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On the Direct-Methods Theory of Single Isomorphous Replacement

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Abstract

The joint probability distribution of six structure factors for a pair of isomorphous structures [Hauptman (1982). *Acta Cryst.* A**38**, 289-294] is used for probability calculations in which doublet invariant phase information (*i.e.* phase-difference information) is employed as conditional information together with intensity data. This information is obtained from the structure-factor magnitudes of the structure formed by the replacement atoms (assumed to be known) and the two isomorphous structures. First, conditional probability distributions of the triplet invariants of the native structure are derived. An alternative to the approach of Fortier, Moore & Fraser [*Acta Cryst.* (1985), A**41**, 571-577] is presented, based on a new enantiomorph-sensitive distribution. It is argued that application of enantiomorph-sensitive distributions obtained by restriction of phase invariants can be widened by using various enantiomorph-defining invariants. Second, the ambiguity in single isomorphous replacement is resolved by calculating the probability of the two possible solutions as was proposed by Fan Hai-fu, Han Fu-son, Qian Jin-zi & Yao Jia-xing [*Acta Cryst.* (1984), A**40**, 489-495], but using a different probabilistic basis. It turns out that the formulae of the latter authors are a special case of formulae derived in the present paper.

1. Introduction

The joint probability distribution of the six structure factors in the first neighbourhood of an isomorphous pair of structures was derived by Hauptman (1982). From this distribution he derived conditional probability distributions of the triplet invariants given the six-magnitude first neighbourhood. These distributions can be used for *ab initio* phasing, yielding estimates of triplet phases having the values 0 or π (Hauptman, Potter & Weeks, 1982). Fortier, Weeks & Hauptman (1984*b*) extended Hauptman's work to the case of triples of isomorphous structures. Hauptman (1982) pointed out that in single isomorphous replacement (SIR) there exist two-phase structure invariants $\varphi_{\mathbf{h}} - \psi_{\mathbf{h}}$ (notated as $\delta_{\mathbf{h}}$ in the present paper) where $\varphi_{\mathbf{h}}$ and $\psi_{\mathbf{h}}$ are the structure-factor phases of the isomorphous pair of structures. Such structure invariants (called doublet invariants in the present paper) play an important role in the case of SIR when the structure-factor magnitudes of the replacement-atom substructure are known, since in this case the magnitudes of these structure invariants can be calculated. By altering Hauptman's (1982) conditional distribution [equation (3.12)], Fortier, Moore & Fraser (1985) obtained eight distributions corresponding to the eight sign combinations associated with $|\delta_{\mathbf{h}}|$, $|\delta_{\mathbf{k}}|$ and $|\delta_{-\mathbf{h}-\mathbf{k}}|$. They demonstrated that application of the latter distributions instead of Hauptman's conditional probability distributions eliminates systematic errors and yields estimates of the cosine invariants in the full range from -1 to $+1$. In the approach of Fan Hai-fu, Han Fu-son, Qian Jin-zi & Yao Jia-xing (1984) probability distributions are constructed based on the Cochran (1955) distribution which exploit the three magnitudes in the first neighbourhood of the native protein or the derivative, together with information about doublet invariants $\varphi_{\mathbf{h}} - \theta_{\mathbf{h}}$ or $\psi_{\mathbf{h}} - \theta_{\mathbf{h}}$ (notated as $\varepsilon_{\mathbf{h}}$ and $\chi_{\mathbf{h}}$ respectively in the present paper) where $\theta_{\mathbf{h}}$ is the structure-factor phase of the substructure formed by the replacement atoms. Formulae were obtained for the calculation of the sign probability of a doublet invariant $\varepsilon_{\mathbf{h}}$ or $\chi_{\mathbf{h}}$. Recently these authors have extended their original procedure by employing the product of the Cochran and the Sim (1959) distributions to incorporate partial structure information (Fan Hai-fu, Han Fu-son, Qian Jin-zi & Yao Jia-xing, 1985).

In the present paper we shall use Hauptman's (1982) joint probability distribution [equation (3.4)] of six structure factors in the first neighbourhood to derive conditional probability distributions of the triplet invariant $\Phi = \varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{-\mathbf{h}-\mathbf{k}}$ given the six magnitudes in the first neighbourhood and the doublet invariants $\delta_{\mathbf{h}}$, $\delta_{\mathbf{k}}$ and $\delta_{-\mathbf{h}-\mathbf{k}}$ or their magnitudes (§ 3). We will give an alternative to the method of estimating cosine invariants proposed by Fortier *et al.* (1985). In § 4 we follow the method of Fan Hai-fu *et al.* (1984) of calculating the sign probability of doublet invariants when the structure formed by the replacement atoms is known. However, our probabilistic basis differs from that of Fan Hai-fu *et al.*, making possible the derivation of a joint probability

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distribution $P(t_1, t_2, t_3)$ of the signs of the doublet invariants $\varepsilon_{\mathbf{h}}$, $\varepsilon_{\mathbf{k}}$ and $\varepsilon_{-\mathbf{h}-\mathbf{k}}$. The probability distributions (16) and (18) of the sign of the doublet invariant $\varepsilon_{\mathbf{h}}$ obtained by Fan Hai-fu *et al.* (1984) will be compared with our conditional probability distribution $P(t_1|t_2, t_3)$ and marginal distribution $P(t_1)$ respectively.

2. Analysis

2.1.

In single isomorphous replacement the following three structures are of interest if replacement atom information is available: the native protein; the derivative; and the structure formed by the replacing atoms. The three structures have atomic scattering powers f_j, g_j and h_j and will be called the f, g and h structure respectively. The reciprocal vector $\mathbf{h}_i$ will be denoted by the subscript i. The structure factor F_i^0 of the f structure is defined as

$$F_i^0 = \sum_{j=1}^{N} f_j \exp[2\pi i \mathbf{h}_i \cdot \mathbf{r}_j], \qquad (1)$$

where N is the number of atoms in the unit cell of the derivative (the g structure). Note that some of the f_j's may be zero. The structure factors G_i^0 and H_i^0 of the g and h structures are defined analogously, with f_j replaced by g_j and h_j respectively. The normalized structure factors F_i, G_i and H_i are defined by

$$F_i = F_i^0/\alpha_{200}^{1/2}, \qquad G_i = G_i^0/\alpha_{020}^{1/2},$$
$$H_i = H_i^0/\alpha_{002}^{1/2}, \qquad (2)$$

where

$$\alpha_{abc} \equiv \sum_{j=1}^{N} f_j^a g_j^b h_j^c. \qquad (3)$$

The phases of F_i, G_i and H_i are denoted by φ_i, ψ_i and θ_i, whereas their magnitudes are denoted by R_i, S_i and T_i.

In general there are 27 triplet invariants associated with three isomorphous structures for the triple of reciprocal vectors $\mathbf{h}_1$, $\mathbf{h}_2$ and $\mathbf{h}_3$ subject to the condition $\mathbf{h}_1+\mathbf{h}_2+\mathbf{h}_3=\mathbf{0}$ (Fortier *et al.*, 1984*b*). The complete set of structure invariants, however, consists of the 27 triplet invariants and nine doublet invariants δ_i, ε_i and χ_i $[i=1,2,3]$, where

$$\delta_i = \varphi_i - \psi_i, \qquad \varepsilon_i = \varphi_i - \theta_i \quad \text{and} \quad \chi_i = \psi_i - \theta_i. \qquad (4)$$

The complete set can be generated by a basis set of seven selected invariants, *e.g.* Φ, δ_i, ε_i $[i=1,2,3]$, where $\Phi = \varphi_1+\varphi_2+\varphi_3$. In the present paper we have $F_i^0 = G_i^0 - H_i^0$. The formulae of Fortier *et al.* (1984*b*) are not valid for this case.

The information associated with the three structures consists of measured structure-factor magnitudes whereas the information associated with the h structure also includes structure-factor phases. The cosines of the doublet invariants δ_i and ε_i [note that $\chi_i = \varepsilon_i - \delta_i$ by (4)] are calculated from the structure-factor magnitudes according to:

$$\cos\delta_i = (|F_i^0|^2 + |G_i^0|^2 - |H_i^0|^2)/2|F_i^0||G_i^0| \qquad (5)$$
$$\cos\varepsilon_i = (-|F_i^0|^2 + |G_i^0|^2 - |H_i^0|^2)/2|F_i^0||H_i^0|. \qquad (6)$$

Probability distributions in which information about doublet invariants is incorporated can be derived *via* the distributions $P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)]$ and $P[\Phi, \varepsilon_1, \varepsilon_2, \varepsilon_3|R_i, T_i\ \ (i=1,2,3)]$ associated with the pairs of structures (f, g) and (f, h) respectively. The first distribution is obtained from the joint probability distribution $P[R_i, S_i, \varphi_i, \psi_i\ (i=1,2,3)]$ of the magnitudes R_i and S_i and the phases φ_i and ψ_i of the normalized structure factors F_i and G_i for the isomorphous pair of structures (f, g), derived by Hauptman [1982, equation (3.4)]. The primitive random variables are the vectors $\mathbf{h}_1$, $\mathbf{h}_2$ and $\mathbf{h}_3$ subject to the condition $\mathbf{h}_1+\mathbf{h}_2+\mathbf{h}_3=\mathbf{0}$. The second distribution is obtained from Hauptman's distribution applied to the pair (f, h). Note that this distribution is useful even though the f and h structures have no atomic positions in common (in this case the f and h structures are non-isomorphous) since doublet invariant information is available.

2.2.

By integrating Hauptman's joint probability distribution with respect to φ_i and ψ_i from 0 to 2π subject to the conditions $\Phi=\varphi_1+\varphi_2+\varphi_3$ and $\delta_i=\varphi_i-\psi_i$ and by fixing the six magnitudes R_i, S_i where i runs from 1 to 3, one may obtain the joint conditional probability distribution of the triplet invariant Φ and the doublet invariants δ_1, δ_2 and δ_3:

$$\begin{aligned} P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)] \\ = C_1 \exp\Big\{ & 2\beta \sum_{i=1}^{3} R_i S_i \cos\delta_i \\ & + 2\beta_0 R_1 R_2 R_3 \cos\Phi \\ & + 2\beta_1 [S_1 R_2 R_3 \cos(\Phi-\delta_1) \\ & + R_1 S_2 R_3 \cos(\Phi-\delta_2) \\ & + R_1 R_2 S_3 \cos(\Phi-\delta_3)] \\ & + 2\beta_2 [S_1 S_2 R_3 \cos(\Phi-\delta_1-\delta_2) \\ & + S_1 R_2 S_3 \cos(\Phi-\delta_1-\delta_3) \\ & + R_1 S_2 S_3 \cos(\Phi-\delta_2-\delta_3)] \\ & + 2\beta_3 S_1 S_2 S_3 \cos(\Phi-\delta_1-\delta_2-\delta_3)\Big\} \qquad (7) \end{aligned}$$

where β, $\beta_0, \ldots, \beta_3$ are defined by Hauptman (1982) and C_1 is a normalizing constant. The set of four structure invariants in the argument of (7) is a basis set of structure invariants for the (f, g) pair of structures from which the complete set, consisting of eight triplet invariants listed by Fortier, Weeks & Hauptman (1984*a*) and Fortier, Moore & Fraser (1985) and three doublet invariants δ_1, δ_2 and δ_3, can be generated. We will denote these triplet invariants by Ω_{klm}, where k, l and m take the values 0 or 1 to specify φ or ψ respectively. As an example, the mixed triplet invariant $\varphi_1+\psi_2+\psi_3$ is notated as Ω_{011}. It is easily verified that

$$\Omega_{klm} = \Phi - k\delta_1 - l\delta_2 - m\delta_3 \tag{8}$$

for each of the eight triplet invariants.

The joint conditional distribution

$$P[\Phi, \varepsilon_1, \varepsilon_2, \varepsilon_3 | R_i, T_i \ (i=1,2,3)] \tag{9}$$

of the basis-set invariants Φ and ε_i $(i=1,2,3)$ for the (f, h) pair can be obtained immediately from (7) by employing the required analogy between (7) and (9). If the h structure is known its triplet invariants are known, so it is advantageous to choose a basis set with $\Theta = \theta_1+\theta_2+\theta_3$ as one of the basis-set invariants: $\{\Theta, \varepsilon_1, \varepsilon_2, \varepsilon_3\}$, for each set of triplet-related reciprocal vectors $\mathbf{h}_1$, $\mathbf{h}_2$ and $\mathbf{h}_3$. The joint conditional distribution $P[\Theta, \varepsilon_1, \varepsilon_2, \varepsilon_3 | R_i, T_i \ (i=1,2,3)]$ can be obtained directly from (9) *via* the relation

$$\Phi = \Theta + \varepsilon_1 + \varepsilon_2 + \varepsilon_3 \tag{10}$$

and reads

$$\begin{aligned} P[\Theta, \varepsilon_1, \varepsilon_2, \varepsilon_3 | R_i, T_i \ (i=1,2,3)] & \\ \sim \exp\Big\{ 2\beta' \sum_{i=1}^{3} R_i T_i \cos \varepsilon_i & \\ + 2\beta_0' R_1 R_2 R_3 \cos(\varepsilon_1+\varepsilon_2+\varepsilon_3+\Theta) & \\ + 2\beta_1' [R_1 R_2 T_3 \cos(\varepsilon_1+\varepsilon_2+\Theta) & \\ + R_1 T_2 R_3 \cos(\varepsilon_1+\varepsilon_3+\Theta) & \\ + T_1 R_2 R_3 \cos(\varepsilon_2+\varepsilon_3+\Theta)] & \\ + 2\beta_2' [R_1 T_2 T_3 \cos(\varepsilon_1+\Theta) & \\ + T_1 R_2 T_3 \cos(\varepsilon_2+\Theta) & \\ + T_1 T_2 R_3 \cos(\varepsilon_3+\Theta)] & \\ + 2\beta_3' T_1 T_2 T_3 \cos \Theta \Big\}. & \end{aligned} \tag{11}$$

The superscript (′) indicates that the β coefficients are now related to the (f, h) pair of structures.

Integration of (7) with respect to δ_i $(i=1,2,3)$ over the range 0 to 2π leads to $P[\Phi | R_i, S_i \ (i=1,2,3)]$ [Hauptman's (1982) formula (3.12)]. From (7), we will derive conditional distributions in which information about the doublet invariants δ_i $(i=1,2,3)$ [*e.g.* their magnitudes calculated *via* (5)] is incorporated, whereas (11) will be used to derive distributions which exploit known triplet invariants Θ as well as information about the doublet invariants ε_i.

3. Conditional distributions derived from $P[\Phi, \delta_1, \delta_2, \delta_3 | R_i, S_i \ (i=1,2,3)]$

3.1.

The cosines of the doublet invariants δ_i, calculated *via* (5), yield magnitudes $|\delta_i|$. We shall examine the distribution $P[\Phi | R_i, S_i, |\delta_i| \ (i=1,2,3)]$ in which the magnitudes $|\delta_i|$ are used as conditional information. The latter distribution is a marginal distribution of $P[\Phi, s_1, s_2, s_3 | R_i, S_i, |\delta_i| \ (i=1,2,3)]$ where s_i is the sign of the doublet invariant δ_i $(-\pi < \delta_i \leq \pi)$, *i.e.* $\delta_i = s_i|\delta_i|$. Thus

$$\begin{aligned} P[\Phi | R_i, S_i, |\delta_i| \ (i=1,2,3)] &= \sum_{s_1, s_2, s_3 = \pm 1} P[\Phi, s_1, s_2, s_3 | R_i, S_i, |\delta_i| \\ &\qquad (i=1,2,3)]. \end{aligned} \tag{12}$$

Application of Bayes's theorem leads to

$$\begin{aligned} P[\Phi, s_1, s_2, s_3 | R_i, S_i, |\delta_i| \ (i=1,2,3)] &= P[s_1, s_2, s_3 | R_i, S_i, |\delta_i| \ (i=1,2,3)] \\ &\quad \times P[\Phi | R_i, S_i, s_i|\delta_i| \ (i=1,2,3)]. \end{aligned} \tag{13}$$

Combination of (12) and (13) yields

$$\begin{aligned} P[\Phi | R_i, S_i, |\delta_i| \ (i=1,2,3)] &= \sum_{s_1, s_2, s_3 = \pm 1} w(s_1, s_2, s_3) \\ &\quad \times P[\Phi | R_i, S_i, s_i|\delta_i| \ (i=1,2,3)] \end{aligned} \tag{14}$$

where

$$w(s_1, s_2, s_3) \equiv P[s_1, s_2, s_3 | R_i, S_i, |\delta_i| \ (i=1,2,3)].$$

We arrive at the conclusion that the distribution $P[\Phi | R_i, S_i, |\delta_i| \ (i=1,2,3)]$ is a weighted sum of the eight distributions $P[\Phi | R_i, S_i, \delta_i \ (i=1,2,3)]$ corresponding to the eight sign combinations of the doublet invariants δ_1, δ_2 and δ_3. The weighting function is the joint conditional distribution $P[s_1, s_2, s_3 | R_i, S_i, |\delta_i| \ (i=1,2,3)]$ of the signs of these doublet invariants.

In the following, we will adopt the notation $M(\Phi | K, \kappa)$ to specify the von Mises distribution

$$M(\Phi | K, \kappa) = [2\pi I_0(K)]^{-1} \exp[K \cos(\Phi - \kappa)]$$

of the random variable Φ with parameters K and κ.

The distribution $P[\Phi | R_i, S_i, \delta_i \ (i=1,2,3)]$ follows directly from (7) and appears to be a von Mises distribution:

$$P[\Phi | R_i, S_i, \delta_i \ (i=1,2,3)] = M(\Phi | A, \xi) \tag{15}$$

where A and ξ follow from (see Appendix I)

$$A \cos \xi = X \quad A \sin \xi = Y \quad A > 0 \tag{16}$$

and

$$X = 2\beta_0 R_1 R_2 R_3 + 2\beta_1[S_1 R_2 R_3 \cos \delta_1 + R_1 S_2 R_3 \cos \delta_2 + R_1 R_2 S_3 \cos \delta_3] + 2\beta_2[S_1 S_2 R_3 \cos (\delta_1 + \delta_2) + S_1 R_2 S_3 \cos (\delta_1 + \delta_3) + R_1 S_2 S_3 \cos (\delta_2 + \delta_3)] + 2\beta_3 S_1 S_2 S_3 \cos (\delta_1 + \delta_2 + \delta_3), \quad (17)$$

$$Y = 2\beta_1[S_1 R_2 R_3 \sin \delta_1 + R_1 S_2 R_3 \sin \delta_2 + R_1 R_2 S_3 \sin \delta_3] + 2\beta_2[S_1 S_2 R_3 \sin (\delta_1 + \delta_2) + S_1 R_2 S_3 \sin (\delta_1 + \delta_3) + R_1 S_2 S_3 \sin (\delta_2 + \delta_3)] + 2\beta_3 S_1 S_2 S_3 \sin (\delta_1 + \delta_2 + \delta_3). \quad (18)$$

I_0 is the modified Bessel function of the first kind and of order zero. With $|\delta_i|$ $(i = 1, 2, 3)$ given, the values of X, Y, A and ξ corresponding to the sign combination s_1, s_2, s_3 are specified by subscripts, *e.g.* A_{s_1,s_2,s_3}. The distributions (15) corresponding to s_1, s_2, s_3 and $-s_1$, $-s_2$, $-s_3$ have modes at opposite values of Φ, because

$$\xi_{s_1,s_2,s_3} = -\xi_{-s_1,-s_2,-s_3}, \quad (19)$$

and equal variances, since

$$A_{s_1,s_2,s_3} = A_{-s_1,-s_2,-s_3}. \quad (20)$$

The weighting function $P[s_1, s_2, s_3|R_i, S_i, |\delta_i|$ $(i = 1, 2, 3)]$ is derived from the distribution $P[\delta_1, \delta_2, \delta_3|R_i, S_i$ $(i = 1, 2, 3)]$ which is obtained *via* Bayes's theorem (Appendix II). The result is

$$P[s_1, s_2, s_3|R_i, S_i, |\delta_i| \, (i = 1, 2, 3)] = L I_0(A_{s_1,s_2,s_3}). \quad (21a)$$

The normalizing constant L is given by

$$L^{-1} = \sum_{s_1,s_2,s_3=\pm 1} I_0(A_{s_1,s_2,s_3}) = 2 \sum_{\substack{s_i,s_j=\pm 1 \\ i\neq j}} I_0(A_{s_1,s_2,s_3}). \quad (21b)$$

From (20) and (21a), it is easily verified that the sign combination s_1, s_2, s_3 has the same probability as the combination $-s_1$, $-s_2$, $-s_3$. This is tantamount to the enantiomorph ambiguity which should exist since no enantiomorph-defining information has so far been incorporated in the distributions.

From (14), (15) and (21a) we obtain

$$P[\Phi|R_i, S_i, |\delta_i| \, (i = 1, 2, 3)] = L \sum_{s_1,s_2,s_3=\pm 1} I_0(A_{s_1,s_2,s_3}) \times M(\Phi|A_{s_1,s_2,s_3}, \xi_{s_1,s_2,s_3}). \quad (22)$$

Thus it is established that the distribution $P[\Phi|R_i, S_i, |\delta_i|$ $(i = 1, 2, 3)]$ is a multi-modal distribution which is symmetrical around zero and which can be expressed as a weighted sum of eight von Mises distributions. Note that this distribution is derived from Hauptman's joint distribution [1982, equation (3.4)], *via* (7), without adding further approximations to those used by Hauptman.

We will show that this distribution can be approximated by a single von Mises distribution for small values of the eight parameters A_{s_1,s_2,s_3}. Using the approximation $\exp x \simeq 1 + x$, we have for small values of A_{s_1,s_2,s_3}

$$P[\Phi|R_i, S_i, |\delta_i| \, (i = 1, 2, 3)] \simeq C_2 \sum_{s_1,s_2,s_3=\pm 1} [1 + A_{s_1,s_2,s_3} \cos (\Phi - \xi_{s_1,s_2,s_3})] \simeq C_3 \exp [\tfrac{1}{8} \sum_{s_1,s_2,s_3=\pm 1} A_{s_1,s_2,s_3} \cos (\Phi - \xi_{s_1,s_2,s_3})] = M(\Phi|K', \kappa'), \quad (23)$$

where C_2 and C_3 are suitable normalizing constants and $K' > 0$ with

$$K' \exp i\kappa' = \tfrac{1}{8} \sum_{s_1,s_2,s_3=\pm 1} A_{s_1,s_2,s_3} \exp i\xi_{s_1,s_2,s_3} = \tfrac{1}{8} \sum_{s_1,s_2,s_3=\pm 1} X_{s_1,s_2,s_3} = \tfrac{1}{4} \sum_{\substack{s_i,s_j=\pm 1 \\ i\neq j}} X_{s_1,s_2,s_3}. \quad (24)$$

The expressions (I.1) and (I.2) have been used together with (16), (19) and (20).

By (24) it is demonstrated that the mode κ' of the distribution $P[\Phi|R_i, S_i, |\delta_i|$ $(i = 1, 2, 3)]$ is restricted to 0 or π owing to the average of the signs of the doublet invariants δ_i over the two possible values -1 and $+1$. The mode of the distribution $P(\Phi|R_i, S_i$ $(i = 1, 2, 3)]$ was also found to be restricted to 0 or π (Hauptman, 1982).

3.2.

The distribution $P[\Phi|R_i, S_i, |\delta_i|$ $(i = 1, 2, 3)]$ examined in § 3.1 is symmetric around zero as a direct consequence of the enantiomorph ambiguity. This ambiguity will be resolved by assigning arbitrarily a sign e to the doublet invariant δ_3, *i.e.* $s_3 = e$ $(e = +1$ or $e = -1)$. As before, the magnitude $|\delta_3|$ is calculated *via* (5). We will examine the distribution $P[\Phi|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3$ $(i = 1, 2, 3)]$ in which the doublet invariant $\delta_3 = e|\delta_3|$ with $\delta_3 \neq 0, \pi$ is used as enantiomorph-defining conditional information. Analogous to (12), we have

$$P[\Phi|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3 \, (i = 1, 2, 3)] = \sum_{s_1,s_2=\pm 1} P[\Phi, s_1, s_2|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3 \, (i = 1, 2, 3)]. \quad (25)$$

From the reasoning developed in § 3.1, it is established that the distribution $P[\Phi|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3$ $(i = 1, 2, 3)]$ is not symmetrical around zero and can be expressed as a weighted sum of the four von Mises distributions (15) corresponding to the sign combinations s_1, s_2, e:

$$P[\Phi|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3\ (i=1,2,3)] = (L/2) \sum_{s_1,s_2=\pm1} I_0(A_{s_1,s_2,e}) \times M(\Phi|A_{s_1,s_2,e}, \xi_{s_1,s_2,e}), \quad (26)$$

where L is defined in (21b).

For small $A_{s_1,s_2,e}$, distribution (26) may be approximated by

$$M(\Phi|K_e, \kappa_e) \quad (27a)$$

where $K_e > 0$ and

$$K_e \exp i\kappa_e = \tfrac{1}{4} \sum_{s_1,s_2=\pm1} A_{s_1,s_2,e} \exp i\xi_{s_1,s_2,e} = Q_r + iQ_i, \quad (27b)$$

where (I.1), (I.2) and (16) have been used. The real and imaginary parts Q_r and Q_i, defined as

$$\left.\begin{aligned} Q_r &\equiv \tfrac{1}{4} \sum_{s_1,s_2=\pm1} X_{s_1,s_2,e} \\ Q_i &\equiv \tfrac{1}{4} \sum_{s_1,s_2=\pm1} Y_{s_1,s_2,e} \end{aligned}\right\} \quad (28)$$

respectively, are given in Appendix III, expressed in terms of R_i, S_i and δ_i [note that Q_r is equal to the right-hand side of (24)]. By (27b) we conclude that the mode κ_e of the distribution $P[\Phi|R_i, S_i, |\delta_1|, |\delta_2|, \delta_3\ (i=1,2,3)]$ is not restricted to 0 or π, but can take any value in the range from 0 to 2π.

Define the set $\mathscr{A}_e(\mathbf{h}_3)$ of triplet invariants

$$\mathscr{A}_e(\mathbf{h}_3) \equiv \{\Phi_{\mathbf{h}_1,\mathbf{h}_2,\mathbf{h}_3}\} \quad (29)$$

where $\mathbf{h}_3$ is a fixed reciprocal-lattice vector, and $\mathbf{h}_1$ and $\mathbf{h}_2$ are arbitrary reciprocal-lattice vectors subject to the condition $\mathbf{h}_1+\mathbf{h}_2+\mathbf{h}_3=\mathbf{0}$. The subscript e indicates that the enantiomorph is fixed by the doublet invariant $\delta_3 = e|\delta_3|$ ($e=1$ or -1). The enantiomorph-sensitive distribution (27a) is employed to estimate the triplet invariants belonging to the set $\mathscr{A}_e(\mathbf{h}_3)$,

$$\Phi_{\mathbf{h}_1,\mathbf{h}_2,\mathbf{h}_3} \cong \kappa_e. \quad (30)$$

(Note that κ_e depends on $\mathbf{h}_1$, $\mathbf{h}_2$ and $\mathbf{h}_3$.) Since the variance of a von Mises distribution $M(\Phi|A, \xi)$ is a decreasing function of the parameter A, the reliability of this estimate is smaller, the smaller the value of K_e. From (27b) we find the expressions

$$\cos \kappa_e = Q_r/K_e \quad (31a)$$

$$\sin \kappa_e = Q_i/K_e \quad (31b)$$

$$K_e = (Q_r^2 + Q_i^2)^{1/2} \quad (31c)$$

for the cosine and sine invariants and their measure of accuracy, K_e. The triplet invariants of any set $\mathscr{A}_e(\mathbf{h}_3)$, estimated *via* (30), correspond to the same enantiomorph.

Consider the sets $\mathscr{A}_e(\mathbf{h}'_3)$ and $\mathscr{A}_e(\mathbf{h}''_3)$. The triplet invariants of these sets are estimated *via* (27a) [*i.e.* *via* (30)], using the enantiomorph definers $\delta_3 = e|\delta_3(\mathbf{h}'_3)|$ and $\delta_3 = e|\delta_3(\mathbf{h}''_3)|$ respectively. As the enantiomorph is unknown, $\delta_3(\mathbf{h}'_3)$ and $\delta_3(\mathbf{h}''_3)$, and hence $\mathscr{A}_e(\mathbf{h}'_3)$ and $\mathscr{A}_e(\mathbf{h}''_3)$, may correspond to opposite enantiomorphs. This 'inter-set' sign ambiguity also exists in connection with the distributions derived by Pontenagel (1984) and Pontenagel, Krabbendam & Heinerman (1984). In these papers enantiomorph-sensitive distributions were derived by restricting a structure-invariant phase sum to the range $[0, \pi]$ or $[\pi, 2\pi]$. Pontenagel *et al.* (1984) remark: 'As an enantiomorph can be chosen only once, it is essential to state explicitly which invariant phase is restricted. This implies that ... the derived enantiomorph-dependent distributions can only be applied to a subset of the available invariants.' Whereas Pontenagel *et al.* (1984) restricted just one invariant, we propose to restrict more than one invariant even though it is unknown whether the different restrictions specify the same enantiomorph. The cosine invariants of the complete set of available invariants can be estimated by employing enantiomorph-sensitive distributions, since cosine invariants are enantiomorph-insensitive, *i.e.* they are not affected by the inter-set sign ambiguity. As an example, consider the case with three restricted invariants, *viz* $\delta_3(\mathbf{h}_3)$, $\delta_3(\mathbf{h}'_3)$ and $\delta_3(\mathbf{h}''_3)$. The cosine invariants of the sets $\mathscr{A}_1(\mathbf{h}_3)$, $\mathscr{A}_1(\mathbf{h}'_3)$ and $\mathscr{A}_1(\mathbf{h}''_3)$ are estimated *via* (31a) and the sine invariants of one of the three sets, say $\mathscr{A}_1(\mathbf{h}_3)$, *via* (31$b$). In a subsequent phasing procedure structure-factor phases are determined from these cosine and sine invariants.

In the previous example, the information provided by enantiomorph-dependent distributions is not exhausted by employing the sine invariants of only one set, together with the cosine invariants of all three sets. By employing the remaining sine invariants, *i.e.* the sine invariants of the sets $\mathscr{A}_1(\mathbf{h}'_3)$ and $\mathscr{A}_1(\mathbf{h}''_3)$ as well, the sign ambiguity of the triplet invariants of these sets is replaced by an inter-set sign ambiguity. If there are n' and n'' triplet invariants in the sets $\mathscr{A}_1(\mathbf{h}'_3)$ and $\mathscr{A}_1(\mathbf{h}''_3)$ respectively, there is a $2^{(n'+n'')}$-fold sign ambiguity in the previous example. If the sine invariants of the sets $\mathscr{A}_1(\mathbf{h}'_3)$ and $\mathscr{A}_1(\mathbf{h}''_3)$ are employed as well, this ambiguity is reduced to a fourfold inter-set sign ambiguity, which is considerably less severe. Thus, with a phasing procedure capable of resolving the inter-set sign ambiguity, optimal use is made of enantiomorph-dependent distributions.

3.3.

Fortier *et al.* (1985) presented a procedure by which cosine invariants in the full range from -1 to $+1$ can be estimated. The distribution defined in their equations (9) and (10), which was obtained *via* modification of Hauptman's (1982) conditional distribution, equation (3.12), is identical to the von Mises approximation (23) of the distribution $P[\Phi|R_i, S_i, |\delta_i|\ (i=1,2,3)]$ of the present paper. Note that $|\alpha_i|$, β_i of Fortier *et al.* (1985) correspond to $|\delta_i|$, β_{i-1} in our notation. Subsequently, these authors constructed four pairs of formulae corresponding to the eight sign combinations of α_1, α_2 and α_3 [where $\alpha_i = \pm(\varphi_i - \psi_i)$] by modifying their distribution (9).

The right-hand side of their expression (11) for $A_1 \cos \Omega_1$ is modified to give two new expressions, *viz* (12) and (13). This modification changes the parameter A_1 in, say, Z, and shifts the mode from 0 or π to, say, λ and $-\lambda$ for (11) and (12) respectively, where the value of λ can be significantly different from 0 or π. Their equations (12) and (13), however, suffer from incorrect notation: the left-hand sides should read $Z \cos(\Omega_1+\lambda)$ and $Z \cos(\Omega_1-\lambda)$ respectively, instead of $A_1 \cos \Omega_1$.

It can be verified that the eight distributions which were constructed by Fortier *et al.* (1985) have the same functional form as the eight conditional distributions $P[\Phi|R_i, S_i, s_i|\delta_i|\ (i=1,2,3)]$ [our distribution (15)] with $s_i = \pm 1\ (i=1,2,3)$. However, consider the case where the doublet invariants δ_1, δ_2, δ_3 are known both in magnitude and sign (*e.g.* a starting set of doublet invariants). From the construction of the eight distributions by Fortier *et al.* (1985), it is impossible to determine which distribution should be used to estimate the value of the triplet invariant Φ, since their distributions are expressed in terms of α_i, and $\alpha_i = \pm\delta_i$. From our derivation it follows that the doublet invariant information can be exploited by estimating Φ *via* the distribution $P[\Phi|R_i, S_i, \delta_i\ (i=1,2,3)]$ [(15)].

Cosine invariants and their measures of accuracy were calculated by Fortier *et al.* (1985) *via* their equations (15) and (16) respectively, which are repeated here for convenience:

$$\cos \Omega_{\text{av}} = \sum_{j=1}^{4} A_j \cos \xi_j / \sum_{j=1}^{4} A_j \tag{32a}$$

$$A_{\text{av}} = \tfrac{1}{4} \sum_{j=1}^{4} A_j \cos(\max|\xi_j - \Omega_{\text{av}}|). \tag{32b}$$

The subscript j labels those four sign combinations s_1, s_2, s_3 for which

$$0 \le \xi_{s_1,s_2,s_3} \le \pi. \tag{33}$$

Instead of comparing these equations directly with (31*a*) and (31*c*) of the present paper we will introduce similar equations which can be compared more easily with (31*a*) and (31*c*).

By restricting the summations in (22) to the four sign combinations for which (33) holds, we obtain the following multimodal distribution:

$$P[\Phi|A_j, \xi_j\ (j=4)] = (L/2) \sum_{j=1}^{4} I_0(A_j) M(\Phi|A_j, \xi_j). \tag{34}$$

This distribution is approximated by the von Mises distribution

$$M(\Phi|K_{\text{av}}, \kappa_{\text{av}}) \tag{35a}$$

for small A_j, with

$$K_{\text{av}} \exp i\kappa_{\text{av}} = \tfrac{1}{4} \sum_{j=1}^{4} A_j \exp i\xi_j. \tag{35b}$$

Thus

$$\cos \kappa_{\text{av}} = \sum_{j=1}^{4} A_j \cos \xi_j / 4K_{\text{av}} \tag{36}$$

and

$$K_{\text{av}} = \tfrac{1}{4} \sum_{j=1}^{4} A_j \cos(\xi_j - \kappa_{\text{av}}). \tag{37}$$

With the approximation

$$K_{\text{av}} \simeq \tfrac{1}{4} \sum_{j=1}^{4} A_j, \tag{38}$$

equation (15) [*i.e.* (32*a*) of the present paper] of Fortier *et al.* (1985) is obtained from (36), whereas their equation (16) [*i.e.* (32*b*)] is obtained from (37) after replacing the arguments of the cosines in (37) by the maximum argument. Instead of A_{av} and Ω_{av}, we will compare K_{av} and κ_{av} with K_e and κ_e respectively.

From the construction in the Argand diagram corresponding to the equations (24), (27*b*) and (35*b*), taking into account (19) and (20), it is readily established that

$$K' \cos \kappa' = K_e \cos \kappa_e = K_{\text{av}} \cos \kappa_{\text{av}} \tag{39a}$$

or, since κ' is restricted to 0 or π,

$$K' = K_e|\cos \kappa_e| = K_{\text{av}}|\cos \kappa_{\text{av}}|. \tag{39b}$$

The closer the value of κ_e (or κ_{av}) to $\pm\frac{1}{2}\pi$, the smaller the value of K' and, hence, the larger the variance of $M(\Phi|K', \kappa')$. This effect, expressed quantitatively by (39*b*), was observed qualitatively by Fortier *et al.* (1985), who remark that 'systematic deviations from the 0 or π estimates ... result in a lowering of the A value or an increase in the variance.'

As noted above, the analysis of Fortier *et al.* (1985) started from Hauptman's [(1982), equation (3.12)] distribution $P[\Phi|R_i, S_i\ (i=1,2,3)]$. This distribution is a *marginal* distribution of $P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)]$ [(7)] and contains therefore less information than (7). By their alteration of Hauptman's distribution, Fortier *et al.* (1985) reconstructed some of the information contained in (7) which led to a distribution identical to (23) of the present paper. Subsequent alterations of the former distribution produced the eight conditional distributions (15) in terms of α_i instead of δ_i. In our approach the formulae of Fortier *et al.* (1985) can be obtained *via* straightforward derivations starting from Hauptman's (1982) *joint* probability distribution, equation (3.1), *via* our distribution (7). Moreover, the new enantiomorph-sensitive distribution (26) was derived.

The equations (15) and (16) of Fortier *et al.* (1985) were obtained by restricting the sign combinations according to (33). However, (33) is a rather arbitrary restriction criterion, devoid of physical meaning. The four contributing terms in the summation in (27*b*) all pertain to the same enantiomorph. The selection criterion (33) of Fortier *et al.* (1985) is thus replaced by the physically meaningful criterion of enantiomorph selection. Sine invariants estimated *via* (35*b*) [replace cos by sin in (36)] have no physical meaning since the contributing terms in (35*b*) will in general correspond to different enantiomorphs. Therefore, *via* (35*b*), only cosine invariants can be estimated. Application of (27*b*), however, not only allows estimation of cosine invariants but also of sine invariants (see § 3.2).

3.4.

The relation between triplet invariants estimated *via* the von Mises approximations of the distributions (22), (26) and (34) was given by (39*a*) and (39*b*). Although the latter distributions are multimodal in general, they can be unimodal depending on the parameters A and ξ of the contributing von Mises distributions. In the latter case the von Mises approximations of the distributions (22), (26) and (34) will be relatively good. For some triplet relations, however, the approximation may be poor.

In their treatment of errors in isomorphous replacement Blow & Crick (1959) have used probability distributions of structure-factor phases. They showed that phases estimated by the centroids of their distributions lead to the least mean-square error in electron density over the unit cell. As an alternative to estimating a triplet invariant *via* the von Mises approximation of its distribution $P(\Phi)$ we will estimate the invariant by the centroid phase ξ of its distribution:

$$m \exp i\xi = \int_0^{2\pi} P(\Phi) \exp(i\Phi)\, \mathrm{d}\Phi \Big/ \int_0^{2\pi} P(\Phi)\, \mathrm{d}\Phi. \tag{40}$$

The magnitude m serves as a measure of the reliability of the estimate.

After substitution of the distributions (22), (26) and (34) in the right-hand side of (40) we obtain respectively

$$m' \exp i\xi' = L \sum_{s_1,s_2,s_3=\pm 1} I_1(A_{s_1,s_2,s_3}) \exp i\xi_{s_1,s_2,s_3} \tag{41}$$

$$m_e \exp i\xi_e = (L/2) \sum_{s_1,s_2=\pm 1} I_1(A_{s_1,s_2,e}) \exp i\xi_{s_1,s_2,e} \tag{42}$$

$$m_{\text{av}} \exp i\xi_{\text{av}} = (L/2) \sum_{j=1}^{4} I_1(A_j) \exp i\xi_j \tag{43}$$

where (19), (20) and (I.3) are used and L is defined in (21*b*). I_1 is the modified Bessel function of the first kind and of order one.

The relation between the estimates ξ', ξ_e and ξ_{av} can be obtained from (41)-(43), analogous to the derivation of (39*a*) and (39*b*) from (24), (27*b*) and (35*b*). Hence the relations (39*a*) and (39*b*) are also valid with κ', κ_e and κ_{av} replaced by ξ', ξ_e and ξ_{av} respectively and K', K_e and K_{av} by m', m_e and m_{av}.

3.5.

In §§ 3.1 and 3.2 we derived distributions of the triplet invariant Φ. This invariant is a member of the set of eight triplet invariants $\{\Omega_{klm}\}$ that exist for the (f, g) pair of structures, where Ω_{klm} is given by (8). (Note that Φ is the member with $klm = 000$, so Φ may be notated by Ω_{000}). A distribution $\mathscr{P}_{klm}$ of the triplet invariant Ω_{klm} analogous to a distribution $\mathscr{P}$ of the triplet invariant Φ may yield the same information as $\mathscr{P}$. This is the case for the distribution $P[\Phi|R_i, S_i, \delta_i\ (i=1,2,3)]$ [(15)] and the analogous distribution $P_{klm}[\Omega_{klm}|R_i, S_i, \delta_i\ (i=1,2,3)]$. The latter distribution can be obtained from the former using (8) and the expressions in Appendix I, leading to

$$\begin{aligned} &P_{klm}[\Omega_{klm}|R_i, S_i, \delta_i\ (i=1,2,3)] \\ &\quad = M(\Omega_{klm}|A_{klm}, \xi_{klm}) \end{aligned} \tag{44}$$

with

$$A_{klm} = A \quad \text{and} \quad \xi_{klm} = \xi - k\delta_1 - l\delta_2 - m\delta_3 \tag{45}$$

where k, l and m take the values 0 or 1 and A and ξ are given by (16)-(18).

We conclude that the eight distributions $P_{klm}[\Omega_{klm}|R_i, S_i, \delta_i\ (i=1,2,3)]$ have equal variances and are merely shifted with respect to each other over known distances. These distributions contain therefore the same information, so no information is lost by considering only one member of the eight distributions (*i.e.* one type of triplet invariant). In contrast to the latter distributions, the distributions $P_{klm}[\Omega_{klm}|R_i, S_i\ (i=1,2,3)]$ have unequal variances. The distributions with $klm = 000$, 001, 011 and 111 are given by Hauptman [(1982), equations (3.12), (3.16), (3.19) and (3.22) respectively]. Appendix IV deals with a simple procedure to obtain the distribution $P_{klm}[\Omega_{klm}|R_i, S_i\ (i=1,2,3)]$ with, for example, $klm = 110$, from that with $klm = 001$ or *vice versa*.

4. Conditional distributions derived from $P[\Theta, \varepsilon_1, \varepsilon_2, \varepsilon_3|R_i, T_i\ (i=1,2,3)]$

4.1.

If the strucutre formed by the replacement atoms (h structure) is known, the remaining phase ambiguity reads

$$\varphi_i = \theta_i \pm |\varepsilon_i| \tag{46}$$

where $-\pi < \varepsilon_i \le \pi$. The phases θ_i are calculated from the known h structure, while $|\varepsilon_i|$ is calculated from (6). The remaining sign ambiguity is resolved by calculating the probability that the sign of ε_i is positive (negative) as was proposed by Fan Hai-fu *et al.* (1984). However, our analysis differs from the analysis of these authors in the probabilistic basis used for the calculation of the sign probability. Their formulae were obtained from Cochran's (1955) distribution, whereas our formulae are obtained from Hauptman's (1982) joint probability distribution for the SIR case, *via* (11).

By fixing the known triplet invariant Θ, we obtain from (11) the joint conditional probability distribution of the doublet invariants ε_1, ε_2 and ε_3,

$$\begin{aligned}
&P[\varepsilon_1, \varepsilon_2, \varepsilon_3|R_i, T_i, \Theta\ (i=1,2,3)]\\
&\quad\sim \exp\{2\beta' \sum_{i=1}^{3} R_iT_i \cos\varepsilon_i\\
&\qquad +2\beta_0' R_1R_2R_3 \cos(\varepsilon_1+\varepsilon_2+\varepsilon_3+\Theta)\\
&\qquad +2\beta_1'[R_1R_2T_3 \cos(\varepsilon_1+\varepsilon_2+\Theta)\\
&\qquad +R_1T_2R_3 \cos(\varepsilon_1+\varepsilon_3+\Theta)\\
&\qquad +T_1R_2R_3 \cos(\varepsilon_2+\varepsilon_3+\Theta)]\\
&\qquad +2\beta_2'[R_1T_2T_3 \cos(\varepsilon_1+\Theta)\\
&\qquad +T_1R_2T_3 \cos(\varepsilon_2+\Theta)\\
&\qquad +T_1T_2R_3 \cos(\varepsilon_3+\Theta)]\}.
\end{aligned} \tag{47}$$

Next, fixing ε_2 and ε_3 results in the von Mises distribution

$$\begin{aligned}
&P[\varepsilon_1|R_i, T_i, \varepsilon_2, \varepsilon_3, \Theta\ (i=1,2,3)]\\
&\quad = M(\varepsilon_1|B,\zeta)
\end{aligned} \tag{48}$$

where B and ζ follow from

$$B\cos\zeta = U \quad B\sin\zeta = V \quad B>0$$

and

$$\begin{aligned}
U &= 2\beta' R_1T_1 + 2\beta_0' R_1R_2R_3 \cos(\varepsilon_2+\varepsilon_3+\Theta)\\
&\quad +2\beta_1'[R_1R_2T_3 \cos(\varepsilon_2+\Theta)\\
&\quad +R_1T_2R_3 \cos(\varepsilon_3+\Theta)]\\
&\quad +2\beta_2' R_1T_2T_3 \cos\Theta\\
V &= -2\beta_0' R_1R_2R_3 \sin(\varepsilon_2+\varepsilon_3+\Theta)\\
&\quad -2\beta_1'[R_1R_2T_3 \sin(\varepsilon_2+\Theta)\\
&\quad +R_1T_2R_3 \sin(\varepsilon_3+\Theta)]\\
&\quad -2\beta_2' R_1T_2T_3 \sin\Theta.
\end{aligned} \tag{49}$$

4.2.

Let t_i be the sign of ε_i $(-\pi < \varepsilon_i \le \pi)$, *i.e.* $\varepsilon_i = t_i|\varepsilon_i|$. After fixing $|\varepsilon_1|$ in (48), a distribution is derived, written as $P(t_1|t_2, t_3)$ in short-hand notation, which gives the probability of the event that the sign of the doublet invariant ε_1 is t_1, given the doublet invariants ε_2 and ε_3, the triplet invariant Θ and the magnitudes R_i, T_i $(i=1,2,3)$ and $|\varepsilon_1|$. With V given by (49) we find

$$P(t_1|t_2, t_3) \sim \exp(t_1 V \sin|\varepsilon_1|), \tag{50}$$

from which follows

$$P(t_1|t_2, t_3) = \tfrac{1}{2} + \tfrac{1}{2} t_1 \tanh(V \sin|\varepsilon_1|). \tag{51}$$

4.3.

The joint probability distribution of the signs of the doublet invariants ε_i derived from (47) is denoted by $P(t_1, t_2, t_3)$ and reads

$$\begin{aligned}
&P(t_1, t_2, t_3)\\
&\quad\sim \exp\{2\beta_0' R_1R_2R_3 \cos(t_1|\varepsilon_1| + t_2|\varepsilon_2| + t_3|\varepsilon_3| + \Theta)\\
&\qquad +2\beta_1'[R_1R_2T_3 \cos(t_1|\varepsilon_1| + t_2|\varepsilon_2| + \Theta)\\
&\qquad +R_1T_2R_3 \cos(t_1|\varepsilon_1| + t_3|\varepsilon_3| + \Theta)\\
&\qquad +T_1R_2R_3 \cos(t_2|\varepsilon_2| + t_3|\varepsilon_3| + \Theta)]\\
&\qquad +2\beta_2'[R_1T_2T_3 \cos(t_1|\varepsilon_1| + \Theta)\\
&\qquad +T_1R_2T_3 \cos(t_2|\varepsilon_2| + \Theta)\\
&\qquad +T_1T_2R_3 \cos(t_3|\varepsilon_3| + \Theta)]\}.
\end{aligned} \tag{52}$$

It can be established* that $t_i = s_i$; the possibility of using $P(t_1, t_2, t_3)$ as a weight in (24) or (27*b*), for example, will be a subject of further investigation.

Formula (51) cannot be used if the signs of ε_2 and ε_3 are unknown. For this case we derive the marginal probability distribution $P(t_1)$ of the sign t_1 of the doublet invariant ε_1,

$$P(t_1) = \sum_{t_2, t_3 = \pm 1} P(t_1, t_2, t_3), \tag{53}$$

which gives the probability that t_1 is positive or negative irrespective of the signs t_2 and t_3. Approximating $\exp(x)$ by $1+x$, we obtain

$$\begin{aligned}
P(t_1) &\simeq \tfrac{1}{2} - \tfrac{1}{2} t_1 \tanh(\sin|\varepsilon_1| \sin\Theta\\
&\quad \times [2\beta_0' R_1R_2R_3 \cos|\varepsilon_2| \cos|\varepsilon_3|\\
&\quad +2\beta_1'(R_1R_2T_3 \cos|\varepsilon_2|\\
&\quad +R_1T_2R_3 \cos|\varepsilon_3|) + 2\beta_2' R_1T_2T_3]\}.
\end{aligned} \tag{54}$$

* Application of the law of sines to the triangle associated with the relation $F_i^0 = G_i^0 - H_i^0$ yields $|H_i^0|/\sin\delta_i = |G_i^0|/\sin\varepsilon_i$. Since $\delta_i = s_i|\delta_i|$ and $\varepsilon_i = t_i|\varepsilon_i|$ we have $s_i = t_i$.

4.4.

If n triplets $\mathbf{h}$, $\mathbf{k}_i$, $-\mathbf{h}-\mathbf{k}_i$ with $i=1,\ldots,n$ are available, the distribution

$$P[\varepsilon_{\mathbf{h}}, \varepsilon_{\mathbf{k}_i}, \varepsilon_{-\mathbf{h}-\mathbf{k}_i}\ (i=1,\ldots,n)|R_{\mathbf{h}}, R_{\mathbf{k}_i}, R_{-\mathbf{h}-\mathbf{k}_i}, T_{\mathbf{h}}, T_{\mathbf{k}_i}, T_{-\mathbf{h}-\mathbf{k}_i}, \Theta_{\mathbf{h},\mathbf{k}_i}\ (i=1,\ldots,n)] \quad (55)$$

may be used instead of (47). If we approximate the former distribution by

$$\prod_{i=1}^{n} P(\varepsilon_{\mathbf{h}}, \varepsilon_{\mathbf{k}_i}, \varepsilon_{-\mathbf{h}-\mathbf{k}_i}|R_{\mathbf{h}}, R_{\mathbf{k}_i}, R_{-\mathbf{h}-\mathbf{k}_i}, T_{\mathbf{h}}, T_{\mathbf{k}_i}, T_{-\mathbf{h}-\mathbf{k}_i}, \Theta_{\mathbf{h},\mathbf{k}_i}), \quad (56)$$

a von Mises distribution analogous to (48) may be derived:

$$P[\varepsilon_{\mathbf{h}}|R_{\mathbf{h}}, R_{\mathbf{k}_i}, R_{-\mathbf{h}-\mathbf{k}_i}, T_{\mathbf{h}}, T_{\mathbf{k}_i}, T_{-\mathbf{h}-\mathbf{k}_i}, \varepsilon_{\mathbf{k}_i}, \varepsilon_{-\mathbf{h}-\mathbf{k}_i}, \Theta_{\mathbf{h},\mathbf{k}_i}\ (i=1,\ldots,n)] = M(\varepsilon_{\mathbf{h}}|B,\zeta) \quad (57)$$

where B and ζ follow from

$$B\cos\zeta = U \quad B\sin\zeta = V \quad B>0,$$

with

$$\begin{aligned} U = 2\beta' R_1 T_1 + \sum_{i=1}^{n} \{&2\beta_0' R_1 R_{2i} R_{3i} \cos(\varepsilon_{2i}+\varepsilon_{3i}+\Theta_i) \\ &+ 2\beta_1'[R_1 R_2 T_{3i}\cos(\varepsilon_{2i}+\Theta_i) \\ &+ R_1 T_{2i} R_{3i}\cos(\varepsilon_{3i}+\Theta_i)] \\ &+ 2\beta_2' R_1 T_{2i} T_{3i}\cos\Theta_i\} \\ V = \sum_{i=1}^{n} -\{&2\beta_0' R_1 R_{2i} R_{3i}\sin(\varepsilon_{2i}+\varepsilon_{3i}+\Theta_i) \\ &+ 2\beta_1'[R_1 R_{2i} T_{3i}\sin(\varepsilon_{2i}+\Theta_i) \\ &+ R_1 T_{2i} R_{3i}\sin(\varepsilon_{3i}+\Theta_i)] \\ &+ 2\beta_2' R_1 T_{2i} T_{3i}\sin\Theta_i\} \end{aligned} \quad (58)$$

and where, for example, $R_{\mathbf{h}}$, $R_{\mathbf{k}_i}$ and $R_{-\mathbf{h}-\mathbf{k}_i}$ are denoted by R_1, R_{2i} and R_{3i} respectively. With V given by (58), equation (51) still holds. Equation (54) may be generalized analogously.

4.5.

Formulae (16) and (18) of Fan Hai-fu *et al.* (1984) are to be compared with our formulae (51) and (54). The invariant phases ε_1, ε_2, ε_3 and Θ are denoted by these authors as $-\Delta\varphi_{\mathbf{H}}$, $\Delta\varphi_{\mathbf{H}'}$, $\Delta\varphi_{\mathbf{H}-\mathbf{H}'}$ and φ_3', whereas the magnitudes R_1, R_2 and R_3 are denoted as $|E_{\mathbf{H}}|$, $|E_{\mathbf{H}'}|$ and $|E_{\mathbf{H}-\mathbf{H}'}|$ respectively. The term containing the product $R_1R_2R_3$ appears both in the aforementioned equations (16) and (18) and in our formulae (51) and (54). Note, however, that the coefficients differ: β_0' in (51) and (54) *vs* $\sigma_3\sigma_2^{-3/2}$ in (16) and (18), where

$$\sigma_a \equiv \sum_{j=1}^{N} f_j^a. \quad (59)$$

The remaining terms in (51) and (54) do not appear in (16) and (18). Probabilities calculated *via* our formulae will deviate more from those calculated by Fan Hai-fu *et al.*, the greater the deviations of β_1' and β_2' from 0, and of β_0' from $\sigma_3\sigma_2^{-3/2}$, *i.e.* the greater α_{a0c} and, hence, the more atomic positions are shared by the associated structures. Formulae (16) and (18) of Fan Hai-fu *et al.* (1984) represent a special case of our formulae, *viz* the case with $\alpha_{a0c}=0$.

In the case of isomorphous addition, all atomic position vectors of the h structure are different from those of the f structure, *i.e.* $\alpha_{a0c}=0$ [with α_{abc} as defined in (3)], implying $\beta_0'=\sigma_3\sigma_2^{-3/2}$ and $\beta_1'=\beta_2'=0$ so that our formulae (51) and (54) reduce to (16) and (18) of Fan Hai-fu *et al.* (1984) respectively. With isomorphous substitution, however, the f structure and the h structure have atomic position vectors in common, so $\alpha_{a0c}\neq 0$, which implies $\beta_1'\neq 0\neq\beta_2'$ and $\beta_0'\neq\sigma_3\sigma_2^{-3/2}$. For this case our formulae do not coincide with those of Fan Hai-fu *et al.* (1984).

According to Fan Hai-fu *et al.* (1984) their analysis applies to the (f, h) pair of structures as well as to the (g, h) pair of structures. The analysis presented in § 4 of the present paper which dealt with the (f, h) pair of structures holds equally well for the (g, h) pair, leading to sign distributions of the doublet invariants χ_i analogous to those of δ_i. The set of atomic position vectors of the h structure is a subset of the set of atomic position vectors of the g structure so that $\alpha_{0bc}\neq 0$, *i.e.* $\beta_1'\neq 0\neq\beta_2'$.

Partial structure information can be incorporated by applying our approach to the (f, h') pair of structures [or the (g, h') pair of structures], where the h' structure is a known partial structure of the f structure (or the g structure). Again, different formulae are obtained from those obtained in a recent paper by Fan Hai-fu *et al.* (1985) who employed the product of Cochran's (1955) and Sim's (1959) distributions to incorporate partial structure information.

In conclusion, our formulae (51) and (54) are generalizations of equations (16) and (18) of Fan Hai-fu *et al.* (1984). The latter formulae represent the special case where the associated structures have no atomic positions in common.

5. Concluding remarks

Application of a newly derived enantiomorph-sensitive distribution with SIR data opens up the ability to estimate both sine and cosine invariants of well defined sets of triplet invariants together with a measure of accuracy. Thus, the sign ambiguity of individual triplet invariants, present in the procedure of Fortier *et al.* (1985), is reduced to an inter-set sign ambiguity. Enantiomorph-sensitive distributions derived by restricting phase invariants have a wider applicability than conceived by Pontenagel (1984) and Pontenagel *et al.* (1984). The statistical analysis employed in the second part of the paper leads to formulae for the resolution of the SIR ambiguity which generalize those of Fan Hai-fu *et al.* (1984). Practical tests of the proposed new formulae will be published in a later paper.

APPENDIX I

Some formulae

As is well known (Hauptman, 1971), a sum of cosines can be expressed as a single cosine by

$$\sum_i A_i \cos(\varphi - \xi_i) = A \cos(\varphi - \xi) \tag{I.1}$$

where

$$A \exp i\xi = \sum_j A_j \exp i\xi_j \tag{I.2}$$

or, equivalently,

$$A^2 = \sum_i \sum_j A_i A_j \cos(\xi_i - \xi_j)$$

$$A \cos \xi = \sum_i A_i \cos \xi_i$$

$$A \sin \xi = \sum_i A_i \sin \xi_i.$$

From Giacovazzo (1980),

$$\int_{\alpha}^{2\pi+\alpha} \exp[in\theta + A \cos\theta]\, d\theta = 2\pi I_n(A) \tag{I.3}$$

where I_n is the modified Bessel function of the first kind and of order n.

APPENDIX II

The derivation of $P[s_1, s_2, s_3|R_i, S_i, |\delta_i|\ (i=1,2,3)]$

With A and ξ obtained from (16) the distribution $P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)]$ [equation (7)] can be expressed as

$$\begin{aligned} P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)] &= C_1 \exp\left(2\beta \sum_{i=1}^{3} R_i S_i \cos \delta_i\right) \\ &\quad \times \exp[A \cos(\Phi - \xi)]. \end{aligned} \tag{II.1}$$

Next, by application of Bayes' theorem and using (15), we obtain

$$\begin{aligned} P[\delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)] &= \frac{P[\Phi, \delta_1, \delta_2, \delta_3|R_i, S_i\ (i=1,2,3)]}{P[\Phi|R_i, S_i, \delta_i\ (i=1,2,3)]} \\ &= 2\pi C_1 I_0(A) \exp\left(2\beta \sum_{i=1}^{3} R_i S_i \cos \delta_i\right). \end{aligned} \tag{II.2}$$

Finally, after fixing $|\delta_1|$, $|\delta_2|$ and $|\delta_3|$, (21*a*) is obtained.

APPENDIX III

The real and imaginary parts defined in (28)

By (17), (18) and (28), we calculate

$$\begin{aligned} Q_r = 2\beta_0 R_1 R_2 R_3 &+ 2\beta_1(S_1 R_2 R_3 \cos \delta_1 + R_1 S_2 R_3 \cos \delta_2 \\ &+ R_1 R_2 S_3 \cos \delta_3) \\ &+ 2\beta_2(S_1 S_2 R_3 \cos \delta_1 \cos \delta_2 \\ &+ S_1 R_2 S_3 \cos \delta_1 \cos \delta_3 \\ &+ R_1 S_2 S_3 \cos \delta_2 \cos \delta_3) \\ &+ 2\beta_3 S_1 S_2 S_3 \cos \delta_1 \cos \delta_2 \cos \delta_3; \end{aligned} \tag{III.1}$$

$$\begin{aligned} Q_i = \sin \delta_3 [2\beta_1 R_1 R_2 S_3 &+ 2\beta_2(S_1 R_2 S_3 \cos \delta_1 + R_1 S_2 S_3 \cos \delta_2) \\ &+ 2\beta_3 S_1 S_2 S_3 \cos \delta_1 \cos \delta_2]. \end{aligned} \tag{III.2}$$

APPENDIX IV

The calculation of $P_{klm}[\Omega_{klm}|R_i, S_i\ (i=1,2,3)]$

A simple procedure to obtain the distribution

$$P_{110}[\Omega_{110}|R_i, S_i\ (i=1,2,3)]$$

from the distribution

$$P_{001}[\Omega_{001}|R_i, S_i\ (i=1,2,3)]$$

consists of interchanging the following parameters:

$$\varphi_i \leftrightarrow \psi_i$$

$$R_i \leftrightarrow S_i$$

$$\beta_0 \leftrightarrow \beta_3$$

$$\beta_1 \leftrightarrow \beta_2.$$

By this procedure the distributions

$$P_{110}[\Omega_{110}|R_i, S_i\ (i=1,2,3)]$$

and

$$P_{100}[\Omega_{100}|R_i, S_i\ (i=1,2,3)]$$

are obtained immediately from the distributions

$$P_{001}[\Omega_{001}|R_i, S_i\ (i=1,2,3)]$$

and

$$P_{011}[\Omega_{011}|R_i, S_i\ (i=1,2,3)]$$

calculated by Hauptman [1982, equations (3.16)-(3.18) and (3.19)-(3.21)].

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Direct Methods in Superspace. I. Preliminary Theory and Test on the Determination of Incommensurate Modulated Structures

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Abstract

The validity of the Sayre equation [Sayre (1952). *Acta Cryst.* **5**, 60-65] for $(3+n)$-dimensional periodic structures is examined. A practical procedure is proposed for the determination of incommensurate modulated structures; this is an extension of the direct method previously proposed for solving superstructures [Fan Hai-fu, He Lao, Qian Jin-zi & Liu Shi-xiang (1978). *Acta Phys. Sin.* **27**, 554-558]. With the newly proposed method, the phase problem for the main as well as the satellite reflections can be solved directly without making particular assumptions about the modulation. A known incommensurate modulated structure, γ-Na_2CO_3, was used in the test. Satisfactory results were obtained.

Introduction

Incommensurate modulated phases are often found in inorganic solids (minerals, alloys, *etc.*) and organic solids. In many cases, the transition to the modulated structure corresponds to a change of certain physical properties. Hence it is essential to know the structure of incommensurate phases in order to understand the mechanism of the transition and properties in the modulated state. Up to the present, methods used in the determination of incommensurate modulated structures, such as the least-squares method of Yamamoto (1982), rely on some assumption about the modulation and on a preliminary knowledge of the main (average) structure. In this paper a method is described which starts by handling X-ray diffraction data and ends in a $(3+n)$-dimensional electron density map revealing the details of the modulated structure objectively. This method is proposed not to replace but to combine with the least-squares method in a way like that for solving ordinary small molecular structures.

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$(3+n)$-dimensional description of modulated structures

A modulated structure is a kind of crystal structure in which the atoms suffer from certain occupational and/or positional fluctuations according to a periodic modulation. In the case that all the wave vectors of the modulation wave are commensurate with unit vectors of the reciprocal cell, a superstructure results, while in the case that the wave vectors are incommensurate with unit vectors of the reciprocal cell, an incommensurate structure is obtained. An n-dimensional $(n=1, 2, \ldots)$ periodic modulation corresponds to an n-dimensional modulated structure. In this section, the descriptions of modulated structure by de Wolff (1974) and by Yamamoto (1982) are briefly reviewed.

For an n-dimensional modulated structure, the reciprocal vector $\mathbf{H}$ of a main or satellite reflection can be expressed in three-dimensional space as

$$\mathbf{H} = h_1\mathbf{a}^* + h_2\mathbf{b}^* + h_3\mathbf{c}^* + \sum_{i=1}^{n} h_{3+i}\mathbf{k}^i, \qquad (1)$$

where

$$\mathbf{k}^i = k_1^i\mathbf{a}^* + k_2^i\mathbf{b}^* + k_3^i\mathbf{c}^*.$$

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