Accurate, robust and reliable calculations of Poisson-Boltzmann binding energies

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Introduction

Poisson-Boltzmann (PB) model is a one of the most used implicit solvent models in biophysical modeling. Making the PB model applicable for the electrostatic solvation (ΔG_{el}) and binding ($\Delta\Delta G_{\text{el}}$) free energy estimation requires reliable and accurate PB solvers. It was warned that the widely used grid spacing of 0.5 Å produces unacceptable errors in $\Delta\Delta G_{\text{el}}$ estimation with the solvent excluded surface (SES) (Harris et al. (2013)). In this work, we investigate the grid dependence of our PB solver (MIBPB) with SESs for estimating both electrostatic solvation free energies and electrostatic binding free energies. Our results indicate that the use of grid spacing 0.7 Å ensures accuracy and reliability in $\Delta\Delta G_{\text{el}}$ calculation. In fact, a grid spacing of 1.1 Å appears to deliver adequate accuracy for high throughput screening (Nguyen et al. (2015)).

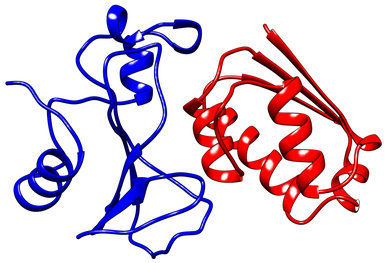

Figure: Mutant Barnase-Barstar complex (pdbid: 1b27)

Poisson-Boltzmann calculation details

Nonlinear PB equation

$$-\nabla\cdot(\epsilon(\mathbf{r})\nabla\Phi(\mathbf{r}))+\bar{\kappa}^2(\mathbf{r})\left(\frac{k_BT}{e_c}\right)\sinh\left(\frac{e_c\Phi(\mathbf{r})}{k_BT}\right)=4\pi\sum_{i=1}^{N_m}q_i\delta(\mathbf{r}-\mathbf{r}_i), \tag{1}$$

where $\Phi(\mathbf{r})$: electrostatic potential, q_i: the ith fractional charge at position $\mathbf{r}_i$, e_c: electronic charge, k_B: Boltzmann constant, T: absolute temperature, N_m: the number of charges in the biomolecule, $\epsilon(\mathbf{r})$: dielectric coefficient ,$\bar{\kappa}(\mathbf{r})$: modified Debye-Hückel parameter function.

Electrostatic solvation free energy

$$\Delta G_{\text{el}}=\frac{1}{2}\sum_i q_i\left(\Phi(\mathbf{r}_i)-\Phi_{\text{home}}(\mathbf{r}_i)\right), \tag{2}$$

where $\Phi_{\text{home}}(\mathbf{r}_i)$ is the electrostatic potential in a homogeneous dielectric environment.

Electrostatic binding free energy

$$\Delta\Delta G_{\text{el}}=(\Delta G_{\text{el}})_{\text{AB}}-(\Delta G_{\text{el}})_{\text{A}}-(\Delta G_{\text{el}})_{\text{B}}+(\Delta\Delta G_{\text{el}})_{\text{Coulomb}}, \tag{3}$$

where $(\Delta G_{\text{el}})_{\text{AB}}$: electrostatic solvation free energy of the bounded complex AB, $(\Delta G_{\text{el}})_{\text{A}}$ and $(\Delta G_{\text{el}})_{\text{B}}$ are the electrostatic solvation free energies of the unbounded components A and B, and $(\Delta\Delta G_{\text{el}})_{\text{Coulomb}}$ is the electrostatic binding free energy of the two components in vacuum:

$$(\Delta\Delta G_{\text{el}})_{\text{Coulomb}}=\sum_{i,j}\frac{q_iq_j}{\epsilon_m r_{ij}},\quad \forall i\in\text{A}, j\in\text{B}, \tag{4}$$

Calculation set-up

- PB solver: MIBPB package with the ionic strength of 100 mM NaCl (Chen et al. (2011); Wang et al. (2015)).
- Data set: DNA-drug, Barnase-Barstar, and RNA-peptide complexes (Harris et al. (2013)).

Acknowledgment

This work was supported in part by NSF Grant Nos. IIS-1302285 and DMS-1160352, and NIH Grant No. R01GM-090208. DN and GWW thank MBI for visiting programs.

Results: Examining the convergence of ΔG_{el}

Surface electrostatic potential

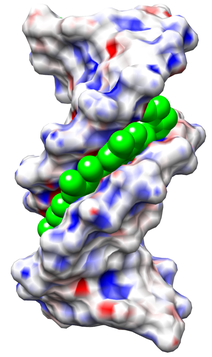

Figure: DNA-drug complex (pdbid: 121d)

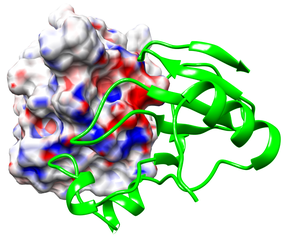

Figure: Barnase-Barstar complex (pdbid: 1b3s)

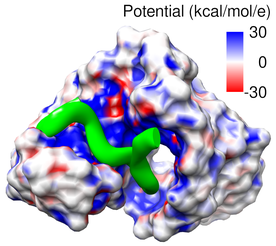

Figure: RNA-peptide complex (pdbid: 1biv)

Accuracy and convergence tests

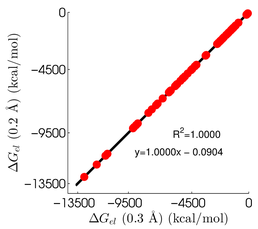

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el} at 0.3 Å

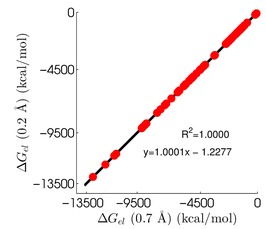

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el}) at 0.7 Å

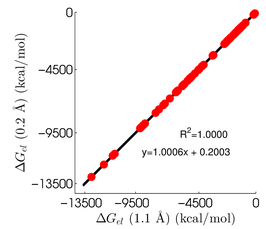

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el} at 1.1 Å

$$\text{Relative absolute error}\doteq\left|\frac{\Delta G_{\text{el},h}-\Delta G_{\text{el},\text{h=0.2}}}{\Delta G_{\text{el,h=0.2}}}\right|. \tag{5}$$

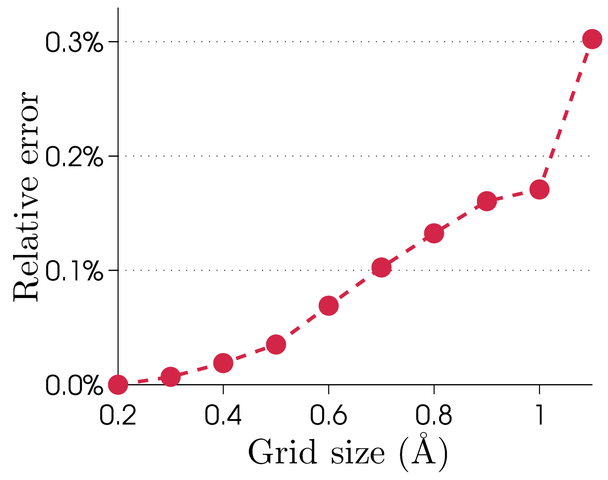

Figure: Averaged relative absolute error for all 153 studied compounds at different grid spacings.

Results: Examining the convergence of $\Delta\Delta G_{\text{el}}$

Accuracy and convergence tests

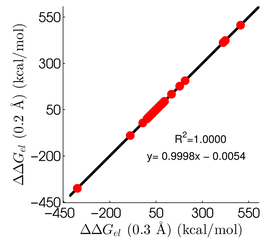

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el} at 0.3 Å

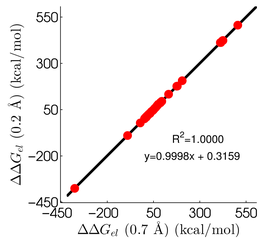

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el}) at 0.7 Å

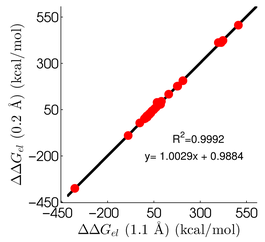

Figure: ΔG_{el} at 0.2 Å plotted against ΔG_{el} at 1.1 Å

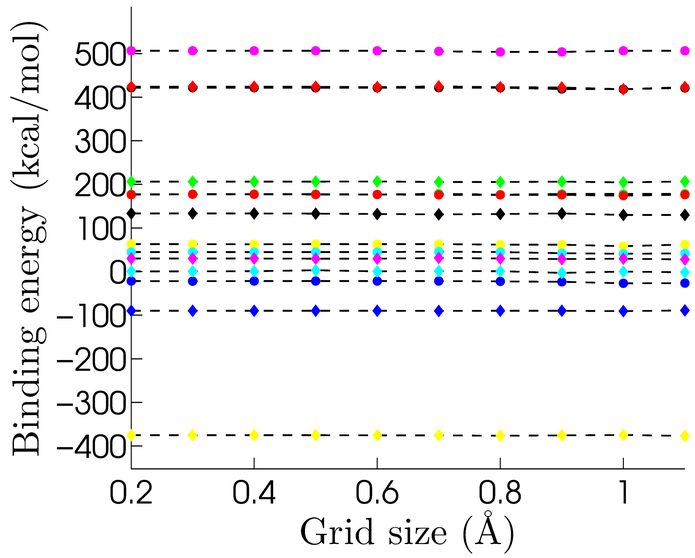

Figure: Binding electrostatic energy for RNA-peptide complexes with grid sizes from 0.2 Å to 1.1 Å.

Conclusion

- The MIBPB solver is essentially grid-size independent.
- Accurate and reliable $\Delta\Delta G_{\text{el}}$ can be obtained at the grid spacing of $h=0.7$ Å and a grid spacing of $h=1.1$ Å is adequate for high throughput screening.

Reference

Chen, D., Chen, Z., Chen, C., Geng, W. H., and Wei, G. W. (2011). MIBPB: A software package for electrostatic analysis. *J. Comput. Chem.*, 32:657 – 670.

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