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REVIEW ARTICLE

Recent Progress in Numerical Methods for the Poisson-Boltzmann Equation in Biophysical Applications

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Abstract. Efficiency and accuracy are two major concerns in numerical solutions of the Poisson-Boltzmann equation for applications in chemistry and biophysics. Recent developments in boundary element methods, interface methods, adaptive methods, finite element methods, and other approaches for the Poisson-Boltzmann equation as well as related mesh generation techniques are reviewed. We also discussed the challenging problems and possible future work, in particular, for the aim of biophysical applications.

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Contents

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1 Introduction

Poisson-Boltzmann (PB) theory has been a well-established model in a broad range of scientific research areas. In electrochemistry, it is known as Gouy-Chapman (GC) theory [1,2]; in solution chemistry, it is known as Debye-Hückel theory [3]; in colloid chemistry, it is known as the Derjaguin-Landau-Verwey-Overbeek (DLVO) theory [4,5]; and in biophysics, it is known as PB theory [6,7]. The Poisson-Boltzmann equation (PBE) represents a typical implicit solvent model, and provides a simplified continuum description of the discrete particle (e.g., water, ion, and protein molecule) distributions in solution. In particular, the PBE describes the electrostatic interaction and ionic density distributions of a solvated system at the equilibrium state. Since the first application of the PBE in a biomolecular system [8], a large amount of literatures and many solution techniques have been produced in this area and directed to studies of diverse biological processes.

A number of excellent review papers can be found that focus on the physical fundamentals, methodologies, and applications of PB electrostatics to molecular structure and dynamics. Here we only list some of recent references. The underlying physics and theories of implicit solvent models are discussed in [9,10]; a brief history of PB can be found in [11]; the PB methodology and applications in biomolecular modeling was summarized briefly in [12,13]; the methodological developments in both generalized Born (GB) and PB models was given by [14]. Ref. [15] focused on the GB models, which are another type of dielectric continuum model with further approximations. This review will focus on the numerical aspects of PB methodology covering several major numerical methods.

The challenges in biomolecular physical applications include macromolecular computations applied to biomolecular binding/association/assembly, (implicit) molecular dynamics (MD) simulations, and multiscale modeling in space and time. Efficiency and accuracy are two central issues in applying the PBE to biophysical modeling. For instance, a typical macromolecule may consist of tens of thousand to millions of atoms (point charges in the PBE), which significantly challenges the current computer memory and speed. Secondly, in order to incorporate the PB electrostatics (on the fly) in a typical MD simulation or Brownian dynamics (BD) simulation for molecular association/dissociation which could involve tens of millions of steps, a single solution of the

PBE has to be completed within no more than a few tenths of a second on a modern workstation to meet the total wall-clock time constraint. Based on this estimation, the current solvers are still, e.g., about one order of magnitude slower [16], although a few trials of PB MD have been made [17–21]. Thirdly, a similar demand of efficiency lies in virtual high throughput screening in drug discovery from many candidate structures and different conformations. This screening is usually based on free energy calculations (e.g., binding affinity) to an accuracy of a few kcal/mol. However, these free energies normally result from the cancellation of energies of several orders of magnitude larger such as electrostatic energies. This demand poses another numerical challenge for electrostatic computations with the PBE.

Solvated biomolecular systems are usually modeled by dielectrically distinct regions with singular charges distributed in the molecular region. Systems without singular charges or dielectric discontinuities are usually found in simplified models with planar or cylindrical boundary geometries in electrochemistry and biopolymer science, and can be regarded as a special case of the systems in this investigation. Fig. 1 schematically illustrates a solvated biomolecular system occupying a domain Ω with a smooth boundary $\partial\Omega$. The solute (molecule) region is represented by Ω_m and the solvent region by Ω_s. The dielectric interface Γ is defined by the molecular surface, and n is the unit normal vector at Γ, pointing from Ω_m to Ω_s. The nonlinear Poisson-Boltzmann equation in Ω reads

$$-\nabla\cdot(\epsilon\nabla u)+\lambda\sum_{j=1}^{K}c_j q_j e^{-\beta q_j u}=\sum_{i=1}^{N}q_i\delta(x-x_i), \tag{1.1}$$

where ϵ is a spatial-dependent dielectric coefficient, the characteristic function $\lambda=0$ in Ω_m (impenetrable to ions) and 1 in Ω_s, c_j is the bulk density of mobile ion species j with charge q_j, $\beta=1/kT$, k is the Boltzmann constant, T is the absolute temperature, q_i is the singular charge located at x_i within solute region. To simplify the presentation we use

$$-\nabla\cdot(\epsilon\nabla u)+\kappa^2\sinh(u)=\rho^f \tag{1.2}$$

for symmetric 1:1 salt and

$$-\nabla\cdot(\epsilon\nabla u)+\kappa^2 u=\rho^f \tag{1.3}$$

for the linearized Poisson-Boltzmann equation in case of weak electrostatic potential, where κ absorbs all the related parameters, and ρ^f and u are the scaled singular charge distribution and electrostatic potential, respectively. Note that $\kappa=0$ in Ω_m because the mobile ions only present in the solvent region Ω_s. An additional region called the Stern layer might be present in some Poisson-Boltzmann models. This Stern layer is part of the solvent but is not penetrable for the mobile ions so $\kappa=0$ there. The transition from the low-dielectric solute region to the high-dielectric solvent region is usually modeled to be abrupt, which gives rise to a dielectric interface Γ. This interface is usually identified as

the molecular surface, and will be discussed in Section 10. There are two conditions on Γ needed to be satisfied from the dielectric theory:

$$[u]=0, \tag{1.4}$$

$$\left[\epsilon\frac{\partial u}{\partial n}\right]=0, \tag{1.5}$$

where $[\cdot]$ denotes the jump on Γ of enclosed quantity from Ω_m to Ω_s. These conditions are explicitly used approaches based on boundary integral equations, but may not be exactly satisfied in other approaches such as the traditional finite difference methods, or finite element methods without an interface-conforming mesh. An approximated Dirichlet boundary condition is normally imposed on $\partial\Omega$. The singular charge distribution within biomolecules, discontinuous dielectric constant, exponential nonlinearity at strong potential, and the highly irregular molecular surface constitute the four most prominent features of the Poisson-Boltzmann equation.

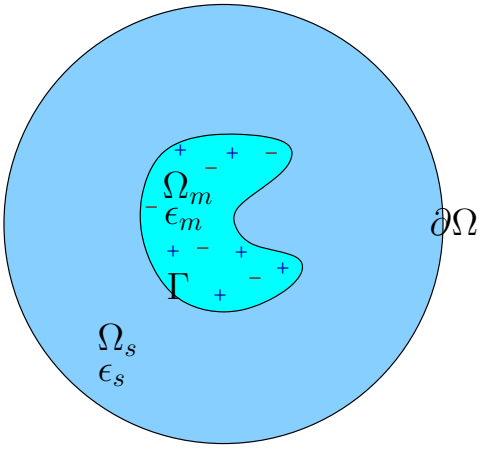

Figure 1: Illustration of the computational domain Ω. The molecular(solute) region is Ω_m with dielectric constant ϵ_m and singular charges denoted by plus and minus signs; the solvent region is Ω_s with dielectric constant ϵ_s; the molecular surface(dielectric interface) is Γ and the boundary of the entire domain is $\partial\Omega$.

The goal of this current review is to summarize the recent advances in PB methods, compare different numerical algorithms, and discuss some major problems arising from solution techniques and from applications of molecular biophysics. We can classify the PB solution techniques into two general categories: direct and indirect strategies. The first one is designed to directly solve the PBE, to which the most numerical efforts have been devoted. Many widely used numerical methods, finite difference method (FD), boundary element method (BEM), and finite element method (FEM), fall into this first category and are the major subjects of this review. The indirect approach strives to explicitly solve alternative equation(s) or mathematical problem, but the solutions can be

proven to be of equivalent to the PB solutions under certain conditions. Direct relaxation of the electrostatic energy represents a typical indirect approach. Although indirect approaches have advantages in their physical interpretations, numerical treatments and model modifications/expansion, they have not been the primary solution techniques, and thus they are only discussed in one section (see 8). Furthermore, some limitations of the PB theory and models of improved/modified PB theory are also briefly mentioned. Speculations are made concerning the directions of future research of PB theory, in both numerical methodology and biophysical applications.

2 Regularization schemes of the Poisson-Boltzmann equation

The presence of the singular charge distribution in the PBE indicates that its solution is not continuous and does not belong to $H^1(\Omega)$ [22, 23], which directly challenges the solution theory of standard finite difference methods, finite volume methods or finite element methods and their applications to the PBE. The practical wide applications of these numerical methods can be attributed to the following two considerations. First, in many applications the solutions of the PBE are used to compute the electrostatic solvation energy ΔG_{ele} only. This energy is defined by [24]

$$\Delta G_{ele} = G_{sys} - G_{ref}, \tag{2.1}$$

where G_{sys} is the electrostatic free energy of the biomolecular system in the solvated state and the G_{ref} is the electrostatic free energy of the system assuming it is in space of uniform dielectric constant ϵ_m and without mobile ions. By using a finite difference method, finite volume method or a finite element method, the PBE is solved twice with corresponding parameters for G_{sys} and G_{ref}, respectively. Linear interpolation or higher order spline interpolation are usually used in these numerical methods for approximating the singular charge distribution. Although the potentials from these two calculations might suffer from large error near the singular charges, it is believed that this error would cancel in computing the ΔG_{ele} via Eq. (2.1) if the same mesh and charge interpolation are used in these two solutions of the PBE. Second, because of the rapid decay of the Coulomb potential induced by these singular charges in solvent with high dielectric constant, the accuracy of the electrostatic potential is believed to be weakly dependent on the specific approximation method to these singular charges. Although the first consideration is somehow validated by many numerical experiments [15, 25–29], the second consideration appears solid only in the region sufficiently away from the molecular surface. In deed, the quality of the potential near the molecular surface is actually critically dependent on the specific treatment of the singular charges [30]. We do note that these singular charges do not pose any difficulty to boundary integral approaches for the PBE [31–33] because of the implementation of the fundamental solutions of the Poisson equation that account for these singular charges in the integral formulation. The reaction field can be extracted from the solution of these integral approaches, from which the energy ΔG can

be directly calculated without incurring any singularity. However, boundary integral approaches also have its own singularity problems in the integrals, and corresponding regularization techniques are also developed in this area. We'll put some discussion on this point in the Section of boundary element methods.

There exist a number of regularization schemes for the PBE aiming at removing the singular component of the potential from the equation such that the remaining component has higher regularity and thus is solvable by using general numerical methods. The straightforward decomposition [22,27,34] considers the singular Coulomb potential u^s of all singular charges

$$-\epsilon_m \Delta u^s = \rho^f \quad \text{in } \Omega. \tag{2.2}$$

The corresponding regular potential component u^r is then found by subtracting Eq. (2.2) from Eq. (1.2) to be

$$\begin{aligned} &-\nabla\cdot(\epsilon\nabla u^r)+\kappa^2\sinh(u^r+u^s)=0 \quad \text{in } \Omega,\\ &[u^r]=0, \quad \left[\epsilon\frac{\partial u^r}{\partial n}\right]=(\epsilon_s-\epsilon_m)\frac{\partial u^s}{\partial n} \quad \text{on } \Gamma. \end{aligned} \tag{2.3}$$

Note that the singular component u^r in this decomposition is defined in the entire Ω. While this simple regularization approach leads to difficulties when used numerically, it was the critical technical tool used to establish a number of new mathematical results about the PBE and numerical approximations recently in [22]. Such results include *a priori* point-wise bounds on the solution to the regularized PBE and on numerical solutions, the first completely rigorous approximation theory for the PBE, and the first provably convergent adaptive method for the PBE.

A more practically useful decomposition [35] defines the singular potential u^s only in the domain Ω_m,

$$\begin{aligned} &u^s = G|_{\overline{\Omega}_m} \quad \text{in } \overline{\Omega}_m,\\ &u^s = 0 \quad \text{in } \Omega_s, \end{aligned} \tag{2.4}$$

where the singular potential G satisfies $-\epsilon_m \Delta G = \rho^f$ in $\mathcal{R}^3$, and uses a harmonic component u^h to compensate the discontinuity of u^s on Γ

$$\begin{aligned} &\Delta u^h = 0 \quad \text{in } \Omega_m,\\ &u^h = -u^s \quad \text{on } \Gamma. \end{aligned} \tag{2.5}$$

Subtracting these two components from Eq. (1.2) one obtains the equation for the regular potential u^r:

$$\begin{aligned} &-\nabla\cdot(\epsilon\nabla u^r)+\kappa^2\sinh(u^r)=0 \quad \text{in } \Omega,\\ &[u^r]=0, \quad \left[\epsilon\frac{\partial u^r}{\partial n}\right]=-\epsilon_m\left(\frac{\partial u^s}{\partial n}+\frac{\partial u^h}{\partial n}\right) \quad \text{on } \Gamma. \end{aligned} \tag{2.6}$$

The first decomposition scheme gives rise to a regular component which is always much larger than the full potential in magnitude. Thus a small relative error in the numerical solution of this regular component appears very large in the full potential. On the contrary, there is no decomposition in Ω_s in the second scheme, and thus it is numerically more stable than the first scheme. Mathematical results analogous to those appearing in [22] for the first decomposition are established for the second more numerically stable decomposition in [23], which also contains a number of numerical experiments illustrating the stable convergent behavior of the second scheme.

In addition to these two general regularization schemes which can be applied to finite difference methods [30, 35], finite element methods [22, 23] and other methods, a third type of decomposition was also proposed for applying a hybrid finite difference/boundary element method [36] and a hybrid finite element/boundary element method [37, 38] for solving the nonlinear PBE. This scheme decomposes the PBE into a Poisson equation

$$\begin{aligned} &-\nabla\cdot(\epsilon\nabla u^s)=\rho^f, \quad \text{in } \Omega, \\ &[u^s]=0, \quad \left[\epsilon\frac{\partial u^s}{\partial n}\right]=0 \quad \text{on } \Gamma, \end{aligned} \tag{2.7}$$

which accounts for the singular charges and can be solved efficiently with boundary element method, and a regularized Poisson-Boltzmann equation

$$\begin{aligned} &-\nabla\cdot(\epsilon\nabla u^r)+\kappa^2\sinh(u^r+u^s)=0 \quad \text{in } \Omega, \\ &[u^r]=0, \quad \left[\epsilon\frac{\partial u^r}{\partial n}\right]=0 \quad \text{on } \Gamma, \end{aligned} \tag{2.8}$$

which can be solved by using finite difference or finite element methods. We would note that the third decomposition differs fundamentally from the first two schemes in their interface conditions on the molecular surface. The regular potential in the first two schemes has a singular source on the molecular surface which must be accounted for in the solution of u^r otherwise the solution does not converge at all [23]. The third decomposition has a vanishing source term on the molecular surface similar to the original nonlinear PBE. Without special treatment of these interface conditions the solution u^r does converge, although at some slowed rate [29]. Furthermore, this third decomposition scheme does not suffer from the numerical instability of the first decomposition because the singular component u^s is usually of the same magnitude as the full potential for small or moderate κ thus its solution accuracy faithfully represents the solution accuracy of the full potential.

It is worth to note that all these interface conditions are determined by the decomposition scheme and the original condition Eqs. (1.4)-(1.5), the latter two are intrinsically satisfied within the PBE describing the electric field in the vicinity of the interface. Therefore, only if the conditions are enforced in the numerical treatment, they can be considered as boundary conditions of the PDE, such as the conditions in Eqs. (2.3)-(2.6). The

interface conditions such as Eqs. (1.4) and (1.5) could be explicitly enforced in boundary element methods, but are not required in many traditional finite difference or finite element methods without adopting the regularization schemes. In the work [37], the PBE form of Eq. (2.8) is directly solved in the whole domain Ω (with boundary conditions on $\partial\Omega$), where the interface conditions are implicitly satisfied and does not need specific treatment.

3 Finite difference methods

Finite difference methods have been the most popular numerical methods for the PBE in bimolecular simulations, most likely due to their simpler implementation than finite volume method or finite element methods since mesh generation and refinement are trivial for finite difference methods. DelPhi [39], GRASP [40], MEAD [41], UHBD [42] and the PBEQ [43] module in CHARMM [44] are among the most successful finite-difference-based PB solvers for computing biomolecular electrostatics, while a finite-volume-based PB solver APBS [45] enjoys increasing popularity over biochemistry and biophysical communities. A number of nice reviews of these well-established numerical methods for the PBE and their applications have been given, for example, in [12, 24, 46, 47].

Several essential features of the Poisson-Boltzmann equation were left untreated in these traditional PB solvers. These features include (1) the exact or approximate position of molecular surface and (2) the continuity condition of electric displacement on the molecular surface, Eq. (1.5), which is also sometimes referred as the potential flux condition [29,30,48]. Lack of the enforcement of this interface condition results in low accuracy of the surface potential and the low convergence rate [29]. In most PB solvers based on structured grids, the molecular surface is used to define the map of the dielectric function only while the position of the molecular surface is not explicitly computed. In PBEQ and APBS, for example, a set of probe spheres centered at sampled points on the van de Waals surface are defined. Any grid point enclosed by these spheres is regarded to be in the solute and is assigned a low dielectric constant. A grid node that is not enclosed by any of van de Waals surface or the probe spheres is in the solvent and has a high dielectric constant. Fig. 2 illustrates that the dielectric constant defined this way might not uniquely map the molecular surface. Moreover, none of the these PB solvers calculates the normal direction of the molecular surface, leading to the neglecting of the continuity conditions on the electric displacement.

The rapid progress of numerical methods for elliptic interface problems on structured meshes and the increasing interest of applied mathematicians in mathematical biology initiated a wave of developing PB solvers with interface methods. One of the earliest interface methods for solving the PBE was developed by Chern *et al.* [35] based on a jump condition capturing scheme(JCCS) [49]. The JCCS assumes that the interface is always aligned with a mesh line and modifies the finite difference scheme at the interface through matching local Taylor expansions of the solution in regions of distinct materi-

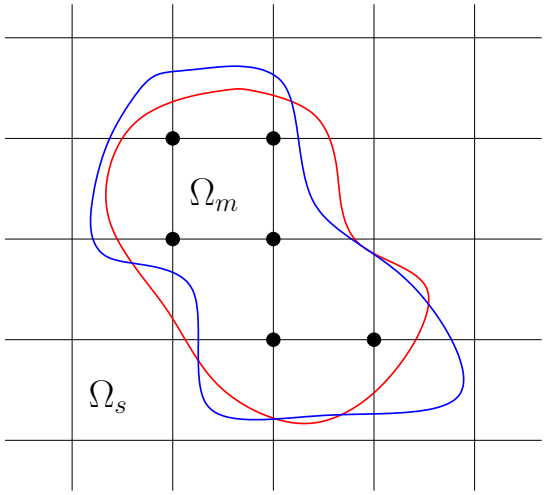

Figure 2: The resolution of molecular surface in traditional finite difference methods for the PBE is limited by the mesh size. Two completely different molecular surfaces could give an identical map of dielectric constants on the same mesh. The grid nodes in the solute are marked with black dots.

als. The modified discretization schemes are monotone and satisfy the discrete maximum principle. Furthermore, the stiff matrix is symmetric and positive definite, therefore standard techniques such as preconditioned conjugate gradient and multigrid can be readily used to accelerate the inversion of the matrix. However, the JCCS does require a body-fitting mapping of the solute region enclosed by an irregular molecular surface onto a ball for aligning the interface with a mesh line, thus its applications are limited to simply-connected molecules with sufficiently smooth surface for which the body-fitting mapping can be found. In deed, the most valuable result in [35] is the new regularization scheme for the Poisson-Boltzmann equation. This scheme not only simplifies the regularity analysis of solutions to the Poisson-Boltzmann equation [22,23,35] but also paves the way to develop convergent and numerically stable Poisson-Boltzmann solvers [23,30,35].

Based on a matched interface and boundary (MIB) method [50–52], Zhou *et al.* had successfully implemented the analytical molecular surface in their interface method for solving the Poisson-Boltzmann equation. These efforts give rise to the first practical Poisson-Boltzmann solver enforcing both interface conditions on the molecular surface [29]. The MIB method implicitly defines the smooth continuation of subdomain separated by an interface and applies the standard central difference scheme on the extended subdomains. Both interface conditions, Eqs. (1.4)-(1.5), are used during this smooth continuation to define the expansion representations of fictitious values located on the extended margins. The molecular surface implemented in [29,53] is a triangulated reduced molecular surface computed from the program MSMS [54] due to Michel Sanner *et al.*, but any molecular surface definitions should also apply because the MIB method needs only the intersections of the molecular surface and the mesh lines, as well as the normal

directions of molecular surface at these intersections. Enhanced with elegant treatments of geometry singularities usually found in the molecular surface [48, 55], MIB-based PB solver showed for the first time a clear second-order convergence rate for computing electrostatics of general biomolecular systems. This MIB Poisson-Boltzmann solver was recently combined with the regularization scheme in [35] to remove the charge singularities in molecules to achieve a higher level of accuracy [30]. Nevertheless, the stiff matrix obtained from the MIB discretization is asymmetric and positive indefinite; this results in losing access to highly efficient linear solvers such as CG and its variants.

The MSMS surface was also successfully implemented with the immersed interface method (IIM) to approximately enforce the interface conditions in discretizing the Poisson-Boltzmann equation in parallel to the implementation of molecular surface with MIB method [53]. IIM was also customized to solving the nonlinear PBE modeling for charged spheres [56], where a 3-D Poisson-Boltzmann equation was reduced to a 2-D equation in cylindrical coordinates by using the symmetry of the geometry. It seems promising to develop a fast IIM-based PB solver by incorporating a number of nice numerical techniques of IIM. These techniques include an optimized finite difference scheme on an enlarged discretization stencil for preserving the maximum principle [57], and the Schur decomposition of the stiff matrix as well as the associated GMRES algorithm [58].

In addition to the enforcing of interface conditions to acquire a highly accurate surface potential and better convergence rate, efforts have also been devoted for accelerating the solution of the Poisson-Boltzmann equation and reducing the memory demand to accommodate dynamics simulations of large biomolecular systems. APBS strives to speed up the solution by adopting an inexact-Newton-algebraic multigrid (AMG) method [59–61] with uniformly refined/coarsened finite volume mesh [59, 62, 63]. As described in detail in [62], a key advantage of Newton-based approaches to discretizations of the nonlinear Poisson-Boltzmann equation is that it can be shown for a large class of nonlinear problems (including the Poisson-Boltzmann equation) that the number of Newton iterations needed to converge to a given tolerance is independent of the discretization parameter. In effect, this means that the computational complexity of any Newton-based approach to the Poisson-Boltzmann equation is completely determined by the complexity of the algorithm used to solve the linear systems at each Newton iteration. As shown in [59–61], the linear systems that arise in a Newton iteration applied to the nonlinear Poisson-Boltzmann equation are effectively discretizations of the linearized Poisson-Boltzmann equation, and as a result they can be solved with AMG-like algorithms with linear $\mathcal{O}(N)$ storage and computational complexity. This class of inexact Newton-AMG algorithms have been demonstrated repeatedly to have this overall optimal storage and computational complexity when applied to the Poisson-Boltzmann equation [45, 59–62].

While Newton-AMG methods achieve the best possible (linear) performance in memory and computational complexity, multigrid-like methods are typically more difficult to implement and tune for a particular application than other iterative methods that can be used for solving the linear Newton systems (or simply for solving the linearized Poisson-

Boltzmann equation as the end goal). These methods are iterative with optimal linear memory complexity, but achieve at best sub-optimal computational complexities that range between $\mathcal{O}(N^{1.25})$ to $\mathcal{O}(N^2)$, and include the (preconditioned) conjugate gradient method (CG or PCG) and classical stationary iterative methods such as SOR, Gauss-Seidel, and Jacobi. Sparse direct methods with sophisticated reordering strategies to reduce fillin also achieve reasonable computational complexity, but have worse than linear memory complexity. By using an modified incomplete Cholesky factorization to precondition the conjugate gradient (MICCG), optimizing the modification parameter and relaxing the convergence criteria, Luo *et al.* reported an efficient linear solver for finite difference PB solvers without interface condition enforcement [19]. More analysis and computations seem necessary to substantiate the mathematical rigors of Luo's approach and improve the accuracy of the potential solution [15].

Another notable work for accelerating the finite-difference PB solver is due to Sayyed-Ahmad *et al*. They regarded the solution of the elliptic PBE as the unique steady state of a parabolic equation, and managed to quickly evolve this parabolic equation to obtained the solution of the PBE [64]. It is worth noting that here the discontinuous dielectric constant on the molecular surface is smoothed so that the diffusion term with variable coefficient in the original Poisson-Boltzmann equation can be split and scaled into a new diffusion term with constant coefficient and a smooth advection term. The smoothing of dielectric interface helps to regularize the problem and alternating direction implicit method results in a substantial reduction of the memory usage. It remains unclear if all these merits are also achievable for discontinuous dielectric models.

In summary, the major concerns in applying the finite difference method in the numerical solution of the Poisson-Boltzmann equation is the large number of unknowns of the order $N=n^3$ (n is the number of mesh points in one of the coordinate directions of a 3D uniform cube of points) and the low efficiency of linear solvers in general. Grid spacings ranging from 0.2Å to 1Å are generally used in biomolecular electrostatic calculations. Hence for large systems of hundreds of angstroms in size the number of unknowns easily approaches to 1000^3, which is prohibitively large. Slightly large grid spacing might be used in the interface methods-based Poisson-Boltzmann solvers because of the increasing of the discretization accuracy on a given mesh [30, 48], but this is limited by the resolution needed to resolve the irregular molecular surface. A number of remedies might be considered to increase the usefulness of finite difference Poisson-Boltzmann solvers for large biomolecular simulations. The first method is to use a non-uniform mesh with local refinement near the active sites on the molecular surface and with large grid spacing in the solvent region far away from the molecules. The second is the so-called telescoping technique [19, 65] with which a very coarse mesh is used in the entire domain to obtain a rough potential distribution. A finer mesh is deployed in the interesting region to solve the Poisson-Boltzmann equation locally with boundary conditions interpolated from the results on coarse mesh. This focusing procedure can be iteratively applied to zoom in the interesting sites. Some of these techniques were developed in [66] and analyzed in [67,68] and shown to be optimal [68].

4 Boundary element methods

Boundary element methods (BEM) invoke Green's theorem to recast the linear PB partial differential equations as certain boundary integral equation (BIE) in u. Therefore, the unknowns and domain discretization are only on a 2D surface. Taking the exterior potential on the molecular surface (boundary) and its derivative as unknowns (denoting as $f=u^{\text{ext}}$, $h=\frac{\partial u^{ext}}{\partial n}$ for brevity), and considering the interface conditions Eqs. (1.4)-(1.5), a set of BIEs are obtained [69]

$$\alpha_p f_p = \oint_\Gamma^{PV} [\nu G_{pt} h_t - \frac{\partial G_{pt}}{\partial n} f_t] dS_t + \frac{1}{\epsilon_m}\sum_k q_k G_{pk}, \quad p\in\Gamma, \tag{4.1}$$

$$(1-\alpha_p) f_p = \oint_\Gamma^{PV} [-F_{pt} h_t + \frac{\partial F_{pt}}{\partial n} f_t] dS_t, \quad p\in\Gamma, \tag{4.2}$$

where n is the unit normal vector at point t, $\nu=\epsilon_s/\epsilon_m$, $G_{pt}=1/4\pi r_{pt}$, $F_{pt}=\exp(-\kappa r_{pt})/4\pi r_{pt}$, r_{pt} denotes the distance between two points p and t, the coefficient constant α_p is dependent on the local surface geometry of the node p. For smooth surface α_p is $1/2$. For a vertex of a polyhedron, which is not a smooth point of the surface, the coefficient α_p is equal to $A_p/4\pi$, where A_p is the interior solid angle at the node. Once f, h are solved, the potential field and energies can be obtained. Compared with this "direct" BEMs, it is noted that another type of "indirect" BIE methods [31] expressed the total electrostatic potential as a surface integral of either the single- or double-layer induced polarization contributions and solved for the unknown surface density.

By linearly combining Eqs. (4.1)-(4.2) and their derivative forms for the smooth surface case, the derivative BIEs (dBIEs) can be obtained [32]:

$$(\frac{1}{2\nu}+\frac{1}{2}) f_p = \oint_\Gamma^{PV} [(G_{pt}-F_{pt}) h_t - (\frac{1}{\nu}\frac{\partial G_{pt}}{\partial n} - \frac{\partial F_{pt}}{\partial n}) f_t] dS_t + \frac{1}{\epsilon_s}\sum_k q_k G_{pk}, \quad p\in\Gamma, \tag{4.3}$$

$$\begin{aligned}(\frac{1}{2}+\frac{1}{2\nu}) h_p = &\oint_\Gamma^{PV} [(\frac{\partial G_{pt}}{\partial n_0} - \frac{1}{\nu}\frac{\partial F_{pt}}{\partial n_0}) h_t - \frac{1}{\nu}(\frac{\partial^2 G_{pt}}{\partial n_0 \partial n} - \frac{\partial^2 F_{pt}}{\partial n_0 \partial n}) f_t] dS_t \\ &+ \frac{1}{\epsilon_s}\sum_k q_k \frac{\partial G_{pk}}{\partial n_0}, \quad p\in\Gamma,\end{aligned} \tag{4.4}$$

where n_0 is the unit normal vector at point p. The dBIEs lead to a well-conditioned system of algebraic equations [70–73], while Eqs. (4.1)-(4.2), so called "normal" BIEs (nBIEs) do not. The dBIEs can also be directly extended to systems with arbitrary numbers of biomolecules [73].

For the nonlinear PBE, 3D volume integrals appear in the integral equations, which reduce the efficiency of BEMs. It is reported that even when accelerated by certain multipole methods, the integral approach for NPBE is still slower than FD [36].

The BIEs are solved either using Galerkin or collocation approaches, but the later are the most commonly used in PBE community.

The advantages of BEM lie in several aspects: the number of unknowns is reduced by an order relative to the methods that involve volume-domain discretization; boundary conditions at infinity (open region problem) are exactly treated and the physical interface conditions (continuity in potential and jump in its normal derivative) on the molecular surface are explicitly treated which results in accurate solution on the interface relative to the FD methods where the jump boundary condition is actually smoothed by the interpolation scheme instead of being enforced; a well-conditioned formulation can be obtained and the pre-conditioner is not necessary to solve the linear system as described in abovementioned references; the singular charges distributed within the biomolecule can be analytically treated.

The disadvantages of BEM are (1) no Green's functions are available for the nonlinear PBE, hence these are only applied to the linear PBE except for that volume integrals are involved; (2) efficiency is not directly achieved because numerous boundary integral operations are required in direct BEMs; (3) singular boundary integrals affect the accuracy and/or stability.

Though the number of unknowns, N, is reduced, discretizing BIEs produces dense linear systems whose memory costs scale as $\mathcal{O}(N^2)$ and solution costs scale with $\mathcal{O}(N^3)$ in the direct solution approach. This is prohibited by either the available computer memory or CPU time for problem sizes of biomolecular systems. Therefore, iteration approaches are applied, and the coefficient matrix is not or just partially saved and the integrations (implicit matrix-vector multiplications) are evaluated at every iteration step [69]. However, even with the acceleration afforded by Krylov subspace methods, direct evaluations of the $N(N-1)/2$ pairs of interactions still requires prohibitive $\mathcal{O}(N^2)$ operations. This is the main hurdle of the wide application of BEM PB approaches. In the 20 years since the first BEM paper [31] on continuum electrostatics of biomolecular system, computational scientists have made extensive contributions to the methodological generalization, optimization, and performance improvements in this area. There are still some issues to be settled to maximize its potential power for biophysical applications.

4.1 Acceleration techniques

The integrations become summation operations (matrix-vector multiplication) after discretization, and these operations are repeated using Krylov subspace methods to solve the inversion of the dense linear system. This forms the most time-consuming part in the solution of the PBE. A number of general techniques have been used to accelerate the summation. These techniques include the fast multipole method (FMM) [74], fast Fourier transform(FFT)-based approaches [75,76], panel clustering method (e.g., see [77]), and the wavelet compression method (e.g., see [78]). The first two techniques have been explored in PBE systems.

Usage of the hierarchical "tree code" [79, 80] can accelerate the calculation to $\mathcal{O}(N\log N)$. Early multipole methods were developed for Coulombic interaction kernel, and thus only applied to BEM Poisson equation solvers instead of PBE solvers, e.g.,

see [81, 82]. Bordner and Huber used an adaptive multipole (low order polynomial expansion) method for force and torque calculations in the 'indirect' BEM [83]. Boschitsch et al. developed the multipole method for screened Coulombic kernel and implemented it in their BEM solver [72]. In the work, in addition to using multipole expansion for far field integration, the calculations were accelerated further by using Taylor expansion again for calculations on points near the evaluation point [72]. The order N algorithm, "new version fast multipole method" (FMM), for screened Coulombic (Yukawa) potential was developed recently [74]. Compared with the original FMM, in the new version FMM, the plane wave expansion-based diagonal translation operators dramatically reduce the prefactor, especially in three dimensions where a break-even point of ~ 600 for 6-digit precision is numerically observed for a direct N-body problem. This $\mathcal{O}(N)$ algorithm was used in the BIE approximations for the PBE in recent papers [16, 73]. In overall performance, the BEM solver (combined with the 'node patch' boundary element method discussed below) breaks even with a direct linear element BEM solution for a value of $N \sim 1000$ [16]. The framework was also extended to systems with arbitrary number of biomolecules. These works would appear to represent a significant advance to overcome the main bottleneck of BEM and make it a competitive tool in application to bio-electrostatics.

The application of FFT based algorithms normally achieves $N \log N$ complexity, such as the precorrected FFT (pFFT) developed by Huo *et al.* in their BEM PB solver [76]. Recently, a more memory efficient and faster algorithm FFTSVD was developed in the same group for bio-microelectromechanical systems design as well as biomolecular simulation [84], in which the memory-efficient Greens-function-independent (for low-frequency kernels) FFT translation method presented by Ying et al. [85] was implemented. FFTSVD is a multiscale algorithm that decomposes the problem domain using an octree and uses sampling to calculate low-rank approximations to dominant source distributions and responses. Long-range interactions at each length scale are computed using the FFT. The performance is illustrated to be better than pFFT-style algorithms or the old version multipole-style algorithms implemented their other programs.

FFT was also used with multipoles [86, 87]. The main idea is to use a wavelet basis such that most of the elements of the collocation and Galerkin matrix will be small enough to be neglected. The main cost of evaluating will be only $\mathcal{O}(n)$ or slightly larger than $\mathcal{O}(n)$ operations. For a general paper on this topic, e.g., see Alpert et al. [88]. Asymptotically optimal $\mathcal{O}(N)$ complexity can be achieved by using the wavelet techniques in the BIE solver for the capacitance extraction of conductors [89, 90]. But it seems there is still no such application to the PBE to our best knowledge.

Re-organizing the raw mesh generated from some software is also a method gaining attention. Reducing the BE number by unifying some nearby elements but with some loss of accuracy was reported [91]. In a recent paper, a 'node patch' BEM [69] was presented by simply re-designing the patch on the original surface mesh, which illustrated good efficiency gains and nearly without loss of accuracy. This method can be considered as the third type of low order BEM, and draws upon both the advantages of constant element

method (fast integral evaluation due to simple constant basis function) and linear element method (only about half of the unknowns as in constant element method). The resulting new mesh is quite similar to the Voronoi mesh used in finite element methods. A 'node patch' construction is illustrated in Fig. 3 on a triangulated surface.

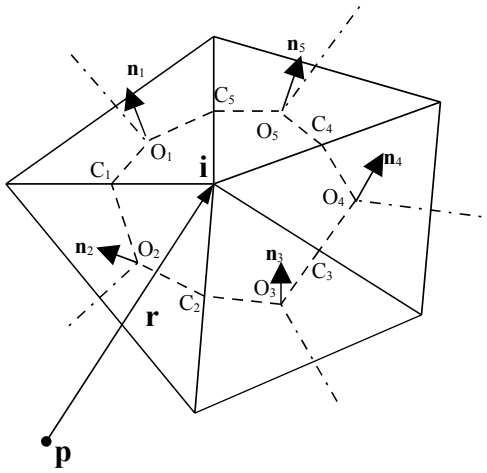

Figure 3: A "node patch" around the i-th corner enclosed by the dashed lines is constructed on a triangular mesh. O and n are the centroid and normal vector of an element respectively, and C is the middle point of an edge.

Conventional piecewise constant and linear element basis functions are often used, but normally result in low-order convergence. High-order convergence may be achieved through a high-order geometric representation for the boundary. And also because a higher order method also achieves high accuracy, it can reduce problem size to maintain the same accuracy level as using conventional flat element method. There is much interest in developing higher order methods in BEM research, e.g., see [75, 92]. In the PBE area Kuo and White's work uses a higher order basis and attains spectral convergence [93]. They describe and demonstrate on a small molecule a spectrally accurate approach for analyzing molecular surfaces described by a collection of surface points. The results demonstrate that for a tolerance of 10^{-3} this new approach requires one to two orders of magnitude fewer unknowns than a flat panel method. And later, Bardhan et al. at the same group present other detailed studies on curved BE approaches to model the 'exact' molecular surface [94]. They conclude that the calculations with their curved elements give exceptional accuracy even for the coarse discretized surfaces. However, the paper did not give the overall performance of curved-element method compared with the flat element method. A common problem is that the integration techniques for curved elements are significantly slower than those required for flat elements, and the generation of curved elements also costs considerable CPU time.

Reformulation of the BIE may improve the numerical stability. In Grandison et al.'s BIE formulation, direct Coulomb contributions to the total potential are treated exactly

and Green's theorem is applied only to the residual reaction field generated by surface polarization charge induced at dielectric boundaries [95]. The implementation shows significantly improved numerical stability over alternative schemes involving the total field or its surface normal derivatives [95].

Krylov subspace methods are commonly used to accelerate the solution of the linear system. Different iterative methods are implemented by Lu *et al.* [73], but detailed comparisons need to be further explored. To the authors' preliminary observation, the restart-GMRES and the biconjugate gradients stabilized (BiCGStab) method perform well in most cases, although GMRES seems to perform better.

4.2 Increasing the accuracy

The accuracy could be trivially improved through increasing the number of BEs, but this will be limited by memory and efficiency considerations. The simple geometric factor correction used in Eqs. (4.1)-(4.2) in the flat BE method shows significant improvement in accuracy without increasing the BEs [69]. This shows that the smooth surface approximation underlying the usual BIE forms using the coefficient $\frac{1}{2}$ can be improved for a practically discretized molecular surface.

Two lowest order BEMs, the constant element and linear element BEs, are the most commonly used flat panel methods, where the last one has better accuracy. Molecular surfaces are typically smooth, and therefore are candidates for use of higher order or especially 'accurate' curved elements. Numerical integration techniques have been presented [94, 96] for curved element suitable for molecular shapes, which the numerical quadrature techniques developed for quadratically curved surfaces (defined by curves along the element edges) [97] and B-splines [98] may not be suitable for. Bardhan et al. found that methods for approximate integration on an exact geometry are far more accurate than exact integration on an approximate geometry. Their results demonstrate that continuum electrostatic calculations with BEM using curved elements, piecewise-constant basis functions, and centroid collocation are several times more accurate than planar-triangle BEM (constant element) for basis sets of comparable size [94].

4.3 Singularity problems in boundary integrals

Integrating singular or near-singular functions over the irregular molecular surface poses a challenge for BEMs. Analytical or accurate treatment of singular integrations affects not only the accuracy but also the stability of the solution.

Normally, the singular integrals are intended to be approximated by simply increasing or specifically choosing quadrature points. But even high-order Gaussian quadrature rules may fail to accurately approximate the singular and near-singular integrals.

A simple way to avoid the singularity is to use a 'cut-off' for local integration (ignoring a small region around the singular evaluation point) or a slightly modified Green's function (e.g., $1/4\pi(r+\sigma)$, σ is a small positive value).

Nearly-singular integrals are not problematic in biomolecular energetics and force calculations, in which evaluations are needed at atomic positions. If the molecular boundary is generated properly, the van der Waals radius of each atom (point charge) inside the molecule guarantees a moderate distance from the atom to the surface. Therefore, the near-singular problem is switched to the qualified mesh generation problem.

Weakly singular integration can be completely settled by coordinate transformation for each panel [97, 99]. Some techniques for regularizations of singular and hypersingular integrals are reviewed in [100, 101]. Guiggiani and Frangi used the Laurent or Taylor expansions in studying the singular patch integration [102, 103]. They presented direct analytical evaluation methods for all the strong singular and hypersingular integrals as well as the other terms such as the additional free terms that appear in the dBIEs with geometrically singular surfaces. In principle, their work can apply to both flat element methods (with collocation point either located within the element or at the corner) or curved element methods. Lu *et al.* implemented similar techniques for PB force calculations in the BEM frame, which involved both singular and hypersingular integrals [99]. The accuracy was demonstrated on a two-sphere model.

In the aforementioned work by Bardhan *et al.*, they described numerical integration techniques designed to treat curved-element singular and near singular integrals for both single-layer and double-layer potentials required for numerical solution of the BIEs suitable for biomolecular shape.

4.4 Some issues and possible improvements

Though significant progress in BEMs has been achieved recently, there are still concerns that might limit the practical application of BEMs in biological and medical research communities. One is the mesh generation. So far, the meshes used in BEM PB solvers are generated in a separate step. The most efficient molecular surface triangulation softwares was developed by Sanner at el. [54], and was not originally designed for numerical solution of PDEs. The quality is not adequate for all cases. Another code of recent development for surface mesh generation can be found in [104]. However, an integrated, fast, "qualified", and (ideally) adaptive mesh generator is still required and is an essential part of BEM PB for biophysical computations.

A completely well-conditioned BIE formulation with geometrical correction factors for discretized mesh (with piecewise smooth boundary) can be derived from Guiggiani [102] and Frangi's work [103]. The implementation including both the free term modification and the hypersingular integration techniques into the dBEM PB (Eqs. (4.3)-(4.4)) solver has not been reported, however.

Several techniques can be pursued to further increase the overall performance of BEM PB, such as parallelization (BIE method and FMM have excellent scalability for parallel computation), generation of curved BEs and the related integral techniques, implementation of adaptive FMM (of the new version) for screening Coulomb (Yukawa) potential to speed the integration and especially to save memory. In addition, because the form

of the well-conditioned BIEs (4.3)-(4.4) was originally intended to avoid the singularity problem, once the singularity problem in boundary integration is solved, a simpler BIE formulation may be constructed just by using Eq. (4.1) and the derivative form of Eq. (4.2) instead of their combination, which is so called the dual BEMs in engineering fields [105, 106]. This treatment can save some CPU time.

In cases where periodic boundary conditions are practical, for instance, modeling the electrostatics of membranes at the atomic level, then the periodic fast multipole method [107] may be implemented to solve the PBE for a fragment of the membrane.

5 Finite element methods

Compared to the finite difference methods and boundary element methods, Finite element methods in general provide more flexibility for local mesh refinement, more rigorous convergence analysis, more selections of efficient iterative solvers for the resultant linear systems and more flexibility for handling nonlinear equations. However, for the Poisson-Boltzmann equation with singular partial charges as treated in this review, its rigorous solution and approximation theory was not established until recently in [22]. Using a decomposition as described earlier in this article, a number of fundamental technical results were established for the PBE in [22], including *a priori* pointwise-bounds on solutions to the continuous and finite element-discretized solutions to the PBE, which made possible the first rigorous *a priori* error estimate for a Galerkin-based finite element method applied to the PBE. This yields the first rigorous convergence result for any numerical method applied to the PBE. In addition, these technical results made it possible in [22] to develop an adaptive algorithm for the PBE, and a rigorous convergence result was also established. This result represents one of only a handful of existing convergence results of this type for nonlinear problems such as the Poisson-Boltzmann equation.

The adaptive finite element method developed by Holst *et al.* in [22, 68, 108, 109] tackled some of the numerically most difficult issues of the Poisson-Boltzmann equation. This method uses the piecewise-linear finite element and a well-defined error indicator for driving the local mesh refinement [22, 68]. The nonlinear Poisson-Boltzmann equation is solved using Newton-AMG iterations [59, 61, 62]. The advantages of the inexact Newton-AMG approach for problems such as the nonlinear PBE was described in detail earlier in this article in the section on finite different methods. After discretization by either finite difference or finite element techniques, the inexact Newton-AMG approach results in linear memory and computational complexity solution of the nonlinear algebraic equations produced by finite difference, finite volume, or finite element discretization methods. In the case of adaptivity, non-standard variations of multigrid solvers must be used to preserve both linear memory and linear computational complexity; see [23, 110] for a detailed discussion.

In [22], the molecular surface was not explicitly calculated in the earlier version of this method but this feature was included in a more recent work of Bond *et al.* [23], where

the new regularization scheme of the Poisson-Boltzmann [35] is used to formulate a convergent adaptive finite element method following the framework in [22]. The harmonic component in this decomposition is solved with a finite element method and the gradient of this harmonic potential on the molecular surface is calculated and supplied to compute the jump of the electric displacement of the regular potential component on the molecular surface. This jump is treated as an additional influx to the solvent region in solving the regular Poisson-Boltzmann equation. The accuracy of the potential near the molecular surface is substantially improved, becoming comparable to that of the interface Poisson-Boltzmann solvers [23, 29]. The finite element method advanced by Cortis *et al.* [111] makes use of the similar Galerkin formulation but lack a treatment of the nonlinear Poisson-Boltzmann equation. Moreover, there is no enforcement of the interface conditions on the molecular surface so the results of this method agree well with those of DelPhi. A recently proposed discontinuous Galerkin method for elliptic interface problems [112] might also be customized for solving the Poisson-Boltzmann equation provided a good description of the molecular surface.

Instead of using the Newton-AMG iterations for the nonlinear PBE, the finite element method of Shestakov *et al.* [113] uses Newton-Krylov iterations for the nonlinearity. The applications of this finite element method have not been extended from colloid systems with rather simple geometry [113] to biomolecular systems with complicated dielectric interfaces.

Most recently a mortar finite element discretization was introduced by Xie *et al.* for numerical solutions of the PBE, this time with explicitly computed dielectric interface so that the interface conditions are satisfied naturally [114]. The constrained mortar space is chosen such that the solute region is the slave subdomain and the solvent region is the master subdomain. Xie's method did not use any of the regularization schemes so a finer mesh is deployed in the solute region to provide a more accurate approximation to the singular charges. Thus the two finite element spaces in the solute and the solvent region do not conform at the molecular surface; while the finite element space on the molecular surface is defined to be the restriction of the finite element space in the solute region. As a result of all these treatments, a nonlinear algebraic system with positive definite Jacobian matrix results, and this nonlinear system is solved by using a minimization technique with preconditioned conjugate gradient method. Xie's method might be applied in combination with the stable regularization scheme of the PBE such that the solute region and the solvent region can be discretized in the same finite element space to improve the accuracy of the solution at reduced degrees of freedom.

6 Hybrid methods

The promising applications of the boundary element methods to the linear Poisson-Boltzmann equation motivate the development of hybrid methods for the nonlinear Poisson-Boltzmann equation. Most of these hybrid methods make use of the decom-

position scheme in Eqs. (2.7)-(2.8). While boundary element method seems to be the best method for the linear Poisson equation (2.7), the numerical methods for Eq. (2.8) can be finite difference methods [36] or finite element methods [37]. The integral equation approach was used early by Vorobjev [115] and Zhou [116] for the solution of the nonlinear PBE. But the possibility of using this method is limited because of a large number of operations necessary for the evaluation of the nonlinear term at all discretization elements in the solvent region Ω_s as discussed in [36].

Considering the fact that the Poisson-Boltzmann equation is a Poisson equation in the solute region and a (nonlinear) equation in the solvent region, it might possible to devise a hybrid method such that the electrostatic potential in the solute region is mapped onto the molecular surface through a Dirichlet-Neumann mapping; thus the numerical solution of the potential is only carried out in the solvent region and the molecular surface. Similar methods have been well established for a large class of transmission problems or exterior problems in physical and engineering sciences [117–120]. The development of this direction is underway by the authors [121].

7 Some other methods

It is expected that the advancing of numerical methods for partial differential equations accomplished in the mathematical community could continue to benefit the numerical solutions of the Poisson-Boltzmann equation for biomolecular electrostatics. Given the complicated structures of biomolecules and the irregular molecular surfaces, the meshless methods such as boundary nodes method [122, 123], boundary knot method (BKM) [124] and element free Galerkin method [125, 126] might be of particular advantage in solving the Poisson-Boltzmann equation. However, the applications of these methods to biomolecular systems have not been reported yet to our knowledge.

8 Indirect approaches

By indirect approaches for the Poisson-Boltzmann equation we mean approaches that manage to solve other equations or systems of equations for electrostatics potentials which under certain circumstances also satisfy the Poisson-Boltzmann equation. The regularization schemes we discussed in Section 2 do not belong to this category because their equivalence to the Poisson-Boltzmann equation is unconditional. The indirect algorithms usually stem from the equivalence between the electrostatics described by the Poisson-Boltzmann equation and other physical models. For instance, the solution of the Poisson-Boltzmann equation can be regarded as the minimization of an energy functional in certain relaxation procedures. As another example, when an electrodiffusion process reaches its equilibrium state, the electric field reduces to the Poisson-Boltzmann description. Therefore, PBE solution can be considered as the final state of an evolving electrodiffusion equation.

The transformation of the elliptic PBE to a parabolic differential equation evolved along a pseudo-time [64,113] is one class of these indirect algorithms. The transformation in [64] leads to

$$\frac{\partial u}{\partial t}=\nabla^2 u+\frac{\nabla\epsilon\cdot\nabla u}{\epsilon}+\frac{\kappa^2}{\epsilon}\sinh(u)+\frac{\rho^f}{\epsilon}, \tag{8.1}$$

where t is the pseudo-time. This equation is then solved with an alternating direction implicit (ADI) method, with an implicitly computed diffusion term and explicitly computed advection term and nonlinear term. The solution of Eq. (8.1) does not necessarily have to be temporally accurate since only the final steady state is of interest; For this reason a regularized technique [127] was applied in the ADI method such that a very large time step can be used to quickly get the steady state of the equation. Similar to this transformation, the nonlinear PBE is also regarded in [113] as the steady state of a parabolic equation

$$\partial_t u=\mathcal{P}(u), \tag{8.2}$$

where $\mathcal{P}(u)$ represents nonlinear Poisson-Boltzmann equation:

$$\mathcal{P}(u)=\nabla\cdot(\epsilon\nabla u)+\rho^f+\kappa^2\sinh(u). \tag{8.3}$$

The derivative $\partial_t u$ is then approximated by $(u-u^0)/\Delta t$ and $\mathcal{P}(u)$ is approximated by

$$\mathcal{P}(u)=\mathcal{P}(u^0)+\frac{\partial\mathcal{P}}{u}|_{u=u^0}(u-u^0), \tag{8.4}$$

where u and u^0 are the potentials of the current and the previous steps, respectively, and Δt is the time increment. These approximations give rise to a linear equation

$$-\nabla\cdot(\epsilon\nabla u)+\left[\frac{1}{\Delta t}+\kappa^2\cosh(u^0)\right]u=\rho^f+\kappa^2\left[u^0\cosh(u^0)-\sinh(u^0)\right]+\frac{u^0}{\Delta t}. \tag{8.5}$$

The time step Δt shall be judiciously chosen such that the steady state can be reached within minimal steps, although a surprisingly large Δt might be used to approximately reach the steady state in a single run [113].

A recent work of Lu *et al.* [37] shows the nonlinear PBE is an equivalent description of the solution of the Poisson-Nernst-Planck equations (PNP) at equilibrium state. The steady state PNP is:

$$\begin{aligned}&-\nabla\cdot(\nabla C_i+\beta C_i q_i\nabla u)=0,\quad \text{in }\Omega_s,\quad i=1,\cdots,K,\\&-\nabla\cdot(\epsilon\nabla u)-\rho^f(r)-\sum_i q^i C^i=0,\quad \text{in }\Omega,\end{aligned} \tag{8.6}$$

where $\beta=1/k_BT$, C_i is the concentration of the i-th species of mobile ion, and K is the number of species considered. The Eqs. (8.6) are to be solved with appropriate initial and boundary conditions for the concentration C_i and the electrostatic potential u.

The transformation of the Poisson-Boltzmann equation to Eqs. (8.6) supplies a useful indirect approach to solve the PBE. This transformation not only captures the underlying relationship between electrostatics and diffusion, but provides flexibility for further extension and modification of the nonlinear PBE to include more physical effects that could affect diffusion and electrostatics, such as the modified PBEs or PNP discussed in Section 11. The model extension can originate from improvement of the free energy expression of the system, which can make it more convenient to start from the energy variational approach. Work on this direction is continuing [128].

The Eqs. (8.6) are solved by finding the fixed point of the mapping $T(C_i,u)=(C_i,u)$ defined by the coupled system via Gauss-Seidel iterations. Since the equations solved within each iteration are linear, this iterative algorithm can be considered as an alternative of the Newton-like algorithms in many finite element approaches for the nonlinear PBE [62,114]. In our experience [37], the performance (number of iterations) to solve the coupled set of equations (using the same setup for equivalent nonlinear PBE) is roughly close to that of direct solution of the nonlinear PBE with finite element methods. However, the numerical properties of such equivalent transformations have not been extensively explored and rigorously proved.

All these indirect approaches might be unified in an energy relaxation scheme, either in real time or pseudo-time.

9 Postprocessing: Energetics and force calculations

Electrostatic energy and, in many cases, the forces are the main concerns in biophysical applications of the PB model. The solvation (charge-solvent) energy, which is defined as the difference of the total energy and a reference energy (e.g., the Coulomb interaction of the singular charges in the molecule) as Eq. (2.1) is of interest. Partially due to this reason, there is no numerical difficulty in energy calculation. In BEMs or FD/FEMs using regularization schemes, the energies are simply obtained once the PBE is solved. In the commonly adopted FDs or FEMs (without invoking the decomposition scheme as described in Section 2), solution of the PBE is performed twice in a nonuniform and a uniform dielectric environment for the solvation energy calculation, e.g., see [65]. In addition, solvation energies can also be obtained from a single PB calculation in FD by using an induced polarization charge rather than electrostatic potential, see, e.g., [129], or using a direct summation on the FD grids for Coulomb interaction to eliminate the need for a second FD calculation [130].

However, there are still numerical issues in force calculations. The discontinuous dielectric coefficient ϵ at the molecular boundary causes a jump of the derivative of the potential. This leads to difficulties in force calculation through direct the numerical derivative of the potential in FD/FEMs. The normal strategies involve using certain smoothed boundaries to substitute for the distinct molecular surface. This naturally avoids the discontinuity problem, and may also accelerate the solution of the PBE and improve the nu-

merical stability in MD simulation. But the potential and force profiles near the molecular surface are very sensitive to the choice of dielectric smoothing function, which always needs a re-parameterization of the force field such as the PB radii [47]. Several smooth boundary dielectric functions are used [20, 131, 132]. Grant *et al.* combine a Gaussian-based dielectric function with fast numerical solvers ZAP [131]. In the comparison, ZAP obtained solutions to the PB equation at speeds that were comparable to those of GB methods at the expense of significant deviations in solvation energies from the other PB solvers [15]. Luo and co-workers also showed the improved speed of the FDPB solver using smooth dielectric functions [19, 20].

In BEM framework, Lu *et al.* recent present rigorous and efficient methods for PB force calculations [33,69,99]. The discontinuous dielectric boundary does not impose difficulty for the force calculation in BEM as shown in these methods. A set of BIEs are presented for the first time for calculation of intermolecular PB (total) force, which are derived using a variational approach from the rigorous intermolecular interaction energies [33]. The efficient Maxwell tensor approaches are also explored by implementing direct singular BI techniques [99], or by constructing a simple interpolation method on the irregular 2D surface [69].

In addition, the choice of outer boundary condition used in the solution of the PBE could influence potential, energy and force evaluation. The outer boundary treatments in most of current nonlinear PBE implementations are to either set the potential at the outer boundaries to zero or estimate it using the (linear) Debye-Hückel (DH) approximation. Firstly, when the outer boundary is sufficiently far away from the solute, these treatments are normally acceptable. Or, a more accurate, in principle, alternative is to iteratively adjust the outer boundary condition according to the salt content enclosed in the outer boundary until convergence. Secondly, for specified outer boundary conditions in certain cases, no matter the boundary is far or close to the solute, the system can be accurately treated by decomposition of the potential and modification the PBE. The work on this is underway. In other cases, as pointed out in Boschitsch and Fenley's recent study, both the outer boundary condition approximations may, under certain conditions, produce erroneous estimates of the potential and energy salt dependencies [133]. They also gave a new outer boundary formulation and energy corrections for the nonlinear Poisson-Boltzmann equation.

10 Mesh generation

All the current numerical methods for differential equations rely on the discretization of space, which is represented as a distribution of points and their connections. The generation of this presentation, called mesh generation, thus is critical to numerical methods. For the Poisson-Boltzmann equation, this generally difficult task is always complicated by the identification of the irregular molecular surface and an appropriate description of this surface for resolving the molecular structures in sufficient details. Once the molec-

ular surface is found and discretized, the remaining procedure of mesh generation depends on the particular numerical method used. For the boundary element method this molecular surface mesh suffices; while for finite element method or its coupling with boundary element methods, a volume mesh in the solvent region and(or) the solute region is also needed. The generation of a volume mesh starting with a boundary discretization can be accomplished following various well-established techniques [134,135], hence in this section we will be focused on the mesh generation on a molecular surface and the implementation of this surface in general numerical methods.

The molecular surface is defined in various senses [136, 137]. Included in the most widely used molecular surfaces are

- the van de Waals surface which is the smallest envelope enclosing a collection of spheres representing all the atoms in the system with their van de Waals radii,
- solvent-accessible surface (sometimes also called the Lee-Richards molecular surface) [138] which is the trace of the centers of probe spheres rolling over the van de Waals surface,
- the solvent-excluded surface (also known as the 'molecular surface' or 'Connolly surface') in Richards' sense [139], which is the surface traced by the inward-facing surface of the probe sphere,
- Skin surface [140–142] which is defined by a set of weighted points representing the atoms and a scalar called the shrink factor controlling hyperboloidal connections between neighboring spheres,
- Gaussian surface [143,144] or "soft-van der Waals" surface (an isosurface of certain density) [145] which is a level-set of the summation of the spherically symmetrical (Gaussian or other type of) density distribution centered at each atom of the biomolecular system,
- the boundary of a domain enclosing the molecule such that a certain energy is minimized over this boundary, such as the surface (surface-determined) free energy [146,147].

The first four definitions are geometrical, and will give rise to a molecular surface comprising of different patches of intersected spheres or hyperboloids. The central issue of generating molecular surfaces in these definitions is to efficiently locate the intersections of a large number of sphere and these patches, either analytically or approximately. Once this is finished, a number of points of prescribed density can be chosen on these patches from which a discretized molecular surface can be generated through, for example, a Delaunay triangulation [54, 148] or level-set based approach [104]. A nice review of these geometrical molecular surfaces is give by Connolly [136]. The last two types of molecular surface are defined by level-set functions, thus it is easier to generate an optimal surface mesh [144, 149].

A quality surface mesh is usually demanded by boundary element methods, especially finite element methods, or their hybrid methods for satisfying the criteria of the

finite element spaces [150] and for enforcing the interface conditions. When an adaptive technique is employed to drive the local mesh refinement, the surface mesh might also be refined. Local mesh refinement is usually accomplished by bisecting selected mesh edges and adding new elements with these middle points [151]. Such a refinement strategy can not provide a more accurate approximation to the molecular surface and the interface conditions, and thus limits the reduction of error of numerical solutions in the vicinity of molecular surface with the mesh refinement [23]. It is possible to move the added nodes from their original positions, the middle points of the selected edges, preferably to the nearest molecular surface in order to provide a more accurate approximation of the molecular surface. The application of this remedy, however, might be complicated if the molecular surface is defined in any of the first four senses because it is difficult to locate a point on the molecular surface close to a mesh node. The molecular surface defined by a level set function, therefore, is preferred for the adaptive algorithms since the manipulations in a level set, such as measuring the distance from an arbitrary point to the level set, involve minimal algebraic operations. It is worth noting that the finite element methods for elliptic interface problems, such as [112, 152], do not rely on the molecular surface discretization for the modified variational formulations used near the interface.

Finite difference methods, regardless of the enforcement of the interface conditions, usually do not demand a surface discretization. In traditional implementations of finite difference methods in this field, random points are positioned on the molecular surface as long as the density of these points is high enough to be able to correctly characterize each grid point as an interior or exterior point of the solute. MIB method [51], for another example, requests only the intersection points of the mesh lines and the molecular surface as well as the outer normal directions at these intersections. Similarly, for each of the irregular nodes IIM needs a point on the molecular surface as well as the normal direction at this point in order to modify the finite difference scheme [153]. The molecular surface defined by a level set thus is a perfect fit for the finite difference method since it is easy to find the intersections of mesh lines with a level set and to find the normal direction at any point in the level set [154]. Any quality of surface triangulation would suffice for the implementation in a finite difference method, and it is essentially not necessary to generate a surface triangulation for a level set molecular surface for the application of finite difference methods. For example, the surface triangulation in the upper left chart of Fig. 4 is apparently not regular due to the large amount of triangles with large aspect ratio. Such a surface mesh would works perfectly with MIB method [29], but has to be smoothed for the application of finite element methods [23, 37, 149] which usually demand a quality surface mesh like that in the upper right chart of Fig. 4. For boundary element methods, the demanded quality of surface mesh sometimes could be not so good as that for finite element methods. For instance, the surface mesh generated by MSMS [54] are directly used in BEM solvers by many groups. A procedure combining existing softwares to generate such surface mesh is described in [37]. We would note that a surface triangulation can help locate the surface nodes and the normal directions efficiently [53], while this triangulation must have sufficiently high resolution such that the approximation error in

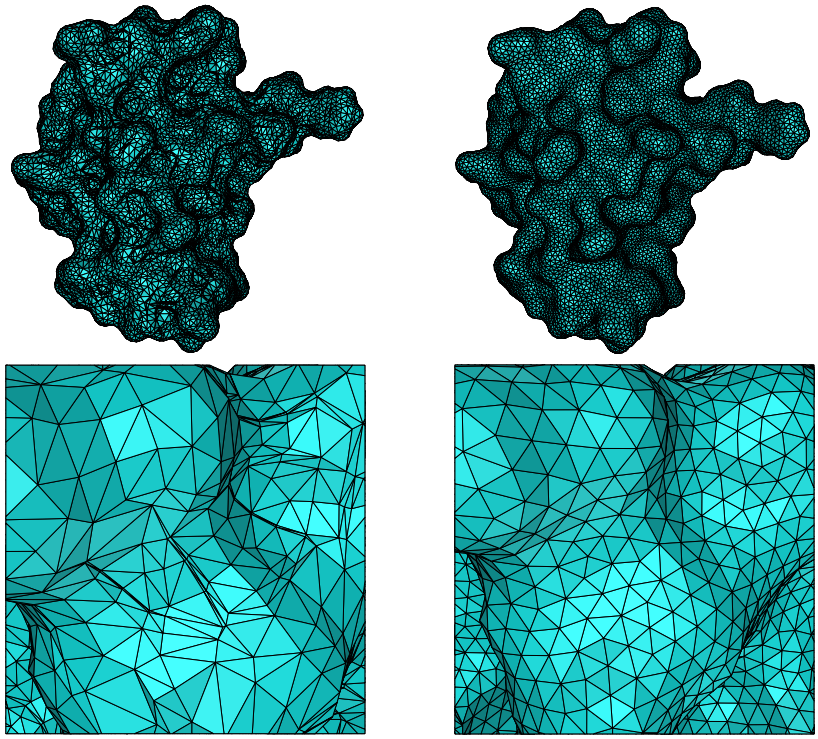

Figure 4: Upper left: A surface mesh with triangles of large aspect ratio suffices for the applications of finite difference interface methods. Such mesh might also be applicable for some boundary element methods. Upper right: The surface mesh should be sufficiently smooth and regular for the application of boundary element methods, or especially finite element methods. Lower: Close view of these two meshes, respectively.

these surface nodes and normal directions would not dominate the approximation error of differential equations with interface methods on a mesh of finite size. It is also important to be able to decimate a given mesh to produce a hierarchy of multiresolution surface and volume meshes for a given biomolecule, where the surface mesh retain interpolatory properties. Algorithms of this type were developed [149, 155].

Finally, considering the facts that the molecular surface itself is a rough approximation to describe the transition from molecular interior region with low dielectric to exterior region with high dielectric, and the electrostatic energy is just a component of the total free energy measurable in experiments, therefore, any type of surface definition would be associated with certain parameterization on such as the atomic radii. This makes it difficult to evaluate different types of molecular surface. Given that the force fields such as CHARMM and AMBER on atomic level have been established, it is possible to explore an alternative approach to avoid the surface mesh problem through interface-free strategy. A physically reasonable model incorporates the van der Waals interactions to extend the PB model, which needs no parameterization procedure and is consistent with the molecular modeling force field [145].

11 Beyond PB model

The physical basis of PBE is a mean field approximation. In this theory, the charged ions are treated as point charges immersed in a continuum dielectric media. The average ionic density distributions and the mean electric potential in solution are determined by each other through the Poisson equation and Boltzmann distribution. However, the real interactions among the ions lead to ion-ion correlations and density fluctuation in the real equilibrium state, which may affect the ionic distributions, and thereby the potential filed. Reviews on this topic can be found, e.g., refs. [156,157]. Because this is not the topic of this paper, we just mention here that a bunch of modified forms to the standard PB theory may also supply new numerical and mathematical problems for computational researchers in this area. For instance, the modified PBE accounts for the effects of ion size [128,158,159], van der Waals interactions between ions and solute [145,160], dispersion and hydrophobicity [147], dipolar solvent [161,162], and a correlation-corrected potential [163]. These extensions will finally lead to more general continuum model of solution systems, and be able to quantitatively analyze the hydrophilicity, hydrophobicity, the total solvation energies of biomolecules, and to explain some novel phenomena including like-charge attraction between biomolecules [164].

12 Conclusions and discussion

Overall, finite difference methods dominate the current applications of PB modeling. FD is relatively easy to implement for the linear, nonlinear and modified PBEs, and is also efficient for not large systems. This method could be a good choice in designing the PBE solver especially in the situation that the mesh generation for biomolecules becomes a difficult task. However, it is hard to improve the efficiency and memory demand for large systems for FDs without incurring parallel computing. The accuracy of solution in the vicinity of molecular surface (supposing at similar grid resolution) is relatively lower than that obtained with the interface methods, boundary element methods, and finite element methods.

Because the linear PBE is a good approximation to the nonlinear PBE for globular proteins under physiological ionic strengths [116], boundary element methods appear to be prospective methods for solution of the linear PBE when intensive computation (for instances in MD simulations) is required. BEMs are also especially proper for the multidomain (molecules) system as met in protein-protein association simulations. But BEMs are not proper for the modified (nonlinear) PBEs.

When qualified mesh generation is available, FEMs seem to be good choice to achieve good performance in the accuracy and memory demands for solution of the PBEs. In addition, some modern finite element method packages such as FETK [68] supply flexible platform to treat the nonlinearity in the standard PBE or even more complicated modified forms such as the modified PBEs, which make it convenient to implement the physical

extensions of the PB model. The main disadvantage of FEM is its inefficiency in treating the nonlinear problems.

For BEMs and FEMs, efficient and accurate mesh generation for molecular surface is still required to make these methodologies to gain popularity. The interface-free method seems a promising solution to avoid the surface mesh problem, which is based on a physically more natural and accurate extension of the PB model [145].

The numerical accuracy of the solution of PBE can be generally improved by increasing the mesh/grid resolution. All the discussed methods can achieve acceptable accuracy for energy calculations. In some cases such as in the diffusion-reaction model [37] where the potential and force on molecular surface are used, the BEM or FEM generally can produce these quantities with higher accuracy. As the accuracy of the PB model itself as a mean field theory, it is in good agreement with experiments for monovalent ions up to energies of order of kT. However, careful measurements of the forces between two charged surfaces at nanometric scale show strong deviation from the simple PB picture [165]. In particular, when the specific binding of ions, size effects, correlation between multivalent ions, the inhomogeneous structure of water around charges, or a more complete free energy continuum model are considered, the beyond PB models should be applied.

Given the rapid improvements in discretization schemes, linear solvers, acceleration techniques, parallelization of algorithms, as well as the advances in computational power, it will not be long before that the PB model (or its beyond) plays active roles in wider areas such as MD simulations and virtual drug designs where accurate solvation model and intensive computations are required.

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