

Advancements in Solving the Generalized Poisson and Poisson-Boltzmann Equations for Continuum Solvation Models

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Abstract

Understanding molecular interactions in different solvents is a complex task in computational chemistry. However, the development of continuum solvation models has helped to reduce the computational expenses of explicit models. This has led to various applications such as drug design, materials science, and understanding biological mechanisms. This study focuses on the evolution of continuum solvation models and the role played by the Generalized Poisson Equation (GPe) and Poisson-Boltzmann Equation (PBe) in bridging the gap between theory and computational techniques. The study examines four seed papers to provide an understanding of how solutes interact with solvents and the mathematical interpretation that comes with them. In addition, the study explores various methodological advances such as the Self-consistent and Pre-conditioned Conjugate Gradient (PCG) methods, the Polarizable Multipole Poisson-Boltzmann (PMPB) model, which integrates the Atomic Multipole Optimized Energies for Biomolecular Applications (AMOEBA) force field to improve the accuracy of the solution, and the domain decomposition approach which accelerates the solution electrostatic models. These methods treat the dielectric function as a continuous function and also consider the polarizability effects in the system. Moreover, the study discusses the Immersed Interface Method (IIM), a technique that solves the GPe and PBe while treating the dielectric function as a function with discontinuities. The IIM is a powerful tool that has been used to solve complex problems in various fields.

1. Introduction

The choreography of molecules in various environments, including vacuums and solvents, is an ongoing challenge and opportunity in computational chemistry. Recent advances have been made in understanding and modeling molecular electrostatics in different phases and environments.

As a result of these advancements, solvation models have evolved from early theoretical constructs to advanced computational algorithms (1). By using implicit solvation models (1; 2), we have gained a deeper understanding of molecular behavior in varied solvent conditions. Conceptualizing the solvent as a continuous dielectric medium (3), these models have simplified computational processes and produced a more accurate representation of molecular interactions.

Models within this field, their development trajectory, and their practical applications cover a wide range of challenges. They cover both theoretical foundations and algorithms for solving elliptic equations with either discontinuous coefficients or even partially varying dielectric functions (4), explaining electrostatic moments in solutes (5), and addressing the complexities of solving elliptic equations with such assumptions. Research has focused on improving accuracy in force field electrostatic models (5; 6), integrating polarization effects, and developing algorithms that can handle detailed and complex simulations.

In addition, these models prove useful in fields such as drug design, material science, and the understanding of biological mechanisms, beyond theoretical speculation (7). It is evident from the reviewed papers that solvation effects play an important role in *ab initio* simulations highlighting the increasing importance of computational models for accurately predicting and understanding molecular behaviors (8; 6; 5).

The discussion revolves around Density Functional Theory (DFT), which Transforms quantum mechanical calculations. By directly correlating a system's ground-state properties with its electron density, DFT avoids the complexities associated with many-body wavefunctions (9). Using this paradigm shift, computational demands have been reduced and a wide range of molecular properties can be predicted. Due to its ability to capture seemingly complex system interactions, DFT has proven essential in chemistry, material science, and physics.

A significant advancement in computational chemistry is continuum solvation models. Instead of using atomistically detailed solvent molecules, these models include solutes within a continuous dielectric medium, as shown in figure 1.1a. Using macroscopic properties of solvents, such as the dielectric constant, the models effectively model solute-solvent interactions electrostatically. Tomasi and co-workers' Polarizable Continuum Model (PCM) enables the computation of solvation energies as well as the prediction of solvent influences on molecules' geometries and reactivity (10) as shown in figure 1.1b. The Conductor-like Screening Model (COSMO) operates similarly to PCM but uses a different approach to handle the solvent's dielectric screening. Due to COSMO's treatment of solvents as infinite conductors, it is particularly effective when simulating reactions in highly polar solvents. It can also be applied to a variety of solvents with the appropriate adjustment of the dielectric constant. The COSMO model is an indispensable tool for computational studies of solvation, despite its simplicity and effectiveness in capturing solvent effects (11). When choosing a model, factors such as the solute and solvent nature, available

computational resources, and desired accuracy level are considered.

New solvation model frameworks beyond PCM and COSMO have been developed to enhance accuracy and applicability across diverse chemical systems. Models such as Surface and Simulation of Volume Polarization for Electrostatics (SS(V)PE) offer a more detailed picture of solvation phenomena by considering surface and volume polarization effects in electrostatics (12). These advances demonstrate the dynamic nature of computational solvation modeling and the constant development of more precise methods to simulate molecules within solvents.

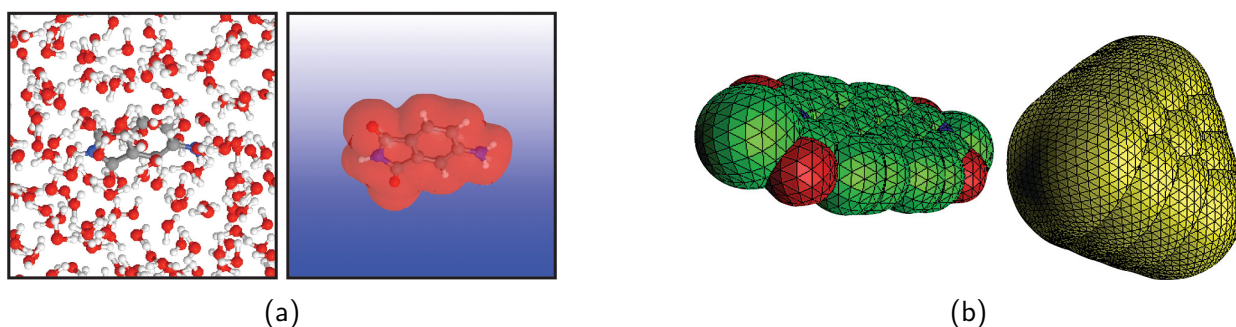


Figure 1.1: (a) Discrete versus Continuum solvation models (b) PCM representation of a molecular system close to a metal nanoparticle of tetrahedral shape (13).

The generalized Poisson equation (GPe) is useful for understanding solvent effects on a molecular scale (6). GPe models solvent impacts on electrostatic potential more accurately by incorporating a spatially varying dielectric constant into the standard Poisson equation. Various solvation models are based on this equation, which explains how electrostatics contribute to solvation energy. The GPe is given by:

$$\nabla \cdot (\epsilon(\mathbf{r}) \nabla \Phi(\mathbf{r})) = -4\pi \rho(\mathbf{r}) \quad (1.0.1)$$

where $\phi(\mathbf{r})$ is the electrostatic potential, $\epsilon(\mathbf{r})$ is the position-dependent dielectric function, and $\rho(\mathbf{r})$ represents the charge density distribution within the system. Solvents, with their characteristic dielectric properties, influence the electrostatic potential generated by and acting on solute molecules through the GPe.

The Poisson-Boltzmann Equation (PBe) further extends the Generalized Poisson Equation (GPe) to account for ionic effects in solvated systems, making it an essential tool for modeling electrostatic interactions in electrolyte solutions (14). The PBe is expressed as:

$$\nabla \cdot (\epsilon(\mathbf{r}) \nabla \Phi(\mathbf{r})) = -4\pi(\rho(\mathbf{r}) + \rho^{\text{ions}}[\Phi](\mathbf{r})) \quad (1.0.2)$$

where $\Phi(\mathbf{r})$ denotes the electrostatic potential, $\epsilon(\mathbf{r})$ is the spatially varying dielectric constant, $\rho(\mathbf{r})$ represents the charge density of the solute, and $\rho^{\text{ions}}[\Phi](\mathbf{r})$ is the charge density due to mobile ions in the solvent. The term $\rho^{\text{ions}}[\Phi](\mathbf{r})$ describes how the electrostatic potential is affected by ion distribution to the solute. The versatility of PBe allows for various modeling approaches, including its linearized versions, which utilize the Debye-Hückel theory to simplify the treatment of electrostatic potential around charged entities in solution (5). The linearized Poisson-Boltzmann equation (LPBE) is represented as:

$$\nabla \cdot [\varepsilon(\mathbf{r}) \nabla \Phi(\mathbf{r})] - \bar{\kappa}^2(\mathbf{r}) = -4\pi\rho(\mathbf{r}) \quad (1.0.3)$$

The linearized form assumes small potential approximations, leading to a modified Debye-Hückel screening factor $\bar{\kappa}^2(\mathbf{r})$

Solving such equations effectively and efficiently cannot be underestimated. Solvated systems require efficient and versatile numerical methods capable of capturing complex solute-solvent interactions precisely. Self-consistent fixed-point iteration (FPI) and preconditioned conjugate gradients (PCG) have been instrumental in addressing the iterative nature of these problems (6). On the other hand, by combining microscale phenomena with macroscale observations, the First Multiple Approach exhibits creativity in the application of multi-scale methods (5). Further, innovative approaches such as Fast Domain Decomposition (DD) provide tailored solutions for these equations' spatial variability and nonlinearity (8). On the other hand, methods such as the Immersed Interface Method (IIM) give a quite divergent approach from the above by considering the dielectric function as a noncontinuous function which creates jumps at the interface. This variation provides a completely different approach towards the solution of these equations (15; 8).

Together, these methods and many more highlight the ongoing advancements in computational strategies, emphasizing the crucial importance of developing better algorithms to unravel molecular behavior in solvated environments, thus enabling more accurate simulations and predictions in chemical research.

An overview of the current landscape in computational solvation dynamics is presented in this review, which synthesizes contributions from four seminal papers and beyond. Synthesized seed papers include;

1. Polarizable atomic multipole solutes in a Poisson-Boltzmann continuum
2. Fast domain decomposition algorithm for continuum solvation models: Energy and first derivatives
3. A generalized Poisson and Poisson-Boltzmann solver for electrostatic environments
4. A fast iterative algorithm for elliptic interface problems

The remainder of this synthesis paper is organized as follows; chapter 2 discusses the advancements in the use of the FPI and PCG as discussed by G. Fiscaro et al; Chapter 3 presents the Polarizable Multiple Poisson Boltzmann model (PMPB) as discussed by Michael J. Schnieders et al; Chapter 4 discusses ideas of Domain decomposition discussed by Filippo Lipparini et al; and chapter 5 provided a discussion on the Immersed Interface method (IIM) as an ongoing trend of this research inspired from the initial works of Zhilin Li and Donna Calhoun about solutions to elliptic problems with discontinuous interfaces.

2. Self-consistent and Preconditioned Conjugate Gradient

At present, there is ongoing research in finding approaches capable of tackling GPEs and PBEs well, particularly in instances where the dielectric properties are subject to change. Certain researchers have employed low-order finite difference discretizations to simplify the Poisson-Boltzmann equation, but this approach overlooks physical influences and incorrectly estimates ionic densities close to highly charged interfaces. Using ideas of Andreussi’s fixed point iteration solver discussed in (16), G. Fiscaro et al utilize a Standard Poisson equation (SPE) solver to effectively handle GPE and linear PBE challenges in just ten iterations. The developed method enhances the dependability of quantum simulations in solvated environments by fusing a self-consistent approach with considerations for ionic steric impacts. Various test configurations subjected to empirical DFT assessments of electrostatic solvation energies demonstrate the efficiency of this approach.

2.1 Generalized Poisson Equation (GPe)

The treatment of the GPe has been revolutionized by the self-consistent (SC) iterative framework introduced by G. Fiscaro et al. This method incorporates spatial variations in the dielectric function $\epsilon(\mathbf{r})$ directly into the calculation process. The core of this method lies in the reformulation of the conventional Poisson equation into an equation that accommodates the polarization charge density, $\rho^{pol}(\mathbf{r})$, alongside the iterative term, $\rho^{iter}(\mathbf{r})$. The equation, presented below, aids in refining the potential $\Phi(\mathbf{r})$, through successive iterations derived from the spatially varying dielectric function.

$$\nabla^2 \Phi(\mathbf{r}) = -4\pi \left[\frac{\rho(\mathbf{r})}{\epsilon(\mathbf{r})} + \rho^{iter}(\mathbf{r}) \right] = -4\pi [\rho(\mathbf{r}) + \rho^{pol}(\mathbf{r})], \quad (2.1.1)$$

The iterative term, $\rho^{iter}(\mathbf{r})$, is defined as:

$$\rho^{iter}(\mathbf{r}) = \frac{1}{4\pi} \nabla \ln \epsilon(\mathbf{r}) \cdot \nabla \Phi(\mathbf{r}). \quad (2.1.2)$$

The method’s stability is enhanced by a linear mixing technique parameterized by η as the residual r_k changes across iterations. This strategy has the inherent advantage of simulating polarization effects within the dielectric medium, bridging the gap between internal and external regions. Its robust framework provides an excellent basis for extensive quantum simulations in a variety of solvated systems using solute densities surrounded by solvent molecules.

Algorithm 1 presents the Preconditioned Conjugate Gradient method’s pseudocode.

Algorithm 1 Self-consistent (SC) iterative procedure

```

1: set  $\rho_0^{iter}$ 
2: for  $k = 0, 1, \dots$  do
3:    $\rho_k^{tot} = \frac{\rho}{\epsilon} + \rho_k^{iter}$ 
4:   solve  $\nabla^2 \Phi_k = -4\pi \rho_k^{tot}$ 
5:    $\rho_{k+1}^{iter} = \frac{1}{4\pi} \nabla \ln \epsilon \cdot \nabla \Phi_k$ 
6:    $\rho_{k+1}^{iter} = \eta \rho_{k+1}^{iter} + (1 - \eta) \rho_k^{iter}$ 
7:    $r_{k+1} = \rho_{k+1}^{iter} - \rho_k^{iter}$ 
8: end for

```

2.1.1 Preconditioned conjugate gradient (PCG). The Preconditioned Conjugate Gradient (PCG) method is a way to improve the refinement of electrostatic potential calculations. According to Fiscaro et al., this approach can solve the generalized Poisson equation (GPe) more efficiently and with greater control over convergence for large systems that typically require extensive computational demands.

PCG uses a preconditioned steepest descent (PSD) approach to refine electrostatic potential calculation by applying preconditioners to the residual vector. The iterative process involved in PCG is defined as follows:

$$v_k = P^{-1}r_k, \quad p_k = v_k + \beta_k p_{k-1}, \quad (2.1.3)$$

where β_k and α_k are dynamically adjusted to steer the minimization path efficiently.

By optimizing the condition number κ , PCG reduces the number of iterations for convergence by relying on a preconditioner based on the standard Poisson solver. The inverse application of the preconditioner to a residual vector helps compute the generalized Poisson operator quickly and accurately from a given charge density.

Furthermore, the PCG method reduces computational complexity by transforming the generalized Poisson operator into simpler vector operations. Computational physics and chemistry may benefit from this approach due to its robustness and speed, as well as ease of parallelization.

Algorithm 2 presents the Preconditioned Conjugate Gradient method's pseudocode.

Algorithm 2 Preconditioned Conjugate Gradient (PCG)

```

1:  $r_0 = -4\pi\rho - A\varphi_0$ ,  $p_{-1} = 0$ 
2: for  $k = 0, 1, \dots$  do
3:    $v_k = P^{-1}r_k$ 
4:    $p_k = v_k + \beta_k p_{k-1}$ 
5:    $\alpha_k = \frac{(v_k, r_k)}{(p_k, Ap_k)}$ 
6:    $\varphi_{k+1} = \varphi_k + \alpha_k p_k$ 
7:    $r_{k+1} = r_k - \alpha_k Ap_k$ 
8: end for

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$$\triangleright \beta_k = \frac{(v_k, r_k)}{(v_{k-1}, r_{k-1})}, k \neq 0$$

2.2 Discussion of Results

The self-consistent iterative procedure and the preconditioned conjugate gradient (PCG) scheme were implemented and tested using the interpolating scaling function (ISF) poisson solver. This solver is known for its $O(N \log(N))$ efficiency and allows for the accurate computation of electrostatic potentials across various boundary conditions. An orthorhombic grid with uniform mesh spacing and dimensions (nx, ny, nz) was used for this purpose.

To benchmark these methods, analytical functions representing the electrostatic potential $\Phi(\mathbf{r})$ and charge density $\rho(\mathbf{r})$ were used. A spatially varying dielectric constant $\epsilon(\mathbf{r})$ was also introduced, characterised by an error function $1 + (\epsilon_0 - 1)h(d_0, \Delta; \mathbf{r})$, where

$$h(d_0, \Delta; \mathbf{r}) = \frac{1}{2} \left[1 + \operatorname{erf} \left(\frac{\mathbf{r} - d_0}{\Delta} \right) \right],$$

to mimic typical dielectric environments. The grid setup for testing encompassed a cubic box with dimensions of 10 atomic units (a.u.) and 300 points per axis. A Gaussian variance of $\sigma = 0.5$ was used for $\Phi(\mathbf{r})$, and parameters $d_0 = 1.7$, $\Delta = 0.3$, and $\epsilon_0 = 78.36$ were used for $\epsilon(\mathbf{r})$.

The PCG solver demonstrated superior convergence efficiency compared to the self-consistent method in the assessment. It achieved an accuracy of approximately 10^{-10} within about ten iterations, irrespective of boundary conditions. This performance advantage highlights the effectiveness of the PCG algorithm, especially in atomistic simulations requiring repeated solutions to the GPe. Implementation details, such as the use of high-order finite difference filters for the nabla operator in the self-consistent method and the pre-calculation of vector $q(\mathbf{r})$ for the PCG scheme, contributed to the observed computational efficiency and accuracy.

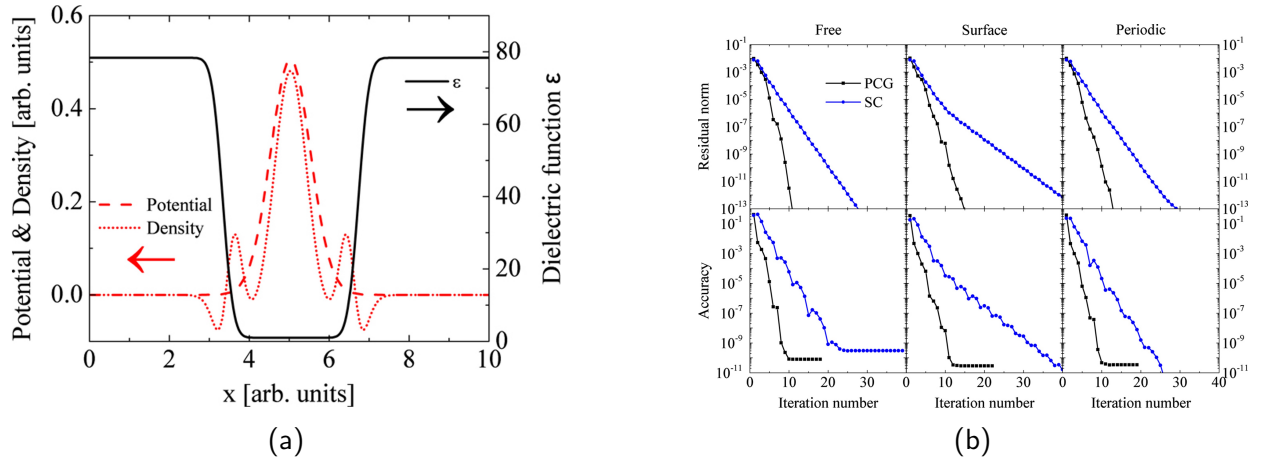


Figure 2.1: (a) shows the analytical 3D functions used in the benchmark for both SC and PCG, (b) shows the residual norm (top) and accuracy (bottom) as functions of the iteration number with free, surface and periodic boundary conditions

2.3 Self-consistent iterative procedure and and Preconditioned Conjugate gradient for the Poisson Boltzmann equation

The self-consistent iterative procedure and the Preconditioned Conjugate gradient (PCG) method were applied to handle the challenges posed by ionic solutions in continuum solvation models. Due to the presence of mobile ions near the solute-solvent interface, the electrostatic potential and charge distribution are greatly affected, resulting in the well-known double-layer effect.

The self-consistent iterative procedure begins with an initial guess for the ionic charge density and iteratively updates it until the potential and the induced ionic charge reach equilibrium. This method is crucial for solving both the Poisson-Boltzmann (PBe) and the modified Poisson-Boltzmann equations, which include considerations for finite ion size effects, thus preventing unrealistic ionic concentrations near highly charged surfaces.

An improved version of this approach optimizes performance by solving the electrostatic problem only for the previous residual vector, thereby ensuring that each iteration builds upon the accuracy of the last. This method proves especially efficient when combined with the PCG solver, designed for the generalized Poisson equation but adaptable to the linear regime of the PBe.

3. Polarizable atomic multipole solutes in a Poisson-Boltzmann continuum

While the FPI and PCG are more general approaches and can be used in a wide range of problems beyond solvation modeling, they might not necessarily offer the specificity necessary for accurately capturing complex solvation dynamics due to their general applicability, especially in systems with polarization and detailed multipole interactions. The polarizable multipole Poisson-Boltzmann (PMPB) model integrates the atomic multipole optimized energies for biomolecular applications (AMOEBA) force field, which accounts for detailed electrostatics through polarizable multipoles. Compared to methods that only take into account point charges or fixed multipoles, this approach allows for a more accurate representation of molecular electrostatics in vacuum and solvent conditions. To provide a comprehensive and accurate illustration of molecular electrostatics, the model also utilizes the Linearized Poisson-Boltzmann Equation (LPBE) presented in equation 1.0.3. Since PMPB builds upon AMOEBA and LPBE, it is inquiry important to understand how the electrostatics are formulated.

3.1 AMOEBA vacuum electrostatics

The Electrostatic energy in a vacuum for an AMOEBA solute is denoted U_{elec}^v . Define vector \mathbf{M} representing a vector of an atomic multipole site. For atomic site i , \mathbf{M}_i encompasses $13N_s$ components of charge (q_i), dipole ($d_{i,x}, d_{i,y}, d_{i,z}$) and quadrupole ($\Theta_{i,xx}, \Theta_{i,xy}, \Theta_{i,xz}, \dots, \Theta_{i,zz}$).

The interaction energy $U(s_{ij})$ between sites i and j is given by the equation:

$$U(s_{ij}) = \mathbf{M}_i^T \cdot \mathbf{T}_{ij} \cdot \mathbf{M}_j$$

where \mathbf{M}_i and \mathbf{M}_j are the multipole vectors of sites i and j , respectively, and \mathbf{T}_{ij} is the tensor describing the interaction between two multipole sites separated by s_{ij} , reflecting their spatial relationship and properties.

Depending on the local electric field strength E_i , the polarizability of each site induces a dipole moment μ_i . As a result of this, both permanent multipole sites and other induced dipoles are taken into account, and mutual influences are managed in a self-consistent manner. That is

$$\mu_i = \alpha_i E_i = \alpha_i \left(\sum_{j \neq i} \mathbf{T}_{d,ij} M_j + \sum_{k \neq i} \mathbf{T}_{ik} \mu_k \right)$$

where α_i is the atomic polarizability. The resulting linear system of equations can be solved using either direct approaches or even iterative schemes such as Successive Over relaxation (SOR).

Therefore, the total electrostatic energy within a vacuum includes both the interactions among permanent multipoles on a pair-wise level and the influence of widespread polarization. Accordingly, we can express this as follows:

$$U_{\text{elec}}^v = \frac{1}{2}[\mathbf{M}^T \mathbf{T} - (\boldsymbol{\mu}^v)^t \mathbf{T}'_p \mathbf{M}],$$

in which the prefactor $\frac{1}{2}$ mitigates the duplication of permanent multipole interactions in the initial term while also reflecting the energetic expenditure necessary for polarizing the system. The vector \mathbf{M} is a columnar aggregation of $13N_s$ multipolar constituents.

3.2 LPBE energies and gradients for fixed partial charge force fields

Researchers have systematically derived energies for fixed partial charge force fields within the LPBE framework. Im et al defines the solvation free energy, ΔG_{elec} for a distribution of permanent charges as follows:

$$\Delta G_{\text{elec}} = \frac{1}{2}(\boldsymbol{\Phi}_s^t - \boldsymbol{\Phi}_v^t) \mathbf{q},$$

where \mathbf{q} is a column vector of site charges, $\boldsymbol{\Phi}_s^t$ and $\boldsymbol{\Phi}_v^t$ represent the transposed vectors of electrostatic potentials in the solvated system and vacuum, respectively. There are a certain number of vectors in this system, and the vectors are made up of points on a cubic grid that is uniformly spaced across the dimensions, despite having variable points along each axis. Using a finite-difference scheme of the LPBE, the potential can be determined as follows:

$$\mathbf{A} \boldsymbol{\Phi} = -4\pi \mathbf{q},$$

where $\mathbf{A} = \nabla \cdot \epsilon \nabla - \bar{\kappa}^2$ is a symmetric matrix. Solving this equation for the potential indicates that \mathbf{A}^{-1} , serving as Green's function, facilitates the computation of solvation energies through the difference between solvated (\mathbf{A}_s^{-1}) and vacuum (\mathbf{A}_v^{-1}) states, yielding:

$$\Delta G_{\text{elec}} = \frac{1}{2}[-4\pi \mathbf{q}^T (\mathbf{A}_s^{-1} - \mathbf{A}_v^{-1}) \mathbf{q}].$$

3.3 Methodological Summary for PMPB Model

With the aid of the AMOEBA and LPBE methodologies as well as prior advances in the representation of solutes with fixed partial charges, a formulation is presented to include electrostatic solvation energies in the PMPB model. Using the parallel multigrid (PMG) package and integrated with adaptive poisson-Boltzmann solver (APBS), the discretized LPBE is solved by discretizing atomic multipoles on a grid and assigning permittivity and a modified Debye-Hückel screening factor after imposing the necessary boundary conditions

3.3.1 Discretization and LPBE Solution. Atomic multipoles are discretized to the charge grid using B-splines, with fifth-order B-splines utilized for quadrupoles to ensure necessary continuity.

$$V(R) = \sum_{i=1}^n \frac{c_i}{|R - r_i|}, \quad (3.3.1)$$

where $V(R)$ is the potential at location R due to charges c_i at positions r_i . The electrostatic solvation energy and gradients are determined from the LPBE solutions, necessitating multiple LPBE solutions for accurate calculation.

3.3.2 Permittivity and Debye-Hückel screening factor. The Permittivity $\epsilon(\mathbf{r})$ and the modified Debye-Hückel screening factor $\bar{\kappa}^2(\mathbf{r})$ are defined through a characteristic function $H(\mathbf{r}_i, \mathbf{s})$. Here, \mathbf{r}_i signifies a grid point's coordinates, and \mathbf{s} the positions of all multipole sites. This characteristic function is zero within the solute cavity, indicating no screening, while it assumes a value of one in the solvent, indicating full screening. During the solvated state, permittivity transitions smoothly from unity inside the solute to ϵ_s in the solvent, modulated by the characteristic function as $\epsilon(\mathbf{r}_i) = 1 + (\epsilon_s - 1)H(\mathbf{r}_i, \mathbf{s})$.

The modified Debye-Hückel screening factor for the solvated scenario is given by $\bar{\kappa}^2(\mathbf{r}_i) = \bar{\kappa}_b^2 H(\mathbf{r}_i, \mathbf{s})$, where $\bar{\kappa}_b^2 = \epsilon_s \kappa_b^2$

To ensure stable energy gradients across the solute-solvent interface, the characteristic function is determined as the product of radially symmetric functions for each atom.

3.3.3 Boundary conditions. To ensure continuity of potential and dielectric displacement across the solute-solvent interface, enforcing boundary conditions is necessary.

$$\begin{aligned} V_{\text{in}} &= V_{\text{out}}, \\ \epsilon_{\text{in}} \frac{\partial V_{\text{in}}}{\partial r} &= \epsilon_{\text{out}} \frac{\partial V_{\text{out}}}{\partial r}. \end{aligned}$$

These conditions ensure the solution is bounded at the origin and approaches a constant at infinity.

Therefore, the Permanent atomic multiple solvation energy and the PMPB electrostatic solvation free energy can be calculated by explicitly designing them with the help of the initial LPBE model description.

4. Advances in Computational Solvation Models through Domain Decomposition

Models such as PCM and COSMO use the apparent surface charge (ASC) method to simplify solute-solvent interactions into a surface-centric problem. The mathematical formulation of these models lead to formulation of integral equations for the potential and field distribution around the solute molecules. Boundary Element method (BEM) comes in play as a numerical technique to solve these integral equations. BEM discretizes the surface of the cavity containing the solute into a set of elements. The discretization process transforms the problem into a system linear equations of the form

$$\mathbf{A}\Phi = \mathbf{B}\sigma,$$

where where \mathbf{A} and \mathbf{B} are dense matrices derived from the BEM formulation, Φ is the potential and σ is the surface charge density.

Since \mathbf{A} and \mathbf{B} are dense, solving such a system of linear equations require a high computational cost, especially as N (the number of elements) increases. Also, storing large dense matrices requires significant memory, making large-scale simulations challenging. Therefore, to simulate larger molecular systems more efficiently, the concept of domain decomposition (DD), borrowed from solution strategies for partial differential equations, offers a promising solution. By breaking the molecular cavity into simpler subdomains, DD allows for localized problem-solving, significantly improving computational performance. This method offers a unique set of advantages for solving large-scale computational problems, complementing the functionality of the Fixed Point Iteration (FPI), Preconditioned Conjugate Gradient (PCG), and Polarizable Multipole Poisson-Boltzmann methods.

4.1 Methodological Innovation

4.1.1 Principles of Domain Decomposition. Domain decomposition addresses the challenge of modeling electrostatic interactions by breaking down the molecular cavity into overlapping spheres, each based on the van der Waals radius of atoms. This subdivision allows for either analytical or numerical resolution of the COSMO equations within these localized regions, resulting in a sparse linear system well-suited for iterative solutions. The advantages of this approach include:

- Enhanced computational efficiency through linear scaling with system size.
- Elimination of the need for fast summation techniques traditionally used in these models.
- Simplified handling of integral equations by focusing on localized surface charge density solutions within each subdomain.

4.1.2 Mathematical Formulation. Consider a molecular system comprised of M atoms, where each atom j possesses a charge q_j located at R_j , the molecular cavity is constructed as a union of spheres. The domain decomposition method iteratively solves for the local ASC, $\sigma_j(s)$, on the surface of each sphere, taking into account the interactions with neighboring spheres. This is formulated as:

$$\sigma_j(s) = \sum_{k \in \mathcal{N}_j} L_{jk} \sigma_k(s), \quad (4.1.1)$$

where \mathcal{N}_j represents the neighboring spheres of sphere j , and L_{jk} denotes the interaction operator between spheres j and k .

4.1.3 Addressing Internal and External Boundary Conditions. Whereas there is an already existing strategy to handle boundary conditions of the external cavity in COSMO, handling the problem at subdomain level would mean that these approaches fail with internal cavities. The domain decomposition method overcomes this by updating boundary conditions for each sphere based on reactions from direct and neighboring interactions.

$$\sigma_j^{(it)}(s) = \begin{cases} -\Phi(s), & s \in \Gamma_{ej} \\ \frac{1}{|\mathcal{N}_j(s)|} \sum_{k \in \mathcal{N}_j(s)} W_k^{(it-1)}(s), & s \in \Gamma_{ij} \end{cases} \quad (4.1.2)$$

Γ_{ej} and Γ_{ij} represent the external and internal surface portions of sphere Ω_j , respectively. $\mathcal{N}_j(s)$ denotes the set of neighboring spheres intersecting at point s , and $W_k^{(it-1)}(s)$ is the reaction potential from sphere k at the previous iteration.

4.1.4 Iterative Boundary Conditions and Linear System Formation. Domain decomposition iteratively refines internal and external boundaries, leading to a comprehensive linear system representing coupled integral equations across the molecular cavity. It efficiently solves the ASC problem, making it suitable for larger molecular simulations.

4.2 Computational Implementation and Benefits

Using domain decomposition, a traditionally complex matrix problem can be transformed into a manageable, sparse system. This not only significantly reduces memory requirements but also computational complexity. Numerical experimentation has validated the linear scaling properties of this method, demonstrating its capability to efficiently tackle complex systems. The introduction of domain decomposition into continuum solvation models is a substantial advancement, offering a scalable and efficient framework for simulating electrostatic interactions.

5. Challenges and future direction

5.1 Challenges of the models

As FPI, PCG, and PMPB are used to solve the GPE and PBE, they suffer from several limitations, even with the adoption of the DD approach.

- The study on FPI and PCG is limited by its reliance on specific computational packages and basis sets like wavelets. Further validation is necessary for accurate results. Also, the solvers have mainly been tested for aqueous environments, and their adaptability to non-aqueous solvents or mixed solvent systems requires additional exploration. Finally, the inclusion of ionic effects through the Poisson-Boltzmann equation may require additional development for high ionic strength or complex ions.
- The PMPB model's effectiveness depends on precise AMOEBA force field parameterization. Comprehensive parameter derivation and extensive validation against experimental data would strengthen the model's credibility. However, accurately parameterizing a wide range of molecules can be a challenge, requiring further research and development. High computational costs can be incurred due to high-level multipole calculations and solving the Poisson-Boltzmann equation. Therefore, it is important to optimize computational strategies or develop approximate methods that reduce computation time without affecting accuracy.
- Lipparini et al assume a simplified model for solute representation, which may not capture certain solute-solvent interactions. The domain decomposition algorithm improves scalability but relies on the proper handling of interactions. However, the use of spherical subdomains may affect the precision of solvation energy calculations.

There is an alternative way to handle systems whose equations [1.0.1](#) and [1.0.2](#) need to be solved. This method takes the dielectric function as purely discontinuous, rather than as a partially varying function as the FPI, PCG, and PMPB methods did.

5.2 The Immersed Interface Method (IIM)

Numerical solutions to partial differential equations (PDEs) can face difficulties when the domain involves interfaces across which coefficients or boundary conditions change abruptly. Traditional methods can lead to significant errors or require complex grid adjustments. The Immersed Interface Method (IIM) offers a promising approach to handle such discontinuities efficiently, providing a robust framework for accurate simulations. This method can be used to handle both equations [1.0.1](#) and [1.0.2](#). The equations' complexity is notably increased in scenarios where there are discontinuities in $\epsilon(\mathbf{r})$ across an interface within the domain. Traditional discretization techniques often fall short in such settings, causing inaccuracies and numerical instabilities.

5.3 Immersed Interface Method (IIM) Formulation

IIM is a numerical approach that provides a refined discretization scheme to solve problems that involve discontinuous domains. The method incorporates jump conditions and interface discontinuities systematically, ensuring second-order accuracy and numerical stability of the solution. This is achieved by embedding the interface conditions (correction term) directly into the finite difference approximation scheme. The method modifies the standard coefficients of the finite difference scheme to account for the effects of the interface.

5.3.1 Correction Term and Jump Conditions. The success of the IIM relies on accurately computing the correction term by enforcing jump conditions. This involves carefully calculating components to bridge any potential and flux discontinuities, ensuring the method's reliability. The formulation follows specific jump conditions to achieve this.

- $[\Phi] = w(s)$, representing a discontinuity in the potential field,
- $[\Phi_n] = v(s)$, signifies a discontinuity in the normal derivative of the potential,

where $w(s)$ and $v(s)$ are predefined functions that describe the jumps along the interface of the preconditioned equation, which is parameterized by s . The mathematical description of such jump conditions implies that the initial equation has been redefined to satisfy an appropriate preconditioner.

The correction term can be formulated using the Taylor series and a linear combination of jump conditions of the preconditioned equation. For example, for a 2D case,

$$C(x_i, y_j) = d_{ij}^1[\Phi] + d_{ij}^2[\Phi_n] + d_{ij}^3[\Phi_s] + d_{ij}^4[\Phi_{ss}] + d_{ij}^5[(\Phi_n)_s] + d_{ij}^6[\nabla^2\Phi]$$

where $C(x, y)$ is the magnitude of the correction term at irregular point (x, y) and d^i is the distance between the particular irregular point and the closest parametrized interface point.

5.4 Implementation

Implementing the IIM for the GPe, or even the PBe, involves an algorithmic procedure that incorporates the interface's geometry, the computation of correction terms for each irregular point, a point that straddles the interface, and the resolution of a modified linear system that reflects the interface's influence. However, to minimize the computational details that come with the increased number of irregular points that have to be corrected when the grid is finer, control points are employed.

The new corrected finite difference scheme around the interface can then be written as;

$$L_h \Phi_{ijk} = \frac{f_{ijk}}{\epsilon_{ijk}} + C_{ijk}, \quad 1 \leq i \leq m-1, \quad 1 \leq j \leq n-1, \quad 1 \leq k \leq l-1,$$

where $L\Phi_{ijk}$ denotes the seven-point stencil of the three-dimensional case of either the PBe or GPe and f_{ijk} represents the right-hand.

Descritization is done on a uniform rectangular grid $[a, b] \times [c, d] \times [e, r]$ where

$$x_i = a + ih, \quad y_j = a + ih, \quad z_k = a + ih, \quad i \in [0, m], \quad j \in [0, n], \quad k \in [0, l] \quad (5.4.1)$$

5.4.1 Numerical Experiments and Accuracy. Zhilin Li's study focused on an approach for solving elliptic interface problems with large jumps in coefficients across irregular interface. The key divergent case that ensures robustness is that there is no formulation of the entire matrix but instead, computing matrix-vector multiplication is employed.

Numerical experiments were conducted to evaluate the algorithm's performance across various interface configurations. These experiments aimed to ascertain the accuracy of computed solutions, the impact of mesh size and discontinuous coefficient ratios on the number of iterations, and the method's capability to handle complex interfaces and significant coefficient jumps.

5.4.2 Accuracy Across Different Interfaces. The method demonstrated remarkable accuracy, particularly in managing jumps in the solution. Grid refinement analysis for cases with significantly different ratios of discontinuous coefficients revealed that the algorithm consistently achieves second-order convergence, even in the presence of large coefficient jumps and complex interface geometries.

5.4.3 Interface Complexity and Solution Accuracy. Investigations into the algorithm's ability to accurately express interfaces through cubic splines or alternative approaches, such as level set formulations, were also discussed. The choice of interface representation method significantly impacts the error distribution and the monotonicity of error reduction across grid refinements.

References

- [1] Jacopo Tomasi, Benedetta Mennucci, and Roberto Cammi. Quantum mechanical continuum solvation models. *Chemical reviews*, 105(8):2999–3094, 2005.
- [2] Christopher J Cramer, Donald G Truhlar, et al. Implicit solvation models: equilibria, structure, spectra, and dynamics. *Chemical Reviews*, 99:2161–2200, 1999.
- [3] Mikhail V Basilevsky, Fedor V Grigoriev, Ekaterina A Nikitina, and Jerzy Leszczynski. Implicit electrostatic solvent model with continuous dielectric permittivity function. *The Journal of Physical Chemistry B*, 114(7):2457–2466, 2010.
- [4] Randall J LeVeque and Zhilin Li. The immersed interface method for elliptic equations with discontinuous coefficients and singular sources. *SIAM Journal on Numerical Analysis*, 31(4):1019–1044, 1994.
- [5] Michael J Schnieders, Nathan A Baker, Pengyu Ren, and Jay W Ponder. Polarizable atomic multipole solutes in a poisson-boltzmann continuum. *The Journal of chemical physics*, 126(12), 2007.
- [6] Giuseppe Fisicaro, Luigi Genovese, Oliviero Andreussi, Nicola Marzari, and Stefan Goedecker. A generalized poisson and poisson-boltzmann solver for electrostatic environments. *The Journal of chemical physics*, 144(1), 2016.
- [7] Jacopo Tomasi. Thirty years of continuum solvation chemistry: a review, and prospects for the near future. *Theoretical chemistry accounts*, 112(4):184–203, 2004.
- [8] Filippo Lipparini, Benjamin Stamm, Eric Cancès, Yvon Maday, and Benedetta Mennucci. Fast domain decomposition algorithm for continuum solvation models: Energy and first derivatives. *Journal of chemical theory and computation*, 9(8):3637–3648, 2013.
- [9] Maylis Orio, Dimitrios A Pantazis, and Frank Neese. Density functional theory. *Photosynthesis research*, 102:443–453, 2009.
- [10] Benedetta Mennucci. Polarizable continuum model. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 2(3):386–404, 2012.
- [11] Andreas Klamt. Conductor-like screening model for real solvents: a new approach to the quantitative calculation of solvation phenomena. *The Journal of Physical Chemistry*, 99(7):2224–2235, 1995.
- [12] Daniel M Chipman. Energy correction to simulation of volume polarization in reaction field theory. *The Journal of chemical physics*, 116(23):10129–10138, 2002.
- [13] Benedetta Mennucci. Continuum solvation models: What else can we learn from them? *The Journal of Physical Chemistry Letters*, 1(10):1666–1674, 2010.
- [14] Gene Lamm. The poisson–boltzmann equation. *Reviews in computational chemistry*, 19:147–365, 2003.

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- [15] Donna Calhoun. A cartesian grid method for solving the two-dimensional streamfunction-vorticity equations in irregular regions. *Journal of computational physics*, 176(2):231–275, 2002.
 - [16] Oliviero Andreussi, Ismaila Dabo, and Nicola Marzari. Revised self-consistent continuum solvation in electronic-structure calculations. *The Journal of chemical physics*, 136(6), 2012.
 - [17] Jacopo Tomasi. Selected features of the polarizable continuum model for the representation of solvation. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 1(5):855–867, 2011.
 - [18] Wonpil Im, Dmitrii Beglov, and Benoit Roux. Continuum solvation model: computation of electrostatic forces from numerical solutions to the poisson-boltzmann equation. *Computer physics communications*, 111(1-3):59–75, 1998.