Rapid Bounds on Electrostatic Energies Using Diagonal Approximations of Boundary-integral Equations

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Abstract—Life as we know it depends critically on electrostatic interactions within and between biological molecules such as proteins. One simple, but surprisingly effective, model for studying these interactions treats a biomolecule of interest as a dielectric continuum of homogeneous low permittivity with some embedded distribution of charges, and the aqueous solvent around it as another homogeneous dielectric with higher permittivity. This gives rise to a mixed-dielectric Poisson problem, widely studied in the mathematics and electromagnetics communities. In this paper we describe some simple analytical approximations to a boundary-integral equation formulation of the mixed-dielectric problem. Remarkably, the approximations (which we call BIBEE, for boundary-integral-based electrostatics estimation) give provable upper and lower bounds for the actual electrostatic energy. Because BIBEE methods preserve interactions between components of the charge distribution, they may represent one approach to rapidly approximate the Green’s function for the geometry of interest.

1. INTRODUCTION

Virtually all biological molecules perform their functions in aqueous solutions — that is, surrounded by water molecules and a mixture of ions and small molecules, the presence of which profoundly impact biomolecular structure and function [1]. Although all-atom molecular dynamics (MD) simulations of biomolecules in explicit solvent are the highest-resolution calculations feasible on a day-to-day basis, unfortunately the majority of computational effort is spent on the solvent molecules rather than the biomolecule of interest. To improve efficiency, alternative methods have been developed to capture the average influence of the solvent on a biomolecule [2, 3], and can be hundreds to thousands of times faster. Implicit-solvent models often (but not always [4]) separate the average solute-solvent energetics into polar and nonpolar components. The polar component, which is the focus of this paper, models the electrostatic interactions between the biomolecule and the solvent, and the nonpolar component captures remaining aspects such as the energy of forming a solvent-free cavity for the molecular volume, and surface-tension effects [3].

The electrostatic interactions between a molecule and surrounding water are frequently modeled using a continuum dielectric framework, in which the solvent is assumed to be a homogeneous dielectric with permittivity approximately that of bulk water, and the molecule is assumed to be a low-dielectric body containing some distribution of charge. This mixed-dielectric Poisson problem has been studied in numerous areas of mathematical physics, particularly in electromagnetics [5, 6]; in this paper, we do not address the nonlinear Poisson-Boltzmann equation [7], or its linearized form, which are commonly used to account for the effects of mobile ions in solution. Given that linear continuum theory is an extreme oversimplification at the molecular scale, neglecting phenomena like dielectric saturation [8, 9] and the molecular nature of the solvent, the success of continuum models, in a variety of contexts, has been surprising [8, 10]. The existence of well-validated numerical software [11–13] has also helped to make continuum electrostatic theory a popular and widely accepted tool for studying molecular structure and function.

Despite the popularity of continuum methods, computational costs have remained a significant bottleneck in spite of rapid growth in CPU power and the development of powerful numerical algorithms. Although any one simulation may require only a minute to an hour, many types of theoretical studies require hundreds to thousands of simulations. For example, some approaches to computational molecular design assess the contribution of each chemical group (such as amino acid side chains or the chemical groups that make up the protein backbone) to the binding affinity between molecules; each such chemical group then requires its own simulation [14]. To make these and other large-scale calculations tractable, many groups have described heuristics capable of estimating electrostatic energies with much less computational effort [15, 16]. The generalized-Born (GB) method [15] is among the most popular of these simplified approaches [17, 18], and has been
extensively tested against accurate simulations [19]. Nevertheless, the essentially empirical nature of these methods and the numerous reports of its shortcomings motivate much work to improve the physical and mathematical rigor of computationally efficient methods to approximate energies within the continuum electrostatic model (e.g., [20]).

In this paper, we describe a widely used boundary-integral equation (BIE) formulation of the problem and present simple approximations, which we call BIBEE (boundary-integral-based electrostatics estimation) methods [21], that make numerical simulation almost trivial. The original BIE is widely known in electrostatics [5], and it is the author’s hope that the electromagnetics community will be able to recognize characteristics of the BIBEE method and contribute to further advances in molecular simulation. In BIBEE, one replaces the dense boundary-integral operator of the BIE with a chosen diagonal operator. One choice for the diagonal gives a provable upper bound for the reaction energy induced by the molecular charge distribution [22]; this method is called BIBEE by the Coulomb-field approximation (BIBEE/CFA). A different choice for approximating the integral equation gives a provable lower bound and is called BIBEE/LB. A third choice, called BIBEE by preconditioning (BIBEE/P) because its numerical implementation is identical to a diagonal preconditioner for BEM solution of the integral equation, gives an effective (but not yet proven) lower bound, much closer to the actual energy than BIBEE/LB.

The next section presents the theoretical background for the BIBEE approach and Section 3 presents the BIBEE approximations themselves. Computational results in Section 4 illustrate how BIBEE approximations compare to full numerical solution and to a simple GB model. A brief discussion in Section 5 concludes the paper.

2. BACKGROUND

2.1. Boundary-integral Equation Formulation of the Mixed-dielectric Problem

Figure 1 is an illustration of the problem of interest [5, 23, 24]. Two dielectric regions, labeled $I$ and $II$, with dielectric constants $\epsilon_I$ and $\epsilon_{II}$, are separated by a boundary $\Omega$. A distribution of fixed charges exists in region $I$, and in this paper it is assumed to be a set of $n_c$ point charges, the $i$th of which is located at $r_i$ and has value $q_i$. These charges polarize the solvent, which in turn creates a reaction potential in the molecule, which gives rise to what is known as the reaction-field energy. In region $I$, the electrostatic potential satisfies the Poisson equation

$$\nabla^2 \varphi(r) = -\sum_{i=1}^{n_c} q_i \delta(r - r_i)$$

(1)

where $\delta(r)$ is the Dirac delta function, and in region $II$ the potential satisfies the Laplace equation $\nabla^2 \varphi_{II}(r) = 0$. At the boundary the potential and the normal displacement field are continuous [25].

Having assumed linear response, the $n_c$-length vector of potentials at the charge locations can be expressed as $\varphi^{\text{reac}} = Lq$ and the reaction-field energy can be expressed as the quadratic expression $\frac{1}{2} q^T L q$, where $q$ is the $n_c$-length vector of the charge values and $L$ is called the reaction-potential matrix, because the matrix entry $L_{i,j}$ represents the reaction potential that a $+1e$ charge at $r_j$ induces at $r_i$. From reciprocity it is clear that $L$ is symmetric, and in addition for $\epsilon_I < \epsilon_{II}$ it can be shown that $L$ is negative definite. Note that eigenvectors of $L$ that correspond to distinct eigenvalues represent charge distributions that do not interact via solvent polarization (although they do interact Coulombically) [21].

Figure 1: The mixed-dielectric Poisson problem.
By Eq. (3), the reaction potential at a point boundary integral at region $I$ (that employs dielectric $\epsilon$) can approach the point charge. Still et al. suggested the generalized-Born (GB) model $R_{\text{Born}}$ where

$$
\int_{\Omega} \sigma(r') 4\pi ||r - r'|| dA' = \sigma(r),
$$

where $\sigma(r)$ represents the layer of surface charge induced on $\Omega$ and $n(r)$ is the outward normal at $r \in \Omega$ (pointing into region $II$ from region $I$). After accounting for the singular nature of the boundary integral at $r = r'$, we may re-write Eq. (2) as

$$\sigma(r) + \hat{\epsilon} \int \frac{\partial}{\partial n(r)} \frac{\sigma(r')}{4\pi ||r - r'||} dA' = -\hat{\epsilon} \sum_i \frac{q_i}{\partial n(r)} \frac{\sigma(r)}{4\pi ||r - r'||},$$

where the notation $\hat{f}$ denotes the principal value of the integral [26] and $\hat{\epsilon} = \frac{2(\epsilon_{II} - \epsilon_{IO})}{\epsilon_{II} + \epsilon_{IO}}$. After solving Eq. (3), the reaction potential at a point $r$ in the molecule is simply the Coulomb potential induced by $\sigma$:

$$\varphi^{\text{reac}}(r) = \frac{1}{\epsilon_I} \int_\Omega \frac{\sigma(r')}{4\pi ||r - r'||} dA'.$$

In operator notation Eq. (3) can be written as $(I + \hat{\epsilon}D^*)\sigma = -\hat{\epsilon}Bq$ and Eq. (4) as $\varphi^{\text{reac}} = C\sigma$.

### 2.2. Numerical Solution of Boundary-integral Equations

To solve Eq. (3) numerically using the boundary-element method (BEM), one discretizes $\Omega$ into a set of $n_B$ boundary elements and then defines a set of compactly supported basis functions $\chi_i(r)$ on the boundary elements so as to represent $\sigma(r)$ approximately as the weighted sum $\sigma(r) = \sum_i x_i \chi_i(r)$ where the weights $x_i$ are unknown. In the present work, we approximate $\Omega$ as a set of planar triangles, and define basis functions such that $\chi_i(r) = 1$ on boundary element $i$ and 0 otherwise. Finally, one enforces a set of $n_p$ independent linear constraints on the weights so that the integral equation is satisfied as closely as possible [26]. Regardless of the choice of constraints (one has some freedom to choose), this process generates the square matrix equation

$$Ax = Bq,$$

where the $n_p$-by-$n_p$ matrix $A$ is the discretized form of the operator $(I + \hat{\epsilon}D^*)$ and the $n_p$-by-$n_c$ matrix $B$ represents the discretization of $\hat{\epsilon}B$. In many BEM simulations, one forces the integral equation to be satisfied exactly at the centers (centroids) of the boundary elements; this is known as centroid collocation [6, 26]. However, as noted by Tausch and White [6], this type of constraint leads to inaccurate results for the electric-field integral operator in Eq. (3), and it is preferable to use a method known as qualocation instead [6, 27–29]. Writing the discretized form of the Coulomb integral operator $C$ as $C$, which maps the $n_p$-length vector $x$ to the $n_c$-length $\varphi^{\text{reac}}$, one can write the reaction-potential matrix as $L = CA^{-1}B$.

The matrices $A$, $B$, and $C$ are all dense, which precludes the use of Gaussian elimination for all but the smallest problems. Instead, one computes sparsiﬁed representations of the matrices using algorithms such as the fast multipole method (FMM) [30, 31], pre-corrected FFT [32], or FFTSVD [33], which allow the matrices to be applied to vectors using only linear time and memory. The linear system in Eq. (5) is then solved approximately using Krylov-subspace iterative methods like GMRES [34], in which one repeatedly applies $A$ to $Bq$ to generate a vector space from which an suitable approximation to the solution is found. A preconditioner matrix $P$ can be employed so that the linear system $PAx = PBq$ yields an acceptable approximate solution $x$ in fewer iterations than would be required to solve the original linear system.

### 2.3. Generalized-born Methods For Estimating Electrostatic Energies

The reaction energy for a sphere of radius $R$ with a central charge $q$ is known as the Born energy $E_{\text{Born}}$:

$$E_{\text{Born}} = \frac{1}{8\pi} \left( \frac{1}{\epsilon_{II}} - \frac{1}{\epsilon_I} \right) \frac{q_i^2}{R_i},$$

where $R_i$, called the Born radius for the ion, is clearly a measure of the degree to which the high dielectric can approach the point charge. Still et al. suggested the generalized-Born (GB) model that employs effective Born radii for molecules [15]. For an atom $i$ in the given molecule, one sets
\( q_1 = 1 \) and the rest to zero, calculates the resulting reaction energy \( E_i \), and then substitutes \( E_i \) into the left-hand side of Eq. (6) to solve for a radius \( R_i \). The reaction-potential matrix entries are then according to

\[
L_{i,j}^{\text{GB}} = \frac{1}{8\pi} \left( \frac{1}{\epsilon_{ii}} - \frac{1}{\epsilon_{lj}} \right) \frac{1}{\sqrt{r_{ij}^2 + R_i R_j \exp(-r_{ij}^2/4R_i R_j)}}. \tag{7}
\]

so that the self-term entries \( L_{i,i}^{\text{GB}} \) recover the original self-energy \( E_i \) in the limit as \( r_{ij} \to 0 \), and for large distances one recovers the difference in Coulomb energies between the same charges interacting in the different dielectrics. The empirical interpolation formula of Eq. (7) is the core equation of Generalized-Born (GB) methods and works surprisingly well to predict reaction energies [15, 19, 35, 36].

Of course, calculating \( L_{ij} \) in such a way requires simulating the electrostatics problem \( n_c \) times, whereas the total energy could be computed in only one simulation, and thus would offer no time savings at all. Instead, the charges’ self-energies are estimated using rapidly computed approximate methods, and then the radii are trivially calculated from Eq. (6). The history of GB methods centers predominantly, but not entirely [37], around finding efficient means to estimate these individual self-energies so that GB reaction energies agree with known analytical results or full numerical simulation [17, 18].

Most approaches to computing a charge’s self energy begin with what is called the Coulomb-field approximation (CFA) [35], in which one integrates the energy density of the bare Coulomb-field in the molecule (omitting the volume interior to the atom itself):

\[
R_i^{-1} \propto \int_V \frac{(r' - r_i)^T n(r')}{|r' - r_i|^4} \, dV'. \tag{8}
\]

Converting Eq. (8) to surface-integral form [16] reveals a direct connection between the CFA and the boundary-integral equation of Eq. (3): the surface-Generalized-Born (SGB)/CFA entails neglecting the integral operator in Eq. (2). In earlier work this was justified by the approximation’s exactness for the sphere with central charge [16] and considered to be a consequence of spherical symmetry.

### 3. BIBEE APPROXIMATIONS

#### 3.1. BIBEE/CFA: A Provable Upper Bound

The SGB/CFA method calculates each charge’s self energy by approximating the induced surface charge via

\[
\sigma^{\text{CFA}} = -\epsilon B q
\]

where again \( q_i = 1 \), \( q_j = 0 \) \( \forall i \neq j \). The second term on the left-hand side arises from the neglect of the integral operator in Eq. (2) — one assumes that all the eigenvalues of \( D^* \) in Eq. (3) are the same extremal eigenvalue associated with the constant normal electric field on the boundary [22]. The crux of the BIBEE/CFA method is to use the same diagonal approximation as in Eq. (9) but with all of the actual charges, rather than just one, so that \( \sigma^{\text{CFA}} \) includes contributions from all charges. The BIBEE/CFA reaction energy is then calculated the same way as in the actual boundary-integral equation approach, i.e., via Eq. (4). BIBEE/CFA is therefore the straightforward extension of the SGB approach to multiple charges, and it appears to be the boundary-integral formulation of the variational Coulomb-field approximation method [38].

The proof that BIBEE/CFA reaction energy is an upper bound to the actual reaction energy proceeds in two main stages [22]. In the first, one re-writes \( C \) in terms of \( B \), and exploits the fact that the normal electric field operator \( D^* \) is similar to a Hermitian operator \( \mathcal{H} \) (see [39]), so that the reaction energy can be expressed as a sum over the modes of \( \mathcal{H} \):

\[
E^{\text{reaction}} = \varepsilon^{-1} \sum_i \left( 1 - 2\lambda_i^D \right)^{-1} \left( 1 + \epsilon \lambda_i^D \right)^{-1} x_i^2
\]

where \( x_i \) represents the projection of \( B q \) onto the \( i \)th eigenvector of \( \mathcal{H} \). It is well known [26] that \( \lambda_i^D \in [-1/2, +1/2] \). In the proof’s second stage, the original operator \( (1 + \epsilon D^*) \) is replaced by
(1 − \epsilon/2) and subjected to the same decomposition by modes to obtain

\[ E_{CFA}^{CFA} = \epsilon^{-1} \sum \frac{1}{2} \left( 1 - 2\lambda_i^D \right)^{-1} \left( 1 - \frac{\epsilon}{2} \right)^{-1} x_i^2. \tag{11} \]

It is then easy to show that each term of the sum in Eq. (11) is greater than the corresponding term in Eq. (10); the full details of the proof are provided elsewhere [22].

3.2. BIBEE/LB and BIBEE/P: Lower Bounds

Other diagonal operators can be chosen to give alternative approximations. The BIBEE/LB approximation solves

\[ (I + \frac{\epsilon}{2}) \sigma_{LB} = -\epsilon B q, \tag{12} \]

dependent on the other extremal eigenvalue of \( D^* \); this can be proven to give a general lower bound for the electrostatic energy [22]. The BIBEE/P approximation arises from

\[ I \sigma_P = -\epsilon B q, \tag{13} \]

giving a provable lower bound to the reaction energy for geometries in which \( D^* \) is known to not possess positive eigenvalues, for instance spheres and prolate spheroids [40]. It is not yet understood why BIBEE/P seems to provide a lower bound for a wide variety of surfaces [22], given that it is known that for some shapes, including oblate spheroids [41], \( D^* \) can be proven to possess eigenvalues arbitrarily close to +1/2.

3.3. Numerical Implementation

As described previously, the reaction-potential matrix can be written as \( L = CA^{-1}B \) where \( B \) maps the vector of charges to the normal electric field at the boundary, \( A \) is the BEM matrix, and \( C \) maps the induced surface charge \( \sigma \) to the reaction potentials at the charge locations. Numerical computations using BIBEE simply employ different diagonal matrices in place of \( A \), where the diagonal entries are the discretized operators in Eqs. (9), (12), and (13). A MATLAB implementation of BIBEE is freely available online [42].

4. RESULTS

All of the numerical simulations performed in this section employed an interior dielectric constant \( \epsilon_I = 4 \) and exterior dielectric constant \( \epsilon_{II} = 80 \). All surfaces were discretized using MSMS [43], and all BEM operators were compressed using FFTSVD [33, 44]. Results for the BIBEE/LB approximation are not plotted because the bound is so loose that other results are obscured [22].

4.1. Charges in a Sphere

The simplest possible case is a single charge in a sphere; we use a sphere of radius 20 Å as a model for a small protein. Figure 2(a) contains plots of the reaction energy of a single +1e charge as a function of the charge’s distance from the sphere center. As explained previously, the SGB/CFA and BIBEE/CFA theories should give identical results for the single-charge case. In Figure 2(a), the numerical results for these theories are slightly different because SGB/CFA energies are calculated by direct numerical integration over the discretized surface [45], whereas the BIBEE/CFA calculations are based on the BEM approach described above. As is well known [37, 46], the CFA is inaccurate for the single charge problem as the charge approaches the sphere surface. Figure 2(b) are plots of the reaction energy of an ion pair in a sphere, as a function of the pair’s distance from the sphere center. The ion pair is composed of two charges, one +1e and one −1e, separated by 3 Å, with the line segment between them pointing radially outward from the sphere center. The CFA approaches are increasingly inaccurate as the ion pair nears the surface, but the BIBEE/P approximation exhibits excellent accuracy throughout; in general, BIBEE/P is most accurate at approximating energies that arise from charge distributions that generate highly localized electric fields on the dielectric boundary [21]. It is also significant that the BIBEE/CFA answers are substantially more accurate near the surface than the SGB/CFA answers. Because each ion taken in isolation would have the two CFA theories agree perfectly (as demonstrated by the results in Figure 2(a)), the BIBEE/CFA improvement must be due to the inclusion of the actual physics of interaction between the ions, by accounting for their mutual induction of surface charge even in the Coulomb-field approximation. The inadequacy of the heuristic Still interpolation formula.
Figure 2: The accuracy of approximate electrostatic models for charges in a sphere. All energies are in kcal/mol. Reaction energies have been computed by BEM solution of Eq. (3), surface-Generalized Born/Coulomb-field approximation (SGB/CFA) theory, and BIBEE approximations. (a) The reaction energy of a single +1\(e\) charge in a sphere of radius 20 Å, as a function of the charge’s distance from the sphere center. (b) The reaction energy of two charges of opposite sign, +1\(e\) and −1\(e\), separated by 3 Å, in a sphere of radius 20 Å, such that the charge locations and the sphere center are collinear. The distance is measured from the sphere center to the midpoint between the charges.

for calculating reaction energies in these cases has motivated the development of improved GB methods (see, e.g., [20, 37, 46]).

4.2. Electrostatics in a Realistic Small Molecule

Most molecules have highly irregular shapes. To illustrate that BIBEE approaches perform well for nonspherical shapes, we use a small molecule, the 22-atom alanine dipeptide [47] and calculate the full \(L\) matrices using BEM, SGB/CFA, and BIBEE/CFA and BIBEE/P. Figure 3(a) contains plots of the magnitudes of the eigenvalues of the computed matrices, sorted in increasing order; physically, all eigenvalues should all be negative, but the final eigenvalues of the SGB/CFA matrix appear to be increasing in magnitude because they are positive (nonphysical). Note that the BIBEE methods exhibit opposite regimes for good accuracy: BIBEE/CFA is most accurate for large-magnitude eigenvalues, whereas BIBEE/P is most accurate for smaller eigenvalues. This behavior suggests that it may be possible to find a physically-motivated, charge-distribution-dependent scheme to interpolate between the two estimates. Figures 3(b) and (c) are pseudocolor plots of the magnitudes of the projections of the eigenvectors of the CFA-based matrices \(L^\text{SGB}\) and \(L^\text{BIBEE}\) onto the eigenvectors of \(L^\text{BEM}\), i.e., the cell \((i, j)\) in Figure 3(b) represents the magnitude of \(V^\text{BEM}_i T V^\text{SGB}_j\). Figure 3(c) appears more “diagonal” than Figure 3(b) because the BIBEE approach more accurately preserves the charge distributions that do not interact via solvent polarization [21]. This example also serves to demonstrate the computational advantages of BIBEE. The total time to compute the BEM matrix was 5.73 seconds, whereas only 0.44 seconds were needed to compute each BIBEE matrix. Comparable performance advantages, showing that BIBEE is at least an order of magnitude faster than BEM, and within a factor of two or three slower than SGB/CFA, were found in [21] for a tripeptide example and for a protein-inhibitor example.

4.3. Interactions between Charges in Two Spheres

We now turn to an example in which one of the conditions of the original proof [22] does not hold: the case of multiple, disconnected, low-permittivity regions. This multiple-region problem could model a situation in which ones wishes to study interactions between multiple bodies that are not in physical contact, such as the interactions between ions, or how two molecules approach each other before binding. Figure 4(a) contains plots of reaction energies for a pair of spheres 1 Å in radius, each with a central +1\(e\) charge, as a function of the separation between them. Similar results are obtained for charges of opposite sign, and for larger spheres containing random charge distributions (results not shown). Figure 4(b) plots the CFA methods’ deviations from BEM simulation. Importantly, BIBEE/CFA appears to continue to offer an upper bound; BIBEE/P and
Figure 3: A comparison of the reaction-potential matrices computed using BEM, SGB/CFA, and BIBEE methods. (a) The eigenvalue magnitudes. The eigenvalues have been sorted in increasing order, and should all be negative; the final SGB/CFA eigenvalues are small and positive, which is why the magnitudes appear to increase. (b) The magnitudes of the projections of the SGB/CFA eigenvectors onto the BEM eigenvectors. (c) The magnitudes of the projections of the BIBEE/CFA eigenvectors onto the BEM eigenvectors. It can be seen that the BIBEE/CFA eigenvectors are well aligned with those from BEM across the entire spectrum.

Figure 4: The reaction energy of two spheres with +1e charges inside, as a function of the spheres’ separation; both spheres are of radius 1 Å. All energies are in kcal/mol. (a) The reaction energies. (b) The deviations of the SGB/CFA and BIBEE/CFA estimates from the BEM solution.

BIBEE/LB appear to offer lower bounds as well (data not shown). One expects the reasonably good agreement between the CFA-based methods and fully detailed numerical solution of the problem that is observed in Figure 4(a), given that the dominant contribution to the reaction energy arises from the spheres’ individual reaction energies. However, the deviations of the CFA-based estimates from the actual BEM results is illustrative of the difference between SGB/CFA and BIBEE/CFA methods (Figure 4(b)). Although in the present example these deviations are small enough to be essentially insignificant as a practical matter (i.e., the energies are so small as to rarely be of importance in studying the function of biological systems), they point again to the improved physical model in BIBEE that employs the CFA using all charges simultaneously.

5. DISCUSSION

This article has described the performance of diagonal approximations to a boundary-integral equation widely used to study electrostatic interactions in mixed dielectrics [5]. This boundary-integral equation is a valuable tool for studying the structure and function of proteins and other biological molecules by modeling both the molecule of interest and the aqueous solvent as dielectric continua, and assuming that the molecule contains some distribution of charge [23, 24]. By replacing the
dense integral operator with a diagonal one (what we call the boundary-integral-based electrostatics estimation, or BIBEE, method), one eliminates the computationally expensive solution of the mixed-dielectric problem and obtains instead a rapidly computed approximation. The choice of diagonal approximation allows one to obtain provable upper and lower bounds to the actual electrostatic energy. Pairwise interactions are remarkably well preserved even in this approximation of the integral operator. We hope that the computational and theoretical electromagnetics communities, which have long history and extensive experience with the theory and practice of boundary-integral equations, may recognize these approximation or similarities they may have to other techniques, and thereby stimulate future advances in modeling molecular interactions. To support this goal, a simple MATLAB implementation of BIBEE is freely available online [42].

The BIBEE/CFA approximation appears to be the boundary-integral form of the variational Coulomb-field approximation (CFA) described by Borgis et al. [38], although a more detailed comparison remains to be performed. One advantage of the boundary-integral analysis is that it allowed direct identification that the CFA exploits the extremal eigenvalue of the electric-field integral operator, immediately giving theoretical support to the BIBEE/P and BIBEE/LB methods [21, 22]. We acknowledge that for reasons of space, we have only compared BIBEE methods to the simplest formulation of the Generalized-Born model, SGB/CFA [16], without using any of the sophisticated correction factors that have been described in the literature [16, 46, 48]; earlier work on BIBEE compared results to the recent GBMV (Generalized Born with Molecular Volume) method [48]. Hopefully, the BIE analysis that clarified the CFA can offer similar support for these new GB methods.

Numerous questions remain for future investigation. It is still not known whether the effective lower bound offered by BIBEE/P is actually a provable lower bound, or if there are conditions under which its apparent bounding properties may be proven. Also, as the last example illustrated, it appears that BIBEE/CFA continues to offer an upper bound for multiple disconnected low-dielectric regions; a proof of this would be a valuable contribution. Finally, in earlier work [22] a simple and purely empirical interpolation between BIBEE/CFA and BIBEE/P was tested and found to give excellent agreement with BEM results for a small peptide. A mathematically justified interpolant, perhaps based on the work of Onufriev and collaborators [20], could obviate the need for much more expensive simulations without the need to resort to largely heuristic approaches like GB. Other extensions for biomolecular electrostatics are also of interest, including problems with more than two dielectric constants and problems in which sources exist in regions with different dielectric constants. The latter, for example, would allow BIBEE to rigorously accelerate Monte Carlo simulations for understanding how ion-channel proteins in cell membranes can selectively pass one kind of ion (e.g., sodium) but not others [49].

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