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Using DelPhi Capabilities to Mimic Protein's Conformational Reorganization with Amino Acid Specific Dielectric Constants

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Abstract. Many molecular events are associated with small or large conformational changes occurring in the corresponding proteins. Modeling such changes is a challenge and requires significant amount of computing time. From point of view of electrostatics, these changes can be viewed as a reorganization of local charges and dipoles in response to the changes of the electrostatic field, if the cause is insertion or deletion of a charged amino acid. Here we report a large scale investigation of modeling the changes of the folding energy due to single mutations involving charged group. This allows the changes of the folding energy to be considered mostly electrostatics in origin and to be calculated with DelPhi assigning residue-specific value of the internal dielectric constant of protein. The predicted energy changes are benchmarked against experimentally measured changes of the folding energy on a set of 257 single mutations. The best fit between experimental values and predicted changes is used to find out the effective value of the internal dielectric constant for each type of amino acid. The predicted folding free energy changes with the optimal, amino acid specific, dielectric constants are within RMSD=0.86 kcal/mol from experimentally measured changes.

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Key words: DelPhi, protein electrostatics, dielectric constant, Poisson-Boltzmann equation, protein flexibility, energy calculations, single point mutations.

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1 Introduction

Electrostatic interactions play significant role in determining the structure, function and interactions of biomolecules [1–4]. Unlike the short-range force as van der Waals (vdW), electrostatic interactions are long ranging and highly sensitive to the surrounding environment such as solvent characteristics and ions concentration [3]. Being long range force, the electrostatics can affect the energetics and structural properties of distant objects ranging from macromolecular assemblages [5] to cluster of interacting amino acids [6]. Furthermore, the electrostatics may be the dominant energy contribution in describing variety of phenomena as pH and salt dependence of protein stability [7–10] and interactions [11, 12]. The last observation allows pH and salt dependent processes to be effectively studied by modeling the electrostatic component of the energy, while ignoring all other contributions [10].

Due to the importance of electrostatic interactions in biomolecular systems, significant efforts were invested to develop methods for modeling the electrostatics and better understanding its contribution to macromolecular properties. Currently there are two distinctive methods for treating the electrostatics in biological macromolecules immersed in water: explicit and implicit methods [13, 14]. The explicit methods describe the water phase explicitly, i.e. as a sea of explicit water molecules [13, 15, 16] and calculate the electrostatic interactions and energies via Coulomb's law. However, these methods demand integration over countless solvent molecules degrees of freedom which requires significant computational time to obtain accurate results. On the other end of the spectrum are so termed implicit solvent models which treat the solvent implicitly as a homogeneous medium with specific dielectric properties and ion concentration [14,17–19]. The implicit models greatly reduce the requirements of computational time while capturing most of the important electrostatics effects, especially for the bulk water phase [20–22]. However, simple implicit models may fail to accurate describe the electrostatic properties of the system of interest in the regions close to macromolecular surface and in cases of macromolecular systems experiencing conformational changes associated with the process being modeled. Because of that, hybrid methods were also developed treating explicitly the water molecules at the molecular surface while the bulk water is modeled as a continuum medium [23–26]. At the same time, fewer efforts were invested to account for the heterogeneity of macromolecules themselves and the effect of intrinsic flexibility on implicit electrostatic calculations. Our work, in conjunction with previously reported investigations [27,28], is devoted to offer better representation of inhomogeneous dielectric properties of macromolecules in the framework of continuum electrostatics.

From point of view of continuum electrostatics, the protein molecules are highly polar objects, because they are made of amino acids carrying electrical charges and dipoles [29]. However, the distribution of charged and polar residues is not homogeneous. Polar and charged residues tend to appear on the surface of the molecules while hydrophobic residues are typically located in the core of the corresponding protein [29]. However, this may not hold in case of membrane proteins which frequently have charged and polar