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Between Algorithm and Model: Different Molecular Surface Definitions for the Poisson-Boltzmann Based Electrostatic Characterization of Biomolecules in Solution

Sergio Decherchi[1], José Colmenares[1], Chiara Eva Catalano[2], Michela Spagnuolo[2], Emil Alexov[3] and Walter Rocchia[1,*]

[1] *Department of Drug Discovery and Development, Istituto Italiano di Tecnologia, via Morego, 30, 16163 Genova, Italy.*
[2] *Institute for Applied Mathematics and Information Technologies, National Research Council of Italy, Genoa, Italy.*
[3] *Department of Physics, Clemson University, Clemson, South Carolina, USA.*

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Abstract. The definition of a molecular surface which is physically sound and computationally efficient is a very interesting and long standing problem in the implicit solvent continuum modeling of biomolecular systems as well as in the molecular graphics field. In this work, two molecular surfaces are evaluated with respect to their suitability for electrostatic computation as alternatives to the widely used Connolly-Richards surface: the *blobby* surface, an implicit Gaussian atom centered surface, and the *skin* surface. As figures of merit, we considered surface differentiability and surface area continuity with respect to atom positions, and the agreement with explicit solvent simulations. Geometric analysis seems to privilege the *skin* to the *blobby* surface, and points to an unexpected relationship between the non connectedness of the surface, caused by interstices in the solute volume, and the surface area dependence on atomic centers. In order to assess the ability to reproduce explicit solvent results, specific software tools have been developed to enable the use of the *skin* surface in Poisson-Boltzmann calculations with the DelPhi solver. The results indicate that the *skin* and Connolly surfaces have a comparable performance from this last point of view.

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*Corresponding author. *Email addresses:* `sergio.decherchi@iit.it` (S. Decherchi), `jose.colmenares@iit.it` (J. Colmenares), `chiara@ge.imati.cnr.it` (C.E. Catalano), `michela.spagnuolo@ge.imati.cnr.it` (M. Spagnuolo), `ealexov@clemson.edu` (E. Alexov), `walter.rocchia@iit.it` (W. Rocchia)

1 Introduction

Biomolecular systems are composed of biological macromolecules, proteins and nucleic acids, and of a number of small organic molecules and electrolytes immersed in aqueous solution. The role of the solvent is sometimes crucial because of the effects it can have on the behavior of the biomolecules while performing their function. Therefore, both in the field of Computational Biological Chemistry and Molecular Visualization, Molecular Surfaces (MSs) play an instrumental role as the separation between the system one wants to monitor and the surrounding environment, whose effect cannot be neglected but that is usually not the focus of the analysis. In Computational Biological Chemistry, the so-called implicit solvent models provide an estimate of the average solvent effect, resulting in a huge computational saving, since the number of degrees of freedom of the solvent is usually much larger than that of the solute. Approaches based on the Poisson-Boltzmann Equation (PBE) [1] and the Generalized Born Approximation [2] are widely used to estimate the reaction of the media to the electric field generated by the partial charges on the solute. In particular, the Poisson-Boltzmann equation reads:

$$\nabla\cdot[\varepsilon(\mathbf{r})\nabla\varphi(\mathbf{r})]=-\left[\rho^{fixed}+e\sum_{i=1}^{N_s}C_i(\infty)z_i\exp\left(-\frac{ez_i}{k_BT}\varphi(\mathbf{r})\right)\right], \tag{1.1}$$

where e is the electron charge, $C_i(\infty)$ is the bulk concentration of the i-th ion type and z_i is its valence, k_B is the Boltzmann constant, T is the temperature, ρ^{fixed} represents the partial charge distribution and $\varphi(\mathbf{r})$ the potential; $\varepsilon(\mathbf{r})$ is the space varying dielectric constant, which is a direct consequence of the adopted surface definition. The solution of this equation is needed to acquire an accurate knowledge of the reaction field and it can also be used to derive the electrostatic forces exerted by the solvent on the solute, which are mostly located at the boundary between high and low dielectric regions, i.e. on the MS.

Traditionally, the simplest molecular models represent classical atoms as hard spheres whose radius, namely the van der Waals radius, indicates the largest distance at which an atom repels its neighbors. The union of these hard spheres is the so-called van der Waals volume and the resulting enclosing surface is termed the van der Waals surface (VDWS). In a real solvent, the solvent molecules have a finite size and small invaginations are not accessible, at least in a static scenario. To account for this fact, other surfaces were identified, in particular the Solvent Accessible Surface, which is the locus of the centers of a spherical probe that rolls over the molecular system. Geometrically, it coincides with the VDWS of the system where each VDW radius is increased by the size of the radius of the probe. In case of aqueous solution, a probe having the average water molecule radius of 1.4Å is considered. A subsequent development consisted in the definition of the Solvent Excluded Surface (SES), often identified with the Molecular Surface; it separates the volume accessible to a finite size solvent probe from the inaccessible one. This definition, based on a hard sphere model of both the solute and the solvent, was suggested