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# A hybrid solver of size modified Poisson–Boltzmann equation by domain decomposition, finite element, and finite difference☆

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ABSTRACT

The size-modified Poisson–Boltzmann equation (SMPBE) is one important variant of the popular dielectric model, the Poisson–Boltzmann equation (PBE), to reflect ionic size effects in the prediction of electrostatics for a biomolecule in an ionic solvent. In this paper, a new SMPBE hybrid solver is developed using a solution decomposition, Schwartz's overlapped domain decomposition, finite element, and finite difference. It is then programmed as a software package in `C`, `Fortran`, and `Python` based on the state-of-the-art finite element library `DOLFIN` from the `FEniCS` project. This software package is well validated on a Born ball model with analytical solution and a dipole model with known physical properties. Numerical results on six proteins with different net charges demonstrate its high performance. Finally, this new SMPBE hybrid solver is shown to be numerically stable and convergent in the calculation of electrostatic solvation free energy for 216 biomolecules and binding free energy for a DNA-drug complex.

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## 1. Introduction

The Poisson–Boltzmann equation (PBE) has been widely applied to the prediction of electrostatics for a biomolecule in an ionic solvent and the calculation of many biophysical quantities, such as electrostatic solvation and binding free energies [1–3], due to the popularity of the PBE software APBS [4], DelPhi [5], PBSA [6,7], UHBD [8], PBEQ [9], MIBPB [10,11] and SDPBS [12]. However, PBE has been known not to work properly in the prediction of ionic concentrations since it simply treats each ion as a volumeless point. To reflect ionic size effects, one variant of PBE, called the size modified PBE (SMPBE), was proposed based on the assumption that each ion and each water molecule occupy the same space of a cube with side length $\Lambda$ [13]. It was revisited in [14] under variational principle to yield a slightly different definition, and shown to be optimal in the sense of minimizing a traditional electrostatic energy. Another modification of SMPBE was given in [15]. We also noted that there existed a nonuniform size modified PBE model [14] and several other SMPBE models studied by the techniques of Monte Carlo and mean-field [16,17], a generalized Poisson–Fermi distribution [18], and statistical mechanics [19,20].

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Even so, the simple SMPBE models from [13–15] remain to be the valuable ones for biomolecular applications due to their similarity to PBE in equation form. Currently, the SMPBE model given in [15] was solved by a finite difference scheme from APBS [21], which had problems of low accuracy and numerical instability [22,23]. In [24], a finite element algorithm was proposed to solve the SMPBE defined in [13], but its numerical tests were limited to a Born ion model and a small molecule with three atoms. As a generalization of our PBE finite element solver [25], we recently developed an effective SMPBE finite element solver [26] according to the definition given in [14], and showed that it worked well for proteins with different net charges. The purpose of this paper is to modify it as a hybrid solver to further improve its performance.

Our new SMPBE hybrid solver was motivated from the following observations. The finite element method with an unstructured interface-matched tetrahedral mesh can be effectively used to deal with the interface conditions of SMPBE defined on an interface $\Gamma$ with very irregular geometry. However, its implementation requires extra arrays to store mesh data and coefficient matrices of finite element linear systems. Multigrid algorithms for solving each involved finite element linear system may be less efficient than the ones for solving a corresponding finite difference linear system [27]. For example, we tested the preconditioned conjugate gradient method (PCG) with an algebraic multigrid preconditioner from the scientific computing library `PETSc` [28]; it was found to take much more CPU run time than the PCG using incomplete LU preconditioning (PCG-ILU). This is the reason why PCG-ILU was selected as the default linear finite element solver in [26]. On the other hand, a finite difference method using a uniform mesh can be solved very efficiently by a geometric multigrid scheme without storing any coefficient matrix or mesh data. However, developing an effective finite difference method for solving SMPBE may become very difficult since it requires advances numerical techniques to treat the complicated flux interface condition.

We further noted that the calculation amount of the SMPBE finite element solver mainly came from solving a linear interface problem (see (6)) for $\Psi$ and a linear variational problem (see (12)) for a search direction, $p_k$, of a modified Newton variational minimization algorithm (see (10)) for computing $\tilde{\Phi}$. Here a sum of $\Psi$ and $\tilde{\Phi}$ with a known function $G$ (see (5)) gives a numerical solution $u$ of SMPBE. Hence, we only need to construct a hybrid algorithm for computing $\Psi$ and $p_k$ to modify the SMPBE finite element solver into a hybrid solver.

To do so, one key step is to reformulate the linear interface problem that defines the search direction $p_k$ (see (1)) from a variational form into a differential form. In this paper, this reformulation is done in Theorem 1. We then construct two overlapped domain decomposition schemes for solving $\Psi$ (see (18)) and $p_k$ (see (21)), respectively, based on a special overlapped seven box partition (see Section 4.1). In this box partition, the central box contains the protein region $D_p$, and is surrounded by six overlapped neighboring boxes. In order to simplify the data exchange between any two neighboring boxes, we next construct a special mesh of the central box, which mixes an unstructured interface-matched tetrahedral mesh with a regular tetrahedral mesh. Furthermore, a finite element scheme is applied to the central box to solve a linear interface problem while a finite difference scheme is applied to each neighboring box to solve a Poisson (or Poisson-like) boundary value problem. In this way, we obtain two finite element and finite difference hybrid algorithms, one for computing $\Psi$ and the other for $p_k$. Using them, we modify the SMPBE finite element solver into a new hybrid one.

From the standard Schwartz's domain decomposition theory [29] it can be known that our overlapped domain decomposition scheme has a fixed rate of convergence for a fixed over-relaxation parameter $\omega$. Thus, its performance mainly depends on the performance of a linear iterative scheme within each box. In our SMPBE hybrid solver, we retain the PCG-ILU as the finite element solver within the central box, and develop an "optimal" scheme, the PCG using multigrid V-cycle preconditioning (PCG-MG), to solve each finite difference linear system within each neighboring box. Because of our special interface-matched tetrahedral mesh of the central box, the data exchange between the finite element and finite difference methods can be carried out easily and efficiently.

We programmed this new SMPBE hybrid scheme in `C`, `Fortran`, and `Python` as a modification of the finite element program package reported in [26]. The new program parts include a `Fortran` program of PCG-MG and a special mesh generation program for the central box, which we developed based on our revised version of the molecular surface and volumetric mesh generation program package `GAMer` [30]. Although PCG-MG is a well known scheme, we did not find any software that is suitable for our case. Thus, we programmed it ourselves. Our PCG-MG program was done based on the `BLAS` library (http://www.netlib.org/blas/). In this implementation, all the required memory arrays are preallocated. It does not require any memory array to store mesh data or coefficient matrices of finite difference linear systems. As a separate software, it can also be easily adopted to solve a general Poisson-like boundary value problem on a rectangular box.

We validated this new hybrid program package using a new SMPBE test model for arbitrarily multiple charges artificially constructed based on a Poisson model from [31], whose analytical solution is given. Numerical results from these tests also confirmed that both PCG-MG and our special overlapped domain decomposition scheme had convergence rates independent of the mesh size $h$, and were very efficient in terms of CPU time and memory usage. To demonstrate that SMPBE is a better model than PBE in the prediction of ionic concentrations, we constructed a more interesting dipole test model than a commonly-used Born ion ball model. In this dipole model, the solute region $D_p$ consists of two overlapped balls with the same radius but two opposite central charges. Our numerical results on this dipole model showed that SMPBE can much better capture physical features of ionic solvent than PBE (see Figs. 2 and 3). Furthermore, we made numerical experiments on six proteins with different net charges in a range from $-35e_c$ to $+6e_c$ to compare the performance of the new hybrid solver with that of the finite element solver. From the numerical results of Table 2 it can be seen that the total CPU runtime of the SMPBE finite element solver was reduced sharply up to 76% by our new SMPBE hybrid solver. For example, it took

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