This Week's Citation Classic®

Scheraga H A. Calculations of conformations of polypeptides.
Advan. Phys. Organ. Chem. 6:103-84, 1968.
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This is a review of early developments in the field of conformational energy calculations on polypeptides and proteins. [The *SCI*® indicates that this paper has been cited in over 440 publications, making it this journal's most-cited paper.]

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In the late-1950s and early-1960s, I was trying to obtain distance constraints by experimental physical chemical methods to determine the three-dimensional structure of ribonuclease in aqueous solution. For example, three specific Tyr...Asp interactions were identified, and subsequently verified when the crystal structure was determined (see Fig. 5 of ref. 1). With this information and knowledge of the location of the four disulfide bonds, it seemed appropriate to try to compute the structure from a knowledge of the amino acid sequence. At the same time (1962), one of my graduate students, George Némethy, had just finished a PhD thesis on the structure of water and hydrophobic bonding (refs. 2-4, two of which have been designated as *Citation Classics*), and we decided to develop methods to compute the conformation of a protein. Our initial efforts were devoted to procedures to generate a polypeptide chain (initially, as a trial calculation, an octapeptide loop of ribonuclease), and used only a hard-sphere potential to determine the sterically-allowed conformations.[5] During that time, the papers of Ramachandran *et al.*[6] and John and Charlotte Schellman[7] on the sterically-allowed conformations of a "dipeptide" appeared, and use was made of this information to reduce the conformational space to be searched in the computations[5] on the ribonuclease loop.

With this initial indication of the feasibility of such a computational approach, and supported by additional calculations on helical structures with Némethy and Syd Leach,[8] we began (together with Ken Gibson, Tatsuo Ooi, Douglas Poland and Roy Scott) to develop more realistic potential functions than the simple hard-sphere potential, and the *Citation Classic* indicated here reviewed this work. Simultaneously, similar efforts were carried on in the laboratories of P.J. Flory, S. Lifson, A.M. Liquori and G.N. Ramachandran.

The cited paper also discussed applications of this methodology to various polypeptide conformational problems; much of the work, cited then as "in progress," was subsequently completed successfully and provided considerable insight into the factors affecting the conformations of polypeptides and proteins.[1]

The basic underlying methodology and approaches are still valid today. However, with the availability of more experimental data, the potential functions have been refined in a self-consistent way. In my own laboratory, this refinement was codified (with the help of Frank Momany, Bob McGuire and Tony Burgess) into ECEPP (Empirical Conformational Energy Program for Peptides),[9] and subsequently updated (ECEPP/2) with even more recent experimental data. Other potential functions have been developed in other laboratories (e.g., AMBER, CHARMM, DISCOVER, etc.). While improvement of these potential functions (including entropy and hydration effects) is an ongoing effort, most of our current work is being devoted to the multiple-minima problem,[10] the solution of which (together with good potential functions) should lead to the prediction of the three-dimensional structure of a globular protein from a knowledge of its amino acid sequence. This methodology has spawned many companies that commercialize these techniques, and has provided the theoretical basis for current work in biotechnology. A summary of recent progress in the computational aspects of protein conformation is provided in references 1 and 11.

1. **Scheraga H A.** Protein structure and function, from a colloidal to a molecular view. *Carlsberg Res. Commun.* 49:1-55, 1984. (Cited 20 times.)
2. **Némethy G & Scheraga H A.** Structure of water and hydrophobic bonding in proteins. I. A model for the thermodynamic properties of liquid water. *J. Chem. Phys.* 36:3382-400, 1962. (Cited 930 times.) [See also: **Némethy G.** Citation Classic. *Current Contents* (22):11, 29 May 1978.]
3. ————. Structure of water and hydrophobic bonding in proteins. II. Model for the thermodynamic properties of aqueous solutions of hydrocarbons. *J. Chem. Phys.* 36:3401-17, 1962. (Cited 780 times.)
4. ————. The structure of water and hydrophobic bonding in proteins. III. The thermodynamic properties of hydrophobic bonds in proteins. *J. Phys. Chem.* 66:1773-89, 1962. (Cited 850 times.) [See also: **Némethy G.** Citation Classic. *Current Contents/Physical, Chemical & Earth Sciences* 28(30):16, 25 July 1988.]
5. ————. Theoretical determination of sterically allowed conformations of a polypeptide chain by a computer method. *Biopolymers* 3:155-84, 1965. (Cited 100 times.)
6. **Ramachandran G N, Ramakrishnan C & Sasisekharan V.** Stereochemistry of polypeptide chain configurations. *J. Mol. Biol.* 7:95, 1963. (Cited 265 times.)
7. **Schellman J A & Schellman C.** The conformation of polypeptide chains in proteins. (Neurath H, ed.) *The proteins: composition, structure, and function.* New York: Academic Press, 1964. Vol. II. p. 1-137. (Cited 205 times.)
8. **Leach S J, Némethy G & Scheraga H A.** Intramolecular steric effects and hydrogen bonding in regular conformations of polyamino acids. *Biopolymers* 4:887-904, 1966. (Cited 40 times.)
9. **Momany F A, McGuire R F, Burgess A W & Scheraga H A.** Energy parameters in polypeptides. VII. Geometric parameters, partial atomic charges, nonbonded interactions, hydrogen bond interactions, and intrinsic torsional potentials for the naturally occurring amino acids. *J. Phys. Chem.* 79:2361-81, 1975. (Cited 525 times.)
10. **Gibson K D & Scheraga H A.** The multiple-minima problem in protein folding. (Sarma M H & Sarma R H, eds.) *Structure & expression. Volume 1: from proteins to ribosomes.* Schenectady, NY: Adenine Press, 1988. p. 67-94.
11. **Scheraga H A.** Approaches to the multiple-minima problem in conformational energy calculations on polypeptides and proteins. (Clementi E & Chin S, eds.) *Biological and artificial intelligence systems.* ESCOM Science. (In press.)