

# 1. GENERAL RELATIONSHIPS AND TECHNIQUES

## 1.3.4.3.5.5. Real antisymmetric transforms

If  $\mathbf{X}$  is real antisymmetric, then its transform  $\mathbf{X}^*$  is purely imaginary and antisymmetric. The double-multiplexing techniques used for real symmetric transforms may therefore be adapted with only minor changes involving signs and factors of  $i$ .

## 1.3.4.3.5.6. Generalized multiplexing

So far the multiplexing technique has been applied to pairs of vectors with similar types of parity-related and/or conjugate symmetry properties, in particular the same value of  $\varepsilon$ .

It can be generalized so as to accommodate mixtures of vectors with different symmetry characteristics. For example if  $\mathbf{X}_1$  is Hermitian-symmetric and  $\mathbf{X}_2$  is Hermitian-antisymmetric, so that  $\mathbf{X}_1^*$  is real-valued while  $\mathbf{X}_2^*$  has purely imaginary values, the multiplexing process should obviously form  $\mathbf{X} = \mathbf{X}_1 + \mathbf{X}_2$  (instead of  $\mathbf{X} = \mathbf{X}_1 + i\mathbf{X}_2$  if both had the same type of symmetry), and demultiplexing consists in separating

$$\begin{aligned}\mathbf{X}_1^* &= \text{Re } \mathbf{X}^* \\ \mathbf{X}_2^* &= i \text{Im } \mathbf{X}^*.\end{aligned}$$

The general multiplexing formula for pairs of vectors may therefore be written

$$\mathbf{X} = \mathbf{X}_1 + \omega \mathbf{X}_2,$$

where  $\omega$  is a phase factor (e.g. 1 or  $i$ ) chosen in such a way that all non-exceptional components of  $\mathbf{X}_1$  and  $\mathbf{X}_2$  (or  $\mathbf{X}_1^*$  and  $\mathbf{X}_2^*$ ) be embedded in the complex plane  $\mathbb{C}$  along linearly independent directions, thus making multiplexing possible.

It is possible to develop a more general form of multiplexing/demultiplexing for more than two vectors, which can be used to deal with symmetry elements of order 3, 4 or 6. It is based on the theory of group characters (Ledermann, 1987).

## 1.3.4.3.6. Global crystallographic algorithms

All the necessary ingredients are now available for calculating the CDFT for any given space group.

### 1.3.4.3.6.1. Triclinic groups

Space group  $P1$  is dealt with by the methods of Section 1.3.4.3.5.1 and  $\bar{P}1$  by those of Section 1.3.4.3.5.4.

### 1.3.4.3.6.2. Monoclinic groups

A general monoclinic transformation is of the form

$$S_g : \mathbf{x} \mapsto \mathbf{R}_g \mathbf{x} + \mathbf{t}_g$$

with  $\mathbf{R}_g$  a diagonal matrix whose entries are  $+1$  or  $-1$ , and  $\mathbf{t}_g$  a vector whose entries are 0 or  $\frac{1}{2}$ . We may thus decompose both real and reciprocal space into a direct sum of a subspace  $\mathbb{Z}^{n_+}$  where  $\mathbf{R}_g$  acts as the identity, and a subspace  $\mathbb{Z}^{n_-}$  where  $\mathbf{R}_g$  acts as minus the identity, with  $n_+ + n_- = n = 3$ . All usual entities may be correspondingly written as direct sums, for instance:

$$\begin{aligned}\mathbf{R}_g &= \mathbf{R}_g^+ \oplus \mathbf{R}_g^-, & \mathbf{N} &= \mathbf{N}^+ \oplus \mathbf{N}^-, & \mathbf{M} &= \mathbf{M}^+ \oplus \mathbf{M}^-, \\ \mathbf{t}_g &= \mathbf{t}_g^+ \oplus \mathbf{t}_g^-, & \mathbf{t}_g^{(1)} &= \mathbf{t}_g^{(1)+} \oplus \mathbf{t}_g^{(1)-}, & \mathbf{t}_g^{(2)} &= \mathbf{t}_g^{(2)+} \oplus \mathbf{t}_g^{(2)-}, \\ \mathbf{m} &= \mathbf{m}^+ \oplus \mathbf{m}^-, & \mathbf{m}_1 &= \mathbf{m}_1^+ \oplus \mathbf{m}_1^-, & \mathbf{m}_2 &= \mathbf{m}_2^+ \oplus \mathbf{m}_2^-, \\ \mathbf{h} &= \mathbf{h}^+ \oplus \mathbf{h}^-, & \mathbf{h}_1 &= \mathbf{h}_1^+ \oplus \mathbf{h}_1^-, & \mathbf{h}_2 &= \mathbf{h}_2^+ \oplus \mathbf{h}_2^-.\end{aligned}$$

We will use factoring by 2, with decimation in frequency when computing structure factors, and decimation in time when computing electron densities; this corresponds to  $\mathbf{N} = \mathbf{N}_1 \mathbf{N}_2$  with  $\mathbf{N}_1 = \mathbf{M}$ ,  $\mathbf{N}_2 = 2\mathbf{I}$ . The non-primitive translation vector  $\mathbf{Nt}_g$  then belongs to  $\mathbf{M}\mathbb{Z}^n$ , and thus

$$\mathbf{t}_g^{(1)} = \mathbf{0} \bmod \mathbf{M}\mathbb{Z}^n, \quad \mathbf{t}_g^{(2)} \in \mathbb{Z}^n / 2\mathbb{Z}^n.$$

The symmetry relations obeyed by  $\rho$  and  $F$  are as follows: for electron densities

$$\rho(\mathbf{m}^+, \mathbf{m}^-) = \rho(\mathbf{m}^+ + \mathbf{N}^+ \mathbf{t}_g^+, -\mathbf{m}^- - \mathbf{N}^- \mathbf{t}_g^-)$$

or, after factoring by 2,

$$\begin{aligned}\rho(\mathbf{m}_1^+, \mathbf{m}_2^+, \mathbf{m}_1^-, \mathbf{m}_2^-) \\ = \rho(\mathbf{m}_1^+, \mathbf{m}_2^+ + \mathbf{t}_g^{(2)+}, \mathbf{M}^- \boldsymbol{\zeta}(\mathbf{m}_1^-) - \mathbf{m}_1^- - \mathbf{m}_2^-, \mathbf{m}_2^- + \mathbf{t}_g^{(2)-});\end{aligned}$$

while for structure factors

$$F(\mathbf{h}^+, \mathbf{h}^-) = \exp[2\pi i(\mathbf{h}^+ \cdot \mathbf{t}_g^+ + \mathbf{h}^- \cdot \mathbf{t}_g^-)] F(\mathbf{h}^+, -\mathbf{h}^-)$$

with its Friedel counterpart

$$F(\mathbf{h}^+, \mathbf{h}^-) = \exp[2\pi i(\mathbf{h}^+ \cdot \mathbf{t}_g^+ + \mathbf{h}^- \cdot \mathbf{t}_g^-)] \overline{F(-\mathbf{h}^+, \mathbf{h}^-)}$$

or, after factoring by 2,

$$\begin{aligned}F(\mathbf{h}_1^+, \mathbf{h}_2^+, \mathbf{h}_1^-, \mathbf{h}_2^-) &= (-1)^{\mathbf{h}_2^+ \cdot \mathbf{t}_g^{(2)+} + \mathbf{h}_2^- \cdot \mathbf{t}_g^{(2)-}} \\ &\times F(\mathbf{h}_1^+, \mathbf{h}_2^+, \mathbf{M}^- \boldsymbol{\zeta}(\mathbf{h}_1^-) - \mathbf{h}_1^- - \mathbf{h}_2^-, \mathbf{h}_2^-)\end{aligned}$$

with Friedel counterpart

$$\begin{aligned}F(\mathbf{h}_1^+, \mathbf{h}_2^+, \mathbf{h}_1^-, \mathbf{h}_2^-) \\ = (-1)^{\mathbf{h}_2^+ \cdot \mathbf{t}_g^{(2)+} + \mathbf{h}_2^- \cdot \mathbf{t}_g^{(2)-}} \overline{F[\mathbf{M}^+ \boldsymbol{\zeta}(\mathbf{h}_1^+) - \mathbf{h}_1^+ - \mathbf{h}_2^+, \mathbf{h}_2^+, \mathbf{h}_1^-, \mathbf{h}_2^-]}.\end{aligned}$$

When calculating electron densities, two methods may be used.

(i) Transform on  $\mathbf{h}^-$  first.

The partial vectors defined by  $X_{\mathbf{h}^+, \mathbf{h}_2^-} = F(\mathbf{h}^+, \mathbf{h}_1^-, \mathbf{h}_2^-)$  obey symmetry relations of the form

$$X(\mathbf{h}_1^- - \mathbf{h}_2^-) = \varepsilon X[\mathbf{M}^- \boldsymbol{\zeta}(\mathbf{h}_1^-) - \mathbf{h}_1^-]$$

with  $\varepsilon = \pm 1$  independent of  $\mathbf{h}_1^-$ . This is the same relation as for the same parity class of data for a (complex or real) symmetric ( $\varepsilon = +1$ ) or antisymmetric ( $\varepsilon = -1$ ) transform. The same techniques can be used to decrease the number of  $F(\mathbf{M}^-)$  by multiplexing pairs of such vectors and demultiplexing their transforms. Partial vectors with different values of  $\varepsilon$  may be mixed in this way (Section 1.3.4.3.5.6).

Once  $F(\mathbf{N}^-)$  is completed, its results have Hermitian symmetry with respect to  $\mathbf{h}^+$ , and the methods of Section 1.3.4.3.5.1 may be used to obtain the unique electron densities.

(ii) Transform on  $\mathbf{h}^+$  first.

The partial vectors defined by  $X_{\mathbf{h}^-, \mathbf{h}_2^+} = F(\mathbf{h}_1^+, \mathbf{h}_2^+, \mathbf{h}^-)$  obey symmetry relations of the form

$$X(\mathbf{h}_1^+ - \mathbf{h}_2^+) = \varepsilon X[\mathbf{M}^+ \boldsymbol{\zeta}(\mathbf{h}_1^+) - \mathbf{h}_1^+]$$

with  $\varepsilon = \pm 1$  independent of  $\mathbf{h}_1^+$ . This is the same relation as for the same parity class of data for a Hermitian symmetric ( $\varepsilon = +1$ ) or antisymmetric ( $\varepsilon = -1$ ) transform. The same techniques may be used to decrease the number of  $F(\mathbf{M}^+)$ . This generalizes the procedure described by Ten Eyck (1973) for treating dyad axes, i.e. for the case  $n_+ = 1$ ,  $\mathbf{t}_g^{(2)-} = \mathbf{0}$ , and  $\mathbf{t}_g^{(2)+} = \mathbf{0}$  (simple dyad) or  $\mathbf{t}_g^{(2)+} \neq \mathbf{0}$  (screw dyad).

Once  $F(\mathbf{N}^+)$  is completed, its results have Hermitian symmetry properties with respect to  $\mathbf{h}^-$  which can be used to obtain the unique electron densities.

Structure factors may be computed by applying the reverse procedures in the reverse order.

### 1.3.4.3.6.3. Orthorhombic groups

Almost all orthorhombic space groups are generated by two monoclinic transformations  $g_1$  and  $g_2$  of the type described in Section 1.3.4.3.6.2, with the addition of a centre of inversion  $-e$  for centrosymmetric groups. The only exceptions are  $Fdd2$  and  $Fddd$

### 1.3. FOURIER TRANSFORMS IN CRYSTALLOGRAPHY

which contain diamond glides, in which some non-primitive translations are 'square roots' not of primitive lattice translations, but of centring translations. The generic case will be examined first.

To calculate electron densities, the unique octant of data may first be transformed on  $\mathbf{h}^+$  (respectively  $\mathbf{h}^-$ ) as in Section 1.3.4.3.6.2 using the symmetry pertaining to generator  $g_1$ . These intermediate results may then be expanded by generator  $g_2$  by the formula of Section 1.3.4.3.3 prior to the final transform on  $\mathbf{h}^-$  (respectively  $\mathbf{h}^+$ ). To calculate structure factors, the reverse operations are applied in the reverse order.

The two exceptional groups  $Fdd2$  and  $Fddd$  only require a small modification. The  $F$ -centring causes the systematic absence of parity classes with mixed parities, leaving only (000) and (111). For the former, the phase factors  $\exp[2\pi i(\mathbf{h}^+ \cdot \mathbf{t}_g^+ + \mathbf{h}^- \cdot \mathbf{t}_g^-)]$  in the symmetry relations of Section 1.3.4.3.6.2 become powers of  $(-1)$  so that one is back to the generic case. For the latter, these phase factors are odd powers of  $i$  which it is a simple matter to incorporate into a modified multiplexing/demultiplexing procedure.

#### 1.3.4.3.6.4. Trigonal, tetragonal and hexagonal groups

All the symmetries in this class of groups can be handled by the generalized Rader/Winograd algorithms of Section 1.3.4.3.4.3, but no implementation of these is yet available.

In groups containing axes of the form  $n_m$  with g.c.d.  $(m, n) = 1$  (i.e.  $3_1, 3_2, 4_1, 4_3, 6_1, 6_5$ ) along the  $c$  direction, the following procedure may be used (Ten Eyck, 1973):

(i) to calculate electron densities, the unique structure factors indexed by

$$[\text{unique } (h, k)] \times (\text{all } l)$$

are transformed on  $l$ ; the results are rearranged by the transposition formula of Section 1.3.4.3.3 so as to be indexed by

$$[\text{all } (h, k)] \times \left[ \text{unique } \left( \frac{1}{n} \right) \text{th of } z \right]$$

and are finally transformed on  $(h, k)$  to produce an asymmetric unit. For a dihedral group, the extra twofold axis may be used in the transposition to produce a unique  $(1/2n)$ th of  $z$ .

(ii) to calculate structure factors, the unique densities in  $(1/n)$ th of  $z$  [or  $(1/2n)$ th for a dihedral group] are first transformed on  $x$  and  $y$ , then transposed by the formula of Section 1.3.4.3.3 to reindex the intermediate results by

$$[\text{unique } (h, k)] \times (\text{all } z);$$

the last transform on  $z$  is then carried out.

#### 1.3.4.3.6.5. Cubic groups

These are usually treated as their orthorhombic or tetragonal subgroups, as the body-diagonal threefold axis cannot be handled by ordinary methods of decomposition.

The three-dimensional factorization technique of Section 1.3.4.3.4.1 allows a complete treatment of cubic symmetry. Factoring by 2 along all three dimensions gives four types (i.e. orbits) of parity classes:

(000)	with residual threefold symmetry,
(100), (010), (001)	related by threefold axis,
(110), (101), (011)	related by threefold axis,
(111)	with residual threefold symmetry.

Orbit exchange using the threefold axis thus allows one to reduce the number of partial transforms from 8 to 4 (one per orbit). Factoring by 3 leads to a reduction from 27 to 11 (in this case, further reduction to 9 can be gained by multiplexing the three

diagonal classes with residual threefold symmetry into a single class; see Section 1.3.4.3.5.6). More generally, factoring by  $q$  leads to a reduction from  $q^3$  to  $\frac{1}{3}(q^3 - q) - q$ . Each of the remaining transforms then has a symmetry induced from the orthorhombic or tetragonal subgroup, which can be treated as above.

No implementation of this procedure is yet available.

#### 1.3.4.3.6.6. Treatment of centred lattices

Lattice centring is an instance of the duality between periodization and decimation: the extra translational periodicity of  $\rho$  induces a decimation of  $\mathbf{F} = \{F_{\mathbf{h}}\}$  described by the 'reflection conditions' on  $\mathbf{h}$ . As was pointed out in Section 1.3.4.2.2.3, non-primitive lattices are introduced in order to retain the same matrix representation for a given geometric symmetry operation in all the arithmetic classes in which it occurs. From the computational point of view, therefore, the main advantage in using centred lattices is that it *maximizes decomposability* (Section 1.3.4.2.2.4); reindexing to a primitive lattice would for instance often destroy the diagonal character of the matrix representing a dyad.

In the usual procedure involving three successive one-dimensional transforms, the loss of efficiency caused by the duplication of densities or the systematic vanishing of certain classes of structure factors may be avoided by using a multiplexing/demultiplexing technique (Ten Eyck, 1973):

(i) for base-centred or body-centred lattices, two successive planes of structure factors may be overlaid into a single plane; after transformation, the results belonging to each plane may be separated by parity considerations;

(ii) for face-centred lattices the same method applies, using four successive planes (the third and fourth with an origin translation);

(iii) for rhombohedral lattices in hexagonal coordinates, three successive planes may be overlaid, and the results may be separated by linear combinations involving cube roots of unity.

The three-dimensional factorization technique of Section 1.3.4.3.4.1 is particularly well suited to the treatment of centred lattices: if the decimation matrix of  $\mathbf{N}$  contains as a factor  $\mathbf{N}_1$  a matrix which 'integerizes' all the non-primitive lattice vectors, then centring is reflected by the systematic vanishing of certain classes of vectors of decimated data or results, which can simply be omitted from the calculation. An alternative possibly is to reindex on a primitive lattice and use different representative matrices for the symmetry operations: the loss of decomposability is of little consequence in this three-dimensional scheme, although it substantially complicates the definition of the cocycles  $\mu_2$  and  $\eta_1$ .

#### 1.3.4.3.6.7. Programming considerations

The preceding sections have been devoted to showing how the raw computational efficiency of a crystallographic Fourier transform *algorithm* can be maximized. This section will briefly discuss another characteristic (besides speed) which a crystallographic Fourier transform *program* may be required to possess if it is to be useful in various applications: a convenient and versatile mode of presentation of input data or output results.

The standard crystallographic FFT programs (Ten Eyck, 1973, 1985) are rather rigid in this respect, and use rather rudimentary data structures (lists of structure-factor values, and two-dimensional arrays containing successive sections of electron-density maps). It is frequently the case that considerable reformatting of these data or results must be carried out before they can be used in other computations; for instance, maps have to be converted from 2D sections to 3D 'bricks' before they can be inspected on a computer graphics display.

The explicitly three-dimensional approach to the factorization of the DFT and the use of symmetry offers the possibility of richer and more versatile data structures. For instance, the use of 'decimation in frequency' in real space and of 'decimation in time' in reciprocal

# 1. GENERAL RELATIONSHIPS AND TECHNIQUES

space leads to data structures in which real-space coordinates are handled by blocks (thus preserving, at least locally, the three-dimensional topological connectivity of the maps) while reciprocal-space indices are handled by parity classes or their generalizations for factors other than 2 (thus making the treatment of centred lattices extremely easy). This global three-dimensional indexing also makes it possible to carry symmetry and multiplicity characteristics for each subvector of intermediate results for the purpose of automating the use of the orbit exchange mechanism.

Brünger (1989) has described the use of a similar three-dimensional factoring technique in the context of structure-factor calculations for the refinement of macromolecular structures.

## 1.3.4.4. Basic crystallographic computations

### 1.3.4.4.1. Introduction

Fourier transform (FT) calculations play an indispensable role in crystallography, because the Fourier transformation is inherent in the diffraction phenomenon itself.

Besides this obligatory use, the FT has numerous other applications, motivated more often by its mathematical properties than by direct physical reasoning (although the latter can be supplied after the fact). Typically, many crystallographic computations turn out to be convolutions in disguise, which can be speeded up by orders of magnitude through a judicious use of the FT. Several recent advances in crystallographic computation have been based on this kind of observation.

### 1.3.4.4.2. Fourier synthesis of electron-density maps

Bragg (1929) was the first to use this type of calculation to assist structure determination. Progress in computing techniques since that time was reviewed in Section 1.3.4.3.1.

The usefulness of the maps thus obtained can be adversely affected by three main factors:

- (i) limited resolution;
- (ii) errors in the data;
- (iii) computational errors.

Limited resolution causes ‘series-termination errors’ first investigated by Bragg & West (1930), who used an optical analogy with the numerical aperture of a microscope. James (1948*b*) gave a quantitative description of this phenomenon as a convolution with the ‘spherical Dirichlet kernel’ (Section 1.3.4.2.1.3), which reflects the truncation of the Fourier spectrum by multiplication with the indicator function of the limiting resolution sphere. Bragg & West (1930) suggested that the resulting ripples might be diminished by applying an artificial temperature factor to the data, which performs a further convolution with a Gaussian point-spread function. When the electron-density map is to be used for model refinement, van Reijen (1942) suggested using Fourier coefficients calculated from the model when no observation is available, as a means of combating series-termination effects.

Errors in the data introduce errors in the electron-density maps, with the same mean-square value by virtue of Parseval’s theorem. Special positions accrue larger errors (Cruickshank & Rollett, 1953; Cruickshank, 1965*a*). To minimize the mean-square electron-density error due to large phase uncertainties, Blow & Crick (1959) introduced the ‘best Fourier’ which uses centroid Fourier coefficients; the associated error level in the electron-density map was evaluated by Blow & Crick (1959) and Dickerson *et al.* (1961*a,b*).

Computational errors used to be a serious concern when Beevers–Lipson strips were used, and Cochran (1948*a*) carried out a critical evaluation of the accuracy limitations imposed by strip methods. Nowadays, the FFT algorithm implemented on digital computers with a word size of at least 32 bits gives results accurate

to six decimal places or better in most applications (see Gentleman & Sande, 1966).

### 1.3.4.4.3. Fourier analysis of modified electron-density maps

Various approaches to the phase problem are based on certain modifications of the electron-density map, followed by Fourier analysis of the modified map and extraction of phase information from the resulting Fourier coefficients.

#### 1.3.4.4.3.1. Squaring

Sayre (1952*a*) derived his ‘squaring method equation’ for structures consisting of equal, resolved and spherically symmetric atoms by observing that squaring such an electron density is equivalent merely to sharpening each atom into its square. Thus

$$F_{\mathbf{h}} = \theta_{\mathbf{h}} \sum_{\mathbf{k}} F_{\mathbf{k}} F_{\mathbf{h}-\mathbf{k}},$$

where  $\theta_{\mathbf{h}} = f(\mathbf{h})/f^{\text{sq}}(\mathbf{h})$  is the ratio between the form factor  $f(\mathbf{h})$  common to all the atoms and the form factor  $f^{\text{sq}}(\mathbf{h})$  for the squared version of that atom.

Most of the central results of direct methods, such as the tangent formula, are an immediate consequence of Sayre’s equation. Phase refinement for a macromolecule by enforcement of the squaring method equation was demonstrated by Sayre (1972, 1974).

#### 1.3.4.4.3.2. Other non-linear operations

A category of phase improvement procedures known as ‘density modification’ is based on the pointwise application of various quadratic or cubic ‘filters’ to electron-density maps after removal of negative regions (Hoppe & Gassmann, 1968; Hoppe *et al.*, 1970; Barrett & Zwick, 1971; Gassmann & Zechmeister, 1972; Collins, 1975; Collins *et al.*, 1976; Gassmann, 1976). These operations are claimed to be equivalent to reciprocal-space phase-refinement techniques such as those based on the tangent formula. Indeed the replacement of

$$\rho(\mathbf{x}) = \sum_{\mathbf{h}} F_{\mathbf{h}} \exp(-2\pi i \mathbf{h} \cdot \mathbf{x})$$

by  $P[\rho(\mathbf{x})]$ , where  $P$  is a polynomial

$$P(\rho) = a_0 + a_1\rho + a_2\rho^2 + a_3\rho^3 + \dots$$

yields

$$P[\rho(\mathbf{x})] = a_0 + \sum_{\mathbf{h}} \left[ a_1 F_{\mathbf{h}} + a_2 \sum_{\mathbf{k}} F_{\mathbf{k}} F_{\mathbf{h}-\mathbf{k}} + a_3 \sum_{\mathbf{k}} \sum_{\mathbf{l}} F_{\mathbf{k}} F_{\mathbf{l}} F_{\mathbf{h}-\mathbf{k}-\mathbf{l}} + \dots \right] \exp(-2\pi i \mathbf{h} \cdot \mathbf{x})$$

and hence gives rise to the convolution-like families of terms encountered in direct methods. This equivalence, however, has been shown to be rather superficial (Bricogne, 1982) because the ‘uncertainty principle’ embodied in Heisenberg’s inequality (Section 1.3.2.4.4.3) imposes severe limitations on the effectiveness of any procedure which operates *pointwise* in *both* real and reciprocal space.

In applying such methods, sampling considerations must be given close attention. If the spectrum of  $\rho$  extends to resolution  $\Delta$  and if the pointwise non-linear filter involves a polynomial  $P$  of degree  $n$ , then  $P(\rho)$  should be sampled at intervals of at most  $\Delta/2n$  to accommodate the full bandwidth of its spectrum.

#### 1.3.4.4.3.3. Solvent flattening

Crystals of proteins and nucleic acids contain large amounts of mother liquor, often in excess of 50% of the unit-cell volume,