Motivation: Electrostatic calculations are an important tool for deciphering many functional mechanisms in proteins. Generalized Born (GB) models offer a fast and convenient computational approximation over other implicit solvent-based electrostatic models. Here we present a novel GB-based web server, using the program Bluues, to calculate numerous electrostatic features including pKa-values and surface potentials. The output is organized allowing both experts and beginners to rapidly sift the data. A novel feature of the Bluues server is that it explicitly allows to find electrostatic differences between wild-type and mutant structures.

Availability: The Bluues server, examples and extensive help files are available for non-commercial use at URL: http://protein.bio.unipd.it/bluues/.

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1 INTRODUCTION

The structure, function [Fersht et al., 1983] stability (Bricker et al., 1994; small molecule binding [Hendler et al., 1992]) and protein–protein interactions [Richter et al., 2004] of a protein is largely dependent on its electrostatics. Electrostatic calculations are computationally impractical when modeling the solvent explicitly, e.g., by analyzing trajectories of a large number of solvent molecules in molecular dynamics simulations. Continuum solvent implicit models based on the Poisson–Boltzmann (PB) equation have been widely used [Davis and MacKerrell, 1999; Fogolari et al., 2003; Honig and Nicholls, 1998]. GB models are computational cheaper but are often very slow, especially for large molecules. When self- and interaction energies and forces are desired, the most widely used approach is based on the Generalized Born (GB) model [Bashford and Case, 1994; Kollman, 1985]. GB approaches are a further approximation to PB methods but are considerably faster with calculations available in reasonable time, even for large molecules. Often the GB approach is benchmarked compared with PB methods due to the improved accuracy of the latter.

Here, we present the Bluues server, a server that uses the program Bluues to perform electrostatic calculations for single-atomic structures with options for point mutations. The tool was conceived to yield accurate yet efficient models. Bluues, which is based on the GB model, was recently proven sufficiently accurate with respect to PB-based solvers [Fogolari et al., 2012]. Bluues currently models: (i) GB radius of each atom; (ii) electrostatic solvation free energy; (iii) pH-dependent properties; (iv) pKa of all titratable groups; and (v) electrostatic potential at the surface of the molecule all in the order of minutes. Upon point mutation, delta values are calculated for the points listed above between the wild-type and mutant structures. It is implemented as a user-friendly web server with output such as downloadable files, molecular graphics and tables sorted by interesting characteristics.

2 SERVER OVERVIEW

Blues requires as input a valid PDB identifier or a user-specified PDB file, from which it calculates a valid PQR protonation state file. Self made PQR files are also supported. The server contains two interfaces. One for analyzing a single-protein structure and the other for mutational analyses of the electrostatic features of two structures. The mutant protein can be derived from the server by point mutation library followed by a branch-and-bound search to remove steric clashes. This simple side chain replacement has been proven more effective than the classical one-step procedure [Krivov et al., 2002]. Bluues server can perform all titratable groups; and (v) electrostatic potential at the surface of the molecule all in the order of minutes. Upon point mutation, delta values are calculated for the points listed above between the wild-type and mutant structures.

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An important characteristic of the mutation output interface are the delta values provided between the wild type and mutant. These simply subtract the wild-type electrostatic features from the mutant ones. They are sorted in order of largest positive difference and may provide clues as to the most relevant electrostatic changes due to the mutation relative to the wild type. Examples of delta values include ΔpKa-values for ionizable groups and Δsurface potential. Moreover, atom distance from the mutation C–β atom is incorporated since long-range effects from the mutation may indicate important residues [Rajagopalan et al. (2005)], especially if they can be found to be conserved. In other words effects nearby the mutation site are expected while distant shifts may indicate an ‘Electrostatic domino’ effect highlighting distantly coupled residues.

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