COMPUTERS AND CRYSTALLOGRAPHY

by

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1. INTRODUCTION

Crystallography is, of course, a very wide subject and embraces all the physical and chemical aspects of research into the nature of crystals.[1] Within this broad field electronic computers have already found many applications. The theoretical treatment of atomic, molecular and crystalline structures has been greatly aided by their use; one can cite particularly the work of D.R. Hartree and his students on atomic structures,[2] and of S.F. Boys and his collaborators on molecular wave functions.[3] Practical calculations have been carried out in Cambridge of the elastic constants of crystals,[4] and the coefficients of transformation for martensitic alloys, for instance, are to be computed in Melbourne.[5] It is easy to foresee that, when sufficient storage becomes readily available, automatic routine identification of substances from X-ray power diffraction data will be a possibility. However, the most important recent advances made in the subject have been in the field of determination of structures from single crystal X-ray diffraction data, and it is with this topic that our paper is mainly concerned.

About five years ago Professor J.D. Bernal, in speaking on crystal structure determination, envisaged the process becoming wholly mechanised. He conceived of the data being automatically recorded and fed into a computer, which rapidly produced the desired result in the form of a set of atomic co-ordinates. Whilst we cannot yet attain quite this degree of mechanisation, we shall discuss how far this has been achieved, and attempt to clarify the limitations of the methods of structure determination put forward by several authors, notably Karle and Hauptmann,[6] Woolfson,[7] and Cochran and Douglas[8].

2. AUTOMATIC RECORDING

In order to implement full mechanisation of structure determination it is, of course, necessary to consider recording the data automatically. The use of power driven Geiger counter apparatus might appear to make this simple but the apparent simplicity is deceptive. Firstly there are the practical problems of sweeping the entire field of diffracted rays in such a way that all intensity maxima are recorded, or of arranging to determine in which positions significant intensities will be observed. Either normally involves a certain prior knowledge of the properties and symmetry of the crystal, although it is possible to devise a 'homing' system for aligning the counter on beams of high intensity. Secondly it is often desirable to apply corrections subsequently to the data for effects such as extinction, and to read again data which appears grossly in error. Procedures of this kind are difficult to codify and thus prove very intractable to mechanise. At present a certain measure of human control over the apparatus is desirable, even if the apparatus is mainly automatic. Once a set of records is produced on some suitable medium then geometrical corrections for the relative positions of the X-ray beam and the Geiger counter, temperature factors and so on can be readily applied by the computer, and the supposed correct mag-

nitudes of the observed intensities can be found on some appropriate scale.

3. AUTOMATIC STRUCTURE DETERMINATION

Given a set of observed intensities we must find a set of atomic positions or a distribution of electron density within the unit cell consistent with observation of those intensities and with any other physical or chemical information about the structure which may be available. At this stage no great accuracy is required in determining the atomic positions, and qualitative satisfaction of the necessary conditions might be regarded as adequate. The size and shape of the unit cell may be found from independent evidence, such as X-ray power diffraction data, or from the single crystal data itself and the symmetry can readily be determined. For simple structures, particularly those possessing a centre of symmetry or showing a centre of symmetry in projection of the electron density on one face of the cell, our problem is considerably simplified, and it is in these cases only that any satisfactory approach has been made to automatic determination of structures.

3.1 Treatment of the general case.

In the general case we may represent the electron density $\rho(\underline{r})$ in the unit cell in the form of a Fourier series. We write

$$\rho(\underline{r}) = \sum_{\underline{h}} A(\underline{h}) \exp\{2\pi i\, \underline{h} \cdot \underline{r}\} \qquad (1)$$

where $\underline{r} = (x, y, z)$, $\underline{h} = (h, k, l)$, h, k, l are integers (the Miller indices), $A(\underline{h})$ is complex, and the summation is over all values of h, k and l independently between $\pm\infty$. From the observed intensity data we can calculate $|A|$ for all observable values of $\underline{h}$. Although equation (1) is an exact definition of ρ, we note that in practice we could not evaluate ρ exactly, even if we knew the phase angle of each observed $A(\underline{h})$, since (i) not all $A(\underline{h})$ are observable, (ii) all the observed $A(\underline{h})$ contain experimental error, and (iii) it is necessary to truncate the series for practical summation. However, our primary problem is to find a set of phase angles to associate with each observed $|A|$ such that (i) ρ is always positive, and (ii) the resulting structure possesses the required physical properties of the substance, e.g. correct number of atoms in the unit cell, interatomic distances reasonable, and so on.

Conversely, we may try to find a structure possessing all the attributes (ii) which also yields the observed intensities on analysis. The Fourier transform of equation (1) yields (omitting a constant),

$$A(\underline{h}) = \int \rho(\underline{r}) \exp\{-2\pi i\, \underline{h} \cdot \underline{r}\}\, dV \qquad (2)$$

where $dV = dx\, dy\, dz$, and the integral is taken through the unit cell. If this approach is used then we may assume a form for each atom, and postulate $\rho = 0$ elsewhere. Each of the resulting integrals can be evaluated in terms of a product of a 'form factor' $f_n(\underline{h})$ and an exponential at the point $\underline{r}_n$, representing the atomic centre of the n^{th} atom. Thus we arrive at the formula (omitting a constant)

$$A(\underline{h}) = \sum_n f_n(\underline{h}) \exp\{-2\pi i\, \underline{h} \cdot \underline{r}_n\} \qquad (3)$$

where n is summed over all atoms in the unit cell, N say. The form factor for each atom is a property of its atomic configuration, and can be calculated for a given configuration from a knowledge of the wave function for that atom. This can, of course, be done to varying degrees of accuracy using either the Hartree-Slater-Fock analysis[9] or the simplified functions of, for instance, Slater, Duncanson and Coulson, or McWeeny[10]. Since not all atomic wave functions have been worked out, interpolation on known form factors has been used to fill in gaps. The accuracy of this has recently been questioned, particularly for the transition metals, and more accurate calculations are now available for Manganese[11].

One possible method of solution emerges from the above treatment. Comparing the values of $|A|$ calculated from equation (3) for a postulated set of $\underline{r}_n$ with those observed, we may set up a process reducing successively the weighted sum of the squares of the differences. We wish to minimise $R = \sum_{\underline{h}} \{ |A_o| - |A_c| \}^2 W(\underline{h})$, where the sum is taken over all observed $|A|$ values each being weighted according to its reliability. This is a well known numerical problem, and may be treated in several different ways. A comprehensive survey and discussion of practical methods is given by Cochran and Lipson[12]. Briefly, these include the 'least squares' technique and the method of steepest descent. Both lead to cumbersome expressions in very many variables (N is seldom less than 10, and, in the case of proteins may be more than 100) and hence have been little used in the three-dimensional form of the equations. The usual difficulties attendant on the minimisation of a function of many variables are in this case enhanced by the known existence of spurious local minima near the required minimum due to the effects of series truncation and experimental error. It is perhaps worth pointing out that, apart from some recent suggestions of Karle and Hauptmann[12], this minimisation technique is the only direct method of solution by calculation of the general problem in three dimensions. Whilst it will not work from an arbitrary choice of the $\underline{r}_n$, if these are chosen sufficiently close to the correct values, the method can be used to improve the the accuracy of the result.

4. THE PATTERSON FUNCTION

Since the principal direct method available can only be used if a fair approximation to the correct result has been found, we seek aids to the finding of such an approximation. One such aid is the Patterson function[14], defined in the unit cell by:

$$P(\underline{r}) = \sum_{\underline{h}} |A|^2 \cos(2\pi \underline{h} \cdot \underline{r}) \qquad (4)$$

The vectors joining the origin to maxima of this function indicate the length and direction of interatomic bonds in the crystal. It would appear, therefore, that it is necessary only to find the co-ordinates of maxima of P. Once again truncation and observational error reduces the usefulness of so simple-minded an approach, but a practised crystallographer can extract much information from looking at the general configuration of P either in section or in projection. It is therefore generally necessary to evaluate P over one or more planes through the unit cell. We shall discuss methods of doing this in connection with Fourier summation in a later section.

5. PROJECTIONS AND SECTIONS

It is difficult to inspect a function evaluated in three dimensions, or to visualise its form. For this reason it is convenient to present both Patterson functions and electron density functions plotted over a plane section through the unit cell. Such a section is normally chosen parallel to one of the cell sides, but need not necessarily be so chosen.

Another aid to visualisation is to plot a projection of the function on one face of the unit cell. In this case, of course, individual atoms cease to appear as distinct aggregates of electrons, and the peak of the projected electron density may overlap. This makes identification of peak positions more difficult. Furthermore it is not necessarily simple to interpret one or even two projections of a structure in terms of a three dimensional pattern.

However, whereas the three-dimensional structure may not possess simple symmetry properties, nevertheless one projection may have, for instance, a centre of symmetry. Methods appropriate to centro-symmetric functions, therefore, are not necessarily restricted in their usefulness to structures which possess a centre of symmetry in three dimensions.

5.1 Treatment of Centro-Symmetric Functions

For convenience we shall deal with centro-symmetric projections only in what follows, it being understood that similar considerations can be applied to centro-symmetric crystals. We can now write the expression for the projected electron density, $\rho(x,y)$ in the form

$$\rho(x,y) = \sum_h \sum_k S(h,k)\,|F(h,k)|\cos 2\pi(hx + ky) \qquad (5)$$

where the summations are for each of h and k running from zero to infinity. The values of the F are derivable from experimental observation, and it is the sign, S(h,k), of each term which is unknown. As before we can express the F(h,k) in terms similar to those of equation (3) for the A(h,k) and can attempt solution by the minimisation method. However, more powerful direct methods have been devised using either a statistical approach (Karle and Hauptmann[6,15]) trial and error (Cochran and Douglas,[16] Woolfson[7]) or inequalities derived from the fact that ρ is everywhere positive (Harker and Kasper[17]). We shall describe first the latter techniques and then discuss these in relation to the statistical approach.

5.1.1 Trial and error.

Normally quite a small number of terms in the summation in equation (5) are sufficient to define ρ well enough to be able to start a minimisation process. The possible number of combinations of sign are then not too large to examine individually in an electronic computer, provided that a criterion for selection of the correct one can be set up. It has not been possible to find a satisfactory criterion by which to distinguish uniquely the correct sign combination in every case. However, it has been possible to introduce a suitable criterion for rejecting a high proportion of the sign combinations as being unlikely to be correct. This criterion is based on a development, proposed simultaneously by

Cochran[18] and by Zachariasen[19], of the Harker-Kasper inequalities[17] For $\underline{h} = (h,k)$ and $\underline{h}' = (h',k')$ chosen such that $|F(\underline{h})\ F(\underline{h}')\ F(\underline{h}+\underline{h}')|$ is sufficiently large, we form the sum:

$$\chi = \sum_{\underline{h}} \sum_{\underline{h}'} P(\underline{h},\underline{h}')\ S(\underline{h})\ S(\underline{h}')\ S(\underline{h}+\underline{h}') \qquad (6)$$

where $P(\underline{h},h')$ is a weighting factor. For a given structure we may determine a value χ_0, and a set of $P(\underline{h},\underline{h}')$ such that there is a high probability that $\chi > \chi_0$ for the correct structure. Clearly the largest value of χ is given by choosing $Y(\underline{h},\underline{h}') = S(\underline{h})\ S(\underline{h}')\ S(\underline{h}+\underline{h}')$ positive for all $\underline{h},\underline{h}'$. The next largest values are given by choosing all but one Y positive and so on. If we can express the S in terms of the Y we can therefore list all the combinations for which $\chi > \chi_0$ without difficulty. Since the S can be only positive or negative we may replace each by a binary variable, multiplication being replaced by arithmetic modulo 2. The problem then reduces to the inversion of a matrix with coefficients and elements each representable by a single binary digit. Inversion can be carried out rapidly and easily in a binary computer, the operations of elimination and back substitution being especially simple if logical instructions are available in the order code of the computer.

For certain simple structures, for which a sufficient number of large $|F|$ are available, this procedure yields the correct set of signs for the highest permissible value of χ. Examples of this are Co_2Al_9 which was solved earlier by direct methods,[20] $MnAl_4$ (which was solved correctly by the computer but the projection could not be interpreted without additional work)[21] and an arsenical bromide.[8] In less favourable cases, the method may yield up to two or three hundred possible combinations. These can, of course, be put into equation (5) one at a time, the projected electron density evaluated, and the results inspected. Apart from the time consumed in such a procedure, it is not simple to sort out 'good' results from 'bad' ones. The results are usually roughly separable into 'families', for which a large block of signs is common to all members of the family, only a few signs altering from one member to the next. In the case of whale myoglobin, to a projection of which the method was applied, four families were distinguished and selected members were used to give electron density maps. It is thought that one of the combinations tried may well be correct, but this cannot at present be proved[22]. In other cases, such as a Kaliophilite, to which the method has been applied, no satisfactory results have been identified as yet; this is almost certainly due to inability to interpret the projections found.

A further selection criterion has been tested out using the EDSAC I. It can be shown that for the correct sign combination we should expect Ψ_0 to be small, where Ψ_0 is defined by:

$$\Psi_0 = \sum_{\underline{k}} \left| \sum_{\underline{h}} F(\underline{h})\ F(\underline{h}+\underline{k}) \right| \qquad (7)$$

where the sum over $\underline{h}$ involves only terms for which signs are given by the χ criterion, and the sum over $\underline{k}$ is over all indices for which $|F(\underline{k})|$ has a small value. The evaluation of Ψ_0 for each of the sets of signs given as probably correct by the χ criterion can be

carried out on the computer, the only complication being to evolve a suitable method of organising the computation efficiently in a computer of limited storage capacity. In this connection use has been made of digital indexing, the position of information in the store being indicated by the presence (or absence) of a digit in a particular word. The criterion was applied successfully to the structure of nitroguanidine, for which the χ criterion yielded 103 possible sign combinations among the 30 terms of largest $|F|$ value. The correct sign combination yielded a value of Ψ_0 very little greater than the lowest recorded, and was readily identified from among the three or four combinations for which the electron density functions were evaluated[23].

As an alternative to the above methods of reducing the number of sign combinations for which the electron density function must be evaluated, Woolfson has proposed a method based on covering theorems for Abelian groups[7]. It was pointed out earlier that selected sign combinations tend to fall into families, and that these families are distinguished by having a block of signs common to all members. Electron density functions belonging to members of a family all bear a resemblance to one another, and it ought to be possible to recognise the broad outlines of any suggested structure from evaluation of the function appropriate to only one member. Let us suppose that differences between the functions corresponding to two different sign combinations are only significant if the two combinations differ in more than three signs out of thirty. We need only evaluate functions for a set of sign combinations covering all the sign combinations in such a way that no combination differs from a member of the set by more than three signs. There are covering theorems which prove the existence of sets in certain cases, and methods are known of selecting particular sets[24]. Woolfson[7] has used such a set, in conjunction with a photographic method of evaluation of the electron density, with success. The most nearly correct sign combination was selected by inspection of the photographs. Such a method only reduces the total number of combinations by one or two orders of magnitude, whereas the method earlier described may reduce 2^{30} possibilities to a matter of a dozen strong candidates.

From our point of view the main drawback of both these methods is the necessity, except in a limited number of cases, for evaluation of the projected electron density for several combinations followed by visual selection among the results. At best the methods used can only be made semi-automatic. What is needed is a better criterion than either of those produced so far, or some additional method of selection from among the results produced. Attempts to introduce additional physical information, such as probable bond lengths, have yielded no new criteria so far.

5.1.2 Statistical methods.

A statistical analysis of the likelihood of a particular set of atomic positions leading to the observed intensities has led Karle and Hauptmann to propose a method of solution of determining signs [6], (or, more recently, phase angles). This involves forming certain sums of products of the observed intensities and combining them so as to determine successively the signs of the terms in the

electron density summation. The validity of the statistical basis has been questioned by Vand and Pepinski[25], whilst Cochran[26] has pointed out that the summations involved can be related to the χ criterion and to certain information obtainable from sections through the Patterson function. Nevertheless, at least one structure, colemanite, has been correctly determined using the method[27], though not using an electronic computer. It is probable that the method is little more powerful for centro-symmetric structures or projections than use of the χ criterion, and less powerful than the combined use of the χ and Ψ_0 criteria in selecting correct sign combinations, but no direct comparison has yet been made. However, it is said to have been used successfully on a non-centro-symmetric structure, and may well prove a powerful method of deriving a starting structure for minimisation. In principle the method might be applied entirely automatically, but, in view of Cochran's criticism, it is unlikely to be infallible in picking out the correct signs in every case, and thus suffers from similar drawbacks to the other methods described.

5.2 Refinement

Once a trial structure has been derived by one of the methods described above, or by some less direct approach, it is possible to proceed to obtain the signs of additional terms in the Fourier series and to effect minimisation of R simultaneously. This process is usually called "refinement" of the structure. The atomic positions are first predicted from the trial structure. The corresponding $A(\underline{h})$ or $F(h,k)$ are calculated for all terms. The terms the signs of which were not determined for the trial structure are now assigned the calculated sign appropriate to each, and the electron density recalculated using observed magnitudes, but calculated signs. Adjustment is now made of the atomic peak positions indicated from evaluation of the electron density function. It is possible to short cut this procedure by one of two methods. Either one may evaluate the electron density function and its derivatives at the trial peak position only and subsequently adjust this position using the derivatives[28], or one may evaluate the 'difference' function $(\rho_0 - \rho_c)$, where ρ_0 is evaluated using observed magnitudes and ρ_c is evaluated using calculated magnitudes[29]. In either case a new trial structure is indicated, which should both decrease R and lead to self-consistency in the signs of the terms. When all the signs are self-consistent, no further refinement is possible.

The whole refinement process, including corrections for anisotropic vibrations of the atoms, can be made automatic or, at least, automatic with a minimal manual control, on a computer with sufficient storage. In particular a series of refinements have been carried out by Cruickshank and his co-workers at Leeds[30] on the Ferranti Mark I at Manchester, and calculations on Vitamin B12 have been done both there and on the SWAC at UCLA. This latter involves more than 100 atoms and has taken much machine time to complete. On small machines it is possible to set up refinements involving card or tape handling and this has been done for LEO[31], DEUCE[32], and Pegasus[33], among British computers.

Once the refinement is complete, presentation of the results in the form of a set of atomic positions is simple enough as far as the heavier atoms are concerned. However, the location of hydrogen atoms is quite difficult to settle by a wholly automatic procedure, and it is for this reason that it is usually desirable to retain some manual control over

the refinement process, particularly if the difference synthesis method is employed. In such a case it is desirable to have available a rapid method of inspecting a contour map of the function in projection or in section. This is also desirable for the stage of selection involved in obtaining the trial structure. We shall, therefore, discuss later the problem of presentation of results. Clearly in order to have any results to present we must first consider the problem of Fourier summation.

6. FOURIER SUMMATION

The first crystallographic Fourier summations on a computer were carried out by Kendrew and Bennett[34] on the EDSAC I. They used the technique of Beevers and Lipson[35], and arranged this in such a way that the whole calculation for a section or projection was carried out inside the computer, the number of points of evaluation of the function over the cell being suitably restricted. In a more recent application on the same machine by Bootle a different technique was used in which the unit cell was divided into suitable strips and the $|F|$ data was run into the machine once for each strip. In this way any desired number of points of evaluation could be used. The method is at present more suitable than that of Kendrew and Bennet for EDSAC I, since fast input apparatus is now available, whilst the store is no larger than it was. In both cases the trigonometric function was tabulated over a quadrant or halfcircle and required cosine and sine valueswere extracted as needed.

The evaluation of 'structure factors' from equations like equation (3) has also been carried out on EDSAC I, as well as other computers. In this case the cosine and sine values needed were also extracted from a table made over a halfcircle at intervals of $\pi/512$. This was adequate to give two figure accuracy in the results. The original program assumed that the general shape of f_n is the same for all atoms, but different ratios were allowed for each class of atom. This technique is quite satisfactory for structures containing only Carbon, Nitrogen and Oxygen. Corrections to the structure factors produced for the general shape of f_n were made after evaluation by the computer. In a later version the f_n are fed in in tabulated form as required. Cruickshank's program on the Ferranti Mark I at Manchester stores all the required f_n on the drum.

The evaluation of a succession of projections or sections for a sequence of sign combinations presents a slightly different problem from the normal Fourier summation. Whilst it is obviously best to start the procedure by summation with a given sign set using the Beevers-Lipson technique, it is best to continue by calculating only the differences due to sign changes from one combination to the next. This requires that the whole grid of points at which the function has been evaluated should be held within the computer, and thus restricts the accuracy of the result that EDSAC I is capable of producing. Nevertheless the results have been satisfactory, each summation being completed and printed out at intervals of 1/32 of the unit cell in about ten minutes.

7. PRESENTATION OF RESULTS

There is no known method of presenting a function of three variables in a satisfactory way, except by construction of a model. It is therefore

normally necessary to present such a function in a series of two dimensional sections through the unit cell. Each such section is, of course, similar in form to the two dimensional function representing the projected electron density. In order to represent such a function numerically it is usually necessary to produce a table of the function at a set of points forming the intersections of a grid covering the area of the section or the face of the unit cell on which the electron density is projected. Such a grid is usually spaced at intervals of 1/30th of the unit cell side, or more closely than this for accurate determinations of the atomic positions. The cell is hardly ever rectangular, although the 'monoclinic angle' does not often depart far from a right angle.

In so far as the results are used as a visual aid to structure determination, only contours showing the general outline of the function are really required, but these are best shown on a unit cell with correct ratios of dimensions and the correct angle. Attempts have been made to present the results on a grid covering the normal printed sheet produced from computer output, but these have not proved very successful. Other attempts have been made to plot the contours directly from the equation for the function. Direct plotting, however, is complicated by the fact that contours are not usually single-valued, and, furthermore, rounding errors do not allow closed contours to be drawn correctly without difficulty.

Some computers possess cathode ray tube outputs. These are usually controlled digitally, and can be used to produce spots on grid points over a grid 1024 x 1024. Each spot is overlapped with the next, but nevertheless it is very difficult to draw a line slightly off one of the axes in a satisfactory manner. Nor is it easy to arrange satisfactory contouring, since the lines become indistinct in regions of steep slope. Also it is difficult to distinguish one contour from another and positive ones from negative ones, since, for reasons connected with photography of the results, it is normally only possible to arrange for two distinct levels of brightness for the contours.

The most promising development would appear to be a fast printer using styli to draw marks on paper on a continuously rotating feed. This is currently being studied by English manufacturers, and should provide a means of plotting contours as well as varying the size of letters or digits used in output.

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DISCUSSION

Professor T.M. Cherry, University of Melbourne.

Is there a clear cut criterion which is logically sufficient to fix the signs which have to be put in front of all the terms? Is it simply that ρ has to be everywhere positive?

Dr. A.S. Douglas (In Reply)

This positiveness of ρ is the only criterion we have used. Other people have looked into other criteria, e.g. whether the inter-atomic distances can be taken into account. I have not used much physical information in this paper. The reason why we cannot get a firm determination is that we have not put enough physical knowledge into it. The only knowledge we have to reach this far is that $\rho > 0$: this might be sufficient if all the F's involved could be taken into account but some are small and some cannot be observed at all.

Professor T.M. Cherry, University of Melbourne.

Do the two criteria you mentioned follow mathematically from $\rho > 0$?

Dr. A.S. Douglas (In Reply)

No; neither of them do! They are both inspired guesses. The high probability that $\Psi > 0$ does follow though. There is no rigid criterion here : it is only a probability criterion. All that follows from $\rho > 0$ are the Harker-Kasper inequalities : these are only valid where the size of the terms is large enough. This is an extrapolation on a probability basis which happens to work.

Professor T.M. Cherry, University of Melbourne.

Apparently a somewhat subjective criterion is used as to whether a condition is sufficiently plausible as a structure to be reckoned to be right.

Dr. A.S. Douglas (In Reply)

Yes, very subjective. The selection from then on is done on a basis of the crystallographer's experience. It is done on a number of valid ideas. He knows what the structure should look like chemically and the distance between the atoms and so on.

We have tried to derive a mathematical expression from the fact that the atoms cannot be too close together, but without satisfactory results.

Mr. I.D. Campbell, Defence Standards Laboratories Melbourne.

Would a two or three dimensional analogue of say the Parseval relation of Fourier Series, shed any light on the problem?

Dr. A.S. Douglas (In Reply)

The nearest way of shedding light by means of Fourier series is to use the related Patterson function mentioned in the paper. A three dimensional Patterson function is of great help. The results of this give vectors between the atoms if measurements can be made in the proper way.

The reason I have not touched very much on this is that it was apparent that there was no automatic process likely to come from this : it was a question of selecting things properly.

The only information to be obtained is due to the distances between the peaks and the directions between the peaks. An experienced person can, from these things, determine a good deal about the structure and particularly the error in his observations, thus enabling him to discard certain information.