2.2. Direct methods

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2.2.1. List of symbols and abbreviations

f_j atomic scattering factor of jth atom
Z_j atomic number of jth atom
N number of atoms in the unit cell
m order of the point group

$$[\sigma_r]_p, [\sigma_r]_q, [\sigma_r]_N, \ldots = \sum_{j=1}^{p} Z_j^r, \sum_{j=1}^{q} Z_j^r, \sum_{j=1}^{N} Z_j^r, \ldots$$

$[\sigma_r]_N$ is always abbreviated to σ_r when N is the number of atoms in the cell

$$\sum_{p}, \sum_{q}, \sum_{N}, \ldots = \sum_{j=1}^{p} f_j^2, \sum_{j=1}^{q} f_j^2, \sum_{j=1}^{N} f_j^2, \ldots$$

s.f.   structure factor
n.s.f.   normalized structure factor
cs.   centrosymmetric
ncs.   noncentrosymmetric
s.i.   structure invariant
s.s.   structure seminvariant
$\mathbf{C} = (\mathbf{R}, \mathbf{T})$ symmetry operator; $\mathbf{R}$ is the rotational part, $\mathbf{T}$ the translational part
$\varphi_{\mathbf{h}}$ phase of the structure factor $F_{\mathbf{h}} = |F_{\mathbf{h}}| \exp(i\varphi_{\mathbf{h}})$

2.2.2. Introduction

Direct methods are today the most widely used tool for solving small crystal structures. They work well both for equal-atom molecules and when a few heavy atoms exist in the structure. In recent years the theoretical background of direct methods has been improved to take into account a large variety of prior information (the form of the molecule, its orientation, a partial structure, the presence of pseudosymmetry or of a superstructure, the availability of isomorphous data or of data affected by anomalous-dispersion effects, . . .). Owing to this progress and to the increasing availability of powerful computers, the phase problem for small molecules has been solved in practice: a number of effective, highly automated packages are today available to the scientific community.

The combination of direct methods with so-called direct-space methods have recently allowed the *ab initio* crystal structure solution of proteins. The present limit of complexity is about 2500 non-hydrogen atoms in the asymmetric unit, but diffraction data at atomic resolution (~1 Å) are required. Trials are under way to bring this limit to 1.5 Å and have shown some success.

The theoretical background and tables useful for origin specification are given in Section 2.2.3; in Section 2.2.4 the procedures for normalizing structure factors are summarized. Phase-determining formulae (inequalities, probabilistic formulae for triplet, quartet and quintet invariants, and for one- and two-phase s.s.'s, determinantal formulae) are given in Section 2.2.5. In Section 2.2.6 the connection between direct methods and related techniques in real space is discussed. Practical procedures for solving small-molecule crystal structures are described in Sections 2.2.7 and 2.2.8, and references to the most extensively used packages are given in Section 2.2.9. The integration of direct methods, isomorphous replacement and anomalous-dispersion techniques is briefly discussed in Section 2.2.10.

The reader interested in a more detailed description of the topic is referred to a recent textbook (Giacovazzo, 1998).

2.2.3. Origin specification

(*a*) Once the origin has been chosen, the symmetry operators $\mathbf{C}_s \equiv (\mathbf{R}_s, \mathbf{T}_s)$ and, through them, the algebraic form of the s.f. remain fixed.

A shift of the origin through a vector with coordinates $\mathbf{X}_0$ transforms $\varphi_{\mathbf{h}}$ into

$$\varphi_{\mathbf{h}}' = \varphi_{\mathbf{h}} - 2\pi\mathbf{h} \cdot \mathbf{X}_0 \tag{2.2.3.1}$$

and the symmetry operators $\mathbf{C}_s$ into $\mathbf{C}_s' = (\mathbf{R}_s', \mathbf{T}_s')$, where

$$\mathbf{R}_s' = \mathbf{R}_s; \quad \mathbf{T}_s' = \mathbf{T}_s + (\mathbf{R}_s - \mathbf{I})\mathbf{X}_0 \quad s = 1, 2, \ldots, m. \tag{2.2.3.2}$$

(*b*) *Allowed* or *permissible origins* (Hauptman & Karle, 1953, 1959) for a given algebraic form of the s.f. are all those points in direct space which, when taken as origin, maintain the same symmetry operators $\mathbf{C}_s$. The allowed origins will therefore correspond to those points having the same symmetry environment in the sense that they are related to the symmetry elements in the same way. For instance, if $\mathbf{T}_s = 0$ for $s = 1, \ldots, 8$, then the allowed origins in *Pmmm* are the eight inversion centres.

To each functional form of the s.f. a set of permissible origins will correspond.

(*c*) A translation between permissible origins will be called a *permissible* or *allowed translation*. Trivial allowed translations correspond to the lattice periods or to their multiples. A change of origin by an allowed translation does not change the algebraic form of the s.f. Thus, according to (2.2.3.2), all origins allowed by a fixed functional form of the s.f. will be connected by translational vectors $\mathbf{X}_p$ such that

$$(\mathbf{R}_s - \mathbf{I})\mathbf{X}_p = \mathbf{V}, \quad s = 1, 2, \ldots, m, \tag{2.2.3.3}$$

where $\mathbf{V}$ is a vector with zero or integer components.

In centred space groups, an origin translation corresponding to a centring vector $\mathbf{B}_v$ does not change the functional form of the s.f. Therefore all vectors $\mathbf{B}_v$ represent permissible translations. $\mathbf{X}_p$ will then be an allowed translation (Giacovazzo, 1974) not only when, as imposed by (2.2.3.3), the difference $\mathbf{T}_s' - \mathbf{T}_s$ is equal to one or more lattice units, but also when, for any s, the condition

$$(\mathbf{R}_s - \mathbf{I})\mathbf{X}_p = \mathbf{V} + \alpha\mathbf{B}_v, \quad s = 1, 2, \ldots, m; \quad \alpha = 0, 1 \tag{2.2.3.4}$$

is satisfied.

We will call any set of cs. or ncs. space groups having the same allowed origin translations a Hauptman–Karle group (H–K group). The 94 ncs. primitive space groups, the 62 primitive cs. groups, the 44 ncs. centred space groups and the 30 cs. centred space groups can be collected into 13, 4, 14 and 5 H–K groups, respectively (Hauptman & Karle, 1953, 1956; Karle & Hauptman, 1961; Lessinger & Wondratschek, 1975). In Tables 2.2.3.1–2.2.3.4 the H–K groups are given together with the allowed origin translations.

(*d*) Let us consider a product of structure factors

$$F_{\mathbf{h}_1}^{A_1} \times F_{\mathbf{h}_2}^{A_2} \times \ldots \times F_{\mathbf{h}_n}^{A_n} = \prod_{j=1}^{n} F_{\mathbf{h}_j}^{A_j}$$

$$= \exp\left(i\sum_{j=1}^{n} A_j\varphi_{\mathbf{h}_j}\right) \prod_{j=1}^{n} |F_{\mathbf{h}_j}|^{A_j}, \tag{2.2.3.5}$$

A_j being integer numbers.

The factor $\sum_{j=1}^{n} A_j \varphi_{\mathbf{h}_j}$ is the phase of the product (2.2.3.5). A *structure invariant* (s.i.) is a product (2.2.3.5) such that

$$\sum_{j=1}^{n} A_j \mathbf{h}_j = 0. \qquad (2.2.3.6)$$

Since $|F_{\mathbf{h}_j}|$ are usually known from experiment, it is often said that s.i.'s are combinations of phases

$$\sum_{j=1}^{n} A_j \varphi_{\mathbf{h}_j}, \qquad (2.2.3.7)$$

for which (2.2.3.6) holds.

F_0, $F_{\mathbf{h}} F_{-\mathbf{h}}$, $F_{\mathbf{h}} F_{\mathbf{k}} F_{\overline{\mathbf{h+k}}}$, $F_{\mathbf{h}} F_{\mathbf{k}} F_{\mathbf{l}} F_{\overline{\mathbf{h+k+l}}}$, $F_{\mathbf{h}} F_{\mathbf{k}} F_{\mathbf{l}} F_{\mathbf{p}} F_{\overline{\mathbf{h+k+l+p}}}$ are examples of s.i.'s for $n = 1, 2, 3, 4, 5$.

The value of any s.i. does not change with an arbitrary shift of the space-group origin and thus it will depend on the crystal structure only.

(*e*) A *structure seminvariant* (s.s.) is a product of structure factors [or a combination of phases (2.2.3.7)] whose value is unchanged when the origin is moved by an allowed translation.

Let $\mathbf{X}_p$'s be the permissible origin translations of the space group. Then the product (2.2.3.5) [or the sum (2.2.3.7)] is an s.s., if, in accordance with (2.2.3.1),

$$\sum_{j=1}^{n} A_j (\mathbf{h}_j \cdot \mathbf{X}_p) = r, \quad p = 1, 2, \ldots \qquad (2.2.3.8)$$

where r is a positive integer, null or a negative integer.

Conditions (2.2.3.8) can be written in the following more useful form (Hauptman & Karle, 1953):

$$\sum_{j=1}^{n} A_j \mathbf{h}_{s_j} \equiv 0 \quad (\text{mod } \boldsymbol{\omega}_s), \qquad (2.2.3.9)$$

where $\mathbf{h}_{s_j}$ is the vector seminvariantly associated with the vector $\mathbf{h}_j$ and $\boldsymbol{\omega}_s$ is the seminvariant modulus. In Tables 2.2.3.1–2.2.3.4, the reflection $\mathbf{h}_s$ seminvariantly associated with $\mathbf{h} = (h, k, l)$, the seminvariant modulus $\boldsymbol{\omega}_s$ and seminvariant phases are given for every H–K group.

The symbol of any group (*cf.* Giacovazzo, 1974) has the structure $\mathbf{h}_s L \boldsymbol{\omega}_s$, where L stands for the lattice symbol. This symbol is underlined if the space group is cs.

By definition, if the class of permissible origin has been chosen, that is to say, if the algebraic form of the symmetry operators has been fixed, then the value of an s.s. does not depend on the origin but on the crystal structure only.

(*f*) Suppose that we have chosen the symmetry operators $\mathbf{C}_s$ and thus fixed the functional form of the s.f.'s and the set of allowed origins. In order to describe the structure in direct space a unique reference origin must be fixed. Thus the phase-determining process must also require a unique permissible origin congruent to the values assigned to the phases. More specifically, at the beginning of the structure-determining process by direct methods we shall assign as many phases as necessary to define a unique origin among those allowed (and, as we shall see, possibly to fix the enantiomorph). From the theory developed so far it is obvious that arbitrary phases can be assigned to one or more s.f.'s if there is at least one allowed origin which, fixed as the origin of the unit cell, will give those phase values to the chosen reflections. The concept of *linear dependence* will help us to fix the origin.

(*g*) n phases $\varphi_{\mathbf{h}_j}$ are *linearly semidependent* (Hauptman & Karle, 1956) when the n vectors $\mathbf{h}_{s_j}$ seminvariantly associated with the $\mathbf{h}_j$ are linearly dependent modulo $\boldsymbol{\omega}_s$, $\boldsymbol{\omega}_s$ being the seminvariant modulus of the space group. In other words, when

$$\sum_{j=1}^{n} A_j \mathbf{h}_{s_j} \equiv 0 \quad (\text{mod } \boldsymbol{\omega}_s), \qquad A_q \not\equiv 0 \quad (\text{mod } \boldsymbol{\omega}_s) \qquad (2.2.3.10)$$

is satisfied. The second condition means that at least one A_q exists that is not congruent to zero modulo each of the components of $\boldsymbol{\omega}_s$. If (2.2.3.10) is not satisfied for any n-set of integers A_j, the phases $\varphi_{\mathbf{h}_j}$ are *linearly semindependent*. If (2.2.3.10) is valid for $n = 1$ and $A = 1$, then $\mathbf{h}_1$ is said to be linearly semidependent and $\varphi_{\mathbf{h}_1}$ is an s.s. It may be concluded that a seminvariant phase is linearly semidependent, and, *vice versa*, that a phase linearly semidependent is an s.s. In Tables 2.2.3.1–2.2.3.4 the allowed variations (which are those due to the allowed origin translations) for the semindependent phases are given for every H–K group. If $\varphi_{\mathbf{h}_1}$ is linearly semindependent its value can be fixed arbitrarily because at least one origin compatible with the given value exists. Once $\varphi_{\mathbf{h}_1}$ is assigned, the necessary condition to be able to fix a second phase $\varphi_{\mathbf{h}_2}$ is that it should be linearly semindependent of $\varphi_{\mathbf{h}_1}$.

Similarly, the necessary condition to be able arbitrarily to assign a third phase $\varphi_{\mathbf{h}_3}$ is that it should be linearly semindependent from $\varphi_{\mathbf{h}_1}$ and $\varphi_{\mathbf{h}_2}$.

In general, the number of linearly semindependent phases is equal to the dimension of the seminvariant vector $\boldsymbol{\omega}_s$ (see Tables 2.2.3.1–2.2.3.4). The reader will easily verify in $(h, k, l) P (2, 2, 2)$ that the three phases φ_{oee}, φ_{eoe}, φ_{eoo} define the origin (o indicates odd, e even).

(*h*) From the theory summarized so far it is clear that a number of semindependent phases $\varphi_{\mathbf{h}_j}$, equal to the dimension of the seminvariant vector $\boldsymbol{\omega}_s$, may be arbitrarily assigned in order to fix the origin. However, it is not always true that only one allowed origin compatible with the given phases exists. An additional condition is required such that only one permissible origin should lie at the intersection of the lattice planes corresponding to the origin-fixing reflections (or on the lattice plane $\mathbf{h}$ if one reflection is sufficient to define the origin). It may be shown that the condition is verified if the determinant formed with the vectors seminvariantly associated with the origin reflections, reduced modulo $\boldsymbol{\omega}_s$, has the value ± 1. In other words, such a determinant should be primitive modulo $\boldsymbol{\omega}_s$.

For example, in $P\bar{1}$ the three reflections

$$\mathbf{h}_1 = (345), \quad \mathbf{h}_2 = (139), \quad \mathbf{h}_3 = (784)$$

define the origin uniquely because

$$\begin{vmatrix} 3 & 4 & 5 \\ 1 & 3 & 9 \\ 7 & 8 & 4 \end{vmatrix} \xrightarrow{\text{reduced mod } (2,2,2)} \begin{vmatrix} 1 & 0 & 1 \\ 1 & 1 & 1 \\ 1 & 0 & 0 \end{vmatrix} = -1.$$

Furthermore, in $P4mm$ [$\mathbf{h}_s = (h + k, l)$, $\boldsymbol{\omega}_s = (2, 0)$]

$$\mathbf{h}_1 = (5, 2, 0), \quad \mathbf{h}_2 = (6, 2, 1)$$

define the origin uniquely since

$$\begin{vmatrix} 7 & 0 \\ 8 & 1 \end{vmatrix} \xrightarrow{\text{reduced mod } (2,0)} \begin{vmatrix} 1 & 0 \\ 0 & 1 \end{vmatrix} = 1.$$

(*i*) If an s.s. or an s.i. has a general value φ for a given structure, it will have a value $-\varphi$ for the enantiomorph structure. If $\varphi = 0, \pi$ the s.s. has the same value for both enantiomorphs. Once the origin has been assigned, in ncs. space groups the sign of a given s.s. $\varphi \neq 0, \pi$ can be assigned to fix the enantiomorph. In practice it is often advisable to use an s.s. or an s.i. whose value is as near as possible to $\pm \pi/2$.

2.2.4. Normalized structure factors

2.2.4.1. Definition of normalized structure factor

The normalized structure factors E (see also Chapter 2.1) are calculated according to (Hauptman & Karle, 1953)

$$|E_{\mathbf{h}}|^2 = |F_{\mathbf{h}}|^2 / \langle |F_{\mathbf{h}}|^2 \rangle, \qquad (2.2.4.1)$$