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Molecular surface-free continuum model for electrodiffusion processes

Benzhuo Lu [a,b,*], J. Andrew McCammon [a,b,c,d]

[a] *Howard Hughes Medical Institute, University of California at San Diego, La Jolla, CA 92093-0365, United States*
[b] *Center for Theoretical Biological Physics, University of California at San Diego, La Jolla, CA 92093-0365, United States*
[c] *Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, CA 92093-0365, United States*
[d] *Department of Pharmacology, University of California at San Diego, La Jolla, CA 92093-0365, United States*

Abstract

Incorporation of van der Waals interactions enables the continuum model of electrodiffusion in biomolecular system to avoid the artifacts of introducing a molecular surface and the painful task of the surface mesh generation. Calculation examples show that the electrostatics, diffusion–reaction kinetics, and molecular surface defined as an isosurface of a certain density distribution can be extracted from the solution of the Poisson–Nernst-Planck equations using this model. The molecular surface-free model enables a wider usage of some modern numerical methodologies such as finite element methods for biomolecular modeling, and sheds light on a new paradigm of continuum modeling for biomolecular systems.
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1. Introduction

Continuum description is commonly used in computational biophysics and chemistry, such as solvation energy prediction, molecular transport studies, signal transduction and metabolism networks simulations. We have recently developed a numerical framework for electrostatics and diffusion modeling for biosystems with realistic spatiotemporal resolution [1]. To use modern numerical methods such as finite element method (FEM) or boundary element method (BEM), generations of the volume-mesh and especially the molecular surface mesh are prerequisites. However, mesh generation is a long standing problem and hinders the wide application of the FEMs and BEMs to biomolecular systems due to the very irregular shape of biomolecules. Many tools are available for volume-mesh generation once the domain boundary mesh (qualified enough) is given. But

to our knowledge, there is still almost no convenient and efficient tool so far for biomolecular surface mesh generation that not only maintains the molecular 'shape' but also satisfies the mesh quality requirement for numerical solution of the related equations, albeit we have supplied a temporary solution for this in our previous paper [1]. And even for the widely used finite difference method (FD), it still needs to identify the molecular surface (no matter if an explicit or implicit surface mesh is generated) to define the solute and solvent regions. The surface mesh requirement is purely due to the convenience for model description and/or visualization. Different types of molecular surface are used in continuum modeling [2]. However, any type of molecular surface is an artifact, and it is recognized that the energy calculation is very sensitive to the choice of surface definition, resulting in variations far beyond the range of chemical accuracy. Moreover, the surface discretization (mesh) introduces further approximation to the surface. Therefore, besides causing the pain to generate a 'qualified' molecular surface mesh, the surface itself is an error source in molecular computations. In this approach, the van der Waals interactions between biomolecule

* Corresponding author. Address: Howard Hughes Medical Institute, University of California at San Diego, La Jolla, CA 92093-0365, United States. Fax: +1 858 534 4974.
E-mail address: blu@mccammon.ucsd.edu (B. Lu).

and solvent molecule, mobile ions or other diffusing particles if involved are incorporated into the continuum model that describes a coupled system of electrostatics and diffusion process. One advantage of this treatment is that the van der Waals interaction as a key ingredient of hydrophobic interaction is included in the continuum studies of particle diffusion, solvent structure and electrostatic field. The other advantage lies in that the molecular surface is then not necessary, because the van der Waals interaction prohibits penetration of the solvent molecules and the other diffusing species into the solute and serves as a natural substitute for the hard-wall approximation (molecular surface). This avoids the difficulties of surface mesh generation, as well as the resulting errors. The latter advantage makes many of state-of-the-art numerical methods applicable to the biomolecular modeling community.

In the latter part of this Letter, some calculation examples are performed to show that this molecular surface-free continuum model is able to give a right description of system's electrostatics, ionic densities, and diffusion–reaction kinetics. Moreover, a novel type of molecular surface defined as an isosurface of a certain density distribution can be as an output of this model. Because no surface exists, the reactivity model introduced in this work (volume-based) differs from the previous surface-base model (reactive surface). This model also gives an interesting profile of diffusion–reaction kinetics that violates the Debye–Hückel limiting law found in our recent work.

2. Methods

As done in our former work [1], to study the diffusion of small molecules (or ions) around a biomolecule, all the charged species in solution are treated as diffusing particles in the model, and the diffusions are influenced by the electrostatic reaction field determined by all the mobile particles and the macromolecule. In that model as well as in many other continuum models, a molecular boundary is required to separate the high and low dielectric regions, and to identify the diffusion region and impenetrable region. The molecular surface serves as a boundary for accessibility of water molecules and other particles, and is equivalent to a wall with infinite potential. This can be considered as a simplification of van der Waals potential between solute and water. From this point, if water molecule is also considered as one of the diffusive species, and the van der Waals interactions are introduced into the model, the density profiles of all species in solution will be automatically determined by the potential field. This is a more realistic situation. As a post-processing, the molecular surface can also be extracted as an isosurface of the density distributions if necessary.

Therefore, the Poisson–Nernst–Planck equations (PNP) describing the coupling of potential field (electrostatics and van der Waals) and diffusion–reaction processes can be modified as follows:

$$\frac{\partial p^i(r,t)}{\partial t} = \nabla \cdot \{D^i(r)e^{-\beta V^i(r,t)}\nabla(e^{\beta V^i(r)}p^i(r,t))\} + \alpha^i(r)p^i(r,t),$$
$$r \in \Omega, \quad i = 1 \ldots K, \tag{1}$$

$$\nabla \cdot \epsilon(r)\nabla \phi(r,t) = -\rho^f(r) - \sum_i q^i p^i(r,t), \quad r \in \Omega, \tag{2}$$

where $p^i(r,t)$ is the density distribution function of the diffusing particles of the ith species with diffusion coefficient $D^i(r)$ and charge q^i, ρ^f is the fixed source charge distribution (usually, the atomic charges of the biomolecule(s) in the system), K is the number of species considered, β is the inverse Boltzmann energy, ϵ is the dielectric coefficient, V^i is the potential that imposes driving forces on the ith diffusing species, which includes both electrostatic and van der Waals contributions $V^i = q^i\phi + V^i_{vdw}$. ϕ is determined by the Poisson equation Eq. (2). V^i_{vdw} is a summation from all of the pair-wise Lennard-Jones (LJ) interactions between the ith species and the macromolecular atoms. The LJ parameters for any pair interaction can be obtained from the force field. In former work, the reaction is described through certain boundary conditions on the 'reactive molecular surface patch' [1,3,4]. Instead, here the last term is added to describe the reaction event, in which an intrinsic reaction rate $\alpha^i(r)$ is nonzero in the 'reactive region' and zero in the nonreactive region. The intrinsic rate should be large in the diffusion-controlled reaction processes.

The Nernst-Planck (NP) equations (also called Smoluchowski equations) Eq. (1) describe the diffusion processes. Now there is one species in this model used for the water modeling. Water molecule is neutral, hence no electrostatic interaction is considered for water diffusion in current work. The force field of single-site model of water has been recently developed [5], in which the LJ parameters are available. As mentioned above, the goal of including water in this work is to identify the molecular surface, which is implicitly done by relating the dielectric coefficient to the water densities. The dielectric coefficient ϵ has complex dependencies on pressure, temperature, and the density, which is definitely a concern in future exploration but out of our current focus. We take a simple linear form here in this work

$$\epsilon = \epsilon_p + \frac{p^w}{p_0^w} * (\epsilon_w - \epsilon_p), \tag{3}$$

where ϵ_p, ϵ_w are the dielectric coefficients of solute and solvent, respectively, p^w is water density and p_0^w is the bulk density which is 55.5 M in standard state. A simple explanation for this form is that the induced dipole moment on the water is approximately proportional to its density. Due to the short range property of LJ interaction, the water density, thereby the ϵ, actually only varies in a limited region around the molecular boundary. In interior, $p^w \sim 0$ (no water penetrates), then $\epsilon \sim \epsilon_p$; in a wide exterior region $p^w \sim p_0^w$, hence $\epsilon \sim \epsilon_w$. This captures the main features in previous electrostatic modeling works, and allows more reasonable dielectric structures (heterogeneous solvent environment) near molecular boundary in this model.

Similarly, the other diffusing species (ions, substrates, ligands) are also subject to the van der Waals interactions with the solute, and will be prohibited to penetrate into solute interior, therefore, no molecular surface is needed.

The numerical approach and volume-mesh generation for solution of the PNP equations have been described in our previous work [1], which used a hybrid FEM/BEM method. In this molecular surface-free continuum model, only FEM is applied. The FEM involves the use of a fairly sophisticated adaptive method within the general finite element modeling library FETK [6]. Generally, the dynamical diffusion process of water can also be studied. The goal in this work is only trying to use its density p^w to naturally identify the different dielectric regions for electrostatic calculations. Therefore, water is supposed to be in equilibrium state, and only the steady-state NP equation for water needs to be solved once to obtain $p^w(r)$, which is then plugged in the Poisson equation. In this specific case, the solution $p^w(r)$ actually follows the Boltzmann distribution $p^w(r) = p_0^w \exp(-\beta V_{vdw})$, which can be directly obtained, rather than through the solution of the NP equation [1]. However, to keep consistency of using the numerical framework, the p^w is also obtained by solving the NP equation for water.

3. Results

In the following, we will show examples for the steady-state PNP calculations described above on electrostatic field, ionic densities around a single or two charged atoms, and the reaction rate coefficient for a spherical reactive region. For the Poisson equation, because the boundary of Ω is normally far away from the solute, the easily calculated Debye–Hückel screening potential (induced by the total source charges) on the boundary $\partial\Omega$ is taken as the (Dirichlet) boundary condition. For the NP equation, Dirichlet boundary conditions are used on $\partial\Omega$ to simulate the bulk conditions of different species. The first test is performed on a single atom (solute) with charge $+e$ immersed in 1:1 salt, and no reaction is considered. An adaptive mesh with 41532 vertices and 259267 tetrahedra is generated. The boundary of the whole spherical mesh has a radius of 100 Å, where the boundary condition is set with the bulk density of each species (co-ion, counter-ion, and water), respectively. The LJ parameters are set as $\epsilon = 0.3$ kcal/mol, $\sigma = 1.0$ Å for all the species (solvent molecule, ions, and the solute atom) in our test system. For the vdw interaction between each pair of species, the LJ parameter ϵ and σ are obtained by employing arithmetic mean combining rule and geometric mean combining rule, respectively. For biomolecular application, the combining rules should be consistent with the force field adopted. Two cases with ionic strengths of zero, and 50 mM are compared. Fig. 1a shows the electrostatic and van der Waals potentials around the solute. The exact electrostatic potential for a unit sphere case (with molecular boundary and no vdw interaction considered) is also plotted for comparison

(green points), where the interior dielectric constant takes ϵ_p, the exterior takes ϵ_w, and the ionic strength is zero. In most region away from the atom, the electrostatic potential calculated in present molecular surface-free model is nearly similar to that in the unit sphere case, which is reasonable because the water density, thereby the dielectric coefficient, is almost the same as the bulk water density due to the short range character of van der Waals interaction. This agreement indicates that in the long range region, the two models lead to similar electrostatic influences on particle diffusions. While in the vicinity of the atomic van der Waals surface, the electrostatic potential of current model is found lower than in the unit sphere case. This is caused by the higher water density, thereby a higher dielectric coefficient, around the solute atom because of van der Waals interaction. This higher density in a narrow band (a similar case can be seen in Fig. 2) corresponds to the first peak of the radial distribution function observed widely in molecular dynamics simulations and experimental studies. In the ionic solution, this model also gives reasonable electric potential (blue points, Fig. 1a), which is lower than that in the case without ionic screening (red points).

Fig. 1b shows the counter-ion and co-ion density distributions in the 50 mM ionic solution, which captures the features of ion density distribution studied in previous models and also clearly shows the automatically vanishing of density in the 'solute' region by introducing the van der Waals interaction.

Fig. 2 shows the water density around two atoms separated by 3 Å. All the parameters are the same as above. Again, the density as a numerical solution of the steady-state PNP equation system follows a Boltzmann distribution in equilibrium state. In the small middle region, the density is a little bit higher than that in the same relative location of the single atom case, which is due to the addition of LJ potentials from two atoms. The two green circles around the blue regions corresponding to 55500 mM of bulk water density are proximate to the atomic vdw surfaces. An isosurface of water density with a value 60000 mM is also shown, which has similar shape as the solvent accessible molecular surface. This indicates that the method through solving the diffusion equation in the vdw potential field can also be used to define a type of molecular surface as an isosurface of density of water (or other diffusing particles).

The PNP is also used to describe the diffusion–reaction processes and reaction rate calculation. In former models using molecular surface representation, the reaction is modeled by using certain boundary condition, such as a sink, applied to a specific 'reactive patch' (active site) on the surface [1,3,4]. In this model, it is also convenient to implement the diffusion–reaction simulations. The reactive site is now represented by a properly selected 'reactive region', and a reaction term as in Eq. (1) is applied in this region. Diffusion–reaction simulations are performed on above single sphere model, in which one reactive species diffuses in a 1:1 salt around the reactive unit sphere with
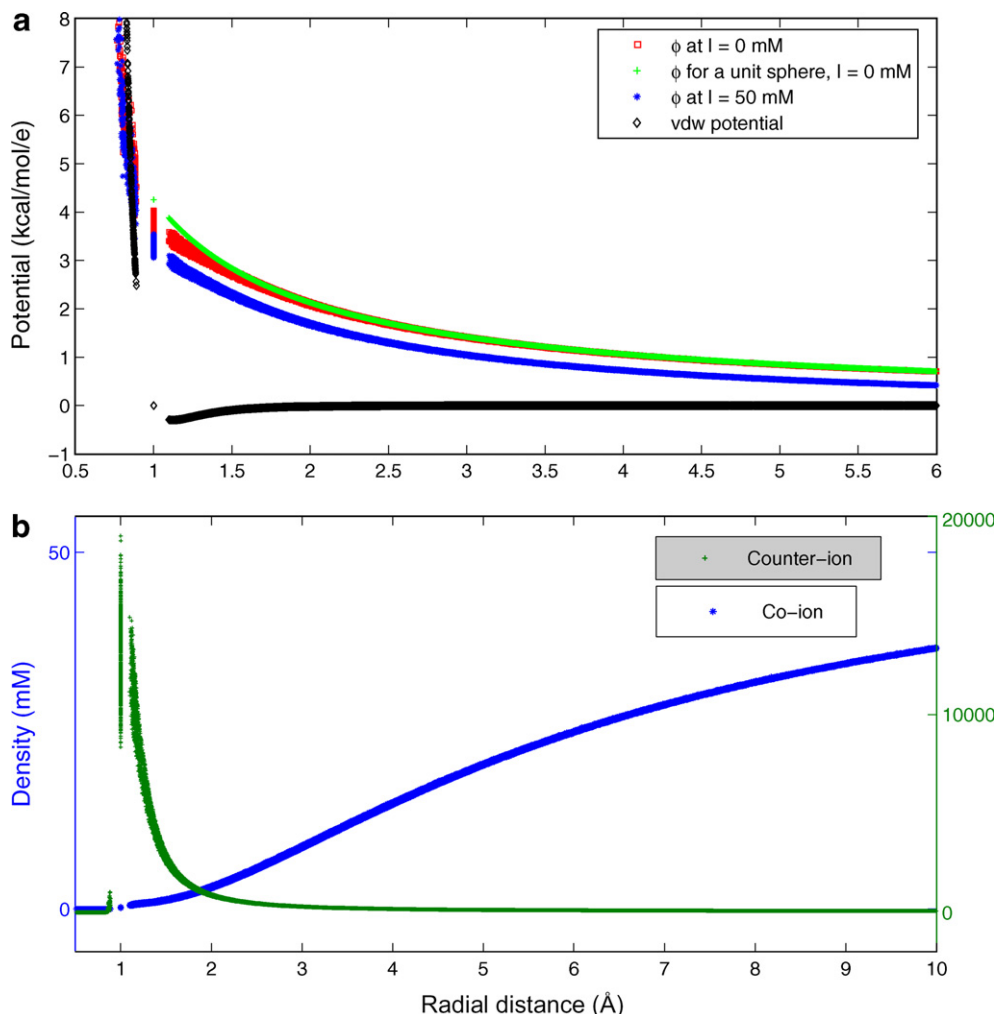
Fig. 1. (a) Electrostatic potential ϕ and van der Waals potential around a single atom (+e) at ionic strength $I = 0$ mM and $I = 50$ mM conditions, (b) ion density distributions as a function of radial distance.
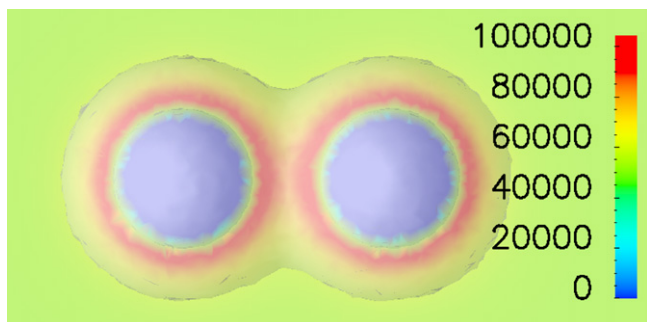

Fig. 2. Water density around two atoms. The isosurface value is 60000 mM.
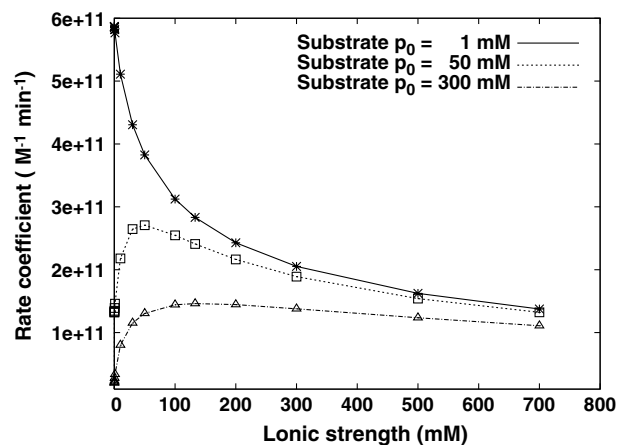

Fig. 3. Reaction rate coefficients for a unit sphere reactive region. The solid line is for a bulk substrate concentration of 1 mM, the dotted line is for 50 mM and the dashed line is for 300 mM.

different bulk densities kept on the domain boundary. The intrinsic reaction rate α is taken as $1.0 \times 10^5 \, \mu \text{s}^{-1}$. The reaction rate coefficient is calculated through $\int_{r<1} \alpha(r) p(r) \mathrm{d}v / p_{\text{bulk}}$ for the reactive species. It is observed that the rate coefficients strongly depend on both the ionic strength and the concentration of the reactive species (see Fig. 3). The Debye-Hückel limiting law that predicts an

exponential decay of the diffusion-controlled reaction rate constant with increase of ionic strength is obviously violated when the (charged) substrate concentration is not

small (>1 mM). For high substrate concentration, the reaction rate coefficient can be even increased by the ionic screening effect in certain range of the strengths due to the competition between the favored substrate-receptor (electrostatic) attraction and the unfavored substrate–substrate (electrostatic) repulsion, both of which interactions are weakened by ionic screening. Similar phenomena was also observed in our recent surface-reaction model [1,7].

4. Conclusions and discussion

The artificial molecular surface is removed in this FEM continuum model. In addition to accuracy improvement, the main benefit is to avoid all the technical concerns about the molecular surface. The similar treatment is also applicable to the widely used FD continuum models. Further improvements can be made to achieve more accurate and realistic description of the water density around the boundary regions of biomolecules. One consideration is to incorporate the interaction between water and electric field due to the polarizability of water molecule. Consistent with above mentioned single-site water model, the dipole, quadrapole, and octapole interactions have been parameterized in the force field [5]. These interactions can be absorbed into the diffusion equation and make correction to the density distribution of water and the dielectric coefficient. Another consideration is the correlation between water molecules, which includes the size effects. For instance, in Fig. 2, when the space between two spheres is small and cannot tolerate inserting of a water molecule, there would be no water density in the small space, but this feature cannot be captured in current continuous model due to the lack of size effects in this model. the model can be extended to cover the size effect using similar idea given by Borukhov et al. [8]. Further work is underway to take into account more general correlation effects in numerical solutions of the PNP for all involved particles including water, ions and other existing particles.

Once accurate solvent and ionic density distributions are obtained, the entropy associated with solvent rearrangement around biomolecule can be calculated, which together with the van der Waals and electrostatic interactions involved, could account for the solvation free energy. Therefore, the model supplies a potential tool to quantitatively analyze the hydrophilicity, hydrophobicity, and solvation energies of (rigid) biomolecules. The Hofmeister effects of ion binding are also expected to be predicted in this model because the individual ionic properties, such as van der Waals interaction and size effect, could be included.

Acknowledgements

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