bond in the non-polar interior of a globular protein is not known with accuracy, and even the planarity of the amide group may not be as invariant as is often assumed.

The resolution normally available from X-ray crystallographic studies of globular proteins is such that electron-density maps do not reveal the positions of individual atoms and can only be interpreted in detail by the use of molecular models incorporating geometrical constraints in the atomic arrangement (such as the planarity of the amide group). In one or two cases there is hope that conventional crystallographic methods of refinement, used with high-resolution X-ray results, may allow these constraints to be dispensed with, leading to atomic arrangements that have not been prejudiced by models used in interpretation. It should then be possible to see how much variation actually occurs in the geometries that are normally assumed to be constant and thus to learn whether the assumptions are valid.

Numerical Methods for Fitting Parameters to Data

By M. J. D. POWELL. (*Building 8.9, Atomic Energy Research Establishment, Harwell, Didcot, Berks., U.K.*)

Theory or a model of a physical system may predict the value $\phi_t(x_1, x_2, \dots, x_n)$ of a measurement y_t , where the x_i ($i = 1, 2, \dots, n$) are parameters of the theory or model. Given a number of measurements, say $y_1, y_2, \dots, y_m$, one may wish to determine the values of the parameters by solving the equations:

$$\phi_t(x_1, x_2, \dots, x_n) = y_t, \quad t = 1, 2, \dots, m \quad (1)$$

In the usual case when $m > n$, it hardly ever happens that one can satisfy all the equations simultaneously, owing to approximations in the theory or model, and owing to errors in the measurements. Indeed one prefers to have m much larger than n , for then one can use methods for calculating $(x_1, x_2, \dots, x_n)$ that tend to smooth out random experimental errors. In this talk we survey the methods that are available for solving the overdetermined system of eqns. (1).

The usual way of allowing for the fact that $m > n$ is to calculate the parameters $(x_1, x_2, \dots, x_n)$ to minimize the sum of squares of residuals:

$$\sum_t \{\phi_t(x_1, x_2, \dots, x_n) - y_t\}^2 = F(x_1, x_2, \dots, x_n) \quad (2)$$

say. The general numerical methods for this calculation are iterative, and a typical iteration improves an estimate, $(\xi_1, \xi_2, \dots, \xi_n)$ say, of the required vector of parameters. Most of the iterative

methods obtain a correction $(\delta_1, \delta_2, \dots, \delta_n)$ to make to $(\xi_1, \xi_2, \dots, \xi_n)$ by using the approximation:

$$F(\xi_1 + \delta_1, \xi_2 + \delta_2, \dots, \xi_n + \delta_n) \approx \sum_t \{\phi_t(\xi_1, \xi_2, \dots, \xi_n) + \sum_j J_{tj}(\xi) \delta_j - y_t\}^2 \quad (3)$$

where $J_{tj}(\xi)$ is the first derivative:

$$J_{tj}(\xi) = [\partial \phi_t(x_1, x_2, \dots, x_n) / \partial x_j]_{(\xi_1, \xi_2, \dots, \xi_n)} \quad (4)$$

The approximation (3) is used because it is a quadratic function of $(\delta_1, \delta_2, \dots, \delta_n)$, and therefore it can be analysed by the methods of linear algebra.

If $(\delta_1, \delta_2, \dots, \delta_n)$ is calculated to minimize the right-hand side of expression (3), then the replacement of ξ_i by $\xi_i + \delta_i$ ($i = 1, 2, \dots, n$) is called the Gauss-Newton iteration. Sometimes it works well, but sometimes it fails to converge, so it has been modified by Levenberg and Marquardt. This modification is described. Also, we mention some methods, based on the approximation (3), that avoid the calculation of first derivatives.

Another approach to solving the overdetermined system (1) is to minimize either the function:

$$F_1(x_1, x_2, \dots, x_n) = \sum_t |\phi_t(x_1, x_2, \dots, x_n) - y_t| \quad (5)$$

or the function:

$$F_\infty(x_1, x_2, \dots, x_n) = \max_t |\phi_t(x_1, x_2, \dots, x_n) - y_t| \quad (6)$$

In these cases if we make the approximation:

$$\phi_t(\xi_1 + \delta_1, \xi_2 + \delta_2, \dots, \xi_n + \delta_n) \approx \phi_t(\xi_1, \xi_2, \dots, \xi_n) + \sum_j J_{tj}(\xi) \delta_j \quad (7)$$

then we find that the iterative methods for calculating the parameters $(x_1, x_2, \dots, x_n)$ are based on linear programming. There are good reasons for occasionally preferring to minimize expression (6) or (7) instead of expression (2), and they are discussed in this paper.

The Conformation of Polynucleotides with Particular Reference to Transfer Ribonucleic Acids

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Structural parameters of RNA. The structural features of double-helical RNA species and their monomer units have been established mainly by X-ray-diffraction studies (Sundaralingam, 1969; Arnott, 1970) and have been supplemented by optical-rotatory-dispersion, circular-dichroism and n.m.r. spectroscopic data.

In RNA the conformation about the glycosidic C-1'-N bond that defines the position of the base relative to the sugar moiety is *anti* with O-2 in pyrimidine and C-4 in purine nucleosides, pointing away from the sugar residue. The five-membered

ribose ring in RNA is not planar but puckered such that C-3' is about 0.5 Å away from the plane through the other four atoms and on the same side as C-5', which is called the C-3'-endo envelope form. The conformation about the C-5'-C-4' bond is such that O-5' is located 'above' the ribose ring. The conformation of the phosphodiester group is *trans* about the C-5'-O-5' bond and *gauche* (approx. 300°) about the O-5'-P and P-O-3' bonds, and the torsional angle about the C-3'-O-3' bond is close to 200° with respect to C-4'.

The base pairs in natural RNA are of the Watson-Crick type and arranged such that their planes are tilted by about 76° with respect to the axis of the double helix with a pitch height of 11 base pairs or 30.9 Å (in A-RNA).

One may assume that in double-helical regions of the tRNA molecule structural parameters similar to those described above are valid. In the loop regions, however, the conformational parameters obtained for monomer nucleosides, which are different in some instances, might be more relevant. Thus the 'rare' tRNA nucleosides 4-thiouridine (Saenger & Scheit, 1970) and inosine (Thewalt, Bugg & Marsh, 1970) were found to crystallize in the unusual *syn* conformation with O-2 and C-4 respectively 'above' the ribose residue. It was established for crystalline dihydrouridine (Saenger & Suck, 1971; Sundaralingam, Rao & Abola, 1971) that the base is puckered because of the saturated C-5-C-6 bond, that the sugar conformation is C-2'-endo and that O-5' is not positioned 'above' the ribose ring. The conformation of the phosphate group was found to differ by 180° or 120° in some nucleotides from the one described for RNA. Further, base pairs other than the Watson-Crick type have been observed for co-crystallized nucleosides or bases

that might be involved when inter-loop base-pairing occurs.

Conformation of tRNA species. From biochemical, chemical and physicochemical experiments, structures for tRNA have been proposed. All of these proposals use the cloverleaf structure as a basic element. The arms of the cloverleaf can be folded in various ways (Cramer, 1971). The final answer on the tertiary structure of tRNA can only come from X-ray-diffraction studies on single crystals, which are now available. In any case, the arrangement must fulfil the specifications of optimum conformational arrangement in the mononucleotide moieties of the macromolecule. A computable optimization has been made for the tRNA conformation that folds together with -C-C-A arm, the dihydrouridine arm and the T-ψ arm (Cramer, Doepner, von der Haar, Schlimme & Seidel, 1968). The structure comprises a long helical stack from the -C-C-A end to the anticodon loop, involving 22 stacked bases. This gives the molecule a length of approx. 70 Å. Such a structure can be built for any of the known sequences of tRNA.

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COMMUNICATIONS

The Combination of Nuclear-Magnetic-Resonance Spectroscopy and Potential-Energy Calculations in the Study of Peptide Conformation in Solution

By G. C. K. ROBERTS and J. FEENEY. (*Medical Research Council Molecular Pharmacology Unit, Medical School, Hills Road, Cambridge CB2 2QH, U.K.*)

N.m.r. spectroscopy can give detailed information about the backbone conformation of peptides in solution. This use of n.m.r. is based on the fact that the magnitude of the spin-spin coupling between the peptide NH and the neighbouring α-CH protons is related to the dihedral angle, φ, of the HN-α-CH fragment. Because of the $\cos^2 \phi$

form of the relationship, a given value of the spin-spin coupling constant, J_{NC} , may correspond to more than one value of φ. In many cases this ambiguity can be removed by eliminating those values of φ that are sterically forbidden, as indicated by 'hard-sphere' calculations (see Ramachandran & Sasisekharan, 1968). Further, the population distribution as a function of φ and ψ (the α-CH-CO dihedral angle) predicted from potential-energy calculations (Scott & Scheraga, 1966; Brant, Miller & Flory, 1967; Ramachandran, Venkatachalam & Krimm, 1966) can be used to calculate a predicted value of J_{NC} . This can provide a useful experimental criterion by which to judge the applicability of a given potential-energy map to a particular system.

This approach will be illustrated by studies of some component peptides of gastrin: Asp-Phe,