Computation of electrostatic forces between solvated molecules determined by the Poisson–Boltzmann equation using a boundary element method

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A rigorous approach is proposed to calculate the electrostatic forces among an arbitrary number of solvated molecules in ionic solution determined by the linearized Poisson–Boltzmann equation. The variational principle is used and implemented in the frame of a boundary element method (BEM). This approach does not require the calculation of the Maxwell stress tensor on the molecular surface, therefore it totally avoids the hypersingularity problem in the direct BEM whenever one needs to calculate the gradient of the surface potential or the stress tensor. This method provides an accurate and efficient way to calculate the full intermolecular electrostatic interaction energy and force, which could potentially be used in Brownian dynamics simulation of biomolecular association. The method has been tested on some simple cases to demonstrate its reliability and efficiency, and parts of the results are compared with analytical results and with those obtained by some known methods such as adaptive Poisson–Boltzmann solver. © *2005 American Institute of Physics*. [DOI: 10.1063/1.1924448]

I. INTRODUCTION

Continuum models of electrostatic interaction, based on the Poisson–Boltzmann equation (PBE), have found increasing application in molecular modeling.[1–4] Several different computational techniques have been developed in the last two decades, such as finite difference (FD) methods,[5–7] finite element (FE) methods,[8,9] and boundary element methods (BEMs).[10,11] In most applications, the stationary solutions of the PBE under fixed conformations were used for calculating the electrostatic potential or solvation energy. However, the PB force can also be used in molecular-dynamics (MD) simulation and other conformational sampling procedure for biomolecules. Gilson *et al.*[12] derived an expression for PB force calculation that is proper for the FD approach. The formula is compatible with the Maxwell stress tensor method, and a smooth dielectric boundary is required in that method. We have previously applied the FDPB force (omitting the boundary pressure) in MD simulation of an insulin dimer.[13]

For some applications involving linear and elliptical problems, the BEM is vastly superior to the FD and FE methods in both efficiency and accuracy. Alternative methods all require discretizing the whole domain, which considerably raises the computational cost, while the BEM only requires discretizing the surface of the molecule. Moreover, the BEM adopts an open boundary condition (not an artificial one as in FD method) and its solution domain is arbitrary in principle (not limited to a cubic box). Such a unique feature enables the BEM to easily account for the interaction between widely separated biomolecules, e.g., in the Brownian dynamics simulation of a protein-protein association process. As will be shown in the following sections, because the discretization of each individual molecule is fixed and can be used repeatedly during multiple rigid conformational sampling in protein-protein interaction, the BEM is especially efficient in saving computational cost. In the normal FD methods the discretization step has to be repeated for every different conformations of a protein pair; this is not practical for multiple protein-protein conformational sampling. In typical calculations using the FDPB method to simulate protein-ligand or protein-protein encounters [as in the widely used program University of Houston Brownian Dynamics[14] (UHBD)], the reaction field is calculated only for a fixed protein conformation using FD method, and the moving ligand/protein is taken as a set of (effective) charges immersed in and interacting with the reaction field. Hence the contribution of the moving ligand/protein to the reaction field is ignored or at least simplified. This may lead to considerable deviation in the interaction calculation for a large

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ligand or protein. The BEM results for multiple molecules can give the full PB interaction between solvated molecules.

For the dynamical study of protein-ligand/protein encounter, the PB forces and torques are essential. In theory, the forces and torques on a rigid-body molecule can be obtained by integrating the stress tensor over the molecular surface. Because the BEM includes an explicit dielectric boundary surface, it looks conceptually straightforward to compute forces (including boundary pressure) using the Maxwell stress tensor. However, the stress tensor calculation in BEM is not trivial, and there are still problems to be tackled. The full electrostatic field on the boundary is required in order to calculate the stress tensor, while only the normal component of the electric field on the surface is directly obtained in the present direct BEM solutions (with both single-layer and double-layer terms). In calculating the component on any other spatial direction (such as the tangential component) on the surface, a hypersingular integration arises and causes complexity in both theory and numerical implementations.[15] The hypersingularity comes from the derivative of the Green's function associated with the double-layer part in the BEM. In the single-layer formulation of the BEM, the hypersingular problem in force and torque calculations can be avoided, such as in the work of Bordner and Huber,[16] who used the "surface charge density" to calculate the force. This "polarized charge" method was described by Zauhar,[17] in which the force included both qE forces and boundary pressures, and this was also incorporated into the BEM Langevin dynamics simulations.[18] The accuracy of the boundary pressure computed by this technique has not yet been demonstrated. More generally, the use of only a single- or double-layer representation of BEM to calculate the forces and torques has still not been adequately tested, although they have been widely applied in electrostatic potential and energy computations.

In this work, we use a variational principle to derive a rigorous algorithm to calculate the forces and torques imposed on a rigid molecule in a solvated molecular system, and avoid the hypersingular problem associated with the stress tensor calculation. The calculated force inherently includes the qE term, the boundary electrostatic pressure, and the ionic concentration pressure.[12] The force computation does not incur much extra computational cost compared to solving the PBE.

II. BOUNDARY INTEGRAL REPRESENTATION OF THE SOLUTION OF THE PBE

In this section, the integral equations governing the electrostatic potential of a system with an arbitrary number of molecules in an ionic solution will be derived. Let us first consider the BEM solution for an isolated molecule, which is surrounded by infinitely homogeneous solvent. For brevity, the electrostatic potential $\phi(x_p)$ is written as ϕ_p, where p is any position inside, outside, or on the boundary of the molecule. The Poisson–Boltzmann equation can be written as

$$\nabla^2 \phi_p^{\text{int}} = -\frac{1}{D_{\text{int}}} \sum_k q_k \delta(r_p - r_k), \quad p \in \Omega, \tag{1}$$

$$\nabla^2 \phi_p^{\text{ext}} = \kappa^2 \phi^{\text{ext}}(r_p), \quad p \in \overline{\Omega}, \tag{2}$$

where ϕ_p^{int} is the potential at position p inside the molecular domain $\Omega, \partial\Omega$ is its boundary, i.e., solvent-accessible surface, ϕ_p^{ext} is the potential at position p outside domain Ω, D_{int} is the interior dielectric constant, r_k is the position of the kth source point charge q_k of the molecule, and κ is the inverse of the Debye–Hückel screening length, which is determined by the ionic strength of the solution. By using Green's second identity

$$\int_\Omega (\phi \nabla^2 \psi - \psi \nabla^2 \phi) dV = \int_{\partial\Omega} (\phi \nabla \psi - \psi \nabla \phi) \cdot dS, \tag{3}$$

the solutions for Eqs. (1) and (2) can be expressed as

$$\phi_p^{\text{int}} = \oint_{\partial\Omega} \left[G_{pt} \frac{\partial \phi_t^{\text{int}}}{\partial n} - \frac{\partial G_{pt}}{\partial n} \phi_t^{\text{int}} \right] dA_t + \frac{1}{D_{\text{int}}} \sum_k q_k G_{pk}, \quad p,k \in \Omega, \tag{4}$$

$$\phi_p^{\text{ext}} = \oint_{\partial\Omega} \left[-u_{pt} \frac{\partial \phi_t^{\text{ext}}}{\partial n} + \frac{\partial u_{pt}}{\partial n} \phi_t^{\text{ext}} \right] dA_t, \quad p \in \overline{\Omega}, \tag{5}$$

where n is the outward normal vector and t is an arbitrary point on the boundary. G and u are the Green functions and also the fundamental solutions of Eqs. (1) and (2), respectively,

$$G_{pq} = \frac{1}{4\pi r_{pq}}, \tag{6}$$

$$u_{pq} = \exp(-\kappa r_{pq})/4\pi r_{pq}. \tag{7}$$

It is straightforward to extend the above boundary integral equations to a system with an arbitrary number of separate domains surrounded by infinite homogeneous solvent,

$$\phi_{p_i}^{\text{int}} = \oint_{\partial\Omega_i} \left[G_{p_i t_i} \frac{\partial \phi_{t_i}^{\text{int}}}{\partial n} - \frac{\partial G_{p_i t_i}}{\partial n} \phi_{t_i}^{\text{int}} \right] dA_{t_i} + \frac{1}{D_{\text{int}}} \sum_k q_{k_i} G_{p_i k_i}, \quad p_i, k_i \in \Omega_i, \tag{8}$$

$$\phi_p^{\text{ext}} = \sum_i \oint_{\partial\Omega_i} \left[-u_{pt_i} \frac{\partial \phi_{t_i}^{\text{ext}}}{\partial n} + \frac{\partial u_{pt_i}}{\partial n} \phi_{t_i}^{\text{ext}} \right] dA_{t_i}, \quad p \in \overline{\Omega 1 \cup \Omega 2 \cup, \ldots}, \tag{9}$$

where p_i and t_i in Eq. (8) denote the points in the ith domain Ω_i and on the ith domain surface $\partial\Omega_i$, respectively, q_{k_i} is the kth point charge in the ith domain, and p is a point outside all the molecules in Eq. (9).

When point p approaches surface $\partial\Omega$, we can utilize the jump discontinuity of the double-layer potential at boundary $\partial\Omega$ (Ref. 19) to obtain the following integral equations for the one-domain case from Eqs. (4) and (5):

$$\frac{1}{2}\phi_p^{\text{int}} = \oint_{\partial\Omega}^{PV}\left[G_{pt}\frac{\partial\phi_t^{\text{int}}}{\partial n} - \frac{\partial G_{pt}}{\partial n}\phi_t^{\text{int}}\right]dA_t + \frac{1}{D_{\text{int}}}\sum_k q_k G_{pk}, \quad p \in \partial\Omega, \tag{10}$$

$$\frac{1}{2}\phi_p^{\text{ext}} = \oint_{\partial\Omega}^{PV}\left[-u_{pt}\frac{\partial\phi_t^{\text{ext}}}{\partial n} + \frac{\partial u_{pt}}{\partial n}\phi_t^{\text{ext}}\right]dA_t, \quad p \in \partial\Omega, \tag{11}$$

where PV denotes the principal-value integral to avoid the singular point when $t \to p$ in the integral equations. Similar expressions can be obtained for a multiple molecular system.

The surface potential and its normal derivative can be solved from Eqs. (10) and (11) with the following two boundary conditions at the dielectric boundary:

$$\phi^{\text{int}} = \phi^{\text{ext}}, \tag{12}$$

$$D_{\text{int}}\frac{\partial\phi^{\text{int}}}{\partial n} = D_{\text{ext}}\frac{\partial\phi^{\text{ext}}}{\partial n}, \tag{13}$$

where D_{ext} is the exterior dielectric constant.

III. NUMERICAL TREATMENT

A. Numerical solution for a single molecule system

Substituting Eqs. (10) and (11) with Eqs. (12) and (13) at the boundary, and through discretizing the boundary, we can get two sets of equations with two kinds of unknown quantities, the surface potential $f = \phi^{\text{int}} = \phi^{\text{ext}}$, and its outside normal derivative $h = \partial\phi^{\text{ext}}/\partial n$. Flat triangular elements are used for the boundary discretization in this work. And a linear element approximation is used, which means that all unknown surface functions, e.g., f and h, are approximated with linear combination of the values at three vertices (nodes) of the element weighted by the local triangle coordinate (ξ, η), $0 \leqslant \xi \leqslant 1$, $0 \leqslant \eta \leqslant 1-\xi$. For example, the value $f(\xi, \eta)$ can be expressed as

$$f(\xi, \eta) = (1 - \xi - \eta)f(x_1) + \xi f(x_2) + \eta f(x_3), \tag{14}$$

where x_1, x_2, and x_3 are the positions of the three vertices of the element.

Denoting f_t and h_t as the unknown potential and its outside normal derivative on the tth node, after discretization, the integral Eqs. (10) and (11) become a set of linear equations:

$$\sum_t^N \left[\left(B_{pt} + \tfrac{1}{2}I\right)f_t - A_{pt}h_t\right] = Q_p, \tag{15}$$

$$\sum_t^N \left[\left(D_{pt} - \tfrac{1}{2}I\right)f_t - C_{pt}h_t\right] = 0, \tag{16}$$

where N is the number of nodes on the triangulated surface, and

$$Q_p = \frac{1}{D_{\text{int}}}\sum_k q_k G_{pk}, \tag{17}$$

and A, B, C, and D are $N \times N$ coefficient matrices that come from integrals on related elements, which are noted as follows:

$$A_{pt} \leftarrow \frac{D_{\text{ext}}}{D_{\text{int}}}\int_{Et} G(x_p, x_t)dA_t, \tag{18}$$

$$B_{pt} \leftarrow \int_{E_t} \frac{\partial G(x_p, x_t)}{\partial n}dA_t, \tag{19}$$

$$C_{pt} \leftarrow \int_{E_t} u(x_p, x_t)dA_t, \tag{20}$$

$$D_{pt} \leftarrow \int_{E_t} \frac{\partial u(x_p, x_t)}{\partial n}dA_t. \tag{21}$$

For example, A_{pt} is a weighted sum of integrations on all elements E_t that include the tth node, and the weight is determined by the numerical quadrature method. The integration on element E_t not containing x_p is trivial, which can be calculated by Gaussian quadrature with a certain number of quadrature base points. When the element E_t contains x_p, the principal-value integral should be applied, and through transformation, the Gaussian quadrature can also be used.[20]

For clarity, matrix and vector representations will be used from now on. Let's us denote matrix H as

$$H = \begin{pmatrix} B' & -A \\ D' & -C \end{pmatrix}, \tag{22}$$

where $B' = B + \frac{1}{2}I$, $D' = D - \frac{1}{2}I$, and I is the identity matrix; the linear equation system can then be simply written as

$$H\begin{pmatrix} f \\ h \end{pmatrix} = \begin{pmatrix} Q \\ 0 \end{pmatrix}. \tag{23}$$

A conventional way to solve Eq. (23) is to use the LU decomposition algorithm. With a fixed boundary discretization, the LU decomposition factors remain the same, thus can be used repeatedly. Much of the matrix computation time can be saved, making it efficient for multiple conformational calculation or Brownian dynamics (BD) simulation, as will be discussed in the later sections.

B. Extension to an interacting system with an arbitrary number of separate molecules in ionic solution

For a system with an arbitrary number of separate molecules, the corresponding equations and solution vectors are similar to Eqs. (22) and (23) but with an expanded matrix and vector. It can be easily found that new matrices A, B', C, and D' in H can be blocked further, and most of the blocks only depend on individual boundaries. We use A^i, B'^i, C^i, D'^i, and H^i to denote the corresponding coeffi-

cient matrices for the ith molecular boundary, with similar meaning as in the isolated molecule case. Matrices A and B' have the forms of

$$A=\begin{pmatrix} A^1 & 0 & & \cdot\cdot \\ 0 & \cdot\cdot & & \\ & & A^1 & \cdot\cdot \\ \cdot\cdot & & \cdot\cdot & \end{pmatrix}, \quad B=\begin{pmatrix} B'^1 & 0 & & \cdot\cdot \\ 0 & \cdot\cdot & & \\ & & B'^i & \cdot\cdot \\ \cdot\cdot & & \cdot\cdot & \end{pmatrix}. \quad (24)$$

Though C and D' have nonzero cross terms, we still use a similar blocked representation. Let us use C^{ij} and $D^{ij}(i\neq j)$ to denote these cross coefficient submatrices, in which the elements correspond to the coefficients between nodes on the ith boundary and nodes on the jth boundary. For example, C^{ij}_{pt} is the interaction coefficient for the pth node on the ith molecular boundary and the tth node on the jth molecular boundary:

$$C^{ij}_{pt} \leftarrow \int_{E_{t_j}} u(x_{p_i}, x_{t_j}) dA_{t_j}. \quad (25)$$

The elements in the D^{ij} are similar. Similarly, the f vector also extends to be $\{f^1,\ldots f^i,\ldots f^j,\ldots\}^T$, and h becomes $\{h^1,\ldots h^i,\ldots h^j,\ldots\}^T$, where T denotes transpose operation, and f^i and h^i are the solution vectors associated with the ith boundary. Then, the linear system has the same form as in Eq. (23).

Suppose that f^i and h^i are the surface potential and the corresponding normal derivative for the ith isolated molecule in ionic solution, and have been solved independently in advance, an iterative procedure can be used to obtain the changes in f^i and h^i, noted as Δf^i and Δh^i, due to the presence of other molecules:[11]

$$H^i\begin{pmatrix}\Delta f^i \\ \Delta h^i\end{pmatrix}=\begin{pmatrix}0 \\ \nu^i\end{pmatrix}, \quad i=1,2,\ldots, \quad (26)$$

where H^i is the same as in Eq. (22)

$$H^i=\begin{pmatrix} B'^i & -A^i \\ D'^i & -C^i \end{pmatrix} \quad (27)$$

and

$$\nu^j=\sum_{j\neq i} -D^{ij}(f^j+\Delta f^j)+C^{ij}(h^j+\Delta h^j). \quad (28)$$

Equation (26) forms the general BEM iterative formulas for the linearized PBE solution for multiple molecules in ionic solution. The solutions f^i and h^i for each individual molecule are required to be solved in advanced for just once, then the individual matrices H^i and its LU decomposition factor can be used repeatedly in the iterative procedure as in Eq. (26) to get Δf and Δh, which determine all the interactions between the molecules (see the following sections). Therefore, for conformations with different relative positions and orientations in a system where only the cross matrices C^{ij} and D^{ij} are needed, this iterative procedure is efficient to get the solution. Moreover, a proper frame has been found to calculate the forces and torques on each molecule using a variational principle (see Sec. III D).

C. The interaction energy between solvated molecules

After Δf and Δh are obtained, the change in the electrostatic potential at any source charge position r_{k_i} in the ith molecule, say, ΔV_{k_i}, can be computed by integration:

$$\Delta V_{k_i}=\oint_{\partial\Omega_i}\left[G_{k_it_i}\frac{D_{\text{ext}}}{D_{\text{int}}}\Delta h_{t_i}-\frac{\partial G_{k_it_i}}{\partial n}\Delta f_{t_i}\right]dA_{t_i}. \quad (29)$$

The interaction energy within the molecular system is given by

$$\Delta U=\frac{1}{2}\sum_i\sum_{k_i} q_{k_i}\Delta V_{k_i}, \quad (30)$$

where q_{k_i} is the partial charge of the kth atom of the ith molecule.

D. Electrostatic forces and torques on molecule

A promising application for this approach is in the BD simulation of protein-protein/ligand encounter, where the forces and torques must be calculated. Instead of calculating the stress tensor on the molecular surface, which will cause hypersingularity due to the second derivatives on Green's function, here the variational principle is used to calculate the forces among molecules. In an encounter study, the typical setup is that the large protein is fixed, and only the small ligand or protein moves relative to the fixed proteins. Assume that a variation in displacement δx_2 on the moving molecule causes a variation in the interaction energy $\delta\Delta U$, then $F=-\delta\Delta U/\delta x_2$. By substitution of Eq. (30), we get

$$F=-\frac{1}{2}\sum_i\sum_{k_i} q_{k_i}\delta\Delta V_{k_i}/\delta x_2. \quad (31)$$

Now the problem is to calculate $\delta\Delta V_{k_i}/\delta x_2$. In Eq. (29), because the variation of δx_2 on the whole moving molecule does not change G_{k_it} and $\partial G_{k_it}/\partial n$, δG_{k_it} and $\delta\partial G_{k_it}/\partial n$ are equal to 0. Therefore, one only needs to calculate $\delta\Delta h/\delta x_2$ and $\delta\Delta f/\delta x_2$. This can be done by taking variations on both sides of Eqs. (26) and (28). Noting that $\delta H^i=0$, $\delta f^j=0$, and $\delta h^j=0$, the only nonzero variational matrices are δD^{ij} and $\delta C^{ij}(i\neq j)$, and these can be obtained from their definitions in the discretization of the integral equations. Because the integral calculations for these two kinds of matrices are only performed between the two molecular boundaries, there is no singularity or hypersingularity involved. A new set of interative equations are derived for solving the unknown $\delta\Delta f^i/\delta x_2$ and $\delta\Delta h^i/\delta x_2$:

$$H^i\begin{pmatrix}\dfrac{\delta\Delta f^i}{\delta x_2} \\ \dfrac{\delta\Delta h^i}{\delta x_2}\end{pmatrix}=\begin{pmatrix}0 \\ \dfrac{\delta v^i}{\delta x_2}\end{pmatrix}, \quad i=1,2,\ldots, \quad (32)$$

and

TABLE I. The BEM solution at the nodes on the spherical surface. Five points are selected to compare the solutions by two surface meshes. f and h are potential and its normal derivative, respectively. f_{analy} and h_{analy} are the corresponding analytical values, and err_f and err_h are relative errors in percentage of f and h, respectively. The corresponding units are in Å, mol, and kcal.

Nodes	x	y	z	f	h	f_{analy}	err_f	h_{analy}	err_h
				Surface mesh with 162 nodes and 320 elements					
1	0.000	0.000	1.000	4.485	−4.202	4.150	8.08	−4.150	1.27
2	0.273	0.000	0.962	4.499	−4.200	4.150	8.41	−4.150	1.21
3	0.084	0.260	0.962	4.500	−4.191	4.150	8.44	−4.149	1.02
4	0.526	0.000	0.851	4.518	−4.173	4.150	8.88	−4.146	0.67
5	0.362	0.263	0.894	4.526	−4.219	4.150	9.08	−4.152	1.62
				Surface mesh with 642 nodes and 1280 elements					
1	0.000	0.000	1.000	4.326	−4.092	4.150	4.24	−4.150	−1.39
2	0.138	0.000	0.990	4.304	−4.220	4.150	3.71	−4.150	1.68
3	0.043	0.131	0.990	4.304	−4.224	4.150	3.71	−4.154	1.68
4	0.273	0.000	0.962	4.314	−4.179	4.150	3.94	−4.150	0.70
5	0.181	0.132	0.975	4.331	−4.094	4.150	4.37	−4.147	−1.26

$$\frac{\delta v^i}{\delta x_2} = \sum_{j \neq i} -\frac{\delta D^{ij}}{\delta x_2}(f^j + \Delta f^j) - D^{ij}\frac{\delta \Delta f^j}{\delta x_2} + \frac{\delta C^{ij}}{\delta x_2}(h^j + \Delta h^j) + C^{ij}\frac{\delta \Delta h^j}{\delta x_2}. \tag{33}$$

Finally, the forces can be computed by subsituting the interative solutions to Eq. (31). Similarly, the torques can be obtained following the same variational approach and interative procedure as in the force calculation, whereas the variations of the potential δV_{k_i} are taken with respect to a small variation of the relative rotational angle $\delta\theta$ of the moving molecule. In fact, the calculation for the torque can be simplified. In Eq. (31), if each term is considered as a component force contributing to the total force on the moving molecule, then the torque M is easily calculated with respect to the center of mass r_c of the molecule as follows:

$$M = -\frac{1}{2}\sum_i \sum_{k_i} q_{k_i}(r_{ck_i} \times \delta \Delta V_{k_i}/\delta x_2), \tag{34}$$

where the r_{ck_i} is a vector from the center of mass r_c to the kth point charge in the ith molecule. The accuracy of this method will be demonstrated in the following simple test cases.

IV. TESTS FOR SOME SIMPLE CASES

The program is first tested on a single sphere model, in which a unit positive charge is positioned at the center of a unit sphere (radius of 1 Å). The relative interior and exterior dielectric constants are set as 2 and 80, respectively. The ionic concentration is 0. We use both 320 boundary elements (BEs) and 1280 BEs to check the computational accuracy. Table I shows the BEM solution values and the analytical values on the first five nodes on the sphere.

It is found that with 1280 BEs the computation accuracy for potential is improved compared with 320 BEs, and the relative error with respect to the analytical results decreases to about half of that obtained with 320 BEs. Note that the derivatives of the potential on the boundary are calculated even more accurately than the potential itself. This is recapitulated in the force calculations described below, and is quite promising for BD trajectory calculation.

Figure 1 shows the potentials calculated using the BEM, adaptive Poisson–Boltzmann solver (APBS)[21] and analytical results plotted along a radial line. The BEM uses a surface mesh with 162 nodes (320 BEs), APBS uses multigrid with grid points $97\times97\times97$, coarse grid dimension $15\times15\times15$ Å^3, and fine grid dimension $6\times6\times6$ Å^3. The APBS potentials for each plotting point are obtained by interpolation from its solutions on grids, while the BEM results are obtained with surface integration according to Eqs. (4) and (5). It is found that in the exterior region away from the boundary (>1.1 Å), both BEM and APBS results coincide very well with the analytical results. In most of the interior domain, the BEM's results still agree with the analytical results, while the APBS results deviate somewhat from the analytical results. In a narrow area very close to the boundary, both numerical methods show larger relative errors from the analytical results relative to other positions, about 8% in BEM, and more than 50% in APBS. The reason may be that at the boundary area, the grid treatment in APBS is expected to produce artifacts. In addition, APBS uses approximate

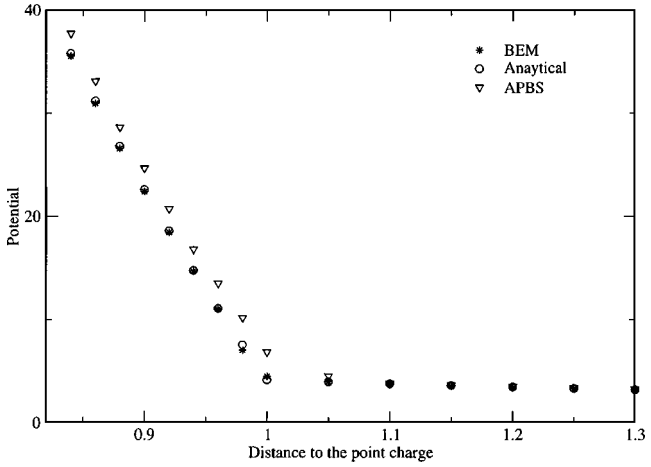

FIG. 1. Potentials at different radial positions in the unit sphere model obtained with BEM, APBS, and analytical results.

boundary conditions, while the correct boundary conditions are enforced in BEM. The solvation energy of this model is also calculated. The analytical solvation energy is −80.92 kcal/mol, BEM gives the result of −81.06 kcal/mol (error 0.14 kcal/mol), and APBS gives −81.58 kcal/mol (error 0.66 kcal/mol).

The CPU time for a whole BEM calculation with 320 BEs is 0.49 s on Intel Pentium IV (2 GHz), but 28.8 s with 1280 BEs. A single APBS solution procedure takes 39.6 s, and the solvation energy usually needs two solutions of APBS with different exterior dielectric settings.

The second test model is a two-unit sphere system with each containing a positive unit charge in the centers. The two spheres are put on the *x* axis symmetrically to the origin with a 4-Å center-to-center distance. The dielectric constants are the same as above. The BEM gives an interaction energy of 1.22 kcal/mol. Using the same treatment for electrostatic interactions as is typically done in BD simulation with the program UHBD, in which only one molecular reaction field (protein) is considered, and the other one (ligand) is represented with a set of point charges that directly interact with the reaction field, one point charge has an interaction energy of 1.02 kcal/mol with the reaction field due to the other one in this model. This is about 0.2 kcal/mol different from the full electrostatic energy calculation in BEM. This amount is expected to be larger for an approaching protein/protein or protein/ligand system. Therefore, if the reaction criteria are defined to be close encounter in a BD simulation, the amount of energy difference calculated by BEM and UHBD (similar to APBS) may significantly influence the encounter kinetics.

To test the force calculation, we set both the interior and exterior dielectric constants to 1 in the above two-sphere model. 320 BEs are used, and all other details are kept the same. Because the energy calculation by BEM has been demonstrated to be of good accuracy in the above tests, we use the "virtual work" principle to get a reliable numerical force to compare with the force calculated with the procedure presented in this work. To get the virtual work, the second charge and its associated sphere are moved by a small displacement of 0.01 Å in the *x* direction, and the difference in the interaction energy ($\Delta\Delta U$) is computed by BEM, then the virtual work force is obtained with $F_x^{\text{virtual}} = -\Delta\Delta U/0.01$. The analytical force $F_x^{\text{analy}} = 20.75$ kcal/mol Å, the virtual work force $F_x^{\text{virtual}} = 19.63$ kcal/mol Å (relative error ~5.4%), and our BEM procedure gives $F_x = 19.58$ kcal/mol Å (relative error ~5.6%). The results show that the forces F_y and F_z along the *y* and *z* directions are indeed 0 in terms of the numerical error ($<10^{-5}$). This means that the accuracy of the force calculation by our procedure is somewhat higher than that of the boundary potential calculation in BEM. Using 1280 BEs, the calculated force is $F_x = 20.20$ kcal/mol Å (relative error 2.6%), and the virtual work force is 20.25 kcal/mol Å (relative error 2.4%).

The last model is a point charge and dipole interaction system. The point charge surrounded by a spherical boundary is located at (−2 0, 0); the dipole is also surrounded by a spherical boundary with its two point charges located at (2, 0, 0.1) and (2, 0, −0.1), respectively. In this model, there are both force and torque acting on the dipole, but only the *z*-direction force component F_z and the *y*-direction torque component M_y are not zero. The analytical solutions are $F_z^{\text{analy}} = -1.04$ kcal/mol Å, and $M_y^{\text{analy}} = -4.15$ kcal/mol. Our BEM results are $F_z = -1.02$ kcal/mol Å and $M_y = -4.08$ kcal/mol. Both relative errors are about 2%.

V. CONCLUSIONS AND DISCUSSION

We apply the variational principle in the BEM frame and present an iterative procedure to calculate the forces and torques among rigid molecules immersed in ionic solution. The direct formulation of the boundary integral equations based on Green's theorem for BEM is used. The calculated force is a full PB force that takes into account the reaction field of all the concerned molecules, and inherently includes the boundary pressure due to the electric field and ion concentration. The computational accuracy for force and torque is demonstrated in sample tests; the accuracy is found to be somewhat higher than that of the BEM potential solution on surface. An advantage of this method is that it totally avoids the hypersingularity problem in direct BEM where the gradient of the potential on surface or the stress tensor is required to be calculated. The code is easily incorporated in an iterative algorithm of ordinary BEM, and the additional computation time is mainly spent on three parts: the derivative calculations of the coefficient matrices C^{ij} and D^{ij}, the iteration procedure to solve Eq. (32), and the summation using Eqs. (31) and (34) to get the force and torque. The iteration usually converges in less than five steps in our sample cases. All these computations are on the order of $\sim N_{\text{nodes}}^2$, or $N_{\text{atom}} \times N_{\text{nodes}}$, which is a small part compared with the CPU cost on the whole BEM solving process that contains several times of $\sim N_{\text{nodes}}^2$ computations for matrices and N_{nodes}^3 computations for LU factorization. However, for large proteins or protein assemblies, $N_{\text{atom}} \times N_{\text{nodes}}$ times of computations are still time consuming, and other accelerating techniques such as the multipole method will be necessary.

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