

A Brief History of Fourier Methods in Crystal-structure Determination*

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Abstract

Fourier methods for the determination of crystal structures were first suggested by Bragg in 1929, and were then successfully used by Beevers and Lipson for determining the structure of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in 1934. It was necessary for methods of summation to be devised, and after some experimentation the Beevers–Lipson strips became established as the best device for the work. They enabled increasingly complicated structures to be derived, but ultimately more elaborate and automatic devices based on digital computers had to be introduced. At the same time, isomorphous-replacement, heavy-atom and direct methods were also developed and these have enabled structures of enormous complexity to be successfully determined.

1. Early Ideas and Their Application to $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

In the early 1930s we were both physics research students at Liverpool. One of the staff, R. W. Roberts, was anxious to extend the research work of the department and asked us to try our hands at crystal-structure determination, then in its early days. He knew nothing about the subject and neither did we, but we soon learned to take oscillation photographs of single crystals; we were, however, at a loss about what to do with them.

As a result we asked for help from W. L. Bragg at Manchester, only 40 miles away. He was very encouraging, and introduced us to his staff, W. H. Taylor in particular. Taylor put us on the right lines and we soon worked out the two tetragonal crystal structures $\text{BeSO}_4 \cdot 4\text{H}_2\text{O}$ and $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$. These, we thought in our enthusiasm, were too easy, and we decided to try something more difficult, say copper sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$), which was triclinic.

In fact, this project was too ambitious, as the crystal involved 33 parameters. By a stroke of luck, however, we recognized regularities in the intensities that allowed placement of the Cu and S atoms, but since little was then known about water of crystallization, and since five was an unusual number of water molecules, we could not make any further progress by packing considerations.

One of us (C.A.B.) then suggested trying the Fourier method that Bragg (1929) had recently advocated. Bragg had tested the method on a known structure, diopside, but no one had used it for an unknown structure. There were, however, two difficulties: we

* Dedicated to Dr A. McL. Mathieson on the occasion of his 65th birthday.

did not have quantitative measurements and we had no experience in summing two-dimensional Fourier series, although from our mathematics lectures we had gained considerable experience in summing one-dimensional series. Two-dimensional work with about 90 terms was a different matter!

The Manchester department came to our rescue for the first problem: we were allowed to use one of their historic ionization spectrometers and several weeks were spent making measurements. For economy we omitted the weaker reflexions. For the calculations, we had to devise our own methods, and this included using long strips of paper and carrying out the summations, which required a period of about a month.

As it was necessary to know the signs of the F values, we used the regularities mentioned above which were, first, that nearly all the strong reflexions had $h+k$ even and, secondly, that reflexions with $k = 3, 4, 7$ and 10 were, on the whole, stronger than the others. These regularities suggested, although they did not prove, that the Cu atoms lay on a C-face-centred lattice at points $(0, 0, 0)$ and $(\frac{1}{2}, \frac{1}{2}, 0)$, and that the parameters of the S atoms were 0.00 and 0.29 ; 0.29 multiplied by $3, 4, 7$ or 10 gives close to a whole number. We then assumed that the signs of the F values were those given by the Cu and S atoms, in spite of the large number of oxygen atoms.

The results exceeded our wildest hopes. The atoms were clearly defined, not perfectly round, but clear nevertheless. There was one small peak, which we called a ghost and which we could not account for, but we later found that it resulted from omitting the weaker reflexions. The Fourier synthesis is shown in Fig. 1.

2. Development of the Fourier Strips

For the calculations, we began very tentatively using only twenty of the lowest order reflexions and working out at first only a limited area of projection. The calculations were very tedious using the straightforward methods. In a structure with a centre of symmetry the quantities to be added together are of the type $F_{hk} \cos(hx + ky)$, where x and y are coordinates in angular measure, h and k are the Miller indices of the planes, and F_{hk} is the experimental amplitude of the wave reflected by the (hk) plane. In the case of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ there are about 90 planes involved in the c -axis projection. If the x and y axes are divided into, say, 60 parts, there are $60 \times 30 = 1800$ points in the cell at which the summation is required. The immediately obvious procedure is to work out $hx + ky$, find the cosine, multiply by the appropriate F_{hk} and add up all the 90 values at each of the 1800 points. Such long additions are exceedingly tedious, especially when carried out mentally, and there was naturally a strong motive to shorten the additions. On the morning of 4 December 1933 one of us (H.L.) suggested that the computation would be made very much easier by expanding $\cos(hx + ky)$ into the well-known form $\cos hx \cos ky - \sin hx \sin ky$. Although this would seem at first glimpse to make matters worse, in that we now have two terms to add instead of one, it did in fact make the computation a great deal easier. For each value of h we could sum all the $F_{hk} \cos ky$ for all values of y , and later use this total as the coefficient for the $\cos hx$ values. For each value of h the summations only involve $2k$ numbers instead of a number of the order of h times k . Furthermore, the symmetry of $\cos ky$ or $\cos hx$ is much higher than the symmetry of $\cos(hx + ky)$ as these functions always have their symmetry points at the value hx or ky equal to $0, 90^\circ$ or 180° . By sub-totalling even and odd values of h and k , the range of x and y can always be reduced to only 90° ; by adding and subtracting the subtotals the range

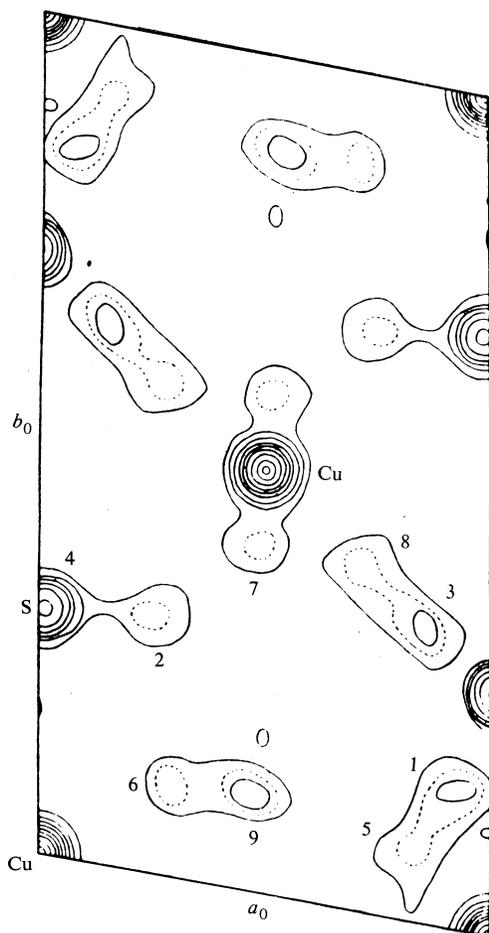


Fig. 1. Fourier synthesis for copper sulfate pentahydrate. [From Lipson and Cochran (1966), p. 207.]

can be extended to 180° . The $F_{hk} \cos ky$ totals are then used as the coefficients for the $\cos hx$ totalling for each value x . Again the number of additions is small and symmetries can and must be used. A good deal of simple book-keeping is involved in the calculations, but this is well worth while in the interests of keeping the additions small. An entirely similar process is required for the sine term summations, and a final subtraction and addition of these terms for each value of (xy) will extend the range of one of the coordinates to the full value of 360° .

The values of $A \cos hx$ and $B \sin hx$ can be printed out in tabular form and then cut into strips, so that the Fourier summation is simply the selection of appropriate strips which are laid down underneath each other and then added to give the various subtotals. Separate tables were used for each value of h , and each table has the value of x across a row and the value of A down a column. The table for $h = 1$ contains all the basic columns of numbers required. To obtain the tables for higher values of h , all that is required is a re-shuffling of the columns. Of course some of the columns have to be repeated many times. The details of ranges and intervals were dealt with in our early papers, starting with a note in the *Philosophical Magazine* fifty years ago (Beever and Lipson 1934*a*; see also Beever and Lipson 1934*b* and Lipson and Beever 1936). For an example of the method, the reader is referred to Lipson and Cochran (1966).

We made the first set of tables from strips actually used in our research, filling in the gaps when the opportunity arose. [We still have an incomplete set written by one of us (H.L.) with some help from his mother.] Several people asked to be allowed to copy them and we therefore explored the possibility of having them printed; Professor Bragg was extremely encouraging and arranged for a loan of £200—then a large sum of money—from the University. The printed strips soon became popular and it was not long before the University loan was completely repaid, leaving a small profit for us.

A second edition was conceived and designed by one of us (C.A.B.) at the University of Edinburgh. These had an interval of division of 3° , thus extending the range of application, and also included extra strips in case three-figure accuracy was required. The strips sold all over the world and were used over a period of more than 20 years before they became obsolescent.

3. Heavy-atom and Isomorphous-replacement Methods

The evaluation of Fourier synthesis maps is, as has been shown, entirely dependent upon a knowledge of the signs of the F values, or indeed in the more general case of their phase values. When a projection does not have a centre of symmetry at the origin the summation involves terms of the form $A \cos(hx + ky) + B \sin(hx + ky)$, where A and B are different parts of the structure factor. Here A is the 'real' part and B the 'imaginary' part, so that $A^2 + B^2 = F^2$. Only the total F value can be deduced from the observed X-ray intensities of reflection; the 'phase problem' is the distribution of the F value between the A and the B terms. In the days before anomalous scattering was understood there were no direct means of knowing the phase angle. If there is a centre of symmetry at the origin of a projection, such as for $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, the B term is zero, and then all that is needed is the sign of the A value.

However, a heavy atom in the structure will have a predominating influence on the sign or on the phase, and if its position in the cell can be deduced it is possible to work out its contribution to the sign or phase, and hence the likely signs or phases of the total F value. These will then give a Fourier map which will not only yield the heavy-atom positions, but also some indication of the lighter atom positions. If these indications are used with care a series of approximations will give the complete structure. A centrosymmetrical projection is likely to give quicker results. In any case, a complete structure determination with two-dimensional maps in several projections is likely to need many Fourier calculations, and the Fourier strips proved most useful in carrying out these calculations.

Isomorphous-replacement methods are an even more certain procedure in attaining a solution to an unknown structure by Fourier methods. There are many cases, especially in the field of inorganic chemistry, where a crystal is a member of a whole series of isomorphs, i.e. of compounds having an almost identical structure but with one atom different. Of course, a change of atom type will cause some change in size or in a re-arrangement of the atoms of the structure. However, the basic structure arrangement may be unchanged, and this can of course be seen in the relevant crystallography and in the general similarity of the X-ray reflexions. The main change, in such cases, is due to the alteration in the scattering factor of the atom concerned, and the change in the F values of the reflexions will give a clear

indication of the position of this atom in the unit cell. The position of the atom will in turn give the sign or phase of the F values. A particularly easy case is when the atom replaced is on a centre of symmetry at the origin. If the F value increases when a change is made from the lighter atom to the heavier, then the F is positive. A difficulty in this method is that a change of atom in a structure also produces a change in the absorption coefficient for the X rays, and this must be taken into account when reducing the observed intensities to F values. When using copper radiation a particularly good substitution is to go from K to Rb in the isomorphic substitutions; although this gives a useful change in scattering factor, it produces practically no change in absorption, as can be seen from the atomic-absorption tables.

4. Competition with Robertson's Method

The Fourier strip method developed had no serious competitor. Robertson (1936) made use of a much slower method, involving eventually one $h = 1$ table, from which values for other values of h would be selected by appropriate stencils. These tables had a three-figure accuracy, opposed to our two figures, but since in those days (and even now?) it was not possible to measure F values to better than a few per cent, this higher accuracy was not needed.

Robertson's method involved recording the numbers that were shown by the stencils, and then adding them with a calculator. With our method, the strips were placed in sequence and added mentally, and although not everyone liked this mental arithmetic, our method soon became generally preferred. We were pleased to find on a visit to Robertson's laboratory in Glasgow that his students were using our methods in preference to his.

5. Direct Methods

Heavy-atom and isomorphous-replacement methods are all very well, but they depend on the ability to make appropriate compounds. It had, however, always been hoped that it might be possible to deduce a structure directly from its diffraction pattern; after all the eye can do this by receiving the diffraction pattern from an object and forming an image.

The reason for the difference, however, is that the eye 'knows' the relative phases of the various parts of the diffraction pattern, whereas in X-ray diffraction patterns this information is lost. W. L. Bragg maintained that this made direct structure determination impossible. There was great excitement therefore when Harker and Kasper (1948) produced a crystal structure ($B_{10}H_{14}$) purely from mathematical considerations!

Once this had been done, others were encouraged to try further ideas. It was soon realized that the Harker and Kasper method was not purely mathematical; it made use of the physical properties that the atomic arrangement must possess. Nevertheless, to contribute to this subject required a considerable degree of mathematical ability. Different groups took up the challenge (for example, Karle and Hauptman, Vand and Pepinsky, Cochran and Woolfson) and extended the methods to more and more complicated structures. These methods filled an important gap. They work best when all the atoms are about equal in size, and so organic compounds containing carbon, nitrogen and oxygen were particularly suitable for investigation.

The most important name in the subject now is that of Woolfson. Germain and Woolfson (1968) described a method later known as MULTAN, which can be used

in three dimensions and for non-centrosymmetric structures, and which has had an enormous impact on problems of moderate (by protein standards!) complexity. For example, the structure of gramicidin (Hull *et al.* 1978), involving over 300 parameters, has been solved by this method; structures with over 400 parameters have also been solved, and 600 parameters does not seem impossible.

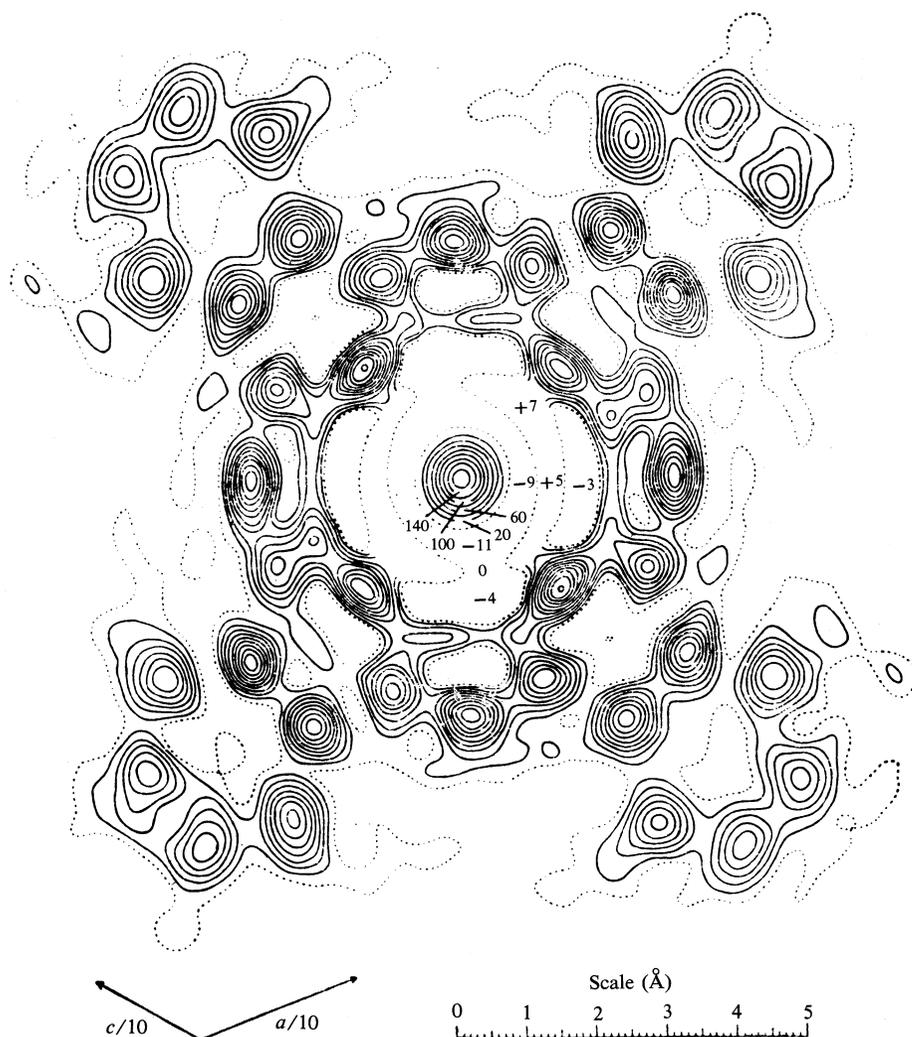


Fig. 2. Fourier synthesis for phthalocyanine. [From Lipson and Cochran (1966), p. 205.]

6. Highlights

The Fourier method opened the floodgates for further work. At first the method was used mainly for refining structures—finding the most accurate coordinates for known structures—but it soon demonstrated its greater power, as exemplified by the work on copper sulfate. To find the phases of the X-ray reflexions, one could use the

heavy-atom method or the isomorphous-replacement method, and both these devices were employed extensively.

The most striking example of this work was that on phthalocyanine by Robertson and Woodward (1937). The molecule is planar and many different metal atoms can be inserted at the centre, which is a centre of symmetry in the crystal; with a metal as heavy as platinum all the phases must be zero and the structure emerges directly (see Fig. 2).

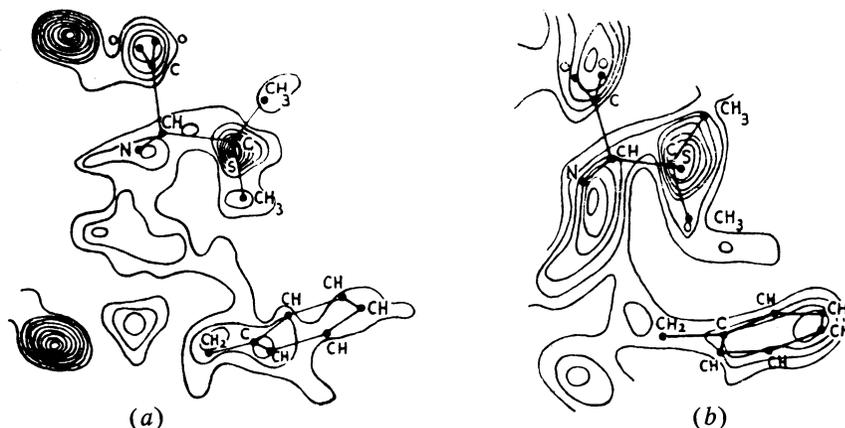


Fig. 3. Partial Fourier syntheses that led to the structure of penicillin: (a) rubidium benzyl penicillin and (b) sodium benzyl penicillin. [From Lipson and Cochran (1966), p. 217.]

During the late 1930s, most work concentrated on organic compounds, but generally the work merely verified what the chemists already knew, albeit with greater accuracy. Sooner or later, however, some new results were bound to arise and one of the first projects of this sort was the structure of penicillin (Crowfoot *et al.* 1949). Penicillin was of obvious importance clinically, but chemically it was rather strange. The chemists managed to attach monovalent atoms such as sodium, potassium and rubidium to the molecule, but unfortunately the compounds were not isomorphous; the first was monoclinic, and the others orthorhombic. The results from the isomorphous-replacement method were not easy to interpret and sodium was not heavy enough to give clear results. However, two outstanding researchers, Dorothy Hodgkin of Oxford and Charles Bunn at I.C.I. in Northwich, found enough similarity in the results (see Fig. 3) to enable the structure to be deduced. (It is now maintained by some that the chemists *had* found the structure just before the crystallographers, but certainly the race was extremely close!)

From that point on, there seemed no limit to the complexity of structures that could be determined. The proteins, involving thousands of atoms, were now open to investigation. In 1960 Kendrew and Perutz produced the detailed atomic structure of myoglobin and haemoglobin (Perutz 1963), molecules involved in the capture and transport of oxygen. Soon after, Blake *et al.* (1965) produced the structure of lysozyme. This was the first structure for an enzyme, a class of chemicals which controls the rate of reactions in the body and which is necessary for life.

All this work was made possible by the introduction of automatic recording

apparatus for the X-ray diffraction patterns and by the use of digital computers for the calculations, which made three-dimensional work commonplace. The Fourier strips were no longer needed. The main problems were of a chemical nature, for example, whether to produce either heavy-atom derivatives or isomorphous compounds. It turned out that the heavy atom need not be all that heavy relative to the rest of the atoms, as many of us had feared, even with thousands of other atoms present. (Perutz has described to us his feelings on seeing by eye that the changes in intensities could be detected in haemoglobin photographs when only a few Hg atoms are introduced into the molecule.)

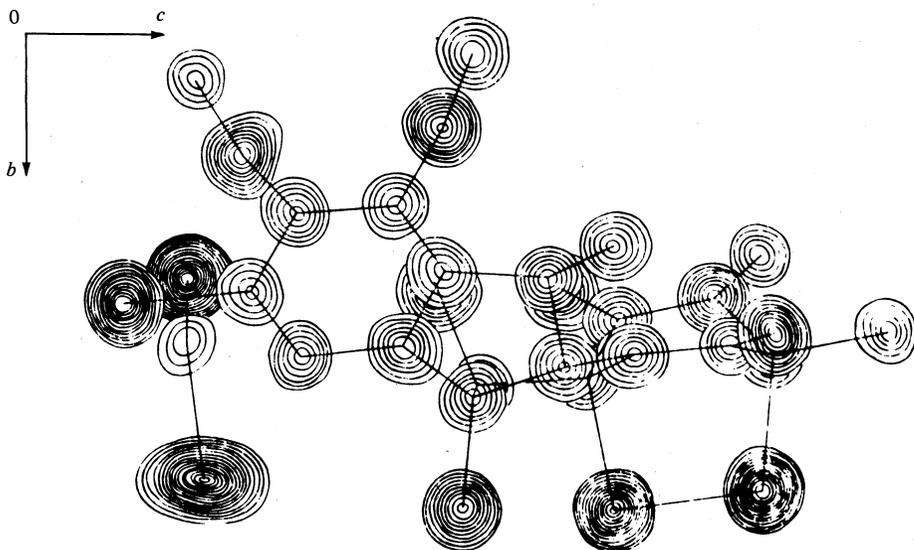


Fig. 4. Fourier synthesis for sporidesmin. [From Fridrichsons and Mathieson (1965).]

In conclusion, we can only briefly mention some of the other important structures that have been worked out—vitamin B₁₂, cholesterol and, in particular, insulin, with which the name of Hodgkin will always be associated (see Dodson *et al.* 1981). Australia was not left behind, as shown by the work of Mathieson on the structures of lanostenol, a constituent of wool wax (Curtis *et al.* 1952). The chemists were initially undecided between three different possibilities, and the Mathieson team was able to produce a definite answer by studying the iodine derivation C₃₂H₅₃O₂I at -150°C . From Patterson projections the precise form of the molecule was found. Another important compound was sporidesmin, a chemical responsible for facial eczema in sheep. An adduct with CH₂Br₂(C₁₈H₂₀O₆N₃S₂Cl.0.65CH₂Br₂) was studied by Fridrichsons and Mathieson (1965) and three-dimensional Patterson synthesis and Harker syntheses enabled the result shown in Fig. 4 to be derived.

Fridrichsons and Mathieson (1967) also derived the structure of gliotoxin, again at -150°C . This compound is related to sporidesmin, but the problem was made more difficult because the asymmetric unit contained two molecules of C₁₃H₁₄O₄N₂S₂. Thus 126 parameters were involved. Three-dimensional Patterson synthesis was used and the absolute configuration was also found by anomalous dispersion.

Thus, the work of Mathieson and his colleagues has been greatly informative about the chemistry of a number of natural products of Australia, and the continent has

been fortunate to have a man of his stature able to direct this work. We like to think that the methods that we devised in 1934 have been ultimately of value in leading to solutions of problems of such complexity.

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