This Week's Citation Classic®

Chou P Y & Fasman G D. Prediction of protein conformation.
Biochemistry—USA 13:222-45, 1974.
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A method is described in which the secondary structure of a protein (α-helix, β-sheet, β-turns) is predicted from the knowledge of its primary sequence. The accuracy of prediction is approximately 80 percent. [The *SCI*® indicates that this paper has been cited in over 1,160 publications, making it the most-cited paper for this journal.]

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I spent several years doing postdoctoral work on the physical-chemical properties of poly-α-amino acids in the laboratories of Ephraim Katchalski and Elkan Blout before moving to Brandeis University in 1961. There I continued these studies, which later led to an experiment demonstrating that leucine formed exceptionally stable α-helices.[1] Peter Chou, a postdoctoral colleague who joined me in 1970, and I wondered whether leucine played a similar role in the structure and function of proteins. Our examination of the conformation of cytochrome C (as determined by X-ray diffraction) revealed that leucine was the most frequent residue in the α-helices that formed the hydrophobic pocket that bound the heme.[2]

We then wondered if this observation was universal, so we examined 15 proteins of known conformation.[3] We discovered that leucine was indeed the most abundant residue in the inner helical cores of proteins. Elaborating on this theme, we conducted a survey in 1974 that resulted in the tabulation of the frequency of all 20 amino acids in each of the α, β, and coil conformations.[3] These frequencies were normalized to yield conformational parameters: P_α for the helix, P_β for the β-sheet, and P_c for the coil conformations. We incorporated these conformational parameters into an algorithm to predict the secondary structure of proteins from their primary sequence. Subsequently, the β-turn parameter P_t, as well as the frequencies of each amino acid in all four positions in the β-turns, was also evaluated.[4] A thorough analysis of β-turns in proteins was carried out in 1977 on the X-ray coordinates of 29 proteins of known sequence and structure, and 459 turns were located.[5] Using these data, an algorithm was written for the prediction of β-turns in proteins.[6] We then applied our predictive algorithm to evaluate the secondary structure of bovine pancreatic trypsin inhibitor (58 residues) and obtained a result that was 87 percent correct for helices and 95 percent correct for the β-sheets. We were more than pleased with these results.

Glucagon (29 residues) was also predicted[7] in 1975 and yielded a fascinating and confusing result. The region 19-29 had nearly equal potential for α-helix and β-sheet: circular dichroism studies showed that, depending on concentration and solvent conditions, either structure could be obtained. Thus, we realized the method had the potential for detecting regions that could undergo conformational changes! We suggested that by changing residues, it should be possible to change potentials and thus lock either the α-helix or β-structure in this 19-29 region. Recently, V.J. Hruby[8] performed experiments that yielded a glucagon with 500 times the activity of the native protein.

In a contest initiated by G.E. Schultz in 1974, individuals were asked to submit predictions for adenylate kinase, which would be published together with the X-ray determined results that he had just completed. We were satisfied when we learned that we had tied for first place for the α- and β-predicted structures and for first place for β-turn prediction.

Our method has now been widely used to choose amino acid replacements for synthetic peptide work, to initiate tertiary structure predictions, to look for homologous secondary conformations in disparate proteins, and to produce models to aid in our understanding of many biological processes.

1. **Chou P Y, Wells M & Fasman G D.** Conformational studies on copolymers of hydroxypropyl-L-glutamine and L-leucine. Circular-dichroism studies. *Biochemistry—USA* 11:3028-343, 1972.
2. **Chou P Y & Fasman G D.** Structural and functional role of leucine residues in proteins. *J. Mol. Biol.* 74:263-81, 1972.
3. ————. Conformational parameters for amino acids in helical, beta-sheet, and random coil regions calculated from proteins. *Biochemistry—USA* 13:211-22, 1974. (Cited 700 times.)
4. **Fasman G D, Chou P Y & Adler A J.** Prediction of conformation of histones. *Biophysical J.* 16:1201-38, 1976.
5. **Chou P Y & Fasman G D.** Beta-turns in proteins. *J. Mol. Biol.* 115:135-75, 1977. (Cited 385 times.)
6. ————. Prediction of beta-turns. *Biophysical J.* 26:367-83, 1979. (Cited 85 times.)
7. ————. Conformation of glucagon-predictions and consequences. *Biochemistry—USA* 14:2536-41, 1975. (Cited 65 times.)
8. **Hruby V J, Krstenansky J L, Gysin B, Pelton J T, Trivedi D & McKee R L.** Conformational considerations in the design of glucagon agonists and antagonists. Examination using synthetic analogs. *Biopolymers* 25:S135-55, 1986.