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Challenges in Binding Free Energy Calculation Using MM-PB/GBSA

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A part of today's routine in computer-aided drug design, particularly in the drug lead identification phase, is protein-ligand binding free energy calculation [1]. The binding free energy calculation methods that combine molecular mechanical force fields with continuum solvent models have gained popularity as they can achieve a good balance between efficiency and accuracy [2-4]. Good examples include MM-PBSA (Molecular Mechanics-Poisson Boltzmann Surface Area) and MM-GBSA (Molecular Mechanics-Generalized Born Surface Area) [5]. Although MM-PB/GBSA is theoretically not as rigorous as free energy perturbation or thermodynamic integration, it is much less computer-resource demanding. In addition, MM-PB/GBSA frequently achieves a much better performance than docking scoring functions, a rationale for using it to re-rank docking poses in molecular docking studies.

In the MM-PB/GBSA theory, the free energy of a molecule is composed of three terms (Eq. 1): the gas phase molecular mechanical energy, the solvation free energy and the configurational entropy term. The gas phase molecular mechanical energy consists of three terms: the bonded, van der Waals, and electrostatic (Eq. 2). The solvation free energy is further decomposed into the polar and nonpolar parts (Eq. 3). The polar part is calculated by solving either the Poisson-Boltzmann equation (Eq. 4) for PBSA or the generalized Born equation (Eq. 5) for GBSA. The nonpolar part in Eq. 3 is typically estimated using solvent accessible surface area (SASA) as the energy for creating a cavity in solvent is proportional to SASA [2].

$$G = \langle E_{gas} \rangle + \langle G_{solv} \rangle - T \langle S_{conf} \rangle \quad (1) \tag{1}$$

$$E_{gas} = E_{bonded} + E_{vdW} + E_{elec} \tag{2}$$

$$G_{solv} = G_{solv}^{pol} + G_{solv}^{nonpol} \tag{3}$$

$$\nabla.\varepsilon(r)\nabla\varphi(r) - \varepsilon(r)\lambda(r)k^2 \sinh\left[\frac{q\varphi(r)}{k_B T}\right] = 4\pi\rho(r) \tag{4}$$

$$G_{GB} = -\frac{1}{2}\left(\frac{1}{\varepsilon_{\text{int}}} - \frac{1}{\varepsilon_{ext}}\right)\sum_i\sum_j \frac{q_i q_j}{\sqrt{r_{ij}^2 + \alpha_i\alpha_j \exp(-\frac{r_{ij}^2}{4\alpha_i\alpha_j})}} \tag{5}$$

There are a lot of successful stories of using this technique to model protein complexes and predict binding affinities [6-8]. It is widely accepted that MM-PB/GBSA can more reliably predict the relative binding free energies of a series of compounds binding to the same target, while the performance of the absolute binding free energy prediction strongly depends on systems [9-11].

As a relatively new technology, MM-PB/GBSA needs to overcome two challenges. The first hurdle is how to wisely set the intrinsic dielectric constant ε_{int}. It has been known that the calculated electrostatic energy ($E_{elec} + G_{solv}^{pol}$) strongly depends on the choice of intrinsic dielectric constant ε_{int}. As illustrated in Figure 1, seven biotin/avidin-protein complexes have wide spread distributions of absolute binding free energies predicted by six MM-PB/GBSA models [10]. The performance of reproducing the experimental relative binding free energy also varies from model to model and the correlation coefficient squares R^2 are 0.87, 0.34, 0.12, 0.86, 0.50 and 0.20 for PBSA (ε_{int}=1), PBSA (ε_{int}=2), PBSA (ε_{int}=4), GBSA (ε_{int}=1), GBSA (ε_{int}=2), and GBSA (ε_{int}=4), respectively. The same system was also studied by Genheden et al. [12] using eight different solvation models (two PBSA, four GBSA and two MM/3D-RISM) and similar results were observed.

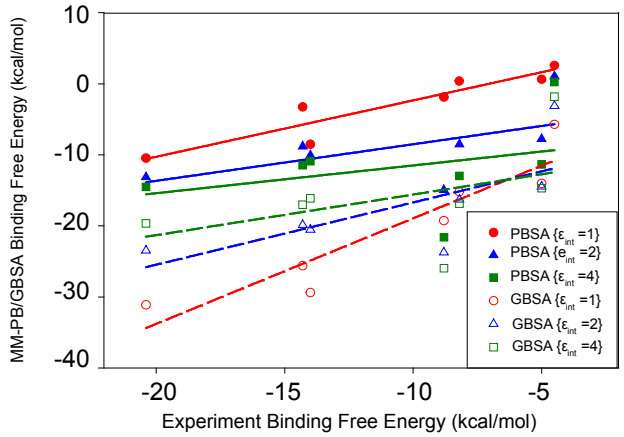

Figure 1: Prediction of the absolute binding free energies of seven biotin/avidin complexes using six MM-PB/GBSA models.

One possible solution to this challenge is to use variable dielectric constants for very heterogeneous environments of a protein. Nevertheless, the use of multiple dielectric constants that depend on subtle chemical environments or functional groups would over kill such a physically simplistic approach. On the other hand, Schutz and Warshel [13] argued that ε_{int} should be model-dependent and the more implicit the model is the larger optimal ε_{int} is needed. If it is the case, more physical model, such as a PBSA model that explicitly considers the induced dipole interaction, could lead to better results.

The second challenge of the MM-PB/GBSA is how to calculate the entropic term efficiently and accurately. Although for large molecules, solving the Poisson-Boltzmann equation does take time, the bottleneck of this technique is to calculate the conformational entropy by normal mode analysis (NMA) or quasiharmonic [14]. For NMA, the structures must be fully minimized in order to make the harmonic assumption valid. Otherwise, the calculation result is meaningless or has a large computational error. A mass-weighted Hessian matrix is generated based on the minimized structure and diagonalized to get vibrational modes. Both the geometrical optimization and the following normal mode analysis are time-consuming and computer memory demanding

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for large biological molecules [15]. The quasi-harmonic approach is even more challenging than NMA because a long molecular dynamics or Monte Carlo simulation is needed to make the fluctuation matrix converge [16]. How to overcome this challenge? It is probably a sound idea to weigh solvent accessible surface areas classified by atom types to estimate the entropy term as researchers do for other molecular properties including solvation free energy, aqueous solubility, etc. Certainly, approaches that can fasten minimization procedure and simplify the diagonalization of Hessian matrix can also break the bottleneck.

In summary, MM-PB/GBSA is a promising technique in calculating the binding affinities in a larger scale. If the two challenges can be overcome, the MM-PB/GBSA technique will be more accurate and efficient, and thus will have more applications in computer-aided drug design.

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