CHAPTER 7

Methods and Problems of Crystal Structure Analysis[*]

7.1. Various Forms of the Problem

a. *Description of the structure.* In the preceding chapter we have paid little attention to the actual configuration of a crystal. We have, in fact, considered the atoms to be point centres of scattering of the incident field which are situated at the lattice points $\mathbf{x}_l = \Sigma l_i\, \mathbf{a}_i$ ($i = 1, 2, 3$; l_i integers varying from $-\infty$ to $+\infty$). There is thus only one atom per cell. In a crystallized compound there must be at least as many atoms in the cell as the chemical formula indicates, or a multiple of this number, corresponding to, say, Z molecules. These atoms form the '*base*' associated with the cell. We distinguish them by a superscript s and their positions relative to the lowest-indexed corner of each cell are given by the 'base-vectors'

$$\mathbf{x}^s = x^s{}_1\mathbf{a}_1 + x^s{}_2\mathbf{a}_2 + x^s{}_3\mathbf{a}_3, \tag{1}$$

where the $x^s{}_i$ are fractional coordinate numbers. The position of the atom of sort s in cell l as seen from the origin of the crystal is then

$$\mathbf{x}^s{}_l = \Sigma_i(l_i + x^s{}_i)\mathbf{a}_i. \tag{2}$$

b. *Atomic factor.* The scattering power for X-rays is not the same for atoms of different sorts. Besides, since the size of the atoms is comparable to the X-ray wave-lengths, the angular distrubution of scattered amplitude is not the same for the atom as for the point scatterer which was considered so far. The wavelets issuing from various parts of the electron cloud of the atoms arrive with phase differences in the direction of observation and this makes the total amplitude received a function of the angle of scattering and of the size and distribution of the electron density in the atom. This function differs from the simple amplitude which, according to a classical calculation by J. J. Thomson, a single electron would give if it were

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[*] See also parts of Ch. 10.

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substituted for the atom; the ratio of the actual amplitude to this fictitious one is called the '*atomic factor*' f. Like all quantities that depend on phase differences caused by differences of optical path, f depends only on the order of diffraction, that is, on the vector **h** if we have to do with a crystal, or on the continuously variable position vector in Fourier space, $\boldsymbol{\eta}$, if we consider a single atom instead of a periodic array of such. The definitions are

$$\begin{aligned} \boldsymbol{\eta} &= \eta_1\mathbf{b}_1 + \eta_2\mathbf{b}_2 + \eta_3\mathbf{b}_3 \\ \eta_h \equiv \mathbf{h} &= h_1\mathbf{b}_1 + h_2\mathbf{b}_2 + h_3\mathbf{b}_3. \end{aligned} \tag{3}$$

The experimental determination of atomic factors from X-ray observations was, and still is, an important aim, even though from 1926 onwards, with the advent of wave mechanics, these factors could be calculated with a fair, but not always sufficient accuracy (Hartree's method of self-consistent fields). By introducing the f-factor explicitly the remaining function of the atom is that of a point-scatterer.

c. *Structure factor.* Since the order of diffraction (h_1, h_2, h_3) indicates the differences of optical path for wavelets scattered by an atom and its neighbours along the directions of the axes $\mathbf{a}_i$, an atom in the cell which is removed only by fractions of $\mathbf{a}_i$ sends out a wavelet whose path length is compounded of the corresponding fractions of h_1, h_2, and h_3, respectively. That is, for the atom of sort s in (1) the path difference, measured in wave-lengths, will be

$$h_1x_1^s + h_2x_2^s + h_3x_3^s = \varphi^s(\mathbf{h}) \text{ (as in } \varphi^s(h^s)). \tag{4}$$

For reasons which need not be explained here the path difference of φ wave-lengths against some standard wave is described mathematically by the exponential function exp with an imaginary argument, namely by exp $(-j\varphi)$, where $j \equiv 2\pi\sqrt{-1}$. Using this symbolism we can now write down the factor by which the amplitude diffracted into an order **h** ($= h_1, h_2, h_3$) will be modified through the superposition of the fields generated by each sort of atom separately. Owing to the definition of the atomic factors f^s, this factor F, which is called the '*structure amplitude*', compares the amplitude of the diffracted wave received from the crystal in any direction to that amplitude which would be obtained if the atoms were all replaced by single electron scatterers. The formal expression of F is

$$F(\mathbf{h}) = \Sigma_s f^s(\mathbf{h}) \exp(-j\varphi^s(\mathbf{h})), \tag{5}$$

the summation extended over all atoms in the cell (the base), be they chemically alike or not.

It should be noted that in the precise direction of the diffraction (h_1, h_2, h_3) all the atoms in the crystal of any one sort s cooperate without any phase differences, and if the direction of observation is changed very slightly, secondary maxima and zero values will be generated by each kind of atom under the same angles. For this reason the factor F multiplies not only the amplitude obtained at the reciprocal lattice point **h** but also the entire distribution of amplitude in the neighbourhood of **h**. The measured intensity of diffraction is therefore proportional to the square of the absolute value of the complex quantity $F(\mathbf{h})$, which is indicated as $|F(\mathbf{h})|^2$. It is from this quantity, and *only* from it, that we gain information about the contents of the cell, that is about the atomic structure of the crystal. Experimentally, between 100 and 20 000 observed intensities may be available, the higher number for the most complex crystals with large cells; each intensity has to be scaled up by division with angle-dependent factors like the Lorentz factor or the temperature factor (see Chapter 6) so as to yield a value proportional to $|F|^2$. If these values are entered as 'weights' at the points of the reciprocal lattice, this weighted lattice shows the data available for the structure determination.

If $F(\mathbf{h})$ itself (i.e. including the sign or the complex phase) could be used as weight, then a simple Fourier synthesis, consisting of the summation of a series of sin and cos functions with the $F(\mathbf{h})$ as coefficients, would lead back to the mass distribution in the crystal. Actually it is the scattering power or electron density which produces the diffraction effect and which we determine in a structure analysis; but we use the term 'mass' in crystal space as opposed to 'weight' in Fourier space. Exploration of the entire Fourier space by experiment would require the use of very long wave vectors, i.e. very short wave-lengths, and this is not feasible, even in principle, because for the shorter wave-lengths, such as gamma rays, the angles of diffraction become very small and, furthermore, classical scattering without change of wave-length gives way to quantum effects involving changes of the states of the atoms, the emission of photoelectrons, and so forth. This means that only a limited region of Fourier space, surrounding the origin, is explorable by X-ray diffraction. Factors like the Lorentz and temperature factors also limit the observable intensities to those of lower orders. Thus the 'aperture' through which we look at reciprocal space is limited and the picture in it incomplete. This means that if this information is transformed back into physical space it will give a somewhat blurred mass distribution. This blurring is often called 'break-off effect' or 'termination of series effect'. It is one of the minor troubles of actual structure analysis. From the large number of intensities observed in most cases it is seen that the available region in Fourier space usually contains many more data than the number of atomic coordinates that have to be determined.

It is this excess of data over the number of unknowns which makes up for the lack of information on the phases of the $F(\mathbf{h})$, but a systematic way of exploiting this overdetermination is still in its trial stage (Karle & Hauptmann's method of 'joint probability', see below).

d. *Algebraic and analytical structure determination.* In practically all of the early work—up to about 1930—the aim of structure analysis was to find the positions of the centres of the atoms in the cell, that is, the base vectors for its Z atoms $s = 1 \ldots Z$. This requires the determination of 3Z coordinates, or rather of $3(Z-1)$ coordinates, since only relative positions count. Besides, the distribution of masses over these sites must be found. In order to speak of point-sites, the atomic factors must be used in reducing the intensities. The finite number of unknowns is hidden away in the reduced intensity values via the structure factor. Their extraction from there is essentially a problem of algebra, but one for which no general solution has been found. Even in the very much simplified case when the same atomic factor may be used for all atoms, as in many organic substances because of the similarity of the atomic factors for C, N, and O, the simultaneous equations to be solved are of a high degree and quite forbidding. One has therefore to proceed by 'trial and error' methods, i.e. by systematic guessing and approximation.

On the other hand, the crystal may be considered as a periodic continuous distribution of scattering power or mass density, $\rho(\mathbf{x})$, and one can see the aim of structure analysis in the determination of this *function.* This is, of course, equivalent to an infinity of unknowns. The structure amplitude produced by such a continuous distribution differs from (5) only in that the summation over individual atoms is replaced by an integration over the contents of the cell, whereby the continuously variable $\varphi(h, x) = \mathbf{h} \cdot \mathbf{x}$ takes the place of $\varphi^s(\mathbf{h})$ from (4); also the lumped atomic factor $f^s(\mathbf{h})$ is replaced by the electron density itself which causes the scattering power in each element dv of the cell volume. Thus the structure amplitude in this case is

$$F(\mathbf{h}) = \int \rho(x) \exp(-j\varphi(h, x)) \, dv. \qquad (6)$$

Again, the intensity is proportional to $|F(\mathbf{h})|^2$, and in this 'structure factor', which is derivable from the experiments, is hidden away the unknown function $\rho(\mathbf{x})$.

Clearly, the determination of this continuous function is an even worse proposition than that of a finite number of coordinate values in the algebraic version of the problem. And yet for many purposes the electron density $\rho(\mathbf{x})$ is what we are really aiming at, for instance in studies of the chemical bond. True, bond lengths and angles can be obtained from the algebraic locating of atomic centres, but only the analytical treatment reveals the actual electron densities on and near the directions of the bonds, for instance an excess density near the midpoints of the C—C bonds in diamond, or the small but definite differences of electron density surrounding the carbon atoms at the end and in the middle of the anthracene molecule (Fig. 10(3c)). $\rho(\mathbf{x})$ also contains information about the spreading of the atoms by the temperature motion.

Since the analytical approach includes the determination of the shape of the electron cloud of each atom, the measured intensity may not be reduced to that of a point scatterer by reduction of the intensities with the atomic factors. On the other hand, it is necessary to attribute the correct sign or phase to each of the $|F|$ before taking them as Fourier coefficients. In many cases this knowledge is obtained from the preceding location of the atomic centres by means of an algebraic structure determination. The two methods are therefore both employed in most cases.

7.2. The Algebraic Structure Determination

The indexing of the geometrical data obtained by any of the methods using monochromatic X-rays leads to the acceptance of a definite shape and size of the cell. Knowledge of the chemical formula, i.e. of the actual weight of the molecule, and of the specific weight of the crystal then tells the number Z of the molecules which are in the cell. This determination is not unique; we could, for instance, double one of the axial lengths, say a_3, and obtain a cell of double the volume and a content of 2Z molecules. With this cell all the h_3-values would have to be doubled and the bigger cell opens up the possibility that between these even h_3-values odd ones could be observed. Only if these are not found, even on close inspection of overexposed photographs, can we be satisfied that the smaller cell is the true one. In this sense the determination of the cell contains an element of intensity discussion besides the use of the geometrical data. In alloys, silicates, long-chain compounds and other structures that are close to possessing an internal periodicity of the base the search for the 'true' cell by means of 'inter-layer lines' or other forms of weak reflections is a very essential step in the crystal analysis.

The next step, which may be determining the placement of some of the atoms, is the determination of the space group. This again does not require a quantitative discussion of intensities, but only the observation of certain zero intensities occurring systematically, the '*absences*'. These are found whenever the structure contains glide symmetry elements because these lead to the interleaving of reflecting atomic planes with similarly populated ones at $\frac{1}{2}$, $\frac{1}{3}$, or $\frac{1}{4}$ of the spacing required by the cell. Not all space groups show absences, and even if such are observed, it does not fully determine the space group, but it restricts the choice.

The early structure determinations dealt with cases where there were only few atoms in the cell, and then their positions were often fully fixed by the knowledge of the space group or groups, especially in cases of high symmetry. Each symmetry element crossing the cell will reproduce an atom placed in the cell, except it is placed on the symmetry element itself; therefore, if the number of atoms in the cell is small, they have to lie on the symmetry elements and often on their points of intersection. In suitable cases, this fully determines the possible positions of the atoms, and since these points of intersection may be the same in related space groups, this may be a unique determination in spite of some indeterminacy of the space group. In other cases, the atomic positions may be restricted to lie on symmetry elements without being fixed otherwise. Any undetermined atomic coordinate is called a '*parameter*', and the value of a parameter can only be assigned from a discussion of the intensities. All modern crystal analyses deal with structures containing a large number of parameters—meaning anything beyond four or five parameters, so that their direct determination from a discussion of the intensities is not possible.

It is here that the '*trial and error*' method sets in, together with methods of '*structure refinement*'. The gist of this procedure is that for any assumed positions of the atoms it is a straightforward, if sometimes lengthy, matter to calculate the structure amplitudes F_h and thence the theoretical intensities $|F_h|^2$. These can then be compared to the observed ones. If the positions chosen were the correct ones the $|F|_{calc}$ and the $|F|_{obs}$ values should show a definite close correlation; coincidence is not to be expected because of the many factors influencing $|F|_{obs}$ which are not too well known (atomic factor, temperature factor, etc.). However, if the assumed atomic positions are in part correct or approximate, some parallelism between the calculated and observed F-values will be noticeable which indicates in which way, by shifting the atoms, a better agreement may be produced. As a measure of the overall agreement a *'residue'* or *'reliability number'* R is formed, usually of the form

$$R = \frac{\Sigma||F_h|_{obs} - |F_h|_{calc}|}{\Sigma|F_h|_{obs}}, \tag{7}$$

the sums being extended over all observed orders of diffraction. It will be noticed that R is really the inverse of a figure for the correctness of the structure proposal, since the correlation is the better the smaller R is.

Special methods have been developed for the refinement of a model structure once this seems to be not too far off the truth. The influence which certain shifts in the atomic positions have on the R-value are studied and improved positions calculated therefrom. This process is simple only in rare cases when the shifts of different atoms can be considered separately; usually all shifts are coupled together and the minimum R-value sought for is a true multidimensional minimum problem in the space of all atomic coordinates. This is a typical computer problem and it has been programmed for a variety of electronic computers:

trial structure – F^2_{calc} — R_1 – proposed shifts – new F^2_{calc} — R_2 – second shifts – third F^2_{calc} — R_3 – etc.

The machine can be programmed to do all this without help, and also to watch that the R-values decrease, and to stop when this is no longer the case or when a certain value of R (often 0.1, i.e. 10%) is reached. Beyond this, it is considered useless to go with algebraic determinations.

7.3. The Analytical Structure Determination

If the positions of the atomic centres have been determined in an algebraic determination, the signs or phases which are needed for converting $|F_h|$ into F_h itself are known from the last cycle of approximation. This information may now be applied to the $|F_{obs}|$ values, uncorrected for atomic factors and, possibly, temperature factor, in order to obtain a set of F-values which can serve as coefficients of a Fourier series representing the actual distribution of the electron density in the crystal. The summation, the *Fourier synthesis*, is required at the points of a conveniently narrow grid in the crystal cell. If the electron density curves are drawn on clear sheets of plastic for the consecutive layers of the grid, and the sheets stacked in the proper positions, the atoms appear floating in the cell as balls of high electron concentration.

The numerical work for a three-dimensional synthesis is so large that it has become a practical proposition only with the advent of the electronic computers. Before that, syntheses were restricted to two dimensions, and these were taken up soon after the first one-dimensional syntheses by Duane and Havighurst showed the usefulness of the method in 1925. The two-dimensional series require observation of intensities only in one zone of crystal planes, that is, in the reciprocal lattice, the knowledge of weights only on one plane passing through the origin. The summed series then represents the mass distribution obtained by projecting the spatial electron density on to a plane in the crystal which is normal to the zone axis. In order to obtain a significant projection, the direction of projection must be a very simple rational one which makes successive layers of cells match in projection. Of course the pictures of atoms may lie very close to one another in projection, even if the atoms are widely separated in the direction of projection. It is therefore not so easy to recognize atoms in the contour lines of the projection as it would be in a three-dimensional synthesis. The early diagram of anthracene (Ch. 10, Fig. 10(3b)) shows in a favourable case of two-dimensional synthesis what kind of indication of atoms can be expected; it may be contrasted with the next diagram showing a section through the same molecule based on a three-dimensional synthesis.

The Fourier summation in two dimensions was first carried out by W. L. Bragg (*Proc. Roy. Soc.* A 1929, *123*, 537) for the monoclinic crystal diopside, $Mg(SiO_3)_2$, using 30–40 reflections and summing at a grid of 24 × 12 points covering one eighth of the (a, c) face of the cell; the remaining parts of the cell follow from symmetry. The signs of the F-values were taken from a previous algebraic determination of the structure by Bragg & Warren. Even in this first try-out the number of numerical operations was quite high. It was inevitable that the repeated application of Fourier synthesis led to the invention of methods for abbreviating this procedure. Beevers and Lipson developed their 'Fourier strip' method which did more for the general introduction of Fourier methods than any other improvement, and remains, for its simplicity and educational value, one of the chief means for evaluating two-dimensional Fourier series of limited complexity. An account of the origin of the method is given by Lipson in Part VII.

The density calculation is always performed for the points of a grid in the cell, which must be fine enough to show individual atoms by their high electron density. Once the densities, measured in electrons per square ångström for the projection, are inscribed in the grid, the curves connecting points of equal density are easily drawn with a convenient height of the contour step.

A different kind of two-dimensional map of electron density is used for building up the mass distribution in three dimensions. For this purpose, *sections* through the crystal cell have to be constructed, each showing the contour lines of the spatial density (in electrons per cube ångström), so that by piling up such sections drawn on plates of clear plastic a vivid impression of the atoms is obtained as they float in the interior of the cell. Models of this type were first shown by Dorothy Hodgkin for the penicillin structure (cf. the remarks in Ch. 8 and 10). One of the many relations of duality between physical and Fourier space is that sectioning in one space corresponds to projecting in the other. We saw above how the projected electron density was obtained from the intensities lying in a cross section through Fourier space; we now obtain the sections through the crystal cell from Fourier series having as coefficients certain sums of the F-values normal to the plane of sectioning. These sums can be formed only if the phases or signs are correctly attached to the observed |F|-values.

7.4. Methods of Phase Determination

We have, so far, assumed that the phase of F_h is known from a preceding algebraic placement of the atoms. This, however, is not always necessary.

If the crystal structure has a centre of symmetry, this can be taken as the origin in crystal space, and, as is easily seen from the expression (5) or (6) of the structure amplitude, F_h will be a *real* quantity, so that only a + or — sign remains undetermined after observing the intensity $|F_h|^2$. The general phase problem is thus greatly reduced, and more centro-symmetric structures have been determined than corresponds to their natural occurrence. One could imagine that it might be possible with the help of computers to synthesize the Fourier series with all possible combinations of signs, and pick out thereafter the most attractive result. But even if only 30 Fourier terms are used, the different combinations of sign will number about 2^{30}, which is of the order of 10^9. Thus, if only one second were allowed for the inspection of each synthesis, it would take about 35 years to get through with it!

A more effective way is the '*heavy atom technique*'. The atomic factors of heavy atoms reach out to higher orders than those of light atoms; this is due to the high concentration of scattering power in the small inner electrons shells of the heavy atoms. By using only high-order reflections it is therefore often possible to locate the heavy atoms alone, of which there are usually few in the cell. From the known positions the phase of the heavy atom contribution to each order of diffraction can be calculated, and with it that part of $|F_{\mathrm{h}}|$ which is due to them. If the observed $|F_{\mathrm{h}}|$ is greater than this value, the likelihood is that the light atom contributions are additive, if it is smaller, they must be subtractive, and that fixes the phase. It is often possible to compare crystals which have essentially the same structure (isomorphous crystals) but contain heavy atoms of different weights. The difference of F-value produced by such changes then show clearly whether the phase to be attributed to a particular $|F_{\mathrm{h}}|_{obs}$ is that produced by the heavy atoms alone, or not.

The classical example for the application of this kind of argument is J. M. Robertson's determination of the phthallocyanine structures in 1935/36. This case is particularly favourable because it is possible to compare the diffracted intensities of the purely organic molecule $C_{32}N_8H_{18}$ to those obtained after insertion of a nickel or platinum atom at the centre of the organic group. The heavy atom contribution outweighs that of the other part in determining the phases and the Fourier synthesis can proceed without any previous model. Even the assumption of the existence of atoms need not be made, since no atomic factor is used; the well rounded-off balls of high electron density appear in the course of the synthesis, and the existence of atoms is thus shown on purely optical grounds.

A similar statement can be made for the most complex structure so far analysed, namely myoglobin whose molecule contains some 2500 light atoms; here various heavy atom groups can be attached to the surface of this enormous globular molecule without appreciably disturbing either its internal constitution or the crystal structure it forms by interaction with adjacent molecules. It is clear that in a case of such complication any attempt at an 'algebraic' structure determination would be hopeless.

While the method of heavy atom substitution has been the most efficient means of supplying the signs or phases required for a Fourier synthesis, other methods have been helpful and are being improved continually. The scattering power of an atom undergoes a change when the wave-length of the incident radiation is shifted across an absorption edge of an atom. This is not a very large change, but Bijvoet showed that with accurate intensity measurements it can be traced and put to the same use as the substitution of a heavy or light atom. A different kind of phase relation near the absorption edge of an atom has been used by Peerdeman, working with Bijvoet, to distinguish between the diffraction by a right-handed and a left-handed structure. In this case measurements are made at only one wave-length, for which one of the atoms has a strong absorption. This is reflected in an imaginary part of the atomic factor of this atom which is always positive. If a right- and a left-handed structure are compared, the geometrical structure factor will change the sign of its phase, since the transition from one structure to the other is made by an inversion, i.e. replacing $+ (x, y, z)$ by $- (x, y, z)$. The addition of the always positive absorption part of the sensitive atomic factor will increase the $|F_h|^2$ in one case and decrease it in the other. A comparison of the intensities from a d- and an l-crystal thus allows to tell which of these is built with right-handed screw axes. This important and rather unexpected method was applied to strychnine by Peerdeman. Instead of using two crystals, the author compared the intensities of several (h, k, l) reflections to those on the back faces, $(\bar{h}, \bar{k}, \bar{l})$; this serves the same purpose since only the product $\mathbf{h}\cdot\mathbf{x}$ appears in the geometrical structure factor.

7.5. The Patterson Method

What happens if the measured $|F_h|^2$ themselves are used as coefficients of a Fourier series? The answer was given in 1934 by A. L. Patterson: the summed series represents the '*convolution*' or '*fold*' of the electron density distribution in the crystal.

To explain this term let us assume that the base of the crystal contains point atoms of masses m^s at positions $\mathbf{x}^s$. We can then draw all the vectors connecting one atom with any other one, i.e. $\mathbf{x}^{ss'} = \mathbf{x}^s - \mathbf{x}^{s'}$, from one origin, letting each end in a weight which is the product mass $m^{ss'} = m^s \cdot m^{s'}$. If the same distance occurs between several atoms, the total weight at the end of this vector will be the sum of the individual product masses. It is easily seen that all vectors will lie within a cell equal to that of the eight crystal cells which have the origin in common. We call the space in which we perform this construction Patterson space, and the distribution of product masses in it the self-convolution or fold of the mass distribution in the crystal cell.

If instead of condensed masses we have a density function $\rho(\mathbf{x})$ in crystal space, the corresponding fold is a continuous function $P(\mathbf{X})$ which is called the Patterson function. Its significance is that it indicates for every vectorial distance $\mathbf{X}$ in Patterson space what total product density will be picked up in crystal space if we let a vector $\mathbf{X}$ roam over all points of the crystal cell, that is,

$$P(\mathbf{X}) = \int \rho(\mathbf{x})\rho(\mathbf{x} + \mathbf{X})dv_x. \tag{8}$$

The origin of Patterson space carries the product mass

$$\Sigma(m^s)^2 \quad \text{or} \quad \int(\rho(\mathbf{x}))^2 dv_x,$$

as the case may be.

If the same construction is continued beyond the confines of one cell for the entire crystal, then the product-mass distribution in Patterson space will be periodic with the same cell as the crystal. For to every pair of masses lying at x^s and $x^{s'}$ in the same cell there exists a pair lying in different cells, so that their relative distance is greater than that of the other pair by a lattice vector x_l of the crystal lattice. This periodic product-mass distribution, appropriately normalized so as not to become infinite, is the self-convolution of the crystal mass distribution; as such it contains the desired information folded away in a multiply superimposed fashion.

The great virtue of the Patterson function is that it can be constructed by Fourier summation with the real, positive, observed values $|F_h|^2$ as coefficients. Therefore also projections and sections can easily be calculated in Patterson space, in contrast to crystal space. Patterson maps, i.e. two-dimensional representations of the projected product mass distribution by means of contour lines, are thus really an alternative representation of the observational data. As such they do not help solve the phase problem, but they change it to a geometrical and often more appealing form, namely to the problem of unfolding the folded distribution.

Much thought has been spent on the problem in this changed form and great progress has been made in its clear perception and in practical methods of unfolding, especially by M. Buerger (see next section).

7.6. The Mathematical and Instrumental Approach to Structure Determination

a. *Discussion of the problem.* Imagine the structure to be known from some source, so that the correct density $\rho(\mathbf{x})$ is known. By means of a

Fourier analysis we can deduce therefrom the coefficients F_h, including signs or phases. The $|F_h|^2$ check with the values obtained from the diffracted intensities. Now imagine the signs or phases to be altered in an entirely arbitrary way. This does not change the agreement with the observed values, but it destroys all the relations between the terms of the Fourier series which, with the correct signs, led to the building-up of very high values of the electron density in the central parts of the atoms. In short, instead of obtaining maps with layer lines showing well rounded and separated atoms, like a dish of fried eggs, we obtain from the changed series a disorganized picture corresponding to scrambled eggs. And yet, the reliability index is unchanged, and would remain so, even if more diffraction data were added.

This discussion shows that there is more to a structure determination than the mere conversion of ever so many intensity data from Fourier space to crystal space. It shows that in the actual procedure of structure determination we add essential information of a non-optical kind, often without being fully aware of its importance. Such information is the *existence* of atoms; their individual size, number and distribution of electrons as expressed by the atomic factor; their kind and number according to the chemical formula. A structure analysis would be rightly rejected if it did not show well rounded atomic peaks, correct electron density distributions in the light and heavy atoms, and acceptable values of bond lengths and angles. In fact, therefore, the criterion for accepting a structure as correct is not so much that the observed intensities of diffraction are well accounted for, but rather that this is the case within the limitations of a whole set of conditions drawn from experience.

Any attempt at making structure analysis a straightforward mathematical procedure which could finally be left entirely to computers has to incorporate at least some of the above restrictions of the non-optical type. The most usual one is the assumption that the observed intensities can be rendered through an algebraic structure determination based on the use of known atomic factors.

b. *Bond distances and bond angles.* The notion that atoms in crystals could be thought of as spheres of certain diameters which are packed so as to touch one another was elaborated by Barlow and Pope before the days of X-ray diffraction. Lothar Meyer's significant curve of the distribution of atomic volumes over the periodic system made such an assumption plausible. With the rapidly accumulating precise data on atomic distances in crystals attempts to assign fixed radii to atoms could be followed up in greater detail, and this was done in various places. W. L. Bragg was the first to use these radii for the construction of trial structures with which to start the trial and error course of determination. V. M. Goldschmidt showed that the 'radius' will vary with the state of ionization and the number of nearest neighbours, the coordination number, of the atom. Finally, some years after the advent of wave-mechanics in 1926, Linus Pauling deduced radii from the approximation of wave-mechanical calculations.

With the wealth of data on atomic distances and bond directions between atoms now established, the structure analyst of today has a fair idea of what values to expect in a particular case, and he generally becomes suspicious of a structure proposal if it leads to deviations of more than a few tenths of an Ångström from the expected distances, or to unusual bond angles or coordination configurations.

It would be an enormous help if this knowledge could be incorporated in some form as a non-optical condition at the beginning, instead of after the completion of a Fourier synthesis, but so far all attempts to achieve this have failed. The only form in which this condition can be made useful from the beginning of the analysis is in the construction of a model of what the molecule might eventually look like, and seeing how this can be fitted into the available space in the cell. This gives an initial structure for the trial and error process which has a chance of being not too far off the truth.

c. *Positiveness.* The electron density is an essentially positive function throughout the cell, and in the case of centrosymmetric structures this leads to some restrictions on the signs of the Fourier coefficients. The first to find how to use the positiveness were D. Harker and J. S. Kasper in 1948. They showed that this property led to relations such as

$$F_H^2 \leqq \tfrac{1}{2} F_O(F_O+F_{2H}) \tag{8a}$$

$$(F_H+F_{H'})^2 \leqq (F_O+F_{H+H'})(F_O+F_{H-H'}) \tag{8b}$$

$$(F_H-F_{H'})^2 \leqq (F_O-F_{H-H'})(F_O-F_{H-H'}) \tag{8c}$$

(H stands for h, k, l; H+H′ for h+h′, k+k′, 1+1′, and 0 for 0, 0, 0.) Now F_O is known from the chemical formula and the density, since it is the total number N of electrons in the cell. (In the forward direction (000) all electrons scatter in phase, without any destructive interference.) The first of the inequalities establishes a restrictive connection between two Fourier coefficients, namely any F_H and F_{2H}.

This may serve to determine the sign of F_{2H}. Let for instance $|F_H| = 0.8\ N$, $|F_{2H}| = 0.45\ N$. Then allowing either sign for F_{2H} one gets from (8a)

$$0.64\ N^2 \leqq \tfrac{1}{2}N\ (N \pm 0.45\ N)$$

or

$$0.64 \leqq \tfrac{1}{2}\ (1 \pm 0.45)$$

The two values which the right hand side can take are 0.725 and 0.275, of which only the first, which corresponds to the + sign of F_{2H}, is possible for the inequality to hold.

The two lower inequalities (b) and (c) involve four Fourier coefficients besides Fo, and in order to be used the signs of at least two coefficients should be known. It will be noticed that inequality (a) follows from (b) when H is put equal to H′. Many special inequalities can be formed with regard to the symmetry of various space groups and they have proved extremely useful in opening up a way to structures to which other approaches had been unsuccessful, like Harker & Kasper's original object, dekaborane $B_{10}H_{14}$. Their applicability is restricted to the large F-values; for the smaller F they are indecisive.

Mathematically the condition that a Fourier series represent a function which is everywhere positive can be expressed as the non-negativity of a series of determinants of increasing order formed from the Fourier coefficients. These more general inequalities include as the simplest cases the ones discussed above, which seem to be the most powerful ones. Much interesting work has been done on the general lines by Karle & Hauptman, McGillavry, Goedkoop, Bertaut, von Eller and others, but it can not be said to have increased the applicability of inequalities for practical purposes.

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There are three further developments which have proved their value for structure analysis. One is the computational aid obtainable nowadays by means of electronic digital computers. A great many lengthy calculations, which it would take years to perform by hand machines, have been programmed for several types of machines, and this service is increasingly used. From the administrative point of view it requires getting used to the idea that the 'desk work' involves expense like the experimental work for which nobody would doubt it. If the man-hour work performed by the machine is converted into salaries, the savings would become apparent, but of course the fact remains that with machine work projects of a complexity can be undertaken which would never be tackled without it.

Of the analogue computers Ray Pepinsky's XRAC (for X-ray analogue computer) is by far the most important. In this ingenious electronic device the magnitudes of a large number of |F|-values are set on dials and they can enter the Fourier synthesis with a positive or negative sign according to the flipping of a switch. The machine then performs instantaneously not only the summation of the two-dimensional Fourier series with these coefficients, but also displays the result in the accustomed form of contour lines on a television screen from where they can be photographed if desired. Besides, the magnification can be varied instantaneously, so that either several cells of the projection are displayed, or one only, or a part of it. With this machine it is possible to try out on the spot whether the change of sign of a Fourier coefficient makes the electron projection more acceptable or less. As a criterion for this, a low background between well separated atoms is usually taken.

A counterpart of this machine is one for Fourier analysis, called SFAC (for Structure factor analogue computer) in which the Fourier coefficients or structure amplitudes are instantaneously calculated after atomic coordinates and atomic factors have been set on dials.

A second important advance in the technique of structure determination is to be seen in Martin Buerger's profound studies of unfolding or deconvoluting of the Patterson function. This function was obtained by searching the cell for vectors leading from one atom to another and then shifting these vectors to the origin of Patterson space and labelling them with the product mass. Therefore, if we imagine one of the atoms to be shifted to the origin of Patterson space, the relative vectors from it to the other atoms of the base will be among the vectors in Patterson space. With Z atoms forming the base, there are $Z-1$ such relative vectors, whereas the Patterson function contains $Z(Z-1)$ peaks because any one of the Z atoms has to be shifted to the origin. (Many of these vectors may coincide, and this makes the unfolding harder.) Buerger succeeded in constructing several 'image seeking functions' with which to find those Patterson peaks which belong together and form an image of the base. His theory is a great step in the direction of systematic unfolding and has been successfully applied in a large number of structure determinations; it presents no automatic solution because it requires attention and ingenuity in its application, especially to the unfolding of projections to which it has been mainly applied.

Finally a few words should be said about the statistical approach to the problem of structure analysis. Since the amount of data for an algebraic determination often exceeds the number of unknowns considerably, one can afford to use the data is a statistical way rather than as single and independent pieces of evidence. A. J. C. Wilson made important contributions by showing how symmetry elements of the structure, including the directly not observable inversion centres, could be deduced from suitable averages of $|F|^2$-values. In a series of papers beginning in 1953 J. Karle and H. Hauptman have developed a method of determining probable sign relations between Fourier coefficients from 'joint probabilities' for the simultaneous appearance of certain sums of $|F|^2$-values. This method has been successfully applied to a number of structure determinations and comes closest to the ideal of a fully automatic derivation of a structure.

Next Section