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NEW INITIATIVES IN THE SOLUTION OF DIFFICULT STRUCTURES: GRADIENT REFINEMENT TECHN112UES APPLIED TO DIRECT METHODS OF SOLVING THE PHASE PROBLEM

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1. Introduction

In a typical X-ray diffraction experiment the intensities, I_{hkl}, are measured of a large number of diffracted beams (reflections) characterised by their Miller indices h, k and 1. This intensity is related to the structure factor, F_{hkl}, by

$$I_{hkl} = | F_{hkl} |^2 \quad (1.1)$$

From a knowledge of the structure factors it is possible to compute the electron density in the crystal as

$$\rho(x, y, z) = \frac{1}{V} \sum_h \sum_k \sum_l F_{hkl} \exp\{-2\pi i(hx + ky + lz)\} \quad (1.2)$$

The electron density gives the positions of the atoms since at the resolution normally achieved the atomic centres are situated at the peaks of almost spherical blobs of electron density. The fundamental drawback, however, is that the structure factor consists of two parts, a magnitude and a phase, and only the magnitude can generally be obtained from experimental measurements:

$$F_{hkl} = | F_{hkl} | \exp i\Phi_{hkl} \quad (1.3)$$

Thus part (in fact, the most important part) of the information required is not available and we must first deduce the phase of each structure factor before the calculation of the electron density can be carried out. This is the well-known 'phase problem' in crystallography, which direct methods seek to resolve using mathematical relationships between phases.

2. The Origins of Direct Methods

The earliest use of mathematical relationships between phases was by Harker and Kasper (1948) when they showed that inequality relationships existed be-tween structure factors. In favourable circumstances these relationships could be used to determine phases for centrosymmetric structure factors. Cochran (1955) later extended the theory to include non-centrosymmetric structure factors, deducing the relationship

$$\Phi_h \approx \Phi_{h'} + \Phi_{h-h'} \quad (2.1)$$

where now we have substituted the vector **h** for Miller Indices (hkl) and '≈' means 'probably equals'. Thus if two phases are known, a third can be deduced and used in turn in equations of type (2. 1) to find others. Such a procedure therefore requires a small basis (or starting set) of phases known *ab initio* and it is fortunate that up to three can be fixed arbitrarily, in order to define an origin within the unit cell to which our atomic positions will eventually refer. As phase determination proceeds and other values are needed to continue the process, they can be included either as symbols which will later assume numerical values (Karle and Karle, 1966) or they are assigned trial numeric values from the start (Germain and Woolfson, 1968). This latter principle forms the basis of some highly successful structure solving computer programs such as MULTAN (Main et al., 1980) and SHELX (Sheldrick, 1976).

3. The YZARC Method

Older methods such as those referred to above have a universal drawback, however, in that in the early stages the phase determination is critically dependent upon one or two relationships. These can seriously disrupt the procedure if they seriously violate equation (2.1) and this may account for the occasional, inexplicable failure of such methods to solve a particular structure. In these cases the solution obtained will most likely be wrong whatever the values used for phases in the starting set. What is needed is a much larger basis of starting phases (up to 100) and consequently more relationships available at the beginning of phase determination, so that individual poor relationships will have a much less damaging effect upon the process. However, it is not feasible to assign these values as in conventional methods, since this would take a great deal of computer time. The solution to this difficulty was found in 1978 by Baggio, Declercq, Germain and Woolfson when they introduced the computer program YZARC (CRAZY spelt backwards). In this method, the equations of type (2.1) are rewritten as follows

$$\Phi_p \pm \Phi_q \pm \Phi_r + b \approx 0 \text{ modulo } 2\pi \qquad (3.1)$$

where the Miller Index notation has been dropped in favour of code numbers represented by *p, q* and *r*. The ± alternatives and the fixed angle *b* occur because phases are taken from only one asymmetric unit of reciprocal space and, depending on the space group, the phases of equivalent reflections may involve changes of sign and a phase shift.

Because of the '2π ambiguity' in,determining phase values, the right-hand side of equation (3.1) is known only within a multiple of 2π and we can write this explicitly as

$$\Phi_p \pm \Phi_q \pm \Phi_r + b \approx 0 \text{ modulo } 2\pi\, n \qquad (3.2)$$

where n is an integer. There are many more relationships than phases and the complete set is conveniently expressed in matrix notation as

$$A\Phi + b \approx n \qquad (3.3)$$

where now, for convenience, the phases are expressed in cycles. It follows that there is a least squares solution for the phases which can be written

$$\Phi = (A^T A)^{-1} A^T (n - b) \qquad (3.4)$$

Equation (3.4) will not yield a solution immediately since the integers, *n*, can only be found from (3.2) and are not known unless the phases are known. This at first appears very circular since one must know the phases in order to be able to determine them. The situation is not as hopeless as it might seem, however, since if approximate phase values are available the *n*'s can be taken to be simply those integers nearest to the actual values of the sums of the three phases in equations. (3.3). It is then necessary to repeat the application of (3.4) until there are no further changes in the phases, so the process assumes the appearance of a refinement method rather than a single step approach. But there still remains the problem of obtaining initial phase values for input to this refinement procedure and this was where a surprise result was found. This was that even random numbers as initial phases would produce a good solution from time-to-time: for most structures a solution could be found in a reasonable number of trials by a Monte Carlo approach with initially random phases. This unexpected and almost absurd discovery provided the program with its name!

4. Gradient Methods in YZARC

Following the success of this new approach it was decided to investigate the use of a gradient refinement procedure in addition to the least squares analysis. Gradient- methods are a class of techniques in which a function is constructed whose minimum point coincides with the solution sought. An approximation is then made to the solution and successive shifts are calculated which carry this point towards the minimum. Figure 4.1 illustrates this process in a two dimensional case.

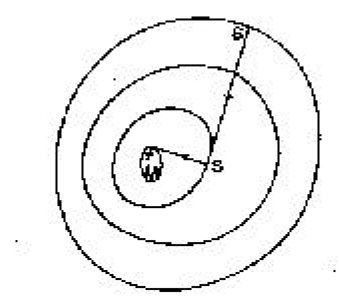

Fig. 4.1 The steepest descents method in a 2-dimensional problem.

There are many ways of deciding how to move the trial solution (S) towards the minimum point (M) and one popular method is to calculate the steepest gradient and follow this direction until the value of the function no longer falls (S'). At this stage the new steepest gradient is calculated and the process repeated. This is the method used in YZARC, but here there is a complication because of the 2π ambiguity. This is because the values of the integers used at each stage are those obtained when currrent values for phases are substituted in an equation such as (3.2). When the initial phase values used are random it isconceivable that the new phases obtained after the first shift is applied will lead to the definition of a

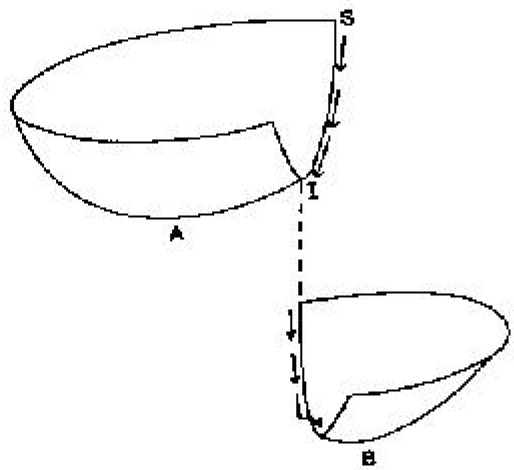

Fig. 4.2. The steepest descents method in a modulo 2π problem.

different set of nearest integers. Consequently the right hand sides of equations (3.3) have changed and therefore the solution sought must be different. Figure 4.2 shows a perspective view of this, where instead of continuing towards the original minimum point (A) the path of descent switches at point I towards a new different minimum (B). This is not a detrimental effect since we are only interested in reaching a solution, not one particular solution. The refinement carries on regardless, as in the least squares case, until the changes in the phases are small enough to consider the process to have converged. Since we know from experience that the integers will change at each cycle, it follows that only the first step of gradient refinement is carried out within a particular minimum. This means that each cycle of the new refinement procedure is equivalent in the present context to a single step of the least squares process, which enables us to make comparisons between the two.

Tests have shown that the new method is effective in refining phases and does not suffer from some of the disadvantages associated with inverting large matrices. It is also slightly faster than the original least-squares method and does not require large amounts of computer storage.

5. Conclusion

Theoretical work of this kind serves to give us an understanding of the working of the phase-determining process, which in turn may allow us to improve the power of the methods being developed. We can, for example, provide a qualitative picture of the operation of the various weighting schemes which are used in these methods and find some explanation for the failure of certain other types of refinement which have also been tried. Perhaps, most importantly, the work has lead to improvements applicable to both the least squares and the gradient refinement techniques and is one small step along the path of an ultimate goal–the solution of the phase problem.

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