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On the Fast Translation Functions for Molecular Replacement

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Abstract

This paper describes the theory and results obtained with the correlation-search technique to solve the translation problem in the molecular-replacement method. The correlation function is expressed in terms of intensities of structure factors and is calculated by fast Fourier transforms.

Introduction

The number of proteins whose three-dimensional structures have been determined by X-ray crystallography and NMR spectroscopy has rapidly increased in recent times. The molecular-replacement method (Rossmann, 1972; Machin, 1985), which is used to determine crystal structures when there exists a homologous molecular structure to the one under study, has become quite important in protein crystallography.

In this paper, attention will be focused on the second step of molecular replacement, *i.e.* the translation function (TF). The term translation function denotes any technique used to determine the position of a properly oriented molecule. The most widely used TFs were presented in the review article of Fitzgerald (1991). A distinction is made between TFs evaluated by Fourier transforms and 'correlation searches' evaluated at each sampling point in real space (the latter category includes *R*-factor searches). Although the higher quality of 'correlation searches' is recognized, their computation with available software is in general very time consuming.

In the present work, the fast TF is reviewed and the advantages of using correlation coefficients in the translation problem are discussed. Finally, the theory and some results obtained with a correlation-function program, calculated by means of fast Fourier techniques, which has been incorporated in the *AMoRe* package (Navaza, 1994) for molecular replacement are described.

Notation

$(\mathbf{M}_s\,|\,\mathbf{t}_s)$, $s = 1, \ldots, g$	Transformation matrix $\mathbf{M}_s$ and translation vector $\mathbf{t}_s$ corresponding to the sth symmetry operation.
$\mathbf{H} = (H,K,L)$	Crystal reciprocal-space (row) vector.
$m_\mathbf{H}$	Multiplicity of reflection $\mathbf{H}$: number of different reciprocal vectors generated by applying to $\mathbf{H}$ all the symmetry operations, including Friedel's.
$F_\mathbf{H}^{\rm obs}$	Fourier coefficient of the crystal electron density.
$I_\mathbf{H}^{\rm obs} = |F_\mathbf{H}^{\rm obs}|^2$	Observed intensity.
$f(\mathbf{H})$	Fourier coefficient of the oriented model placed in the crystal cell with its center of mass at the origin, assuming $P1$ symmetry.

Different types of fast translation function

This section presents a short review of some translation functions that are computed by fast-Fourier-transform techniques. In all of them, the observed Fourier coefficients are compared with the calculated ones,

$$F_\mathbf{H}(\mathbf{x}) = \sum_s f(\mathbf{HM}_s)\exp(2\pi i\mathbf{Ht}_s)\exp(2\pi i\mathbf{HM}_s\mathbf{x}) \quad (1)$$

for each translation $\mathbf{x}$ of the center of mass of the oriented model.

Two main types of fast TF may be distinguished.

(1) *Overlap functions*

These are the most widely used translation functions in macromolecular crystallography, based on that proposed by Crowther & Blow (1967), which measures the overlap between observed and calculated Patterson functions:

$$\begin{aligned} T(\mathbf{x}) &= \sum_\mathbf{H} m_\mathbf{H} I_\mathbf{H}^{\rm obs}|F_\mathbf{H}(\mathbf{x})|^2 \\ &= \sum_{s,s'}\sum_\mathbf{H} m_\mathbf{H} I_\mathbf{H}^{\rm obs} f(\mathbf{HM}_s)^* f(\mathbf{HM}_{s'}) \\ &\quad \times \exp\{-2\pi i\mathbf{H}[(\mathbf{M}_s - \mathbf{M}_{s'})\mathbf{x} + (\mathbf{t}_s - \mathbf{t}_{s'})]\}, \quad (2) \end{aligned}$$

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where indexes s and s' run over all symmetry operations. The multiplicity $m_{\mathbf{H}}$ of reflection **H** is introduced in order to restrict the sum to the asymmetric unit. $T(\mathbf{x})$ is evaluated by a simple Fourier summation, with **x** taking values in the Cheshire cell (Hirshfeld, 1968). For a complete review of several modifications of this basic function, see Tickle (1985, 1992).

Another overlap function, although based on a quite different physical approach, is the full-symmetry phased translation function (Cygler & Desrochers, 1989). Its reciprocal-space version (Bentley & Houdusse, 1992) is computationally similar to T(**x**):

$$\begin{aligned}\mathrm{PT}(\mathbf{x}) = \sum_{s,s'}\sum_{\mathbf{H}} m_{\mathbf{H}}[|F_{\mathbf{H}}^{\mathrm{obs}}/f(\mathbf{HM}_s)| \\ + |F_{\mathbf{H}}^{\mathrm{obs}}/f(\mathbf{HM}_{s'})| - 2\sigma] \\ \times f(\mathbf{HM}_s)^* f(\mathbf{HM}_{s'}) \exp\{-2\pi i\mathbf{H}[(\mathbf{M}_s - \mathbf{M}_{s'})\mathbf{x} \\ + (\mathbf{t}_s - \mathbf{t}_{s'})]\},\end{aligned} \qquad (3)$$

with σ a scaling factor. We note that $T(\mathbf{x})$ is quadratic in the intensities, whereas PT(**x**) is quadratic in the amplitudes.

(2) *Method of Harada, Lifchitz, Berthou & Jolles* (1981)

These authors have provided a number of improvements to $T(\mathbf{x})$, based on an approximation to the correlation coefficient in terms of intensities. They ended up with an expression that may be evaluated by Fourier transforms. They have introduced the function

$$\mathrm{HC}(\mathbf{x}) = T(\mathbf{x})/O(\mathbf{x}), \qquad (4)$$

where $T(\mathbf{x})$ is given by (2) and

$$O(\mathbf{x}) = \sum_{\mathbf{H}} m_{\mathbf{H}} |F_{\mathbf{H}}(\mathbf{x})|^2. \qquad (5)$$

The only difference between HC(**x**) and $T(\mathbf{x})$ is the denominator $O(\mathbf{x})$. As discussed by the above authors, this function can be regarded as a measure of the intermolecular overlap within the crystal.

The cumulated experience with the *AMoRe* package has demonstrated the advantages of selecting solutions according to the values of the correlation coefficient in terms of amplitudes. The strategy developed in *AMoRe* consists in using the values of the translation functions, based on the overlap functions discussed above, only as a means of selecting a reasonable number of potential peaks, but the output is the correlation coefficient, in terms of amplitudes, corresponding to the top values of the TF. If the correct solution is very low in the list of overlap TF peaks, it may not appear in the output.

Correlation searches in the translation problem

Perhaps the simplest measure of agreement between the sets of observed $\{|F_{\mathbf{H}}^{\mathrm{obs}}|\}$ and calculated $\{|F_{\mathbf{H}}(\mathbf{x})|\}$ Fourier coefficients, depending on **x**, is the quadratic misfit

$$\begin{aligned}Q &= \left\{\sum_{\mathbf{H}} m_{\mathbf{H}}[|F_{\mathbf{H}}^{\mathrm{obs}}| - \lambda|F_{\mathbf{H}}(\mathbf{x})| - \mu]^2\right\}\left[\sum_{\mathbf{H}} m_{\mathbf{H}}\right]^{-1} \\ &= \langle[|F_{\mathbf{H}}^{\mathrm{obs}}| - \lambda|F_{\mathbf{H}}(\mathbf{x})| - \mu]^2\rangle.\end{aligned} \qquad (6)$$

λ and μ are introduced to correct scale and shift mismatch. Q is a quadratic function of λ and μ, therefore it has a unique minimum.

Since data are given in arbitrary units, the role of λ is obvious but that of μ is not so evident within the crystallographic context (one would expect $\mu = 0$ for normal data). The optimum of μ is

$$\mu = \langle|F_{\mathbf{H}}^{\mathrm{obs}}| - \lambda|F_{\mathbf{H}}(\mathbf{x})|\rangle, \qquad (7)$$

which leads to

$$\begin{aligned}Q &= \langle\{|F_{\mathbf{H}}^{\mathrm{obs}}| - \langle|F_{\mathbf{H}}^{\mathrm{obs}}|\rangle - \lambda[|F_{\mathbf{H}}(\mathbf{x})| - \langle|F_{\mathbf{H}}(\mathbf{x})|\rangle]\}^2\rangle \\ &= \langle[\Delta|F_{\mathbf{H}}^{\mathrm{obs}}| - \lambda\Delta|F_{\mathbf{H}}(\mathbf{x})|]^2\rangle.\end{aligned} \qquad (8)$$

The optimum of (8) with respect to λ now gives

$$Q = \langle(\Delta|F_{\mathbf{H}}^{\mathrm{obs}}|)^2\rangle(1 - C^2), \qquad (9)$$

where C is the correlation coefficient:

$$C = \langle\Delta|F_{\mathbf{H}}^{\mathrm{obs}}|\Delta|F_{\mathbf{H}}(\mathbf{x})|\rangle/\{\langle(\Delta|F_{\mathbf{H}}^{\mathrm{obs}}|)^2\rangle\langle[\Delta|F_{\mathbf{H}}(\mathbf{x})|]^2\rangle\}^{1/2}. \qquad (10)$$

Expression (6) makes clear the origin of the main characteristic of the correlation coefficient, *i.e.* the independence with respect to both the scale and the absolute value of the data. C is intrinsically a cosine, $-1 \leq C \leq 1$; it is a normalized measure of agreement: $C = 1$ corresponds to a total agreement between $\{|F_{\mathbf{H}}^{\mathrm{obs}}|\}$ and $\{|F_{\mathbf{H}}(\mathbf{x})|\}$. However, some authors do not use 'centered' variables $\Delta|F_{\mathbf{H}}|$, as in the method of Harada *et al.* (1981).

The correlation coefficient in terms of amplitudes seems appropriate for the molecular-replacement method. Unfortunately, it cannot be calculated by simple Fourier summations because of the numerator in (10).

In the program *BRUTE*, Fujinaga & Read (1987) use the correlation coefficient in terms of 'centered' intensities:

$$\langle\Delta I_{\mathbf{H}}^{\mathrm{obs}}\Delta|F_{\mathbf{H}}(\mathbf{x})|^2\rangle\{\langle(\Delta I_{\mathbf{H}}^{\mathrm{obs}})^2\rangle\langle[\Delta|F_{\mathbf{H}}(\mathbf{x})|^2]^2\rangle\}^{-1/2}, \qquad (11)$$

which is (10) with amplitudes replaced by intensities. This function is computed for each sample point in real space. But, as explained in the next section, it can be evaluated by using fast Fourier techniques, resulting in a considerable saving of CPU time for the three-dimensional calculations.

Fast correlation function

We will consider the general case where the asymmetric unit contains several molecules, and call $F_{\mathbf{H}}^{m}$ the structure factors corresponding to the models already placed, $F_{\mathbf{H}}(\mathbf{x})$ being as before the contribution of the oriented model when its center of mass is placed at $\mathbf{x}$.

We define the correlation function in terms of structure-factor intensities as follows:

$$\begin{aligned}\mathrm{CC}(\mathbf{x}) = {} & \sum_{\mathbf{H}} m_{\mathbf{H}} \Delta I_{\mathbf{H}}^{\mathrm{obs}} \Delta |F_{\mathbf{H}}(\mathbf{x}) + F_{\mathbf{H}}^{m}|^2 \\ & \times \left[\sum_{\mathbf{H}} m_{\mathbf{H}} (\Delta I_{\mathbf{H}}^{\mathrm{obs}})^2\right]^{-1/2} \\ & \times \left\{\sum_{\mathbf{H}} m_{\mathbf{H}} [\Delta |F_{\mathbf{H}}(\mathbf{x}) + F_{\mathbf{H}}^{m}|^2]^2\right\}^{-1/2}. \end{aligned} \tag{12}$$

Then we write the $\mathbf{x}$-dependent part of the denominator as

$$\begin{aligned} & \sum_{\mathbf{H}} m_{\mathbf{H}} |F_{\mathbf{H}}(\mathbf{x}) + F_{\mathbf{H}}^{m}|^4 \\ & - \left[\sum_{\mathbf{H}} m_{\mathbf{H}} |F_{\mathbf{H}}(\mathbf{x}) + F_{\mathbf{H}}^{m}|^2\right]^2 \left(\sum_{\mathbf{H}} m_{\mathbf{H}}\right)^{-1} \end{aligned} \tag{13}$$

and note that the sum within square brackets and the numerator of (12) involve essentially the same terms. The latter can be written as

$$\begin{aligned} & \sum_{\mathbf{H}} m_{\mathbf{H}} \Delta I_{\mathbf{H}}^{\mathrm{obs}} \{F_{\mathbf{H}}(\mathbf{x}) F_{\mathbf{H}}(\mathbf{x})^* \\ & \quad + [F_{\mathbf{H}}(\mathbf{x}) F_{\mathbf{H}}^{m*} + \mathrm{c.c.}] + F_{\mathbf{H}}^{m} F_{\mathbf{H}}^{m*}\} \\ & \quad = \sum_{\mathbf{H}} m_{\mathbf{H}} \Delta I_{\mathbf{H}}^{\mathrm{obs}} \sum_{s,s'} \tilde{f}(\mathbf{h}_s)^* \tilde{f}(\mathbf{h}_{s'}) \\ & \quad \times \exp[-2\pi i \mathbf{H}(\mathbf{M}_s - \mathbf{M}_{s'})\mathbf{x}] \\ & \quad + \left[\sum_{\mathbf{H}} m_{\mathbf{H}} \Delta I_{\mathbf{H}}^{\mathrm{obs}} \sum_{s} \tilde{f}(\mathbf{h}_s)^* F_{\mathbf{H}}^{m} \right. \\ & \quad \left. \times \exp(-2\pi i \mathbf{H}\mathbf{M}_s\mathbf{x}) + \mathrm{c.c.}\right] \\ & \quad + \sum_{\mathbf{H}} m_{\mathbf{H}} \Delta I_{\mathbf{H}}^{\mathrm{obs}} F_{\mathbf{H}}^{m} F_{\mathbf{H}}^{m*}, \end{aligned} \tag{14}$$

with $\tilde{f}(\mathbf{h}_s) = f(\mathbf{H}\mathbf{M}_s) \exp(2\pi i \mathbf{H}\mathbf{t}_s)$ and c.c. stands for complex conjugate. A similar expression, with $\Delta I_{\mathbf{H}}^{\mathrm{obs}} = 1$, gives the sum between brackets in (13). This involves reciprocal vectors up to twice the data resolution.

The first sum in (13) is then developed as follows:

$$\begin{aligned} & \sum_{\mathbf{H}} m_{\mathbf{H}} |F_{\mathbf{H}}(\mathbf{x}) + F_{\mathbf{H}}^{m}|^4 \\ & \quad = \sum_{\mathbf{H}} m_{\mathbf{H}} \sum_{s,s',s'',s'''} \tilde{f}(\mathbf{h}_s)^* \tilde{f}(\mathbf{h}_{s'}) \tilde{f}(\mathbf{h}_{s''})^* \tilde{f}(\mathbf{h}_{s'''}) \\ & \quad \times \exp[-2\pi i \mathbf{H}(\mathbf{M}_s - \mathbf{M}_{s'} + \mathbf{M}_{s''} - \mathbf{M}_{s'''})\mathbf{x}] \\ & \quad + 2\left\{ \sum_{\mathbf{H}} m_{\mathbf{H}} \sum_{s,s',s''} \tilde{f}(\mathbf{h}_s)^* \tilde{f}(\mathbf{h}_{s'}) \tilde{f}(\mathbf{h}_{s''})^* F_{\mathbf{H}}^{m} \right. \\ & \quad \left. \times \exp[-2\pi i \mathbf{H}(\mathbf{M}_s - \mathbf{M}_{s'} + \mathbf{M}_{s''})\mathbf{x}] + \mathrm{c.c.} \right\} \\ & \quad +4 \sum_{\mathbf{H}} m_{\mathbf{H}} \sum_{s,s'} \tilde{f}(\mathbf{h}_s)^* \tilde{f}(\mathbf{h}_{s'}) F_{\mathbf{H}}^{m*} F_{\mathbf{H}}^{m} \\ & \quad \times \exp[-2\pi i \mathbf{H}(\mathbf{M}_s - \mathbf{M}_{s'})\mathbf{x}] \\ & \quad + \left\{ \sum_{\mathbf{H}} m_{\mathbf{H}} \sum_{s,s'} \tilde{f}(\mathbf{h}_s)^* \tilde{f}(\mathbf{h}_{s'})^* (F_{\mathbf{H}}^{m})^2 \right. \\ & \quad \left. \times \exp[-2\pi i \mathbf{H}(\mathbf{M}_s + \mathbf{M}_{s'})\mathbf{x}] + \mathrm{c.c.} \right\} \\ & \quad + 2\left\{ \sum_{\mathbf{H}} m_{\mathbf{H}} \sum_{s} \tilde{f}(\mathbf{h}_s)^* (F_{\mathbf{H}}^{m})^2 F_{\mathbf{H}}^{m*} \right. \\ & \quad \left. \times \exp[-2\pi i \mathbf{H}\mathbf{M}_s\mathbf{x}] + \mathrm{c.c} \right\} \\ & \quad + \sum_{\mathbf{H}} m_{\mathbf{H}} (F_{\mathbf{H}}^{m*})^2 (F_{\mathbf{H}}^{m})^2. \end{aligned} \tag{15}$$

These terms involve reciprocal vectors up to four times the data resolution.

In summary, three fast Fourier transforms suffice to recover the correlation function. The overall computing time is about 24 times longer than a standard overlap calculation; this includes the use of a finer grid than in the standard calculation.

Test examples

The results obtained with four different translation functions are now compared; the centered-overlap function CO [with $\Delta I_{\mathbf{H}}^{\mathrm{obs}}$ instead of $I_{\mathbf{H}}^{\mathrm{obs}}$ in (2)], the full-symmetry phased translation function PT, the Harada *et al.* (1981) correlation function HC and the correlation function CC described in this paper. All these functions are now incorporated into the *AMoRe* package. As before, the output of *AMoRe* is the correlation coefficient, in terms of amplitudes, corresponding to the highest peaks.

Several tests were performed using real data. The results obtained with erabutoxin-b, solved by molecular replacement (Saludjian, Prangé, Navaza, Ménez, Guilloteau, Riès-Kautt & Ducruix, 1992) are as follows. Erabutoxin-b crystallizes in space group $P2_12_12_1$ ($a = 53.36$, $b = 40.89$, $c = 66.71$ Å), with two molecules in the asymmetric unit. Data were used between 10 and 3.5 Å resolution. The orientations of the two independent molecules were determined by the rotation function. For each of these two orientations, the above-mentioned translation functions were calculated. The first orientation is a trivial case of molecular replacement: the first separated peak in the rotation function and the translation function. On the contrary, the second orientation, appearing rather low in the rotation-function output, illustrates a common feature observed in difficult cases: most TFs are poorly contrasted and the correct solution is not among the first peaks. The critical dependence of the outputs on the parameters that define the TF implies that, in such situations, the peak height is not a reliable criterion to select the correct solution.

Table 1. *Results of the CO translation function*

The correct solution is ranked ninth.

Peak rank	Correlation (amplitudes)	Correlation (intensities)	*R* factor (%)	Peak height (in σ units)
1	7.97	10.09	54.42	5.90
2	8.55	9.12	54.33	4.38
3	9.99	9.75	54.46	4.25
4	8.29	9.61	54.52	4.06
5	9.42	10.20	54.19	3.96
6	7.53	9.64	54.83	3.94
7	8.85	9.24	54.60	3.83
8	10.30	9.36	54.69	3.79
9	13.21	11.76	53.33	3.73
10	10.90	9.20	53.38	3.64

Table 2. *Results of the PT translation function*

The correct solution is ranked 21st.

Peak rank	Correlation (amplitudes)	Correlation (intensities)	*R* factor (%)	Peak height (in σ units)
1	10.98	9.20	54.42	4.29
2	5.45	5.17	54.33	4.03
3	8.8	8.04	54.46	4.01
4	7.53	5.68	54.52	3.97
5	7.95	8.08	54.19	3.90
6	7.88	7.06	54.83	3.83
7	8.82	9.96	54.60	3.70
8	8.20	7.23	54.69	3.55
9	9.49	10.42	53.33	3.55
10	6.67	7.74	53.38	3.52
⋮	⋮	⋮	⋮	⋮
21	11.94	10.69	53.30	3.33

Table 3. *Results of the HC translation function*

The correct solution is ranked first.

Peak rank	Correlation (amplitudes)	Correlation (intensities)	*R* factor (%)	Peak height (in σ units)
1	13.10	12.30	53.11	4.62
2	9.95	11.41	54.35	4.51
3	10.76	11.56	53.96	4.34
4	8.29	11.51	54.84	4.24
5	11.07	10.57	53.80	4.24
6	7.83	8.82	54.31	3.86
7	10.76	9.59	54.51	3.82
8	8.21	9.36	54.73	3.78
9	9.85	10.07	53.50	3.68
10	7.43	9.39	55.23	3.58

Table 4. *Results of the CC translation function*

The correct solution is ranked first.

Peak rank	Correlation (amplitudes)	Correlation (intensities)	*R* factor (%)	Peak height (100 × correlation)
1	13.15	12.24	53.07	12.24
2	10.80	11.65	53.91	11.65
3	9.79	11.39	54.34	11.39
4	8.10	11.06	54.44	11.06
5	11.07	10.58	53.82	10.58
6	9.60	10.09	53.43	10.09
7	8.62	9.87	53.63	7.87
8	8.57	8.78	53.82	9.78
9	8.52	9.77	54.33	9.77
10	9.71	9.76	53.67	9.76

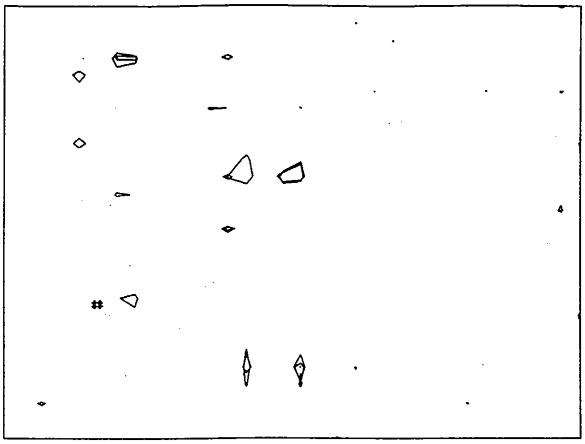

Fig. 1. CO translation-function map. The whole Cheshire cell is projected along the *b* axis. The contour level is 1σ below the maximum value. The correct solution is indicated by symbol #; it is ranked ninth.

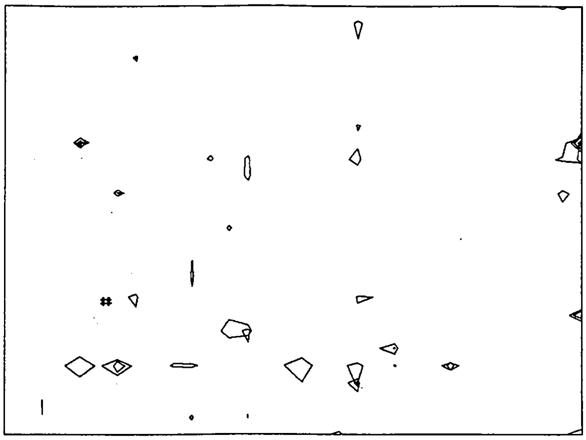

Fig. 2. Same conditions as Fig. 1 but for PT translation function. The correct solution is ranked 21st.

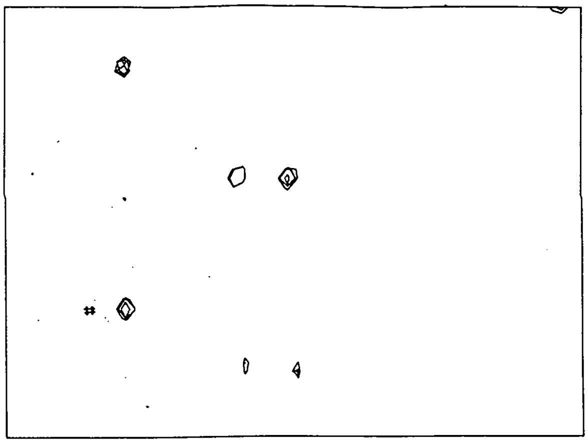

Fig. 3. Same conditions as Fig. 1 but for HC translation function. The correct solution is ranked first.

The results show (Tables 1 to 4) that the correlation coefficients, in terms of either amplitudes or intensities, have the greatest contrast, the correct peak being systematically at the top of the CC output. In the case reported here, the HC function gave the solution in first rank too, with essentially the same contrast. The TF maps (Figs. 1 to 4) show that, although computed in a finer grid, the correlation function has almost the same spatial resolution.

In some 'pathological' examples, the correct solution is absent from the CO output. This is the case with the low-resolution neutron data corresponding to the cubic form of the tRNA$^{\mathrm{Asp}}$–synthetase complex. This complex crystallizes in space group $I432$ ($a = 354$ Å) with one dimer in the asymmetric unit. The correlation function, computed with data from 500 to 20 Å, gave the correct solution as first rank. The solution also appeared with the PT function but its rank in the output list was very low (below 50) and extremely sensitive to the scaling parameter σ. The Harada method also failed to give the correct solution. A detailed investigation of TF problems for this structure was presented by Urzhumtsev, Podjarny & Navaza (1994).

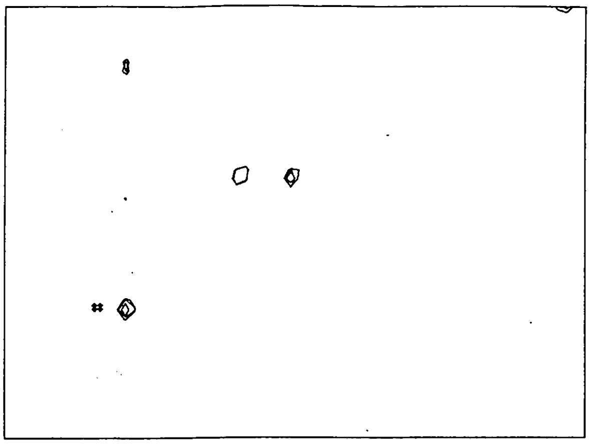

Fig. 4. Same conditions as Fig. 1 but for CC translation function. The correct solution is ranked first.

Concluding remarks

The paper has shown the advantages of using the correlation function as the main criterion to select solutions in the translation problem of molecular replacement. Its computation by fast Fourier transforms allows one to explore many potential orientations in reasonable computing times. This is particularly interesting for the pseudo-many-body searches, where it is crucial to detect the starting correct position of at least one individual molecule. Also, the technique appears as the only realistic one to deal with very low resolution data.

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