Modeling Proteins Conformation in Solution. Part II: A Solvent Effect Model Based on the Evaluation of Solvent-Accessible Surface Area and Generalized Born Equation

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Abstract

This is the second of a series of articles describing our system for prediction of protein conformation in solution. Here we propose a force field for studying protein folding in solution. Our force field is made up of an internal force field (MM2) and a solvent force field which sums up the constrains that solvent imposes to protein structure in solution, as compared with the gas phase.

1 Modelling Proteins Conformation in Solution

The concept of hydrophobic interaction plays an important role in the development of a theory for protein folding[1]. Hydrophobic interaction idea is used to describe a variety of biological processes[2], e.g. (i) the change in conformation of a biopolymer in a solvent, (ii) the binding of a substrate to an enzyme, (iii) the association of subunits to form a multisubunit enzyme, and processes involving high levels of aggregation, such as (iv) the formation of biological membranes and (v) the aggregation of molecules to form a functional unit in a living system. From the observation that the aggregation of hydrophobic solutes in water leads to a decrease in solvent-accessible surface area of the protein (SASA), many researchers proposed empirical relationships between solvent- accessible surface area of the protein and thermodynamics of cavity formation or solvation. In this paper we propose a force field for studying protein folding in solution. Our force field is made up of an internal force field (MM2) and a solvent force field which sums up the constrains that solvent imposes to protein structure in solution, as compared with the gas phase. The solvent effect model allows us (a) to

explore the conformational map of the protein in solution by locating the stationary points on the constrained potential energy hypersurface of solvent-protein ensemble, and (b) to evaluate solvation thermodynamics (free energy, enthalpy and entropy). Our conformational search engine is based on a procedure which implements the genetic algorithm[3]. The solvent-protein interaction energy is defined as a sum of hydrophobic and electrostatic interaction terms. The hydrophobic interaction term is calculated as a function of solvent-accessible surface area of the protein, while generalized-Born equation is used to evaluate protein-solvent interaction. We proposed to evaluate also the solvation enthalpy with a linear relationship based on the calculation of protein SASA while the generalized-Born equation was adapted for nonspherical molecules by evaluating the Born term with a numerical procedure based on the calculation of the exposed area of a protein atom. Solvent saturation effects near the protein surface are taking into account by means of a variable solvent dielectric constant. In our modification we keep the identity of Born and Coulomb terms which are associated with distinct electrostatic processes and modify the Born term by introducing a variable dielectric constant. The shape of the protein is taken into account by excluding the dielectric from the space region occupied by neighboring atoms. As a novelty, we introduce in this model a new kind of solvent-accessible surface for water, i.e. we use a 'two radii' water probe sphere. For C, S and H atoms (connected to C) we use a water sphere with a radius of 1.6 A, while for the other atoms a radius of 1.4 A is used. Our computational results lead to the conclusion that SASA of the peptide backbone decreases while that for all residues increases. SASA for hydrophobic residues increases several times more than that of hydrophilic residues. Finally, we introduce the concept of 'fluctuating' SASA of a protein and show that this idea can be used to incorporate structural information about solvent packing around protein in a solvent effect model based on the continuum representation of the solvent. In the 'fluctuating' SASA solvent effect model many configurations of solvent-protein system are generated and the thermodynamics quantities are obtained by averaging over solvent-protein ensemble. The 'fluctuating' SASA of a protein is our first step in the definition of a solvent effect model which incorporates a dynamic behavior of the solvent.

References

[1] (a)R.T. Ingwall and M. Goodman, "Amino Acids Peptides and Related Compounds", International Review of Science,Organic Chemistry Series Two, Vol. 6, N.H. Rydon (ed), Butterwarths, London, 1976, p. 153; (b) J.F. Kennedy, "Proteoglycans-Biological and Chemical Aspects in Human Life", Elsevier, Amsterdam, 1979, p. 145.

[2] (a) J.L. Rivail(Ed.),"Modelling of Molecular Structures and Properties", Elsevier, Amsterdam, 1990; (b) W.F. van Gunsteren, P.K. Weiner and A. J. Wilkinson(Eds), "Computer Simulation of Biiomolecular Systems, ESCOM Science Publishers B.V., Leiden, 1993.

[3] Del Carpio C.A., Gogonea V., Proceedings of the Seventh Workshop on Genome Informatics. 1996.