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On developing stable finite element methods for pseudo-time simulation of biomolecular electrostatics

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ABSTRACT

The Poisson–Boltzmann Equation (PBE) is a widely used implicit solvent model for the electrostatic analysis of solvated biomolecules. To address the exponential nonlinearity of the PBE, a pseudo-time approach has been developed in the literature, which completely suppresses the nonlinear instability through an analytic integration in a time splitting framework. This work aims to develop novel Finite Element Methods (FEMs) in this pseudo-time framework for solving the PBE. Two treatments to the singular charge sources are investigated, one directly applies the definition of the delta function in the variational formulation and the other avoids numerical approximation of the delta function by using a regularization formulation. To apply the proposed FEMs for both PBE and regularized PBE in real protein systems, a new tetrahedral mesh generator based on the minimal molecular surface definition is developed. With a body-fitted mesh, the proposed pseudo-time FEM solvers are more accurate than the existing pseudo-time finite difference solvers. Moreover, based on the implicit Euler time integration, the proposed FEMs are unconditionally stable for solvated proteins with source singularities and non-smooth potentials, so that they could be more efficient than the existing pseudo-time discontinuous Galerkin method based on the explicit Euler time stepping. Due to the unconditional stability, the proposed pseudo-time algorithms are free of blow-up or overflow issues, without resorting to any thresholding technique. Numerical experiments of several benchmark examples and free energy calculations of protein systems are conducted to validate the stability, accuracy, and robustness of the proposed PBE solvers.

1. Introduction

The Poisson–Boltzmann (PB) equation is commonly used in biomolecular simulations to describe the electrostatic interactions and ionic density distributions of solvated biomolecules at the equilibrium state [1,2]. By treating the macromolecule and its aqueous surroundings as continuum, the PB equation combines the classical Gauss's law in electrodynamics with the fundamental Boltzmann distribution in statistical thermodynamics. Mathematically, the PB model takes the form of a nonlinear elliptic equation on multiple domains with discontinuous dielectric coefficients across the molecular surface or solute–solvent interface [3,4]. A brief history of PB model can be found in [5]. The PB methodology and applications in biomolecular modeling are summarized briefly in [2,6].

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The PB equation admits analytic solutions only for a few simple shapes [7], so that for simulating biomolecules with complex geometries, numerical solution is indispensable. Driven by practical needs, tremendous advances have been made in developing PB numerical solvers over the last few decades, giving rise to a variety of fast computational approaches, including finite difference methods [8–13], finite element methods [14–18], boundary element methods [19–23], and discontinuous Galerkin methods [24–26]. Moreover, many numerical algorithms for the PB equation have been incorporated into popular molecular simulation software packages or online web servers, such as DelPhi [8,11], UHBD [27], CHARMM [10], APBS [28], AMBER [12], MIBPB [29], and SDPBS [30]. Even though a great success has been achieved in the aforementioned studies, the numerical solution of the PB equation remains to be challenging, due to the consideration of discontinuous coefficients, complex geometry of protein structures, singular source terms, infinite domain, and strong non-linearity [31].

The non-linearity associated with the PB equation is of exponential form, and is critical when the underlying electrostatic potential is strong. An improper numerical treatment of the PB non-linearity could introduce instability or ill-conditioning in the computation. Two different approaches have been developed in the literature for handling the PB non-linearity. In a usual approach [32], the PB equation is discretized into a nonlinear algebra system, which is then solved by nonlinear algebraic solvers, including nonlinear relaxation methods [10,11], nonlinear conjugate gradient method [9], and inexact Newton method [33].

The other approach is based on the pseudo-time solution of the PB equation [34–36]. In such solutions, a time dependent PB equation is constructed by introducing a pseudo-time derivative. A long time integration is carried out, so that the resulting steady state solution converges to the solution of the original nonlinear boundary value system. Nevertheless, by using an explicit or semi-implicit time integration scheme [34–36], the nonlinear term has to be linearized or evaluated at a previous time, which undermines both stability and efficiency.

Recently, a novel nonlinear treatment in the pseudo-time approach has been developed [37,38] to completely suppress the nonlinear instability. The success lies in an analytic integration of the nonlinear term, after the time-dependent PB equation is split into linear and nonlinear subsystems. Being free of blow-up or overflow problems which may be encountered in the nonlinear algebraic methods [39], this tailored nonlinear treatment finally makes the pseudo-time solution a viable approach for electrostatic analysis of biomolecules [37,38,40].

In particular, both pseudo-time finite difference [37,38,40] and discontinuous Galerkin (DG) [26] methods have been developed in this framework. Using implicit time stepping schemes, the finite difference methods are very efficient for large protein systems, but are quite inaccurate. Based on a body-fitted mesh, the DG variational formulation offers great accuracy and flexibility in handling complex geometries and nonsmooth potentials. However, by integrating with an explicit Euler scheme, the pseudo-time DG method [26] is quite inefficient in steady state simulations.

The objective of this work is to develop stable finite element methods (FEMs) for solving the PB equation. To this end, Nodal-Based Finite Element Method (NBFEM) [41–44] will be introduced for pseudo-time simulation of biomolecular electrostatics, by overcoming the difficulties associated with the existing pseudo-time approaches [26,37,38,40]. In the framework of continuous Galerkin (CG) weak formulations, the implicit Euler time discretization is constructed, giving rise to more stable and efficient pseudo-time FEMs for solving the PB equation. Moreover, rigorous treatment of solute–solvent interface will be adopted by using unstructured tetrahedra meshes, so that the numerical accuracy could be greatly improved, compared with the finite difference results [37,38,40]. Furthermore, significant effort will be devoted to attack other challenging features of the PB equation. In particular, we will investigate and compare different treatments for singular partial charges. A new tetrahedral mesh generator based on the minimal molecular surface [3,4] will be developed, so that the proposed pseudo-time FEMs can be applied to protein structures downloaded from the protein data bank.

It is well known that the singular charge sources of the PB model, in terms of a sum of Dirac delta functions, not only impose great difficulty in numerical analysis [16], but also introduce a large approximation error in 3D mesh based algorithms [31]. The most commonly used technique in the PB literature is using a trilinear approximation to distribute a singular source to the vertices of the cube or element containing the source point [8]. In a FEM variational form, one can apply the definition of the delta function so that a singular source can be evaluated through the trial functions [17]. Being cheap and efficient, these treatments may not guarantee second order accuracy [13], because the potential function changes rapidly near the singular poles. A more elegant way to handle singular charges is using regularization approaches [13,16,18,39,45,46]. In these approaches, the potential function is decomposed into a singular component plus one or two other components. The singular Coulomb potential satisfies a Poisson equation with the same PB singular sources, and can be analytically solved in terms of Green's functions. After removing the singular component, the other potential components satisfy elliptic equations with a higher regularity so that their discretization by general numerical methods becomes more accurate [31]. In the present study, both the trial function method [17] and a regularization approach [39] will be studied in the proposed pseudo-time FEMs.

In the PB model, a molecular surface is needed to distinguish the molecular domain from the solvent domain. The classical molecular surfaces are hard sphere models including Van der Waals (VdW) surface, solvent-accessible surface [47], and solvent-excluded surface [48]. On the other hand, the soft sphere models, such as Gaussian surface [49] and minimal molecular surface (MMS) [3,4], are more suitable for the FEM tetrahedral mesh generation, because these surfaces are free of geometrical singularities and the underlying level set functions allow simpler algebraic calculations in generating volumetric meshes [18,50,51]. The MMS will be employed in this work, which is defined as the unique surface that is of the smallest area and encloses all VdW balls. However, in the previous MMS generation [52], only Cartesian grid type volumetric meshes have been considered for finite difference PB solvers.