Communications in Information and Systems
Volume 22, Number 3, 305–315, 2022

Benchmarking electrostatic free energy of the nonlinear Poisson-Boltzmann model for the Kirkwood sphere

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Various numerical packages have been developed to solve the Poisson-Boltzmann equation (PBE) for the electrostatic analysis of solvated biomolecules. A common benchmark test for the PBE solvers is the Kirkwood sphere, for which analytical potential and free energy are available for the linearized PBE. However, the Kirkwood sphere does not admit analytical solution for the nonlinear PBE involving a hyperbolic sine term. This paper proposes a simple numerical approach, so that the energy of the Kirkwood sphere for the nonlinear PBE can be calculated at a very high precision. This provides a new benchmark test for the future developments of nonlinear PBE solvers.

Keywords and phrases: Nonlinear Poisson-Boltzmann equation, Kirkwood sphere, matched interface and boundary (MIB), electrostatic free energy.

1. Introduction

The Poisson-Boltzmann (PB) equation, as a mean field model, is widely used as the governing equation of electrostatics for solvated biomolecules in a solvent environment with dissolved electrolytes [9, 1]. Under the assumption that all mobile ions are univalent in the solvent, the Boltzmann distribution terms of the PB equation can be combined into a hyperbolic sine term, giving rise to a nonlinear elliptic boundary value problem. When the underlying electrostatic potential u is weak, the nonlinear PB model can be approximated by the linearized PB model, obtained by replacing $\sinh(u)$ with u. If the solvent is free of mobile ions, the PB equation reduces to a Poisson equation.

Due to the complex geometries of three-dimensional (3D) biomolecules, the solution of the PB equation has to be conducted numerically for real

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protein systems. Furthermore, several numerical difficulties are well known in solving the PB equation, including unbounded domain, nonlinearity, singular sources, complex molecular surface, discontinuous dielectric coefficients, etc. To overcome these difficulties, various PB solvers have been developed in the literature, such as [10, 3, 13, 8, 11, 4].

To validate the PB solvers, the Kirkwood sphere [7, 10, 6] is frequently adopted as a benchmark test, in which a partial charge is assumed at the center of a dielectric spherical cavity immersed in the solvent. For both linearized PB (LPB) and Poisson equations, the Kirkwood sphere admits analytical solutions for both potential and electrostatic free energy. Moreover, for Kirkwood sphere with off-center charges, series solutions are also available [10]. However, for the nonlinear PB (NPB) model, no analytical solution is known for the Kirkwood sphere.

The goal of this paper is to develop a highly accurate numerical procedure for calculating electrostatic free energy of the Kirkwood sphere for the NPB model. Taking advantage of the rotational symmetry, the 3D boundary value problem (BVP) of the NPB equation will be first reduced to a one-dimensional (1D) BVP over an unbounded domain. By truncating the unbounded domain into a bounded one with sufficient length, a new NPB-BVP is proposed. By resolving the resulting Neumann and Dirichlet boundary conditions through the matched interface and boundary (MIB) scheme [15, 12], a high order finite difference discretization is formulated, which could provide an estimation of electrostatic free energy up to double precision limit. Therefore, the proposed numerical approach for the Kirkwood sphere provides a new benchmark test for the PB solvers [10, 3, 13, 8, 11, 4] so that their performance for solving the NPB model could be accurately assessed.

The rest of this paper is structured as the follows. The proposed numerical approach is discussed in Section 2. Numerical validation for both LPB and NPB energies is reported in Section 3. Finally, this paper ends with a conclusion.

2. Theory and algorithm

Consider a dielectric molecule or Kirkwood sphere with a radius a being immersed in the solvent with mobile ions. A partial charge q is assumed at the spherical center, which is also the origin of the coordinate system. The spherical interface Γ divides the domain $\Omega = \mathbb{R}^3$ into a molecule region Ω^- and a solvent region Ω^+. The electrostatic interaction of this system is

governed by the nonlinear Poisson-Boltzmann (NPB) equation [7, 9, 1].

$$(1)\qquad \begin{cases} -\nabla\cdot(\epsilon\nabla u(\vec{r}))+\kappa^2\sinh(u(\vec{r}))=4\pi Cq\delta(\vec{r}-\vec{0}), & \vec{r}\in\Omega \\ [u]=0, \quad \text{and} \quad \left[\epsilon\frac{\partial u}{\partial n}\right]=0, & \vec{r}\in\Gamma \\ u(\vec{r})=0, & |\vec{r}|\to\infty \end{cases}$$

where u is the electrostatic potential which vanishes at infinity. Here ϵ is a piecewise dielectric constant, i.e., $\epsilon=\epsilon^-$ and $\epsilon=\epsilon^+$, respectively, in Ω^- and Ω^+, and C is a constant. The Debye-Huckel parameter κ vanishes in Ω^- and it is a constant depending on the ionic strength I_s of the solvent in Ω^+. The reader can refer to [7] for more details about definition and units of these coefficients. Across the dielectric interface Γ, the potential u satisfies two jump conditions in (1), where the notation $[f]=f^+-f^-$ represents the difference of the functional value across the interface Γ, and the directional derivative $\frac{\partial u}{\partial n}$ is along the outer normal direction of Γ.

In a spherical coordinate system (r,θ,φ), the Kirkwood system is invariant in θ and φ directions, so that the potential is actually a function in radial direction $r=|\vec{r}|$ only, i.e., $u(r)$. Thus, the NPB equation (1) can be reduced to an ordinary differential equation (ODE). Moreover, $u^-(r)$ and $u^+(r)$ for $r<a$ and $r>a$, respectively, can be solved separately. In particular, the potential $u^-(r)$, that satisfies

$$(2)\qquad -\epsilon^-\frac{1}{r^2}\frac{d}{dr}(r^2\frac{d}{dr}u^-)=4\pi Cq\delta(r), \quad r<a,$$

in Ω^- and has a bounded reaction field component, can be analytically given as [6]

$$(3)\qquad u^-(r)=G(r)+C_1=\frac{Cq}{\epsilon^- r}+C_1, \quad r<a,$$

where $G(r)=\frac{Cq}{\epsilon^- r}$ is the Green's function and the constant C_1 is unknown.

For $r\in[a,\infty)$, $u^+(r)$ satisfies a nonlinear ODE. We note that the flux jump condition given in (1) now becomes $[\epsilon\frac{du}{dr}]=0$ at $r=a$. For $r<a$, the solution (3) gives rise to $\frac{du^-}{dr}=-\frac{Cq}{\epsilon^- r^2}$. Using the jump condition, we have $\frac{du^+}{dr}(a)=\frac{\epsilon^-}{\epsilon^+}\frac{du^-}{dr}(a)=-\frac{Cq}{\epsilon^+ a^2}$, which will be treated as a boundary condition at $r=a$. Thus, $u^+(r)$ satisfies the following nonlinear boundary value problem (BVP)

$$(4)\qquad \begin{cases} -\epsilon^+\frac{1}{r^2}\frac{d}{dr}(r^2\frac{d}{dr}u^+)+\kappa^2\sinh(u)=0, & r\in[a,\infty) \\ \frac{du^+}{dr}(a)=-\frac{Cq}{\epsilon^+ a^2}, \quad \text{and} \quad \lim_{r\to\infty}u^+=0. \end{cases}$$

Since the BVP Eq. (4) does not admit an analytical solution, we will solve it numerically. Because the potential u is known to be exponentially decaying as $r \to \infty$ [7, 6], we will first truncate the infinity domain $[a, \infty)$ to a finite one $[a, b]$, with b being sufficiently large. Then, a Dirichlet zero boundary condition can be assumed at $r = b$. Therefore, we propose to solve the following 1D BVP with notations $u(r) = u^+(r)$, $u'(r) = \frac{du}{dr}$, and $\lambda = \sqrt{\kappa^2/\epsilon^+}$

$$\begin{cases} u'' + \frac{2}{r}u' - \lambda^2 \sinh(u) = 0, & r \in [a, b] \\ u'(a) = -\frac{Cq}{\epsilon^+ a^2}, \quad \text{and} \quad u(b) = 0. \end{cases} \tag{5}$$

In the present study, the Newton's scheme [11] will be employed for solving the NPB equation and a high order finite difference approximation will be considered. A uniform grid is employed to partition $[a, b]$ with a spacing h. By treating the Neumann and Dirichlet boundary conditions by the Matched Interface and Boundary (MIB) scheme [15, 12], central difference discretization with orders being two, four, six, and eight will be constructed. We note that $C_1 = u^-(a) - \frac{Cq}{\epsilon^- a} = u^+(a) - \frac{Cq}{\epsilon^- a}$, in which the potential jump condition has been applied. Thus, after solving $u^+(r)$ numerically, a numerical value of C_1 is available based on $u^+(a)$. This allows us to calculate the electrostatic free energy of the Kirkwood system [10]

$$E = \frac{k_B T}{2} \int q\delta(\vec{r})[u^-(\vec{r}) - G(\vec{r})]\, d\vec{r} = \frac{k_B T}{2} \int q\delta(\vec{r}) C_1 d\vec{r} = \frac{1}{2} k_B T q C_1, \tag{6}$$

where k_B is the Boltzmann constant and T is the room temperature. With a proper unit conversion [11], the electrostatic free energy will be reported in the unit of kcal/mol.

3. Numerical validation

Consider a Kirkwood sphere with radius $a = 2$Å and a point charge at the atom center. The dielectric constant for the molecule and solvent is, respectively, $\epsilon^- = 1$ and $\epsilon^+ = 80$. The ionic strength is taken as $I_s = 0.15$M.

We first validate the proposed procedure by studying the linearized Poisson-Boltzmann (LPB) equation, which is obtained by replacing $\sinh(u)$ by u in Eq. (1). In particular, the LPB version of the BVP Eq. (4) has an analytical solution $u^+(r) = \frac{C_2}{r} \exp(-\lambda r)$ for $r > a$. By imposing two jump conditions at $r = a$, the unknown constants C_1 and C_2 can be uniquely determined. Then, the analytical potential and electrostatic free energy are

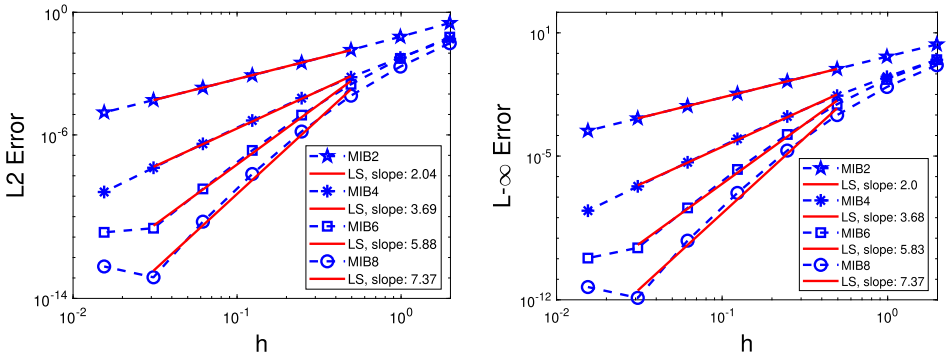

Figure 1: Numerical accuracy in approximating electrostatic potential of the LPB equation for the Kirkwood sphere with $q = 1$. Left: L_2 error; Right: L_∞ error.

given as [6]

$$(7)\quad u^+(r) = \frac{Cqe^{\lambda(a-r)}}{\epsilon^+(\lambda a+1)r},\ r > a,\ \text{and}\ E = \frac{1}{2}k_BTq\left(\frac{Cq}{\epsilon^+(\lambda a+1)a} - \frac{Cq}{\epsilon^- a}\right).$$

Our first test involves numerically solving the LPB version of the BVP Eq. (5) by the MIB method, and comparing the numerical potential with the analytical one given in Eq. (7). A sufficiently large $b = 100a$ is employed so that the error associated with the truncation of the infinity domain is negligibly small. By taking $q = 1$ and using different spacing h or mesh size N, numerical errors in terms of L_2 and L_∞ norms are reported in Fig. 1. Four MIB finite difference discretizations are employed, with the designed order of accuracy being two, four, six and eight, namely the MIB2, MIB4, MIB6 and MIB8 schemes. It can be seen that as h decreases, the errors decay quickly. The MIB8 scheme reaches the precision limit of the iterative algebra solver so that its error becomes larger when h is further refined. To verify the convergence, a least squares (LS) linear fitting is considered in the logarithm scale, and the corresponding LS slope indicates the numerical order. The LS slopes of four schemes are reported in Fig. 1. It is clear that all four MIB methods achieve the desired convergence orders in approximating the potential u.

To investigate the impact of charge value q, we repeat the LPB study of the Kirkwood sphere by taking $q = -2$. By using the same numerical setup, the numerical errors and convergence rates are shown in Fig. 2. It can be seen that the results of Fig. 2 are almost identical to those of Fig. 1. This

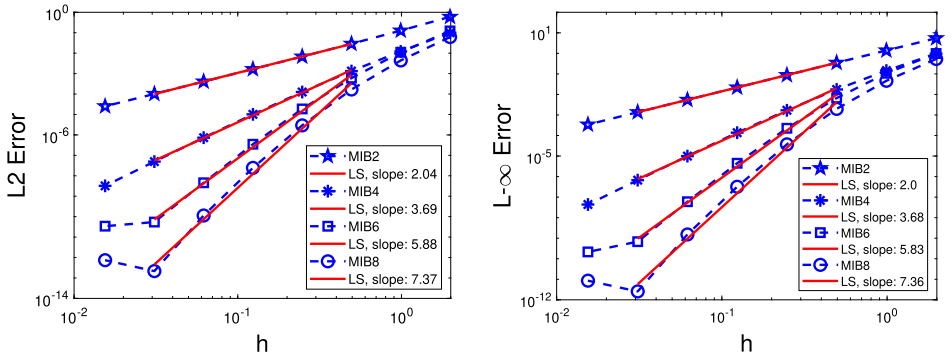

Figure 2: Numerical accuracy in approximating electrostatic potential of the LPB equation for the Kirkwood sphere with $q = -2$. Left: L_2 error; Right: L_∞ error.

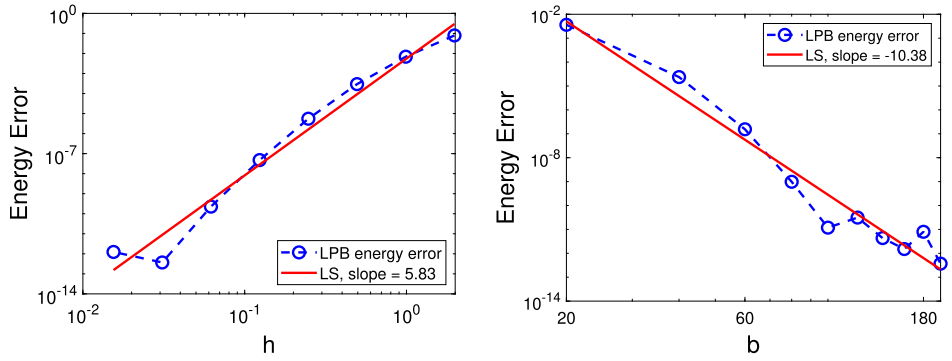

Figure 3: Numerical error in approximating the LPB energy for different h with a fixed $b = 100a$ (left) and for different b with a fixed mesh size N (right). The energy is benchmarked with the analytical value.

suggests that the convergence of the present approach is not affected by the charge value q. In the following, we will only consider $q = 1$.

We next approximate the electrostatic free energy of the LPB model, whose analytical value is $E = -82.188683337726175$ kcal/mol according to Eq. (7). To this end, the LPB version of the BVP Eq. (5) is solved by the MIB8 scheme only. By fixing $b = 100a$, it can be seen from Fig. 3 that the absolute error in energy decays quickly as h decreases, and the double precision limit is reached. The LS fitting shows that the numerical convergence order in energy of the MIB8 scheme is about six. By fixing the

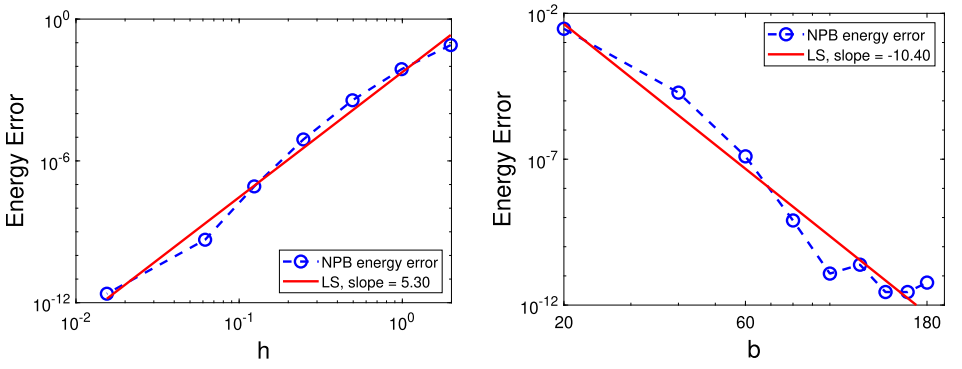

Figure 4: Numerical error in approximating the NPB energy for different h with a fixed $b = 100a$ (left) and for different b with a fixed mesh size N (right). The energy is benchmarked with the reference value generated by the proposed MIB8 scheme.

number of mesh size as $N = 6401$, we have also examined the impact of parameter b to the energy error. By taking several b values in $[10a, 100a]$, the energy error is depicted in Fig. 3. When b is small, the approximation of the infinity domain BVP Eq. (4) by the finite domain BVP Eq. (5) produces a large systematic error, indicating that a sufficiently large b is indispensable for the proposed procedure. When b becomes larger, this error decays very rapidly and is almost vanishing for $b = 100a$.

Based on the LPB results, a set of optimized parameter values will be employed in the proposed MIB8 method to generate a reference energy for the present Kirkwood sphere. In particular, we will take $b = 100a$ and $N = 6401$ or $h = 0.0309$. The corresponding LPB energy is $E_r = -82.188683337726545$ kcal/mol with an error 3.69E-13. For the NPB case, the reference energy is $E_r = -82.212210771856221$ kcal/mol, whose error is estimated to be about 2.4E-12 by comparing with other NPB energies. By using the NPB reference energy, the numerical errors of the MIB8 scheme with respect to the changes of h and b are depicted in Fig. 4. The convergence patterns are very similar to those of the LPB case. This suggests that the proposed procedure performs equally well for the NPB equation.

We finally consider a study to demonstrate the significance of the proposed approach. To this end, the present Kirkwood sphere is numerically solved by the 3D rMIB package [11], which is known to produce second order convergence in electrostatic potential. In particular, a tight domain $\Omega = [-4, 4]^3$ is employed, for which a Dirichlet zero boundary condition is

Table 1: The Kirkwood energy calculated by the rMIB package [11] and the present MIB8 scheme with successive mesh refinements. Here, the error is calculated against the reference values generated by the MIB8 scheme

	LPB			
	rMIB [11]		MIB8	
h	energy	error	energy	error
1.0	−82.1660026	2.27E-2	−82.1958558	7.17E-3
0.5	−82.1769841	1.17E-2	−82.1889936	3.10E-4
0.25	−82.1825212	6.16E-3	−82.1886892	5.89E-6
0.125	−82.1861310	2.55E-3	−82.1886834	5.14E-8
0.0625	−82.1893892	7.06E-4	−82.1886833	2.45E-10
	NPB			
	rMIB [11]		MIB8	
h	energy	error	energy	error
1.0	−82.4181454	2.06E-1	−82.2201108	7.90E-3
0.5	−82.4285045	2.16E-1	−82.2125964	3.86E-4
0.25	−82.4351523	2.23E-1	−82.2122193	8.58E-6
0.125	−82.4365766	2.24E-1	−82.2122109	8.94E-8
0.0625	−82.4368539	2.25E-1	−82.2122108	4.99E-10

obviously invalid. Thus, a Dirichlet boundary condition is employed in the rMIB package [10, 3, 11] for both LPB and NPB Kirkwood systems, i.e., $u(\vec{r}) = Cq \exp(\lambda(a - |\vec{r}|)) / \left(\epsilon^+(\lambda a + 1)|\vec{r}|\right)$ for $\vec{r} \in \partial\Omega$, which is obtained by the analytical LPB potential Eq. (7). Benchmarked by the reference energies generated by the MIB8 scheme, the errors of the rMIB energies are listed in Table 1. For a comparison, the energies calculated by the present MIB8 scheme at the same spacing h are reported together with the corresponding errors. For the LPB case, the rMIB energy converges rapidly to the reference energy. This is in agreement with the original rMIB study [11]. As a high order scheme, the MIB8 method converges even faster for the LPB energy. A similar high order convergence can be observed in the MIB8 for the NPB energy. Nevertheless, the rMIB energy for the NPB case clearly converges to a different value so that the error is non-diminishing. Such a non-convergence issue is unknown to the rMIB developers, until the present test. This issue is believed to be due to the use of a LPB boundary condition for the NPB solver. While there exist some remedies in the literature [14, 2, 5], the development of appropriate boundary conditions for the NPB equation deserves further study.

4. Conclusion

This study introduces a highly accurate numerical approach for calculating the energy of the Kirkwood sphere for the NPB equation. This provides a new benchmark test for validating the PB solvers. A quick benchmark test indicates that for a well-established PB solver with verified accuracy in solving the LPB equation, the NPB energy is non-converging. We will explore the boundary condition issue of the NPB equation in the future.

A remark about the convergence rate of energy estimation is in order. It can be seen from Fig. 3 and Fig. 4 that the convergence rate of the MIB8 with respect to h is about 5.83 and 5.30, respectively, for the LPB and NPB cases. For lower order methods, such rates become 2.00 and 1.99 for MIB2, 3.52 and 3.47 for MIB4, and 4.96 and 4.79 for MIB6. We note that except for the MIB2, the other three schemes all experience some order reduction. The same can be observed in Table 1 that the order of the rMIB energy estimation is clearly less than two, while the rMIB method is known to produce second order accurate potential solution [11]. This indicates that energy estimation is numerically more challenging than approximating electrostatic potential. Nevertheless, although a higher order method usually suffers a larger order reduction, we can see that a higher order method still produces a more accurate energy. This is why we have adopted up to 8th order MIB scheme in the present study.

Acknowledgments

Zhao's research is partially supported by the National Science Foundation (NSF) of USA under grant DMS-2110914. Geng's research is partially supported by the NSF under grant DMS-2110922.

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Received March 5, 2022