external field. Accounting for these explicit interactions are important because they tend to decrease ϵ directly, but increase it indirectly by inducing higher values of ρ . Non-local effects are also important as they tend to lower the effective permittivity at the interface for reasons seemingly unrelated to saturation.⁶² Finally, electrostriction can be represented by changing the effective molecular volume in strong fields (cf. Sec. II). All these phenomenological refinements will lead to a more sophisticated Eq. (1), but the impact on the computational performance is not expected to be large since the time-limiting step in the self-consistent calculation is the numerical solutions of the Poisson equation, at least in the absence of non-local effects.

Benchmarking of the model would require prediction of physico-chemical data of processes involving redistribution of

charge close to the solute–liquid interfaces. Three studies are here proposed that will challenge the model and provide guidance for improvements: calculations of pKa shifts of water-accessible groups in proteins; calculations of redox potentials in metalloproteins; and quantum chemical geometry optimization of highly polar molecules.

Extension of the method to the Poisson–Boltzmann equation (PBE) presents no technical difficulties. The PBE is an adequate approximation to modeling non-specific ion effects originated in the bulk phase, and has been used to modeling salt effects on proteins. However, ions at interfaces can strongly affect intermolecular forces and stabilization through specific ion-solute interactions,⁴² and such effects are not amenable to mean-field approximations or other continuum assumptions.^{63,64} Realistic modeling of salt effects might ultimately require an explicit treatment of ions due to their unique actions at interfaces.⁴⁶ With this important caveat in mind, the method can be used in combination with the Smoluchowski equation to study electrostatic-mediated diffusion of ions or small ligands. In particular, the Nernst–Planck equation can be combined with PBE to calculate local ion currents, e.g., through trans-membrane channels,⁶⁵ or to estimate protein-ligands association rates.⁶⁶ In all these problems interfacial electrostatic effects are important components of the underlying physics. The method may also be useful in situations where dielectric gradients are important or when transient, local liquid density variations affect electrostatics, e.g., in biological samples under the action of pressure shocks.

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