Commun. Comput. Phys.
doi: 10.4208/cicp.220711.041011s

Vol. **13**, No. 1, pp. 195-206
January 2013

# Numerical Optimization of a Walk-on-Spheres Solver for the Linear Poisson-Boltzmann Equation

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Received 22 July 2011; Accepted (in revised version) 4 October 2011

Available online 12 June 2012

**Abstract.** Stochastic walk-on-spheres (WOS) algorithms for solving the linearized Poisson-Boltzmann equation (LPBE) provide several attractive features not available in traditional deterministic solvers: Gaussian error bars can be computed easily, the algorithm is readily parallelized and requires minimal memory and multiple solvent environments can be accounted for by reweighting trajectories. However, previously-reported computational times of these Monte Carlo methods were not competitive with existing deterministic numerical methods. The present paper demonstrates a series of numerical optimizations that collectively make the computational time of these Monte Carlo LPBE solvers competitive with deterministic methods. The optimization techniques used are to ensure that each atom's contribution to the variance of the electrostatic solvation free energy is the same, to optimize the bias-generating parameters in the algorithm and to use an epsilon-approximate rather than exact nearest-neighbor search when determining the size of the next step in the Brownian motion when outside the molecule.

**PACS**: 02.70.Uu, 41.20Cv, 05.40.Fb

**Key words**: Poisson-Boltzmann equation, walk-on-spheres, solvation.

## 1 Introduction

Implicit-solvent models, like the Poisson-Boltzmann equation (PBE) are commonly used to account for the aqueous environments and ionic atmospheres of biomolecules in elec-

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trostatic calculations without requiring the explicit inclusion of water molecules and ions [1–3]. Instead, the water is represented as a high-dielectric continuum, the ions are represented as a continuous charge distribution that obeys the Boltzmann distribution and the biomolecule is represented as a low-dielectric cavity containing point charges at the atomic centers. Unfortunately, the PBE is a nonlinear partial differential equation (PDE), which presents challenges to numerical solvers. Instead, the PBE is often linearized in the limit of small potentials, producing the linearized Poisson-Boltzmann equation, LPBE [4]. The LPBE has been applied to many biophysical problems and has been solved with several different numerical methods, including finite-difference [5–10], finite element [11–13], boundary element [14–19] and stochastic methods [20–24].

In particular, walk-on-spheres (WOS) [20–24], methods can compute the electrostatic solvation free energy, $\Delta G_{el}$, accurately with several features unavailable in deterministic methods, including natural parallelizability, low memory overhead, easily computed Gaussian error bars and the ability to compute $\Delta G_{el}$ across multiple solvent conditions simultaneously, accounting for both changes in the dielectric environment and salt concentration. However, previously-reported timings for WOS methods were not competitive with deterministic alternatives. The present paper illustrates that numerically optimizing WOS methods by dividing the variance of $\Delta G_{el}$ evenly over all atoms, optimizing the bias generating parameters in the algorithm and including an epsilon-approximate rather than exact nearest-neighbor search when computing the size of the next Markov step during the walk outside the molecule produces computational times competitive with deterministic methods while retaining all of the previously-mentioned advantages.

## 2 Computational methods

### 2.1 Structure preparation and Poisson-Boltzmann calculations

The 55 proteins in this study were a data set used by Tjong and Zhou [25], which in turn were taken from the RCSB Protein Databank, PDB [26], with charges taken from the AMBER force field [27] and the radii taken from the set used by Bondi [28]. Unless otherwise stated, all calculations in this paper used a temperature of 298.15K, 0.5M 1:1 salt (NaCl), an interior dielectric constant of 1 and an exterior dielectric constant of 80. The selection of these parameters does not significantly affect the results presented here. All WOS calculations were performed on a single core of an Intel Core 2 Duo T6500 processor operating at 2.10GHz with 4GB of random access memory. The deterministic calculations used to compare to the WOS solver were performed with either the ACG [29] or APBS [3] programs. The calculations in ACG were performed on a grid that was 3 times larger than the largest dimension of the molecule with a minimum grid spacing of 0.3Å. To verify that these electrostatic solvation free energies are converged, the same calculations were performed at a minimum grid spacing of 0.2Å and the two sets of calculations fit to a best-fit line with a slope of 1.0 and $R^2 = 0.999$ (data not shown). All calculations were performed with double precision.