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The method of joint probability distribution functions applied to MAD techniques. The two-wavelength case for acentric crystals

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MAD (multiple-wavelength anomalous dispersion) techniques are often considered as a special MIR (multiple isomorphous replacement) case. The rigorous method of the joint probability distribution functions is applied to solve the phase problem for acentric crystals, on the assumption that the anomalous scatterer's substructure is *a priori* known. The two-wavelength case is considered: errors in measurements and in the model substructure are handled. The probabilistic approach provides a very simple and efficient formula for estimating structure-factor phases.

1. Notation

N: number of atoms in the unit cell.
a: number of anomalous scatterers in the unit cell.
$na = N - a$: number of non-anomalous scatterers.
$f_j = f_j^0 + \Delta f_j + if_j'' = f_j' + if_j''$: scattering factor of the jth atom. f' is its real, f'' is its imaginary part. The thermal factor is included.
Σ_a, Σ_{na}, $\Sigma_N = \sum (f_j'^2 + f_j''^2)$, where the summation is extended to a, na and N atoms.

$$F^+ = |F^+| \exp(i\varphi^+) = F_{\mathbf{h}} = \sum_{j=1}^{N} f_j \exp(2\pi i \mathbf{hr}_j)$$

$$F_a^+ = |F_a^+| \exp(i\varphi_a^+) = \sum_{a} f_j \exp(2\pi i \mathbf{hr}_j)$$

$$F^- = |F^-| \exp(i\varphi^-) = F_{-\mathbf{h}} = \sum_{j=1}^{N} f_j \exp(-2\pi i \mathbf{hr}_j)$$

$$F_a^- = |F_a^-| \exp(i\varphi_a^-) = \sum_{a} f_j \exp(-2\pi i \mathbf{hr}_j)$$

$$\Delta_{\text{ano}} = |F^+| - |F^-|.$$

2. Introduction

The increasing power and tunability of synchrotron beamlines have strongly improved the efficiency of the MAD (multiple-wavelength anomalous dispersion) method for solving the phase problem in protein crystallography. The technique exploits the differences among structure-factor moduli generated, at wavelengths around the absorption edges, by the anomalously scattering atoms present in the unit cell (Hendrickson & Ogata, 1997; Smith, 1997). The first step of the procedure aims at locating the anomalously scattering atoms (Terwilliger *et al.*, 1987; Miller *et al.*, 1994; Sheldrick & Gould, 1995). The second step tries to determine the phase values on assuming the partial structure of the anomalously scattering atoms as prior information. Previous probabilistic approaches consider MAD data as special MIR (multiple isomorphous replacement) cases (Blow & Crick, 1959; Terwilliger & Eisenberg, 1987) or adapt Karle's (1980) algebraic analysis to a probabilistic description (Pähler *et al.*, 1990; Chiadmi *et al.*, 1993). This paper applies the rigorous method of the joint probability distribution function to the two-wavelength case on assuming that the anomalously scattering atoms are located. The paper follows:

(*a*) a contribution by Giacovazzo & Siliqi (2001*a*), from now on paper I, where the joint probability distribution method has been applied to the SAD (single-wavelength anomalous dispersion) case, on the assumption that the positions of all or a part of the anomalous scatterers have been found *via* one of the current methods;

(*b*) a contribution by Giacovazzo & Siliqi (2001*b*), from now on paper II, where the MAD case has been treated for symmetry-restricted reflections.

The two-wavelength case is crucial for MAD data treatment: the algebraic aspects have been studied by several authors (*i.e.* Singh & Ramaseshan, 1968; Unangst *et al.*, 1967; Bartunik, 1978; Cascarano *et al.*, 1982; Klop *et al.*, 1989). The probabilistic aspects of this case are here investigated: the joint probability distribution functions $P(F_1^+, F_2^+, F_1^-, F_2^- | F_a^+, F_a^-)$ will be derived, from which the

marginal distributions $P(\varphi_1^+||F_1^+|, |F_2^+|, |F_1^-|, |F_2^-|, F_a^+, F_a^-)$ will be obtained. The first application of the conclusive formulas are also described.

By analogy with the probabilistic approach described in papers I and II, the positions of the non-anomalous scatterers will be the primitive random variables. For each wavelength, we will make the following assumptions:

(*a*)

$$F^+ = F_a^+ + F_{na}^+ + \mu^+ = F_a^+ + F_q^+, \tag{1}$$

where F_{na}^+ is the structure factor corresponding to the non-anomalous scatterers, all supposed non-located. Furthermore, $\mu^+ = |\mu|^+ \exp(i\theta^+)$ represents the cumulative error arising from errors in measurements and in the substructure model of the anomalous scatterers: it is incorporated into $F_q^+ = F_{na}^+ + \mu^+$.

(*b*) Equivalently,

$$F^- = F_a^- + F_{na}^- + \mu^- = F_a^- + F_q^-, \tag{2}$$

where $F_q^- = F_{na}^- + \mu^-$.

(*c*) F_a, F_{na}, μ^+, are uncorrelated with each other. The same assumption is made for $\langle\mu^+\rangle = \langle\mu^-\rangle = 0$.

(*d*) $\langle\mu^+\mu^-\rangle = 0$. This implies that errors on F^+ and F^- are uncorrelated. Accordingly,

$$\langle|F^+|^2\rangle = |F_a^+|^2 + \Sigma_{na} + \langle|\mu^+|^2\rangle,$$
$$\langle|F^-|^2\rangle = |F_a^-|^2 + \Sigma_{na} + \langle|\mu^-|^2\rangle.$$

(*e*) $\langle\mu_1^+\mu_2^+\rangle = \langle\mu_1^-\mu_2^-\rangle = \langle\mu_1^+\mu_2^-\rangle = 0$.

In the absence of any prior information, all the assumptions (*a*)–(*e*) are quite reasonable. In practice, the errors are not uncorrelated, whether because of possible systematic errors in measurements or because of unavoidable errors in the assumed structural model of the anomalous atoms.

As in papers I and II, we will normalize the structure factors with respect to the unknown part of the structure. Accordingly,

$$R\exp(i\varphi^+) = (A^+ + iB^+) = F^+\Big/\textstyle\sum_{na}^{1/2}$$
$$G\exp(i\varphi^-) = (A^- + iB^-) = F^-\Big/\textstyle\sum_{na}^{1/2},$$

where R and G are the pseudo-normalized moduli of $|F^+|$ and $|F^-|$, respectively, and

$$A^+ = \left[\sum_{j=1}^{N}(f_j'\cos 2\pi\mathbf{hr}_j - f_j''\sin 2\pi\mathbf{hr}_j) + |\mu^+|\cos\theta^+\right]\Big/\textstyle\sum_{na}^{1/2},$$
$$B^+ = \left[\sum_{j=1}^{N}(f_j'\sin 2\pi\mathbf{hr}_j + f_j''\cos 2\pi\mathbf{hr}_j) + |\mu^+|\sin\theta^+\right]\Big/\textstyle\sum_{na}^{1/2},$$
$$A^- = \left[\sum_{j=1}^{N}(f_j'\cos 2\pi\mathbf{hr}_j + f_j''\sin 2\pi\mathbf{hr}_j) + |\mu^-|\cos\theta^-\right]\Big/\textstyle\sum_{na}^{1/2},$$
$$B^- = \left[\sum_{j=1}^{N}(-f_j'\sin 2\pi\mathbf{hr}_j + f_j''\cos 2\pi\mathbf{hr}_j) + |\mu^-|\sin\theta^-\right]\Big/\textstyle\sum_{na}^{1/2}.$$

Equivalently,

$$R_a\exp(i\varphi_a^+) = (A_a^+ + iB_a^+) = F_a^+/\Sigma_{na}^{1/2},$$
$$G_a\exp(i\varphi_a^-) = (A_a^- + iB_a^-) = F_a^-/\Sigma_{na}^{1/2},$$
$$R_q\exp(i\varphi_q^+) = (A_q^+ + iB_q^+) = F_q^+/\Sigma_{na}^{1/2},$$
$$G_q\exp(i\varphi_q^-) = (A_q^- + iB_q^-) = F_q^-/\Sigma_{na}^{1/2},$$

where

$$A_q^+ = [\Re(F_{na}^+) + |\mu^+|\cos\theta^+]/\Sigma_{na}^{1/2},$$
$$B_q^+ = [\Im(F_{na}^+) + |\mu^+|\sin\theta^+]/\Sigma_{na}^{1/2},$$
$$A_q^- = [\Re(F_{na}^-) + |\mu^-|\cos\theta^-]/\Sigma_{na}^{1/2},$$
$$B_q^- = [\Im(F_{na}^-) + |\mu^-|\sin\theta^-]/\Sigma_{na}^{1/2}.$$

$\Re(\ldots)$ and $\Im(\ldots)$ stand for real part of and imaginary part of, respectively.

3. The joint probability distribution $P(F_1^+, F_2^+, F_1^-, F_2^-|F_{a1}^+, F_{a2}^+, F_{a1}^-, F_{a2}^-)$

Under the assumptions specified in §2, the characteristic function

$$C(u_1^+, u_2^+, u_1^-, u_2^-, \mathrm{v}_1^+, \mathrm{v}_2^+, \mathrm{v}_1^-, \mathrm{v}_2^-)$$

(in short C) of the distribution

$$P(A_1^+, A_2^+, A_1^-, A_2^-, B_1^+, B_2^+, B_1^-, B_2^-|A_{a1}^+, \ldots, B_{a2}^-)$$

(in short P) may be calculated, where $u_1^+, u_2^+, \ldots, \mathrm{v}_1^-, \mathrm{v}_2^-$ are carrying variables associated with A_1^+, A_2^+, …, B_1^-, B_2^-, respectively. We have

$$\begin{aligned} C &= \langle\exp i(u_1^+A_1^+ + u_2^+A_2^+ + \ldots + \mathrm{v}_2^-B_2^-)\rangle \\ &\approx \exp[i(u_1^+A_1^+ + u_2^+A_{a2}^+ + u_1^-A_{a1}^- + u_2^-A_{a2}^- + \ldots + \mathrm{v}_2^-B_{a2}^-)] \\ &\quad\times\exp\left\{-\tfrac{1}{4}\sum_{j=1}^{2}[e_j^+(u_j^{+2} + \mathrm{v}_j^{+2}) + e_j^-(u_j^{-2} + \mathrm{v}_j^{-2})]\right. \\ &\quad -\tfrac{1}{2}(u_1^+u_2^+ + u_1^+u_1^- + u_1^+u_2^- + u_2^+u_1^- + u_2^+u_2^- + u_1^-u_2^-) \\ &\quad\left.-\tfrac{1}{2}(\mathrm{v}_1^+\mathrm{v}_2^+ - \mathrm{v}_1^+\mathrm{v}_1^- - \mathrm{v}_1^+\mathrm{v}_2^- - \mathrm{v}_2^+\mathrm{v}_1^- - \mathrm{v}_2^+\mathrm{v}_2^- - \mathrm{v}_1^-\mathrm{v}_2^-)\right\}, \end{aligned}$$

where

$$e_j^+ = 1 + (\sigma_{\mu j}^+)^2, \qquad e_j^- = 1 + (\sigma_{\mu j}^-)^2,$$
$$(\sigma_{\mu j}^+)^2 = \langle\mu_j^{+2}\rangle/\Sigma_{na}^{1/2}, \quad (\sigma_{\mu j}^-)^2 = \langle(\mu_j^-)^2\rangle/\Sigma_{na}^{1/2}.$$

Then

$$\begin{aligned} P \approx (2\pi)^{-8}\int_{-\infty}^{-\infty}\ldots\int_{-\infty}^{+\infty}\exp\Big\{ &-i[u_1^+(A_1^+ + A_{a1}^+) + u_2^+(A_2^+ - A_{a2}^+) \\ &+ \ldots + \mathrm{v}_2^-(B_2^- - B_{a2}^-)] \\ &-\tfrac{1}{4}\sum_{j=1}^{2}[e_j^+(u_j^{+2} + \mathrm{v}_j^{+2}) + e_j^-(u_j^{-2} + \mathrm{v}_j^{-2})] \\ &-\tfrac{1}{2}(u_1^+u_2^+ + u_1^+u_1^- + u_1^+u_2^- + u_2^+u_1^- + u_2^+u_2^- + u_1^-u_2^-) \\ &-\tfrac{1}{2}(\mathrm{v}_1^+\mathrm{v}_2^+ - \mathrm{v}_1^+\mathrm{v}_1^- - \mathrm{v}_1^+\mathrm{v}_2^- - \mathrm{v}_2^+\mathrm{v}_1^- - \mathrm{v}_2^+\mathrm{v}_2^- \\ &+ \mathrm{v}_1^-\mathrm{v}_2^+)\Big\}\,\mathrm{d}u_1^+\ldots\mathrm{d}\mathrm{v}_2^-. \end{aligned} \tag{3}$$

Define

$$u_j^+ = (2/e_j^+)^{1/2}u_j^{+\prime}, \quad u_j^- = (2/e_j^-)^{1/2}u_j^{-\prime},$$
$$\mathrm{v}_j^+ = (2/e_j^+)^{1/2}\mathrm{v}_j^{+\prime}, \quad \mathrm{v}_j^- = (2/e_j^-)^{1/2}\mathrm{v}_j^{-\prime}.$$

Then (3) may be written as

$$P = (2\pi)^{-8}2^4(e_1^+e_2^+e_1^-e_2^-)\int_{-\infty}^{-\infty}\cdots\int_{-\infty}^{+\infty}\exp(-i\overline{\mathbf{T}}\mathbf{U}' - \tfrac{1}{2}\overline{\mathbf{U}}'\mathbf{k}\mathbf{U}')\,\mathrm{d}\overline{\mathbf{U}}'$$
$$= \pi^{-4}(e_1^+e_2^+e_1^-e_2^-)^{-1}(\det\mathbf{k})^{-1/2}\exp(-\tfrac{1}{2}\overline{\mathbf{T}}\mathbf{k}^{-1}\mathbf{T}), \qquad (4)$$

where

$$\overline{\mathbf{U}} = (u_1^{+\prime}, u_2^{+\prime}, u_1^{-\prime}, u_2^{-\prime}, \mathrm{v}_1^{+\prime}, \ldots, \mathrm{v}_2^{-\prime}),$$
$$\overline{\mathbf{T}} = [(A_1^+ - A_{a1}^+)(2/e_1^+)^{1/2}, \ldots, (B_2^- - B_{a2}^-)(2/e_2^-)^{1/2}],$$

$$\mathbf{k} = \begin{vmatrix} 1 & (e_1^+e_2^+)^{-1/2} & (e_1^+e_1^-)^{-1/2} & (e_1^+e_2^-)^{-1/2} \\ (e_1^+e_2^+)^{-1/2} & 1 & (e_2^+e_1^-)^{-1/2} & (e_2^+e_2^-)^{-1/2} \\ (e_1^+e_1^-)^{-1/2} & (e_2^+e_1^-)^{-1/2} & 1 & (e_1^-e_2^-)^{-1/2} \\ (e_1^+e_2^-)^{-1/2} & (e_2^+e_2^-)^{-1/2} & (e_1^-e_2^-)^{-1/2} & 1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{vmatrix}$$
$$\begin{vmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ (e_1^+e_2^+)^{-1/2} & -(e_1^+e_1^-)^{-1/2} & -(e_1^+e_2^-)^{-1/2} \\ 1 & -(e_2^+e_1^-)^{-1/2} & -(e_2^+e_2^-)^{-1/2} \\ -(e_2^+e_1^-)^{-1/2} & 1 & (e_1^-e_2^-)^{-1/2} \\ -(e_2^+e_2^-)^{-1/2} & (e_1^-e_2^-)^{-1/2} & 1 \end{vmatrix}$$
$$= \begin{vmatrix} \mathbf{Q}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{Q}_2 \end{vmatrix}. \qquad (5)$$

$\mathbf{Q}_1$ and $\mathbf{Q}_2$ are 4×4 matrices.

In accordance with the results of Appendix A, we write down the explicit form of (4):

$$P \approx \pi^{-4}q^{-1}\exp\Big(-q^{-1}\Big\{\sum_{i=1}^{2}\lambda_{ii}[(A_i^+ - A_{ai}^+)^2 + (B_i^+ - B_{ai}^+)^2]$$
$$+ \sum_{i=3}^{4}\lambda_{ii}[(A_i^- - A_{ai}^-)^2 + (B_i^- - B_{ai}^-)^2]$$
$$+ 2\lambda_{12}[(A_1^+ - A_{a1}^+)(A_2^+ - A_{a2}^+) + (B_1^+ - B_{a1}^+)(B_2^+ - B_{a2}^+)]$$
$$+ 2\lambda_{13}[(A_1^+ - A_{a1}^+)(A_1^- - A_{a1}^-) - (B_1^+ - B_{a1}^+)(B_1^- - B_{a1}^-)]$$
$$+ 2\lambda_{14}[(A_1^+ - A_{a1}^+)(A_2^- - A_{a2}^-) - (B_1^+ - B_{a1}^+)(B_2^- - B_{a2}^-)]$$
$$+ 2\lambda_{23}[(A_2^+ - A_{a2}^+)(A_1^- - A_{a1}^-) - (B_2^+ - B_{a2}^+)(B_1^- - B_{a1}^-)]$$
$$+ 2\lambda_{24}[(A_2^+ - A_{a2}^+)(A_2^- - A_{a2}^-) - (B_2^+ - B_{a2}^+)(B_2^- - B_{a2}^-)]$$
$$+ 2\lambda_{34}[(A_1^- - A_{a1}^-)(A_2^- - A_{a2}^-) - (B_1^- - B_{a1}^-)(B_2^- - B_{a2}^-)]\Big\}\Big). \qquad (6)$$

The change of variables

$$A_i^+ = R_i\cos\varphi_i^+, \quad A_i^- = G_i\cos\varphi_i^-,$$
$$A_{ai}^+ = R_{ai}\cos\varphi_{ai}^+, \quad A_{ai}^- = G_{ai}\cos\varphi_{ai}^-$$

reduces (6) to

$$P \approx \pi^{-4}q^{-1}\prod_{i=1}^{2}(R_iG_i)\exp\Big(-q^{-1}\Big\{\sum_{i=1}^{2}\lambda_{ii}[R_i^2 + G_i^2 + R_{ai}^2 + G_{ai}^2$$
$$- 2R_iR_{ai}\cos(\varphi_i^+ - \varphi_{ai}^+) - 2G_iG_{ai}\cos(\varphi_i^- - \varphi_{ai}^-)]$$
$$+ 2\lambda_{12}[R_1R_2\cos(\varphi_1^+ - \varphi_2^+) - R_1R_{a2}\cos(\varphi_1^+ - \varphi_{a2}^+)$$
$$- R_2R_{a1}\cos(\varphi_2^+ - \varphi_{a1}^+) + R_{a1}R_{a2}\cos(\varphi_{a1}^+ - \varphi_{a2}^+)]$$
$$+ 2\lambda_{13}[R_1G_1\cos(\varphi_1^+ + \varphi_1^-) - R_1G_{a1}\cos(\varphi_1^+ + \varphi_{a1}^-)$$
$$- G_1R_{a1}\cos(\varphi_1^- + \varphi_{a1}^+) + R_{a1}G_{a1}\cos(\varphi_{a1}^+ + \varphi_{a1}^-)]$$
$$+ 2\lambda_{14}[R_1G_2\cos(\varphi_1^+ + \varphi_2^-) - R_1G_{a2}\cos(\varphi_1^+ + \varphi_{a2}^-)$$
$$- G_2R_{a1}\cos(\varphi_2^- + \varphi_{a1}^+) + R_{a1}G_{a2}\cos(\varphi_{a1}^+ + \varphi_{a2}^-)]$$
$$+ 2\lambda_{23}[R_2G_1\cos(\varphi_2^+ + \varphi_1^-) - R_2G_{a1}\cos(\varphi_2^+ + \varphi_{a1}^-)$$
$$- G_1R_{a2}\cos(\varphi_1^- + \varphi_{a2}^+) + R_{a2}G_{a1}\cos(\varphi_{a2}^+ + \varphi_{a1}^-)]$$
$$+ 2\lambda_{24}[R_2G_2\cos(\varphi_2^+ + \varphi_2^-) - R_2G_{a2}\cos(\varphi_2^+ + \varphi_{a2}^-)$$
$$- G_2R_{a2}\cos(\varphi_2^- + \varphi_{a2}^+) + R_{a2}G_{a2}\cos(\varphi_{a2}^+ + \varphi_{a2}^-)]$$
$$+ 2\lambda_{34}[G_1G_2\cos(\varphi_1^- - \varphi_2^-) - G_1G_{a2}\cos(\varphi_1^- - \varphi_{a2}^-)$$
$$- G_2G_{a1}\cos(\varphi_2^- - \varphi_{a1}^+) + G_{a1}G_{a2}\cos(\varphi_{a1}^- - \varphi_{a2}^-)]\Big\}\Big). \qquad (7)$$

4. The conditional probability $P(\varphi_1^+, \varphi_2^+, \varphi_1^-, \varphi_2^-, |E_{ai}^+, E_{ai}^-, R_i, G_i,\ i = 1, 2)$

In order to derive the main property of the joint probability distribution (7), we reconsider (6). Since $\sigma^2 = \langle\mu^2\rangle/\sum_N$ is usually quite a small quantity, we can introduce the following approximation:

$$\lambda_{11} = -(\lambda_{12} + \lambda_{13} + \lambda_{14}), \quad \lambda_{22} = -(\lambda_{12} + \lambda_{23} + \lambda_{24}),$$
$$\lambda_{33} = -(\lambda_{13} + \lambda_{23} + \lambda_{34}), \quad \lambda_{44} = -(\lambda_{14} + \lambda_{24} + \lambda_{34}).$$

Then (6) may be rewritten (see Appendix B) as

$$P \approx \pi^{-4}q^{-1}\exp\big(+(\lambda_{12}/q)\{[(A_1^+ - A_2^+) - (A_{a1}^+ - A_{a2}^+)]^2$$
$$+ [(B_1^+ - B_2^+) - (B_{a1}^+ - B_{a2}^+)]^2\} + (\lambda_{13}/q)\{[(A_1^+ - A_1^-)$$
$$- (A_{a1}^+ - A_{a1}^-)]^2 + [(B_1^+ + B_1^-) - (B_{a1}^+ + B_{a1}^-)]^2\}$$
$$+ (\lambda_{14}/q)\{[(A_1^+ - A_2^-) - (A_{a1}^+ - A_{a2}^-)]^2 + [(B_1^+ + B_1^-)$$
$$- (B_{a1}^+ + B_{a1}^-)]^2\} + (\lambda_{23}/q)\{[(A_2^+ - A_1^-) - (A_{a2}^+ - A_{a1}^-)]^2$$
$$+ [(B_2^+ + B_1^-) - (B_{a2}^+ + B_{a1}^-)]^2\} + (\lambda_{24}/q)\{[(A_2^+ - A_2^-)$$
$$- (A_{a2}^+ - A_{a2}^-)]^2 + [(B_2^+ + B_2^-) - (B_{a2}^+ + B_{a2}^-)]^2\}$$
$$+ (\lambda_{34}/q)\{[(A_1^- - A_2^-) - (A_{a1}^- - A_{a2}^-)]^2$$
$$+ [(B_1^- - B_2^-) - (B_{a1}^- - B_{a2}^-)]^2\}\big). \qquad (8)$$

We observe:

(a) Equation (8) is maximized when the differences $(A_i^+ - A_j^+)$, $(A_i^- - A_j^-)$, $(A_i^+ - A_j^-)$, …, $(B_i^+ + B_j^-)$, $(B_i^- - B_j^-)$ are equal to the corresponding differences among structure factors of the anomalous atom substructure. In a more appealing form, (8) may be rewritten as

$$
\begin{aligned}
P \approx \pi^{-4} q^{-1} \exp[&(\lambda_{12}/q)|(E_1^+ - E_2^+) - (E_{a1}^+ - E_{a2}^+)|^2 \\
&+ (\lambda_{13}/q)|(E_1^+ - E_1^{-*}) - (E_{a1}^+ - E_{a1}^{-*})|^2 \\
&+ (\lambda_{14}/q)|(E_1^+ - E_2^{-*}) - (E_{a1}^+ - E_{a2}^{-*})|^2 \\
&+ (\lambda_{23}/q)|(E_2^+ - E_1^{-*}) - (E_{a2}^+ - E_{a1}^{-*})|^2 \\
&+ (\lambda_{24}/q)|(E_2^+ - E_2^{-*}) - (E_{a2}^+ - E_{a2}^{-*})|^2 \\
&+ (\lambda_{34}/q)|(E_1^- - E_2^-) - (E_{a1}^- - E_{a2}^-)|^2],
\end{aligned}
$$

where E^* stands for the complex conjugate of E. The above equation perfectly complies with expectations. At the same time, the expectations work in the formula as a lack-of-closure criterion.

(*b*) Each term is modulated by a sensitive weight, correlated with the errors in the anomalous atom substructure and/or in measurements. For example, the contribution of the difference

$$[(A_1^+ - A_2^+) - (A_{a1}^+ - A_{a2}^+)]^2 + [(B_1^+ - B_2^+) - (B_{a1}^+ - B_{a2}^+)]^2$$

to the probability density P will be large if the product $\sigma_1^{-2}\sigma_2^{-2}$ is large, in agreement with common sense.

The conditional probability

$$P(\varphi_1^+, \varphi_2^+, \varphi_1^-, \varphi_2^- | E_{ai}, R_i, G_i, i = 1, 2)$$

is then

$$
\begin{aligned}
&P(\varphi_1^+, \varphi_2^+, \varphi_1^-, \varphi_2^- | \ldots) \\
&\quad \approx L^{-1} \exp\{-2(\lambda_{12}/q)[R_1 R_2 \cos(\varphi_1^+ - \varphi_2^+) \\
&\qquad - R_1 R_{a2} \cos(\varphi_1^+ - \varphi_{a2}^+) - R_2 R_{a1} \cos(\varphi_2^+ - \varphi_{a1}^+)] \\
&\qquad - 2(\lambda_{13}/q)[R_1 G_1 \cos(\varphi_1^+ + \varphi_1^-) \\
&\qquad - R_1 G_{a1} \cos(\varphi_1^+ + \varphi_{a1}^-) - G_1 R_{a1} \cos(\varphi_1^- + \varphi_{a1}^+)] \\
&\qquad - 2(\lambda_{14}/q)[R_1 G_2 \cos(\varphi_1^+ + \varphi_2^-) \\
&\qquad - R_1 G_{a2} \cos(\varphi_1^+ + \varphi_{a2}^-) - G_2 R_{a1} \cos(\varphi_2^- + \varphi_{a1}^+)] \\
&\qquad - 2(\lambda_{23}/q)[R_2 G_1 \cos(\varphi_2^+ + \varphi_1^-) \\
&\qquad - R_2 G_{a1} \cos(\varphi_2^+ + \varphi_{a1}^-) - G_1 R_{a2} \cos(\varphi_1^- + \varphi_{a2}^+)] \\
&\qquad - 2(\lambda_{24}/q)[R_2 G_2 \cos(\varphi_2^+ + \varphi_2^-) \\
&\qquad - R_2 G_{a2} \cos(\varphi_2^+ + \varphi_{a2}^-) - G_2 R_{a2} \cos(\varphi_2^- + \varphi_{a2}^+)] \\
&\qquad - 2(\lambda_{34}/q)[G_1 G_2 \cos(\varphi_1^- - \varphi_2^-) \\
&\qquad - G_1 G_{a2} \cos(\varphi_1^- - \varphi_{a2}^-) - G_2 G_{a1} \cos(\varphi_2^- - \varphi_{a1}^-)] \\
&\qquad - (2/q)[(\lambda_{12} + \lambda_{13} + \lambda_{14}) R_1 R_{a1} \cos(\varphi_1^+ - \varphi_{a1}^+) \\
&\qquad + (\lambda_{12} + \lambda_{23} + \lambda_{24}) R_2 R_{a2} \cos(\varphi_2^+ - \varphi_{a2}^+)] \\
&\qquad - (2/q)[(\lambda_{13} + \lambda_{23} + \lambda_{34}) G_1 G_{a1} \cos(\varphi_1^- - \varphi_{a1}^-) \\
&\qquad + (\lambda_{14} + \lambda_{24} + \lambda_{34}) G_2 G_{a2} \cos(\varphi_2^- - \varphi_{a2}^-)]\}, \qquad (9)
\end{aligned}
$$

where L is a scaling factor which does not depend on the phases.

Since

$$\sum_k C_k \cos(\varphi + \alpha_k) = Z \cos(\varphi + \xi),$$

where

$$Z^2 = \left[\sum_k C_k \cos\alpha_k\right]^2 + \left[\sum_k C_k \sin\alpha_k\right]^2$$

and

$$\tan\xi = \left[\sum_k C_k \sin\alpha_k\right] \Big/ \left[\sum_k C_k \cos\alpha_k\right],$$

we can rewrite (9) in a form more useful for practical applications:

$$
\begin{aligned}
&P(\varphi_1^+, \varphi_2^+, \varphi_1^-, \varphi_2^- | \ldots) \\
&\quad \approx L^{-1} \exp\{-(2/q)[\lambda_{12} R_1 R_2 \cos(\varphi_1^+ - \varphi_2^+) \\
&\qquad + \lambda_{13} R_1 G_1 \cos(\varphi_1^+ + \varphi_1^-) + \lambda_{14} R_1 G_2 \cos(\varphi_1^+ + \varphi_2^-) \\
&\qquad + \lambda_{23} R_2 G_1 \cos(\varphi_2^+ + \varphi_1^-) + \lambda_{24} R_2 G_2 \cos(\varphi_2^+ + \varphi_2^-) \\
&\qquad + \lambda_{34} G_1 G_2 \cos(\varphi_1^- - \varphi_2^-)] + (2/q)[R_1 Z_1^+ \cos(\varphi_1^+ - \xi_1^+) \\
&\qquad + R_2 Z_2^+ \cos(\varphi_2^+ - \xi_2^+) + G_1 Z_1^- \cos(\varphi_1^- - \xi_1^-) \\
&\qquad + G_2 Z_2^- \cos(\varphi_2^- - \xi_2^-)]\}, \qquad (10)
\end{aligned}
$$

where

$$
\begin{aligned}
Z_1^+ \cos\xi_1^+ &= [\lambda_{12} R_{a2} \cos\varphi_{a2}^+ + \lambda_{13} G_{a1} \cos\varphi_{a1}^- + \lambda_{14} G_{a2} \cos\varphi_{a2}^-, \\
&\quad - (\lambda_{12} + \lambda_{13} + \lambda_{14}) R_{a1} \cos\varphi_{a1}^+], \\
Z_1^+ \sin\xi_1^+ &= [+\lambda_{12} R_{a2} \sin\varphi_{a2}^+ - \lambda_{13} G_{a1} \sin\varphi_{a1}^- - \lambda_{14} G_{a2} \sin\varphi_{a2}^-, \\
&\quad - (\lambda_{12} + \lambda_{13} + \lambda_{14}) R_{a1} \sin\varphi_{a1}^+], \\
Z_2^+ \cos\xi_2^+ &= [\lambda_{12} R_{a1} \cos\varphi_{a1}^+ + \lambda_{23} G_{a1} \cos\varphi_{a1}^- + \lambda_{24} G_{a2} \cos\varphi_{a2}^-, \\
&\quad - (\lambda_{12} + \lambda_{23} + \lambda_{24}) R_{a2} \cos\varphi_{a2}^+], \\
Z_2^+ \sin\xi_2^+ &= [+\lambda_{12} R_{a1} \sin\varphi_{a1}^+ - \lambda_{23} G_{a1} \sin\varphi_{a1}^- - \lambda_{24} G_{a2} \sin\varphi_{a2}^-, \\
&\quad - (\lambda_{12} + \lambda_{23} + \lambda_{24}) R_{a2} \sin\varphi_{a2}^+], \\
Z_1^- \cos\xi_1^- &= [\lambda_{13} R_{a1} \cos\varphi_{a1}^+ + \lambda_{23} R_{a2} \cos\varphi_{a2}^+ + \lambda_{34} G_{a2} \cos\varphi_{a2}^-, \\
&\quad - (\lambda_{13} + \lambda_{23} + \lambda_{34}) G_{a1} \cos\varphi_{a1}^-], \\
Z_1^- \sin\xi_1^- &= [-\lambda_{13} R_{a1} \sin\varphi_{a1}^+ - \lambda_{23} R_{a2} \sin\varphi_{a2}^+ + \lambda_{34} G_{a2} \sin\varphi_{a2}^-, \\
&\quad - (\lambda_{13} + \lambda_{23} + \lambda_{34}) G_{a1} \sin\varphi_{a1}^-], \\
Z_2^- \cos\xi_2^- &= [\lambda_{14} R_{a1} \cos\varphi_{a1}^+ + \lambda_{24} R_{a2} \cos\varphi_{a2}^+ + \lambda_{34} G_{a1} \cos\varphi_{a1}^-, \\
&\quad - (\lambda_{14} + \lambda_{24} + \lambda_{34}) G_{a2} \cos\varphi_{a2}^-] \\
Z_2^- \sin\xi_2^- &= [-\lambda_{14} R_{a1} \sin\varphi_{a1}^+ - \lambda_{24} R_{a2} \sin\varphi_{a2}^+ + \lambda_{34} G_{a1} \sin\varphi_{a1}^-, \\
&\quad - (\lambda_{14} + \lambda_{24} + \lambda_{34}) G_{a2} \sin\varphi_{a2}^-].
\end{aligned}
$$

The coefficients Z_j^+, Z_j^-, ξ_j^+, ξ_j^- do not depend on the phases φ_i^+, φ_i^-, for $i, j = 1, 2$: they take into account the correlation among the phases φ_i and the phases φ_{aj} arising from the anomalous scatterers substructure. Equation (10) is the main result of this paper.

5. The conditional probability $P(\varphi_1^+ | E_{ai}^+, E_{ai}^-, R_i, G_i,\ i = 1, 2)$

The accurate derivation of $P(\varphi_1^+ | E_{ai}^+, E_{ai}^-, R_i, G_i, i = 1, 2)$ from (10) requires the progressive integration over φ_2^-, φ_2^+, φ_1^-. The first integration gives rise to

$$
\begin{aligned}
&P(\varphi_1^+, \varphi_2^+, \varphi_1^- | \ldots) \\
&\quad \approx L^{-1} \exp\{-(2/q)[\lambda_{12} R_1 R_2 \cos(\varphi_1^+ - \varphi_2^+) \\
&\qquad + \lambda_{13} R_1 G_1 \cos(\varphi_1^+ + \varphi_1^-) + \lambda_{23} R_2 G_1 \cos(\varphi_2^+ + \varphi_1^-)] \\
&\qquad + (2/q)[R_1 Z_1^+ \cos(\varphi_1^+ - \xi_1^+) + R_2 Z_2^+ \cos(\varphi_2^+ - \xi_2^+) \\
&\qquad + G_1 Z_1^- \cos(\varphi_1^- - \xi_1^-)]\} 2\pi I_0(S), \qquad (11)
\end{aligned}
$$

where I_0 is the modified Bessel function of order zero and

$$
\begin{aligned}
S^2 = 4G_2^2[&\lambda_{14}^2R_1^2+\lambda_{24}^2R_2^2+\lambda_{34}^2G_1^2+Z_2^{-2}\\
&+2\lambda_{14}\lambda_{24}R_1R_2\cos(\varphi_1^+-\varphi_2^+)\\
&+2\lambda_{14}\lambda_{34}R_1G_1\cos(\varphi_1^++\varphi_1^-)-2\lambda_{14}R_1Z_2^-\cos(\varphi_1^++\xi_2^-)\\
&+2\lambda_{24}\lambda_{34}G_1R_2\cos(\varphi_1^-+\varphi_2^+)-2\lambda_{24}R_2Z_2^-\cos(\varphi_2^++\xi_2^-)\\
&-2\lambda_{34}G_1Z_2^-\cos(\varphi_1^--\xi_2^-)].
\end{aligned}
$$

The integration of (11) over φ_1^- requires the approximation

$$I_0(S)\approx\exp(S^2/4). \tag{12}$$

Equation (12) is also necessary for the next integration over φ_2^+. The final result is the probability density

$$P(\varphi_1^+|\ldots)\approx L^{-1}\exp[\zeta(\varphi_1^+)], \tag{13}$$

where $\zeta(\varphi_1^+)$ is a quite intricate polynomial of order eight (in terms of R_i, G_i).

There are several reasons that discourage the use of (13): (*a*) P is very sensitive to experimental errors, owing to the high degree of ζ; (*b*) P should be a rough approximation of the true distribution. Indeed, (12) is only valid when S is sufficiently small, and this is not the case in practical applications: in fact, the quantities $|\lambda_{ij}/q|, Z_j^+/q, Z_j^-/q$ have the same order of magnitude as $(\sigma^2)^{-1}=\sum_N/\langle\mu^2\rangle$, which is expected to be a quite large number; (*c*) The procedure will provide worse results when more than two wavelengths are used: ζ shoud be a very complicated polynomial of order 12 for a three-wavelength case, and of order 16 for a four-wavelength case.

Two alternatives to the above procedure are indicated below:

(*a*) We vary φ_1^+ from zero to 2π. For each trial value of φ_1^+, the values of φ_2^+, φ_1^- and φ_2^- are derived (owing to the prior knowledge of φ_{ai}^+ and φ_{ai}^-, $i=1,2$):

$$
\begin{aligned}
\tan\varphi_2^+ &= \frac{R_1\sin\varphi_1^+ + R_{a2}\sin\varphi_{a2}^+ - R_{a1}\sin\varphi_{a1}^+}{R_1\cos\varphi_1^+ + R_{a2}\cos\varphi_{a2}^+ - R_{a1}\cos\varphi_{a1}^+},\\
\tan\varphi_1^- &= \frac{-R_1\sin\varphi_1^+ + G_{a1}\sin\varphi_{a1}^- + R_{a1}\sin\varphi_{a1}^+}{R_1\cos\varphi_1^+ + G_{a1}\cos\varphi_{a1}^- - R_{a1}\cos\varphi_{a1}^+},\\
\tan\varphi_2^- &= \frac{-R_1\sin\varphi_1^+ + G_{a2}\sin\varphi_{a2}^- + R_{a1}\sin\varphi_{a1}^+}{R_1\cos\varphi_1^+ + G_{a2}\cos\varphi_{a2}^- - R_{a1}\cos\varphi_{a1}^+}.
\end{aligned}
$$

The result is the probability density $P(\varphi_1|\ldots)$, calculated in the selected values between zero and 2π: standard numerical techniques provide the mean and the variance of the distribution. In particular, φ_1 is obtained by calculating

$$
\begin{aligned}
x^+ &= \int P(\varphi_1^+|\ldots)\cos\varphi_1^+\,\mathrm{d}\varphi_1^+,\\
y^+ &= \int P(\varphi_1^+|\ldots)\sin\varphi_1^+\,\mathrm{d}\varphi_1^+,\\
\theta_1^+ &= \tan^{-1}(y^+/x^+).
\end{aligned} \tag{14}
$$

θ_1^+ is the best estimate of φ_1^+. The classical figure of merit m^+, assessing the reliability of the estimate, is obtained as

$$m_1^+ = (x^{+2}+y^{+2}). \tag{15}$$

The above procedure (from now on PROC1) does not explore the full space $(\varphi_1^+,\varphi_1^-,\varphi_2^+,\varphi_2^-)$ but only a line of it, just the line around which that probability density is concentrated. To make a simple (ideal) example, let us consider (see Fig. 1) a two-dimensional case: $P(\varphi_1^+|\ldots)$ is evaluated from $P(\varphi_1^+,\varphi_2^+|\ldots)$. The plane $(\varphi_1^+,\varphi_2^+)$ is explored only along the full line in Fig. 1, where $P(\varphi_1^+,\varphi_2^+|\ldots)$ is concentrated. The line is very close to $\varphi_1^+=\varphi_2^+$: indeed, $P(\varphi_1^+,\varphi_2^+|\ldots)$ is vanishing in the regions where $\varphi_1^+\approx\varphi_2^+$ is highly violated.

(*b*) We assume in (9) that

$$\varphi_1^+=\varphi_2^+=-\varphi_1^-=-\varphi_2^-. \tag{16}$$

Then,

$$P(\varphi_1^+|\ldots)\approx[2\pi I_0(G_1^+)]^{-1}\exp[G_1^+\cos(\varphi_1^+-\theta_1^+)], \tag{17}$$

where

$$
\begin{aligned}
\tan\theta_1^+ &= \frac{c_1R_{a1}\sin\varphi_{a1}^+ + c_2R_{a2}\sin\varphi_{a2}^+ - c_3G_{a1}\sin\varphi_{a1}^- - c_4G_{a2}\sin\varphi_{a2}^-}{c_1R_{a1}\cos\varphi_{a1}^+ + c_2R_{a2}\cos\varphi_{a2}^+ + c_3G_{a1}\cos\varphi_{a1}^- + c_4G_{a2}\cos\varphi_{a2}^-}\\
&= \frac{T}{B},
\end{aligned} \tag{18}
$$

$$
\begin{aligned}
G_1^+ &= (T^2+B^2)^{1/2},\\
c_1 &= 2[\lambda_{12}(R_2-R_1)+\lambda_{13}(G_1-R_1)+\lambda_{14}(G_2-R_1)]/q,\\
c_2 &= 2[\lambda_{12}(R_1-R_2)+\lambda_{23}(G_1-R_2)+\lambda_{24}(G_2-R_2)]/q,\\
c_3 &= 2[\lambda_{34}(G_2-G_1)+\lambda_{13}(R_1-G_1)+\lambda_{23}(R_2-G_1)]/q,\\
c_4 &= 2[\lambda_{34}(G_1-G_2)+\lambda_{14}(R_1-G_2)+\lambda_{24}(R_2-G_2)]/q.
\end{aligned} \tag{19}
$$

Equation (17) is a von Mises distribution: it is unimodal, θ_1^+ is the most probable value of φ_1^+ and G_1^+ is the concentration parameter.

The two proceduces for phase estimation involve different approximations. The formulas (17)–(19) are more fascinating: their application is very easy and they show how the probabilistic estimates depend on the diffraction moduli differences. However, the assumption (16) is not always valid: it may be violated mostly when the moduli R_a and G_a are comparable with the moduli R and G. Since R_a and G_a are usually small with respect to R and G, largest errors in the phase estimates are expected for small R and G moduli. This is not crucial for the success of the phasing process.

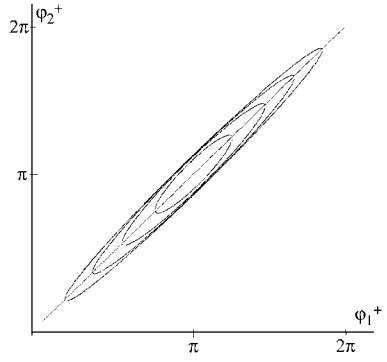

Figure 1
Probablility contours of the probability distribution (ideal case) $P(\varphi_1^+,\varphi_2^+|\ldots)$.

6. Experimental tests

To check the correctness of our probabilistic approach, we first applied our conclusive formulas [*i.e.* equations (14)–(15) and (17)–(19)] to the calculated (without error) data of 1SRV (Walsh *et al.*, 1999), space group $C222_1$, a = 63.470, b = 65.960,

Table 1
1SRV: expected $\Delta f'$ and f'' values for each λ value.

λ	$\Delta f'$	f''
1.1271	−1.805	0.646
0.9793	−8.582	3.843
0.9791	−7.663	3.841
0.9465	−2.618	3.578

Table 2
SRV calculated data, acentric reflections.

Estimates according to formulas (14) and (15). NR is number of reflections for which $m^+ >$ ARG, $\langle|\Delta\varphi|\rangle$ is the average phase error of the estimates.

ARG	NR	$\langle|\Delta\varphi|\rangle$ (°)
0.00	6345	20.32
0.05	4233	12.51
0.20	1980	8.31
0.35	1217	6.68
0.50	855	5.56
0.65	586	4.78
0.80	383	3.80
0.95	97	2.29

Table 3
1SRV calculated data, acentric reflections.

Estimates according to formulas (17)–(19). NR is the number of phased reflections under various conditions, $\langle|\Delta\varphi|\rangle^\circ$ is the average phase error of the estimates.

	Conditions		
	$R_1 > 0.0$	$R_1 > 0.2$	$R_1 < 0.2$
NR	6345	6090	255
$\langle|\Delta\varphi|\rangle$ (°)	2.69	2.37	10.53

Table 4
1SRV experimental data.

Number of phased reflections and corresponding phase errors for the pairs of wavelengths λ_i–λ_j accordingly to equations (17)–(19) (rows 2 and 3) and to *MLPHARE* (rows 4 and 5)

i–*j*	1–2	1–3	1–4	2–3	2–4	3–4
NR	7125	7149	7193	7552	7178	7203
ERR(W-ERR)	72 (62)	68 (59)	78 (70)	74 (66)	71 (62)	70 (62)
NR	6879	7059	4999	7047	7028	7003
ERR(W-ERR)	70 (60)	66 (55)	88 (82)	80 (69)	71 (61)	65 (54)

$c = 75.030$ Å, 1186 non-hydrogen atoms and 3 Se atoms in the asymmetric unit. The crystal structure solution was originally undertaken to push MAD to the extreme, that is to check the feasibility of ultrafast protein crystal structure solution. The positions of the two Se atoms were found automatically using a Patterson technique implemented in the program *RSPS* in the CCP4 suite (Collaborative Computation Project, Number 4, 1994) and refined by the program *MLPHARE* of the same CCP4 suite. A subsequent test by *CNS* (Brünger *et al.*, 1998) revealed the third Se site, which turned out to be disordered (B factor refined to 62.4 Å^2). Multiwavelength data were collected by Walsh *et al.* (1999) up to 1.70 Å resolution: we used for our tests the wavelengths λ_i and the expected parameters $\Delta f_i'$ and f_i'' quoted in Table 1. Structure factors were calculated for the 7589 (centric and acentric) reflections. To avoid singularities in our probabilistic equations (14)–(15) and (17)–(19), we assumed $e = 1 + (0.1|E_{\rm calc}|)^2$. We note that the two-wavelength case is algebraically determined in the absence of errors: therefore, the calculations of the joint probability distribution $P(F_1^+, F_2^+, F_1^-, F_2^-|F_a^+, F_a^-)$ needs the introduction of the supplementary error variable μ to avoid singularities. The results of our tests are shown in Table 2 for equations (14) and (15) and in Table 3 for equations (17)–(19): for both the tables we used the pair λ_1–λ_3. In Table 2, we give the number of reflections with $m^+ >$ ARG and the corresponding average phase error ($\langle|\Delta\varphi|\rangle$ measures the discrepancy between estimated and published phases). Errors larger than 10° are only found at very low values of m^+. In Table 3, we show the average phase error for a number of reflections selected according to various conditions. The error is larger than 10° only at very small R_1 values. The comparison of Table 2 with Table 3 suggests that equations (17)–(19) are more efficient than (14)–(15): these last equations will not be employed in the next calculations.

Formulas (17)–(19) have been applied to 1SRV experimental data for each pair of wavelengths. In Table 4, we give the number of phased reflections (NR) and the relative unweighted and weighted phase errors (ERR and W-ERR, respectively). The corresponding values obtained by applying *MLPHARE* to the experimental data are shown in the last two lines of the tables. We observe that equations (17)–(19) have the following properties.

(*a*) They have been derived without taking into account the correlations of the errors at different wavelengths. Since such errors are usually highly correlated, disregarding them reduces the efficiency of our equations. However, our probabilistic approach can take error correlation into account: in this case the matrix (5) would no more assume the form of a block-diagonal matrix.

(*b*) They have been applied without a previous refinement of the $\Delta f'$ and f'' values quoted in Table 1 and of the occupancy of the Se atoms. Parameter refinement can add efficiency to the formulas but requires the integration of our approach with a specific refinement program still not available.

In spite of the above two handicaps, the phase errors relative to (17)–(19) are competitive with those obtained *via* *MLPHARE*. A future paper will be devoted to the n-wavelength case and the correlation of the errors by fully integrating our approach with a refinement procedure.

7. Conclusions

A new probabilistic approach has been described aiming at phasing structure factors under the assumption that the anomalous scattering substructure is known. The two-wavelength case has been studied and simple and appealing formulas have been derived. The approach may be easily

extended to treat the multiwavelength case: this will be the subject of a future paper.

APPENDIX *A*

The value of $\det(\boldsymbol{\lambda})$ in equation (4) and the estimate of the elements of the matrix $\boldsymbol{\lambda}^{-1}$ may be obtained *via* the following theorem: if $\mathbf{D}$ is a diagonal matrix of order m whose ith diagonal element is d_i and $\mathbf{g}$ is an $m \times 1$ column matrix, then

$$\det(\mathbf{D} + \mathbf{g}\bar{\mathbf{g}}) = \det(\mathbf{D})\left\{1 + \sum_{i=1}^{m} g_i^2/d_i\right\}.$$

Let us denote

$$\mathbf{G} = [(e_1^+)^{-1/2}, (e_2^+)^{-1/2}, (e_1^-)^{-1/2}, (e_2^-)^{-1/2}],$$
$$d_1 = (\sigma_1^+)^2/e_1^+, d_2 = (\sigma_2^+)^2/e_2^+, d_3 = (\sigma_1^-)^2/e_1^-, d_4 = (\sigma_2^-)^2/e_2^-.$$

Then [see (5)],

$$\det(\mathbf{Q}_1) = \frac{\sigma_1^{+2}\sigma_2^{+2}\sigma_1^{-2}\sigma_2^{-2}}{e_1^+e_2^+e_1^-e_2^-}\left(1 + \frac{1}{\sigma_1^{+2}} + \frac{1}{\sigma_2^{+2}} + \frac{1}{\sigma_1^{-2}} + \frac{1}{\sigma_2^{-2}}\right).$$

By analogy denote

$$\mathbf{G} = [(e_1^+)^{-1/2}, (e_2^+)^{1/2}, -(e_1^-)^{-1/2}, -(e_2^-)^{-1/2}]$$
$$d_1 = (\sigma_1^+)^2/e_1^+, d_2 = (\sigma_2^+)^2/e_2^+, d_3 = (\sigma_1^-)^2/e_1^-, d_4 = (\sigma_2^-)^2/e_2^-.$$

Then

$$\det(\mathbf{Q}_2) = \det(\mathbf{Q}_1)$$

and

$$\det(\boldsymbol{\lambda}) = [\det(\mathbf{Q}_1)]^2.$$

The elements Λ_{ij} of the matrix $\mathbf{k}^{-1}$ may be obtained by observing that

$$\mathbf{k}^{-1} = \begin{vmatrix} \mathbf{Q}_1^{-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{Q}_2^{-1} \end{vmatrix}.$$

Accordingly,

$$\begin{aligned}
&\Lambda_{11} = e_1^+\lambda_{11}/q, && \Lambda_{22} = e_2^+\lambda_{22}/q,\\
&\Lambda_{33} = e_1^-\lambda_{33}/q, && \Lambda_{44} = e_2^-\lambda_{44}/q,\\
&\Lambda_{12} = (e_1^+e_2^+)^{1/2}\lambda_{12}/q, && \Lambda_{13} = (e_1^+e_1^-)^{1/2}\lambda_{13}/q,\\
&\Lambda_{14} = (e_1^+e_2^-)^{1/2}\lambda_{14}/q, && \Lambda_{23} = (e_2^+e_1^-)^{1/2}\lambda_{23}/q,\\
&\Lambda_{24} = (e_2^+e_2^-)^{1/2}\lambda_{24}/q, && \Lambda_{34} = (e_1^-e_2^-)^{1/2}\lambda_{34}/q,
\end{aligned}$$

$$\Lambda_{4+i,4+i} = \Lambda_{ii} \quad \text{for} \quad i = 1, \ldots, 4,$$
$$\Lambda_{56} = \Lambda_{12}, \quad \Lambda_{57} = -\Lambda_{13}, \quad \Lambda_{58} = -\Lambda_{14},$$
$$\Lambda_{67} = -\Lambda_{23}, \quad \Lambda_{68} = -\Lambda_{24}, \quad \Lambda_{78} = -\Lambda_{38},$$

$$\begin{aligned}
q &= \sigma_1^{+2}\sigma_2^{+2}\sigma_1^{-2}\sigma_2^{-2} + \sigma_1^{-2}\sigma_2^{+2}\sigma_2^{-2} + \sigma_1^{+2}\sigma_2^{+2}\sigma_2^{-2}\\
&\quad + \sigma_1^{+2}\sigma_1^{-2}\sigma_2^{-2} + \sigma_1^{+2}\sigma_1^{-2}\sigma_2^{+2},\\
\lambda_{11} &= \sigma_1^{-2}\sigma_2^{+2}\sigma_2^{-2} + \sigma_1^{-2}\sigma_2^{-2} + \sigma_1^{-2}\sigma_2^{+2} + \sigma_2^{+2}\sigma_2^{-2},\\
\lambda_{22} &= \sigma_1^{+2}\sigma_1^{-2}\sigma_2^{-2} + \sigma_1^{+2}\sigma_1^{-2} + \sigma_1^{+2}\sigma_2^{-2} + \sigma_1^{-2}\sigma_2^{-2},\\
\lambda_{33} &= \sigma_1^{+2}\sigma_2^{+2}\sigma_2^{-2} + \sigma_1^{+2}\sigma_2^{+2} + \sigma_1^{+2}\sigma_2^{-2} + \sigma_2^{+2}\sigma_2^{-2},\\
\lambda_{44} &= \sigma_1^{+2}\sigma_2^{+2}\sigma_1^{-2} + \sigma_1^{+2}\sigma_2^{+2} + \sigma_1^{+2}\sigma_1^{-2} + \sigma_2^{+2}\sigma_1^{-2},
\end{aligned}$$

$$\begin{aligned}
\lambda_{12} &= -\sigma_1^{-2}\sigma_2^{-2}, \quad \lambda_{13} = -\sigma_2^{+2}\sigma_2^{-2},\\
\lambda_{14} &= -\sigma_2^{+2}\sigma_1^{-2}, \quad \lambda_{23} = -\sigma_1^{+2}\sigma_2^{-2},\\
\lambda_{24} &= -\sigma_1^{+2}\sigma_1^{-2}, \quad \lambda_{34} = -\sigma_1^{+2}\sigma_2^{+2}.
\end{aligned}$$

APPENDIX *B*

From

$$\begin{aligned}
&[(A_1^+ - A_{a1}^+) - (A_2^+ - A_{a2}^+)]^2\\
&\quad = (A_1^+ - A_{a1}^+)^2 + (A_2^+ - A_{a2}^+)^2 - 2(A_1^+ - A_{a1}^+)(A_2^+ - A_{a2}^+),\\
&[(B_1^+ - B_{a1}^+) - (B_2^+ - B_{a2}^+)]^2\\
&\quad = (B_1^+ - B_{a1}^+)^2 + (B_2^+ - B_{a2}^+)^2 - 2(B_1^+ - B_{a1}^+)(B_2^+ - B_{a2}^+),
\end{aligned}$$

the relation

$$\begin{aligned}
&2[(A_1^+ - A_{a1}^+)(A_2^+ - A_{a2}^+) + (B_1^+ - B_{a1}^+)(B_2^+ - B_{a2}^+)]\\
&\quad = (A_1^+ - A_{a1}^+)^2 + (A_2^+ - A_{a2}^+)^2 + (B_1^+ - B_{a1}^+)^2\\
&\qquad + (B_2^+ - B_{a2}^+)^2 - [(A_1^+ - A_{a1}^+) - (A_2^+ - A_{a2}^+)]^2\\
&\qquad - [(B_1^+ - B_{a1}^+) - (B_2^+ - B_{a2}^+)]^2.
\end{aligned}$$

Similarly, from

$$\begin{aligned}
&[(A_1^+ - A_{a1}^+) - (A_1^- - A_{a1}^-)]^2\\
&\quad = (A_1^+ - A_{a1}^+)^2 + (A_1^- - A_{a1}^-)^2 - 2(A_1^+ - A_{a1}^+)(A_1^- - A_{a1}^-),\\
&[(B_1^+ - B_{a1}^+) + (B_1^- - B_{a1}^-)]^2\\
&\quad = (B_1^+ - B_{a1}^-)^2 + (B_1^- - B_{a1}^-)^2 + 2(B_1^+ - B_{a1}^+)(B_1^- - B_{a1}^-),
\end{aligned}$$

the relation

$$\begin{aligned}
&2[(A_1^+ - A_{a1}^+)(A_1^- - A_{a1}^-) - (B_1^+ - B_{a1}^+)(B_1^- - B_{a1}^-)]\\
&\quad = (A_1^+ - A_{a1}^+)^2 + (A_1^- - A_{a1}^-)^2 + (B_1^+ - B_{a1}^+)^2\\
&\qquad + (B_1^- - B_{a1}^-)^2 - [(A_1^+ - A_{a1}^+) - (A_1^- - A_{a1}^-)]^2\\
&\qquad - [(B_1^+ - B_{a1}^+) - (B_1^- - B_{a1}^-)]^2.
\end{aligned}$$

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