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Including implicit solvation in the bond capacity polarization model

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ABSTRACT

We derive expressions corresponding to a coupling of the recently proposed Bond Capacity polarization model with implicit solvation by means of the generalized Born and conductor-like polarizable continuum models. The original bond capacity interaction kernel is in both cases augmented with a term that accounts for the reaction potential arising from the continuum. The expressions for energy gradients are derived within the recently introduced Lagrangian formalism for the efficient evaluation of energy gradients of nonvariational force fields.

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I. INTRODUCTION

The description of solvation effects is an active field of research in molecular modeling as all biochemically relevant reactions and processes occur in solution.¹ The description of bulk solvation effects with explicit solvent molecules requires the inclusion of several solvation shells and leads to a rapid increase of the system size. In classical Molecular Dynamics (MD) simulations of biological systems, the number of atoms arising from explicit water molecules is often larger than the number of atoms from the solute, and an adequate sampling requires long simulations that become unfeasible for large systems.² In solvent-drop models, where the system of interest is placed in a sphere of solvent molecules, special care must be taken as surface effects can be significant for small systems where the surface/volume ratio of the simulation drop is relatively high.³ The use of periodic boundary conditions is a standard tool for eliminating surface effects but may introduce other artifacts due to the enforced periodicity.⁴

A significant reduction in the system size can be obtained by replacing the atomistic description of the solvent by a continuum medium (implicit solvent) where the solute is accommodated within a cavity and is subjected to a solvent reaction field. Such implicit solvent models are characterized by a dielectric constant that includes the statistical average of the solvent configurations to account for the electrostatic interactions and possibly also

empirical corrections for modeling the exchange and dispersion interactions.^{5–9}

The Born model is one of the earliest implicit solvent models and predicts the free-energy stabilization of an ion upon placing it in a spherical cavity in a dielectric medium.¹⁰ Subsequent approaches by Onsager, Kirkwood, and Westheimer extended the model to include a multipolar expansion in a spherical cavity^{11,12} and a dipole in an ellipsoidal cavity.¹³ The Born model has been used as a starting point for constructing Generalized Born (GB) models where the cavity for polyatomic solutes is derived from the union of atomic spheres and employing fractional atomic charges.¹⁴ When combined with exchange and dispersion terms parameterized by the surface area (SA) of the cavity, this defines the GB/SA model. The GB/SA model usually only increases the total computational cost by a few percent and has been successfully implemented and employed in classical MD simulation packages to model solvation effects^{15–19} as well as in quantum mechanical calculations with the SM-X versions of the GB/SA model.^{20–22}

A computationally more expensive alternative of implicit solvent models is represented by the apparent surface charge class of methods where the solvent reaction field is assumed to arise from a fictitious charge distribution spread on the cavity surface, which is in practice represented by a mesh of point charges.⁷ The values of the apparent charges on the surface depend on the electrostatic potential at each point of the mesh due to the charge

density of the solute and this leads to a self-consistent mutual polarization in the case of a polarizable solute. Apparent surface charge models are popular for modeling solvent effects in connection with electronic structure methods, and different versions of the Polarizable Continuum Model (PCM)⁹ are implemented in many program packages. PCM and related Poisson-Boltzmann methods²³ are computationally more expensive than GB/SA models but have been used for simulations using massive parallel implementations.²⁴

Production type simulations currently employ fixed charge force fields, but there is increasing evidence that the neglect of electric polarization may be a limiting factor for the accuracy of the results.^{25–28} Polarizable force fields have the potential capability of higher accuracy than nonpolarizable ones but also carry an increased computational cost.²⁹ Replacing all or part of the solvent molecules by an implicit solvent model is one possibility for reducing the computational cost, and this has been investigated by several groups in connection with different polarization models.^{24,30–32}

We have recently proposed a Bond Capacity (BC) polarization model, where the anisotropic molecular polarizability is represented by (only) atomic charges that are allowed to respond to changes in the electrostatic potential.³³ Off-nuclei sites are included for modeling out-of-plane polarization. While similar in spirit to the fluctuating charge model,³⁴ the BC model is free from artificial long range charge transfer and nonlinear scaling of the polarizability with system size. The BC model has been implemented in the Tinker-HP package³⁵ employing periodic boundary conditions³⁶ and thus allowing for explicit solvation, but for the reasons discussed above, it may be useful also to couple the BC model with implicit solvent models. In the present work, we derive the equations for combining the BC polarizable model with the GB and the conductorlike PCM³⁷ (C-PCM) implicit solvation models for representing continuum solvent electronic effects. The inclusion of implicit solvation modifies the BC interaction kernel by an extra term arising from the reaction potential, and the expressions for energy gradients are obtained by means of the general Lagrange formalism recently introduced for nonvariational force fields.³⁶

II. THEORY

The BC model is built upon the assumption that the charge transferred between an atom pair is proportional to a bond capacity times an electrostatic potential difference between the involved pair in analogy with classical capacitors.³³ The bond capacity is closely related to the bond order and contains an attenuation function that decays to zero as the bond length is elongated. The atomic electrostatic potential consists of an intrinsic potential (an atomic electronegativity), a screened Coulomb potential from all other charges, and a Coulomb self-interaction term (an atomic hardness). As derived in detail in Ref. 33, the set of N atomic charges $\mathbf{Q}$ can be obtained from the following equation:

$$\begin{aligned}\mathbf{Q} &= -\mathbf{C}\mathbf{V} + \mathbf{Q}_0, \\ \mathbf{V} &= \chi + \tilde{\phi}.\end{aligned}\quad (1)$$

In the above equation, $\mathbf{C}$ represents Maxwell's capacitance matrix³⁸ composed of all the bond capacities as shown in Eq. (2), where ξ_{ij}^0 represents the bond capacity parameter for the ij pair of atoms

at equilibrium distance and $g(R_{ij})$ is an attenuation function that takes a value of one at equilibrium bond length and decays exponentially to zero as R_{ij} increases. This ensures that charge transfer can only take place between atom pairs within wave function overlap, and the structure of the $\mathbf{C}$ matrix automatically ensures charge conservation,³³

$$C_{ij} = \begin{cases} \sum_{k \neq j} \xi_{ik}^0 g(r_{ik}), & i = j, \\ -\xi_{ij}^0 g(r_{ij}), & i \neq j. \end{cases} \quad (2)$$

The quantity $\mathbf{V}$ represents the electrostatic potential arising from atomic electronegativity parameters χ and an intermolecular and intramolecular Coulomb potential $\tilde{\phi}$ [Eq. (3)] containing a short range screening factor $h(R_{ij})$ and augmented with self-interaction parameters J_i that are equivalent to atomic hardness parameters in conceptual density functional theory.³⁹ $\mathbf{Q}_0$ is a vector of reference charges used to model non-neutral systems,

$$\tilde{\phi} = \tilde{\mathbf{J}}\mathbf{Q}, \quad (3)$$

$$\tilde{\phi}_i = \sum_{j \neq i} J_{ij} Q_j + J_i Q_i = \sum_{j \neq i} \frac{1 - h(r_{ij})}{r_{ij}} Q_j + J_i Q_i.$$

The atomic charges are obtained by inserting Eq. (3) in Eq. (1) and isolating $\mathbf{Q}$ as shown in the following equation:

$$\begin{aligned}\mathbf{Q} &= \mathbf{A}_{BC}^{-1} \mathbf{b}, \\ \mathbf{A}_{BC} &= (\mathbf{I} + \tilde{\mathbf{C}}\tilde{\mathbf{J}}), \\ \mathbf{b} &= -\mathbf{C}\chi + \mathbf{Q}_0.\end{aligned}\quad (4)$$

The $\mathbf{A}_{BC}$ matrix represents the specific BC interaction kernel that couples all the charges via the intermolecular and intramolecular potential $\tilde{\phi}$ modulated by the capacitance matrix $\mathbf{C}$. Once the set of charges $\mathbf{Q}$ have been obtained from Eq. (4), the energy is computed from Eq. (5), where the absence of the tilde denotes that the self-interactions parameters are not included in the screened Coulomb matrix $\mathbf{J}$ ($J_i = 0$),

$$\mathcal{E}_{el} = \frac{1}{2} \mathbf{Q}^\dagger \mathbf{J} \mathbf{Q}. \quad (5)$$

Unlike other polarization models, the BC charges in Eq. (4) are non-variational in the sense that are not obtained by making the energy in Eq. (5) stationary. The energy gradient of nonvariational polarization models needed to perform MD simulations formally requires calculation of a cumbersome polarization response term, but we have shown that this can be avoided by using a general Lagrange formalism.³⁶ By solving for the set of Lagrange multipliers shown in Eq. (6), which is of the same computational complexity as solving for the atomic charges in Eq. (4), the energy gradient in Eq. (7) ($\mathbf{r}_i$ being an atomic coordinate) can be obtained at a computational cost comparable to that for variational ones. The equation for the charges and multipliers must be converged to $\sim 10^{-6}$ in order to ensure energy conservation, as shown in Ref. 36,

$$\lambda = -(\mathbf{A}_{BC}^\dagger)^{-1} \mathbf{J} \mathbf{Q}, \quad (6)$$

$$\begin{aligned}\frac{\partial \mathcal{L}(\mathbf{Q}, \lambda)}{\partial \mathbf{r}_i} &= \frac{1}{2} \mathbf{Q}^\dagger \frac{\partial \mathbf{J}}{\partial \mathbf{r}_i} \mathbf{Q} + \lambda^\dagger \left[\frac{\partial \mathbf{A}_{BC}}{\partial \mathbf{r}_i} \mathbf{Q} - \frac{\partial \mathbf{b}}{\partial \mathbf{r}_i} \right], \\ \frac{\partial \mathbf{A}_{BC}}{\partial \mathbf{r}_i} &= \frac{\partial \mathbf{C}}{\partial \mathbf{r}_i} \tilde{\mathbf{J}} + \mathbf{C} \frac{\partial \tilde{\mathbf{J}}}{\partial \mathbf{r}_i}, \\ \frac{\partial \mathbf{b}}{\partial \mathbf{r}_i} &= -\frac{\partial \mathbf{C}}{\partial \mathbf{r}_i} \chi.\end{aligned}\quad (7)$$

In the last equation, it has been assumed that the electronegativity parameters are geometry independent. It can also be noted that the derivatives of $\tilde{\mathbf{J}}$ are identical to the derivatives of $\mathbf{J}$ if the Coulomb self-interaction parameters are assumed to be independent of geometry.

The goal of the present work is to couple the effects of implicit solvation to the BC equations by identifying the expression for the reaction potential ψ that contributes to the potential $\mathbf{V}$ both for the GB and C-PCM implicit solvent models. Once ψ is identified, the interaction kernel $\mathbf{A}$ and thus the new BC charge equations can be derived. The energy in Eq. (5) is augmented with the implicit solvation contribution $\mathcal{G}$, and the Lagrange formalism is applied to derive the energy gradient expressions.

A. The BC/GB equations

The electrostatic contribution to the solvation energy in the GB model is given by the following equation:¹⁴

$$\begin{aligned}\mathcal{G}_{GB}(\mathbf{Q}) &= -\frac{1}{2} \sum_{i \neq j}^N \left(1 - \frac{1}{\varepsilon} \right) \frac{Q_i Q_j}{f_{ij}} = -\frac{1}{2} \mathbf{Q}^\dagger \mathbf{F}_{GB} \mathbf{Q}, \\ f(r_{ij}) &= \sqrt{r_{ij}^2 + \alpha_i \alpha_j \exp(-r_{ij}^2 / 4\alpha_i \alpha_j)}.\end{aligned}\quad (8)$$

In the above equation, α_i represents the effective Born radius of atom i , r_{ij} is the distance between a pair of atoms, and ε is the dielectric constant of the medium. The reaction potential ψ arising from the solvation is obtained by differentiating Eq. (8) with respect to $\mathbf{Q}$ to get the following equation:

$$\psi = -\mathbf{F}_{GB} \mathbf{Q}. \quad (9)$$

Inserting Eq. (9) in Eq. (1) and isolating $\mathbf{Q}$ provide the interaction kernel $\mathbf{A}_{GB}$ in Eq. (10) that couples the BC charges to the GB model, where $\mathbf{b}$ is given in Eq. (4),

$$\begin{aligned}\mathbf{Q} &= \mathbf{A}_{GB}^{-1} \mathbf{b}, \\ \mathbf{A}_{GB} &= [\mathbf{I} + \mathbf{C}(\tilde{\mathbf{J}} - \mathbf{F}_{GB})].\end{aligned}\quad (10)$$

The total electrostatic energy of the solvated system is the sum of the vacuum Coulomb interaction in Eq. (5) and the GB solvation energy in Eq. (8), as shown in the following equation:

$$\mathcal{E}_{tot} = \mathcal{E}_{el} + \mathcal{G}_{GB} = \frac{1}{2} \mathbf{Q}^\dagger \mathbf{J} \mathbf{Q} - \frac{1}{2} \mathbf{Q}^\dagger \mathbf{F}_{GB} \mathbf{Q}. \quad (11)$$

The atomic charges $\mathbf{Q}$ from Eq. (10) do not make the energy in Eq. (11) stationary, and calculating energy gradients thus requires the use of the Lagrangian formalism for nonvariational polarization models.³⁶ A Lagrange function is defined by augmenting the total energy in Eq. (11) with the first equality in Eq. (10) premultiplied by a set of Lagrange multipliers, as shown in the following equation:

$$\mathcal{L}(\mathbf{Q}, \lambda) = \frac{1}{2} \mathbf{Q}^\dagger (\mathbf{J} - \mathbf{F}_{GB}) \mathbf{Q} + \lambda^\dagger [\mathbf{A}_{GB} \mathbf{Q} - \mathbf{b}]. \quad (12)$$

The Lagrange function has the same numerical value as the total energy and is made stationary with respect to $\mathbf{Q}$, leading to the equation for the Lagrange multipliers λ shown in the following equation:

$$\begin{aligned}\frac{\partial \mathcal{L}(\mathbf{Q}, \lambda)}{\partial \mathbf{Q}} &= (\mathbf{J} - \mathbf{F}_{GB}) \mathbf{Q} + \mathbf{A}_{GB}^\dagger \lambda = \mathbf{0}, \\ \lambda &= -(\mathbf{A}_{GB}^\dagger)^{-1} (\mathbf{J} - \mathbf{F}_{GB}) \mathbf{Q}.\end{aligned}\quad (13)$$

The Lagrange function provides the required energy gradient shown in Eq. (14) by differentiation with respect to an atomic Cartesian coordinates $\mathbf{r}_i$ and making use of Eq. (13) to avoid the calculation of response terms,

$$\begin{aligned}\frac{\partial \mathcal{L}}{\partial \mathbf{r}_i} &= \frac{1}{2} \mathbf{Q}^\dagger \left(\frac{\partial \mathbf{J}}{\partial \mathbf{r}_i} - \frac{\partial \mathbf{F}_{GB}}{\partial \mathbf{r}_i} \right) \mathbf{Q} + \lambda^\dagger \left(\frac{\partial \mathbf{A}_{GB}}{\partial \mathbf{r}_i} \mathbf{Q} - \frac{\partial \mathbf{b}}{\partial \mathbf{r}_i} \right), \\ \frac{\partial \mathbf{A}_{GB}}{\partial \mathbf{r}_i} &= \frac{\partial \mathbf{C}}{\partial \mathbf{r}_i} (\tilde{\mathbf{J}} - \mathbf{F}_{GB}) + \mathbf{C} \left(\frac{\partial \tilde{\mathbf{J}}}{\partial \mathbf{r}_i} - \frac{\partial \mathbf{F}_{GB}}{\partial \mathbf{r}_i} \right).\end{aligned}\quad (14)$$

The $\partial \mathbf{b} / \partial \mathbf{r}$ term is given in Eq. (7). Incorporation of the GB solvent model thus only requires that the Coulomb matrices $\mathbf{J}$ and $\tilde{\mathbf{J}}$ and their derivatives are modified by the $\mathbf{F}_{GB}$ matrix and its derivatives. We note that the same derivation can be used for different choices of the effective Coulomb operator $f(r)$ in Eq. (8).⁴⁰ Equations (10) and (13) involve the inversion of $\mathbf{A}_{GB}$ and $\mathbf{A}_{GB}^\dagger$ having the same (N, N) dimension as the original kernel $\mathbf{A}_{BC}$. The increase in computational cost by coupling the GB model to the BC equations is thus expected to be very small.

B. The BC/C-PCM equations

The solvation energy functional^{7,31} in the C-PCM framework is given in the following equation:

$$\mathcal{G}_{PCM}(\sigma, \rho(\mathbf{r})) = \frac{1}{2f(\varepsilon)} \sigma^\dagger \mathbf{S} \sigma + \sigma^\dagger \mathbf{V}^S[\rho(\mathbf{r})]. \quad (15)$$

Here, σ represents a vector of N_σ charges at positions $\mathbf{s}_1, \dots, \mathbf{s}_i, \dots, \mathbf{s}_{N_\sigma}$ on the surface of the cavity accommodating the solute, while $\mathbf{S}$ is a Coulomb matrix of size (N_σ, N_σ) that accounts for the electrostatic interactions of the surface charges, as shown in the following equation:

$$S_{ij} = \frac{1}{|\mathbf{s}_i - \mathbf{s}_j|}. \quad (16)$$

The function $f(\varepsilon) = (\varepsilon - 1)/\varepsilon$ represents a scaling factor that ensures the correct dielectric behavior to the C-PCM that is derived from the assumption that the medium behaves like a conductor.^{7,37} The quantity $\mathbf{V}^S[\rho(\mathbf{r})]$ is a vector of size N_σ representing the electric potential at the surface charge positions arising from the molecular charge density $\rho(\mathbf{r})$ in the cavity. This potential is in the present case generated by the set of BC point charges $\mathbf{Q}$. The resulting vector $\mathbf{V}^S(\mathbf{Q})$ can be expressed by introducing the rectangular Coulomb matrix Ω shown in the following equation:

$$V_i^S = \sum_j^{N_Q} \frac{1}{|\mathbf{r}_j - \mathbf{s}_i|} Q_j = \sum_j^{N_Q} \Omega_{ij} Q_j. \quad (17)$$

The reaction potential ψ at the atomic charge positions due to the surface charges σ is defined in the following equation:

$$\psi_j = \sum_i^{N_\sigma} \frac{1}{|\mathbf{r}_j - \mathbf{s}_i|} \sigma_i = \sum_i^{N_\sigma} \Omega_{ji}^\dagger \sigma_i. \quad (18)$$

The surface charges σ are obtained by minimizing the solvation energy in Eq. (15) with the insertion of V^S to give the following equation:

$$\begin{aligned} \frac{\partial \mathcal{G}_{PCM}}{\partial \sigma} &= \frac{1}{f(\epsilon)} \mathbf{S} \sigma + \mathbf{\Omega} \mathbf{Q} = \mathbf{0}, \\ \sigma &= -f(\epsilon) \mathbf{S}^{-1} \mathbf{\Omega} \mathbf{Q}. \end{aligned} \quad (19)$$

Equation (19) allows expressing ψ in terms of $\mathbf{Q}$, as shown in the following equation:

$$\psi = -f(\epsilon) \mathbf{\Omega}^\dagger \mathbf{S}^{-1} \mathbf{\Omega} \mathbf{Q} = -\mathbf{F}_{PCM} \mathbf{Q}. \quad (20)$$

The potential $\mathbf{V}$ in Eq. (1) can be augmented with the reaction potential ψ and the set of BC charges $\mathbf{Q}$ isolated as shown in Eq. (21), together with the PCM interaction kernel $\mathbf{A}_{PCM}$ that includes the C-PCM solvation effects, while $\mathbf{b}$ is given in Eq. (4),

$$\begin{aligned} \mathbf{Q} &= \mathbf{A}_{PCM}^{-1} \mathbf{b}, \\ \mathbf{A}_{PCM} &= [\mathbf{I} + \mathbf{C}(\tilde{\mathbf{J}} - \mathbf{F}_{PCM})]. \end{aligned} \quad (21)$$

Once the charges $\mathbf{Q}$ are computed, the apparent surface charges σ can be obtained from Eq. (19). The total energy of the system shown in Eq. (22) represents the sum of the electrostatic interaction of the solute within the cavity and the solvation energy in Eq. (15),

$$\mathcal{E}_{tot}(\mathbf{Q}, \sigma) = \mathcal{E}_{el} + \mathcal{G}_{PCM} = \frac{1}{2} \mathbf{Q}^\dagger \mathbf{J} \mathbf{Q} + \frac{1}{2f(\epsilon)} \sigma^\dagger \mathbf{S} \sigma + \sigma^\dagger \mathbf{\Omega} \mathbf{Q}. \quad (22)$$

The total energy $\mathcal{E}_{tot}$ is stationary with respect to σ [Eqs. (23) and (19)] but is not stationary with respect to the set of atomic charges $\mathbf{Q}$,

$$\frac{\partial \mathcal{E}_{tot}}{\partial \sigma} = \frac{\partial \mathcal{G}_{PCM}}{\partial \sigma} = \mathbf{0}. \quad (23)$$

It is convenient to rewrite Eq. (22) similarly to Eq. (11) by making use of Eq. (19) to get Eq. (24) where the set of surface charges σ have been explicitly written in terms of $\mathbf{Q}$,

$$\mathcal{E}_{tot}(\mathbf{Q}) = \frac{1}{2} \mathbf{Q}^\dagger \mathbf{J} \mathbf{Q} - \frac{1}{2} \mathbf{Q}^\dagger \mathbf{F}_{PCM} \mathbf{Q}. \quad (24)$$

In analogy to Eq. (12), the energy gradient is obtained by defining a Lagrange function by adding the equality in Eq. (21) multiplied by a set of Lagrange multipliers to the total energy in Eq. (24) to get the following equation:

$$\mathcal{L}(\mathbf{Q}, \lambda) = \frac{1}{2} \mathbf{Q}^\dagger (\mathbf{J} - \mathbf{F}_{PCM}) \mathbf{Q} + \lambda^\dagger [\mathbf{A}_{PCM} \mathbf{Q} - \mathbf{b}]. \quad (25)$$

Making the Lagrange function stationary with respect to $\mathbf{Q}$ provides an equation for λ , as shown in the following equation:

$$\begin{aligned} \frac{\partial \mathcal{L}(\mathbf{Q}, \lambda)}{\partial \mathbf{Q}} &= (\mathbf{J} - \mathbf{F}_{PCM}) \mathbf{Q} + \mathbf{A}_{PCM}^\dagger \lambda = \mathbf{0}, \\ \lambda &= -(\mathbf{A}_{PCM}^\dagger)^{-1} (\mathbf{J} - \mathbf{F}_{PCM}) \mathbf{Q}. \end{aligned} \quad (26)$$

The energy gradient shown in Eq. (27) is obtained by differentiating Eq. (25) with respect to an atomic Cartesian coordinates $\mathbf{r}_i$,

$$\begin{aligned} \frac{\partial \mathcal{L}}{\partial \mathbf{r}_i} &= \frac{1}{2} \mathbf{Q}^\dagger \left(\frac{\partial \mathbf{J}}{\partial \mathbf{r}_i} - \frac{\partial \mathbf{F}_{PCM}}{\partial \mathbf{r}_i} \right) \mathbf{Q} + \lambda^\dagger \left(\frac{\partial \mathbf{A}_{PCM}}{\partial \mathbf{r}_i} \mathbf{Q} - \frac{\partial \mathbf{b}}{\partial \mathbf{r}_i} \right), \\ \frac{\partial \mathbf{A}_{PCM}}{\partial \mathbf{r}_i} &= \frac{\partial \mathbf{C}}{\partial \mathbf{r}_i} (\tilde{\mathbf{J}} - \mathbf{F}_{PCM}) + \mathbf{C} \left(\frac{\partial \tilde{\mathbf{J}}}{\partial \mathbf{r}_i} - \frac{\partial \mathbf{F}_{PCM}}{\partial \mathbf{r}_i} \right), \\ \frac{\partial \mathbf{F}_{PCM}}{\partial \mathbf{r}_i} &= 2f(\epsilon) \mathbf{\Omega}^\dagger \mathbf{S}^{-1} \frac{\partial \mathbf{\Omega}}{\partial \mathbf{r}_i}. \end{aligned} \quad (27)$$

The $\partial \mathbf{b} / \partial \mathbf{r}$ term is again given in Eq. (7).

III. DISCUSSION

The GB is a continuum model, where the interaction between the solute and cavity for a given atom is parameterized by the radius of the corresponding atomic sphere. The coupling of the BC and GB models is expected to add only a small computational cost as it corresponds to simply adding a contribution from an effective Coulomb operator. The coupling provides a way to include polarization in the solvent (and implicitly in the solute) without including a large number of explicit solvent molecules, and this may be a way to retain high accuracy in terms of solvation energies without a large reduction in computational efficiency.⁴⁰

The C-PCM model, on the other hand, is a continuum model, where all solute charges interact with all the surface charges. The exact definition of the cavity surface depends on the specific model^{7,9} but will usually be allowed to change if the solute structure changes. The cavity surface enters the expression for the energy gradient by the $\mathbf{S}^{-1}$ matrix in Eq. (27), where $\mathbf{S}$ has a dimension corresponding to the number of surface charges. This is often larger than the number of solute charges, and constructing $\mathbf{S}^{-1}$ may become the computational bottleneck. While this formally must be done in each time step, it may in analogy with the use of neighboring lists for calculating nonbonded interactions be done only at suitable intervals.⁴¹ It can also be noted that the dd-COSMO model (closely related to C-PCM) has already been successfully coupled to the AMOEBA force field for MD simulations, as discussed in Ref. 24. The coupling of the BC and PCM models may also be useful for solvent-drop models where the cavity is held fixed, and the $\mathbf{S}$ matrix consequently only needs to be inverted once, as discussed in Ref. 31. In the case of a fixed cavity, the computational cost of inverting $\mathbf{A}_{PCM}$ and $\mathbf{A}_{PCM}^\dagger$ is the same as for the uncoupled case and for the coupling to the GB model. The BC/PCM combination, with or without a fixed cavity, may also be useful for QM/MM methods, where the computational cost arising from the QM region is expected to dominate over the calculation of $\mathbf{S}^{-1}$.

The present work focuses on the electrostatic component of implicit solvent models and can in analogy with existing models be augmented with terms representing exchange and dispersion interactions, as well as terms depending on the electric field aimed at modeling hydrogen bonding.⁴²

IV. CONCLUSIONS

The present work shows how the bond capacity model describing molecular polarization by electrostatic potential dependent atomic charges can be coupled to two commonly used implicit solvent models, the GB and C-PCM. The equations are derived by identifying the solvent reaction potential and including it in the total electrostatic potential V from which new kernels and bond capacity atomic charges are derived. Inclusion of solvation effects via the GB model leads to only a small increase in computational cost, in analogy with its use in other force field applications, and to our knowledge, this is the first time that the GB/SA model has been coupled to a polarizable force field. Introduction of implicit solvation via the C-PCM model formally requires inversion of a Coulomb matrix describing the interaction of all the surface charges at each time step, and this will in most cases lead to a large computational overhead. If the cavity is fixed, however, the computational cost will be only slightly higher than the uncoupled case. The fixed-cavity case has previously been adopted in conjunction with the fluctuating charge model as an alternative to periodic boundary conditions in multiscale molecular modeling.^{31,43,44} Given that the bond capacity model is similar in spirit to the fluctuating charge model, but does not display artificial long range charge transfer and nonlinear scaling of the polarizability with system size, the combination of a charge-only polarization model with continuum solvation models may find similar uses.

As the original bond capacity model, the BC/GB and BC/C-PCM versions represent nonvariational models where the atomic charges do not minimize the energy function. The energy gradients required for performing molecular dynamics simulations are obtained by applying a general Lagrange formalism introduced in Ref. 36. This reference shows that it is possible to obtain energy gradients with only a small additional computational overhead compared to variational energy models. Despite the similarity in the name, this formalism should not be confused with the extended Lagrangian method where thermostats and short time steps are required for the integration of the equations of motion. Our Lagrange formalism is a general method to avoid the calculation of response terms in the gradient and can be coupled to longtime step strategies that are able to significantly reduce the computational cost for a given amount of sampling as has been discussed for the polarizable point dipole model in Ref. 45. The present work defines new interaction kernels A_{GB} and A_{PCM} for calculating the bond capacity atomic charges and augments the bond capacity energy expression with solvation contributions arising from the GB and C-PCM models, respectively.

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