

# Efficient and Accurate Simulation for Molecular Electrostatics.

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The Poisson-Boltzmann equation (PBE) is a critical tool for modeling electrostatic interactions in biophysics, colloidal science, and materials science. It describes the mean-field electrostatic potential created by fixed charges in a dielectric medium with mobile ions, playing a vital role in applications such as protein interactions, enzyme activity, and the behavior of colloidal particles. The PBE is nonlinear and challenging to solve, even in its linearized form (LPBE), which is a reasonable approximation for systems with low surface potentials. Advances in computational methods have improved the accuracy and efficiency of solving the PBE, but challenges persist, including computational cost, scalability to large systems, and agreement with experimental data. Here, we analyze some advancements in solving the LPBE, improving accuracy without increasing computational costs. By leveraging analytical techniques and optimizing computational approaches, this enhanced method has been validated through comparison with analytical solutions and applied to biological systems such as proteins and nucleic acids. These developments are implemented in the recently released LPBE solver NextGenPB.

*Index Terms*—Poisson-Boltzmann, FEM

## I. INTRODUCTION

The Poisson-Boltzmann equation (PBE) is a model commonly used to estimate the electrostatic energy of biomolecular systems immersed in electrolytic solutions. It is often applied to giant molecules, such as proteins or viruses, comprised of even millions of atoms, with a complex surface geometry. The nonlinearities in the PBE make it particularly challenging to solve, but its linearized form (LPBE) is a reasonable approximation for systems with low surface potentials. Due to the extreme simulation sizes, implementing efficient yet accurate solvers is daunting, even for the linearized model. Most existing state-of-the-art software packages for solving the PBE [1], [2] are based on structured Cartesian grids that reduce computational costs and memory footprint by removing the need for an explicit data structure for mesh representation. Achieving high accuracy in structured grid-based methods may lead to many degrees of freedom and significant computational costs. NextGenPB [3] is a recently developed parallel solver for the PBE that exploits properties of Cartesian grids with hierarchical local refinement [4] to maximize accuracy-to-cost efficiency applying tailored quadrature rules near interface discontinuities and optimized boundary conditions. The present contribution expands the discussion of the numerical methods used in NextGenPB to deal with non-grid-aligned permittivity discontinuities, validating their accuracy and efficiency.

## II. MODEL

The PBE models solute molecules in ionic solutions by explicitly considering the fixed charges in the solute and, implicitly, the mobile ions in the solvent. The computational domain  $D = \Omega_m \cup \Omega_s \cup \Gamma$  is comprised of the solute ( $\Omega_m$ ), solvent ( $\Omega_s$ ), and their interface ( $\Gamma$ ). The electric permittivity is assumed to be uniform within each volume region,  $\varepsilon_m =$

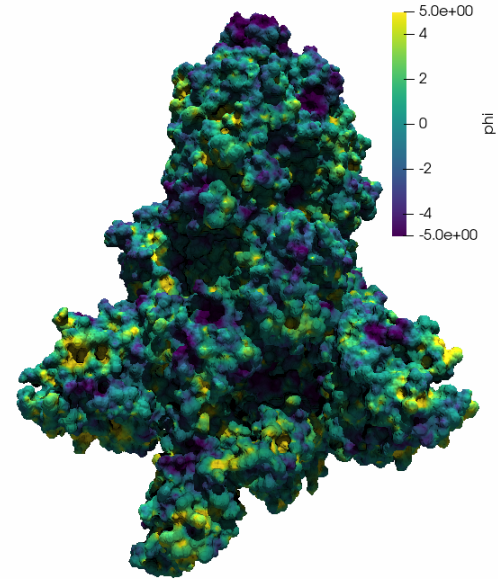


Fig. 1. Electrostatic potential on the molecular surface of the spike protein of the SARS-CoV-2 virus (Omicron variant of concern).

$\varepsilon_0 \varepsilon_{r,m}$ ,  $\forall \mathbf{r} \in \Omega_m$ , while  $\varepsilon_s = \varepsilon_0 \varepsilon_{r,s}$ ,  $\forall \mathbf{r} \in \Omega_s$  and therefore displays a discontinuity across the interface. Quantitatively,  $\varepsilon_{r,m}$  (solute) is usually smaller (around 2–4) than  $\varepsilon_{r,s}$  (solvent) ( $\sim 80$ ), to reflect the fact that water is much more easily polarized than most solutes. Fixed charges in the solute are represented as a set of point charges, while ions in the solvent are modeled as continuous charge densities combined with

Boltzmann weights

$$\begin{aligned}\rho^f(\mathbf{r}) &= \sum_{i=1}^N q_i \delta(\mathbf{r} - \mathbf{r}_i), \\ \rho^s(\mathbf{r}) &= \sum_{j=1}^J e z_j \rho_j^b \exp\left(-\frac{e z_j \phi(\mathbf{r})}{k_B T}\right) \chi_{\Omega_s}(\mathbf{r}),\end{aligned}\quad (1)$$

where  $z_j$  and  $\rho_j^b$  denote the valence and the bulk concentration of ions, respectively. For low-charge systems,  $\rho^s$  can be approximated as:  $\rho^s(\mathbf{r}) \approx -\varepsilon_s k_D^2 \chi_s(\mathbf{r}) \phi(\mathbf{r}) = -\kappa^2(\mathbf{r}) \phi(\mathbf{r})$ , where  $k_D$  is the Debye screening factor, and  $\chi_s(\mathbf{r})$  is the indicator function of the region that is accessible to ions. Applying the linearization and plugging (1) into Poisson's equation yields the LPBE model

$$-\nabla \cdot (\varepsilon(\mathbf{r}) \nabla \phi) + \kappa^2(\mathbf{r}) \phi(\mathbf{r}) = \sum_{i=1}^N q_i \delta(\mathbf{r} - \mathbf{r}_i). \quad (2)$$

Thus, the LPBE is a linear elliptic PDE which is computationally less demanding than its nonlinear counterpart. Yet, it is widely used to study biomolecular electrostatics, including charge screening and ion effects, and it can still be challenging to solve numerically due to the considerable size and geometric complexity of the systems to be considered.

#### A. Numerical method

We will focus here on some aspects of the discretization strategy that was used in [3] for the LPBE (2), having in mind two key objectives: maximizing accuracy near molecular surfaces, where discontinuities occur, and minimizing computational complexity for large-scale problems. To this aim, we start with a *primal mixed* Galerkin formulation of (2): Find  $(\mathbf{D}_h, \phi_h) \in U_h \times V_h$  s.t.

$$\begin{aligned}\int_D \frac{1}{\varepsilon} \mathbf{u}_h \cdot \mathbf{D}_h + \int_D \mathbf{u}_h \cdot \nabla \phi_h &= 0 \quad \forall \mathbf{u}_h \in U_h \\ \int_D \nabla v_h \cdot \mathbf{D}_h - \int_{\Omega_m} \kappa^2 v_h \phi_h &= - \int_{\Omega_s} v_h \rho^f \quad \forall v_h \in V_h\end{aligned}\quad (3)$$

where  $\mathbf{D}_h$  and  $\phi_h$  denote the approximation to the dielectric displacement vector and electrostatic potential, which are sought for in the Finite Element (FE) spaces  $U_h$  and  $V_h$ , respectively. As a compromise between the simplicity of structured tensor-product grids and the flexibility of locally refined unstructured meshes, we define our FE spaces on a hierarchically (de)refined cartesian Oct-tree type grid. It is well known that a suitable compatibility condition must hold between the spaces  $U_h$  and  $V_h$  for the discretization to be stable. The simplest choice for such a condition holds is to select piece-wise bi-linear continuous functions for  $V_h$  and suitable edge-element functions for  $U_h$ . Upon the latter choice, solving (3) amounts to solving a linear algebraic system of the form

$$\begin{bmatrix} A & B^T \\ B & -C \end{bmatrix} \begin{bmatrix} D \\ \phi \end{bmatrix} = \begin{bmatrix} 0 \\ -R \end{bmatrix} \quad (4)$$

By approximating the integrals in (3) by a trapezoidal quadrature rule, the matrix  $A$  can be made diagonal so that (3) can be simplified to

$$(BA^{-1}B^T + C) \phi = R, \quad D = (-A^{-1}B^T) \phi \quad (5)$$

In the poster presentation of this contribution, we show that (5) is equivalent to a standard FE discretization with nodal basis functions in regions where the permittivity is uniform, and it amounts to a suitable averaging of the permittivity along the edges of grid cells where discontinuities occur. We further show that by modifying the quadrature rule to account for the position along the edges where the discontinuity occurs, the accuracy of the computed approximation of the potential and of the energy are greatly improved.

### III. RESULTS

In the full version of this contribution, we will expand on the implications of different discretization strategies on the computational cost-to-accuracy trade-off. Moreover, we will briefly resume from [3] the validation of the proposed numerical method by evaluating its accuracy concerning analytical solutions [5] and results obtained with other state-of-the-art simulators. Finally, we will demonstrate the viability of implementing such a method in NextGenPB to solve the electrostatic potential for extensive systems. For example, Figure 1) shows the electrostatic potential on the molecular surface of the spike protein of the Sars-Cov-2 virus. The ability of an LPBE solver to provide high-resolution electrostatic maps is crucial for understanding molecular interactions and identifying molecular determinants of relevant biological features.

### IV. CONCLUSION

We describe relevant enabling features of a novel framework for solving the Poisson-Boltzmann equation, leveraging NanoShaper's [6] molecular surface accurate determination and ensuing analytical corrections to enhance Cartesian FEM discretization. This approach improves accuracy, accelerates energy evaluations, and allows efficient computation of ionic contributions.

Validation shows NextGenPB achieves superior precision at a lower computational cost, making it highly effective for biomolecular electrostatics and other PDEs with sharp boundary discontinuities.

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