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DelPhi Web Server: A Comprehensive Online Suite for Electrostatic Calculations of Biological Macromolecules and Their Complexes

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Abstract. Here we report a web server, the DelPhi web server, which utilizes DelPhi program to calculate electrostatic energies and the corresponding electrostatic potential and ionic distributions, and dielectric map. The server provides extra services to fix structural defects, as missing atoms in the structural file and allows for generation of missing hydrogen atoms. The hydrogen placement and the corresponding DelPhi calculations can be done with user selected force field parameters being either Charmm22, Amber98 or OPLS. Upon completion of the calculations, the user is given option to download fixed and protonated structural file, together with the parameter and Delphi output files for further analysis. Utilizing Jmol viewer, the user can see the corresponding structural file, to manipulate it and to change the presentation. In addition, if the potential map is requested to be calculated, the potential can be mapped onto the molecule surface. The DelPhi web server is available from `http://compbio.clemson.edu/delphi_webserver`.

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Key words: DelPhi, electrostatics, proteins, continuum models, electrostatic potential, finite-difference Poisson-Boltzmann solver.

1 Introduction

Electrostatic force has profound role in molecular biology [1–4]. However, computing electrostatic properties of biological objects have always posed challenging and signif-

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icant problems to the biomedical computational community [5, 6]. The main reason for this difficulty is that biological macromolecules are made of thousands/millions of atoms, with different size and partial charge. More importantly, these molecules perform their function in a water phase. Since the individual positions and orientations of the water molecules are not know *a priori*, modeling the water phase is not trivial.

The importance of electrostatic interactions and energies is illustrated by the fact that proteins, DNAs, and RNAs are made of charged atoms and frequently the entire molecule(s) carry significant net charge as well. Since all atoms have charge, along with the small (angstrom scale) distances that are prevalent in biological systems, the magnitude of electrostatic interactions is typically very large and frequently surpasses other energy components [7–9]. Also, many biological phenomena are predominantly electrostatic in origin as is salt-dependence of binding [10–13] and folding [14], pH-dependence [15, 16], and pKa shifts in proteins [17, 18] and RNAs [19]. Moreover, electrostatics is the only long range force that is present within biological systems. All of these factors illuminate the importance of electrostatics in biology, which ultimately leads to the necessity of determining accurate electrostatic energy of biological systems and objects within these systems.

A major difficulty that is posed within the area of electrostatic calculations is modeling the solvent surrounding the biological macromolecules. Two general approaches [20, 21] are currently being used, explicit [22, 23] and implicit models [24–27], although hybrid approaches were introduced as well [28–31]. Without focusing on the differences (both advantages and disadvantages) of these methods (interested readers are referred to excellent papers [20, 24, 32–35]), we briefly outline a particular resource, DelPhi [36, 37], version 5, which is based on the continuum approach and solves the Poisson-Boltzmann equation via the Finite-Difference algorithm [38]. The biological entities (proteins, DNAs, RNAs, lipid membranes and other small molecules), are treated at an atomistic level of detail and considered a low dielectric cavity region surrounded by a water phase modeled as a continuum media with a high dielectric constant. The mobile ions in the water phase are treated as non-interacting particles and their effect is calculated through the Boltzmann law. The corresponding equations are solved on a grid and the electrostatic components of a variety of energies are calculated [37, 39]. While being user-friendly, the usage of DelPhi (as a stand-alone software package) still requires the user to have a local computer to be able to protonate the 3D structure of interest, and perhaps fix structural defects if they are present. Selection of the input parameters and output quantities can also be problematic for some inexperienced users. All of these factors motivated us to create a Delphi web server which is aimed to provide easy access to performing electrostatic calculations in biological systems without prior knowledge and without having a computational infrastructure in place.

With the development of modern internet connection technology, a large amount of web server based methods within computational biology have been on the rise [40–46]. These listed servers provide the biomedical community with tools for sequence alignment [47–51], structure alignment and prediction [52–55], estimation of the folding en-