PROTEIN FOLDING, an hypothesis

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One of the major scientific challenges about protein structures remains: how do they fold? Different approaches of the question are made in the literature[1,2,3,4] and up to now the most successful ones do not consider the mechanism of folding per se but rather they predict structures from direct or indirect sequence homology. Therefore we are still facing the question of the mechanism of protein folding. Pure *ab initio* trials are good to predict helical folds[1,2,3] but they are obviously facing a problem when sheet structures are calculated. The most reasonable hypothesis is that the helix turn resulting from local interactions(n-4 to n+4 sequence partners) is statistically more frequently observed than strand interactions to make sheets that require less local partners. The rules that guide the formation of sheets are still unclear.

In a series of recent studies[5,6], we have been investigating the 3D structures of proteins trying to identify on a statistical point of view what are the common and what are the specific rules of residue interactions. This led us to revise the steric limits of the Ramachandran maps and to distinguish the H-bond geometry of helices and sheets. From there, we are tempted to suggest that protein folding could start from a 3-10 helix structure.

In order to test this hypothesis, we have analyzed a series of sequences (31cb, 1ppt, 1ubq 1enh and 1aan). Their 3D structures was forced into a 3-10 structure and we analyzed the steric, the electrostatic and the hydrophobic properties of the structures and compared them with those of the native folds. For this analysis we have developed a Pex file in which the van der Walls, the Coulomb term of the force field together with the hydrophobicity potentials are calculated for all amino acids along the sequence.

Van der Waals energy: we used the Morse equation. The initial 3-10 structures calculated with standard bond lengths and standard valence angles have steric clashes. Most clashes correspond to the occurrence of polar residues. A rapid optimization of the geometry decreases the van der Walls energy. It results in a shift of the chi1 chi2. The optimized structures still have a higher van der Walls energy than the native folds.

The electrostatic energy of the structure is negative in most instances: we are now comparing the energy profiles with all alpha and all beta folded structures with special attention to the structure breaker residues such as proline, glycine, but also polar residues.

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[1] Srinivasan R. Rose G.D. 1995 Linus : a hierarchic procedure to predict the fold of a protein. Proteins : Struct. Funct. & Genet. 22 : 81-99

[2] Yue K. Dill K.A. 1996 Folding protein with a simple energy function and extensive conformational search Protein Science 5 : 254-261

[3] Brasseur R. 1995 simulating the folding of small protein by use of the local minimum energy and the free solvation enerdy yields native-like structure. J. Mol. Graph. 13: 312-322

[4] Simons K.T., Bonneau R, Ruczinski I., Baker D. 1999 Ab initio protein structure prediction of CASP III targets using ROSETTA. Proteins 37 : 171-176

[5] Bosco K.H., Thomas, A. Brasseur.R. Submitted. Revisiting the Ramachandran plot : hard sphere repulsion, electrostatics and H-bonding in the alpha helix.

[6] Thomas A., Benhabiles N., Meurisse R., Ngawabije R. and Brasseur R. 2001. PEX analytical tools for pdb files. II. H-PEX : non canonical H-bonds in alpha helices. Proteins : Struct. Funct. & Genet. 43 : 37-44

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