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A Fast and Robust Poisson−Boltzmann Solver Based on Adaptive Cartesian Grids

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Supporting Information

ABSTRACT: An adaptive Cartesian grid (ACG) concept is presented for the fast and robust numerical solution of the 3D Poisson−Boltzmann equation (PBE) governing the electrostatic interactions of large-scale biomolecules and highly charged biomolecular assemblies such as ribosomes and viruses. The ACG offers numerous advantages over competing grid topologies such as regular 3D lattices and unstructured grids. For very large biological molecules and their assemblies, the total number of grid points is several orders of magnitude less than that required in a conventional lattice grid used in the current PBE solvers, thus allowing the end user to obtain accurate and stable nonlinear PBE solutions on a desktop computer. Compared to tetrahedral-based unstructured grids, ACG offers a simpler hierarchical grid structure, which is naturally suited to multigrid, relieves indirect addressing requirements, and uses fewer neighboring nodes in the finite difference stencils. Construction of the ACG and determination of the dielectric/ionic maps are straightforward and fast and require minimal user intervention. Charge singularities are eliminated by reformulating the problem to produce the reaction field potential in the molecular interior and the total electrostatic potential in the exterior ionic solvent region. This approach minimizes grid dependency and alleviates the need for fine grid spacing near atomic charge sites. The technical portion of this paper contains three parts. First, the ACG and its construction for general biomolecular geometries are described. Next, a discrete approximation to the PBE upon this mesh is derived. Finally, the overall solution procedure and multigrid implementation are summarized. Results obtained with the ACG-based PBE solver are presented for (i) a low dielectric spherical cavity, containing interior point charges, embedded in a high dielectric ionic solvent—analytical solutions are available for this case, thus allowing rigorous assessment of the solution accuracy; (ii) a pair of low dielectric charged spheres embedded in an ionic solvent to compute electrostatic interaction free energies as a function of the distance between sphere centers; (iii) surface potentials of proteins, nucleic acids, and their larger-scale assemblies such as ribosomes; and (iv) electrostatic solvation free energies and their salt sensitivities—obtained with both linear and nonlinear Poisson−Boltzmann equations—for a large set of proteins. These latter results along with timings can serve as benchmarks for comparing the performance of different PBE solvers.

INTRODUCTION

The efficient and accurate implicit solvent-based electrostatic modeling of large complex and highly charged biomolecules in an aqueous electrolyte solution at finite ionic strengths remains an important and difficult challenge in computational molecular biophysics. Considerable success in modeling the long-range and nonspecific electrostatic interactions of biomolecules in ionic solution has been achieved on the basis of the Poisson−Boltzmann equation (PBE), which provides the electrostatic potential and other important derived quantities (e.g., electrostatic solvation free energies, electrostatic binding free energies, forces, and pK shifts) under varying ionic conditions.[1] Nevertheless, two challenges persist in the numerical calculation of such systems. First, for large molecules, the mesh topologies used to date—regular lattices and unstructured tetrahedral grids—are subject to various inefficiencies and/or mesh generation challenges that can be improved upon by considering an alternate mesh structure as well as selecting a representation of the solution that reduces the mesh resolution demands. In the current development, the PBE is solved upon a hierarchical mesh structure variously referred to as an adaptive Cartesian grid (ACG) or octree or simply a Cartesian mesh. The ACG terminology is adopted here to distinguish it from regular lattices, which are also commonly called Cartesian grids. The second challenge is achieving reliable and rapid solution convergence for highly charged biomolecular systems. The current article describes a methodology that addresses both challenges, resulting in a robust nonlinear PBE analysis capable of properly modeling salt-mediated and nonspecific electrostatic effects in nucleic acids and their associations with charged ligands such as cationic drugs, peptides, and larger proteins.

One goal of the ACG-based PBE solver is to facilitate computation of electrostatic properties for large-scale biomolecular systems at the atomic level of detail using readily accessible computational resources. For example, a recent experimental study suggests that the electrostatic interactions in the ribosomal exit tunnel can modulate the elongation rates of nascent peptides.[2] For such large-scale ribosomal systems, most Poisson−Boltzmann studies have necessarily been based on coarse-grained molecular

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