General quadratic functions in real and reciprocal space and their application to likelihood phasing

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A general multivariate quadratic function of the structure factors is constructed and transformed to obtain a quadratic function of the continuous electron density. Two special cases, where structure factors are independent and where electron-density values are independent, are examined. These results are related to the new likelihood-based framework of Terwilliger [Terwilliger (1999), *Acta Cryst*. D**55**, pp. 1863–1871] for employing structural information which was previously exploited by means of conventional density-modification calculations. The treatment here involves different assumptions and highlights new features of Terwilliger's calculation. The generalization quadratic construction allows the generation of cross terms relating all reflections and electron densities. Other applications of this approach are considered.

1. Introduction

The Fourier transform relationship between real and reciprocal space means that any function which can be represented in terms of parameters in one space can generally be represented in terms of the corresponding parameters in the other space. Some functions may be transformed between spaces more conveniently than others. This paper examines a set of generalized quadratic functions which are particularly simple to express in either space.

These functions have a particularly useful property: if the exponential is taken of a general multivariate quadratic function, the result is a general multivariate Gaussian. Multivariate Gaussians are often used to represent probability distributions, either because they arise from the central limit theorem or because they represent a convenient approximation. Thus, by this method probability distributions may be easily transformed between real and reciprocal space. This approach was inspired by the work of Terwilliger (1999), although the approach described here involves different approximations which lead to a more general set of results (although whether these approximations will be as useful in practice is yet to be seen).

Many optimization algorithms involve the assumption that the function to be optimized is at least locally quadratic and therefore, give extremely good convergence when the function to be optimized is genuinely quadratic (with a general second-order method converging in a single step). The maximum of a probability function which is based on a product of Gaussian probabilities arising from various sources of information in either space may therefore be efficiently located by optimization of the logarithm of the probability function, which is a quadratic function.

The methods described here differ from the likelihood approach of Bricogne (1984) in that the probability functions are approximated to obtain a computationally convenient form. Some of the limitations of this approximation will be discussed. The probability distributions will initially be considered in terms of electron densities and structure factors rather than atomic positional probabilities. The parameter space is therefore one step closer to the experimental data whilst being one step further away from the atomic model parameters which will ultimately be used to describe the data. It will be shown later that atomic positional probabilities lead to simplifications in the treatment of density correlation.

2. The general multivariate quadratic function in real and reciprocal space

2.1. Space group P1

Consider a general quadratic summation Q calculated in reciprocal space over all reflections. Let the minima of the quadratic function be at $F_m(\mathbf{h})$ and the curvatures in each direction be described by terms $W(-\mathbf{h}, -\mathbf{k})$, *i.e.*

$$Q(F) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} [F(\mathbf{h}) - F_m(\mathbf{h})][F(\mathbf{k}) - F_m(\mathbf{k})]W(-\mathbf{h}, -\mathbf{k}), \quad (1)$$

where the arguments of W are negative for future convenience. If $W(-\mathbf{h}, -\mathbf{k})$ is Hermitian in six dimensions [*i.e.* $W(-\mathbf{h}, -\mathbf{k}) = W(-\mathbf{h}, -\mathbf{k})^*$], then $Q(F)$ will be real. An offset structure factor is defined which is the difference between the actual value and the value at the minimum $D(h) = F(\mathbf{h}) - F_m(\mathbf{h})$; then,

$$Q(D) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} D(\mathbf{h})D(\mathbf{k})W(-\mathbf{h}, -\mathbf{k}). \quad (2)$$

The same summation may be written in terms of offset densities $d(\mathbf{x})$, where

$$d(\mathbf{x}) = (1/V) \sum_{\mathbf{h}} D(\mathbf{h}) \exp(-2\pi i \mathbf{h} \cdot \mathbf{x}) \quad (3)$$

and

$$D(\mathbf{h}) = \int_V d(\mathbf{x}) \exp(2\pi i \mathbf{h} \cdot \mathbf{x}) \, d\mathbf{x}, \quad (4)$$

giving

$$Q(d) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} W(-\mathbf{h}, -\mathbf{k}) \int_V d(\mathbf{x}) \exp(2\pi i \mathbf{h} \cdot \mathbf{x}) \, d\mathbf{x}$$
$$\times \int_V d(\mathbf{y}) \exp(2\pi i \mathbf{k} \cdot \mathbf{y}) \, d\mathbf{y} \quad (5)$$

$$= \int_V \int_V d(\mathbf{x}) \, d(\mathbf{y}) \sum_{\mathbf{h}} \sum_{\mathbf{k}} W(-\mathbf{h}, -\mathbf{k})$$
$$\times \exp[2\pi i(\mathbf{h} \cdot \mathbf{x} + \mathbf{k} \cdot \mathbf{y})] \, d\mathbf{x} \, d\mathbf{y} \quad (6)$$

$$= V^2 \int_V \int_V d(\mathbf{x}) \, d(\mathbf{y}) \, w(\mathbf{x}, \mathbf{y}) \, d\mathbf{x} \, d\mathbf{y}, \quad (7)$$

where $w(\mathbf{x}, \mathbf{y})$ is the six-dimensional Fourier transform of $W(\mathbf{h}, \mathbf{k})$,

$$w(\mathbf{x}, \mathbf{y}) = (1/V^2) \sum_{\mathbf{h}} \sum_{\mathbf{k}} W(\mathbf{h}, \mathbf{k}) \exp[-2\pi i(\mathbf{h} \cdot \mathbf{x} + \mathbf{k} \cdot \mathbf{y})] \quad (8)$$

and therefore

$$W(\mathbf{h}, \mathbf{k}) = \int \int w(\mathbf{x}, \mathbf{y}) \exp[2\pi i(\mathbf{h} \cdot \mathbf{x} + \mathbf{k} \cdot \mathbf{y})] \, d\mathbf{x} \, d\mathbf{y}. \quad (9)$$

2.2. General space groups

Space-group symmetry introduces relationships between terms distributed throughout real or reciprocal space. These relationships between different parameters in real or reciprocal space impose constraints on the values of w and W. These may be handled by allowing w or W to be defined generally and imposing the symmetry through modified Fourier transforms.

First, we define symmetry-generating Fourier transforms which will generate correct terms in one space from any arbitrary asymmetric unit or more of the other space as long as any duplicated terms are divided by their multiplicity,

$$D(\mathbf{h}) = \int_V d(\mathbf{x}) \sum_i \exp\{2\pi i[\mathbf{h} \cdot (\mathbf{R}_i \mathbf{x} + \mathbf{T}_i)]\} \, d\mathbf{x}, \quad (10)$$

$$d(\mathbf{x}) = (1/V) \sum_{\mathbf{h}} D(\mathbf{h}) \sum_i \exp\{-2\pi i[\mathbf{h} \cdot (\mathbf{R}_i \mathbf{x} + \mathbf{T}_i)]\}, \quad (11)$$

where $\mathbf{R}_i$ and $\mathbf{T}_i$ are the ith crystallographic symmetry-rotation matrix and translation vector, respectively.

Substituting (10) in (2) and comparing with (7), an expression for $w(\mathbf{x}, \mathbf{y})$ is obtained in terms of $W(\mathbf{h}, \mathbf{k})$ in the presence of space-group symmetry,

$$w(\mathbf{x}, \mathbf{y}) = (1/V^2) \sum_{\mathbf{h}} \sum_{\mathbf{k}} W(\mathbf{h}, \mathbf{k}) \quad (12)$$
$$\times \sum_i \sum_j \exp\{-2\pi i[\mathbf{h} \cdot (\mathbf{R}_i \mathbf{x} + \mathbf{T}_i) + \mathbf{k} \cdot (\mathbf{R}_j \mathbf{y} + \mathbf{T}_j)]\}.$$

Similarly, substituting (10) in (2) and comparing with (7), an expression for $W(\mathbf{h}, \mathbf{k})$ is obtained in terms of $w(\mathbf{x}, \mathbf{y})$,

$$W(\mathbf{h}, \mathbf{k}) = \int_V \int_V w(\mathbf{x}, \mathbf{y}) \sum_i \sum_j \exp\{2\pi i[\mathbf{h} \cdot (\mathbf{R}_i \mathbf{x} + \mathbf{T}_i)$$
$$+ \mathbf{k} \cdot (\mathbf{R}_j \mathbf{y} + \mathbf{T}_j)]\} \, d\mathbf{x} \, d\mathbf{y}. \quad (13)$$

3. Special cases of the general quadratic function

3.1. Real-space terms independent

Consider the case when Q is a known function of $d(\mathbf{x})$, represented by $w(\mathbf{x}, \mathbf{y}) = \delta(\mathbf{x}, \mathbf{y})w'(\mathbf{x})$. In other words, the contribution to Q from the value of d at any point in the map is independent of the value of d at any other point in the map.

Substituting for w' in (9) gives

$$W(\mathbf{h}, \mathbf{k}) = \int_V w'(x) \exp[2\pi i(\mathbf{h} + \mathbf{k}) \cdot \mathbf{x}] \, d\mathbf{x} \quad (14)$$

$$= W'(\mathbf{h} + \mathbf{k}), \quad (15)$$

where $W'(\mathbf{h})$ is the Fourier transform of $w'(\mathbf{x})$. Therefore, if

$$Q(d) = V^2 \int_V d(\mathbf{x})^2 w'(\mathbf{x}) \, d\mathbf{x} \quad (16)$$

then

$$Q(D) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} D(\mathbf{h})D(\mathbf{k})W'(-\mathbf{h} - \mathbf{k}). \quad (17)$$

Enough terms of D must be calculated to exactly represent d.

For a general space group, w' is substituted in (13) giving

$$Q(D) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} D(\mathbf{h}) D(\mathbf{k}) \sum_i \sum_j W'(-\mathbf{h}\mathbf{R}_i - \mathbf{k}\mathbf{R}_j)$$
$$\times \exp[2\pi i(-\mathbf{h} \cdot \mathbf{T}_i - \mathbf{k} \cdot \mathbf{T}_j)]. \qquad (18)$$

This expression has not been tested in practice, but may be easily verified by substituting $D(\mathbf{h})$ with a symmetry-equivalent reflection and verifying that the result is unchanged (see *Appendix B*).

3.2. Reciprocal-space terms independent

Similar reasoning applies if Q is a known function of $D(\mathbf{h})$ where the contributions to Q from different terms in reciprocal space are independent. However, there are two complications.

(i) Each term in reciprocal space consists of two components, one real and one imaginary. Even when individual reflections are independent, the real and imaginary parts of an individual reflection will usually not be independent.

(ii) The Hermitian symmetry of $D(\mathbf{h})$ must be considered, *i.e.* $D(\mathbf{h})$ and $D(-\mathbf{h})$ cannot be considered independent.

The second problem is addressed by including terms in $(\mathbf{h}, \mathbf{h})$, $(-\mathbf{h}, \mathbf{h})$, $(\mathbf{h}, -\mathbf{h})$ and $(-\mathbf{h}, -\mathbf{h})$ in the calculation of Q. The two independent complex terms $W(\mathbf{h}, \mathbf{h})$ and $W(\mathbf{h}, -\mathbf{h})$ then provide the freedom required to represent the dependence between real and imaginary parts of the reflection, solving the first problem, as shown below.

Retaining just the terms described above, (2) becomes

$$Q(D) = \sum_{\mathbf{h}\in\text{hemi}} D(\mathbf{h})D(\mathbf{h})W(-\mathbf{h}, -\mathbf{h}) + D(-\mathbf{h})D(-\mathbf{h})W(\mathbf{h}, \mathbf{h})$$
$$+ D(\mathbf{h})D(-\mathbf{h})W(-\mathbf{h}, \mathbf{h}) + D(-\mathbf{h})D(\mathbf{h})W(\mathbf{h}, -\mathbf{h}), \qquad (19)$$

where 'hemi' symbolizes a hemisphere of reflections.

Expanding in terms of real and imaginary components, labelled by use of the subscripts A and B, and using the Hermitian symmetry of D in three dimensions and W in six dimensions,

$$Q(D) = 2 \sum_{\mathbf{h}\in\text{hemi}} D_A(\mathbf{h})^2 [W_A(\mathbf{h}, \mathbf{h}) + W_A(\mathbf{h}, -\mathbf{h})]$$
$$+ D_B(\mathbf{h})^2 [-W_A(\mathbf{h}, \mathbf{h}) + W_A(\mathbf{h}, -\mathbf{h})]$$
$$+ 2D_A(\mathbf{h})D_B(\mathbf{h})[W_B(\mathbf{h}, \mathbf{h})], \qquad (20)$$

giving a general quadratic in $D_A(\mathbf{h})$, $D_B(\mathbf{h})$ for each reflection individually.

This is equivalent to the exponent of the electron-density log-likelihood expression given by Cowtan (2000), although the similarity is obscured by the fact that v_{ri} in that paper is antisymmetric and therefore corresponds to the imaginary component $W_B(\mathbf{h}, \mathbf{h})$ in the complex expression above.

The same expression may be more conveniently expressed in terms of magnitudes and phase angles,

$$Q(D) = 2 \sum_{\mathbf{h}\in\text{hemi}} |D(\mathbf{h})|^2 \{|W(\mathbf{h}, \mathbf{h})| \cos[2\varphi_D(\mathbf{h}) - \varphi_W(\mathbf{h}, \mathbf{h})]$$
$$+ |W(\mathbf{h}, -\mathbf{h})| \cos[\varphi_W(\mathbf{h}, -\mathbf{h})]\}, \qquad (21)$$

where φ_D and φ_W are the phases of D and W. Note that the first term is dependent on $\varphi_D(\mathbf{h})$, while the second is independent of the phase of D. Thus, in the second term the magnitude of $W(\mathbf{h}, -\mathbf{h})$ determines the mean curvature of Q and in the first term the magnitude of $W(\mathbf{h}, \mathbf{h})$ determines the anisotropy of the curvature. The directions of most and least curvature are determined by the phase $\varphi_W(\mathbf{h}, \mathbf{h})$. $\varphi_W(\mathbf{h}, -\mathbf{h})$ may arbitrarily be set to zero, since the imaginary part of this term has no effect.

Any of these expressions may be equivalently expressed in real space by taking (19) and substituting $W(\mathbf{h}, \mathbf{k}) = \delta_{\mathbf{h},\mathbf{k}} W'(\mathbf{h}) + \delta_{\mathbf{h},-\mathbf{k}} W''(\mathbf{h})$. The four terms may then be written in terms of $d(\mathbf{x})$, $w'(\mathbf{x})$ and $w''(\mathbf{x})$ using (7),

$$Q(d) = V^2 \int_V \int_V d(\mathbf{x})d(\mathbf{y})[w'(\mathbf{x} + \mathbf{y}) + w''(\mathbf{x} - \mathbf{y})]\,d\mathbf{x}\,d\mathbf{y}, \qquad (22)$$

where w' and w'' are the three-dimensional Fourier transforms of W' and W''. In practice, $Q(d)$ will usually be calculated by summation over a grid, which must be fine enough to avoid aliasing effects.

For a general space group, w is substituted in (12) giving

$$Q(d) = V^2 \int_V \int_V d(\mathbf{x})\, d(\mathbf{y}) \sum_i \sum_j [w'(\mathbf{R}_i\mathbf{x} + \mathbf{T}_i + \mathbf{R}_j\mathbf{y} + \mathbf{T}_j)$$
$$+ w''(\mathbf{R}_i\mathbf{x} + \mathbf{T}_i - \mathbf{R}_j\mathbf{y} - \mathbf{T}_j)]\,d\mathbf{x}\,d\mathbf{y}. \qquad (23)$$

This expression may be verified by the same approach used in *Appendix B*, although the absence of phase factors makes the expression self-evident.

4. Connection with statistical methods in crystallography

Suppose the probability of a set of structure factors can be represented by a multivariate Gaussian function centred on some set of expected values for the structure factors. Such a distribution might arise through the central limit theorem or through some approximation. The logarithm of this probability is then a general quadratic in terms of the structure factors. This quadratic function may be represented in turn by a general quadratic function in real space based on the electron density across the whole map.

Furthermore, the whole procedure may be reversed. Thus, a probability distribution in real or reciprocal space may be represented in the other space by the following series of steps:
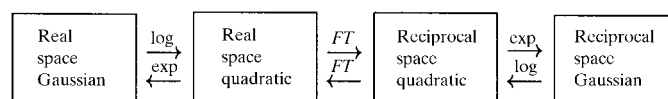
By this means, probability distributions may be constructed in either space as a general multivariate Gaussian and applied in the other space. The real-space joint probability distribution of offset densities

$$P[d(\mathbf{x}) \ \forall \ \mathbf{x}] \propto \exp[-Q(d)] \qquad (24)$$

may be written in reciprocal space as

$$P[D(\mathbf{h}) \ \forall \ \mathbf{h}] \propto \exp[-Q(D)] \qquad (25)$$

and *vice versa*. Information about the electron-density distribution in real space leads directly to a joint probability distribution of structure factors, which may be used to refine phases or predict missing reflections. Applying the opposite transformation, any structure-factor magnitude-and-phase probability distribution leads directly to a joint probability distribution of electron-density values, from which electron-density variances and covariances may be derived.

The joint probability distribution of structure factors is the basis of structure-factor statistics. As more information is incorporated into the joint probability distribution, the statistical model becomes a better description of the observed structure factors. Wilson statistics (Wilson, 1949) depend on the assumption that the atomic coordinates are independent random variables uniformly distributed across the unit cell. By construction of the appropriate joint probability of electron densities, two deviations from these assumptions may be examined.

(i) The atomic coordinates are not independent; rather, atomic positions are strongly related by bonding constraints. In particular, atoms do not approach closer than the appropriate minimum bond length. Peptide geometry affects the probabilities of certain interatomic separations beyond the range of a single atomic bond.

(ii) The distribution of atomic coordinates throughout the cell is non-uniform. The most common case of a non-uniform atomic distribution occurs when the unit cell contains known regions of solvent.

The calculation of structure-factor statistics using this approach is outlined in §5.

Alternatively, the same approach may be applied in the opposite direction; the joint probability distribution of electron-density values may be calculated using probability distributions constructed in reciprocal space; for example, phase probability distributions from some source of experimental phasing. This gives rise to variance estimates for the electron density at any point in the map, as well as covariance estimates between different points. The electron-density variance may be used to calculate a likelihood that a map feature arises from some density model, such as bulk solvent or a fragment model.

Both these techniques may be combined in techniques for phase improvement by use of known structural information, *i.e.* a statistical density-modification calculation as described by Terwilliger (1999). Electron-density variance estimates may be used in the estimation of solvent and non-crystallographic symmetry envelopes, which in turn provide probability distributions for electron densities in real space which may be transformed to reciprocal space to update experimental phase probability distributions. This approach is discussed further in §6.

5. Application to structure-factor statistics

The structure-factor statistics given by Wilson (1949) are based on a random-walk model for the contributions of individual atoms to the total scattering. In the case where the number of scatterers is large, the probability distribution for the value of an individual structure factor is Gaussian, in accordance with the central limit theorem. The width of the Gaussian is a function of resolution and atomic shape and in the case of a uniform random distribution the Gaussian is centred at the origin of the Argand diagram. Blessing *et al.* (1996) extended this work to deal with the case where the atomic shape varies according to a Gaussian spread of B factors. Srinivasan & Parthasarathy (1976) provide more general formulae which are valid even when a small number of scatterers dominate and the resulting probability distributions are non-Gaussian.

In this work, the value of a structure factor is already assumed to obey a Gaussian distribution and so the problem of a small number of scatterers cannot be addressed; however, the problem of a non-uniform distribution of atoms is ideally suited to treatment here.

Initially, the case where density values are independent will be considered (16, 17). If the Wilson assumption of a uniform random distribution of scatterers is made, then $D(\mathbf{h}) = F(\mathbf{h})$ for non-origin terms, w' is constant and W' is a delta function at the origin, so the joint probability distribution of offset structure factors is given by

$$P[D(\mathbf{h}) \ \forall \ \mathbf{h}] \propto \exp[-Q(D)]$$
$$Q(D) = \sum_{\mathbf{h}} D(\mathbf{h})D(-\mathbf{h})W'(000)$$
$$= W'(000) \sum_h |D(\mathbf{h})|^2. \qquad (26)$$

Thus, the marginal distribution for an individual (offset) structure factor is given by

$$P[D(\mathbf{h})] \propto \exp[-W'(000)|D(\mathbf{h})|^2]. \qquad (27)$$

Note that this model predicts that the distribution of complex structure factors will be Gaussian and that the width of the Gaussian will be constant for all reflections and independent of resolution.

This result is of course only true if the scattering is from point (delta function) atoms. However, it is interesting to note that the assumption of independent density values in real space is identically equivalent to the assumption of point scatterers often used in earlier direct-methods work. This implies that to obtain a realistic distribution of structure-factor magnitudes as a function of resolution, the correlation between neighboring values in an electron-density map must be modelled.

The simplest approach to modelling the correlation of neighboring map points is to apply a simple correction which gives the correct distribution in the case of a uniform distribution of atomic positions and then apply the same correction to the non-uniform case. This may be achieved by rescaling each reflection to produce the desired flat distribution with resolution, in a manner analogous to the K-curve scaling used

in the *MULTAN* direct-methods package (Main *et al.*, 1980). In this case, (17) would be rewritten as

$$Q(D) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} K(\mathbf{h})D(\mathbf{h})K(\mathbf{k})D(\mathbf{k})W'(-\mathbf{h} - \mathbf{k}), \qquad (28)$$

where $K(\mathbf{h})$ is the factor which normalizes the offset structure factor $D(\mathbf{h})$, *i.e.* $K(\mathbf{h}) = 1/\langle|D(\mathbf{h})|^2\rangle_s^{1/2}$, and the expectation value is calculated by an average over a resolution shell. This is equivalent to (2) with

$$W(\mathbf{h}, \mathbf{k}) = K(-\mathbf{h})K(-\mathbf{k})W'(-\mathbf{h} - \mathbf{k}), \qquad (29)$$

i.e. the six-dimensional array of cross terms is constructed from two three-dimensional arrays, one describing local correlation in the map and the other describing the variance as a function of map coordinate.

The real-space representation of the same function is

$$Q(d) = V^3 \int_V \int_V d(\mathbf{x})k(\mathbf{u} - \mathbf{x})\,\mathrm{d}\mathbf{x} \int_V d(\mathbf{y})k(\mathbf{u} - \mathbf{y})\,\mathrm{d}\mathbf{y}\, w'(\mathbf{u})\,\mathrm{d}\mathbf{u}, \qquad (30)$$

which is equivalent to (7) with

$$w(\mathbf{x}, \mathbf{y}) = \int_V k(\mathbf{u} - \mathbf{x})k(\mathbf{u} - \mathbf{y})w'(\mathbf{u})\,\mathrm{d}\mathbf{u}. \qquad (31)$$

In the case where the density distribution is uniform [*i.e.* $w'(\mathbf{x})$ is constant], (28) gives the normal Wilson distribution and after a change of variable (31) becomes

$$w(\mathbf{x}, \mathbf{y}) = w' \int_V k(\mathbf{u}')k[\mathbf{u}' - (\mathbf{x} - \mathbf{y})]\,\mathrm{d}\mathbf{u}' = k'(\mathbf{x} - \mathbf{y}), \qquad (32)$$

where k' is the autocorrelation function of k and the Fourier transform of K^2.

Note that since K is the reciprocal of the expected offset structure-factor magnitude, K is a function which *increases* with resolution and as a result k and k' feature high-resolution ripples. In practice, these functions will be aliased and will depend on both resolution and grid sampling. k is in fact the function which when convoluted with an average atomic shape function gives rise to a delta function; this is not possible in the continuous case. The calculation of k on a discrete grid in real space is probably not useful; however, it is helpful to understand that k contains information about the pattern of correlation amongst neighboring densities.

In practical calculations, independent probability distributions should be constructed for the values of the sharpened map where possible and the offset structure factors rescaled in reciprocal space according to an appropriate function of resolution K. This rescaling of the structure factors is equivalent to the use of unitary structure factors (Us) and atomic positional probabilities by Bricogne (1984).

Bond-length restrictions and common interatomic distances will lead to a deviation from Wilson statistics and corresponding variations in the pattern of correlations amongst neighboring densities. These may therefore be introduced by calculating a modified curve K using structure factors from a model cell filled with representative protein-like density.

Once an appropriate resolution-dependent scaling has been determined, the effect of a non-uniform distribution of atoms

may be included by simply adjusting $w'(\mathbf{x})$ appropriately, *e.g.* to exclude atoms from the solvent region.

To determine probability distributions for the observed structure factors, the scattering from the whole cell must be considered. This may include contributions from several different types of density: for example, the unit cell may be known to consider some regions of low thermal motion, some regions of high thermal motion and some regions of solvent. Each of these will have its own K curve. A joint probability distribution for the total scattering from the cell can be constructed either by convolution of probability distributions of partial structure factors or by multiplication of probability distributions of independent components of the scattering. Both multiplication and convolution of Gaussian distributions may be performed analytically. This is equivalent to the 'multi-channel' approach proposed by Bricogne (1988).

6. Application to phase improvement

A solvent envelope or the combination of a non-crystallographic symmetry operator and envelope provide structural information in real space which may be framed in terms of probabilities for electron-density values. In the case of a solvent envelope, the probability of an electron-density value may be considered to be a Gaussian about the expected solvent mean, whose width varies from the expected solvent standard deviation for map points which are definitely solvent to infinity for map points which are definitely protein. (A protein mean and variance constraint could also be introduced, in which case the expected mean density would vary across the map.)

Non-crystallographic symmetry is only slightly more complex. In order to obtain independent indications of NCS-related density, the expected mean density for a NCS-related map point will be the mean of the *other* NCS-related copies only. (Thus, in the case of twofold NCS only one independent estimate of the density is available.) The expected variance will depend on the variances of the other copies of the density (plus an additional term for non-isomorphism) and will decrease as the number of copies increases. The non-isomorphism term may be estimated from the agreement of the NCS-related densities in comparison to the expected variance of the map. To obtain accurate statistics in reciprocal space, $w(\mathbf{x}, \mathbf{y})$ should include covariance terms for the NCS-related map points.

The variance of the solvent density is used by Terwilliger (1999) and Roversi *et al.* (2000) to estimate the probability of a density point belonging to the solvent. In the case of Terwilliger, this is estimated from the current map; in the case of Roversi and coworkers, the global formula of Blow & Crick (1959) is used. Calculation of the probability distribution of electron densities gives rise to a variance estimate which varies as a function of position in the map.

A similar approach may be used to determine a non-crystallographic symmetry-averaging mask by testing whether regions of the map related by the non-crystallographic symmetry operator agree at a statistically significant level.

This approach leads naturally to a probability-based version of Abrahams' weighted averaging approach (Abrahams, 1996).

Once the probability distribution has been assembled in real space, it may be converted to reciprocal space with a resolution-weighting function and combined with other sources of reciprocal-space phase information, such as phasing from experimental sources.

This approach is in essence the 'reciprocal-space solvent-flattening' approach demonstrated by Terwilliger (1999), with a different representation of the probability distributions. However, additional covariance terms have been derived, the need to rescale the offset structure factors has been demonstrated and map-variance information has been incorporated.

6.1. Comparison with reciprocal-space solvent flattening

The general multivariate Gaussian function of the offset structure factors arising from independent Gaussian functions of the density values in real space {*i.e.* $\exp[-Q(D)]$ where $Q(D)$ is given by (18)} is closely related to the likelihood expression used by Terwilliger (1999). $Q(D)$ is therefore related to the log-likelihood expression in that paper. If all cross terms between reflections are neglected except for the cross terms between Friedel opposites, which may not be neglected, then the six-dimensional summation in (18) becomes a three-dimensional summation and a summation over two reflections

$$
\begin{aligned}
Q(D) &= \sum_{\mathbf{h}} \sum_{\mathbf{k}=\pm\mathbf{h}} D(\mathbf{h})D(\mathbf{k}) \sum_i \sum_j W'(-\mathbf{h}\mathbf{R}_i - \mathbf{k}\mathbf{R}_j) \\
&\quad \times \exp[2\pi i(-\mathbf{h}\cdot\mathbf{T}_i - \mathbf{k}\cdot\mathbf{T}_j)] \\
&= \sum_{\mathbf{h}} D(\mathbf{h})D(\mathbf{h}) \sum_i \sum_j W'(-\mathbf{h}\mathbf{R}_i - \mathbf{h}\mathbf{R}_j) \\
&\quad \times \exp(-2\pi i\mathbf{h}\cdot\mathbf{T}_i)\exp(-2\pi i\mathbf{h}\cdot\mathbf{T}_j) \\
&\quad + \sum_{\mathbf{h}} D(\mathbf{h})D(-\mathbf{h}) \sum_i \sum_j W'(-\mathbf{h}\mathbf{R}_i + \mathbf{h}\mathbf{R}_j) \\
&\quad \times \exp(-2\pi i\mathbf{h}\cdot\mathbf{T}_i)\exp(2\pi i\mathbf{h}\cdot\mathbf{T}_j).
\end{aligned} \tag{33}
$$

Writing in terms of real and imaginary components and collecting the terms in $\pm\mathbf{h}$,

$$
\begin{aligned}
Q(D) &= 2 \sum_{\mathbf{h}\in\text{hemi}} D_A(\mathbf{h})^2 \\
&\quad \times \sum_i \sum_j \text{Re}[W'(-\mathbf{h}\mathbf{R}_i - \mathbf{h}\mathbf{R}_j)\exp(-i\Delta_{i,\mathbf{h}})\exp(-i\Delta_{j,\mathbf{h}}) \\
&\quad + W'(-\mathbf{h}\mathbf{R}_i + \mathbf{h}\mathbf{R}_j)\exp(-i\Delta_{i,\mathbf{h}})\exp(i\Delta_{j,\mathbf{h}})] \\
&\quad + D_B(\mathbf{h})^2 \sum_i \sum_j \text{Re}[-W'(-\mathbf{h}\mathbf{R}_i - \mathbf{h}\mathbf{R}_j)\exp(-i\Delta_{i,\mathbf{h}}) \\
&\quad \times \exp(-i\Delta_{j,\mathbf{h}}) + W'(-\mathbf{h}\mathbf{R}_i + \mathbf{h}\mathbf{R}_j)\exp(-i\Delta_{i,\mathbf{h}}) \\
&\quad \times \exp(i\Delta_{j,\mathbf{h}})] \\
&\quad + 2D_A(\mathbf{h})D_B(\mathbf{h}) \sum_i \sum_j \text{Im}[W'(-\mathbf{h}\mathbf{R}_i - \mathbf{h}\mathbf{R}_j) \\
&\quad \times \exp(-i\Delta_{i,\mathbf{h}})\exp(-i\Delta_{j,\mathbf{h}})],
\end{aligned} \tag{34}
$$

where the symmetry phase shifts $2\pi\mathbf{h}\cdot\mathbf{T}_i$ are written as $\Delta_{i,\mathbf{h}}$.

The first two terms in this equation are equivalent to Terwilliger (1999) equations (16) and (19) for $\varphi_{\mathbf{h}} = 0$, with the

obvious sign change in the arguments of W'. The third term allows the directions of maximum and minimum curvature in the Argand diagram to lie along an arbitrary direction, rather than along the directions defined by $\varphi_{\mathbf{h}}$ and $\varphi_{\mathbf{h}} + \pi/2$. The corresponding expression in Cowtan (2000) is incorrect, omitting the phase-shift term.

One notable difference between the approach described here and that of Terwilliger is that the density probability distribution is approximated here before changing from real to reciprocal space. As a result, no Taylor series expansion is required: the resulting distribution is correct across the whole of the Argand diagram. The disadvantage of this approach is that some information about the probability distribution of density values is discarded. For example, a bimodal probability distribution for the value of the electron density at some point in the map will be approximated by a single broad distribution. The practical implications of these changes have yet to be investigated. However, for the simple application of solvent flattening, the differences between a fixed-width Gaussian plus constant and variable-width Gaussian model are likely to be small.

Using this model, it is possible to ask what information can be gained from a solvent-flatness constraint, by considering the variation in log-likelihood across the whole of the Argand diagram for each reflection. Suppose real-space probability distributions are constructed to represent flat density in the solvent region and completely unknown density in the protein. The probability distribution for the electron density at any position in the map is therefore a Gaussian centred on the solvent density whose width increases with the probability that the density belongs to the protein.

When expressed in reciprocal space, the likelihood maximum will be centered at the origin of the Argand diagram for each non-origin reflection. [Since the maximum-likelihood electron density is flat and at the solvent level, the maximum-likelihood structure factors will be zero, *i.e.* $F_m(\mathbf{h}) = 0$ and $D(\mathbf{h}) = F(\mathbf{h})$ for $\mathbf{h} \neq 0$.] Therefore, in the case of unobserved reflections for which both magnitude and phase are unknown, this information alone cannot predict non-zero values for unobserved reflections. In the case of reflections whose magnitude is known, the Gaussian probability centred on the origin can give rise to at best a symmetrical bimodal phase distribution (*i.e.* in terms of Hendrickson–Lattman coefficients, $A = B = 0$). Combination of this probability distribution with an experimental phase probability distribution can provide some phase improvement.

Terwilliger, however, describes non-zero predicted magnitudes for unmeasured reflections. These predictions arise through *implicit* use of the inter-reflection cross-terms, even those terms are not included in the curvature expression. The second-order approximation to the log-likelihood function in reciprocal space provides an accurate local estimate of the log-likelihood gradient, which is in turn dependent on all the inter-reflection cross terms. The omission of cross terms in the curvature expression only limits the rate of convergence on the log-likelihood maxima. The result is a computationally economic algorithm; however, the approximation will affect

the estimated shape of the log-likelihood around the maximum.

This behaviour is illustrated in Fig. 1. The axes in this figure represent two separate reflections. Although the maximum of the log-likelihood function is at the origin, as soon as one reflection is constrained to a non-zero value the constrained maximum for the other becomes non-zero through the action of the inter-reflection cross terms.

6.1.1. Example: reciprocal-space solvent flattening with known origin term. The effect of cross terms in reciprocal space solvent flattening can be illustrated in $P1$ by examining the behavior when a smooth 'solvent-probability' mask and an origin term [*i.e.* $F(000)$] are known.

In the Gaussian model, the probability distributions for densities across the whole map will be centred on ρ_{solv} and have a variance which is low in the solvent region and high in the protein region. The quadratic coefficient $w(\mathbf{x}, \mathbf{x})$ will be the reciprocal of the variance at that point. The quadratic terms will be independent in real space.

Therefore, the log-likelihood is described by (16) with $w'(\mathbf{x})$ large and positive in the solvent region and small and positive in the protein region. The centre of the distribution $\rho_m(\mathbf{x}) = \rho_{solv}$.

Transforming to reciprocal space gives a distribution centred on

$$F_m(\mathbf{h}) = \begin{cases} V\rho_{solv} & \mathbf{h} = 0 \\ 0 & \mathbf{h} \neq 0 \end{cases}. \qquad (35)$$

The quadratic coefficients $W'(\mathbf{h})$ are the Fourier transform of $w'(\mathbf{x})$ and therefore correspond closely to the G function of Rossmann & Blow (1962) with non-origin terms inverted.
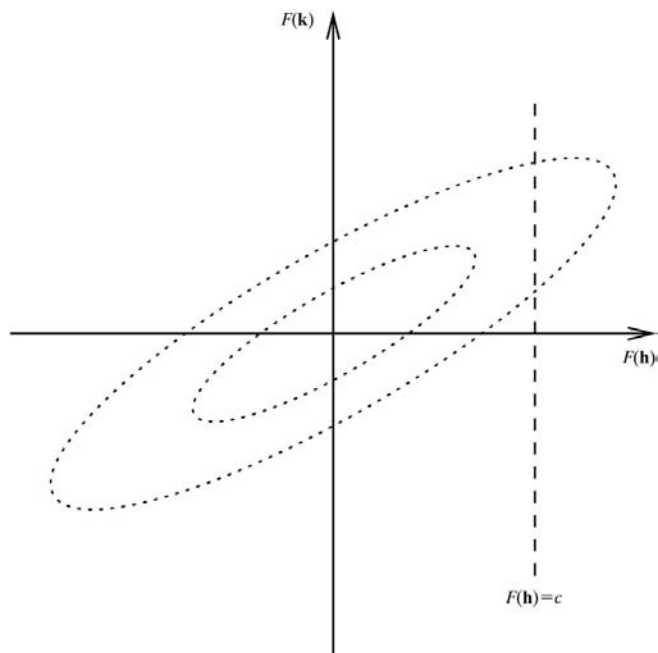

Figure 1
Illustration of how inter-reflection cross-terms in the curvature lead to a non-zero estimate of a reflection when another reflection is fixed.

Substituting $D(\mathbf{h}) = F(\mathbf{h}) \forall \mathbf{h} \neq 0$ and $D(000) = F(000) - F_m(000)$, where $F_m(000) = V\rho_{solv}$ in (16), gives

$$\begin{aligned} Q(D) &= [F(000) - F_m(000)]^2 W'(000) \\ &\quad + 2[F(000) - F_m(000)] \sum_{\mathbf{h} \neq 0} F(\mathbf{h}) W'(-\mathbf{h}) \\ &\quad + \sum_{\mathbf{h} \neq 0} \sum_{\mathbf{k} \neq 0} F(\mathbf{h}) F(\mathbf{k}) W'(-\mathbf{h} - \mathbf{k}). \qquad (36) \end{aligned}$$

The value of $[F(000) - F_m(000)]$, while smaller than $F(000)$, should still be larger than any non-origin reflection for real problems. Since W' is related to the G function it will be a low-resolution function dominated by the origin term. The most significant terms in determining the minimum of the quadratic (and therefore the likelihood maximum) are $\sum_{\mathbf{h} \neq 0} F(\mathbf{h}) W'(-\mathbf{h})$, which must be as negative as possible and $\sum_{\mathbf{h} \neq 0} F(\mathbf{h}) F(-\mathbf{h}) W'(000)$, which cannot be negative and so must be close to zero.

The expression $\sum_{\mathbf{h} \neq 0} F(\mathbf{h}) W'(-\mathbf{h})$ is the Fourier transform of $V \int_V \rho(\mathbf{x}) w'(\mathbf{x}) \, d\mathbf{x}$. For this expression to be small or negative, $\rho(\mathbf{x})$ must be small or negative when $w'(\mathbf{x})$ is large and positive, *i.e.* in the solvent region. The value of $\rho(\mathbf{x})$ is far less important when $w'(\mathbf{x})$ is small, *i.e.* in the protein region.

The expression $\sum_{\mathbf{h} \neq 0} F(\mathbf{h}) F(-\mathbf{h}) W'(000)$ is least positive when $\sum_{\mathbf{h} \neq 0} |F(\mathbf{h})|^2$ is small, *i.e.* the map is as smooth and featureless as possible.

Therefore, it can be seen that fixing just the origin term gives a constrained likelihood maximum corresponding to a smooth map with lower density in the solvent region and larger and more variable density in the protein region.

A similar analysis can be made in the case when a single reflection is fixed and gives rise to a familiar G function-like relationship [see, for example, Cowtan (1999), equation (16)].

7. Alternative approaches to likelihood-based phase improvement

7.1. General phasing approach with Gaussian contributions

Suppose probability distributions are available for both structure-factor magnitudes and phases and for electron-density values. If each of these distributions can be represented as a general multivariate Gaussian in the space concerned (with cross terms if necessary), then the information can be combined by transforming all the multivariate Gaussians to a single space. If the probability distributions are independent, they may be combined by multiplication; in other words, by simply summing the corresponding quadratic coefficients.

Information which does not give rise to a multivariate Gaussian probability in one space may also be incorporated by construction of an appropriate Gaussian approximation to the probability distribution.

The maximum of the resulting multivariate Gaussian may be located by finding the minimum of the corresponding polyquadratic function. In the general case, this involves inverting a six-dimensional matrix of the structure-factor curvatures [$W(\mathbf{h}, \mathbf{k})$] or electron-density curvatures [$w(\mathbf{x}, \mathbf{y})$];

however, most practical cases will consist of combinations of probabilities which are independent in either real or reciprocal space and the resulting system is amenable to efficient solution (see *Appendix A*). Inversion of the full curvature matrix will be required to obtain complete variance and covariance information for all parameters in either real or reciprocal space, although it may be possible to calculate the diagonal elements of the inverse matrix and therefore the parameters variances more efficiently.

The choice between real and reciprocal space for the calculation is probably only a matter of computational convenience: reciprocal space offers advantages in that the structure factors and phases are used at most stages of the structure-solution process. However, calculation in real space allows immediate calculation of maps for interpretation and may have advantages when combined with automatic updating of solvent and averaging masks or density fitting.

7.2. General phasing approach with non-Gaussian contributions

If non-Gaussian probability information is available in one space, then the obvious approach is to perform the calculation in that space. The Gaussian probability information from the other space must be transformed and may be combined with the non-Gaussian information. Direct determination of the global maximum will not be possible in this case; however, standard gradient methods may be used. Local maxima may present problems in this case.

The most common case in which this approach may be adopted is the use of conventional MIR or MAD data. This information is usually represented by the product of a Hendrickson–Lattman distribution for the phase multiplied by a Gaussian distribution for the magnitude based on the experimental standard deviation for the structure-factor magnitude; however, a general two-dimension probability distribution as employed by *SHARP* (La Fortelle & Bricogne, 1997) could be used. This distribution is multiplied by the multivariate Gaussian obtained from density constraints in real space. Since the Hendrickson–Lattman distribution may be strongly bimodal, local minima may provide a significant difficulty. Phase permutation or simulated annealing could be used; however, a simpler approach may be to obtain an initial estimate for the global maximum using the Gaussian approximation to the MIR/MAD probability distribution, as described previously, and use this as a starting point for locating the minima of the true combined distribution. This is somewhat analogous to the use of quadratic underestimation to find the global minima of a function with many local minima (Dill *et al.*, 1997).

Non-Gaussian probabilities may arise in real space if density estimates arise from several sources; for example, the total probability at a coordinate may be a weighted sum of Gaussians based on whether the coordinate is in solvent or protein and whether it is in an NCS-related domain. In this case, the Gaussian probabilities may be transformed to reciprocal space and then summed; however, the logarithm of

the resulting probability will no longer be a quadratic function. Terwilliger's electron-density likelihood expression could be expressed exactly by this approach, since the Gaussian-plus-constant probability function [Terwilliger, 1999, equation (3)] is a special case of a sum of Gaussians.

If non-Gaussian probabilities are present in both spaces then an approximation will have to be made in one space. In this case, the approach of calculating a Taylor series approximation to the gradient and curvature around the current estimates, as used by Terwilliger, may be more useful.

8. Other applications

The approaches described here to the representation of probability distributions between real and reciprocal space have a number of other applications.

Any application which makes use of Sim-like weights (Sim, 1959) can be adapted to use reflection-by-reflection phase probability distributions calculated directly from the real-space fragment with corresponding variances attached. These variances may be estimated on the basis of positional and other uncertainties associated with the fragment density. A full σ_A-like usage (Read, 1986) would involve determination of the atomic positional uncertainty and using it to explicitly calculate density variances and covariances on the basis of the possible positions of every atom. This is probably impractical except for isolated atoms.

The calculation of electron-density variances across the unit cell also has applications. This information could be used to calculate a probability that a volume of density is associated with a particular model, leading to a likelihood-based version of the fragment-searching algorithm of Cowtan (1999). This information may also be useful in model-building programs to distinguish between features in the map which are well determined and therefore should be fitted by the model and those which are poorly determined and therefore are more likely to contain artifacts.

9. Limitations

The approaches described here are limited by the restriction that all probability distributions must be Gaussian.

In reciprocal space, this means that the common case of a Hendrickson–Lattman phase probability distribution with an accurately measured structure-factor magnitude can only be represented by a two-dimensional Gaussian about the centroid of the distribution. The bimodality and radial nature of the distribution are lost.

In real space, the use of Gaussian probabilities for electron densities precludes any effective use of positivity until the density is known very accurately. Bricogne (1984) showed that the combination of positivity (through entropy maximization) and the known origin term allows the derivation of a joint probability distribution which embodies the phase relationships used in traditional direct methods. These relationships are inaccessible using the methods described here, although local curvatures of a non-Gaussian probability function could

still be calculated using the same approach as Terwilliger (1999).

10. Conclusions

A mathematically simple and computationally efficient framework has been described for combining probability or likelihood distributions originating in both real and reciprocal space. This framework is closely related to methods which have already been demonstrated by Terwilliger (1999) as a powerful alternative to traditional density-modification procedures. The new treatment provides an alternative perspective on that work.

The same approach allows the calculation of variances for electron densities derived from the magnitude-and-phase probability distribution in reciprocal space.

A full six-dimensional representation allows an arbitrary multivariate Gaussian to be transformed between real and reciprocal space without loss of information. This general form is probably impractical except at very low resolution at the moment; however, some calculations will be amenable to sparse-matrix methods.

The approaches described here cannot replace the methods of Terwilliger (1999) or Bricogne (1984), because the Gaussian representation of the probability functions precludes the use of certain types of information such as positivity; however, the computational convenience of the Gaussian model may render it valuable for some applications. Implementation of the ideas described here has not yet been attempted.

APPENDIX *A*
Locating the minimum of combined quadratic sum functions

The quadratic sum functions used in this paper have been formulated in terms of a distribution about the minimum by the change of variable from F to D or ρ to d. For multiple distributions to be combined, they must all be written in terms of the same set of variables; therefore, we must transform back to F or ρ.

Consider a function Q which is represented in reciprocal space,

$$Q(D) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} D(\mathbf{h})D(\mathbf{k})W(-\mathbf{h}, -\mathbf{k}) \qquad (37)$$

or

$$Q(F) = \sum_{\mathbf{h}} \sum_{\mathbf{k}} [F(\mathbf{h}) - F_m(\mathbf{h})][F(\mathbf{k}) - F_m(\mathbf{k})]W(-\mathbf{h}, -\mathbf{k}). \quad (38)$$

This equation can be written in matrix form

$$Q = (\mathbf{F} - \mathbf{F}_m)^T \mathbf{W} (\mathbf{F} - \mathbf{F}_m), \qquad (39)$$

where $\mathbf{F}$ is the vector of structure factors, $\mathbf{F}_i = F(\mathbf{h}_i)$ and $\mathbf{W}$ is the matrix of curvatures $\mathbf{W}_{i,j} = W(-\mathbf{h}_i, -\mathbf{k}_j)$. The gradient with respect to the vector of structure factors is then

$$\frac{\delta Q}{\delta F} = 2(\mathbf{F} - \mathbf{F}_m)^T \mathbf{W}. \qquad (40)$$

For quadratic functions originating in reciprocal space, $F_m(\mathbf{h})$ is available since it was used in the construction of the function. For quadratic functions originating in real space, $F_m(\mathbf{h})$ may be obtained by taking the Fourier transform of the parameters of the minimum in real space $\rho_m(\mathbf{h})$.

Suppose several quadratic functions with different centres and curvatures (possibly arising from different spaces) are summed; the gradient of the resultant function at any point in the parameter space will be the sum of the gradients of the individual functions. The curvature matrix (which is independent of the parameters) is also the sum of the curvatures of the individual functions. To obtain the centre of the composite function, the gradient vector at any point must be pre-multiplied by the inverse of the curvature matrix to obtain the shift required to reach the minimum (multiplied by -2).

Direct inversion of the matrix of curvatures (whose rank is the number of reflections) will be impractical in most cases. However, the problem is amenable to almost any first- or second-order optimization method as a consequence of the following.

(i) In practice, the individual matrices of curvatures will always be non-negative definite. After combination of quadratic functions formed in real and reciprocal space, the combined matrix will almost always be positive definite.

(ii) The product of the matrix of curvatures and an arbitrary vector may be calculated directly for functions which are independent in reciprocal space and by convolutions for functions which are independent in real space. For the combined function, the result may be summed over all contributors.

(iii) The gradient of the combined function may be calculated from the product of the matrix of curvatures with the distance to the centre of each quadratic function. Again, the combined gradient is simply a sum over the contributors.

An obvious candidate for the solution of such systems is the conjugate-gradient technique as employed by Zhang & Main (1990) in the solution of Sayre's equation for large structures. An advanced Newton-like method such as *BFGS* (Fletcher, 1987), which forms an estimate of the inverse matrix from which parameter variances may be calculated, may also be useful if the inverse matrix can be represented in a compact manner (*e.g.* as a sparse matrix).

APPENDIX *B*
Verification of general symmetry relationships

The space-group-general expressions for the special case quadratic distributions (in particular equation 18) are not self-evident. For example, Cowtan (2000) omits the phase shift factors in this equation. (18) will therefore be demonstrated to be invariant under symmetry transformation of the reciprocal-space terms $D(\mathbf{h})$.

The set of symmetry operators is closed, so two symmetry operators applied in turn always give a third symmetry operator; thus, there exists i for all m, n such that

$$\mathbf{R}_n(\mathbf{R}_m\mathbf{x} + \mathbf{T}_m) + \mathbf{T}_n = \mathbf{R}_i\mathbf{x} + \mathbf{T}_i. \tag{41}$$

Collecting terms in powers of $\mathbf{x}$,

$$\mathbf{R}_n\mathbf{R}_m = \mathbf{R}_i \tag{42}$$

$$\mathbf{R}_n\mathbf{T}_m + \mathbf{T}_n = \mathbf{T}_i. \tag{43}$$

If (18) is invariant under symmetry transformation of the terms, then substituting $D(\mathbf{hR}_n)\exp(2\pi i\mathbf{h}\cdot\mathbf{T}_n)$ for $D(\mathbf{h})$ should not affect the value of the expression. (18) becomes

$$
\begin{aligned}
Q(D) &= \sum_\mathbf{h}\sum_\mathbf{k} D(\mathbf{hR}_n)\exp(2\pi i\mathbf{h}\cdot\mathbf{T}_n)D(\mathbf{k}) \\
&\quad \times \sum_i\sum_j W'(-\mathbf{hR}_i - \mathbf{kR}_j)\exp[2\pi i(-\mathbf{hT}_i - \mathbf{kT}_j)] \\
&= \sum_\mathbf{h}\sum_\mathbf{k} D(\mathbf{hR}_n)D(\mathbf{k})\sum_i\sum_j W'(-\mathbf{hR}_i - \mathbf{kR}_j) \\
&\quad \times \exp\{2\pi i[-\mathbf{h}(\mathbf{T}_i - \mathbf{T}_n) - \mathbf{kT}_j]\}. \tag{44}
\end{aligned}
$$

From (42) and (43), substitute $\mathbf{T}_i - \mathbf{T}_n = \mathbf{R}_n\mathbf{T}_m$ and $\mathbf{R}_i = \mathbf{R}_n\mathbf{R}_m$,

$$
\begin{aligned}
Q(D) &= \sum_\mathbf{h}\sum_\mathbf{k} D(\mathbf{hR}_n)D(\mathbf{k})\sum_i\sum_j W'(-\mathbf{hR}_n\mathbf{R}_m - \mathbf{kR}_j) \\
&\quad \times \exp[2\pi i(-\mathbf{hR}_n\mathbf{T}_m - \mathbf{kT}_j)]. \tag{45}
\end{aligned}
$$

Let $\mathbf{h}' = \mathbf{hR}_n$. The summation over i becomes a summation over m because i is a function of m,

$$
\begin{aligned}
Q(D) &= \sum_{\mathbf{h}'}\sum_\mathbf{k} D(\mathbf{h}')D(\mathbf{k})\sum_m\sum_j W'(-\mathbf{h}'\mathbf{R}_m - \mathbf{kR}_j) \\
&\quad \times \exp[2\pi i(-\mathbf{h}'\mathbf{T}_m - \mathbf{kT}_j)], \tag{46}
\end{aligned}
$$

which is equivalent to the original expression.

Therefore, it is clear that this expression may be assembled from an arbitrary unique set of terms in reciprocal space without altering the result. (Friedel opposites should still be included to obtain a real result or, alternatively, the real part of the expression can be calculated and doubled.)

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