A different approach has been suggested in two recent papers (Burla *et al.*, 2002; Burla, Carrozzini *et al.*, 2003): the estimates of the amplitudes of the structure factors of the anomalously scattering substructure are derived, *via* the rigorous method of the joint probability distribution functions, from the experimental diffraction moduli relative to n wavelengths. To do that, first the joint distribution

$$\begin{aligned} P_n = P(&A_{\rm oa}, A_1^+, A_2^+, \ldots, A_n^+, A_1^-, A_2^-, \ldots, A_n^-, \\ &B_{\rm oa}, B_1^+, B_2^+, \ldots, B_n^+, B_1^-, B_2^-, \ldots, B_n^-) \\ &= \pi^{-(2n+1)}(\det\, K)^{1/2} \exp(-\tfrac{1}{2}\mathbf{T}^T\mathbf{K}^{-1}\mathbf{T}) \end{aligned}$$

is calculated, where $A_{\rm oa}, B_{\rm oa}, E_{\rm oa}, A_i^+, B_i^+, A_i^-, B_i^-$ are the real and imaginary components of $E_{\rm oa}$, E_i^+, E_i^-, respectively, $\mathbf{K}$ is a symmetric square matrix of order $(4n + 2)$, $\mathbf{K}^{-1} = \{\lambda_{ij}\}$ is its inverse, and $\mathbf{T}$ is a suitable vector with components defined in terms of the variables $A_{\rm oa}, A_1^+, A_2^+, \ldots, B_n^-$. $E_{\rm oa}$ is the normalized structure factor of the anomalous scatterer substructure calculated by neglecting anomalous scattering components. Then the conditional distribution

$$P(R_{\rm oa}|R_1, \ldots, R_n, G_1, \ldots, G_n)$$

is derived, from which

$$\langle R_{\rm oa}|R_1, \ldots, G_n\rangle = \tfrac{1}{2}(\pi/\lambda_{11})^{1/2}[1 + 4X^2/(\pi\lambda_{11})]^{1/2} \quad (2.2.10.12)$$

is obtained, where

$$\begin{aligned} X^2 &= Q_1^2 + Q_2^2 \\ Q_1 &= \lambda_{12}R_1 + \lambda_{13}R_2 + \ldots + \lambda_{1,n+1}R_n + \lambda_{1,n+2}G_1 + \ldots \\ &\quad + \lambda_{1,2n+1}G_n \\ Q_2 &= \lambda_{1,2n+3}R_1 + \lambda_{1,2n+4}R_2 + \ldots + \lambda_{1,3n+2}R_n + \ldots - \lambda_{1,3n+3}G_1 \\ &\quad - \ldots - \lambda_{1,4n+2}G_n. \end{aligned}$$

The standard deviation of the estimate is also calculated:

$$\sigma_{R_{\rm oa}} = \left[\langle R_{\rm oa}^2|\ldots\rangle - \langle R_{\rm oa}|\ldots\rangle^2\right]^{1/2} = \left[\left(1 - \frac{\pi}{4}\right)\lambda_{11}^{-1}\right]^{1/2},$$

from which

$$\frac{\langle R_{\rm oa}|\ldots\rangle}{\sigma_{R_{\rm oa}}} = \left[\frac{(\pi/4) + (X^2)/\lambda_{11}}{1 - (\pi/4)}\right]^{1/2}. \quad (2.2.10.13)$$

The advantage of the above approach is that the estimates can simultaneously exploit both the anomalous and the dispersive differences. The computing procedure proposed by Burla, Carrozzini *et al.* (2003) is the following:

(i) The sets S_j, $j = 1, \ldots, n$, of the observed magnitudes (say $|F^+|$, $|F^-|$) are stored for all the n wavelengths.

(ii) The Wilson method is applied to put the sets S_j on their absolute scales.

(iii) Equations (2.2.10.12) and (2.2.10.13) are applied to obtain the values $\langle R_{\rm oa}|\ldots\rangle$ and $\langle R_{\rm oa}|\ldots\rangle/\sigma_{R_{\rm oa}}$.

(iv) The triplet invariants involving the reflections with the highest $\langle R_{\rm oa}|\ldots\rangle/\sigma_{R_{\rm oa}}$ values are evaluated and the tangent formula is applied *via* a random starting approach.

(v) The direct-space refinement techniques of *SIR2002* (Burla, Camalli *et al.*, 2003) are used to extend the phase information to a larger set of reflections: only 30% of the reflections with the smallest values of $\langle R_{\rm oa}|\ldots\rangle$ remain unphased. Automatic cycles of least-squares refinement improve the substructure model provided by the trial solutions.

(vi) Suitable figures of merit are used to recognize the correct substructure models.

The application of the above procedure to several MAD cases showed that the various wavelength combinations are not equally informative. A criterion based on the correlation among the various $\Delta_{\rm ano}$ values was also provided (see also Schneider & Sheldrick, 2002) for predicting the most informative combinations.

2.2.10.10. SAD–MAD case: protein phasing by direct methods

Once the anomalous-scatterer substructure has been found, the corresponding structure factors $E_{a1}^+, \ldots, E_{an}^+, E_{a1}^-, \ldots, E_{an}^-$ are known in modulus and phase. Then the conditional joint probability distribution

$$P\left(E_1^+, \ldots, E_n^+, E_1^-, \ldots, E_n^-|E_{a1}^+, \ldots, E_{an}^+, E_{a1}^-, \ldots, E_{an}^-\right)$$

may be calculated (Giacovazzo & Siliqi, 2004), from which the conditional distribution

$$P\left(\varphi_1^+|E_{ai}^+, E_{ai}^-, R_i, G_i, i = 1, \ldots, 2\right)$$

may be derived.

It has been shown that the most probable phase of φ_1^+, say θ_1^+, is the phase of the vector

$$\begin{aligned} &\sum_{j=1}^{n}\left[w_j^+E_{aj}^+ + w_j^-E_{aj}^{-*}\right] \\ &\quad + \sum_{j,p=1,p>j}^{n}\left[w_{jp}(E_{aj}^+ - E_{ap}^+) + w_{n+j,n+p}\left(E_{aj}^{-*} - E_{ap}^{-*}\right)\right] \\ &\quad + \sum_{j,p=1}^{n} w_{j,n+p}\left(E_{aj}^+ - E_{ap}^{-*}\right)] \end{aligned} \quad (2.2.10.14)$$

and the reliability parameter of the phase estimate is nothing other than the modulus of (2.2.10.14). The first term in (2.2.10.14) is a Sim-like contribution; the other terms, through the weights w, take into account the errors and the experimental differences $(R_j - R_p)$, $(G_j - G_p)$ and $(R_j - G_p)$.

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