

(1) the components of the vectors  $\mathbf{h}$ , seminvariantly associated with  $\mathbf{h}=(h,k,l)$ ; it can be useful to preserve this information in the symbol of the H-K group.

(2) The type of the cell ( $P$  primitive, *etc.* . . .): following Rogers (1950, 1965), the lattice symbol is underlined if the point group is centrosymmetric.

(3) The seminvariant modulus  $\omega_s$ .

The meaning of the symbols ( $\|2\|$ ,  $\|\infty\|$ , . . .) used in the Tables 1-4 is the same as in Karle (1970).

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## Geometric Sources of Redundancy in Intensity Data and Their Use for Phase Determination

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Linear equations are derived in direct space, which express the relation between the electron densities of crystals built from the same molecule, but with different lattices or several identical subunits in their asymmetric units. They are shown to be equivalent to the most general 'molecular-replacement' phase equations in reciprocal space. The solution of these phase equations by the method of successive projections is discussed. This algorithm, best implemented in direct space by averaging operations, is shown to be convergent for over-determined problems, and to be equivalent to a least-squares solution of the phase equations.

### Introduction

The 'molecular-replacement' method has now a well documented literature, which has recently been collected in a book (Rossmann, 1972). It aims at exploiting the redundancies of geometrical origin which may be present in X-ray intensity data, in order to determine or refine phases. Such redundancies arise if a protein can crystallize with several identical molecules in the asymmetric unit, or in several crystal forms.

The basic equations expressing the phase constraints thus generated were derived by Rossmann & Blow (1963), Main & Rossmann (1966), and Crowther (1967). Their implementation was investigated by Rossmann & Blow (1963, 1964), Main (1967), Crowther (1969) and Jack (1973). All this work was done in reciprocal space *only*, although Main (1967) and Rossmann (1972) suggested that direct-space methods should be formally equivalent but of greater practical utility.

In this work, a rigorous proof of this formal equivalence is presented. The equations are first written in direct space, using an adequate linear operator formalism. A Fourier transformation then yields equations in reciprocal space, which are found to be the most general molecular-replacement equations in Crow-

ther's linear formulation. This proves the equivalence in question.

In both direct and reciprocal spaces, the equations express the fact that a certain vector, representing a set of structures built from a common subunit, is constrained to lie in the eigenspace of a certain orthogonal projector. In reciprocal space, this projector is represented by a matrix. In direct space, the projection operation consists in averaging the electron densities of all the crystallographically independent molecules present in all crystals, then rebuilding each crystal from this averaged molecule, the density outside the molecular boundaries being set to a uniform background value. The direct-space method has considerable computational advantages. Indeed, averaging is a simple operation, and the molecular boundaries can easily be given any desired shape.

If  $N$  subunits are thus averaged, the signal-to-noise ratio of the electron-density maps will increase, by a factor of at least  $\sqrt{N}$  since we also remove noise from the solvent regions. Therefore, combining the experimental amplitudes with the phases recomputed from these averaged maps - or, equivalently, with the phases of the projected structure factors - may be expected to give improved maps.

This algorithm will be shown to be convergent for over-determined problems having a unique solution, and to be equivalent to a least-squares solution of the phase equations in which the constraints of geometric redundancy and agreement with observed amplitudes are treated separately.

## 1. Geometric sources of redundancy

### 1.1 Redundancy and its sources

A crystal structure is defined at resolution  $\Delta$  by those structure factors  $F_{hkl}$  for which  $d_{hkl}^* \leq \Delta^{-1}$ . In most cases, we find that not all these structure factors need to be determined separately, because relations exist between them. Thus, if the structure has no anomalous scatterers, Friedel's law applies; and if it has symmetry other than  $P1$ , structure factors with point-group-related indices differ only by known phase shifts. In both cases, these relations between structure factors can be decomposed into two sets of relations, one involving moduli only, the other involving phases only. We shall say that relations between structure factors are *split* if they can be decomposed in this way into separate relations between the moduli and the phases. Friedel's law and space-group symmetries are the only general sources of split relations.

Other relationships between structure factors may follow from the positivity of the electron density, the existence of equal resolved atoms in a structure, the existence of molecular boundaries, local symmetries and polymorphism. These relations cannot be decomposed into separate relations between moduli and phases: such relations will be called *mixed*. A set of mixed relations will be called *irreducible* if it cannot be factored into a smaller mixed set, and a split set. Intensity data will be called *redundant* if they are involved in an irreducible set of mixed relations.

Of the types of redundancy mentioned, only those which follow from molecular boundaries, local symmetries and polymorphism, and which may be called geometric, will be considered in this paper. As the positivity of electron density is ignored, the  $F_{000}$  term will be adjusted so that the mean electron density outside molecular boundaries is zero. When several crystal forms are involved, it will be assumed that this mean density is the same for all.

### 1.2. A quantitative estimate of redundancy

A real structure with unit cell  $V$  in space group  $P1$  is defined, at resolution  $\Delta$ , by those structure factors  $F_{hkl}$  for which  $d_{hkl}^* \leq \Delta^{-1}$ . By Friedel's law, their number is:

$$N_{\Delta}(V) = \frac{1}{2} \cdot \frac{4\pi}{3} \left( \frac{1}{\Delta} \right)^3 \cdot \frac{1}{V^*} = \frac{2\pi}{3\Delta^3} \cdot V = k_{\Delta} \cdot V^{\dagger}$$

† More exactly,  $N_{\Delta}(V) = [k_{\Delta} \cdot V]$ , i.e. the greatest integer less than  $k_{\Delta} \cdot V$ . But we gloss over that point.

so that such a structure may be considered as a system with  $k_{\Delta}$  complex (hence  $2k_{\Delta}$  real) degrees of freedom per unit volume of its unit cell. An X-ray study of this structure will yield  $N_{\text{obs}} = N_{\Delta}(V)$  independent and non-redundant real parameters: the moduli  $|F_{hkl}|$ . If a space group of multiplicity  $m$  is present, all these numbers are to be divided by  $m$ , which can be done by formally substituting the asymmetric unit  $v$  for the unit cell  $V$  in the preceding formulae; thus, we have  $N_{\text{obs}} = N_{\Delta}(v)$  independent moduli, while the number  $N_{\text{free}}$  of actual real degrees of freedom is  $2N_{\Delta}(v)$ .

If the electron density is zero in part of  $v$  owing to molecular boundaries, or if local symmetries relate different parts of  $v$ ,  $N_{\text{free}}$  will decrease; indeed, if  $U$  is the volume of the subunit from which  $v$  is built, the preceding rule of formal substitution yields the estimate:  $N_{\text{free}} \simeq 2N_{\Delta}(U)$ . Conversely, observation of several crystal forms containing the same structural unit will increase  $N_{\text{obs}}$ . The phase problem will become over-determined if  $N_{\text{obs}} \geq N_{\text{free}}$ .

We may define a redundancy criterion  $\sigma$  by:

$$\sigma = 2 \cdot \frac{N_{\text{obs}}}{N_{\text{free}}} - 1.$$

For non-redundant data,  $\sigma = 0$ , and over-determination will occur for  $\sigma \geq 1$ .

## 2. Notations and preliminaries

Paradoxically enough, writing equations in direct space is more difficult than in reciprocal space, if we want them to be amenable to mathematical manipulation. Indeed, functions in direct space, and especially linear operations on them, have to be thought of abstractly; whereas in reciprocal space we can handle Fourier coefficients and matrices.

The aim of these sections is to introduce the symbolism which will be used in writing these equations, and to illustrate how it makes some invariance properties expressible in the form of eigenvalue equations. The use of distributions at an elementary level, and of their convolutions and Fourier transforms, yields a convenient notation for periodic electron densities and their diffraction patterns. We shall use these notations, but with as little reference to distribution theory as possible.

### 2.1. Projectors

Let  $E$  be ordinary (direct) space, and  $C(E)$  be the vector space of complex-valued functions over  $E$ . A linear operator  $P$  in  $C(E)$  will be called a *projector* if  $P^2 = P$ . An eigenvalue  $\lambda$  of  $P$  has to satisfy  $\lambda^2 = \lambda$ , so that  $\lambda$  equals 0 or 1. Any function  $f \in C(E)$  can be written uniquely as:  $f = f_0 + f_1$ , with  $Pf_0 = 0$  and  $Pf_1 = f_1$ ; indeed,  $f_0 = f - Pf$  and  $f_1 = Pf$ .

Let  $L^2(E)$  be the subspace of  $C(E)$  formed by those functions  $f$  for which the integral  $\int_E |f(\mathbf{x})|^2 d^3\mathbf{x}$  conver-

ges. We can define in  $L^2(E)$  the notion of orthogonality, using the scalar product:

$$\langle f|g\rangle = \int_E \overline{f(\mathbf{x})}g(\mathbf{x})d^3\mathbf{x}$$

where the bar denotes complex conjugation. A projector  $P$  will then be called orthogonal if any eigenvector of  $P$  for eigenvalue 1 is orthogonal to any eigenvector of  $P$  for eigenvalue 0. A linear operator  $A$  in  $L^2(E)$  is called *Hermitian* if

$$\langle Af|g\rangle = \langle f|Ag\rangle \quad \text{for all } f, g \in L^2(E).$$

A projector is orthogonal if and only if it is Hermitian.

### 2.2. Indicators and envelopes

If  $U$  is any domain of  $E$ , we shall call the *indicator* of  $U$  the function  $\chi_U$  defined by:

$$\chi_U(\mathbf{x}) = 1 \text{ if } \mathbf{x} \in U, \quad \chi_U(\mathbf{x}) = 0 \text{ if } \mathbf{x} \notin U.$$

The operation of multiplication by  $\chi_U$  is a linear operator in  $C(E)$ , which is Hermitian in  $L^2(E)$  since

$$\langle \chi_U f|g\rangle = \langle f|\chi_U g\rangle = \int_U \overline{f(\mathbf{x})}g(\mathbf{x})d^3\mathbf{x}.$$

This operator will be denoted by  $\chi_U$ .

The identity  $\chi_U^2 = \chi_U$  implies that  $(\chi_U)^2 = \chi_U$ , so that  $\chi_U$  is a projector in  $C(E)$ , orthogonal in  $L^2(E)$ .

We shall say that a function  $f \in C(E)$  admits  $U$  as an *envelope* if  $f$  vanishes identically outside  $U$ . This can be written:

$$\chi_U \cdot f = f$$

which states that  $f$  is an eigenfunction of projector  $\chi_U$  for eigenvalue 1.

### 2.3. Functional representation of geometrical operations

To any invertible transformation  $T$  of  $E$  we can associate a linear transformation  $T^*$  of  $C(E)$ , defined by:

$$(T^*f)(\mathbf{x}) = f(T^{-1}\mathbf{x}) \quad \text{for all } f \in C(E).$$

This correspondence has the property that:

$$(T_1 T_2)^* = T_1^* T_2^*, \quad (T^{-1})^* = (T^*)^{-1}.$$

Therefore, if we have a group  $\mathcal{G} = \{T_1, \dots, T_n\}$  of transformation of  $E$ , the set  $\mathcal{G}^* = \{T_1^*, \dots, T_n^*\}$  will also be a group.

If  $T$  is a translation by a vector  $\mathbf{u}$  ( $T\mathbf{x} = \mathbf{x} + \mathbf{u}$ ),  $T^*$  will be denoted  $\tau_{(\mathbf{u})}$ . If  $T$  is a displacement ( $T\mathbf{x} = C\mathbf{x} + \mathbf{d}$ , where  $C$  is a rotation), and if  $f$  and  $g$  are in  $L^2(E)$ , we have the identity (proved by simple change of variable):

$$\langle f|T^*g\rangle = \langle (T^{-1})^*f|g\rangle. \quad (\mathcal{I}_1)$$

The invariance of a function  $f \in C(E)$  under a transformation  $T$  can be written:  $T^*f = f$ , which states that  $f$  is an eigenfunction of  $T^*$  for eigenvalue 1.

The invariance of  $f$  by a group  $\mathcal{G} = \{T_1, \dots, T_n\}$  of transformations of  $E$  is equivalent to its invariance by the operator  $G = \frac{1}{n} \sum_{i=1}^n T_i^*$ ; this follows easily from

identity:

$$T_j^* G = G \quad \text{for all } j = 1, \dots, n \quad (\mathcal{I}_2)$$

as  $T_j \mathcal{G} = \{T_j T_1, \dots, T_j T_n\} = \mathcal{G}$  by the group property. This same identity shows that  $G^2 = G$ , and  $(\mathcal{I}_1)$  shows that  $G$  is Hermitian in  $L^2(E)$  since as well  $G = \frac{1}{n} \sum_{k=1}^n (T_k^{-1})^*$ . Thus  $G$  is a projector in  $C(E)$ , orthogonal in  $L^2(E)$ . The invariance of  $f$  under group  $\mathcal{G}$  reads  $Gf = f$ , i.e. states that  $f$  is an eigenfunction of projector  $G$  for eigenvalue 1.

### 2.4. Convolution and lattices

The convolution of two functions  $f$  and  $g$ , if defined, will be denoted by  $f * g$ :

$$(f * g)(\mathbf{x}) = \int_E f(\mathbf{y})g(\mathbf{x} - \mathbf{y})d^3\mathbf{y}.$$

Dirac's  $\delta$  distribution is the unity of convolution:

$$\delta * f = f \quad \text{for all } f \text{'s}.$$

and one has the identity:  $\tau_{(\mathbf{u})}f = \delta_{(\mathbf{u})} * f$  if  $\delta_{(\mathbf{u})} \equiv \tau_{(\mathbf{u})}\delta$ .

This yields a concise notation for the electron density  $\rho$  in a crystal with lattice  $\mathcal{R}$  and motif  $\rho^0$ . Indeed, we can write:

$$\rho = \sum_{\mathbf{u} \in \mathcal{R}} \tau_{(\mathbf{u})}\rho^0 = \sum_{\mathbf{u} \in \mathcal{R}} \delta_{(\mathbf{u})} * \rho^0 = R * \rho^0$$

where  $R$  is the *lattice-distribution* associated with  $\mathcal{R}$ :

$$R = \sum_{\mathbf{u} \in \mathcal{R}} \delta_{(\mathbf{u})} = \sum_{\substack{m, n, p \\ \text{integers}}} \delta_{(m\mathbf{a} + n\mathbf{b} + p\mathbf{c})} \quad \text{if } \mathcal{R} \text{ is based on } (\mathbf{a}, \mathbf{b}, \mathbf{c}).$$

We shall also need the 'unit lattice-distribution':  $r = \sum_{m, n, p} \delta_{(m\mathbf{i} + n\mathbf{j} + p\mathbf{k})}$ , where  $(\mathbf{i}, \mathbf{j}, \mathbf{k})$  is a right-handed orthonormal frame.

### 2.5. Fourier transform and reciprocal lattices

We shall denote as  $\mathcal{F}$  and  $\overline{\mathcal{F}}$  the Fourier transform and its inverse respectively:

$$\mathcal{F}[\varphi](\xi) = \int_E \varphi(\mathbf{x}) \exp(-2\pi i \xi \cdot \mathbf{x}) d^3\mathbf{x}$$

$$\overline{\mathcal{F}}[\varphi](\xi) = \int_E \varphi(\mathbf{x}) \exp(+2\pi i \xi \cdot \mathbf{x}) d^3\mathbf{x}$$

and use their extensions to distributions (see Schwartz, 1966, chap. 7).

If  $T$  is an invertible linear transformation of  $E$ , one has the identities (Schwartz, 1966, p. 252):

$$\overline{\mathcal{F}}[T^*\varphi] = (\det T) \cdot ({}^c T)^* \overline{\mathcal{F}}[\varphi]$$

$$\mathcal{F}[T^*\varphi] = (\det T) \cdot ({}^c T)^* \mathcal{F}[\varphi] \quad (\mathcal{I}_3)$$

where  ${}^c T = {}^t T^{-1}$  is the inverse of the transpose of  $T$ . In particular, if  $T$  is a rotation,  $\det T = 1$  and  $T = {}^c T$ , so that

$$\overline{\mathcal{F}}[T^*\varphi] = T^* \overline{\mathcal{F}}[\varphi], \quad \mathcal{F}[T^*\varphi] = T^* \mathcal{F}[\varphi].$$

With the notations of § 2.4, we can write:

$$R = T^*r$$

where  $T$  is defined by  $T\mathbf{i} = \mathbf{a}$ ,  $T\mathbf{j} = \mathbf{b}$ ,  $T\mathbf{k} = \mathbf{c}$ . Using identities ( $\mathcal{F}_3$ ) and the fact that  $\overline{\mathcal{F}}[r] = r$  (Schwartz, 1966, p. 254), we have

$$\overline{\mathcal{F}}[R] = (\det T) \cdot ({}^cT)^*r = V \cdot R',$$

where  $V$  is the volume of the unit cell of  $\mathcal{R}$ , and  $R' = ({}^cT)^*r$  is a lattice distribution. Indeed,

$$R' = \sum_{\mathbf{p} \in \mathcal{R}'} \delta_{(\mathbf{p})}$$

where  $\mathcal{R}'$ , the *reciprocal lattice* of  $\mathcal{R}$ , is based on vectors  $\mathbf{a}^* = {}^cT\mathbf{i}$ ,  $\mathbf{b}^* = {}^cT\mathbf{j}$ ,  $\mathbf{c}^* = {}^cT\mathbf{k}$ .

This yields the well-known expression for the diffraction pattern  $F$  of a crystal  $\varrho = R^*\varrho^0$ :

$$F = \overline{\mathcal{F}}[\varrho] = \overline{\mathcal{F}}[R] \cdot \overline{\mathcal{F}}[\varrho^0] = V \cdot R' \cdot \overline{\mathcal{F}}[\varrho^0].$$

### 2.6 Shannon's (1949) interpolation formula

Let  $\varphi$  be a function whose Fourier transform  $\Phi = \overline{\mathcal{F}}[\varphi]$  vanishes identically outside the unit cell  $V$  of a lattice  $\mathcal{R}$ . This can be written:

$$\Phi = \chi_V \cdot (R^*\Phi).$$

Transforming both sides by  $\overline{\mathcal{F}}$  yields the formula:

$$\varphi = \frac{1}{V} \overline{\mathcal{F}}[\chi_V]^*(R' \cdot \varphi)$$

which shows that  $\varphi$  can be calculated everywhere once its values on  $\mathcal{R}'$  are known, since it can be written:

$$\varphi(\xi) = \frac{1}{V} \sum_{\mathbf{p} \in \mathcal{R}'} \overline{\mathcal{F}}[\chi_V](\xi - \mathbf{p})\varphi(\mathbf{p}) \quad \text{for all } \xi \in E.$$

In particular, this formula enables us to calculate 'structure factors' at non-integral points of reciprocal space from the usual structure factors.

## 3. Deduction of the equations in space group P1

For the sake of clarity, structure factors, their moduli and phases, will be written as explicit functions of vectors of the reciprocal lattice, *e.g.*  $F(\mathbf{p}) = |F|(\mathbf{p}) \times \exp[i\varphi(\mathbf{p})]$ .

### 3.1. Hypotheses

A molecule  $M$  is able to crystallize in  $\nu$  ( $\nu \geq 1$ ) different forms, with lattices  $\mathcal{R}_\alpha$  and motifs  $\varrho_\alpha^0$  ( $\alpha = 1, \dots, \nu$ ). This molecule is described, in a reference position, by electron density  $\mu$  with envelope  $U$ . Each motif  $\varrho_\alpha^0$  consists of  $n_\alpha$  such molecules, in positions deduced from the reference position by a set of local transformations  $T_{j_\alpha}$  ( $j_\alpha = 1, \dots, n_\alpha$ ), such that their envelopes  $T_{j_\alpha}U$  be non-overlapping.

This constitutes a general statement of the types of redundancies envisaged by Rossmann & Blow (1963).

### 3.2. Equations in direct space

The first two assumptions are fully expressed in the formulae:

$$\varrho_\alpha = R_\alpha^* \varrho_\alpha^0 \quad \alpha = 1, \dots, \nu \quad (3.1)$$

$$\varrho_\alpha^0 = \sum_{i_\alpha=1}^{n_\alpha} T_{i_\alpha}^* \mu \quad \alpha = 1, \dots, \nu. \quad (3.2)$$

The third one can be expressed by writing that the content of each envelope  $T_{j_\alpha}U$  is equal to  $T_{j_\alpha}^* \mu$ ; *i.e.* there is no contribution from neighbouring molecules:

$$\chi_{T_{j_\alpha}U} \cdot \varrho_\alpha = T_{j_\alpha}^* \mu \quad \alpha = 1, \dots, \nu; j_\alpha = 1, \dots, n_\alpha. \quad (3.3)$$

A relation between  $\varrho_\alpha$  and  $\varrho_\beta$  will result if we eliminate  $\mu$  between (3.1) and (3.2) written for  $\alpha$  and  $\beta$ , using (3.3) written for  $\beta$ . The latter yields:

$$\mu = (T_{i_\beta}^{-1})^* (\chi_{T_{i_\beta}U} \cdot \varrho_\beta) = \chi_U \cdot (T_{i_\beta}^{-1})^* \varrho_\beta \quad (3.4)$$

so that:

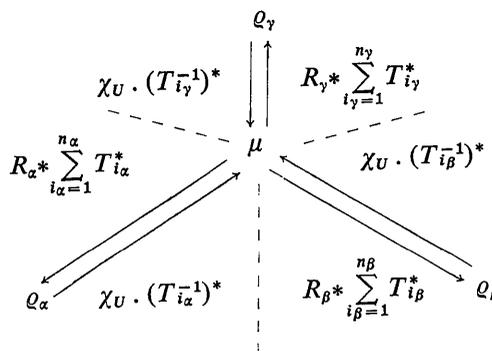
$$\varrho_\alpha = R_\alpha^* \sum_{i_\alpha=1}^{n_\alpha} T_{i_\alpha}^* \chi_U \cdot (T_{i_\beta}^{-1})^* \varrho_\beta \quad (3.5)$$

for all  $\alpha, \beta = 1, \dots, \nu$  and  $i_\beta = 1, \dots, n_\beta$ .

We shall write these equations in condensed form as:

$$\varrho_\alpha = B_{\alpha\beta}^{(i_\beta)} \varrho_\beta \quad (3.6a)$$

and visualize them on the diagram:



If applied to an arbitrary function  $f$ , the linear operator  $B_{\alpha\beta}^{(i_\beta)}$  would build a structure of type  $\alpha$  from that part of  $f$  contained in  $T_{i_\beta}U$ , brought back to the reference position.

This makes obvious the following fundamental identity: for *any*  $i_\beta = 1, \dots, n_\beta$ , one has

$$B_{\alpha\beta}^{(i_\beta)} B_{\beta\gamma}^{(i_\gamma)} = B_{\alpha\gamma}^{(i_\gamma)}$$

for all

$$\alpha, \beta, \gamma = 1, \dots, \nu, \quad i_\gamma = 1, \dots, n_\gamma. \quad (3.7a)$$

The independence of  $i_\beta$  comes from the fact that all the intermediate subunits produced by  $B_{\beta\gamma}^{(i_\gamma)}$  are identical.

This identity will enable us to condense system (3.6a) into an *equivalent* system of  $\nu$  equations, by two averaging operations: over  $i_\beta$ , for constant  $\alpha$  and  $\beta$ ; then over  $\beta$ , for constant  $\alpha$ .

Indeed, let us define:  $B_{\alpha\beta} = \frac{1}{n_\beta} \sum_{i_\beta=1}^{n_\beta} B_{\alpha\beta}^{(i_\beta)}$ . We shall use later the explicit expression:

$$B_{\alpha\beta} f = R_\alpha^* \sum_{i_\alpha=1}^{n_\alpha} T_{i_\alpha}^* \chi_U \cdot \frac{1}{n_\beta} \sum_{i_\beta=1}^{n_\beta} (T_{i_\beta}^{-1})^* f \quad (3.8)$$

which shows that the action of  $B_{\alpha\beta}$  on an arbitrary function  $f$  is to build a structure of type  $\alpha$  from the average of the contents of the  $T_{i_\beta} U$ 's, brought back to the reference position.

By successively averaging identities (3.7a) over  $i_\gamma$  and  $i_\beta$ , one gets:

$$B_{\alpha\beta}^{(i_\beta)} B_{\beta\gamma} = B_{\alpha\gamma} \quad \text{for any } i_\beta = 1, \dots, n_\beta \quad (3.7b)$$

and

$$B_{\alpha\beta} B_{\beta\gamma} = B_{\alpha\gamma}. \quad (3.7c)$$

If  $\alpha = \beta = \gamma$ , identities (3.7c) show that  $B_{\alpha\alpha}^2 = B_{\alpha\alpha}$ , so that the  $B_{\alpha\alpha}$ 's are *projectors*.

We can now proceed to condense system (3.6a).

The exactness of this system obviously implies that of the system:

$$Q_\alpha = B_{\alpha\beta} Q_\beta \quad \alpha, \beta = 1, \dots, v. \quad (3.6b)$$

To show that the converse is true, we suppose that (3.6b) is satisfied, so that  $Q_\beta = B_{\beta\gamma} Q_\gamma$  for all  $\beta, \gamma = 1, \dots, v$ , then multiply both sides by  $B_{\alpha\beta}^{(i_\beta)}$  and use identity (3.7b):

$$B_{\alpha\beta}^{(i_\beta)} Q_\beta = B_{\alpha\beta}^{(i_\beta)} B_{\beta\gamma} Q_\gamma = B_{\alpha\gamma} Q_\gamma = Q_\alpha \quad \text{for any } i_\beta = 1, \dots, n_\beta$$

so that (3.6a) is fully verified.

The exactness of system (3.6b) in its turn implies that of system:

$$Q_\alpha = \frac{1}{v} \sum_{\beta=1}^v B_{\alpha\beta} Q_\beta \quad \alpha = 1, \dots, v. \quad (3.6c)$$

Conversely, if (3.6c) is satisfied, we have  $Q_\beta = \frac{1}{v} \sum_{\gamma=1}^v B_{\beta\gamma} Q_\gamma$  for all  $\beta = 1, \dots, v$ ; multiplying both sides by  $B_{\alpha\beta}$  and using identity (3.7c) yields:

$$B_{\alpha\beta} Q_\beta = \frac{1}{v} \sum_{\gamma=1}^v B_{\alpha\beta} B_{\beta\gamma} Q_\gamma = \frac{1}{v} \sum_{\gamma=1}^v B_{\alpha\gamma} Q_\gamma = Q_\alpha \quad \text{by (3.6c)}$$

which shows that (3.6b) is fully verified.

Thus system (3.6c) still expresses *all* the initial hypotheses. It can be rewritten:

$$\mathbf{q} = \mathbf{B}\mathbf{q} \quad (3.6d)$$

using the notation:

$$\mathbf{q} = \begin{pmatrix} Q_1 \\ \vdots \\ Q_v \end{pmatrix} \quad \text{and} \quad \mathbf{B} = \frac{1}{v} \begin{pmatrix} B_{11} & \dots & B_{1v} \\ \vdots & & \vdots \\ B_{v1} & \dots & B_{vv} \end{pmatrix}.$$

$\mathbf{B}$  operates in the product  $C = C(E_1) \times \dots \times C(E_v)$ , and identities (3.7c) imply that it is a *projector* in this space. Indeed, if we call  $\{\mathbf{B}\}_{\alpha\beta}$  the element of line  $\alpha$  and column  $\beta$  of  $\mathbf{B}$ , we have:

$$\begin{aligned} \{\mathbf{B}^2\}_{\alpha\beta} &= \sum_{\gamma=1}^v \{B\}_{\alpha\gamma} \{B\}_{\gamma\beta} = \sum_{\gamma=1}^v \frac{B_{\alpha\gamma}}{v} \cdot \frac{B_{\gamma\beta}}{v} \\ &= v \cdot \frac{B_{\alpha\beta}}{v^2} = \{\mathbf{B}\}_{\alpha\beta} \end{aligned}$$

that is:

$$\mathbf{B}^2 = \mathbf{B}. \quad (3.7d)$$

### 3.3. Equations in reciprocal space

Equations may be obtained in reciprocal space by Fourier transformation of the direct space equations.

#### 3.3.1. Deduction

Let  $F_\alpha$  be the column vector of structure factors of  $Q_\alpha$ :

$$F_\alpha(\mathbf{p}_\alpha) = \overline{\mathcal{F}}[Q_\alpha](\mathbf{p}_\alpha) = V_\alpha \cdot \overline{\mathcal{F}}[Q_\alpha^0](\mathbf{p}_\alpha), \quad \mathbf{p}_\alpha \in \mathcal{R}'_\alpha.$$

Then systems (3.6a), (3.6b) and (3.6d) are respectively equivalent to:

$$F_\alpha = H_{\alpha\beta}^{(i_\beta)} F_\beta \quad \alpha, \beta = 1, \dots, v; i_\beta = 1, \dots, n_\beta \quad (3.9a)$$

$$F_\alpha = H_{\alpha\beta} F_\beta \quad \alpha, \beta = 1, \dots, v \quad (3.9b)$$

$$\mathbf{F} = \mathbf{H}\mathbf{F} \quad (3.9d)$$

where we have used the notation:

$$\begin{aligned} H_{\alpha\beta}^{(i_\beta)} &= \overline{\mathcal{F}} B_{\alpha\beta}^{(i_\beta)} \overline{\mathcal{F}} \\ H_{\alpha\beta} &= \overline{\mathcal{F}} B_{\alpha\beta} \overline{\mathcal{F}} \end{aligned}$$

(which shows that the  $H$ 's and the  $B$ 's are related by a similarity transformation) and:

$$\mathbf{F} = \begin{pmatrix} F_1 \\ \vdots \\ F_v \end{pmatrix}, \quad \mathbf{H} = \frac{1}{v} \begin{pmatrix} H_{11} & \dots & H_{1v} \\ \vdots & & \vdots \\ H_{v1} & \dots & H_{vv} \end{pmatrix}.$$

The evaluation of the matrix elements of these linear operators is immediate. For instance, using (3.8), we can write for  $H_{\alpha\beta} = \overline{\mathcal{F}} B_{\alpha\beta} \overline{\mathcal{F}}$  the explicit expression:

$$H_{\alpha\beta} = V_\alpha \cdot R'_\alpha \cdot \frac{1}{n_\beta} \sum_{i_\beta=1}^{n_\beta} \sum_{i_\alpha=1}^{n_\alpha} \overline{\mathcal{F}} T_{i_\alpha}^* \chi_U \cdot (T_{i_\beta}^{-1})^* \overline{\mathcal{F}}. \quad (3.10)$$

The basis vectors in the space of structure factors for crystal  $\alpha$  are the  $\delta_{(\mathbf{p}_\alpha)}$ , where  $\mathbf{p}_\alpha$  runs through  $\mathcal{R}'_\alpha$ ; their Fourier transforms are:

$$\overline{\mathcal{F}}[\delta_{(\mathbf{p}_\alpha)}](\mathbf{x}) = \frac{1}{V_\alpha} \exp(-2\pi i \mathbf{p}_\alpha \cdot \mathbf{x}).$$

Using identity ( $\mathcal{J}_1$ ) of § 2.3 and the definition of a matrix element, we have:

$$\begin{aligned}
H_{\alpha\beta}(\mathbf{p}_\alpha, \mathbf{q}_\beta) &= \langle \delta_{(\mathbf{p}_\alpha)} | H_{\alpha\beta} \delta_{(\mathbf{q}_\beta)} \rangle \\
&= V_\alpha \cdot \frac{1}{n_\beta} \sum_{i_\beta=1}^{n_\beta} \sum_{i_\alpha=1}^{n_\alpha} \langle \delta_{(\mathbf{p}_\alpha)} | \overline{\mathcal{F}} T_{i_\alpha}^* \chi_U \cdot (T_{i_\beta}^{-1})^* \mathcal{F} \delta_{(\mathbf{q}_\beta)} \rangle \\
&= \frac{1}{n_\beta V_\beta} \sum_{i_\alpha=1}^{n_\alpha} \sum_{i_\beta=1}^{n_\beta} \langle (T_{i_\alpha}^{-1})^* \exp \{-2\pi i \mathbf{p}_\alpha \cdot \mathbf{x}\} | \chi_U (T_{i_\beta}^{-1})^* \exp \{-2\pi i \mathbf{q}_\beta \cdot \mathbf{x}\} \rangle \\
&= \frac{1}{n_\beta V_\beta} \sum_{i_\alpha=1}^{n_\alpha} \sum_{i_\beta=1}^{n_\beta} \int_U \exp \{2\pi i (\mathbf{p}_\alpha \cdot T_{i_\alpha} \mathbf{x} - \mathbf{q}_\beta \cdot T_{i_\beta} \mathbf{x})\} d^3 \mathbf{x}.
\end{aligned}$$

We can rearrange the scalar product, if we write  $T_K \mathbf{x} = C_K \mathbf{x} + \mathbf{d}_K$ , as:

$$(\mathbf{p}_\alpha \cdot \mathbf{d}_{i_\alpha} - \mathbf{q}_\beta \cdot \mathbf{d}_{i_\beta}) + ({}^t C_{i_\alpha} \mathbf{p}_\alpha - {}^t C_{i_\beta} \mathbf{q}_\beta) \cdot \mathbf{x},$$

whence

$$\begin{aligned}
H_{\alpha\beta}(\mathbf{p}_\alpha, \mathbf{q}_\beta) &= \frac{1}{n_\beta V_\beta} \sum_{i_\alpha=1}^{n_\alpha} \sum_{i_\beta=1}^{n_\beta} \\
&\times \exp \{2\pi i (\mathbf{p}_\alpha \cdot \mathbf{d}_{i_\alpha} - \mathbf{q}_\beta \cdot \mathbf{d}_{i_\beta})\} \\
&\times \overline{\mathcal{F}}[\chi_U] ({}^t C_{i_\alpha} \mathbf{p}_\alpha - {}^t C_{i_\beta} \mathbf{q}_\beta). \quad (3.11)
\end{aligned}$$

This expression, which could be put in an explicitly adimensional form using the 'interference function'  $G = (1/U) \overline{\mathcal{F}}[\chi_U]$ , generalizes both those given by Crowther (1967) and Main & Rossmann (1966).

It also shows that we may write:

$$\begin{aligned}
H_{\alpha\beta} &= \frac{h_{\alpha\beta}}{n_\beta V_\beta}, \\
\text{with} \quad h_{\alpha\beta}^\dagger &= h_{\beta\alpha} \quad (3.12)
\end{aligned}$$

where  $\dagger$  denotes Hermitian conjugation. Therefore, the matrices  $H_{\alpha\alpha}$  are Hermitian, whereas matrix  $H$  is not.

Identities (3.7a) to (3.7d) between  $B$  operators give rise to similar identities among the  $H$  operators, since the two families correspond to each other by a similarity transformation. In particular:

$$H_{\alpha\beta} H_{\beta\gamma} = H_{\alpha\gamma} \quad (\text{whence } H_{\alpha\alpha}^2 = H_{\alpha\alpha}) \quad (3.13c)$$

$$\mathbf{H}^2 = \mathbf{H}. \quad (3.13d)$$

This shows that the  $H_{\alpha\alpha}$ 's and  $H$  are *projectors* in their respective spaces. The  $H_{\alpha\alpha}$ 's have Hermitian matrices, and are therefore orthogonal projectors for the ordinary scalar products defined by:

$$\langle F_\alpha | F'_\alpha \rangle = \sum_{\mathbf{p}_\alpha \in \mathcal{R}'_\alpha} \overline{F_\alpha(\mathbf{p}_\alpha)} F'_\alpha(\mathbf{p}_\alpha).$$

To make  $\mathbf{H}$  orthogonal, let us introduce the *weighted* scalar product:

$$\langle \mathbf{F} | \mathbf{F}' \rangle_w = \sum_{\alpha=1}^v \frac{\langle F_\alpha | F'_\alpha \rangle}{n_\alpha V_\alpha}.$$

Then, using (3.12), it is easily seen that  $\langle \mathbf{H} \mathbf{F} | \mathbf{F}' \rangle_w = \langle \mathbf{F} | \mathbf{H} \mathbf{F}' \rangle_w$ , so that  $\mathbf{H}$  is Hermitian - hence orthogonal - for this product.

If we now define the scalar product of two crystals  $\varrho_\alpha$  and  $\varrho'_\alpha$  having the same lattice  $\mathcal{R}_\alpha$  by:

$$\langle \varrho_\alpha | \varrho'_\alpha \rangle = \int_E \varrho_\alpha^0(\mathbf{x}) \overline{\varrho'_\alpha^0(\mathbf{x})} d^3 \mathbf{x}$$

we have by Plancherel's theorem:  $\langle F_\alpha | F'_\alpha \rangle = V_\alpha^2 \langle \varrho_\alpha | \varrho'_\alpha \rangle$ , (see Titchmarsh, 1933). Therefore, we see that the  $B_{\alpha\alpha}$ 's are orthogonal, and that  $\mathbf{B}$  is orthogonal for the weighted scalar product:

$$\langle \varrho | \varrho' \rangle_w = \sum_{\alpha=1}^v \frac{V_\alpha}{n_\alpha} \langle \varrho_\alpha | \varrho'_\alpha \rangle.$$

### 3.3.2. Case of 'proper' symmetries

Let us consider the particular case where the motif  $\varrho^0$  of a crystal  $\varrho$  is invariant under a *group*  $\mathcal{G} = \{C_1, \dots, C_n\}$  of local rotations around a point, which we shall take as the origin for convenience. As we have seen in § 2.3, this is equivalent to the invariance of  $\varrho^0$  by

$$G = \frac{1}{n} \sum_{i=1}^n C_i^*.$$

The logical union  $\mathcal{U} = \bigcup_{i=1}^n C_i U$  of the  $n$  molecular envelopes is also invariant under  $\mathcal{G}$ , which can be written:  $G \chi_{\mathcal{U}} = \chi_{\mathcal{U}}$ , with  $\chi_{\mathcal{U}} = \sum_{i=1}^n C_i^* \chi_U$  since the envelopes are non-overlapping.

Then we have:  $B = G \chi_{\mathcal{U}} \cdot = \chi_{\mathcal{U}} \cdot G, \dagger$  whence:

$$H(\mathbf{p}, \mathbf{q}) = \frac{1}{nV} \sum_{j=1}^n \overline{\mathcal{F}}[\chi_{\mathcal{U}}](C_j^{-1} \mathbf{p} - \mathbf{q})$$

which gives to equation  $F = HF$  the aspect of a convolution equation:

$$F(\mathbf{p}) = \frac{1}{n} \sum_{j=1}^n \sum_{\mathbf{q} \in \mathcal{R}'} \frac{1}{V} \overline{\mathcal{F}}[\chi_{\mathcal{U}}](C_j^{-1} \mathbf{p} - \mathbf{q}) F(\mathbf{q}). \quad (3.14)$$

This can be interpreted as an averaging in reciprocal space by the group  $\mathcal{G}$  of local rotations. Indeed,  $\overline{\mathcal{F}}[\varrho^0]$  is also invariant by  $G$ , i.e.:

$$\overline{\mathcal{F}}[\varrho^0](\xi) = \frac{1}{n} \sum_{i=1}^n \overline{\mathcal{F}}[\varrho^0](C_i^{-1} \xi) \quad \text{for all } \xi.$$

$\dagger$  It is clear, here, that  $B$  is an orthogonal projector, since it is the product of two commuting orthogonal projectors,  $G$  and  $\chi_{\mathcal{U}}$ .

But equation (3.14) can be written identically:

$$F(\mathbf{p}) = \frac{1}{n} \sum_{i=1}^n F(C_i^{-1}\mathbf{p}),$$

where the structure factors at those points  $C_i^{-1}\mathbf{p}$  which do not belong to  $\mathcal{R}'$  are calculated by Shannon's interpolation formula (§ 2.6):

$$F(\xi) = \frac{1}{V} \sum_{\mathbf{r} \in \mathcal{R}'} \overline{\mathcal{F}}[\chi_{\mathcal{Q}}](\xi - \mathbf{r})F(\mathbf{r}).$$

Here, the use of  $\chi_{\mathcal{Q}}$  instead of  $\chi_V$  expresses the envelope constraints.†

### 3.3.3. Reduction of the equations by Friedel's law

All the equations written so far are valid even for a complex electron density. If  $\varrho$  is now supposed to be real, these equations are reducible (in the sense of § 1.1).

For each crystal, we choose a 'positive' half in reciprocal space, containing the origin. We denote by  $F_{\alpha}^{+}$  the column vector of structure factors belonging to this half-space, with  $F_{\alpha}(\mathbf{0})$  divided by 2, and define  $F_{\alpha}^{-}$  as  $\overline{F_{\alpha}^{+}}$ . We define in the same way the matrices  $H_{\alpha\beta}^{++}$ ,  $H_{\alpha\beta}^{+-}$ ,  $H_{\alpha\beta}^{-+}$ ,  $H_{\alpha\beta}^{--}$ , according to whether their arguments are in positive or negative half-spaces, and with the convention that a matrix element is to be divided by 2 whenever one of its arguments is  $\mathbf{0}$ . Then, by Friedel's law, the system

$$\begin{pmatrix} F_{\alpha}^{+} \\ F_{\alpha}^{-} \end{pmatrix} = \begin{pmatrix} H_{\alpha\beta}^{++} & H_{\alpha\beta}^{+-} \\ H_{\alpha\beta}^{-+} & H_{\alpha\beta}^{--} \end{pmatrix} \begin{pmatrix} F_{\beta}^{+} \\ F_{\beta}^{-} \end{pmatrix} \quad (3.15b)$$

is equivalent to system (3.9b). Indeed, they differ only in the fact that the equation for  $F_{\alpha}(\mathbf{0})$  is duplicated in (3.15b).

But equation (3.11) shows that:

$$H_{\alpha\beta}^{-+} = \overline{H_{\alpha\beta}^{++}} \quad \text{and} \quad H_{\alpha\beta}^{+-} = \overline{H_{\alpha\beta}^{--}}$$

so that equations (3.15b) separate into two groups, which are equivalent since related simply by complex conjugation. We have therefore factored equations (3.9b) into the split equations expressing Friedel's law, and the smaller system:

$$F_{\alpha}^{+} = H_{\alpha\beta}^{++} F_{\beta}^{+} \quad (3.16b)$$

where

$$H_{\alpha\beta}^{++} = (H_{\alpha\beta}^{++} H_{\alpha\beta}^{+-}) \quad \text{and} \quad F_{\beta}^{+} = \begin{pmatrix} F_{\beta}^{+} \\ F_{\beta}^{-} \end{pmatrix}.$$

System (3.16b) is irreducible, since no relation exists between  $H_{\alpha\beta}(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta})$  and  $H_{\alpha\beta}(\mathbf{p}_{\alpha}, -\mathbf{q}_{\beta})$ .

Similarly, system (3.9d) can be reduced to:

$$\mathbf{F}^{+} = \mathbf{H}^{+} \mathbf{F}' \quad (3.16d)$$

where

$$\mathbf{F}^{+} = \begin{pmatrix} F_1^{+} \\ \vdots \\ F_v^{+} \end{pmatrix}, \quad \mathbf{F}' = \begin{pmatrix} F_1' \\ \vdots \\ F_v' \end{pmatrix}$$

and

$$\mathbf{H}^{+} = \frac{1}{v} \begin{pmatrix} H_{11}^{+} & \dots & H_{1v}^{+} \\ \vdots & & \vdots \\ H_{v1}^{+} & \dots & H_{vv}^{+} \end{pmatrix}.$$

### 3.3.4. A reciprocal-space estimate of redundancy

Any line of matrix  $\mathbf{H}^{+}$  has an infinite number of non-zero elements, unless all the crystals are identical and all the local symmetries and envelope constraints are trivial. Thus, equations (3.16d) constitute an irreducible set of mixed relations between structure factors, so that intensity data from these crystals are indeed redundant in the sense of § 1.1.

The fact that  $\mathbf{H}$  and the  $H_{\alpha\alpha}$ 's are projectors gives a means of computing the number of actual complex degrees of freedom of our structures. Indeed, as the eigenvalues of a projector are 0 or 1, its trace will be equal to the complex dimension of the subspace onto which it projects.

Thus, ignoring Friedel's law, structure  $\alpha$  will possess, at resolution  $\Delta$ ,  $N_{\Delta}^{(\alpha)}$  complex degrees of freedom, with

$$N_{\Delta}^{(\alpha)} \sim \text{Tr} (H_{\alpha\alpha}^{\Delta})_{\Delta \rightarrow 0}.$$

$H_{\alpha\alpha}^{\Delta}$  is the matrix obtained by truncating  $H_{\alpha\alpha}$  at resolution  $\Delta$ , that is:

$$H_{\alpha\alpha}^{\Delta}(\mathbf{p}_{\alpha}, \mathbf{q}_{\alpha}) = \begin{cases} H_{\alpha\alpha}(\mathbf{p}_{\alpha}, \mathbf{q}_{\alpha}) & \text{if } \|\mathbf{p}_{\alpha}\| \leq \Delta^{-1} \text{ and } \|\mathbf{q}_{\alpha}\| \leq \Delta^{-1} \\ 0 & \text{otherwise} \end{cases}$$

and we take the limit as  $\Delta \rightarrow 0$  to eliminate truncation errors which will result in  $H_{\alpha\alpha}^{\Delta}$  not being exactly a projector.

We then have:

$$\text{Tr} (H_{\alpha\alpha}^{\Delta}) = \sum_{\|\mathbf{p}_{\alpha}\| \leq \Delta^{-1}} \frac{1}{n_{\alpha} V_{\alpha}} \sum_{i=1}^{n_{\alpha}} \sum_{j=1}^{n_{\alpha}} \exp\{2\pi i \mathbf{p}_{\alpha} \cdot (\mathbf{d}_i - \mathbf{d}_j)\} \times \overline{\mathcal{F}}[\chi_U]\{(C_i - C_j)\mathbf{p}_{\alpha}\}.$$

As  $\overline{\mathcal{F}}[\chi_U]$  is very small for large moduli of its argument, the only terms which will contribute to the sum at large values of  $\|\mathbf{p}_{\alpha}\|$  will be those where  $i=j$ ; they are all equal to  $U$ , and their number is  $2n_{\alpha}N_{\Delta}(V_{\alpha})$ . Therefore,

$$\text{Tr} (H_{\alpha\alpha}^{\Delta})_{\Delta \rightarrow 0} \sim 2N_{\Delta}(V_{\alpha}) \cdot \frac{U}{V_{\alpha}} = 2N_{\Delta}(U)$$

which is independent of  $\alpha$ .

Since  $\text{Tr} (\mathbf{H}^{\Delta}) = \frac{1}{v} \sum_{\alpha=1}^v \text{Tr} (H_{\alpha\alpha}^{\Delta})$ , we also have:

$$\text{Tr} (\mathbf{H}^{\Delta})_{\Delta \rightarrow 0} \sim 2N_{\Delta}(U).$$

† The results of this section were obtained independently by Dr Peter Colman (private communication).

If we now recall Friedel's law, this result confirms our direct-space estimate of § 1.2 for the number of *real* degrees of freedom of our set of structures. These degrees of freedom have now been identified as being the coordinates of  $\mathbf{F}$  in a basis of eigenvectors of  $\mathbf{H}$  for eigenvalue 1.

We shall introduce for later use the relative complex dimensions of the eigenspaces of  $\mathbf{H}$  and the  $H_{\alpha\alpha}$ 's, defined by:

$$\kappa_{\alpha} = \lim_{A \rightarrow 0} \frac{\text{Tr}(H_{\alpha\alpha}^A)}{2N_A(V_{\alpha})} \quad \text{and} \quad \mathbf{\kappa} = \lim_{A \rightarrow 0} \frac{\text{Tr}(\mathbf{H})}{\sum_{\alpha=1}^{\nu} 2N_A(V_{\alpha})}.$$

By the preceding results:

$$\kappa_{\alpha} = \frac{U}{V_{\alpha}}, \quad \mathbf{\kappa} = \frac{U}{\sum_{\alpha=1}^{\nu} V_{\alpha}}.$$

We shall call these ratios the *convergence indices* of projectors  $H_{\alpha\alpha}$  and  $\mathbf{H}$ , for reasons which will become clear later.

The ratio  $N_{\text{free}}/N_{\text{obs}}$ , which Crowther (1967, 1969) calls the 'gradient of the  $(m, N)$  plot', is thus:

$$2\kappa_{\alpha} = \frac{2U}{V_{\alpha}} \quad \text{for structure } \alpha,$$

$$2\mathbf{\kappa} = \frac{2U}{\sum_{\alpha=1}^{\nu} V_{\alpha}} \quad \text{for the set of structures,}$$

so that overdetermination of the phase problem will occur for  $\mathbf{\kappa} \leq \frac{1}{2}$ .

#### 4. The equations for non-trivial space groups

When space-group symmetries are present in the set of structures of § 3, equations can be written in a reduced form involving only independent reflexions of each crystal.

##### 4.1. Preliminary identities

Let  $\Gamma$  be a displacement in  $E(\Gamma\mathbf{x} = G\mathbf{x} + \mathbf{g})$ ,  $\Phi$  any function of  $C(E)$ . Then the following identities are readily proved:

$$(\overline{\mathcal{F}}\Gamma^*\mathcal{F}\Phi)(\xi) = \exp(2\pi i\xi \cdot \mathbf{g})(G^*\Phi)(\xi) \quad (4.1)$$

$$(\overline{\mathcal{F}}(\Gamma^{-1})^*\mathcal{F}\Phi)(\xi) = \exp(2\pi i(G\xi) \cdot \mathbf{g})((G^{-1})^*\Phi)(\xi). \quad (4.2)$$

If moreover rotation  $G$  belongs to the point group of a crystal  $\varrho = R^*\varrho^0$ , that is if  $G^*R = (G^{-1})^*R = R$ , we have the identity:

$$R^*(\Gamma^*\varrho^0) = \Gamma^*(R^*\varrho^0), \quad (4.3)$$

*i.e.*  $\Gamma$  'commutes' with the lattice.

##### 4.2. The equations

Let us suppose that each of the crystals of § 3.1 has a non-trivial space group, so that its motif  $\varrho_{\alpha}^0$  is built

from the asymmetric motif  $\varrho_{\alpha}^{00}$  by  $m_{\alpha}$  operations  $\Gamma_{K_{\alpha}}$  – explicitly  $\Gamma_{K_{\alpha}}\mathbf{x} = G_{K_{\alpha}}\mathbf{x} + \mathbf{g}_{K_{\alpha}}$ . The identity operation corresponds to  $K_{\alpha} = 1$ . The asymmetric motif  $\varrho_{\alpha}^{00}$  is in its turn built, as in § 3.1, by  $n_{\alpha}$  local operations  $T_{i_{\alpha}}$  – explicitly  $T_{i_{\alpha}}\mathbf{x} = C_{i_{\alpha}}\mathbf{x} + \mathbf{d}_{i_{\alpha}}$  – from molecule  $M$ , described in a reference position by density  $\mu$ , with envelope  $U$ .

We therefore have:

$$\varrho_{\alpha} = R_{\alpha}^* \sum_{K_{\alpha}=1}^{m_{\alpha}} \Gamma_{K_{\alpha}}^* \left( \sum_{i_{\alpha}=1}^{n_{\alpha}} T_{i_{\alpha}}^* \mu \right)$$

or, using (4.3):

$$\varrho_{\alpha} = \sum_{K_{\alpha}=1}^{m_{\alpha}} \Gamma_{K_{\alpha}}^* (R_{\alpha}^* \sum_{i_{\alpha}=1}^{n_{\alpha}} T_{i_{\alpha}}^* \mu). \quad (4.4)$$

The non-overlapping of the various envelopes reads:

$$\chi U_{K_{\alpha}, i_{\alpha}} \cdot \varrho_{\alpha} = \Gamma_{K_{\alpha}}^* T_{i_{\alpha}}^* \mu \quad \text{for all } K_{\alpha}, i_{\alpha} \quad (4.5)$$

with

$$U_{K_{\alpha}, i_{\alpha}} = \Gamma_{K_{\alpha}} T_{i_{\alpha}} U.$$

Reasoning from (4.4) and (4.5) as in § 3.2, and with the *same* notations, it is easily shown that the system of equations:

$$\varrho_{\alpha} = \sum_{K_{\alpha}=1}^{m_{\alpha}} \Gamma_{K_{\alpha}}^* B_{\alpha\beta} (\Gamma_{K_{\alpha}}^{-1})^* \varrho_{\beta} \equiv \mathcal{B}_{\alpha\beta}^{(K_{\alpha})} \varrho_{\beta} \quad \text{for all } K_{\alpha} \quad (4.6a)$$

expresses all our hypotheses, and that *equivalent* systems are obtained by successive averagings over  $K_{\beta}$  and  $\beta$ , namely:

$$\varrho_{\alpha} = \frac{1}{m_{\beta}} \sum_{K_{\beta}=1}^{m_{\beta}} \sum_{K_{\alpha}=1}^{m_{\alpha}} \Gamma_{K_{\alpha}}^* B_{\alpha\beta} (\Gamma_{K_{\beta}}^{-1})^* \varrho_{\beta} \equiv \mathcal{B}_{\alpha\beta} \varrho_{\beta} \quad (4.6b)$$

and

$$\varrho = \mathcal{B} \varrho \quad (4.6d) \quad \text{where} \quad \mathcal{B} = \frac{1}{\nu} \begin{pmatrix} \mathcal{B}_{11} & \dots & \mathcal{B}_{1\nu} \\ \vdots & & \vdots \\ \mathcal{B}_{\nu 1} & \dots & \mathcal{B}_{\nu\nu} \end{pmatrix}.$$

Here again,  $\mathcal{B}$  and the  $\mathcal{B}_{\alpha\alpha}$ 's are *projectors*. The  $\mathcal{B}_{\alpha\alpha}$ 's are orthogonal (since Hermitian), and  $\mathcal{B}$  can be made orthogonal for a suitably weighted scalar product.

The corresponding equations in reciprocal space are readily obtained. We shall therefore limit ourselves to the calculation of some matrix elements to be used in their reduction.

Equations (4.6a) become:

$$F_{\alpha} = \mathcal{H}_{\alpha\beta}^{(K_{\alpha})} F_{\beta} \quad (4.7a)$$

with

$$\mathcal{H}_{\alpha\beta}^{(K_{\alpha})} = \overline{\mathcal{F}} \mathcal{B}_{\alpha\beta}^{(K_{\alpha})} \mathcal{F} = \sum_{K_{\alpha}=1}^{m_{\alpha}} (\overline{\mathcal{F}} \Gamma_{K_{\alpha}}^* \mathcal{F}) H_{\alpha\beta} (\overline{\mathcal{F}} (\Gamma_{K_{\alpha}}^{-1})^* \mathcal{F}), \quad (4.8)$$

whence, using (4.1) and (4.2):

$$\mathcal{H}_{\alpha\beta}^{(K_{\alpha})}(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta}) = \sum_{K_{\alpha}=1}^{m_{\alpha}} \exp(2\pi i \mathbf{p}_{\alpha} \cdot \mathbf{g}_{K_{\alpha}}) \times H_{\alpha\beta}(G_{K_{\alpha}}^{-1} \mathbf{p}_{\alpha}, G_{K_{\alpha}} \mathbf{q}_{\beta}) \exp(-2\pi i \mathbf{q}_{\beta} \cdot \mathbf{g}_{K_{\alpha}}). \quad (4.9)$$

This expression can be used to show, as in § 3.3.3, that the projectors  $\mathcal{H}_{\alpha\alpha}$  and  $\mathcal{H}$  all have eigenspaces for eigenvalue 1 whose dimensions are asymptotically equal to  $2N_{\alpha}(U)$  as  $\Delta \rightarrow 0$ , and whose convergence indices are  $\kappa_{\alpha} = \frac{U}{v_{\alpha}}$  and  $\mathbf{\kappa} = U \sum_{\alpha=1}^{\nu} v_{\alpha}$ .

#### 4.3. The reduction of equations in reciprocal space

Let  $\mathcal{A}'_{\alpha}$  be the reciprocal asymmetric unit of crystal  $\alpha$  (ignoring Friedel's law), and let us define the partial column vectors  $F_{\alpha}^{(K_{\alpha})}$  by:

$$F_{\alpha}^{(K_{\alpha})}(\mathbf{p}_{\alpha}) = F_{\alpha}(\mathbf{p}_{\alpha}) \text{ for } \mathbf{p}_{\alpha} \in G_{K_{\alpha}} \mathcal{A}'_{\alpha}.$$

Equations (9a) can then be written:

$$\begin{pmatrix} F_{\alpha}^{(1)} \\ \vdots \\ F_{\alpha}^{(m_{\alpha})} \end{pmatrix} = \begin{pmatrix} \mathcal{H}_{\alpha\beta}^{(K_{\beta})} (1, 1) & \dots & \mathcal{H}_{\alpha\beta}^{(K_{\beta})} (1, m_{\beta}) \\ \vdots & & \vdots \\ \mathcal{H}_{\alpha\beta}^{(K_{\beta})} (m_{\alpha}, 1) & \dots & \mathcal{H}_{\alpha\beta}^{(K_{\beta})} (m_{\alpha}, m_{\beta}) \end{pmatrix} \begin{pmatrix} F_{\beta}^{(1)} \\ \vdots \\ F_{\beta}^{(m_{\beta})} \end{pmatrix} \quad \text{for all } K_{\beta} \quad (4.10)$$

with

$$\mathcal{H}_{\alpha\beta}^{(K_{\beta})} (l_{\alpha}, l_{\beta})(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta}) = \mathcal{H}_{\alpha\beta}^{(K_{\beta})}(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta}) \text{ for } \mathbf{p}_{\alpha} \in G_{l_{\alpha}} \mathcal{A}'_{\alpha} \text{ and } \mathbf{q}_{\beta} \in G_{l_{\beta}} \mathcal{A}'_{\beta}.$$

But this system (4.10) can be deduced from its first line by applying to it the operators  $\overline{\mathcal{F}} \Gamma_{K_{\alpha}}^* \mathcal{F}$ ; also, operators  $\overline{\mathcal{F}} (\Gamma_{K_{\beta}}^{-1})^* \mathcal{F}$  induce the same permutation on the lines of the r.h.s. vector and the columns of the matrix, leaving the  $F_{\alpha}^{(K_{\alpha})}$ 's unchanged.

It is therefore equivalent to its first line written for  $K_{\beta} = 1$ . Using the identity:

$$F_{\beta}^{(1\beta)}(\mathbf{q}_{\beta}) = \exp(2\pi i \mathbf{q}_{\beta} \cdot \mathbf{g}_{l_{\beta}}) F_{\beta}^{(1)}(G_{l_{\beta}}^{-1} \mathbf{q}_{\beta}) \text{ if } \mathbf{q}_{\beta} \in G_{l_{\beta}} \mathcal{A}'_{\beta},$$

we obtain the reduced equation:

$$F_{\alpha}^{(1)} = \mathcal{H}_{\alpha\beta}^{(R)} F_{\beta}^{(1)} \quad (4.11)$$

where

$$\mathcal{H}_{\alpha\beta}^{(R)}(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta}) = \sum_{K_{\beta}=1}^{m_{\beta}} \mathcal{H}_{\alpha\beta}^{(1)}(\mathbf{p}_{\alpha}, G_{K_{\beta}} \mathbf{q}_{\beta}) \times \exp\{2\pi i(G_{K_{\beta}} \mathbf{q}_{\beta}) \cdot \mathbf{g}_{K_{\beta}}\},$$

i.e.

$$\mathcal{H}_{\alpha\beta}^{(R)}(\mathbf{p}_{\alpha}, \mathbf{q}_{\beta}) = \sum_{K_{\alpha}=1}^{m_{\alpha}} \sum_{K_{\beta}=1}^{m_{\beta}} \exp(2\pi i \mathbf{p}_{\alpha} \cdot \mathbf{g}_{K_{\alpha}}) \times H_{\alpha\beta}(G_{K_{\alpha}}^{-1} \mathbf{p}_{\alpha}, G_{K_{\beta}} \mathbf{q}_{\beta}) \exp\{2\pi i(G_{K_{\beta}} \mathbf{q}_{\beta}) \cdot \mathbf{g}_{K_{\beta}}\} \quad (4.12)$$

with

$$\mathbf{p}_{\alpha} \in \mathcal{A}'_{\alpha}, \mathbf{q}_{\beta} \in \mathcal{A}'_{\beta}.$$

This matrix can in its turn be reduced by Friedel's law, as explained in § 3.3.3.

## 5. Discussion

### 5.1. Summary of the main results

Relations have been obtained between structure factors of crystals built from the same molecule, but with different lattices or with several identical subunits in

their asymmetric units. These relations are of the general form:

$$\mathbf{F} = \mathbf{H}\mathbf{F} \quad (5.1)$$

where  $\mathbf{F}$  is a vector of structure factors, and  $\mathbf{H}$  is an orthogonal projector (for a suitable scalar product  $\langle \mathbf{F} | \mathbf{G} \rangle$ ). They are *mixed* (see § 1.1) since each line of matrix  $\mathbf{H}$  has an infinite number of non-zero elements. Therefore, they constitute constraints imposed upon the phases of the structure factors, once the moduli are known.

Equation (5.1) has been shown to be equivalent to the direct-space equation:

$$\mathbf{q} = \mathbf{B}\mathbf{q} \quad (5.2)$$

where  $\mathbf{q}$  is a column vector of electron densities, and  $\mathbf{B}$  is an orthogonal projector (for a suitable scalar product  $\langle \mathbf{q} | \boldsymbol{\sigma} \rangle$ ) which rebuilds each crystal from the average of all the molecules present in all the crystals.

The relative dimension of the subspaces onto which  $\mathbf{B}$  and  $\mathbf{H}$  project is what we have called their convergence index:

$$\mathbf{x} = U \sum_{\alpha=1}^{\nu} v_{\alpha}.$$

A Fourier transformation connects these two formulations, as illustrated by the diagram:

$$\begin{array}{ccc} & \mathbf{B} & \\ \mathbf{q} & \longrightarrow & \mathbf{B}\mathbf{q} \\ \mathcal{F} \uparrow & \overline{\mathcal{F}} & \mathcal{F} \uparrow \\ & \mathbf{H} & \\ \mathbf{F} & \longrightarrow & \mathbf{H}\mathbf{F} \end{array} \quad (5.3)$$

### 5.2. The method of successive projections

Relations (5.1) considered as phase equations, form a system of simultaneous transcendental equations, for which no general method of solution exists. But advantage can be taken of the fact that  $\mathbf{H}$  is an orthogonal projector to solve these equations iteratively.

#### 5.2.1. Outline of the method

Crowther (1969) has proposed such an iterative procedure, in which the current phases are combined with the observed moduli, and the structure factors thus obtained are projected; the phases of the projected vector are then taken as the current phases for the next cycle. This method was used successfully by Jack to calculate *ab initio* signs for a centric projection of the disks of tobacco mosaic virus protein (Jack, 1973) and to refine single isomorphous replacement phases for the enzyme barnase (Jack, 1972).

#### 5.2.2. Direct-space vs. reciprocal-space implementation

In Crowther's method the projection operation consists in multiplying the vector of structure factors by

matrix  $\mathbf{H}$ . From the computational point of view, this is a source of severe limitations. As shown in § 4.3, the minimum size to which an  $H$  matrix can be reduced is  $N \times 2N$  for  $N$  independent reflexions. Moreover, it is natural to ask that the shape of the molecular boundaries be defined with at least the resolution  $\Delta$  at which we want to determine phases. This implies that the function  $\overline{\mathcal{F}}[\chi_U]$  should not be truncated for arguments less than  $\Delta^{-1}$  in length, which means that almost all the matrix elements should be used. This becomes impractical as soon as more than about 2000 reflexions are present. Neglecting all but the largest elements of  $\mathbf{H}$  introduces errors which are difficult to estimate and certainly harm the convergence of the process.

Also, if the matrix elements are to be easily computed, the molecular envelope  $U$  has to allow an analytical expression of  $\overline{\mathcal{F}}[\chi_U]$ . It is then difficult to avoid the overlapping of such crude envelopes, which will make the equations inaccurate.

If the local symmetries are *proper*, an intermediate expansion of the structure factor vectors on suitable eigenvectors of the  $H$  matrix can reduce the amount of permanent storage required by a factor of  $\kappa^{-1}$ , and the amount of calculation by  $\frac{1}{2}\kappa^{-1}$  (Jack, 1973). But both of these quantities will still vary as  $\Delta^{-6}$ .

These difficulties can be overcome if the projection is performed in direct space, using the correspondence between  $\mathbf{H}$  and  $\mathbf{B}$  illustrated by diagram (5.3). Indeed, since  $\mathbf{H} = \overline{\mathcal{F}}\mathbf{B}\overline{\mathcal{F}}$ , we can project  $\mathbf{F}$  in three steps:

- step ( $\mathcal{F}$ ): a set of electron density maps  $\varrho$  is computed from  $\mathbf{F}$ ;
- step ( $B$ ): the electron densities of all crystallographically independent molecules are averaged, and each crystal is rebuilt from this averaged molecule; the density outside the molecular boundaries is set to its average value;
- step ( $\overline{\mathcal{F}}$ ): structure factors are recomputed from these averaged densities.

Fast Fourier transform programs can be used in steps ( $\mathcal{F}$ ) and ( $\overline{\mathcal{F}}$ ). The electron densities can be over-sampled in step ( $\mathcal{F}$ ), so that all the averaging operations in step ( $B$ ) can be performed using linear eight-point interpolations. Then the amounts of permanent storage and calculation involved in ( $B$ ) both vary as  $\Delta^{-3}$ . Also, no restrictions whatsoever are imposed on the shape of the molecular envelope.

Therefore, this direct-space procedure will be considerably more powerful and more flexible than its reciprocal-space counterpart. Its superiority ultimately lies in the fact that it handles the envelope constraints by multiplication, whereas in reciprocal space this is done by convolution.

### 5.2.3. Convergence of the algorithm

Crowther (1969) has given some numerical counter-examples in one dimension, which show that the prob-

lem of phase determination using geometrical redundancies may not have a unique answer.

He also discussed the problems which may arise if a non-centrosymmetric structure possesses a centrosymmetric arrangement of subunits. We shall limit our attention to the case where a unique solution exists, and show that the algorithm will converge for small enough values of the convergence index  $\kappa$  ( $\kappa^{-1}$  is at least equal to the number of independent molecules present in the crystals).

Indeed, we can separate in the current structure factors a 'signal' (the solution) and a 'noise' (the difference). If the noise can be assumed to be *white*, i.e. to have a uniform power spectrum over the eigenvectors of  $\mathbf{H}$  (or  $\mathbf{B}$ ), each projection will increase the signal-to-noise ratio by a factor  $\kappa^{-1/2}$ . The convergence problem can then be phrased: will the recombination of the phases of the projected vector with the observed moduli reintroduce more or less noise than the projection has removed?

Let  $\mathbf{p}$  be any reciprocal-lattice point. We denote (see Fig. 1):

- by  $\mathbf{F}_i(\mathbf{p})$  the structure factor estimate for cycle  $i$ ;
- by  $\delta\mathbf{F}_i(\mathbf{p})$  the correction to be added to the projected structure factor  $\mathbf{H}\mathbf{F}_i(\mathbf{p})$  to obtain  $\mathbf{F}_{i+1}(\mathbf{p})$ ;
- by  $\mathbf{F}(\mathbf{p})$  the solution;
- by  $\Delta\mathbf{F}_i(\mathbf{p})$  the difference  $\mathbf{F}(\mathbf{p}) - \mathbf{H}\mathbf{F}_i(\mathbf{p})$ ;
- by  $\varepsilon_i$  the quadratic error for step  $i$ , defined by

$$\varepsilon_i^2 = \langle \mathbf{F} - \mathbf{F}_i | \mathbf{F} - \mathbf{F}_i \rangle.$$

Writing  $\mathbf{F} - \mathbf{F}_{i+1} = (\mathbf{F} - \mathbf{H}\mathbf{F}_i) - (\mathbf{F}_{i+1} - \mathbf{H}\mathbf{F}_i) = \Delta\mathbf{F}_i - \delta\mathbf{F}_i$ , we have:

$$\varepsilon_{i+1}^2 = \langle \Delta\mathbf{F}_i | \Delta\mathbf{F}_i \rangle + \langle \delta\mathbf{F}_i | \delta\mathbf{F}_i \rangle - \langle \Delta\mathbf{F}_i | \delta\mathbf{F}_i \rangle - \langle \delta\mathbf{F}_i | \Delta\mathbf{F}_i \rangle.$$

Since the noise  $\mathbf{F} - \mathbf{F}_i$  has been supposed to be white, and  $\Delta\mathbf{F}_i = \mathbf{H}(\mathbf{F} - \mathbf{F}_i)$ , we have

$$\langle \Delta\mathbf{F}_i | \Delta\mathbf{F}_i \rangle = \kappa \cdot \varepsilon_i^2.$$

Also, since  $\mathbf{F}_{i+1}(\mathbf{p})$  is the nearest point to  $\mathbf{H}\mathbf{F}_i(\mathbf{p})$  on the phase circle, we have the rigorous inequality:  $|\delta\mathbf{F}_i(\mathbf{p})| \leq |\Delta\mathbf{F}_i(\mathbf{p})|$  for all  $\mathbf{p}$ . We can in fact average over an angle  $\theta$ , and obtain the better estimate:

$$\langle \delta\mathbf{F}_i | \delta\mathbf{F}_i \rangle \sim \frac{1}{2} \langle \Delta\mathbf{F}_i | \Delta\mathbf{F}_i \rangle = \frac{\kappa}{2} \varepsilon_i^2.$$

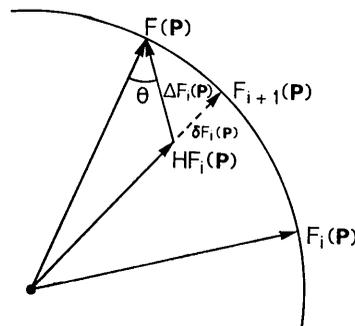


Fig. 1. Notation in reciprocal space.

The last two scalar products can be estimated as follows: from the definition of  $\Delta F_i$  we have  $H\Delta F_i = \Delta F_i$ , so that:

$\langle \Delta F_i | \delta F_i \rangle = \langle H\Delta F_i | \delta F_i \rangle = \langle \Delta F_i | H\delta F_i \rangle$  since  $H$  is Hermitian. If  $\delta F_i$  is also supposed to be a white noise,  $\langle H\delta F_i | H\delta F_i \rangle = \kappa \langle \delta F_i | \delta F_i \rangle$  and Schwarz's inequality gives:

$$\begin{aligned} |\langle \Delta F_i | H\delta F_i \rangle| &\leq \langle \Delta F_i | \Delta F_i \rangle^{1/2} \langle H\delta F_i | H\delta F_i \rangle^{1/2} \\ &= \kappa \cdot \left(\frac{\kappa}{2}\right)^{1/2} \cdot \varepsilon_i^2. \end{aligned}$$

Since

$$|\langle \delta F_i | \Delta F_i \rangle| = |\langle \Delta F_i | \delta F_i \rangle|,$$

we finally have:

$$\varepsilon_{i+1}^2 \leq \kappa \cdot \left[ \frac{3}{2} + \left(\frac{\kappa}{2}\right)^{1/2} \right] \varepsilon_i^2.$$

For  $\kappa \leq \frac{1}{2}$ , we have  $\kappa \left[ \frac{3}{2} + \left(\frac{\kappa}{2}\right)^{1/2} \right] \leq 1$ . Therefore as soon as the problem is overdetermined (*i.e.*  $\kappa < \frac{1}{2}$ ), the quadratic error will decrease geometrically from one iteration to the next. The same applies to the 'quadratic  $R$  value'  $\langle \delta F_i | \delta F_i \rangle / \langle F | F \rangle$ .

#### 5.2.4. Relation to the least-squares method

An alternative method of solution of equations (5.1) was used by Main (1967) on a trial structure. Phases  $\varphi_{\text{calc}}$  are determined iteratively in order to minimize the quadratic lack of closure  $\langle A | A \rangle$ , where

$$A = |F|_{\text{obs}} \exp(i\varphi_{\text{calc}}) - H[|F|_{\text{obs}} \exp(i\varphi_{\text{calc}})].$$

This is a least-squares phase refinement under the joint constraints of geometric redundancy and agreement with the observed moduli.

It is easily seen that the method of successive projections is also a least-squares method. However, it treats the two types of constraints *separately*.

Indeed, let us consider the cycle illustrated in Fig. 1:

$$\begin{array}{ccc} (H) & & (\delta) \\ \rightarrow F_i & \rightarrow & HF_i \rightarrow F_{i+1} \rightarrow. \end{array}$$

Since  $H$  is an orthogonal projector,  $HF_i$  is the best least-squares fit to  $F_i$  which satisfies the geometric re-

dundancy constraints. Similarly, because of the extremal property of the  $\delta F_i$ 's already mentioned,  $F_{i+1}$  is the best fit to  $HF_i$  having the required moduli. Thus, steps ( $H$ ) and ( $\delta$ ) are two least-squares fittings, treating separately the two constraints between which a compromise is sought.

Therefore, Main's method should in principle be the more powerful. But in practice, this theoretical superiority will be outweighed by the inherent computational inaccuracies of reciprocal-space methods (Main, 1967).

#### 5.3. Conclusion

The molecular replacement equations can be solved by the method of successive projections as soon as they are overdetermined, *i.e.* if more than two crystallographically independent copies of the same molecule can be observed. This method can be applied most easily if the projections are performed in direct space. The solution may not be unique, but as in any least-squares method, false solutions will play no role if the starting phases are close enough to the true one.

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