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An Analytical Packing Function Employing Fourier Transforms

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Abstract

An analytical expression for molecular overlap as a function of position is presented; it can be calculated by means of Fourier transforms. Overlap functions between pairs of symmetry elements can be combined to give a crystallographic packing function. Multiplication of this packing function with the translation function increases the significance of the latter, as shown for a trigonal test example.

Introduction

Patterson-search (Hoppe, 1957*a*, *b*; Nordman & Nakatsu, 1963; Huber, 1965) or reciprocal-space (Rossmann & Blow, 1962; Crowther & Blow, 1967; Lattman & Love, 1970; see Rossmann, 1972) molecular-replacement techniques are used increasingly for macromolecular structure solution when a partial or similar structure is known. The method is carried out in two stages: determination of the model orientation in the new crystal (rotation function), followed by translation of the rotated model with respect to the new cell axes (translation function). It is not infrequent that a reasonable solution to the rotation function can be obtained with no corresponding translation vector. Use has been made of packing functions in order to discriminate peaks in the translation function on the grounds of reasonable crystallographic packing. A short summary of available packing algorithms has been given by Fitzgerald (1990); they operate as follows.

(i) Cohen & Suh (unpublished). The shape of the protein is approximated by a number of spheres, from which intersphere distances are calculated.

(ii) Bott & Sarma (1976). A criterion is defined for bad contacts; when the number of bad contacts exceeds a user-defined number, the translation vector $\mathbf{t}$ is abandoned.

(iii) Hendrickson & Ward (1976). The molecular shape is defined by a shape function $M(\mathbf{r})$, where

$$M(\mathbf{r}) = \begin{cases} 1 & \text{if } \mathbf{r} \text{ is intramolecular} \\ 0 & \text{otherwise.} \end{cases}$$

The packing function is then calculated using the relation

$$P(\mathbf{t}) = \frac{\int M(\mathbf{r}) \cup M([R]\mathbf{r}+\mathbf{t})\, \mathrm{d}^3\mathbf{r}}{\int M(\mathbf{r})\, \mathrm{d}^3\mathbf{r}}$$

where $[R]$ denotes a crystallographic rotation matrix and $\mathbf{t}$ the translation vector.

(iv) Harada, Lifchitz, Berthou & Jolles (1981). In investigating the use of a correlation coefficient to determine the translation function,

$$\mathscr{C}(\mathbf{t}) = \frac{\sum_{h}^{S} F_o^2(\mathbf{h}) \| F_c(\mathbf{h}, \mathbf{t}) \|^2}{\left[\sum_{h}^{S} F_o^4(\mathbf{h}) \sum_{h}^{S} \| F_c(\mathbf{h}, \mathbf{t}) \|^4 \right]^{1/2}},$$

approximations were made to allow utilization of FFT methods, resulting in a function

$$\mathscr{C}(\mathbf{t}) \simeq TO(\mathbf{t})/O(\mathbf{t})$$

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where $TO(\mathbf{t})$ is a product translation function and

$$O(\mathbf{t}) = \frac{\sum_{h}^{S} \|F_c(\mathbf{h},\mathbf{t})\|^2}{N \sum_{h}^{S} \|F_m(\mathbf{h})\|^2}$$

is sensitive to packing. The summations are over the reciprocal-space sphere S bounded by the resolution limit of the observed intensities $F_o^2(\mathbf{h})$ with $F_c(\mathbf{h},\mathbf{t})$ the calculated cell transform for a translation vector $\mathbf{t}$, $F_m(\mathbf{h})$ the molecular transform and N the number of molecules in the unit cell.

In this paper, we present an analytical form for the overlap of two molecules. The overlap is seen to be a convolution and can thus be calculated easily and efficiently using Fourier transforms. A packing function is constructed from this overlap, which can be used in turn to modify translation-function results.

The overlap function

Given two molecular density functions $\rho_1(\mathbf{r})$ and $\rho_2(\mathbf{r})$, the overlap or correlation of the two molecules when separated by a vector $\mathbf{t}$ may be written

$$\psi_{12}(\mathbf{t}) = \int_{\text{cell}} \rho_1(\mathbf{r})\rho_2(\mathbf{r}+\mathbf{t})\, \mathrm{d}^3\mathbf{r}. \qquad (1)$$

This function has a maximum value when ρ_1 and ρ_2 overlap maximally, and is zero when they do not touch. It is recognized as a convolution of $\rho_1(\mathbf{r})$ and $\rho_2(-\mathbf{r})$; making use of the convolution theorem

$$\mathcal{T}[\psi_{12}(\mathbf{t})] = F_1^*(\mathbf{h})F_2(\mathbf{h}) \qquad (2)$$

where $F_i^{(*)}$ denotes (the complex conjugate of) the Fourier transform $\mathcal{T}$ of $\rho_i(\mathbf{r})$. The overlap function for the two molecules as a function of their relative position can therefore be calculated readily through Fourier inversion of the above product. It is worthy of note that the function $\psi_{12}(\mathbf{t})$ can be used for the translation function (see below).

In particular, if two molecules are related by crystallographic symmetry, then

$$\rho_1(\mathbf{r}) = \rho\{[C_j](\mathbf{r}+\mathbf{t})+\mathbf{u}_j\}$$

and

$$\rho_2(\mathbf{r}) = \rho\{[C_k](\mathbf{r}+\mathbf{t})+\mathbf{u}_k\}$$

where $[C_i]$ and $\mathbf{u}_i$ are respectively the crystallographic rotation matrix and the translation vector for the ith symmetry element and $\mathbf{t}$ is the translation vector relating the model to the crystallographic origin. Substitution into (1) then gives the crystallographic overlap function for two symmetry elements.

This function is demonstrated for a two-dimensional example in Fig. 1. The 'molecule' is an equilateral triangle of unit density, placed in a rectangular *pm* unit cell. Even for such a simple example, the overlap function is not trivial. It exhibits three distinct regions: one linear (zero) and two parabolic, of opposite curvature. The overlap function does not obey the target space-group symmetry; its symmetry is in this case $p1$. As with the corresponding Patterson function, the overlap function shows a halving of the unit cell, due to alternative choices of origin.

Expanding (2) using these crystallographic density terms gives the transform of the overlap function as

$$\mathcal{T}\{\psi_{jk}(\mathbf{t})\} = F^*(\mathbf{h}[C_j]^{-1})F(\mathbf{h}[C_k]^{-1}) \times \exp[2\pi i\mathbf{h}\,.\,(\mathbf{u}_j-\mathbf{u}_k)] \times \exp\{2\pi i\mathbf{h}([C_j]-[C_k])\,.\,\mathbf{t}\}. \qquad (3)$$

This equation therefore allows simple calculation of the crystallographic overlap for any molecular form.

By way of example, data from the complex of papain and human stefin B (Stubbs *et al.*, 1990) are used. This structure was solved using Patterson-search techniques, with papain (212 residues) as search model (total asymmetric unit 310 residues). The space group is $P3_121$ with $a = b = 67{\cdot}02$, $c = 169{\cdot}34$ Å, $\alpha = \beta = 90$, $\gamma = 120°$. The overlap function for a twofold axis is shown for this example in Fig. 2.

As already noted for the theoretical example, the function does not exhibit the crystal symmetry; it is

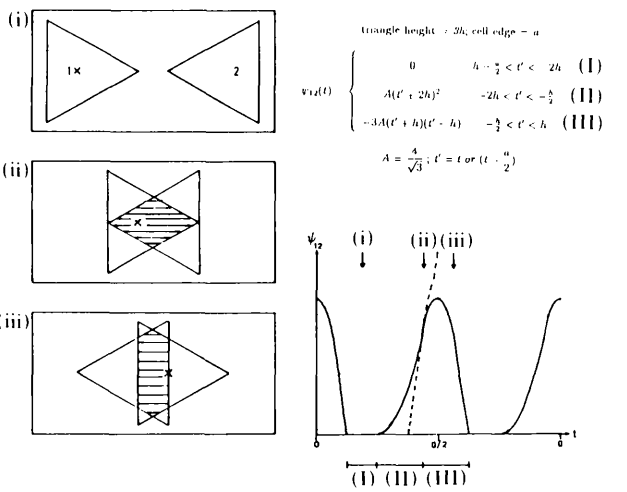

Fig. 1. The overlap function for a simple planar *pm* unit cell. The 'molecule' is an equilateral triangle of unit density, with one edge parallel to the crystallographic mirror line. Three positions for the centre of gravity (c.g., ×) of 'molecule 1' are shown [(i)-(iii)]; the shaded regions indicate the degree of overlap. Although their c.g.s are related by the mirror symmetry, positions (ii) and (iii) are dissimilar. The equation for the overlap function is given above right; three areas exist [(I), (II), (III)], exemplified by sections (i), (ii), (iii) respectively; position (ii) is the transition between these regions. The function for translations perpendicular to the mirror line is sketched lower right. The function itself does not possess mirror symmetry, but shows a repeat for t and $t \pm a/2$, corresponding to equivalent choices of origin. The mirror image of the function would be obtained if 'orientation 2' were placed at 'position 1'.

asymmetric because only one orientation of the asymmetric molecule is considered. The function is negative for some translation vectors. This is a result of termination errors, due to finite resolution limits (8–3·5 Å data). Regions of overlap with negative value may be conferred a degree of significance, however. The function changes sign when the two molecules touch; one would expect molecules that are 'optimally packed' to lie between these points. A negative value of the overlap function could therefore be viewed as a measure of 'better' packing. Such results must be viewed with caution, however, in particular if the search molecule does not represent the whole of the asymmetric unit.

Defining the packing function

The overlap function can be inverted to yield the packing function

$$\varphi_{jk}(\mathbf{t}) = 1 - \psi_{jk}(\mathbf{t})/\kappa \qquad (4)$$

where the term κ is a scale factor. For a true analytical form of the packing function, $\kappa = \psi_{11}(0) = \int \rho^2(\mathbf{r})\, d^3\mathbf{r}$, the overlap of the unrotated molecule on itself at zero translation.

In practice, this measure of κ is so large that the packing function has little dynamic range (values between ~90 and 100% in our test example). A more discriminatory procedure is to equate κ with the maximum value of $\psi_{jk}(\mathbf{t})$, allowing a full dynamic range between 0 and 100%. With this choice of κ, the function φ_{jk} has zero value for molecules with maximum overlap, unity for those that touch and

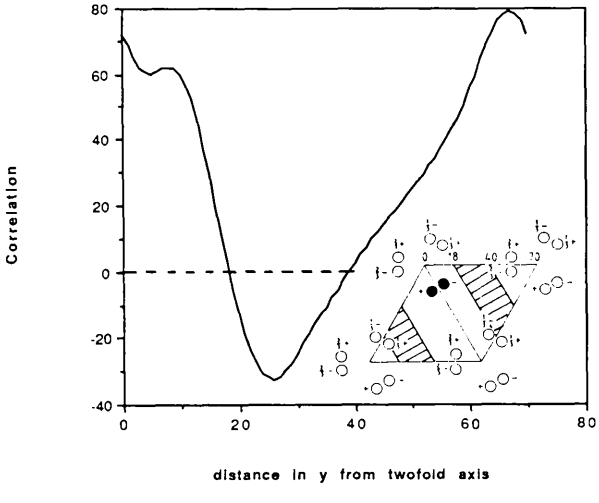

Fig. 2. The correlation function for the twofold axis on the plane $z = 0$. Coordinates are in grid units from the twofold axis in the y direction (unit cell 70 grid points in y). A B factor of 10^2 has been applied. Inset: regions of $\psi_{jk} \leq 0$ (shaded) on plane $z = 0$ for the two filled positions. The asymmetry of the shaded regions about the diagonal diad reflects the molecular asymmetry.

greater than unity for 'optimally packed' molecules. Values of $\varphi_{jk} > 1$ can be truncated to 1, resulting in a modified packing function $\varphi'_{jk}(\mathbf{t})$, *i.e.* giving equal probability to all allowed regions. An additional modification is to set to zero any values of the packing function $\varphi_{jk} < \xi$, where ξ is a selected fraction.

For a total of n symmetry elements, the combined correlation is given by the product

$$\Phi(\mathbf{t}) = \prod_{j>k}^{n(n-1)/2} \varphi_{jk}(\mathbf{t}) \qquad (5)$$

using the same value of κ for each jk. Such a packing function is illustrated in Fig. 3. Its convoluted form is related to the underlying molecular shape. The space available for the molecule is seen to be fairly large, although it should be remembered that only 2/3 of the asymmetric unit was used in the calculation. The maximum of the calculated packing function is therefore not that of optimal packing for the entire asymmetric unit, demonstrating the possible dangers of using values of $\varphi > 1$.

The product function above indicates the correct way of combining packing functions from different symmetry elements: for example, if $\varphi_{jk}(\mathbf{t}_1) = 0$ at some position $\mathbf{t}_1$ for the symmetry pair jk, then the combined packing function $\Phi(\mathbf{t}_1)$ should also take the value zero. Similarly, if $\varphi_{jk}(\mathbf{t}_2) = \xi$ and $\varphi_{lm}(\mathbf{t}_2) = 1$ at some position $\mathbf{t}_2$ for symmetry pairs jk and lm respectively, their combined value should be ξ. These identities are obtained with the product function. Of course, a sum function is easier to evaluate, in that it requires only one transform; it does not possess the same powers of discrimination however.

For a direct comparison of the packing function derived here with the function $O(\mathbf{t})$ of Harada, Lifchitz, Berthou & Jolles (1981), one can rewrite the equation as

$$O(\mathbf{t}) = 1 + \frac{\sum_{k>j} \psi_{jk}(\mathbf{t})}{\sum_{j} \psi_{jj}(0)}.$$

This is therefore a sum of the independent overlaps, with extreme values of 1 (no overlap) and 2 (full overlap). As indicated by our example above, use of the scale factor $\kappa = \psi_{11}(0)$ would result in a maximum value of $O(\mathbf{t})$ far less than 2. An increase in sensitivity in this function could be gained by allowing optimization of κ.

Modification of the translation function

The packing function $\Phi(\mathbf{t})$ can be used to modify a previously obtained translation function $T(\mathbf{t})$ through simple point-by-point multiplication:

$$T^{\Phi}(\mathbf{t}) = T(\mathbf{t})\Phi(\mathbf{t}). \qquad (6)$$

We have used a version of the translation function of Crowther & Blow (1967) which calculates a direct vector in the target unit cell instead of cross vectors (see Appendix). Table 1 gives an analysis of modified translation functions using the packing function and its truncated forms. It is quite clear that the modified functions enhance peak discrimination. The signal-to-noise ratio (defined as the ratio of signal peak height

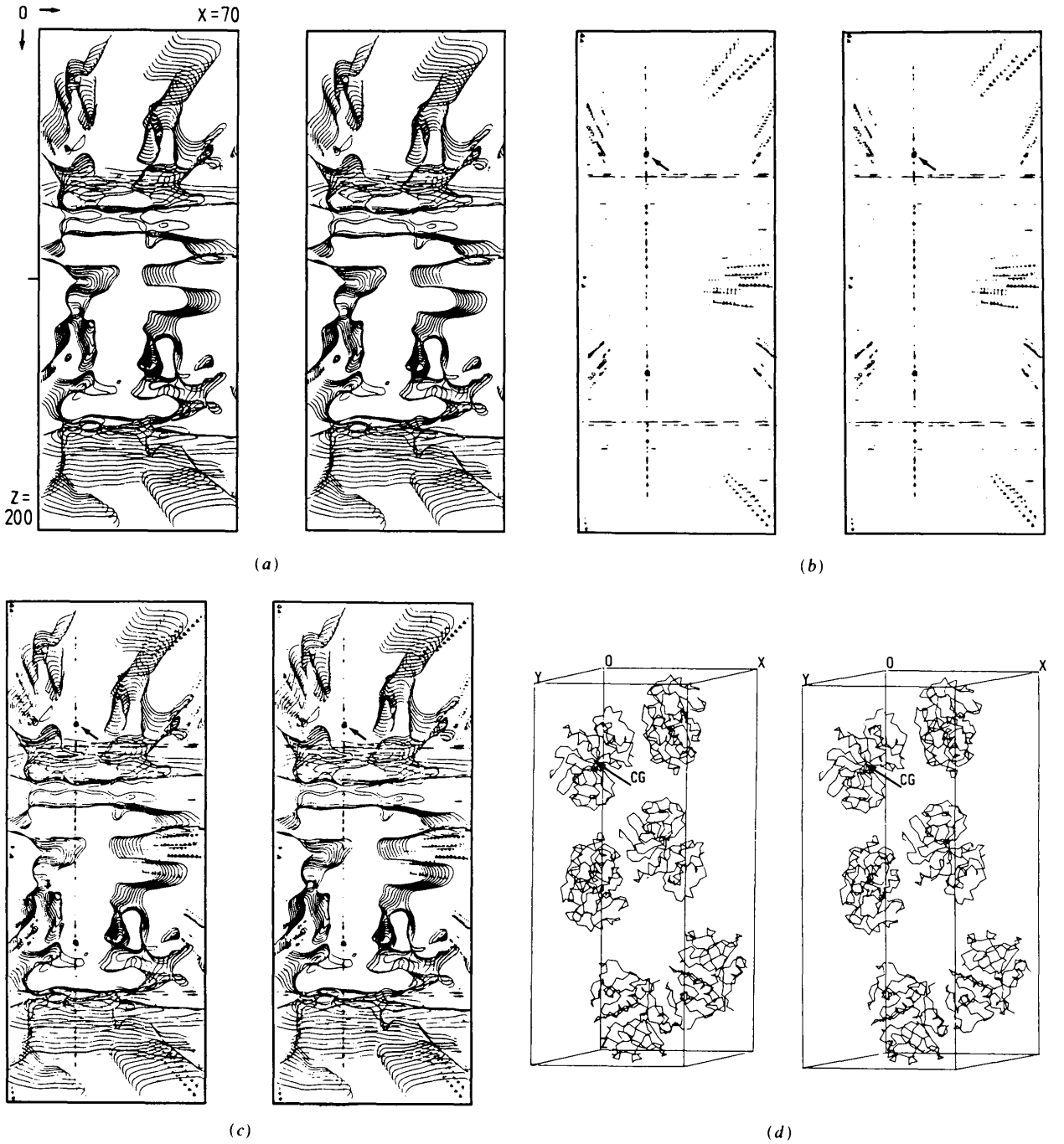

Fig. 3. (*a*) The packing function for papain in papain-stefin B complex crystals. A stereoplot is given for grid layers 55-65 in the direction of *y*. The single contour delineates regions of $\Phi(\mathbf{t}) > 1$. The function shows a halving in the *z* direction, corresponding to equivalent choices of axes. (*b*) The three-dimensional translation function for the same region as (*a*); contour levels start at 9σ above mean and are incremented in steps of 2σ. The highest peak in the translation function is at (22·2, 58·1, 41·6) (arrowed; see Table 1). (*c*) Superposition of (*a*) and (*b*); the highest peak is well within the allowed packing region. (*d*) C_α plot of papain, showing the unit cell built using this vector (arrow shows position of centre of gravity); it is the correct solution of the structure.

Table 1. *Comparison of the translation function $T(\mathbf{t})$, the modified translation function $T^{\Phi}(\mathbf{t})$ and the truncated translation functions $T^{\Phi}(\mathbf{t})$, $T^{\Phi>\xi}(\mathbf{t})$, $T^{\Phi'>\xi}(\mathbf{t})$, as described in the text*

The trigonal grid has units of 70, 70 and 200 in x, y and z respectively; only one half of the unit cell in the z direction is given (equivalent origins for the translation function). Peak heights are given as units of σ above mean. $T(\mathbf{t})$ is calculated by means of a full-symmetry translation function written by one of us (MTS); such a function has previously been described by Rius & Miravitlles (1986). Peak 1 is the correct position of the molecule in the unit cell.

			$T(\mathbf{t})$ $\sigma = 5{\cdot}73$, mean = 0·00			$T^{\Phi}(\mathbf{t})$ $\sigma = 5{\cdot}81$, mean = 0·05		$T^{\Phi'}(\mathbf{t})$ $\sigma = 4{\cdot}97$, mean = 0·02		$T^{\Phi>0.9}(\mathbf{t})$ $\sigma = 5{\cdot}34$, mean = 0·09		$T^{\Phi'>0.9}(\mathbf{t})$ $\sigma = 3{\cdot}99$, mean = 0·06	
Peak rank	Height σ	x	t (grid) y	z	Height σ	Original rank	Height σ	Original rank	Height σ	Original rank	Height σ	Original rank
1	19·1	22·2	58·1	41·6	23·9	1	21·6	1	26·0	1	25·4	1
2	11·0	22·1	58·1	73·0	11·7	6	11·5	4	12·7	6	14·3	4
3	10·1	22·2	58·1	81·0	11·4	7	11·4	3	12·4	7	14·2	3
4	10·0	22.1	58·2	93·1	11·1	9	11·4	5	12·0	9	14·1	5
5	9·93	22·2	58·1	96·2	11·1	14	11·2	7	12·0	14	13·9	7
6	9·82	22·2	58·1	44·9	11·0	3	11·0	6	11·9	3	13·7	6
7	9·77	22·1	58·1	33·8	10·9	17	11·0	8	11·9	17	13·6	8
8	9·68	22·1	58·1	50·0	10·9	4	10·9	13	11·8	4	13·5	13
9	9·58	45·6	34·9	57·1	10·8	26	10·9	14	11·8	26	13·5	14
10	9·53	22·1	58·1	76·1	10·8	5	10·8	12	11·7	5	13·5	12

to that of the highest noise peak) for the various functions is as follows:

$$2{\cdot}05[T^{\Phi>0.9}(\mathbf{t})] > 2{\cdot}04[T^{\Phi}(\mathbf{t})] > 1{\cdot}88[T^{\Phi'}(\mathbf{t})] > 1{\cdot}78[T^{\Phi'>0.9}(\mathbf{t})] > 1{\cdot}74[T(\mathbf{t})].$$

The 'unprimed' functions, however, give greater weights to 'better packed' noise peaks. Although the original solution is in this case unambiguous, it is obvious that the effective decrease in noise would be valuable in cases that are not so clear cut.

The use of a product is not the only method for combining packing and translation-function terms. As cited in the *Introduction*, Harada, Lifchitz, Berthou & Jolles (1981) employ a quotient. This leaves translation-function-solution peaks that exhibit no overlap unmodified and halves those showing maximum overlap. It has already been pointed out that this maximum overlap may not be achieved in practice so that badly packed solutions of the translation function might not be sufficiently downweighted. The present formulation leaves unmodified (or even accentuates) solutions representing good packing, with the important advantage of eliminating totally those that would give rise to bad contacts.

It was previously noted that the terms necessary to calculate $\psi_{jk}(\mathbf{t})$ are the same as those for the translation function: in fact, the translation function of Crowther & Blow (1967) can be written

$$T_{jk}(\mathbf{t}) = \int P_{\rm obs}(\mathbf{u})\psi_{jk}(\mathbf{u}+\mathbf{t})\,{\rm d}^3\mathbf{u} \qquad (7)$$

$$\mathcal{T}[T_{jk}(\mathbf{t})] = I_{\rm obs}(\mathbf{h})F_j^*(\mathbf{h})F_k(\mathbf{h}). \qquad (8)$$

One could therefore modify the translation function by subtraction of the overlap:

$$T_{jk}^{\Delta}(\mathbf{t}) = \int [P_{\rm obs}(\mathbf{u}) - k]\psi_{jk}(\mathbf{u}+\mathbf{t})\,{\rm d}^3\mathbf{u} \qquad (9)$$

$$\mathcal{T}[T_{jk}^{\Delta}(\mathbf{t})] = [I_{\rm obs}(\mathbf{h}) - k]F_j^*(\mathbf{h})F_k(\mathbf{h}) \qquad (10)$$

where k is a scaling constant. Such a modified translation function has the advantage of more straightforward calculation: it requires only one transform, with no resultant multiplication. Trial calculations using various scaling constants k failed to produce significant differentiation between signal and background peaks. This may well be due to a problem of scaling between observed and model data. The observed data were scaled to the calculated data as follows

$$I_{\rm obs}^{\rm scaled}(\mathbf{h}) = [I_{\rm obs}(\mathbf{h}) - \langle I_{\rm obs}(\mathbf{h})\rangle]\frac{\sum_{\mathbf{h}} F_c^2(\mathbf{h})}{\sum_{\mathbf{h}} I_{\rm obs}(\mathbf{h})} - F_c^2(\mathbf{h})$$

where subtraction of the average intensity corresponds to origin removal in Patterson space, whilst the final term represents removal of the self-vector set, as in the translation function $T_1(\mathbf{t})$ of Crowther & Blow (1967). It has been pointed out (Harada, Lifchitz, Berthou & Jolles, 1981; Fujinaga & Read, 1987) that translation-function results may be enhanced significantly by using normalized $E(\mathbf{h})$s as opposed to $F(\mathbf{h})$s; we have not tested this, however.

Use of the packing function can help remove peaks that lead to particularly bad contacts, thereby increasing the significance of correct translation-function peaks. It may also find use in the case of docking or molecular-dynamics calculations.

APPENDIX

The programs which were used for the given example are described here. Equation (3) can be written

$$\mathcal{T}\{\psi_{jk}(\mathbf{t})\} = A_{jk}\exp\{2\pi i\mathbf{h}([C_j]-[C_k])\,.\,\mathbf{t}\} \quad (A1)$$

where

$$A_{jk} = F^*(\mathbf{h}[C_j]^{-1})F(\mathbf{h}[C_k]^{-1}) \times \exp[2\pi i\mathbf{h}.(\mathbf{u}_j - \mathbf{u}_k)]. \quad (A2)$$

Equation (A1) can be transformed either with respect to the reciprocal-space vectors **h**, resulting in a transform with vectors $([C_j]-[C_k])\mathbf{t}$, or with respect to the reciprocal-space cross vectors $\mathbf{h}([C_j]-[C_k])$, giving rise to a transform with vectors **t**. The main advantage of the latter lies in the ease of combination of different symmetry elements. A Fourier synthesis with modified coefficients of this sort has been described previously by Rius & Miravitlles (1986).

The translation and packing functions are calculated as follows.

(i) Structure factors are calculated for the correctly oriented molecule, placed in a triclinic unit cell of identical lattice constants as the target cell; this avoids interpolation in the ensuing steps.

(ii) The structure factors are sorted according to resolution such that symmetry-related reflections are grouped together.

(iii) For a given vector **h** in the asymmetric unit, the structure factors are found for all symmetry-related vectors $\mathbf{h}[C_j]^{-1}$. The complex coefficients (A2) are evaluated for each symmetry element [using (3) and (8) for the packing and translation functions respectively] and assigned to cross vectors $\mathbf{h}([C_j]-[C_k])$.

(iv) The resulting difference vector coefficients are added together (from all symmetry elements for the translation function, pairwise for the overlap function) and Fourier transformed. The packing-function coefficients must be weighted by an artificial *B* factor to dampen spurious ripples, resulting in a smooth function (see Fig. 2); this is necessary for the combination with the translation function as outlined in (6).

(v) The packing function is evaluated according to (4) and (5), using an appropriate value for κ.

(vi) Modified translation functions are calculated according to (6).

The current translation-function package requires ~4 min CPU on a VAX 8550 from atomic coordinates to translation function for the example given here (29 823 structure factors between 8 and 3·5 Å, 6 symmetry operations); the packing function currently takes <20 min CPU for the same problem (15 cross vectors), although the use of external programs, with consequent multiple file conversions, represents a considerable fraction of retrievable computation time.

Programs for the packing and translation functions described here are available on request.

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On the Application of Direct Methods to Complex Structures. XXXI. Properties and Limitations of Sayre's Equation

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Abstract

Since Sayre's equation is the basis of some direct-methods procedures, the applicability of Sayre's equation has been tested in various circumstances. When a structure contains a heavy atom, it is found that Sayre's equation does not hold well, which is expected since the condition of equal resolved atoms does not apply. However, what is not expected is that with a heavy atom present the equation actually holds better at low resolution than at high resolution. The cause of this apparent anomaly is discussed and it is shown that there exists a modified Sayre's equation which holds far better in the presence of one kind of

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