95. Native loop conformation recognition by MM/PBSA energy calculation

Federico Fogolari, [1] **Silvio Tosatto,** [2] **Alessandro Cestaro,** [3] **Giorgio Valle,** [4] **Henriette Molinari** [5]

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1 Introduction

The fold prediction problem can be divided in two parts: the generation of alternative conformations and the estimation of the stability of every available structure. We show that the latter task can be accomplished by a a hybrid method (molecular mechanics/Poisson-Boltzmann solvent accessibility (MM/PBSA)) method.

2 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],[2],[3]). In this approach only solute degrees of freedom are explicitly represented, so that the potential of mean force W is written as the sum of a solute energy term $U(\vec{r}_1, \vec{r}_2, ..., \vec{r}_n)$, estimated after minimization, using the classical forcefield CHARMM (v. 27b2) and a solvation free energy term which can be further split in a polar (electrostatic) and a non-polar (hydrophobic) term:

$W = U(\vec{r}_1, \vec{r}_2, ..., \vec{r}_n) + \Delta G^{polar} + \Delta G^{non-polar}$ [1]

ΔG^{polar} has been computed according to the Poisson-Boltzmann theoretical framework ([4],[5]) as the difference in free energy for the hypothetical charging process of the solute in vacuo and in ionic solvent. $\Delta G^{non-polar}$ is taken to be proportional to the solvent accessible surface area A i.e. $\Delta G^{non-polar} = \gamma A$ ([6]). The potential of mean force may be used to estimate the free energy of each conformation, except for the entropic part associated with solute degrees of freedom. This choice is roughly equivalent to assume that the entropy of each conformation is the same.

3 Results

In analysing results obtained on a database of 726 loops of d1.3 antibody (available from http://dd.stanford.edu/), it must be considered that only low energy conformations should

[1]Dipartimento Scientifico-Tecnologico, Universita' di Verona. Strada Le Grazie 15, 37134 Verona (Italy). E-mail: `fogolari@sci.univr.it`

[2]CRIBI and Dipartimento di Biologia, Universita' di Padova. Viale G. Colombo 3, 35131 - Padova (Italy), E-mail: `silvio@cribi.unipd.it`

[3]CRIBI and Dipartimento di Biologia, Universita' di Padova. Viale G. Colombo 3, 35131 - Padova (Italy), E-mail: `adepto@cribi.unipd.it`

[4]CRIBI and Dipartimento di Biologia, Universita' di Padova. Viale G. Colombo 3, 35131 - Padova (Italy), E-mail: `giorgio.valle@unipd.it`

[5]Dipartimento Scientifico-Tecnologico, Universita' di Verona. Strada Le Grazie 15, 37134 Verona (Italy). E-mail: `Henriette.molinari@ismac.cnr.it`

be taken into account, due to the fact that many conformations have poor local geometry and therefore their MM energy is high. When all the minima at increasing RMSDs are considered a very strong correlation between energy and RMSD from native structure is found. These results prove that MM/PBSA may play a relevant role in protein structure prediction and refinement.

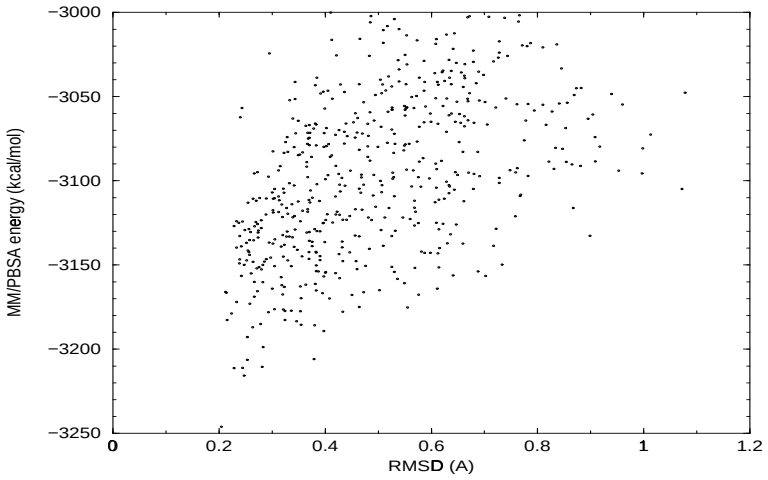

Figure 1: MM/PBSA energy plotted versus overall RMSD from native structure.

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