Fast Boundary Element Method for the Linear Poisson−Boltzmann Equation

Alexander H. Boschitsch,*,† Marcia O. Fenley,*,‡,|| and Huan-Xiang Zhou§,⊥

Continuum Dynamics, Inc., 34 Lexington Avenue, Ewing, New Jersey 08618-2302, Department of Physics, Washington University, St. Louis, Missouri 63130-4899, and Department of Physics, Drexel University, Philadelphia, Pennsylvania 19104

Received: September 24, 2001; In Final Form: December 13, 2001

This article summarizes the development of a fast boundary element method for the linear Poisson−Boltzmann equation governing biomolecular electrostatics. Unlike previous fast boundary element implementations, the present treatment accommodates finite salt concentrations thus enabling the study of biomolecular electrostatics under realistic physiological conditions. This is achieved by using multipole expansions specifically designed for the exponentially decaying Green's function of the linear Poisson−Boltzmann equation. The particular formulation adopted in the boundary element treatment directly affects the numerical conditioning and thus convergence behavior of the method. Therefore, the formulation and reasons for its choice are first presented. Next, the multipole approximation and its use in the context of a fast boundary element method are described together with the iteration method employed to extract the surface distributions. The method is then subjected to a series of computational tests involving a sphere with interior charges. The purpose of these tests is to assess accuracy and verify the anticipated computational performance trends. Finally, the salt dependence of electrostatic properties of several biomolecular systems (alanine dipeptide, barnase, barstar, and coiled coil tetramer) is examined with the method and the results are compared with finite difference Poisson−Boltzmann codes.

I. Introduction

The properties and function of numerous charged biomolecules and their complexes with other molecules are dependent on the ionic strength of the environment. For example, the conformational stability of highly charged peptides and proteins is greatly affected by changes in salt concentration. Similarly, the binding affinities and association rates of biomolecular complexes are also strongly dependent on salt concentration. Therefore, computational tools that reliably and accurately predict ionic strength dependent electrostatic interactions are essential for an improved understanding of many biological processes. Moreover, to offer the user the ability to address large molecules using readily accessible computers, the CPU and storage demands imposed by such tools must be kept at a minimum.

The different theoretical approaches used to model salt effects in biomolecular systems can be divided into two broad categories according to whether they employ an explicit or implicit solvent model. Explicit solvent models adopt microscopic representations of both solute (e.g., biomolecule) and solvent molecules. Typically, explicit solvent-based approaches employ potential energy functions and sample the conformational space by either molecular dynamics or Monte Carlo techniques. Explicit solvent approaches produce accurate results, but are very computer intensive. Molecular dynamics of biomolecules immersed in salt solutions entail considerable computational effort since they involve a large number of ions and water molecules and require accurate ion−water, ion−ion, and ion−solute potential functions. Obtaining thermodynamic quantities, such as solvation and binding free energies, from free energy simulations of biomolecules immersed in aqueous salt solutions is even more challenging. The introduction of efficient particle-mesh Ewald (PME) algorithms[1,2] which accurately account for long-range Coulombic interactions has promoted the popularity of biomolecular dynamics simulations and allowed larger systems to be considered. However, despite the advent of such tools and advances in computer power, molecular dynamics simulations of ionic strength effects in biomolecular systems are still not practical using an explicit solvent model.[3]

Implicit solvent models adopt a semi-microscopic treatment of the solute, but characterize the solvent in terms of its macroscopic physical properties (e.g., dielectric constant, ionic strength). This allows ionic strength effects to be accurately reproduced at much lower computational cost than with explicit solvent approaches. For this reason, implicit solvent models such as those based on the Poisson−Boltzmann equation (PBE) are now widely used. In particular, the linear Poisson−Boltzmann approach considered here has been successfully used to account for the salt dependence of a variety of thermodynamic quantities such as binding free energies,[4] pK shifts,[5−7] and biomolecular association rate constants.[8,9] The Poisson−Boltzmann equation has also been coupled to quantum chemistry methods (e.g., ref 10) and used in conjunction with molecular dynamics to obtain relative free energies (e.g., binding free energies), which include both molecular mechanical free energies and solvation free energies.[11]

Analytical solutions to the linear Poisson−Boltzmann equation are only available for a limited number of cases involving

* Correspondence should be addressed to A.H.B: telephone: (609) 538-0444, fax: 538-0464, e-mail: alex@continuum-dynamics.com; and MOF: telephone: (850) 644-7961, fax: (850) 644-7244, e-mail: mfenley@sb.fsu.edu.

† Continuum Dynamics, Inc.

‡ Washington University.

§ Drexel University.

|| Current address: Institute of Molecular Biophysics, Florida State University, Tallahassee, FL 32306.

⊥ Address after July 1, 2001: Institute of Molecular Biophysics and Department of Physics, Florida State University, Tallahassee, FL 32306.

10.1021/jp013607q CCC: $22.00
Published on Web 00/00/0000 PAGE EST: 13.5