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Influence of Grid Spacing in Poisson−Boltzmann Equation Binding Energy Estimation

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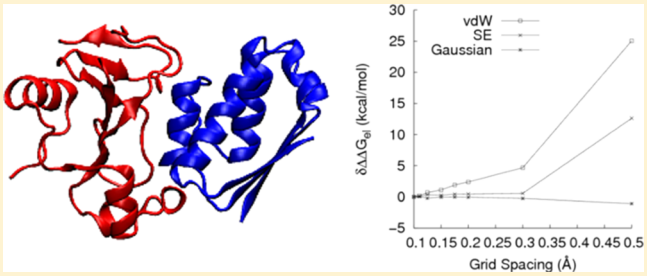
ABSTRACT: Grid-based solvers of the Poisson−Boltzmann, PB, equation are routinely used to estimate electrostatic binding, $\Delta\Delta G_{el}$, and solvation, ΔG_{el}, free energies. The accuracies of such estimates are subject to grid discretization errors from the finite difference approximation to the PB equation. Here, we show that the grid discretization errors in $\Delta\Delta G_{el}$ are more significant than those in ΔG_{el}, and can be divided into two parts: (i) errors associated with the relative positioning of the grid and (ii) systematic errors associated with grid spacing. The systematic error in particular is significant for methods, such as the molecular mechanics PB surface area (MM-PBSA) approach, that predict electrostatic binding free energies by averaging over an ensemble of molecular conformations. Although averaging over multiple conformations can control for the error associated with grid placement, it will not eliminate the systematic error, which can only be controlled by reducing grid spacing. The present study indicates that the widely used grid spacing of 0.5 Å produces unacceptable errors in $\Delta\Delta G_{el}$, even though its predictions of ΔG_{el} are adequate for the cases considered here. Although both grid discretization errors generally increase with grid spacing, the relative sizes of these errors differ according to the solute−solvent dielectric boundary definition. The grid discretization errors are generally smaller on the Gaussian surface used in the present study than on either the solvent-excluded or the van der Waals surfaces, which both contain more surface discontinuities (e.g., sharp edges and cusps). Additionally, all three molecular surfaces converge to very different estimates of $\Delta\Delta G_{el}$.



INTRODUCTION

Many cellular processes, such as signal transduction, gene expression, and protein synthesis, are governed by the binding of biomolecules. In pharmaceutical applications, accurate and fast predictions of the binding free energy, $\Delta\Delta G$, of drugs to biomolecular targets, such as proteins and nucleic acids, are necessary, particularly in the final stages of the structure-based drug discovery. Predicting $\Delta\Delta G$ accurately is, however, challenging because it usually involves combining several energies, each of which is subject to numerical and model errors. Some of these energy terms, such as the Coulombic interactions between binding partners, usually favor binding, while others, such as the desolvation penalty of removing charged residues from the solvent environment upon binding, oppose it. Frequently, $\Delta\Delta G$ is much smaller than the contributing energy terms, so that errors judged small when compared against these individual contributions assume much greater significance when estimating $\Delta\Delta G$.

The present study illustrates this general problem by examining the numerical computation of the electrostatic component, $\Delta\Delta G_{el}$, of $\Delta\Delta G$, estimated by the Poisson−Boltzmann, PB, equation.[1−7] Typically, one obtains $\Delta\Delta G_{el}$ from $\Delta\Delta G_{el} = (\Delta G_{el})_c - (\Delta G_{el})_1 - (\Delta G_{el})_2 + (\Delta\Delta G_{el})_{coulomb}$, where $(\Delta G_{el})_c$ is the electrostatic solvation free energy of the complex, $(\Delta G_{el})_1$ and $(\Delta G_{el})_2$ are the corresponding electrostatic solvation free energies of the unbound components, and $(\Delta\Delta G_{el})_{coulomb}$ is the electrostatic binding free energy of the two components in vacuum. Here we assume that there are no conformational changes upon binding and thus, the bound and unbound states of the binding partners are the same. This same assumption is made in the most popular single trajectory MM-PBSA protocol, where only a single all-atom molecular dynamics of the complex is performed to compute $\Delta\Delta G$. Many studies assume that the differences in $\Delta\Delta G$ between closely related complexes, such as the binding of similarly charged organic drugs to a single protein or nucleic acid target or the mutation of polar or charged side chains in protein−ligand complexes, are dominated by the change in $\Delta\Delta G_{el}$.[8,9] However, many of these studies have used grid spacings of 0.5 Å or larger under the justification that ΔG_{el} estimates computed with these grid spacings are consistent with free energy methods using explicit solvent molecular dynamics simulations[10] or experimental solvation free energy data.[11] As demonstrated below, however, such coarse grids produce estimates of $\Delta\Delta G_{el}$ with unacceptably large errors because the magnitude of $\Delta\Delta G_{el}$ is typically orders of magnitude smaller than $(\Delta G_{el})_1$, $(\Delta G_{el})_2$, and $(\Delta G_{el})_c$.

Finite difference estimates of $\Delta\Delta G_{el}$ by the PB equation contain two kinds of numerical grid discretization error. The

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