

Acta Crystallographica Section A

**Foundations of  
Crystallography**

ISSN 0108-7673

Editor: **D. Schwarzenbach**

## **The mean-square Friedel intensity difference in $P1$ with a centrosymmetric substructure**

**H. D. Flack and U. Shmueli**

Copyright © International Union of Crystallography

Author(s) of this paper may load this reprint on their own web site provided that this cover page is retained. Republication of this article or its storage in electronic databases or the like is not permitted without prior permission in writing from the IUCr.

# The mean-square Friedel intensity difference in $P1$ with a centrosymmetric substructure

H. D. Flack<sup>a\*</sup> and U. Shmueli<sup>b</sup>

<sup>a</sup>Laboratoire de Cristallographie, University of Geneva, Switzerland, and <sup>b</sup>School of Chemistry, Tel Aviv University, Israel. Correspondence e-mail: howard.flack@cryst.unige.ch

For non-centrosymmetric structures in space group  $P1$  containing a centrosymmetric substructure, analytical expressions have been obtained for various functions of the diffraction intensity of Friedel opposites. These functions are the average intensity of Friedel opposites, the mean difference in intensity of Friedel opposites and the mean-square difference in intensity of Friedel opposites. A Bijvoet intensity ratio is defined for the evaluation of resonant-scattering effects in non-centrosymmetric and pseudo-centrosymmetric structures. Analysis of these expressions confirms that both resonant and non-resonant atoms are necessary to produce differences in intensity between Friedel opposites and also shows that in some circumstances atoms may lie on a centrosymmetric substructure without diminishing the Bijvoet intensity ratio. The effects of the real component of resonant scattering, of the variation of the scattering factors with  $\sin \theta/\lambda$ , of isotropic atomic displacement parameters, of a crystal twinned by inversion, of atoms in special positions and of weak reflections are considered. Software is available for the evaluation of the Bijvoet intensity ratio.

© 2007 International Union of Crystallography  
Printed in Singapore – all rights reserved

## 1. Introduction

It is useful to be able to make *a priori* estimates of the average intensity difference between Friedel opposites prior to experimentation. Such estimates may be used to select the most suitable compound or derivative and to optimize the choice of wavelength of the radiation. In the field of biological crystallography, one wishes to know whether it is in principle possible to solve the crystal structure using techniques such as MAD and SAD especially if it is intended to rely only on the resonant-scattering (anomalous diffraction) effects from the S atoms in the native protein. The article of Dauter (2006) treats the practical applications of such matters in protein crystallography where often the elemental composition of a salt-soaked protein crystal is not known. In the area of chemical and organo-metallic crystallography, it is the question of the possibility of absolute-configuration determination which is the driving force for the need for an *a priori* estimate. Flack *et al.* (2006) have found for a limited class of compounds that the standard uncertainty of the Flack (1983) parameter obtained by least-squares refinement shows a clear dependence on the estimate of  $\langle |\Delta F| \rangle / \langle F \rangle$  given by a formula of Girard *et al.* (2003).

Various formulae for estimating  $\langle |\Delta F| \rangle / \langle F \rangle$  of Friedel opposites may be found in the literature. All derivations are based on the approach of Crick & Magdoff (1956) for the estimation of mean structure-factor-amplitude differences between an isomorphous derivative and a native protein. Moreover, available formulae are all based on the hypothesis

of a non-centrosymmetric crystal structure without pseudo-symmetry containing few types of resonant scatterers in a sea of non-resonant scatterers. In particular, Hendrikson & Teeter (1981) gave an approximate formula for a single resonant scatterer in a molecule as part of their determination of the structure of crambin using resonant-scattering techniques. Olczak *et al.* (2003) give a formula applicable to two kinds of resonant scatterer, and Weiss *et al.* (2001) and Girard *et al.* (2003) extended the estimate to include any number of resonant scatterers. Shen *et al.* (2003) treat differences in atomic displacement parameters between heavy and light atoms, and also show how allowance may be made for certain structural features (*e.g.* disulfide bridge or metal cluster) in the resonant part of the structure. A practical application to phasing protein structures by way of  $\text{Ta}_6\text{Br}_{12}$  clusters is presented by Banumathi *et al.* (2003). Zwart (2005) gives a thorough review of resonant signal indicators in protein crystallography and provides a Monte Carlo procedure for their estimation.

Although the formula of Girard *et al.* (2003) gave significant results in the study of Flack *et al.* (2006), it is apparent that it has shortcomings if applied outside its intended domain of application. In particular, it gives the same estimate of mean Friedel difference whether the crystal structure is non-centrosymmetric, centrosymmetric or pseudo-centrosymmetric. Also it may give large estimates of Friedel differences where in practice none exist. For example, in the spherical-atom approximation there is no difference in intensity between Friedel opposites for elemental Se in its helical chiral crystal structure. Consequently, we decided to reanalyse the

intensity differences between Friedel opposites from first principles with as few approximations as possible for the case of a non-centrosymmetric structure in space group  $P1$  but containing a centrosymmetric substructure. All atoms present in the compound are allowed to display resonant scattering.

## 2. Analysis

The unit cell of the crystal contains  $N$  atoms, of which  $M$  atoms are arranged non-centrosymmetrically,  $Q$  are arranged centrosymmetrically with  $N = Q + M$ , the centre of symmetry applicable to the  $Q$  atoms being placed at the origin of a primitive basis. We choose to number the atoms starting from the  $Q$  centrosymmetrically arranged atoms and finishing with the  $M$  non-centrosymmetrical ones. Thus atoms 1 to  $Q$  are arranged centrosymmetrically and atoms  $Q + 1$  to  $N$  are arranged non-centrosymmetrically. Moreover, atoms  $i$  and  $i + Q/2$  for  $1 \leq i \leq Q/2$  are centrosymmetrically related. Let  $\mathbf{x}_j$  be the vector of coordinates of the  $j$ th atom. Let the real non-resonant contribution to the scattering factor of the  $j$ th atom be  $f_j$  with the imaginary component of the resonant scattering being  $f_j''$ . In order to concentrate on the essentials of the analysis, we initially make several simplifying assumptions.

- (i) The real component of the resonant scattering is ignored.
- (ii) All theory and calculations are undertaken in the spherical-atom approximation at  $\sin \theta/\lambda = 0$ , where for X-ray scattering  $f_j = Z_j$  the atomic number of the  $j$ th atom.
- (iii) The structure is not disordered and all site occupation factors are unity.
- (iv) The crystal is monodomain and not twinned by inversion.
- (v) All the atoms are located in general positions, *i.e.* no atom is located on a centre of symmetry of the  $Q$  atoms.

The analysis is completed in §4 by consideration of the ways to remove these simplifications.

We write the complex structure factor  $\mathbf{F}(\mathbf{h})$  of reflection  $\mathbf{h}$  as  $\mathbf{F}(\mathbf{h}) = \mathbf{F}_C(\mathbf{h}) + \mathbf{F}_N(\mathbf{h})$ , where  $\mathbf{F}_C(\mathbf{h})$  and  $\mathbf{F}_N(\mathbf{h})$  represent respectively the contributions from the centrosymmetric and non-centrosymmetric substructures,

$$\mathbf{F}_C(\mathbf{h}) = 2 \sum_{j=1}^{Q/2} (f_j + if_j'') \cos(2\pi\mathbf{h} \cdot \mathbf{x}_j),$$

$$\mathbf{F}_N(\mathbf{h}) = \sum_{j=Q+1}^N (f_j + if_j'') [\cos(2\pi\mathbf{h} \cdot \mathbf{x}_j) + i \sin(2\pi\mathbf{h} \cdot \mathbf{x}_j)].$$

Setting  $c_j = \cos(2\pi\mathbf{h} \cdot \mathbf{x}_j)$ ,  $s_j = \sin(2\pi\mathbf{h} \cdot \mathbf{x}_j)$ ,

$$\begin{aligned} C_C &= 2 \sum_{j=1}^{Q/2} f_j c_j, & C_N &= \sum_{j=Q+1}^N f_j c_j, & C &= C_C + C_N = \sum_{j=1}^N f_j c_j, \\ C_C'' &= 2 \sum_{j=1}^{Q/2} f_j'' c_j, & C_N'' &= \sum_{j=Q+1}^N f_j'' c_j, & C'' &= C_C'' + C_N'' = \sum_{j=1}^N f_j'' c_j, \\ S &= \sum_{j=Q+1}^N f_j s_j, & S'' &= \sum_{j=Q+1}^N f_j'' s_j \end{aligned}$$

and expanding gives

$$\mathbf{F}(\mathbf{h}) = C_C + C_N + iC_C'' + iC_N'' + iS - S'' = C + iC'' + iS - S'' \quad (1)$$

In the structure factor of the antireflection  $-\mathbf{h}$ , the *sine* terms change sign giving  $\mathbf{F}(-\mathbf{h}) = C + iC'' - iS + S''$ . In the model of a monodomain single crystal, the mean intensity of Friedel opposites  $\mathbf{h}$  and  $-\mathbf{h}$  is given by

$$\begin{aligned} A(\mathbf{h}) &= \frac{1}{2} (|\mathbf{F}(\mathbf{h})|^2 + |\mathbf{F}(-\mathbf{h})|^2) \\ &= \frac{1}{2} [(C - S'')^2 + (C'' + S)^2] + \frac{1}{2} [(C + S'')^2 + (C'' - S)^2] \\ &= C^2 + S^2 + C''^2 + S''^2, \end{aligned} \quad (2)$$

and the difference in intensity between Friedel opposites  $\mathbf{h}$  and  $-\mathbf{h}$  is given by

$$D(\mathbf{h}) = |\mathbf{F}(\mathbf{h})|^2 - |\mathbf{F}(-\mathbf{h})|^2 = 4(C''S - CS''). \quad (3)$$

### 2.1. Average values

We now proceed to the calculation of mean values  $\langle A \rangle$ ,  $\langle D \rangle$ ,  $\langle D^2 \rangle$  of  $A(\mathbf{h})$ ,  $D(\mathbf{h})$ ,  $D^2(\mathbf{h})$ , respectively, the mean being taken assuming uniform and uncorrelated probability density functions of the  $\mathbf{h} \cdot \mathbf{x}_j$ . This implies either fixed  $hkl$  and uniformly distributed atomic coordinates *or* fixed atomic coordinates and a large number of reflections.

From (1) and (2), the average intensity of Friedel opposites is given by

$$\begin{aligned} \langle A \rangle &= \langle A(\mathbf{h}) \rangle = \langle C^2 \rangle + \langle S^2 \rangle + \langle C''^2 \rangle + \langle S''^2 \rangle \\ &= \langle C_C^2 \rangle + \langle C_N^2 \rangle + 2\langle C_C C_N \rangle + \langle S^2 \rangle + \langle C_C''^2 \rangle \\ &\quad + \langle C_N''^2 \rangle + 2\langle C_C'' C_N'' \rangle + \langle S''^2 \rangle. \end{aligned} \quad (4)$$

The details of the derivation of the mean values are given in Appendix A and leads to a result one would anticipate from Wilson's statistics:

$$\langle A \rangle = \sum_{j=1}^N f_j^2 + \sum_{j=1}^N f_j''^2. \quad (5)$$

From (3), and noting that  $D(\mathbf{h}) = -D(-\mathbf{h})$ , we show it is clear that  $\langle D \rangle = 0$ . Also from (3), the squared intensity difference between Friedel opposites is given by  $D^2(\mathbf{h}) = 16(C^2 S''^2 + S^2 C''^2 - 2CS C'' S'')$ , and from (1)

$$\begin{aligned} \frac{1}{16} \langle D^2 \rangle &= \frac{1}{16} \langle D^2(\mathbf{h}) \rangle \\ &= \langle C_C^2 S''^2 \rangle + \langle C_N^2 S''^2 \rangle + 2\langle C_C C_N S''^2 \rangle + \langle S^2 C_C''^2 \rangle \\ &\quad + \langle S^2 C_N''^2 \rangle + 2\langle S^2 C_C'' C_N'' \rangle - 2\langle C_C S C_C'' S'' \rangle \\ &\quad - 2\langle C_N S C_N'' S'' \rangle - 2\langle C_C S C_N'' S'' \rangle - 2\langle C_N S C_C'' S'' \rangle. \end{aligned} \quad (6)$$

The details of the derivation of the mean values are given in Appendix A and leads to

$$\langle D^2 \rangle = 4 \sum_{j=1}^N \sum_{l=1}^N (f_j f_l'' - f_l f_j'')^2 - 4 \sum_{j=1}^Q \sum_{l=1}^Q (f_j f_l'' - f_l f_j'')^2. \quad (7)$$

Appendix B presents the derivation of  $\langle A_z \rangle$  and  $\langle D_z^2 \rangle$ , similar to  $\langle A \rangle$  and  $\langle D^2 \rangle$ , but based on normalized rather than ordinary structure factors.

## 2.2. Bijvoet intensity ratio

The formula of Girard *et al.* (2003) for the estimation of Friedel-difference effects resulted from a derivation of  $\langle |\Delta F| \rangle / \langle F \rangle$ . We can proceed in the same manner to obtain a value based on intensities rather than structure-factor amplitudes by using (5) and (7):

$$\begin{aligned} \chi &= \langle D^2 \rangle^{1/2} / \langle A \rangle \\ &= 2 \left[ \sum_{j=1}^N \sum_{l=1}^N (f_j f_l'' - f_l f_j'')^2 - \frac{Q}{j=1} \frac{Q}{l=1} \sum_{j=1}^Q \sum_{l=1}^Q (f_j f_l'' - f_l f_j'')^2 \right]^{1/2} \\ &\quad \times \left( \sum_{j=1}^N f_j^2 + \sum_{j=1}^N f_j'^2 \right)^{-1/2}. \end{aligned} \quad (8)$$

Appendix B shows that for  $\chi_z$ , based on normalized rather than ordinary structure factors,  $\chi_z = \langle D_z^2 \rangle^{1/2} = \chi$ , implying that  $\chi$  is already correctly normalized.

## 3. Behaviour of mean-square Friedel intensity difference and Bijvoet intensity ratio

Equation (7) is the principal result of this analysis. It is an exact form of two previous approximate analyses. Flack & Bernardinelli (1999) showed that both resonant and non-resonant atoms were necessary for giving intensity differences between Friedel opposites. Further, Flack *et al.* (2006) undertook a preliminary analysis of the effect of a centrosymmetric substructure on Friedel differences. Equation (7) of Olczak *et al.* (2003), applicable to two kinds of resonant scatterer, is the only one known to us in the literature containing the all important difference factor  $(f_j f_l'' - f_l f_j'')$ .

Taking (7) as written, the first term corresponds to having all atoms arranged non-centrosymmetrically and the second term reduces the value of  $\langle D^2 \rangle$  for those atoms which are arranged centrosymmetrically. From (7), it is clear that the largest value is obtained when all the atoms are arranged non-centrosymmetrically, *i.e.*  $M = N$ ,  $Q = 0$ , and a zero value applies when all atoms are arranged centrosymmetrically, *i.e.*  $M = 0$ ,  $Q = N$ . The form of (7) with two sums of quadratic terms ensures that a partially centrosymmetric structure will take a value of  $\langle D^2 \rangle$  intermediate between that of an entirely non-centrosymmetric structure and that of a centrosymmetric structure of the same chemical composition.

If all atoms are of the same type, *i.e.* the same chemical element, all terms  $(f_j f_l'' - f_l f_j'') = 0$  in (7) and (8), and  $\langle D^2 \rangle$  is zero in the spherical-atom approximation regardless of whether the structure is centrosymmetric or non-centrosymmetric. This corresponds to the results of McIntyre (1978), who carried out a full analysis of the Friedel intensity differences in a chiral crystal structure of elemental Se. In the case of the crystal structure of a chemical element, the form of the terms  $(f_j f_l'' - f_l f_j'')$  does not allow any diffraction contrast between atoms in the intensity difference between Friedel opposites despite a large imaginary resonant-scattering contribution as in the case of Se.

It is instructive to write the principal factors in (7) as  $(f_j f_l'' - f_l f_j'') = f_j f_l (f_l''/f_l - f_j''/f_j)$ , from which it can be seen that Friedel intensity differences are conditioned by differences between the imaginary parts of the resonant scattering of an atom relative to their own non-resonant scattering. Thus in a very real way H atoms help to augment the difference in intensity of Friedel opposites although the imaginary component of their resonant scattering contribution is zero. As an example, let us now see how the intensity differences between Friedel opposites appear in the case of a crystal structure containing two atom types. As an example, we use the hydrocarbon decane ( $C_{10}H_{22}$ ) studied with Cu  $K\alpha$  radiation.  $10^4 \chi$  in (8) takes a value of zero if only the C atoms or only the H atoms are taken into consideration. It also takes a value of zero if all atoms are arranged centrosymmetrically. With all atoms in a non-centrosymmetric arrangement, the value of  $10^4 \chi$  is 10 and it remains at 10 if either any or all of the C atoms or any or all of the H atoms are placed on a centrosymmetric substructure. In the general case of  $T$  atom types, the diffraction contrast is undiminished if any or all of the atoms of one type are arranged centrosymmetrically.

As a further example, take the case of the compound of composition  $C_5H_{11}Cl_2NO_2PtS$  whose CSD refcode is OCARAL (Llorca *et al.*, 2001). This was one of those pseudo-centrosymmetric structures used in the study of Flack *et al.* (2006) on centrosymmetric and pseudo-centrosymmetric structures refined as being non-centrosymmetric. Its crystal structure was determined to be in space group  $P1$  with  $Z = 2$  and gave a *PLATON* (Spek, 2003) fit parameter for space group  $P\bar{1}$  of 100% (see Flack *et al.*, 2006, for details). The structure was deemed to be non-centrosymmetric on account of the proven enantiopurity of the bulk compound, there being just one chiral C centre in the molecule. The value of  $10^4 \chi$  with all atoms being arranged non-centrosymmetrically is 1054. Although the molecule has no symmetry of its own, in the crystal structure two molecules are arranged approximately centrosymmetrically. On taking a worst-case situation that all atoms apart from the chiral C atoms in the two molecules of the asymmetric unit are arranged centrosymmetrically, the value of  $10^4 \chi$  drops to 193. This is a considerable reduction but nevertheless  $10^4 \chi$  is still appreciable. On carrying out the superposition of one molecule of the asymmetric unit with the inverted image of the other, a more reasonable approximation to the number of non-centrosymmetric atoms is  $C_2H_7$  giving  $10^4 \chi = 286$  or  $C_2H_7N$  giving  $10^4 \chi = 364$ . Another approach to the symmetry of OCARAL could be intensity statistics. Wilson's (1949) statistics would most probably indicate that OCARAL is non-centrosymmetric (*e.g.* the experimental fourth moment of  $|E|$  would be closer to 2 than to 3). However, the presence of the outstandingly heavy Pt atom would invalidate this statistic (*e.g.* Shmueli & Wilson, 1981) and it is interesting to find out if the exact symmetry- and composition-dependent probability density functions (p.d.f.s) of  $|E|$  (Shmueli *et al.*, 1984) would show the correct symmetry. There is a related example in the latter reference which supports such an application.

#### 4. Further analysis

We now return to the extension of (7) in terms of atom types, and to allow for the real component of resonant scattering, for the variation of scattering factors with  $\sin \theta/\lambda$ , for isotropic atomic displacement parameters, for atomic site occupation parameters, for crystals twinned by inversion and for atoms occupying special positions.

##### 4.1. Mean-square Friedel intensity difference in terms of atom types

Equation (7) for  $\langle D^2 \rangle$  is given in terms of sums over the individual atoms whereas sums over atom types (chemical elements) would provide a useful simplification. So suppose that  $N_j^a$  is the total number of atoms of type  $j$ ,  $Q_j^a$  is the number of centrosymmetrically arranged atoms of type  $j$  and  $T$  is the number of atom types in the structure. By substitution in (7),

$$\langle D^2 \rangle = 4 \sum_{j=1}^T \sum_{l=1}^T N_j^a N_l^a (f_j f_l'' - f_l f_j'')^2 - 4 \sum_{j=1}^T \sum_{l=1}^T Q_j^a Q_l^a (f_j f_l'' - f_l f_j'')^2. \quad (9)$$

On expanding the quadratic terms in (9) and rearranging, one obtains

$$\begin{aligned} \langle D^2 \rangle &= 4 \sum_{j=1}^T Y_j - 4 \sum_{j=1}^T V_j; \\ Y_j &= (N_j^a f_j^2) \sum_{l=1}^T N_l^a f_l''^2 \\ &\quad - 2(N_j^a f_j f_j'') \sum_{l=1}^T N_l^a f_l f_l'' + (N_j^a f_j''^2) \sum_{l=1}^T N_l^a f_l^2; \\ V_j &= (Q_j^a f_j^2) \sum_{l=1}^T Q_l^a f_l''^2 \\ &\quad - 2(Q_j^a f_j f_j'') \sum_{l=1}^T Q_l^a f_l f_l'' + (Q_j^a f_j''^2) \sum_{l=1}^T Q_l^a f_l^2. \end{aligned} \quad (10)$$

##### 4.2. Real component of resonant scattering

Equations (7) and (8) may be readily adapted to make allowance for the effect of  $f'$  the real part of the resonant-scattering contribution. This is achieved by replacing  $f_j$  by  $(f_j + f_j')$ . In general,  $f'$  is negative and only a few percent of  $f$ , so the terms  $(f_j f_l'' - f_l f_j'')$  in (7) and (8) will diminish somewhat when  $f'$  is included, as will the denominator in (8).

##### 4.3. Dependence of scattering factors on $\sin \theta/\lambda$

The real and imaginary components of the resonant scattering,  $f'$  and  $f''$ , are independent of  $\sin \theta/\lambda$  whereas the non-resonant atomic scattering factors are monotonically decreasing functions of  $\sin \theta/\lambda$ . A crude approximation to the non-resonant atomic scattering factors is to take  $f_j = Z_j G(\sin \theta/\lambda)$ , where  $G$  is a monotonically decreasing function of  $\sin \theta/\lambda$  having  $G(0) = 1$ , i.e. all atomic scattering factors have the same shape but with values scaled to the atomic number of

the chemical element. Inspection of (8) shows that  $\chi$  varies approximately as  $1/G$ . Consequently, a general trend is for a monotonic increase in  $\chi$  as  $\sin \theta/\lambda$  increases. For practical considerations on many of these points, the reader is referred to Dauter (2006).

It is of course not difficult to take explicit account of the  $\sin \theta/\lambda$  variation of the non-resonant atomic scattering factors by using either a five-term or a seven-term parametric representation and evaluating  $\chi$  at a series of values of  $\sin \theta/\lambda$ . If available, Debye–Waller factors could also be included as described in §4.4 as these also have a contribution which varies with  $\sin \theta/\lambda$ . For  $\langle D_z^2 \rangle$  and  $\chi_z$ , similar to  $\langle D^2 \rangle$  and  $\chi$  but based on normalized rather than ordinary structure factors, Appendix B shows that  $\chi_z = \langle D_z^2 \rangle^{1/2} = \chi$ . Clearly these three functions depend more weakly on  $\sin \theta/\lambda$  than does  $\langle D^2 \rangle$ .

##### 4.4. Isotropic atomic displacements

In the approximation of an overall isotropic atomic displacement parameter, a Debye–Waller factor  $t = \exp\{-8\pi^2 U \sin^2 \theta/\lambda^2\}$  premultiplies every  $f_j$  and  $f_j''$  and  $t$  cancels out in the expression for  $\chi$  in (8). Consequently, an overall isotropic atomic displacement has no effect on the variation of  $\chi$  with  $\sin \theta/\lambda$ .

One may also allow for individual isotropic atomic displacements without difficulty. To achieve this it is sufficient in (7) and (8) to replace each  $f_j$  and  $f_j''$  by  $t_j f_j$  and  $t_j f_j''$ , respectively, where  $t_j = \exp\{-8\pi^2 U_j \sin^2 \theta/\lambda^2\}$  is the individual Debye–Waller factor and  $U_j$  is the isotropic atomic displacement parameter for the  $j$ th atom. If this substitution is carried out in (7) and (8), each factor  $(f_j f_l'' - f_l f_j'')$  becomes  $t_j t_l (f_j f_l'' - f_l f_j'')$ . So although the contrast factor  $(f_j f_l'' - f_l f_j'')$  is unaffected by isotropic atomic displacement parameters, the prefactor  $t_j t_l$  allows the contribution of certain pairs of atoms to be modified. As heavy atoms tend to have smaller atomic displacement parameters than light atoms, their contribution to the contrast terms in (7) and (8) is upweighted with respect to the light atoms. As before, the effect will be greatest at larger values of  $\sin \theta/\lambda$ . This analysis is in agreement with those of Dauter (2006) and Shen *et al.* (2003).

##### 4.5. Atomic site occupation parameters

In like manner to the analysis of atomic displacement parameters, the effect of atomic site occupation parameters may be taken into account in (7) and (8) by replacing each  $f_j$  and  $f_j''$  by  $p_j f_j$  and  $p_j f_j''$ , respectively, where  $p_j$  is the site occupation parameter for the  $j$ th atom. So with this substitution carried out, the first term in equation (7)  $\langle D^2 \rangle_1 = 4 \sum_{j=1}^N \sum_{l=1}^N (f_j f_l'' - f_l f_j'')^2$  becomes  $\langle D^2 \rangle_1 = 4 \sum_{j=1}^N \sum_{l=1}^N p_j^2 p_l^2 (f_j f_l'' - f_l f_j'')^2$ . It is thus easy to see that the contribution to  $\langle D^2 \rangle$  of sites with partial atomic occupation is diminished with respect to full occupation of the site. As in §4.1, it is of particular interest to express  $\langle D^2 \rangle$  in terms of atom types in order to understand how arranging the same total number of atoms of each type over sites with partial occupation modifies (7) and (8). As in §4.1, let  $N_j^a$  be the total number of atoms of type  $j$  and  $T$  be the number of atom types in the

structure. We also need to define  $N_j^s$  as the total number of sites occupied by atoms of type  $j$  and double index the atomic site occupation parameters so  $p_{ij}$  refers to site  $j = 1, \dots, N_i^s$  occupied by an atom of type  $i = 1, \dots, T$ . It follows that  $\sum_{j=1}^{N_i^s} p_{ij} = N_i^a$  and in the expression for  $\langle D^2 \rangle_1$  each sum over all atomic sites  $\sum_{j=1}^N$  may be replaced by the double summation over atom types and sites of each atom type,  $\sum_{i=1}^T \sum_{j=1}^{N_i^s}$ . Substitution and rearrangement leads to

$$\langle D^2 \rangle_1 = 4 \sum_{j=1}^T \sum_{l=1}^T N_j^a N_l^a (f_j f_l'' - f_l f_j'')^2 \sum_{i=1}^{N_j^s} \frac{p_{ji}^2}{N_j^a} \sum_{k=1}^{N_l^s} \frac{p_{lk}^2}{N_l^a}.$$

Let us examine one of the two factors like  $\sum_{i=1}^{N_j^s} p_{ji}^2 / N_j^a$  remembering that  $\sum_{i=1}^{N_j^s} p_{ji} = N_j^a$ . The best case occurs when all sites of atom type  $j$  are fully occupied giving  $p_{ji} = 1$  for  $i = 1, \dots, N_j^s$ ,  $N_j^s = N_j^a$  and  $\sum_{i=1}^{N_j^s} (p_{ji}^2 / N_j^a) = 1$ . Clearly, if all atomic sites of all atomic types are fully occupied, the same result is obtained for  $\langle D^2 \rangle_1$  and by extension for  $\langle D^2 \rangle$  as in §4.1. It is possible to show that the worst case occurs for  $N_j^s > N_j^a$  when all sites of atom type  $j$  are equally occupied with  $p_{ji} = N_j^a / N_j^s$  for  $i = 1, \dots, N_j^s$  so  $\sum_{i=1}^{N_j^s} p_{ji}^2 / N_j^a = N_j^a / N_j^s$ ,

$$\begin{aligned} \langle D^2 \rangle &= 4 \sum_{j=1}^T \sum_{l=1}^T \left( \frac{N_j^a}{N_j^s} \right) \left( \frac{N_l^a}{N_l^s} \right) N_j^a N_l^a (f_j f_l'' - f_l f_j'')^2 \\ &\quad - 4 \sum_{j=1}^T \sum_{l=1}^T \left( \frac{Q_j^a}{Q_j^s} \right) \left( \frac{Q_l^a}{Q_l^s} \right) Q_j^a Q_l^a (f_j f_l'' - f_l f_j'')^2. \end{aligned}$$

In fact, the latter equation covers both the best case when  $N_j^s = N_j^a$  and the worst case which can be calculated as in §4.1 by diminishing  $N_j^a$  by a factor  $N_j^a / N_j^s < 1$  and likewise for  $Q$ . Such a reduction of the mean-square Friedel intensity difference resulting from disorder in atomic positions is in agreement with the observations of Olczak *et al.* (2003, 2007).

#### 4.6. Crystal twinned by inversion

In a crystal twinned by inversion, the intensities of the reflection  $\mathbf{h}$  and its Friedel opposite  $-\mathbf{h}$  are given by  $I(\mathbf{h}) = (1-x)|\mathbf{F}(\mathbf{h})|^2 + x|\mathbf{F}(-\mathbf{h})|^2$  and  $I(-\mathbf{h}) = x|\mathbf{F}(\mathbf{h})|^2 + (1-x)|\mathbf{F}(-\mathbf{h})|^2$ . So the average intensity of a pair of Friedel opposites  $A(\mathbf{h}) = \frac{1}{2}I(\mathbf{h}) + \frac{1}{2}I(-\mathbf{h}) = \frac{1}{2}[|\mathbf{F}(\mathbf{h})|^2 + |\mathbf{F}(-\mathbf{h})|^2]$  is unchanged from that of the untwinned crystal given by (2). However, for the Friedel difference  $D(\mathbf{h}) = I(\mathbf{h}) - I(-\mathbf{h}) = (1-2x)[|\mathbf{F}(\mathbf{h})|^2 - |\mathbf{F}(-\mathbf{h})|^2]$ , a prefactor  $(1-2x)$  multiplies the value of an untwinned crystal given by (3). As  $0 \leq x \leq 1$ ,  $|1-2x|$  takes its largest value of unity when  $x = 0$  or  $x = 1$  for an untwinned crystal. The corresponding values of  $\langle D^2 \rangle$  and  $\chi$  are given by (7) and (8), respectively, for the untwinned crystal.  $|1-2x|$  takes its smallest value of zero when  $x = 0.5$  for a crystal composed of equal amounts of the two domain states which are inversion images one of another. The corresponding values of  $\langle D^2 \rangle$  and  $\chi$  are also zero, confirming that a crystal twinned by inversion in the ratio 50:50 shows no difference in intensity between Friedel opposites.

#### 4.7. Atoms in special positions

The analysis in the following subsections proves that no modification of (7) and any equation resulting from it is necessary to allow atoms to occupy special positions in the current model. Although there are no special positions in space group  $P1$ , its centrosymmetric supergroup  $P\bar{1}$  on a primitive basis with a centre of symmetry at the origin has only centres of symmetry as special positions with coordinates  $m/2, n/2, p/2$ , where  $m, n$  and  $p$  are integers,  $0 \leq m, n, p \leq 1$ . As the coordinates of these special positions are fixed, the calculation of the average values of  $c_j$  and its powers is taken over reflection indices  $\mathbf{h}$ . Here,  $c_i = \cos(2\pi\mathbf{h} \cdot \mathbf{x}_i) = \cos\{\pi(hm_i + kn_i + lp_i)\} = \pm 1$ , the sign depending on the parity of  $hm_i + kn_i + lp_i$ . Consequently,  $c_j^2 = 1$ ,  $\langle c_j^2 \rangle = 1$ , whereas  $c_i c_j = \pm 1$ ,  $i \neq j$ , the sign changing regularly as  $h, k, l$  are increased by unity, implying that  $\langle c_i c_j \rangle \approx 0$ ,  $i \neq j$ . The definitions of  $M, N$  and  $Q$  as given in §2 are unchanged but we also define  $W$  to be the number of atoms in the unit cell sitting on special positions of site symmetry  $\bar{1}$  and these  $W$  atoms are put at the end of the list of centrosymmetrically arranged atoms. Thus, atoms 1 to  $Q$  are arranged centrosymmetrically, of which atoms 1 to  $Q - W$  are atoms arranged centrosymmetrically in pairs,  $Q - W + 1$  to  $Q$  are atoms located on the centres of symmetry and atoms  $Q + 1$  to  $N$  are arranged non-centrosymmetrically. We are of course aware of the fact that in this case setting  $\langle c_i c_j \rangle \approx 0$ ,  $i \neq j$ , is possibly a serious approximation because of the strong rational dependence of the coordinates of the centres of symmetry. However, this seems to be the closest attainable description of  $\langle D^2 \rangle$  in the presence of atoms in the above special positions. On the other hand, the average  $\langle c_j^2 \rangle = 1$  is correct and in addition the important case of a single centre of symmetry being occupied does not involve any approximation. We look forward to a confrontation of the result to be presented with experiment or, at least, with a simulation.

**4.7.1. Average Friedel intensity with special positions.** This subsection needs to be understood as an adjunct to Appendix A to take account of atoms in special positions. From Appendix A, the only terms in the expression for  $\langle A \rangle$  in (4) that are affected by atoms in special positions are  $\langle C_C^2 \rangle$  and  $\langle C_C'^2 \rangle$ . Allowing for the special positions  $C_C = 2 \sum_{j=1}^{(Q-W)/2} f_j c_j + \sum_{j=Q-W+1}^Q f_j c_j \equiv C_{Cg} + C_{Cs}$ , where  $C_{Cg}$  is the contribution of the general positions and  $C_{Cs}$  that of the special ones, we have

$$\begin{aligned} \langle C_C^2 \rangle &= \langle C_{Cg}^2 \rangle + \langle C_{Cs}^2 \rangle + 2\langle C_{Cg} C_{Cs} \rangle \\ &= 4 \sum_{j=1}^{(Q-W)/2} \sum_{k=1}^{(Q-W)/2} f_j f_k \langle c_j c_k \rangle + \sum_{j=Q-W+1}^Q \sum_{k=Q-W+1}^Q f_j f_k \langle c_j c_k \rangle \\ &\quad + 4 \sum_{j=1}^{(Q-W)/2} \sum_{k=Q-W+1}^Q f_j f_k \langle c_j c_k \rangle. \end{aligned}$$

For the first double summation in  $\langle C_C^2 \rangle$ ,  $\langle c_j^2 \rangle = \frac{1}{2}$  and  $\langle c_j c_k \rangle = 0$ ,  $j \neq k$ ; for the second double summation in  $\langle C_C^2 \rangle$ ,  $\langle c_j^2 \rangle = (\pm 1)^2 = 1$  and  $\langle c_j c_k \rangle \approx 0$ ,  $j \neq k$ ; the third term in  $\langle C_C^2 \rangle$  vanishes since  $j$  never equals  $k$ , and  $\langle c_j c_k \rangle = \langle c_j \rangle \langle c_k \rangle = 0$ . We thus have  $\langle C_C^2 \rangle \approx 2 \sum_{j=1}^{(Q-W)/2} f_j^2 + \sum_{j=Q-W+1}^Q f_j^2 = \sum_{j=1}^Q f_j^2$ , so

$\langle C_C^2 \rangle$ , and by comparison  $\langle C_C'^2 \rangle$ , are unchanged from the analysis of Appendix A. Hence we obtain  $\langle A \rangle \approx \sum_{j=1}^N f_j^2 + \sum_{j=1}^N f_j'^2$  even if there are  $W$  atoms located on the special positions, the only very slight modification from Appendix A being the replacement of the equality by an approximate equality.

**4.7.2. Mean-square Friedel intensity difference with special positions.** This subsection needs to be understood as an adjunct to Appendix A to take account of atoms in special positions. One writes (6) as

$$\langle D^2 \rangle / 16 = \langle C_C^2 \rangle \langle S'^2 \rangle + \langle C_N^2 S'^2 \rangle + \langle S^2 \rangle \langle C_C'^2 \rangle + \langle S^2 C_N'^2 \rangle - 2 \langle C_C C_C' \rangle \langle S S' \rangle - 2 \langle C_N S C_N' S' \rangle,$$

in which the only averages that can be affected by atoms in special positions are those containing  $\langle C_C^2 \rangle$ ,  $\langle C_C'^2 \rangle$  and  $\langle C_C C_C' \rangle$ . We have already shown in §4.7.1 that  $\langle C_C^2 \rangle$  and, by inspection,  $\langle C_C'^2 \rangle$  are approximately unchanged by the presence of atoms occupying special positions. By inspection it is also clear that  $\langle C_C C_C' \rangle$  is unmodified as the averaging in the above three quantities takes place only over the trigonometric terms, and is unaffected by the particular scattering-factor components concerned. All in all,  $\langle D^2 \rangle$  is approximately unchanged by the presence of atoms in special positions.

## 5. Weak reflections

In resolving centrosymmetric–non-centrosymmetric ambiguities in the determination of a crystal structure, Marsh (1981) has argued forcibly concerning the importance of retaining weak reflections. In this he follows the more general opinion of Hirshfeld & Rabinovich (1973) on the cosmetic effect of ignoring weak reflections and the introduction of systematic errors or bias into structural parameters. An interesting modern experimental demonstration that weak reflections are indeed critical in such circumstances is to be found in the work of Walker *et al.* (1999). In the latter, the crystal structure of emycin E was known to be non-centrosymmetric since the compound was a mixture of two epimers having the same chirality at C(3) and opposite chirality at C(12), but which was nevertheless very close indeed to being centrosymmetric. Walker *et al.* (1999) noted that refinement in a centrosymmetric space group led to the observed intensities of the weak reflections being systematically larger than the corresponding model intensities whereas this was not the case for refinement in the correct non-centrosymmetric space group. If weak reflections are so important in resolving centrosymmetric–non-centrosymmetric ambiguities, it is tempting to imagine that they might also be critical in choosing a subset of reflections that have maximal Friedel intensity differences. However, we know of no report in the literature suggesting that weak reflections are of particular importance in obtaining significant Friedel differences. Consequently, we analyse the two cases to understand better their similarities and differences.

Following Marsh (1981), the appropriate intensity difference to calculate for reflection  $\mathbf{h}$  of a pseudo-centrosymmetric

structure is that between the intensity corresponding to the electron density  $\rho(\mathbf{r})$  of the whole unit-cell contents and that corresponding to the centrosymmetric component of the real electron density,  $\rho_c(\mathbf{r}) = \frac{1}{2}[\rho(\mathbf{r}) + \rho(-\mathbf{r})]$ , for an inversion point at the origin. We shall call this a Marsh difference intensity denoted by  $M(\mathbf{h})$ . Using the notation and results of §2, the structure factor  $\mathbf{F}(\mathbf{h})$  of reflection  $\mathbf{h}$  corresponding to the electron density  $\rho(\mathbf{r})$  is  $\mathbf{F}(\mathbf{h}) = C + iC'' + iS - S''$  and its component corresponding to  $\rho_c(\mathbf{r})$  is  $\Phi(\mathbf{h}) = C + iC''$ . For the corresponding intensities, we set  $M(\mathbf{h}) = A(\mathbf{h}) - |\Phi(\mathbf{h})|^2 = S^2 + S''^2$ . Examination of this equation shows that there is no functional relationship between  $M(\mathbf{h})$  and  $A(\mathbf{h})$  but that the Marsh difference intensity is always positive or zero, within the limits  $0 \leq M(\mathbf{h}) \leq A(\mathbf{h})$  or  $0 \leq M(\mathbf{h})/A(\mathbf{h}) \leq 1$ , as confirmed by Walker *et al.* (1999) for the weak reflections in emycin E. For a pseudo-centrosymmetric structure,  $M(\mathbf{h})$  will in general be small, so it is likely to be of the same magnitude for a weak reflection as for a strong reflection and the largest values of  $M(\mathbf{h})/A(\mathbf{h})$  occur for weak reflections. By way of comparison, we find from §2 that the Friedel intensity difference  $D(\mathbf{h}) = 4(C''S - CS'')$  with  $\langle D \rangle = 0$ . Again, for  $D(\mathbf{h})$ , there is no functional relationship between  $D(\mathbf{h})$  and  $A(\mathbf{h})$ , but  $D(\mathbf{h})$  may be positive or negative within the limits  $-2A(\mathbf{h}) \leq D(\mathbf{h}) \leq +2A(\mathbf{h})$  or  $-1 \leq D(\mathbf{h})/2A(\mathbf{h}) \leq +1$ .  $D(\mathbf{h})$  is in general small [like  $M(\mathbf{h})$  for a pseudo-centrosymmetric structure] and  $D(\mathbf{h})/2A(\mathbf{h})$  is largest for weak reflections. The important difference between  $M(\mathbf{h})$  and  $D(\mathbf{h})$  is that the former is zero or positive whereas the latter may take both positive and negative values with a mean value of zero.

It seems to be commonly accepted that the importance of weak reflections in centrosymmetric–non-centrosymmetric ambiguities is due to  $M(\mathbf{h})/A(\mathbf{h})$  being largest for weak reflections. In this respect, we need to make two comments. Firstly,  $M(\mathbf{h})/A(\mathbf{h})$  is large for weak reflections not because  $M(\mathbf{h})$  is large but because  $A(\mathbf{h})$  is small. Secondly, in the calculation of normalized structure factors (for intensity statistical tests and direct methods of structure solution) and least-squares refinement of structural parameters, one uses intensities as such and not relative to some average or expected value. The paper of McCandlish *et al.* (1975) on the statistics of derived intensities is of the utmost importance in this respect. They showed that the need to bring data to a common scale engenders a relative dependence on the uncertainties or systematic errors in the data with respect to the value of the datum.

So it seems to us that the most plausible explanation for the importance of weak reflections in resolving centrosymmetric–non-centrosymmetric ambiguities runs as follows.  $M(\mathbf{h})$  is always positive and, for both the calculation of  $E(\mathbf{h})$  and the least-squares refinement of structural parameters, a scale factor is used to bring the observed and model intensities to the same scale. The strong/medium reflections will dominate the determination of the scale factor because they are measured more accurately and because residuals between observed and model values tend to be proportional to the observed value. Consequently, the value obtained for the scale factor is biased because  $M(\mathbf{h})$  is always positive. This bias in

the scale factor leads to residuals on the strong/medium reflections having a mean of zero, *i.e.* part of the effect of  $M(\mathbf{h})$  is absorbed into the biased scale factor. However, for the weak reflections this is not the case because the bias in the scale factor only produces a small effect proportional to the intensity of the weak reflection, *i.e.* next to none of the contribution of  $M(\mathbf{h})$  to a weak reflection is lost by a biased scale factor. Consequently, weak reflections remain the key to resolving centrosymmetric–non-centrosymmetric ambiguities even in the presence of a biased scale factor.

On the other hand, for Friedel differences,  $\langle D(\mathbf{h}) \rangle$  is zero and consequently there is no mechanism for producing a biased scale factor. Consequently, weak reflections have no particular importance in choosing reflections with a significant Friedel intensity difference.

The problem of weak reflections can also be regarded from the point of view of intensity statistics. Briefly, if Wilson's (1949) p.d.f.s are applicable and the structure is centrosymmetric, the p.d.f. is a simple Gaussian and the greatest probabilities of occurrence are assigned to weak reflections. If the exact p.d.f. is used, there is still a finite probability assigned to the weak reflections. If, however, weak reflections are omitted, the p.d.f. – whether asymptotic (Wilson, 1949) or exact (Shmueli *et al.*, 1984) – is distorted towards appearing more acentric and indicates a nearly or completely non-centrosymmetric structure. The not infrequent omission of intensities smaller than 3 standard uncertainties may be a source of such problems.

## 6. Software

A spreadsheet application<sup>1</sup> has been written for Microsoft Excel<sup>™</sup> 2003 running under Microsoft Windows XP<sup>™</sup>. Using (10), the spreadsheet calculates the value of  $10^4\chi$  for the two cases of all atoms arranged non-centrosymmetrically, labelled *Friedif*, and allowing for the centrosymmetric substructure, labelled *Friedif-centro*. The real part of the resonant atomic scattering factor and atomic displacement parameters are not taken into account. The spreadsheet also calculates the molecular mass and  $10^4(|\Delta F|)/\langle F \rangle$  of Girard *et al.* (2003) labelled *Rescat*. The calculation is undertaken for the wavelengths of Cu  $K\alpha$  and Mo  $K\alpha$  using values of  $f''$  given by Creagh (2004). The user has to enter the total elemental composition of the compound in the form of its stoichiometry and optionally the elemental composition of the centrosymmetric substructure.

## 7. Concluding remarks

An important and essential feature concerning the difference in intensity between Friedel opposites as displayed by (7) is that the effect is one of contrast. One needs both atoms with significant resonant scattering and atoms with a small resonant

effect to produce the largest measurable effects. Another surprising result from (7) concerns arrangements of atoms that do not affect the differences between Friedel opposites. Non-centrosymmetric crystal structures of chemical elements produce no difference in intensity between Friedel opposites. In like manner, a centrosymmetric arrangement of identical resonant scatterers in an otherwise non-centrosymmetric structure does not diminish the mean-square Friedel intensity difference.

In §5, we have confirmed the underlying theoretical soundness of Marsh's demonstration of the importance of weak reflections in resolving centrosymmetric–non-centrosymmetric ambiguities and the mechanism by which their model intensities are biased. Moreover, Walker *et al.* (1999) have provided convincing experimental confirmation of this effect. From this and other work, we judge that it would be opportune for publications of crystal structures solved as being centrosymmetric to contain statistics on weak reflections such as those presented by Walker *et al.* (1999). If these statistics show a marked tendency for the observed intensities of weak reflections to be larger than the model ones, the structure may in fact be non-centrosymmetric. A typical example would be that of a structure, solved as being centrosymmetric and composed of a racemate, perhaps disordered, which is in fact a non-centrosymmetric chiral crystal structure of an enantiopure compound, probably ordered. Physicochemical characterization of the 'racemate' in the bulk and in the single crystal used for the diffraction experiment provides additional evidence as to the real state of the crystal structure.

The application of (7) and (8) to the prediction of the value of the standard uncertainty of the Flack parameter, as in Flack *et al.* (2006), is under way.

## APPENDIX A

### Derivation of the average intensity and mean-square difference intensity of Friedel opposites

Following the definitions in §2, we shall first derive the average intensity of Friedel opposites. The starting equation is

$$\begin{aligned} \langle A \rangle &= \langle C^2 \rangle + \langle C'^2 \rangle + \langle S^2 \rangle + \langle S'^2 \rangle \\ &= \langle C_C^2 \rangle + \langle C_N^2 \rangle + 2\langle C_C C_N \rangle + \langle C'_C{}^2 \rangle + \langle C'_N{}^2 \rangle \\ &\quad + 2\langle C'_C C'_N \rangle + \langle S_N^2 \rangle + \langle S'_N{}^2 \rangle \end{aligned}$$

but  $\langle C_C C_N \rangle$  and  $\langle C'_C C'_N \rangle$  vanish since they are products of odd independent summations. We now retain and simplify the non-vanishing summations:

$$\langle C_C^2 \rangle = 4 \sum_{j=1}^{Q/2} f_j^2 \langle c_j^2 \rangle = \sum_{j=1}^Q f_j^2 \quad (11)$$

$$\langle C'_C{}^2 \rangle = 4 \sum_{j=1}^{Q/2} f_j'^2 \langle c_j'^2 \rangle = \sum_{j=1}^Q f_j'^2 \quad (12)$$

<sup>1</sup> Supplementary data for this paper are available from the IUCr electronic archives (Reference: SH5056). Services for accessing these data are given at the back of the journal.



$$\langle C_N^2 \rangle = \sum_{j=Q+1}^N f_j^2 \langle c_j^2 \rangle = \frac{1}{2} \sum_{j=1}^N f_j^2 - \frac{1}{2} \sum_{j=1}^Q f_j^2 \quad (13)$$

$$\langle C_N'^2 \rangle = \sum_{j=Q+1}^N f_j'^2 \langle c_j^2 \rangle = \frac{1}{2} \sum_{j=1}^N f_j'^2 - \frac{1}{2} \sum_{j=1}^Q f_j'^2 \quad (14)$$

$$\langle S_N^2 \rangle = \sum_{j=Q+1}^N f_j^2 \langle s_j^2 \rangle = \frac{1}{2} \sum_{j=1}^N f_j^2 - \frac{1}{2} \sum_{j=1}^Q f_j^2 \quad (15)$$

$$\langle S_N'^2 \rangle = \sum_{j=Q+1}^N f_j'^2 \langle s_j^2 \rangle = \frac{1}{2} \sum_{j=1}^N f_j'^2 - \frac{1}{2} \sum_{j=1}^Q f_j'^2 \quad (16)$$

and equations (11) through (16) add up to

$$\langle A \rangle = \sum_{j=1}^N (f_j^2 + f_j'^2) = \sum_{j=1}^N |f_j + if_j''|^2, \quad (5)$$

in agreement with Wilson's statistics.

We now turn to the mean-square intensity difference of a Friedel pair. Starting again from §2, we have

$$\langle D^2 \rangle / 16 = \langle (CS'' - SC'')^2 \rangle = \langle C^2 S''^2 \rangle + \langle S^2 C'^2 \rangle - 2 \langle CS'' C'' S' \rangle.$$

The first term of  $\langle D^2 \rangle / 16$  is

$$\langle C^2 S''^2 \rangle = \langle (C_C^2 + C_N^2) S_N'^2 \rangle = \langle C_C^2 \rangle \langle S_N'^2 \rangle + \langle C_N^2 S_N'^2 \rangle$$

since  $C_C$  and  $S_N'$  are independent. The averages to be calculated are

$$\begin{aligned} \langle C_C^2 \rangle &= 4 \sum_{j=1}^{Q/2} \sum_{k=1}^{Q/2} f_j f_k \langle c_j c_k \rangle = 4 \sum_{j=1}^{Q/2} f_j^2 \langle c_j^2 \rangle = \sum_{j=1}^Q f_j^2, \\ \langle S_N'^2 \rangle &= \sum_{l=Q+1}^N \sum_{m=Q+1}^N f_l' f_m' \langle s_l s_m \rangle = \sum_{l=Q+1}^N f_l'^2 \langle s_l^2 \rangle = \frac{1}{2} \sum_{l=Q+1}^N f_l'^2, \\ \langle C_N^2 S_N'^2 \rangle &= \sum_{j=Q+1}^N \sum_{k=Q+1}^N \sum_{l=Q+1}^N \sum_{m=Q+1}^N f_j f_k f_l' f_m' \langle c_j c_k s_l s_m \rangle \\ &= \begin{cases} \frac{1}{8} \sum_{l=Q+1}^N f_l^2 f_l'^2 & \text{for } j = k = l = m \\ \frac{1}{4} \sum_{j=Q+1}^N \sum_{l=Q+1}^N f_j^2 f_l'^2 & \text{for } j = k, l = m, j \neq l. \end{cases} \end{aligned}$$

The non-vanishing summations in the first term of  $\langle D^2 \rangle / 16$  are

$$\langle C^2 S''^2 \rangle = \frac{1}{2} \sum_{j=1}^Q \sum_{l=Q+1}^N f_j^2 f_l'^2 + \frac{1}{8} \sum_{l=Q+1}^N f_l^2 f_l'^2 + \frac{1}{4} \sum_{j=Q+1}^N \sum_{l=Q+1}^N f_j^2 f_l'^2 \quad (17)$$

with  $j \neq l$  in the third summation (in the first this is so by definition). If we follow similar algebraic manipulations, the non-vanishing summations in the second term of  $\langle D^2 \rangle / 16$  are

$$\langle S^2 C'^2 \rangle = \frac{1}{2} \sum_{j=Q+1}^N \sum_{l=1}^Q f_j^2 f_l'^2 + \frac{1}{8} \sum_{l=Q+1}^N f_l^2 f_l'^2 + \frac{1}{4} \sum_{j=Q+1}^N \sum_{l=Q+1}^N f_j^2 f_l'^2 \quad (18)$$

with  $j \neq l$  in the third summation, and the non-vanishing summations in the third term are obtained by decomposing the third term prior to the averaging and following similar steps to the above, as

$$\begin{aligned} -2 \langle CSC'' S'' \rangle &= -\frac{2}{2} \sum_{j=1}^Q \sum_{k=Q+1}^N f_j f_k f_j'' f_k'' - \frac{2}{8} \sum_{k=Q+1}^N f_k^2 f_k''^2 \\ &\quad - \frac{2}{4} \sum_{j=Q+1}^N \sum_{(k \neq j)=Q+1}^N f_j f_k f_j'' f_k''. \end{aligned} \quad (19)$$

If we now collect the summations from equations (17), (18) and (19), take care of the dummy indices and rearrange the summations, the mean-square intensity difference is obtained as

$$\langle D^2 \rangle = 8 \sum_{j=1}^Q \sum_{l=Q+1}^N (f_j f_l' - f_l f_j'')^2 + 4 \sum_{j=Q+1}^N \sum_{l=Q+1}^N (f_j f_l'' - f_l f_j')^2.$$

We omitted  $l \neq j$  from the last summation since, for  $j = l$ ,  $(f_j f_l'' - f_l f_j') = 0$ . If we now replace  $\sum_{l=Q+1}^N$  with  $\sum_{l=1}^N - \sum_{l=1}^Q$ , we readily obtain

$$\langle D^2 \rangle = 4 \sum_{j=1}^N \sum_{l=1}^N (f_j f_l' - f_l f_j'')^2 - 4 \sum_{j=1}^Q \sum_{l=1}^Q (f_j f_l'' - f_l f_j')^2. \quad (7)$$

## APPENDIX B

### Derivation of the average normalized intensity and the mean-square difference normalized intensity of Friedel opposites

Analogously to the analysis in §2, the complex normalized structure factor  $E(\mathbf{h})$  can be written as  $E(\mathbf{h}) = E_C(\mathbf{h}) + E_N(\mathbf{h})$ , where

$$E_C(\mathbf{h}) = 2 \sum_{j=1}^{Q/2} (n_j + in_j'') c_j, \quad E_N(\mathbf{h}) = \sum_{j=Q+1}^N (n_j + in_j'') (c_j + is_j)$$

and the non-resonant and imaginary resonant parts of the normalized scattering factor are given, for space group  $P1$ , by

$$n_j = \frac{f_j}{(\Sigma)^{1/2}}, \quad n_j'' = \frac{f_j''}{(\Sigma)^{1/2}}, \quad \Sigma = \sum_{j=1}^N |f_j + if_j''|^2.$$

The trigonometric terms  $c_j$  and  $s_j$  have the same meaning as in §2. If we now define

$$\begin{aligned} \xi_C &= 2 \sum_{j=1}^{Q/2} n_j c_j, & \xi_N &= \sum_{j=Q+1}^N n_j c_j, & \xi &= \xi_C + \xi_N = \sum_{j=1}^N n_j c_j, \\ \xi_C'' &= 2 \sum_{j=1}^{Q/2} n_j'' c_j, & \xi_N'' &= \sum_{j=Q+1}^N n_j'' c_j, & \xi'' &= \xi_C'' + \xi_N'' = \sum_{j=1}^N n_j'' c_j, \end{aligned}$$

$$\eta_N = \sum_{j=Q+1}^N n_j s_j, \quad \eta_N'' = \sum_{j=Q+1}^N n_j'' s_j,$$

the normalized structure factor of reflection  $\mathbf{h}$  can be brought to the form

$$E(\mathbf{h}) = \xi + i\xi'' + i\eta - \eta'' \quad (20)$$

while

$$E(-\mathbf{h}) = \xi + i\xi'' - i\eta + \eta'', \quad (21)$$

in analogy with the development in §2. The corresponding normalized intensities are  $z(\mathbf{h}) = |E(\mathbf{h})|^2$  and  $z(-\mathbf{h}) = |E(-\mathbf{h})|^2$ . If we now make use of equations (20) and

(21), it follows, after some straightforward algebra, that the mean normalized intensity of a Friedel pair  $\mathbf{h}$  and  $-\mathbf{h}$  is

$$A_z(\mathbf{h}) = \frac{1}{2}[z(\mathbf{h}) + z(-\mathbf{h})] = \xi^2 + \eta^2 + \xi'^2 + \eta'^2 \quad (22)$$

and that the difference between the normalized intensities of the Friedel opposites is

$$D_z(\mathbf{h}) = z(\mathbf{h}) - z(-\mathbf{h}) = 4(\xi'\eta - \xi\eta'). \quad (23)$$

The evaluation of the required averages now follows exactly Appendix A if we identify  $\xi$  with  $C$  and  $\eta$  with  $S$  etc.

The average Friedel normalized intensity is obtained as

$$\langle A_z \rangle = \sum_{j=1}^N |n_j + in_j''|^2 = 1, \quad (24)$$

which is just the well known second moment of  $|E(\mathbf{h})|$ .

Finally, the mean square difference of normalized intensities of Friedel opposites is obtained by an algebra exactly analogous to that presented in Appendix A. The result is

$$\langle D_z^2 \rangle = 4 \sum_{j=1}^N \sum_{l=1}^N (n_j n_l'' - n_l n_j'')^2 - 4 \sum_{j=1}^Q \sum_{l=1}^Q (n_j n_l'' - n_l n_j'')^2. \quad (25)$$

It is analogous to equation (7) in the text but thanks to the expression of (25) in terms of normalized scattering factors its dependence on the scattering angle, *via* Debye–Waller and trigonometric structure factors, is weaker than that of  $\langle D^2 \rangle$ . In a similar manner, we can obtain the ratio  $\chi_z = \langle D_z^2 \rangle^{1/2} / \langle A_z \rangle$  as

$$\chi_z = 2 \left[ \sum_{j=1}^N \sum_{l=1}^N (n_j n_l'' - n_l n_j'')^2 - \sum_{j=1}^Q \sum_{l=1}^Q (n_j n_l'' - n_l n_j'')^2 \right]^{1/2}, \quad (26)$$

since, as shown in (24), the average  $\langle A_z \rangle$  equals unity. This is analogous to equation (8) in the text, there expressed in terms of conventional scattering factors. Moreover, by back-substitution of  $n_j$  and  $n_j''$ , from their definitions, in (26) it can be readily shown that  $\chi_z = \chi = \langle D_z^2 \rangle^{1/2}$ .

C. Flack is thanked for her help with programming the advanced features of *Excel*. The idea to undertake the development presented in this paper came to HDF during a

conversation with M. Schiltz. The authors have pleasure in acknowledging the spontaneous help of the editor, D. Schwarzenbach, in drawing their attention to some fundamental discrepancies in some last-minute additions to the text.

## References

- Banumathi, S., Dauter, M. & Dauter, Z. (2003). *Acta Cryst.* **D59**, 492–498.
- Creagh, D. C. (2004). *International Tables for Crystallography*, Vol. C, *Mathematical, Physical and Chemical Tables*, edited by E. Prince, Table 4.2.6.8. Dordrecht: Kluwer Academic Publishers.
- Crick, F. H. C. & Magdoff, B. S. (1956). *Acta Cryst.* **9**, 901–908.
- Dauter, Z. (2006). *Acta Cryst.* **D62**, 867–876.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Flack, H. D. & Bernardinelli, G. (1999). *Acta Cryst.* **A55**, 908–915.
- Flack, H. D., Bernardinelli, G., Clemente, D. A., Linden, A. & Spek, A. L. (2006). *Acta Cryst.* **B62**, 695–701.
- Girard, E., Stelter, M., Vicat, J. & Kahn, R. (2003). *Acta Cryst.* **D59**, 1914–1922.
- Hendrikson, W. A. & Teeter, M. M. (1981). *Nature (London)*, **290**, 107–113.
- Hirshfeld, F. L. & Rabinovich, D. (1973). *Acta Cryst.* **A29**, 510–513.
- Llorca, J., Molins, E., Espinosa, E., Mata, I., Miravittles, C., Cervantes, G., Caubet, A. & Moreno V. (2001). *Acta Cryst.* **C57**, 804–806.
- McCandlish, L. E., Stout, G. H. & Andrews, L. C. (1975). *Acta Cryst.* **A31**, 245–249.
- McIntyre, G. (1978). *Acta Cryst.* **A34**, 936–939.
- Marsh, R. E. (1981). *Acta Cryst.* **B37**, 1985–1988.
- Olczak, A., Cianci, M., Hao, Q., Rizkallah, P. J., Raftery, J. & Helliwell, J. R. (2003). *Acta Cryst.* **A59**, 327–334.
- Olczak, A., Glówka, M. L., Szczesio, M., Bojarska, J., Duax, W. L., Burkhart, B. M. & Wawrzak, Z. (2007). *Acta Cryst.* **D63**, 319–327.
- Shen, Q., Wang, J. & Ealick, S. E. (2003). *Acta Cryst.* **A59**, 371–373.
- Shmueli, U., Weiss, G. H., Kiefer, J. E. & Wilson, A. J. C. (1984). *Acta Cryst.* **A40**, 651–660.
- Shmueli, U. & Wilson, A. J. C. (1981). *Acta Cryst.* **A37**, 342–353.
- Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
- Walker, M., Pohl, E., Herbst-Irmer, R., Gerlitz, M., Rohr, J. & Sheldrick, G. M. (1999). *Acta Cryst.* **B55**, 607–616.
- Weiss, M. S., Sicker, T. & Hilgenfeld, R. (2001). *Structure*, **9**, 771–777.
- Wilson, A. J. C. (1949). *Acta Cryst.* **2**, 318–320.
- Zwart, P. H. (2005). *Acta Cryst.* **D61**, 1437–1448.