Loop predictions using molecular mechanics/Poisson- Boltzmann solvent accessible surface area (MM/PBSA)

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Introduction

In many predictive tasks accurate free energy estimation is needed. The molecular mechanics/ Poisson-Boltzmann solvent accessible surface area (MM/PBSA) approach has proven to be one of the most accurate. However, the correlation between the estimated free energy and the distance (e.g. root mean square deviation (RMSD)) from the most stable conformation is hindered by the strong free energy dependence on minor conformational variations.

In the present paper a protocol for MM/PBSA free energy estimation is designed and tested successfully on several loop decoy sets. Further integration of MM/PBSA free energy estimator with the "colony energy" approach makes the correlation between free energy and RMSD from the native structure apparent, thus making the method both accurate and robust.

Materials and methods

The free energy corresponding to each alternative conformation (involving in the present study only limited loop regions of the protein) has been estimated using the MM/PBSA (molecular mechanics/ Poisson Boltzmann Solvent Accessible surface area) methodology (see e.g.[1-3]). In this approach the solute potential of mean force W is written as the sum of a molecular mechanics energy term and a solvation free energy term which can be further split in a polar (electrostatic) and a non-polar (hydrophobic) term:

$$W = U(\vec{r}_1, \vec{r}_1, ..., \vec{r}_n) + \Delta G^{polar} + \Delta G^{non-polar}$$

ΔG^{polar} is computed according to the Poisson-Boltzmann theoretical framework ([4,5]). $\Delta G^{non-polar}$ is taken to be proportional to the solvent accessible surface area A ([6]) i.e.: $\Delta G^{non-polar} = \gamma A$. Each conformation is considered as representative of a colony of similar conformations and its energy ΔG_i is reassigned, based on the potential of mean force W_j of all other conformations j, according to the following rule [7]:

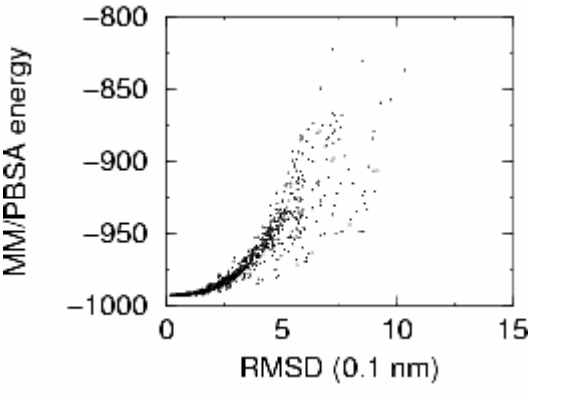
$$\Delta G_i = -kT \ln \frac{\sum e^{-\frac{W_j}{kT} - \frac{rmsd_j^3}{kT}}}{\sum e^{-\frac{W_j}{kT}}}$$

Twenty decoys for all octamers of protein A immunoglobin binding protein (PDB code: 1igd), a small 61-residue protein containing both α-helices and β-strands, were generated with a fast divide and conquer method ([8]). Sidechain atoms were predicted using the SCWRL3 method ([9]).

Results

Many decoys' sets have been analysed using both MM/PBSA free energy and its colony version. The effect of the application of the colony approach is reported in Figure 1.

The colony energy approach has two main beneficial effects. First, it takes into account entropic effects, albeit in a heuristic way. Second it greatly hampers the dependence of the estimated free energy on conformational variations and therefore gives the long sought robustness to free energy estimation. The typical plots obtained after application of the colony energy approach are rather impressive when compared to typical scatter plots reported in this kind of works. The counterpart of these benefits is the requirement of a rather large enesemble of models (typically in the order of one thousand).



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References

[1] Fogolari, F., A. Brigo and H. Molinari. 2002. The Poisson-Boltzmann equation for biomolecular electrostatics: a tool for structural biology. *J. Mol. Rec.* 15:377-392.

[2] Baginski, M., F. Fogolari and J. M. Briggs. 1997. Electrostatic and non-electrostatic contributions to the binding free energies of anthracycline antibiotics to DNA. *J. Mol. Biol.* 274:253-67.

[3] Kollman, P. A., I. Massova, C. Reyes, B. Kuhn, S. Huo, L. Chong, M. Lee, T. Lee,Y. Duan, W. Wang, O. Donini, P. Cieplak, J. Srinivasan, D. A. Case and T. E. 3rd Cheatham. 2000. Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models. *Acc. Chem. Res.* 33:889-897.

[4] Sharp, K. A. and B. Honig. 1990. Calculating total electrostatic energies with the non-linear Poisson-Boltzmann equation. *J. Phys. Chem.* 94:7684-7692.

[5] Fogolari, F. and J. M. Briggs. 1997. On the variational approach to the Poisson-Boltzmann free energies, *Chem. Phys. Lett.* 281:135-139.

[6] Nicholls, A., K. A. Sharp and B. Honig. 1991. Protein folding and association: insights from the interfacial and thermodynamic properties of hydrocarbons. *Proteins: Struct. Funct. Genet.* 11:281-96.

[7] Xiang, Z., Soto S. C. and B. Honig. 2002. Evaluating free energies: the colony energy and its application to the problem of loop prediction. *Proc. Natl. Acad. Sci. USA*. 99:7432-7437.

[8] Tosatto, S. C. E., Bindewald, E., Hesser, J. and R. Maenner. 2002. A divide and conquer approach to fast loop modeling. *Protein Eng.* 15:279-286.

[9] Canutescu, A. A., Shelenkov, A. A. and R. L. Dunbrack. 2003. A graph-theory algorithm for rapid protein side-chain prediction. *Protein Sci.* 12:2001-2014.