The Direct Methods of X-ray Crystallography

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The electron density function $\rho(\mathbf{r})$ in a crystal determines its diffraction pattern, that is, both the magnitudes and phases of its x-ray diffraction maxima, and conversely. If, however, as is always the case, only magnitudes are available from the diffraction experiment, then the density function $\rho(\mathbf{r})$ cannot be recovered. If one invokes prior structural knowledge, usually that the crystal is composed of discrete atoms of known atomic numbers, then the observed magnitudes are, in general, sufficient to determine the positions of the atoms, that is, the crystal structure.

THE INTENSITIES OF A SUFFICIENT NUMBER OF X-RAY DIFFRACTION maxima determine the structure of a crystal. The available intensities usually exceed the number of parameters needed to describe the structure. From these intensities a set of numbers $|E_{\mathbf{H}}|$ can be derived, one corresponding to each intensity. However, the elucidation of the crystal structure also requires a knowledge of the complex numbers $E_{\mathbf{H}} = |E_{\mathbf{H}}| \exp(i\phi_{\mathbf{H}})$, the normalized structure factors, of which only the magnitudes $|E_{\mathbf{H}}|$ can be determined from experiment. Thus, a "phase" $\phi_{\mathbf{H}}$, unobtainable from the diffraction experiment, must be assigned to each $|E_{\mathbf{H}}|$, and the problem of determining the phases when only the magnitudes $|E_{\mathbf{H}}|$ are known is called "the phase problem." Owing to the known atomicity of crystal structures and the redundancy of observed magnitudes $|E_{\mathbf{H}}|$, the phase problem is solvable in principle.

The Phase Problem

Just as the plane may be tiled by congruent parallelograms (Fig. 1), so three-dimensional space may be tiled by congruent parallelepipeds, the vertices of which constitute a lattice. If one imagines atoms to be identically distributed in these parallelepipeds, the resulting electron density distribution $\rho(\mathbf{r})$ may be regarded as the mathematical description of a crystal structure. Clearly, $\rho(\mathbf{r})$ is a three-dimensional periodic function of the position vector $\mathbf{r}$ and may therefore be represented by the three-dimensional Fourier series:

$$\rho(\mathbf{r}) = \frac{1}{V} \sum_{\mathbf{H}} F_{\mathbf{H}} \exp(-2\pi i \mathbf{H} \cdot \mathbf{r}) \tag{1}$$

where V is the volume of the fundamental parallelepiped, the so-called unit cell of the crystal (Fig. 2), and the three components of the vector $\mathbf{H}$ range over all the integers. The Fourier coefficient $F_{\mathbf{H}}$, said to be the structure factor corresponding to the reciprocal lattice vector $\mathbf{H}$, may then be calculated in the usual way:

$$F_{\mathbf{H}} = \int_V \rho(\mathbf{r}) \exp(2\pi i \mathbf{H} \cdot \mathbf{r}) dV \tag{2}$$

where the integration is carried out over the unit cell V. Clearly, each $F_{\mathbf{H}}$ is a complex number that may be written in polar form

$$F_{\mathbf{H}} = |F_{\mathbf{H}}| \exp(i\phi_{\mathbf{H}}) \tag{3}$$

where $\phi_{\mathbf{H}}$ is the phase of the structure factor $F_{\mathbf{H}}$.

When a beam of monochromatic x-rays is incident on a crystal, the radiation is scattered in discrete directions determined by the crystal lattice and labeled by the reciprocal lattice vectors $\mathbf{H}$. Both the amplitude and phase of each scattered ray, or reflection, depend on the crystal structure. The amplitude, or intensity, of a reflection leads in a straightforward way to the magnitude $|F_{\mathbf{H}}|$ of the complex structure factor $F_{\mathbf{H}}$. However, the phases $\phi_{\mathbf{H}}$, which are also needed if one is to determine $\rho(\mathbf{r})$ from Eq. 1, are lost in the diffraction experiment. If one uses the known values of the magnitudes $|F_{\mathbf{H}}|$ but arbitrary values for the phases $\phi_{\mathbf{H}}$ in Eq. 1, then density functions $\rho(\mathbf{r})$ consistent with the observed values of the diffraction intensities are obtained. Thus, diffraction intensities alone do not determine a unique density function $\rho(\mathbf{r})$. Even if the known nonnegativity of $\rho(\mathbf{r})$ is assumed, thus greatly restricting the values of the phases (*1*, *2*), the observed diffraction intensities are, in general, still not sufficient to determine $\rho(\mathbf{r})$ uniquely. It follows that the phase problem, to determine the values of the phases $\phi_{\mathbf{H}}$ of the structure factors $F_{\mathbf{H}}$ when only the magnitudes $|F_{\mathbf{H}}|$ are given, is, in principle, unsolvable when formulated in these terms. It was this argument that led the crystallographic community, prior to 1950, to believe also that crystal structures could not, even in principle, be determined from the diffraction intensities alone. However, by invoking the prior structural knowledge that crystals consist of discrete atoms, one readily refutes this argument, as shown below.

If one replaces the real crystal, with continuous electron density $\rho(\mathbf{r})$, by an idealized one, the unit cell of which consists of N discrete, nonvibrating point atoms, then the structure factor $F_{\mathbf{H}}$ is replaced by the normalized structure factor $E_{\mathbf{H}}$ and Eqs. 3, 2, and 1 are replaced by

$$E_{\mathbf{H}} = |E_{\mathbf{H}}| \exp(i\phi_{\mathbf{H}}) \tag{4}$$

$$E_{\mathbf{H}} = \frac{1}{\sigma_2^{1/2}} \sum_{j=1}^{N} Z_j \exp(2\pi i \mathbf{H} \cdot \mathbf{r}_j) \tag{5}$$

$$\begin{aligned} \langle E_{\mathbf{H}} \exp(-2\pi i \mathbf{H} \cdot \mathbf{r}) \rangle_{\mathbf{H}} &= \frac{1}{\sigma_2^{1/2}} \langle \sum_{j=1}^{N} Z_j \exp[2\pi i \mathbf{H} \cdot (\mathbf{r}_j - \mathbf{r})] \rangle_{\mathbf{H}} \\ &= \frac{Z_j}{\sigma_2^{1/2}} \text{ if } \mathbf{r} = \mathbf{r}_j \\ &= 0 \text{ if } \mathbf{r} \neq \mathbf{r}_j \end{aligned} \tag{6}$$

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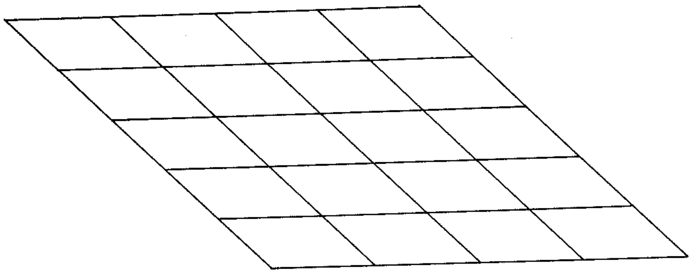

Fig. 1. Tiling the plane with congruent parallelograms.

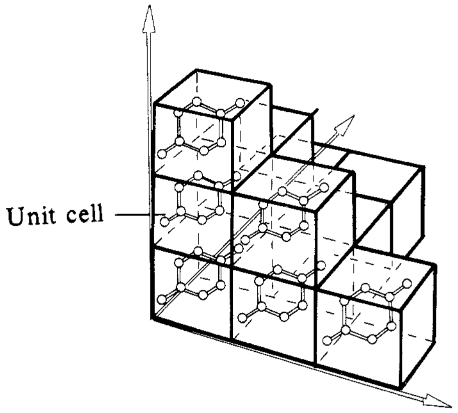

Fig. 2. A three-dimensional periodic function of position defines a crystal structure.

respectively, where Z_j is the atomic number and $\mathbf{r}_j$ is the position vector of the atom labeled j, and

$$\sigma_n = \sum_{j=1}^{N} Z_j^n,\ n = 1, 2, 3, \ldots \tag{7}$$

In practice, the magnitudes $|E_\mathbf{H}|$ of the normalized structure factors $E_\mathbf{H}$ are obtainable (at least approximately) from the observed magnitudes $|F_\mathbf{H}|$, while the phases $\phi_\mathbf{H}$, as defined by Eqs. 4 and 5, cannot be determined experimentally. Since one now requires only the $3N$ components of the N position vectors $\mathbf{r}_j$ rather than the much more complicated electron density function $\rho(\mathbf{r})$, it turns out that, in general, the known magnitudes are more than sufficient. This is most readily seen if we equate the magnitudes of both sides of Eq. 5, thus eliminating the unknown phases $\phi_\mathbf{H}$, in order to obtain

$$|E_\mathbf{H}| = 1/\sigma_2^{1/2} \left| \sum_{j=1}^{N} Z_j \exp(2\pi i \mathbf{H}\cdot\mathbf{r}_j) \right| \tag{8}$$

a system of equations in which the only unknowns are the $3N$ components of the position vectors $\mathbf{r}_j$. Since the number of Eq. 8, equal to the number of reciprocal lattice vectors $\mathbf{H}$ for which the magnitudes $|E_\mathbf{H}|$ are observed, usually exceeds the number of unknowns, $3N$, by far, the system in Eq. 8 is redundant. Thus the phase problem is, in principle, solvable when reformulated in terms of fixed point atoms, as reference to Eq. 5 shows.

The system of Eq. 5 implies the existence of relationships among the normalized structure factors $E_\mathbf{H}$ since the (relatively few) unknown position vectors $\mathbf{r}_j$ may, at least in principle, be eliminated. By the term "direct methods" is meant that class of methods that exploits relationships among the normalized structure factors in order to go directly from the observed magnitudes $|E|$ to the needed phases ϕ.

The Structure Invariants

Equation 6 implies that the normalized structure factors $E_\mathbf{H}$ determine the crystal structure. However, Eq. 5 does not imply that, conversely, the crystal structure determines the values of the normalized structure factors $E_\mathbf{H}$ since the position vectors $\mathbf{r}_j$ depend not only on the structure but on the choice of origin as well. It turns out, nevertheless, that the magnitudes $|E_\mathbf{H}|$ of the normalized structure factors are in fact uniquely determined by the crystal structure and are independent of the choice of origin, but that the values of the phases $\phi_\mathbf{H}$ depend also on the choice of origin. Although the values of the individual phases depend on the structure and the choice of origin, there exist certain linear combinations of the phases, the so-called structure invariants, whose values are determined by the structure alone and are independent of the choice of origin.

If the origin of coordinates is shifted to a new point having position vector $\mathbf{r}_0$ with respect to the old origin, then, from the definition (Eq. 5) of $E_\mathbf{H}$, it follows readily that the phase $\phi_\mathbf{H}$ of the normalized structure factor $E_\mathbf{H}$ with respect to the old origin is replaced by the new phase $\phi'_\mathbf{H}$ with respect to the new origin given by

$$\phi'_\mathbf{H} = \phi_\mathbf{H} - 2\pi\mathbf{H}\cdot\mathbf{r}_0 \tag{9}$$

Equation 9 implies that the linear combination of three phases

$$\psi_3 = \phi_\mathbf{H} + \phi_\mathbf{K} + \phi_\mathbf{L} \tag{10}$$

is a structure invariant (triplet) provided that

$$\mathbf{H} + \mathbf{K} + \mathbf{L} = 0 \tag{11}$$

the linear combination of four phases

$$\psi_4 = \phi_\mathbf{H} + \phi_\mathbf{K} + \phi_\mathbf{L} + \phi_\mathbf{M} \tag{12}$$

is a structure invariant (quartet) provided that

$$\mathbf{H} + \mathbf{K} + \mathbf{L} + \mathbf{M} = 0 \tag{13}$$

and so on.

Since the values of the individual phases depend not only on the structure but on the choice of origin, it follows that magnitudes $|E|$ alone cannot determine unique values of the individual phases. It is clear that magnitudes $|E|$ alone determine only the values of the structure invariants (and not even uniquely at that, because of the enantiomorph problem, as clarified below) and only then, after suitable specification of the origin (and enantiomorph when necessary), may the individual phases be determined.

The theory of the structure invariants leads directly to recipes for origin specification called for by the techniques of direct methods. For example, when no crystallographic element of symmetry is present (space group $P1$), the rule states simply that the values of any three phases

$$\phi_{h_1k_1\ell_1},\ \phi_{h_2k_2\ell_2},\ \phi_{h_3k_3\ell_3}$$

where the determinant

$$\begin{vmatrix} h_1k_1\ell_1 \\ h_2k_2\ell_2 \\ h_3k_3\ell_3 \end{vmatrix} = \pm 1$$

are to be specified arbitrarily, thus fixing the origin uniquely.

The Fundamental Principle of Direct Methods

It is known that the values of a sufficiently extensive set of cosine invariants (the cosines of the structure invariants) lead unambiguously to the values of the individual phases (*3*). Magnitudes $|E|$ are capable of yielding estimates of the cosine invariants only or, equivalently, the magnitudes of the structure invariants; the signs of the structure invariants are ambiguous because the two enantiomorphous structures (related to each other by reflection through a point) that are permitted by the observed magnitudes $|E|$ correspond to two values of each structure invariant differing only in sign. However, once the enantiomorph has been selected by specifying arbitrarily the sign of a particular enantiomorph-sensitive structure invariant (that is, one different from 0 or π), then the magnitudes $|E|$ determine both signs and magnitudes of the structure invariants consistent with the chosen enantiomorph. Thus, for fixed enantiomorph, the observed magnitudes $|E|$ determine unique values for the structure invariants; the latter, in turn, as certain well-defined linear combinations of the phases, lead to unique values of the individual phases. In short, the structure invariants serve to link the observed magnitudes $|E|$ with the desired phases ϕ (the fundamental principle of direct methods). It is this property of the structure invariants that accounts for their importance and justifies the stress placed on them here.

The Neighborhood Principle

It has long been known that, for fixed enantiomorph, the value of any structure invariant ψ is, in general, uniquely determined by the magnitudes $|E|$ of the normalized structure factors. Recently it has become clear that, for fixed enantiomorph, there corresponds to ψ one or more small sets of magnitudes $|E|$, the neighborhoods of ψ, on which, in favorable cases, the value of ψ most sensitively depends; that is to say that, in favorable cases, ψ is primarily determined by the values of $|E|$ in any of its neighborhoods and is relatively independent of the values of the great bulk of remaining magnitudes. The conditional probability distribution of ψ, assuming as known the magnitudes $|E|$ in any of its neighborhoods, yields an estimate for ψ that is particularly good in the favorable case in which the variance of the distribution happens to be small (*4*, *5*) (the neighborhood principle).

The first neighborhood of the triplet ψ_3 (Eq. 10) consists of the three magnitudes

$$|E_{\mathbf{H}}|, |E_{\mathbf{K}}|, |E_{\mathbf{L}}| \tag{14}$$

The first neighborhood of the quartet ψ_4 (Eq. 12) consists of the four magnitudes

$$|E_{\mathbf{H}}|, |E_{\mathbf{K}}|, |E_{\mathbf{L}}|, |E_{\mathbf{M}}| \tag{15}$$

The second neighborhood of the quartet consists of the four magnitudes (magnitude set 15) plus the three additional magnitudes

$$|E_{\mathbf{H+K}}|, |E_{\mathbf{K+L}}|, |E_{\mathbf{L+H}}| \tag{16}$$

that is, seven magnitudes $|E|$ in all (*5*).

The neighborhoods of all the structure invariants are now known.

The Solution Strategy

One starts (*6*) with the system of Eq. 5. By equating real and imaginary parts of Eq. 5, one obtains two equations for each reciprocal lattice vector **H**. The magnitudes $|E_{\mathbf{H}}|$ and the atomic numbers Z_j are presumed to be known. The unknowns are the atomic position vectors $\mathbf{r}_j$ and the phases $\phi_{\mathbf{H}}$. Owing to the redundancy of the system (Eq. 5), one naturally invokes probabilistic techniques to eliminate the unknown position vectors $\mathbf{r}_j$, and in this way to obtain relationships among the unknown phases $\phi_{\mathbf{H}}$, dependent on the known magnitudes $|E|$, having probabilistic validity.

Choose a finite number of reciprocal lattice vectors **H**, **K**, . . . in such a way that the linear combination of phases

$$\psi = \phi_{\mathbf{H}} + \phi_{\mathbf{K}} + \ldots \tag{17}$$

is a structure invariant whose value we wish to estimate. Choose satellite reciprocal lattice vectors **H′**, **K′**, . . . in such a way that the collection of magnitudes

$$|E_{\mathbf{H}}|, |E_{\mathbf{K}}|, \ldots; |E_{\mathbf{H}'}|, |E_{\mathbf{K}'}|, \ldots \tag{18}$$

constitutes a neighborhood of ψ. The atomic position vectors $\mathbf{r}_j$ are assumed to be the primitive random variables that are uniformly and independently distributed. Then the magnitudes $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$, . . .; $|E_{\mathbf{H}'}|$, $|E_{\mathbf{K}'}|$, . . .; and phases $\phi_{\mathbf{H}}$, $\phi_{\mathbf{K}}$, . . .; $\phi_{\mathbf{H}'}$, $\phi_{\mathbf{K}'}$, . . . of the complex, normalized structure factors $E_{\mathbf{H}}$, $E_{\mathbf{K}}$, . . .; $E_{\mathbf{H}'}$, $E_{\mathbf{K}'}$, . . ., as functions (Eq. 5) of the position vectors $\mathbf{r}_j$, are themselves random variables, and their joint probability distribution P may be obtained by techniques that are now standard. From the distribution P one derives the conditional joint probability distribution

$$P(\Phi_{\mathbf{H}},\Phi_{\mathbf{K}}, \ldots \,|\, |E_{\mathbf{H}}|, |E_{\mathbf{K}}|, \ldots; |E_{\mathbf{H}'}|, |E_{\mathbf{K}'}|, \ldots) \tag{19}$$

of the phases $\phi_{\mathbf{H}}$, $\phi_{\mathbf{K}}$, . . ., given the magnitudes $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$, . . .; $|E_{\mathbf{H}'}|$, $|E_{\mathbf{K}'}|$, . . ., by fixing the known magnitudes, integrating with respect to the unknown phases $\Phi_{\mathbf{H}'}$, $\Phi_{\mathbf{K}'}$, . . . from 0 to 2π, and multiplying by a suitable normalizing parameter. Distribution 19 in turn then leads directly to the conditional probability distribution

$$P(\Psi \,|\, |E_{\mathbf{H}}|, |E_{\mathbf{K}}|, \ldots; |E_{\mathbf{H}'}|, |E_{\mathbf{K}'}|, \ldots) \tag{20}$$

of the structure invariant ψ, if we assume as known the magnitudes 18 constituting a neighborhood of ψ. Finally, distribution 20 yields an estimate for ψ (for example, the mode) that is particularly good in the favorable case that the variance of distribution 20 happens to be small.

Estimating the Triplet

Let the three reciprocal lattice vectors **H**, **K**, and **L** satisfy Eq. 11. Refer to magnitude set 14 for the first neighborhood of the triplet ψ_3 and to the previous paragraph for the probabilistic background.

Suppose that R_1, R_2, and R_3 are three specified nonnegative numbers. Denote by

$$P_{1/3} = P(\psi | R_1, R_2, R_3)$$

the conditional probability distribution of the triplet ψ_3, given the three magnitudes in its first neighborhood:

$$|E_{\mathbf{H}}| = R_1, \; |E_{\mathbf{K}}| = R_2, \; |E_{\mathbf{L}}| = R_3 \tag{21}$$

Then, carrying out the program described earlier, one finds (*7*)

$$P_{1/3} = P(\Psi | R_1, R_2, R_3) \approx \frac{1}{K} \exp{(A \cos\Psi)} \tag{22}$$

where

$$A = \frac{2\sigma_3}{\sigma_2^{3/2}} R_1 R_2 R_3 \tag{23}$$

K is a normalizing constant not needed for the present purpose, and σ_n is defined by Eq. 7. Since $A > 0$, $P_{1/3}$ has a unique maximum at $\Psi = 0$, and it is clear that the larger the value of A, the smaller the variance of the distribution (see Fig. 3, where $A = 2.316$ and Fig. 4, where $A = 0.731$). Hence in the favorable case that A is large, say, for example, $A > 3$, the distribution leads to a reliable estimate of the structure invariant ψ_3, zero in this case:

$$\psi_3 \approx 0 \text{ if } A \text{ is large} \tag{24}$$

Furthermore, the larger the value of A, the more likely the probabilistic statement (Eq. 24). It is remarkable how useful this relationship has proven to be in the applications (*8*); and yet Eq. 24 is severely limited because it is capable of yielding only the zero estimate for ψ_3, and only those estimates are reliable for which A is large, the favorable cases. Note that the previously specified numbers R_1, R_2, R_3, identified with observed magnitudes $|E|$ by Eq. 21, as well as the atomic numbers Z_j, presumed to be known, appear via Eq. 23 as parameters of the distribution (Eq. 22).

A distribution closely related to Eq. 22 leads directly to the so-called tangent formula (*9*), which is universally used by direct methods practitioners:

$$\tan \phi_{\mathbf{h}} = \frac{\langle |E_{\mathbf{K}}E_{\mathbf{h-K}}| \sin(\phi_{\mathbf{K}} + \phi_{\mathbf{h-K}})\rangle_{\mathbf{K}}}{\langle |E_{\mathbf{K}}E_{\mathbf{h-K}}| \cos(\phi_{\mathbf{K}} + \phi_{\mathbf{h-K}})\rangle_{\mathbf{K}}} \tag{25}$$

in which **h** is a fixed reciprocal lattice vector, the averages are taken over the same set of reciprocal lattice vectors **K**, usually restricted to those vectors **K** for which $|E_{\mathbf{K}}|$ and $|E_{\mathbf{h-K}}|$ are both large, and the sign of sin $\phi_{\mathbf{h}}$ is the same as the sign of the numerator on the right-hand side (the sign of cos $\phi_{\mathbf{h}}$ is the same as the sign of the denominator on the right-hand side). The tangent formula is usually used to refine and extend a basis set of phases, presumed to be known. Because it uses the zero estimate of the triplet ψ_3, together with a measure *(A)* of variance, to link observed magnitudes $|E|$ with desired phases ϕ, the tangent formula serves as the simplest illustration of the fundamental principle of direct methods.

Closely related to the tangent formula is Sayre's equation (*10*), recently shown (*11, 12*) to be useful in the refinement and extrapolation of a low-resolution phase set to higher resolution for macromolecules.

Estimating the Quartet

Two conditional probability distributions are described, one assuming as known the four magnitudes $|E|$ in the first neighborhood of the quartet, the second assuming as known the seven magnitudes $|E|$ in its second neighborhood.

Suppose that **H**, **K**, **L**, and **M** are four reciprocal lattice vectors that satisfy Eq. 13. Refer to magnitude set 15 for the first neighborhood of the quartet ψ_4 (Eq. 12). Suppose that R_1, R_2, R_3, and R_4 are four specified nonnegative numbers. Denote by

$$P_{1/4} = P(\Psi | R_1, R_2, R_3, R_4)$$

the conditional probability distribution of the quartet ψ_4, given the four magnitudes in its first neighborhood:

$$|E_{\mathbf{H}}| = R_1,\ |E_{\mathbf{K}}| = R_2,\ |E_{\mathbf{L}}| = R_3,\ |E_{\mathbf{M}}| = R_4 \tag{26}$$

Then (*4, 5, 13*)

$$P_{1/4} = P(\Psi | R_1, R_2, R_3, R_4) \approx \frac{1}{K} \exp\,(B \cos \Psi) \tag{27}$$

where

$$B = \frac{2\sigma_4}{\sigma_2^2} R_1R_2R_3R_4 \tag{28}$$

K is a normalizing parameter not relevant here, and σ_n is defined by Eq. 7. Thus $P_{1/4}$ is identical with $P_{1/3}$, but B replaces A. Hence similar remarks apply to $P_{1/4}$. In particular, Eq. 27 always has a unique maximum at $\Psi = 0$ so that the most probable value of ψ_4, given the four magnitudes (Eq. 26) in its first neighborhood, is zero; the larger the value of B, the more likely that $\psi_4 \approx 0$. Since B values, of order $1/N$, tend to be less than A values, of order $1/\sqrt{N}$, at least for large values of N, the estimate (zero) of ψ_4 is in general less reliable than the estimate (zero) of ψ_3. Hence the goal of obtaining a reliable nonzero estimate for a structure invariant is not realized by Eq. 27. The decisive step in this direction is made next.

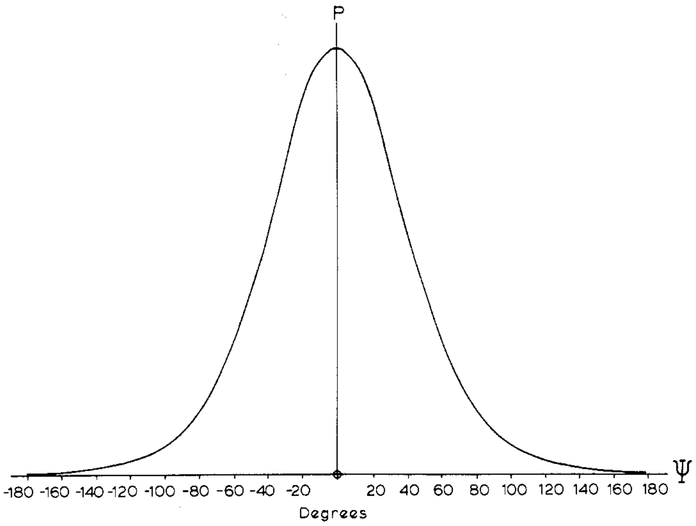

Fig. 3. The distribution $P_{1/3}$, Eq. 22, for $A = 2.316$.

Let us use the same notation as in the previous paragraph but refer now to magnitude sets 15 and 16 for the second neighborhood of the quartet ψ_4. Suppose that $R_1, R_2, R_3, R_4, R_{12}, R_{23}$, and R_{31}, are seven nonnegative numbers. Denote by

$$P_{1/7} = P(\Psi | R_1, R_2, R_3, R_4; R_{12}, R_{23}, R_{31}) \tag{29}$$

the conditional probability distribution of the quartet ψ_4, given the seven magnitudes in its second neighborhood:

$$|E_{\mathbf{H}}| = R_1,\ |E_{\mathbf{K}}| = R_2,\ |E_{\mathbf{L}}| = R_3,\ |E_{\mathbf{M}}| = R_4 \tag{30}$$

$$|E_{\mathbf{H+K}}| = R_{12},\ |E_{\mathbf{K+L}}| = R_{23},\ |E_{\mathbf{L+H}}| = R_{31} \tag{31}$$

The explicit form for $P_{1/7}$ has been found (*4, 5, 13*) but is too long to be given explicitly here. Instead, Figs. 5 through 7 show the distribution (Eq. 29) (solid line) for typical values of the seven parameters (Eqs. 30 and 31). For comparison, the distribution (Eq. 27) (broken line) is also shown. Since the magnitudes $|E|$ have been

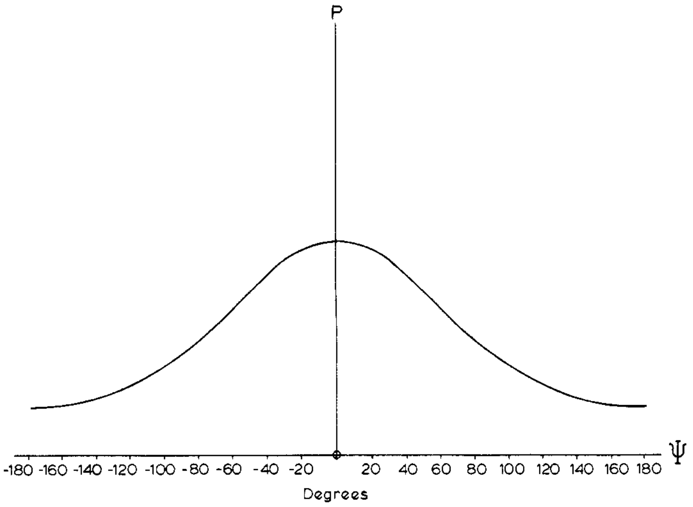

Fig. 4. The distribution $P_{1/3}$, Eq. 22, for $A = 0.731$.

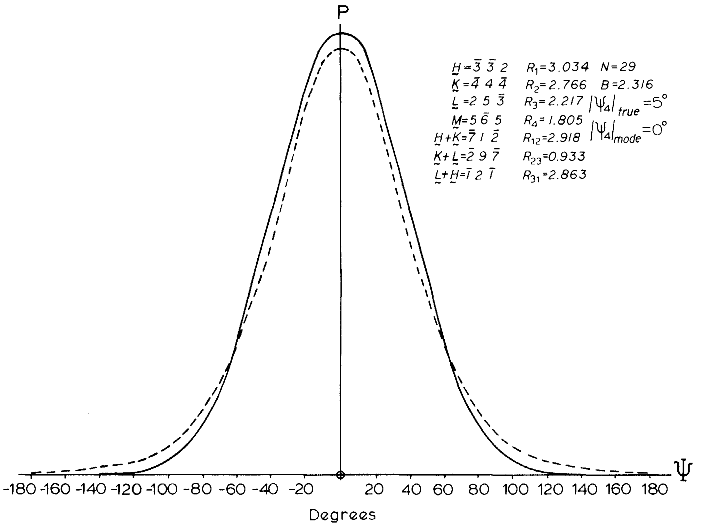

Fig. 5. The distributions Eq. 29 (——) and Eq. 27 (------) for the values of the seven parameters (Eqs. 30 and 31) shown. The mode of Eq. 29 is 0, the mode of Eq. 27 is always 0.

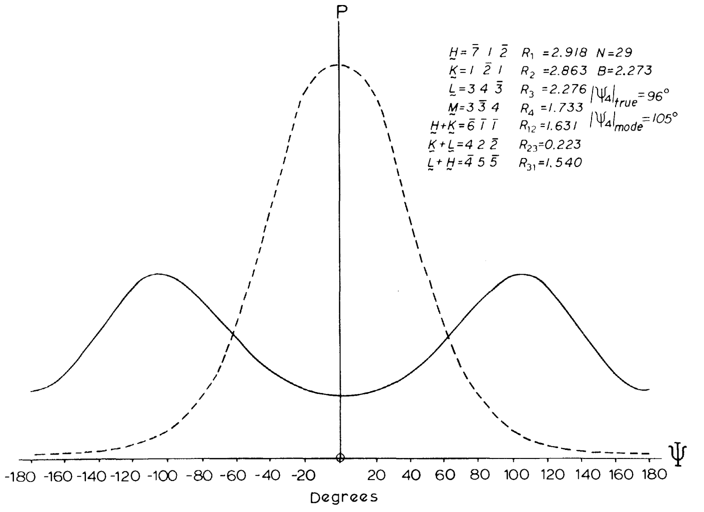

Fig. 6. The distributions Eq. 29 (——) and Eq. 27 (------) for the values of the seven parameters (Eqs. 30 and 31) shown. The mode of Eq. 29 is 105°, the mode of Eq. 27 is always 0.

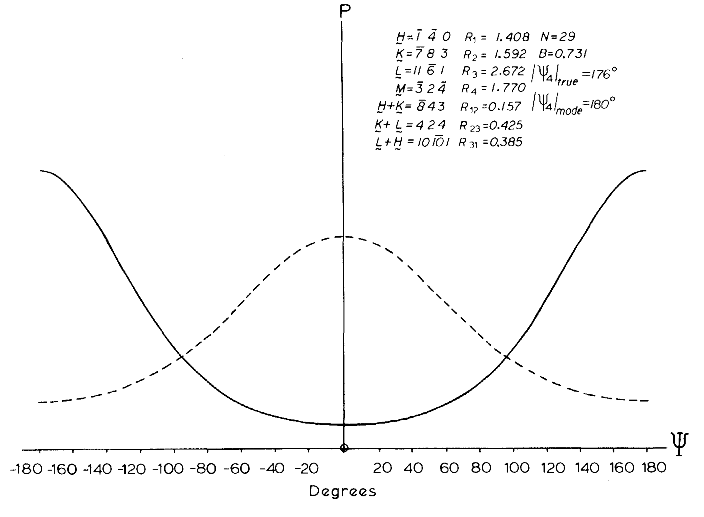

Fig. 7. The distributions Eq. 29 (——) and Eq. 27 (------) for the values of the seven parameters (Eqs. 30 and 31) shown. The mode of Eq. 29 is 180°, the mode of Eq. 27 is always 0.

obtained from a real structure with $N = 29$, comparison with the true value of the quartet is also possible. As already emphasized, the distribution (Eq. 27) always has a unique maximum at $\Psi = 0$. The distribution (Eq. 29), on the other hand, may have a maximum at $\Psi = 0$, or π, or any value between these extremes, as shown by Figs. 5 through 7. Roughly speaking, the maximum of Eq. 29 occurs at 0 or π according as the three parameters R_{12}, R_{23}, R_{31} are all large or all small, respectively. These figures also clearly show the improvement that may result when, in addition to the four magnitudes (Eq. 30), the three magnitudes (Eq. 31) are also assumed to be known. Not unexpectedly, when more information is available, that is, seven magnitudes $|E|$ rather than only four, the potential for determining more reliable estimates of the structure invariants is increased. Finally, in the special case that

$$R_{12} \approx R_{23} \approx R_{31} \approx 0 \tag{32}$$

the distribution (Eq. 29) reduces simply to

$$P_{1/7} \approx \frac{1}{L} \exp\left(-2B'\cos\Psi\right) \tag{33}$$

where

$$B' = \frac{1}{\sigma_2^3}\left(3\sigma_3^2 - \sigma_2\sigma_4\right)R_1R_2R_3R_4 \tag{34}$$

and L is a normalizing parameter not relevant here, which has a unique maximum at $\Psi = \pi$ (Fig. 7).

The Effect of Crystallographic Symmetry

When crystallographic elements of symmetry are present, the origin may not be chosen arbitrarily if the simplification permitted by the space group symmetries is to be realized. For example, if a crystal has a center of symmetry, it is natural to place the origin at such a center while, if a twofold axis but no other symmetry element is present, the origin would normally be situated on this symmetry axis. In such cases the permissible origins are greatly restricted and it is therefore plausible to assume that many linear combinations of the phases will remain unchanged in value when the origin is shifted only in the restricted ways allowed by the space group symmetries. One is thus led to the notion of the structure semi-invariant, the linear combinations of the phases whose values are independent of the choice of permissible origin. Explicitly then, the structure semi-invariants are those linear combinations of the phases whose values are uniquely determined by the crystal structure alone, no matter what the choice of permissible origin.

The structure semi-invariants have been tabulated for all the space groups (*6, 14–17*). For example, if a center of symmetry is present (space group $P\bar{1}$), then a single phase $\phi_{\mathbf{H}}$ is a structure semi-invariant if and only if the three components of $\mathbf{H}$ are even integers; the linear combination of two phases, $\phi_{\mathbf{H}} + \phi_{\mathbf{K}}$, is a structure semi-invariant if and only if the three components of $\mathbf{H} + \mathbf{K}$ are even integers, and so on.

By embedding a structure semi-invariant T and its symmetry-related variants in suitable structure invariants Q, one obtains the extensions (*18, 19*) Q of the semi-invariant T [also called representations (*20*)]. Owing to the space group–dependent relations among the phases, the value of T is simply related to the values of its extensions. In this way the probabilistic theory of the structure semi-invariants is reduced to that of the structure invariants, which is well developed. In particular, the neighborhoods of the structure semi-invariant T are defined in terms of the neighborhoods of its extensions.

Concluding Remarks

The estimate (zero) of the triplet ψ_3 (Eq. 24) and the related tangent formula (Eq. 25) are the cornerstones of most computer programs (*21, 22*) used for the direct solution of crystal structures. However, estimates of the quartets, in particular (Eq. 33), used to identify those quartets whose values are close to π (the so-called negative quartets because their cosines are negative), as well as of the higher order structure invariants and semi-invariants, often play an important (sometimes indispensable) role (*23–25*), particularly for complex structures when diffraction data may be limited in number and quality (*26–36*).

Major emphasis has been placed on the neighborhood principle and the important role played by the structure invariants. The conditional probability distribution of a structure invariant T, given the magnitudes $|E|$ in any of its neighborhoods, yields a reliable estimate for T in the favorable case that the variance of the distribution happens to be small. Since the structure invariants are the essential link between magnitudes $|E|$ and phases ϕ, probabilistic methods play the central role in the solution of the phase problem.

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