book *Symmetry in Science and Art*, thus greatly facilitating the present work.

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Problems of Resolution and Bias in the Experimental Determination of the Distribution of Electron Density and Other Densities in Crystals

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Abstract

The limited 'window' in reciprocal space through which it is possible to observe diffraction phenomena sets a reciprocal limit to the resolution of detail in density distributions. The limit of resolution depends on whether the detail is one-, two-, or three-dimensional, and to some extent it is possible to choose between (i) lack of resolution associated with a large central maximum representing a point-object and (ii) false details associated with a smaller central maximum and more pronounced diffraction troughs. In any case, however, the limit of resolution is about one-quarter to one-half of the wavelength of the radiation used. Intensities measured by photon or particle counting are unbiased estimates of the true intensities, but their square roots are not unbiased estimates of the structure factors, and this bias may carry over into parameters based on structure factors rather than intensities. A satisfactory correction can be made for the strong reflexions, but weak reflexions (which are required if the theoretical limit of resolution is to be reached) remain a problem.

1. Introduction

1.1. The positional parameters of atoms in crystals can be determined with considerable accuracy, and in general they are remarkably little affected by systematic errors and statistical fluctuations (Wilson, 1976*b*, 1977*a*,*b*). The scaling factor and the thermal parameters, on the other hand, are sensitive to systematic errors and are biased by statistical fluctuations unless special precautions are taken (Wilson, 1975, 1976*b*, 1977*a*,*b*, 1978*b*; Lomer & Wilson, 1975). The measurement of the distribution of electron density is even more sensitive to systematic errors and statistical bias, and there is a fundamental limitation of resolving power: only reflexions with spacings greater than $\frac{1}{2}\lambda$ can be measured, where λ is the wavelength of the radiation employed, and sometimes the geometrical design of the apparatus imposes a higher limit $\lambda/2\sin\theta_{\max}$, where $\theta_{\max}$ is the largest Bragg angle that can be attained. One cannot expect, therefore, to be able to resolve details of the charge distribution on a scale much less than $\frac{1}{2}\lambda$. Naturally it is possible to fit models to the observed intensities of reflexion that imply detail on a smaller scale, but the measurements would give no criterion for deciding between rival models giving approximately the same goodness of fit. These remarks apply equally, *mutatis mutandis*, to measurements of the distribution of momentum density, of spin density, and of atomic-centre distribution in imperfect structures, and to diffraction measurements with electrons, neutrons *etc.* as well as to measurements with X-rays.

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1.2. There is a considerable literature dealing with the experimental difficulties in obtaining intensity measurements of sufficient accuracy for determining density distributions. That up to about 1965 has been reviewed by Weiss (1966) [see also the opening chapters of Azároff, Kaplow, Kato, Weiss, Wilson & Young (1974)]. More recent papers are by Dawson (1967*a*,*b*), Dietrich (1972), Stevens & Coppens (1975), and Rees (1976, 1978), but this list is not exhaustive. The present paper is concerned with the theoretical difficulties of resolution (§ 2) and bias (§ 3). Some early theoretical papers are those of Booth (1946, 1947) and Cruickshank (1949).

2. The fundamental limitation in density-distribution determination

2.1. Most crystallographers are aware of the 'diffraction ripples' or 'series-termination effects' exhibited when an electron-density (or other) distribution is represented by a Fourier series consisting of a finite number of terms. The spherical 'window' in reciprocal space through which the density is viewed has a maximum radius of $2/\lambda$ or $2 \sin \theta_{\max}/\lambda$ (§ 1.1). Let us call this maximum radius s. If no other influences intervened, the observed density distribution would be the true density convoluted with the Fourier transform of a function that has the value unity within the limiting sphere and the value zero outside. This Fourier transform takes three different forms, depending on whether the density distribution is one-, two-, or three-dimensional.

In the one-dimensional case the Fourier transform is given by

$$T(r) = \int_{-s}^{+s} \exp(2\pi i r s)\, \mathrm{d}s, \qquad (1)$$

which is readily integrated to give the expression

$$T(r) = (\sin 2\pi r s)/\pi r, \qquad (2)$$

familiar in all sorts of contexts. The first zero of $T(r)$ occurs for

$$2\pi r s = \pi = 3\cdot 14159\ldots, \qquad (3)$$

so that one-dimensional syntheses cannot be expected to resolve detail on a scale much smaller than

$$r = 1/2s \geq 0\cdot 25\lambda. \qquad (4)$$

The criterion of using the peak-to-first-zero distance as an indication of resolving power seems to have been introduced by Rayleigh (1879).

2.2. In the two-dimensional case the integration is over the interior of a circle of radius s, and is most conveniently performed in polar coordinates:

$$\begin{aligned} T(r) &= \int_0^s \int_0^{2\pi} \exp(2\pi i r s \cos \varphi)\, s\, \mathrm{d}s\, \mathrm{d}\varphi \qquad (5) \\ &= 2\pi \int_0^s J_0(2\pi r s)\, s\, \mathrm{d}s \\ &= 2\pi s^2 \{J_1(2\pi r s)\}/(2\pi r s), \qquad (6) \end{aligned}$$

where J_0 and J_1 are Bessel functions of the first kind. This expression has been familiar for a century in connexion with the resolving power of optical instruments with circular apertures, and its importance for two-dimensional crystallographic Fourier syntheses was emphasized by James (1948, pp. 399–410). The first zero occurs for

$$2\pi r s = 3\cdot 83171\ldots, \qquad (7)$$

so that two-dimensional syntheses cannot be expected to resolve detail on a scale much smaller than

$$r = 3\cdot 83171\ldots/2\pi s \geq (0\cdot 30491\ldots)\,\lambda. \qquad (8)$$

2.3. In the three-dimensional case the integration is over the interior of a sphere of radius s, giving, in spherical polar coordinates,

$$T(r) = \int_0^s \int_0^{2\pi} \int_0^{\pi} \exp(2\pi i r s \cos \varphi)\, s^2 \sin \varphi\, \mathrm{d}s\, \mathrm{d}\varphi\, \mathrm{d}\psi. \qquad (9)$$

The integration is easily performed in terms of elementary functions, giving

$$T(r) = 4\pi s^3 \{\sin 2\pi r s - 2\pi r s \cos 2\pi r s\}/(2\pi r s)^3, \qquad (10)$$

but for comparison with equation (6) the expression may be written

$$T(r) = 4\pi s^3 \{j_1(2\pi r s)\}/(2\pi r s), \qquad (11)$$

where j_1 is a spherical Bessel function. The first zero occurs for

$$2\pi r s = 4\cdot 49340\ldots, \qquad (12)$$

so that three-dimensional syntheses cannot be expected to resolve detail on a scale much smaller than

$$r = 4\cdot 49340\ldots/2\pi s \geq (0\cdot 35757\ldots)\,\lambda. \qquad (13)$$

The minimum resolutions in one-, two-, and three-dimensional syntheses are thus in the ratios

$$1 : 1\cdot 22 : 1\cdot 43. \qquad (14)$$

Criteria other than the peak-to-first-zero distance, such as the width at half-height for $T(r)$, could be chosen, but would not alter the relative resolving powers substantially.

2.4. At first sight it may seem surprising that the resolving power of a one-dimensional synthesis, for the problems to which it is applicable, is greater than that of a three-dimensional. It will not seem so odd to those familiar with the theory of small-particle-size broadening, who will recognize that equations (2), (6) and (10) are, within appropriate scale factors, the amplitude of diffraction by, respectively, a cylinder of unit length and diameter diffracting from planes parallel to its ends, the same diffracting from planes parallel to its axis, and a sphere of unit diameter diffracting from any set of planes {Patterson (1939) and Wilson [1952, equations (6) and (14); 1970, equation (10–29)]}. The line breadths for small crystallites of these shapes increase in the same order as the widths of the smearing functions.

2.5. Attempts to determine electron density in interatomic bonds are likely to necessitate three-dimensional syntheses, but other problems may involve only one- or two-dimensional syntheses. A recent example of a one-dimensional problem is the attempt to determine the distribution of the density of atomic (halogen-atom) centres along the *c* axis of cadmium analogues of apatite (Wilson, Sudarsanan & Young, 1977). Here it was confirmed that a one-dimensional synthesis based on the equivalent of the 00*l* reflexions only gave better resolution than a line section through a complete three-dimensional synthesis. It may be that there are problems (some types of two-dimensional disorder? some features of the bonding electrons in graphite?) that are somewhat better resolved by two-dimensional than by three-dimensional syntheses.

2.6. If the observed density is ideally the convolution of the true density with the smearing function $T(r)$ and $T(r)$ is known, why is it impossible to deconvolute by the standard methods, such as the iteration method of Burger & van Cittert (1932), the Fourier method introduced by Smith (1934) but better known through the work of Stokes (1948), or the relaxation method of Paterson (1950)? These are all equivalent, in theory if not in practice, and the problem is most easily understood through the Fourier approach. The Fourier transform of a convolution is the simple product of the Fourier transforms of the convoluted functions [for an elementary treatment see Wilson (1963, pp. 82–84); the generalization to three dimensions is easy]. If the convolution is observed, and the smearing function is known, the Fourier transform of the true function is therefore

$$\frac{\text{Fourier transform of convolution}}{\text{Fourier transform of smearing function}}, \qquad (15)$$

and the true function should be obtained immediately by taking the Fourier transform of the ratio (15). In the present problem, however, this process simply reproduces the convolution. The argument of Jones & Misell (1970) is readily generalized from one to two or three dimensions. Within the range of observation the Fourier transform of $T(r)$ is unity, and outside this range it is zero. The ratio (15) thus gives the Fourier transform of the convolution, without change, up to the limit of observation. Beyond that limit it gives

$$\frac{\text{some quite unknown quantity}}{\text{zero}}, \qquad (16)$$

and it would clearly be meaningless to include such ratios in a Fourier transform. Deconvolution, therefore, cannot remove termination-of-series effects from the observed density synthesis; the best objectively determinable estimate of the true density is the truncated Fourier series with coefficients as free as possible from systematic error and statistical bias. Attempts like those of Scheringer (1977) need to be made with great caution; either they are pointless, as leading back to the smeared distribution, or they allow the crystallographer to insert (consciously or unconsciously) some of his pre-judgements of what the density ought to be into his estimate of what it is. Bayesian statisticians would presumably approve of the conscious use of the latter process.

Similar remarks, *mutatis mutandis*, apply to some types of $F_o - F_c$ synthesis.

2.7.1. It is well known that the troughs of high and low density surrounding the central maximum of $T(r)$, and hence surrounding any reasonably concentrated feature of a density distribution (such as the electron cloud around an atomic nucleus), can be made less conspicuous by weighting down the higher-order reflexions. As has been repeatedly pointed out [for example, by Wilson (1970, pp. 176–177)], the use of an 'artificial temperature factor' worsens the agreement, in the least-squares sense, between the Fourier-series representation and the function represented; the supposed gain through removal of the troughs is paid for by a broadening of the central maximum and a general blurring of the image. The corresponding process in optical instruments is known as apodization (from a Greek word constructed to mean 'removal of the feet'), and there is an extensive theory [see, for example, the references cited by Jacquinot (1958), and Ross, Fiddy, Nieto-Vesperinas & Wheeler (1978)]. By selective suppression, such as the use of a square aperture instead of a circular one, it is often possible to shift the troughs from a region where they are a nuisance to a region where they are not, and thus, for example, to resolve the dark companion of Sirius from Sirius itself – at the expense of turning Sirius from a circularly symmetric object into a cross.

2.7.2. The analogy with particle-size broadening (§ 2.4) may serve to suggest the regions of reciprocal space that should be used to obtain reduction of troughs in specified directions. For example, in the case of the cadmium analogues of apatite, the optimum simple region would be the interior of a cube inscribed within the limiting sphere and oriented so that one of its triad axes is parallel to the hexad axis of the apatite. Troughs along the hexad axis would be practically suppressed, the central maximum would be enlarged, and there would be gross distortions in directions perpendicular to the cube faces – but these directions are not relevant in the particular problem.

2.7.3. It is not so well known that the central maximum of $T(r)$ can be reduced in size, at the expense of enhancing the pattern of troughs, by selective weighting down of the low-order reflexions. The theory for the simplest case was worked out by Airy (1841), but it was Strutt (later Lord Rayleigh) (1872) who pointed out the increase in resolving power of a telescope produced by masking off the central part of the objective. It is readily seen that if the low orders are completely suppressed over the range 0 to $t < s$, equations (2), (6) and (11) are replaced by

$$T(r) = (\sin 2\pi rs)/\pi r - (\sin 2\pi rt)/\pi r, \tag{17}$$

$$T(r) = 2\pi s^2\{J_1(2\pi rs)\}/(2\pi rs) - 2\pi t^2\{J_1(2\pi rt)\}/(2\pi rt), \tag{18}$$

and

$$T(r) = 4\pi s^3\{j_1(2\pi rs)\}/(2\pi rs) - 4\pi t^3\{j_1(2\pi rt)\}/(2\pi rt) \tag{19}$$

for one, two and three dimensions respectively. Each shows an improvement in resolution, as defined by the Rayleigh criterion, but with more pronounced subsidiary peaks and troughs. There is no easy way of representing the first zeros as functions of t and s simultaneously, but it is perhaps instructive to look at the limiting cases as t approaches s – that is, when only the outermost reflexions are used. The limiting forms are, with d written for $s - t$,

$$T(r) = 2d \cos 2\pi rs, \tag{20}$$

$$T(r) = 2\pi ds J_0(2\pi rs), \tag{21}$$

and

$$T(r) = 4\pi ds^2\, j_0(2\pi rs) = 4\pi ds^2(\sin 2\pi rs)/(2\pi rs). \tag{22}$$

The first zeros are at

$$2\pi rs = \tfrac{1}{2}\pi,\ 2{\cdot}40482\ldots,\ \pi, \tag{23}$$

corresponding to minimum resolutions of

$$r \geq 0{\cdot}125\lambda,\ (0{\cdot}191369\ldots)\,\lambda,\ 0{\cdot}25\lambda \tag{24}$$

respectively. These all show improvements on equations (4), (8) and (13), the improvement being least in the three-dimensional case.

2.8. The 'improvement' described in the preceding paragraph is a reduction in the diameter of the central maximum, called the Airy disk in astronomical applications. A different picture emerges if a criterion based on the nuisance value of the troughs is used, say the ratio of the depth of the first trough to the peak height. For equations (2), (6) and (10) this ratio takes the values 0·217, 0·123, 0·085, which are very favourable in comparison with the values 1·000, 0·402, 0·217 for equations (20)–(22).

2.9. In § 2.7.1 the low-order reflexions were supposed completely suppressed, and there seems to have been no crystallographic application of the procedure. For the sake of completeness, however, it should be mentioned that, before the introduction of powerful computers and direct methods, there was considerable interest in weighting up the high-order reflexions, in order to produce 'sharpened' Patterson syntheses. These show the expected decrease in the diameter of the Patterson peaks and the more pronounced troughs. The process is discussed in Lipson & Cochran (1953, pp. 170–174). The calculation of unitary or normalized structure factors [see Wilson (1970, pp. 158–160) for an elementary account] is much used in direct methods, but rarely for density syntheses [see, however, Main & Hull (1978)]. An exception is the work on halogen-atom distribution in apatites, already mentioned in § 2.5.

3. Bias

3.1. Any physical measurement is subject to errors of two types, systematic and random. In crystallographic measurements statistical fluctuation in the number of photons counted is likely to be the largest random error, but there can be irregular backlash in positioning mechanisms and so on. 'Bias' will be used here to indicate a particular type of systematic error, arising from inadequacy of mathematical techniques, whereby random errors, of mean value zero in the raw data, become a systematic bias in derived quantities – in the present case in the distribution of electron or other density. The density is given by a Fourier series in one, two or three dimensions; such as, for the three-dimensional case,

$$\rho(x,y,z) = U^{-1} \sum_{hkl} F(hkl) \times \exp\{-2\pi i(hx + ky + lz) + i\varphi(hkl)\}, \tag{25}$$

where ρ is the electron *etc.* density, U is the volume of the unit cell, $F(hkl)$ is the modulus of the structure *etc.* factor of the *hkl* reflexion, $\varphi(hkl)$ is its phase, and x,y,z are fractional coordinates within the unit cell. Difficulties in determining φ will be ignored; for the simple structures for which high-quality density determinations are desired the phase will often be fully determined by the symmetry, or restricted to one of the two values 0 and π. Some more complex situations have been considered [for example, by Blow & Crick (1959), Rae (1974), Ross *et al.* (1978) and Price (1978)], but there is much to be said about the modulus of F without adding the complication of its phase. Since $\rho(x,y,z)$ is a linear function of the F's, if the F's as observed are unbiased estimates of the 'true' structure factors, $\rho(x,y,z)$ will be an unbiased estimate of the 'true' density.

3.2. In most crystallographic measurements the structure factor is not observed directly, but is inferred from measurements of an intensity proportional to the square of its modulus. The main exception to this statement is the direct determination of F from the spacing of *Pendellösung* fringes [see, for example, Kato (1969)], a technique applicable only to substances that can be prepared in the form of nearly perfect single crystals. Presumably structure factors so obtained are unbiased estimates. The situation is different for structure factors obtained from intensity measurements.

3.3. Intensities measured by counting photons are in principle unbiased. The form of the distribution function for the fluctuations about the mean differs for different counting modes (Wilson, 1978*c*), and the following discussion is based on unmodified fixed-time counting. There will be differences in detail for fixed-count timing and intermediate modes, but no differences in principle. If the number of counts that ought to be have been registered is N, the actual number observed in any particular case is

$$N_o = N + \varepsilon, \tag{26}$$

where ε is the fluctuation. Theory indicates that, for fixed-time counting and in the absence of disturbing effects, N_o has a Poisson distribution with mean and variance N, so that the mean value of ε is zero, and the observed number of counts is thus an unbiased estimate of the 'true' number N, though the number found in any particular measurement may be greater or less. This property of absence of bias is preserved by any linear transformation of N_o, such as (i) subtraction of background; (ii) division by counting time in order to obtain a counting rate; and (iii) division by the Lorentz–polarization factor (see, however, § 3.5.2). Subtraction of background, which also has a Poisson distribution of counts in fixed-time counting, leads to an hyperbolic Bessel distribution, and the distributions for fixed-count timing are even more complex (Wilson, 1978*a*,*c*). As a result of the statistical fluctuations, the observed background count may be greater than the total reflexion-plus-background count, so that some reflexions are recorded as having negative intensity. However, if the negative intensity observations are counted in, the recorded intensity is still an unbiased estimate of the 'true' intensity [compare Hirshfeld & Rabinovich (1973)]. French & Wilson (1978) have suggested a method of estimating the probable positive value of an intensity recorded as negative. The method rests on a Bayesian combination of the *a priori* distribution of the probability of an intensity (Wilson, 1949) with the probability of an intensity of a given positive value being recorded as negative.

3.4. The property of lack of bias is lost if any non-linear transformation is applied to the measured intensity. The two non-linear transformations commonly used in crystallography are (i) taking the square root of the intensity in order to obtain the modulus of the corresponding structure factor; and (ii) using weights that depend on the observed values of the intensity or of its square root (Wilson, 1976*b*). Only the first of these is of primary interest in the present context. Positive and negative fluctuations in the intensity have equal average values, but a negative fluctuation in the intensity depresses the square root by more than the amount that an equal positive fluctuation increases it. One can write

$$F_o = I_o^{1/2} = (I + \varepsilon)^{1/2}, \tag{27}$$

where F_o is the observed modulus of the structure factor, I_o is the observed intensity, I is the 'true' intensity and ε is the fluctuation. If the fluctuations are small in comparison with the intensity, one can expand the square root in a power series, obtaining

$$F_o = I^{1/2} + \tfrac{1}{2}\varepsilon I^{-1/2} - \tfrac{1}{8}\varepsilon^2 I^{-3/2} + \ldots. \tag{28}$$

The average value of ε is zero, so that the expected value of the second term is zero, but the average value of ε^2 is positive and finite; it is, of course, the variance of the intensity, $\sigma^2(I_o)$. The expected value of the modulus of the structure factor, estimated as the square root of the observed intensity, is thus biased to low values. An estimate, unbiased to the second order in the fluctuations, is

$$F_{\text{corr}} = I_o^{1/2} + \tfrac{1}{8}\sigma^2(I_o)\, I^{-3/2} + \ldots. \tag{29}$$

A correction equivalent to this was given without derivation by Ibers & Hamilton (1964), and Rees (1977*a*,*b*) has attempted a closer approximation, based on the assumption of a Gaussian intensity distribution.

It is obvious that the correction in equation (29) is greatest, both relatively and absolutely, for the weaker reflexions. It is therefore unfortunate that it is just for these reflexions that it is impossible to use it. The series (28) converges only if $\varepsilon < I$, which in practice means that it cannot be used for I_o less than about $3\sigma(I_o)$. There seems to be, as yet, no practicable means of correcting for the bias in structure factors derived from weak or measured-as-negative intensities. Possibly the French & Wilson (1978) procedure could be modified to provide an unbiased estimate; French (private communication) believes that there is a small positive bias.

3.5.1. One can make some qualitative probable deductions about the effect of the above underestimate (if not allowed for) on the derived electron density. In equation (25), any particular F_o may be larger or smaller than its true value, but on the whole the coefficients will be too small, and the general level of the electron-density maxima will be too low. This is, of course, an effect quite distinct from the distortion, generally amounting to a lowering, resulting from the finiteness of the series. Further, the higher-order coefficients, which trim the electron-density maxima into shape, are likely to be smaller, and therefore underestimated to a greater extent, than are the lower-order coefficients, which determine the general position of the maxima. The 'observed' electron-density maxima may thus be expected to be lower and more diffuse than the 'true'. Variation of the parameters of the calculated electron density to match the observed is thus likely to lead to (i) a scale factor that is too low, in an attempt to match the too-low general level of the electron-density maxima, and (ii) temperature parameters (B or β) that are too big, in an attempt to match the too-diffuse maxima. The first of these effects was noticed by Wilson (1975). He showed that if the scale factor had originally been adjusted to make

$$\sum I_c = \sum I_o, \qquad (30)$$

equivalent to

$$\langle I_c \rangle = \langle I_o \rangle, \qquad (31)$$

then least-squares refinement in

$$R_1 = \sum (F_o - EF_c)^2 / \sum F_o^2 \qquad (32)$$

of the scaling factor E would not confirm the value unity, as would naïvely be expected, but would lead instead to the lower value

$$E = \sum F_o F_c / \sum F_o^2 = \langle F_o F_c \rangle / \langle I_o \rangle \qquad (33)$$

{Wilson [1975, equation (9), with change of notation]}. This result has been independently rediscovered by Rees [1978, equation (3)] and Davis, Maslen & Varghese [1978, equation (15)]. The numerical value of E is found to be $1 - \frac{1}{2}R_1$, where R_1 is the value of the residual without adjustment [Wilson, 1975, equation (10)], and is thus some tenths of a percent less than unity (Wilson, 1978*b*). The residual is reduced by the adjustment to

$$(R_1)_{\text{adj}} = R_1 - \tfrac{1}{4}R_1^2 \qquad (34)$$

[Wilson, 1975, equation (11)]. Equation (16) of Davis, Maslen & Varghese leads to the same expression when use is made of the equivalence of direct-space and reciprocal-space least-squares refinements [Wilson (1976*a*); Davis, Maslen & Varghese (1978, Appendix)].

3.5.2. Nielsen (1977) describes a process of optimizing weights for use in least-squares analysis. The process is analytical rather than numerical, but the resultant weights are in principle similar to the optimum filtering function of Davis, Maslen & Varghese (see § 3.6). In the particular example given by Nielsen both the high-order and the low-order reflexions are weighted down relatively to those of medium order. Nielsen (private communication) considers the weighting down of the low-order reflexions 'primarily as an effect of the poor Lorentz correction' for these reflexions.

3.5.3. Equation (33) does not depend on the source of the differences between F_o and F_c, and is valid whether they arise from statistical fluctuations or from systematic errors (defects in the model from which F_c is calculated) or from both. It is, however, of interest to confirm that in the absence of systematic errors equation (33) would follow directly from the bias in F_o if this is not corrected in accordance with equation (29). In the formulation of Wilson (1973, 1976*b*) an uncorrected bias is a systematic error, and the bias in any derived parameter is [Wilson, 1973, equation (8)]

$$-\sum w\delta F_c' / \sum w(F_c')^2 \qquad (35)$$

in the notation of the present paper; the w's are weights if desired, δ is the amount of the bias, and primes indicate differentiation of the calculated structure factor with respect to the parameter in question. In the present instance, with the scaling factor near unity, the derivative of the structure factor with respect to the scaling factor is practically equal to the structure factor, so that the expression (35) becomes

$$-\tfrac{1}{8} \sum wF_c\, \sigma^2(I)\, I^{-3/2} / \sum wF_c^2. \qquad (36)$$

Since $\sigma^2(I) \sim 4F^2\,\sigma^2(F)$ this becomes, nearly enough,

$$-\tfrac{1}{2} \sum w\sigma^2(F) / \sum wF^2, \qquad (37)$$

which is $-\frac{1}{2}R_1$ if there is statistical bias only. The approximation is rather better than might have been expected from the restrictions on the convergence of the series (28) and (29). This is explained by the additional factor F_c arising from F_c', which reduces the effects of the dubious terms with small intensity. A similar argument shows that the general magnitude of the thermal parameters (B's or β's) is increased by a fraction of the same order of magnitude (Wilson, 1977*a*).

3.6. Davis, Maslen & Varghese (1978) evaluate E (in their notation M) for about two-dozen successive shells of $(\sin\theta)/\lambda$, thus, in effect, allowing themselves about two-dozen parameters to represent the bias in the F_o's, not merely a scaling and an overall temperature factor. The resultant, which they call a minimum-variance or optimum filtering function, is thus an 'apodization' in the sense described in § 2.7. Their Fig. 3 shows the predicted broadening of the central image and the reduction of the troughs; the resolution of the former is reduced from the equivalent of $s = 1{\cdot}07$ Å^{-1} to the equivalent of about $s = 0{\cdot}90$ Å^{-1}. Clearly this may be considered an improvement in applications where the troughs are a nuisance, and a worsening in applications where lack of resolution of the peaks is a greater nuisance. It would be interesting to know the effect of correcting the observed structure factors for bias before calculating the values of M.

3.7.1. Least-squares refinement in reciprocal space is exactly equivalent to obtaining a least-squares match of the corresponding observed and calculated densities in direct space, any weights used in the reciprocal-space refinement appearing as distortions of the Fourier coefficients of the density in direct space (Wilson, 1976*a*, in *Effect of weights*). In discussions of bias of electron or other densities, therefore, unit weights should be assigned to the Fourier coefficients involved; this will be assumed in the discussion of bias in positional parameters derived from least-squares refinement in R_1 (§§ 3.8–3.11). Because of the reciprocity just invoked the results are equally applicable to parameters derived from electron-density maps.

3.7.2. It should be noted, however, that non-unit weights may be used when it is deliberately intended to obtain parameters 'biased' by giving greater emphasis to some features of the electron density than to other features. For example, Cochran (1948) showed that weights proportional to the reciprocal of an atomic scattering factor led to parameters corresponding to the maximum (as distinguished from the centroid or other measure of location) of the electron density of that atom. This idea has been greatly developed by Dunitz & Seiler (1973), who showed how weights could be used to accentuate particular features of the electron cloud in estimating the atomic parameters. Such deliberately induced biases are conceptually different from those introduced by inadequate mathematical techniques for handling the raw data. Ideally refinement procedures should compare observed and calculated counts, rather than observed and calculated intensities or structure factors, so that each detected photon receives equal weight. This would be technically possible, though perhaps inconvenient, for least-squares or maximum-likelihood refinements, but it is difficult to see how it could be applied to electron-density mapping.

3.8. Equation (35) applies to the bias in positional parameters also. Consider first the space group $P1$. The derivative of F_c with respect to a positional parameter, say x for the ith atom, is in this case

$$F_c' = 2\pi h f_i \sin\theta_i, \tag{38}$$

where f_i is the atomic scattering factor of the ith atom and θ_i is the difference in phase between its scattering and that of the complete unit cell. From equation (35) the bias of this parameter arising from the bias in the structure factors is

$$-\frac{\sum \delta h f_i \sin\theta_i}{2\pi \sum h^2 f_i^2 \sin^2\theta_i}. \tag{39}$$

The terms in the bottom line are all positive, but those in the top line are of random sign, so the expected value of the bias in the positional parameters is zero, though for any particular parameter it may be considerable. It has been suggested that the statistical fluctuations allow the atom, or rather its Fourier representation, to slide a little way down the slope of the electron density [Wilson, 1977*a*, discussion of equations (82)–(85)], but the argument is based on a very crude approximation.

In equation (39) the number of terms top and bottom is the same, and equal to the total number of reflexions measured, say N. The root-mean-square (r.m.s.) bias thus increases as $N^{1/2}$ through the top line, and decreases as N^{-1} through the bottom line, so that overall the r.m.s. bias decreases as $N^{-1/2}$, the inverse square root of the number of reflexions measured. One thus has

$$\text{r.m.s. bias in } x_i = \frac{\langle \delta^2 h^2 f_i^2 \sin^2\theta_i\rangle^{1/2}}{2\pi N^{1/2}\langle h^2 f_i^2 \sin^2\theta_i\rangle}, \tag{40}$$

where the averaging is over the N values of hkl. Substitution of δ from

$$\delta \sim -\tfrac{1}{8}\sigma^2(I_o)\, I^{-3/2} \sim -\tfrac{1}{2}\sigma^2(F_o)\, F^{-1} \tag{41}$$

gives

$$\text{r.m.s. bias in } x_i \sim \frac{\langle \sigma^4(F_o)\, F^{-2} h^2 f_i^2 \sin^2\theta_i\rangle^{1/2}}{4\pi N^{1/2}\langle h^2 f_i^2 \sin^2\theta_i\rangle}. \tag{42}$$

There is no reason to expect any correlation between $\sin\theta_i$ and h and f_i, and $\sigma^2(F_o)$ does not vary greatly with hkl, at any rate for fixed-time counting. It is difficult to demonstrate that there is *no* correlation between $\sin\theta_i$ and F, but any correlation must be small, since (i) the contribution of the ith atom to F is of the order of $f_i/\Sigma^{1/2}$ of the total [where Σ is the sum of the squares of the atomic scattering factors (Wilson, 1942)], and is thus of the order of the inverse square root of the number of atoms in the unit cell, say $n^{-1/2}$, and (ii) the contribution of the ith atom to F varies as $\cos\theta_i$, and is thus in quadrature to $\sin\theta_i$. Neglecting correlations and putting $\langle\sin^2\theta\rangle = \frac{1}{2}$ gives

$$\text{r.m.s. bias in } x_i \sim \frac{\sigma^2(F_o)\langle I^{-1}\rangle^{1/2}}{8^{1/2}\,\pi N^{1/2}\langle h^2 f_i^2\rangle^{1/2}}. \tag{43}$$

Since the statistical contribution to R_1 is $\sigma^2(F_o)/\langle I\rangle \sim \sigma^2(F_o)/\Sigma$, equation (43) becomes

$$\text{r.m.s. bias of } x_i \sim R_1 \frac{\Sigma\langle I^{-1}\rangle^{1/2}}{8^{1/2}\,\pi N^{1/2}\langle h^2 f_i^2\rangle^{1/2}}. \tag{44}$$

If reflexions measured as zero were to be included, the mean value of I^{-1} would be infinite, giving infinite bias. However, in actual refinements in R_1, reflexions of less than some minimum value $I_{\min}$ [often $3\sigma(I_o)$] are omitted, so that $\langle I^{-1}\rangle$ remains finite. For the acentric distribution (Wilson, 1949)

$$\langle I^{-1}\rangle \sim \frac{\Sigma^{-1}\int_{I_{\min}}^{\infty} I^{-1}\exp(-I/\Sigma)\,\mathrm{d}I}{\Sigma^{-1}\int_{I_{\min}}^{\infty}\exp(-I/\Sigma)\,\mathrm{d}I} \tag{45}$$

$$= \Sigma^{-1}\frac{E_1(I_{\min}/\Sigma)}{\exp(-I_{\min}/\Sigma)}, \tag{46}$$

where $E_1(x)$ is the exponential integral. Since $I_{\min}/\Sigma$ is ordinarily small, to a first approximation

$$\langle I^{-1}\rangle = \Sigma^{-1}[\log_e(\Sigma/I_{\min}) - \gamma] \tag{47}$$

where $\gamma = 0{\cdot}577\ldots$ is Euler's constant (Abramowitz & Stegun, 1964, formula 5.1.11). One then has

$$\text{r.m.s. bias of } x_i \sim R_1\frac{\Sigma^{1/2}[\log_e(\Sigma/I_{\min}) - \gamma]^{1/2}}{8^{1/2}\,\pi N^{1/2}\langle h^2 f_i^2\rangle^{1/2}}. \tag{48}$$

For a quasi-equiatom structure $\Sigma \sim nf^2$, where n is the number of atoms in the unit cell and f is a mean structure factor, so that

$$\text{r.m.s. bias of } x_i \sim R_1\, n^{1/2}[\log_e(\Sigma/I_{\min}) - \gamma]^{1/2}/8^{1/2}\,\pi N^{1/2}\, h_{\text{r.m.s.}}. \tag{49}$$

The bias thus increases as the square root of the number of atoms to be located and decreases rather faster than the square root of the number of reflexions available to locate them ($h_{\text{r.m.s.}}$ increases with increasing n and N). This behaviour seems very reasonable, as does the linear increase with R_1.

3.9. If the space group is $P\bar{1}$ the treatment in § 3.8 needs modification in two respects. First, the expression for F_c', equation (38), is doubled; θ_i retains its interpretation as the phase of scattering of the ith atom (not that of the ith centrosymmetric pair). Secondly, the centric distribution must be used instead of the acentric in equation (45), giving

$$\langle I^{-1}\rangle = \frac{(2\pi\Sigma)^{-1/2}\int_{I_{\min}}^{\infty} I^{-3/2}\exp(-I/2\Sigma)\,\mathrm{d}I}{(2\pi\Sigma)^{-1/2}\int_{I_{\min}}^{\infty} I^{-1/2}\exp(-I/2\Sigma)\,\mathrm{d}I}. \tag{50}$$

The integrals are incomplete Γ functions (Abramowitz & Stegun, 1964, pp. 260–263). However, a series can be obtained by repeated integration by parts, giving

$$\langle I^{-1}\rangle = \Sigma^{-1}[(2\Sigma/\pi I_{\min})^{1/2} + 2/\pi - 1 + \ldots] \tag{51}$$

with sufficient accuracy for estimating the bias in x_i; the terms not written down are in ascending powers of $(I_{\min}/2\Sigma)^{1/2}$. One thus obtains

$$\text{r.m.s. bias of } x_i \sim R_1\,\Sigma^{1/2}[(2\Sigma/\pi I_{\min})^{1/2} + 2/\pi - 1]^{1/2}/4\pi N^{1/2}\langle h^2 f_i^2\rangle^{1/2}, \tag{52}$$

which differs from equation (48) through a factor $2^{-1/2}$ and in the form of the function of $\Sigma/I_{\min}$ in the square bracket. Earlier estimates of r.m.s. bias (Wilson, 1977*a*,*b*) used cruder approximations, equivalent to putting $\langle I^{-1}\rangle = \Sigma^{-1}$, so that the factors in square brackets in equations (48) and (52) did not appear. The present estimates, therefore, are several times as big.

3.10. The arguments leading to equations (38)–(52) are based on the assumption that the atoms are in general positions in the space group $P1$ or $P\bar{1}$. Atoms in special positions have one or more positional parameters fixed by the symmetry, and for such parameters the bias vanishes. If the atoms are in a Wyckoff position of multiplicity p, the bias is reduced by a factor of $p^{-1/2}$ (acentric) or $(\frac{1}{2}p)^{-1/2}$ (centric) (Wilson, 1977*a*). In §§ 3.8 and 3.9 it was tacitly assumed that interactive effects between dispersion (Wilson, 1975, 1978*d*) and bias could be neglected. It was also assumed that the N reflexions entering into equation (39) and later equations were non-equivalent. If a full set of reflexions is used the equations for the r.m.s. bias must be multiplied by the square root of the multiplicity factor for the general reflexions of the space group in question.

3.11. It would be of great interest to obtain an expression for the bias in the electron density [equation (25)] resulting from the bias $-\frac{1}{2}\sigma^2(F_o)/F$ in the structure factors. For fixed-time counting the variance of the structure factors does not vary greatly with hkl, so that the bias synthesis has coefficients approximately proportional to the reciprocals of the true coefficients. A search of several textbooks on Fourier analysis did not reveal any general properties relating syntheses with coefficients F and F^{-1}. The only obvious remark, therefore, is that the bias in the scaling factor will reduce the mean density and the r.m.s. variation about the mean by a fraction $\frac{1}{2}R_1$, as qualitatively anticipated in § 3.5. The effect is not, however, a trivial change in scale; the peak shapes are distorted by the selective weighting down of the weaker reflexions.

4. Discussion

Since the biases discussed in § 3 depend on the variance of the observations, they can be reduced to any desired extent by improving the stability of the apparatus and increasing the counting times. They are thus likely to be of little importance in highly accurate investigations of elements or simple compounds in space groups of high symmetry, but may render suspect deductions from observations of ordinary quality on more complex compounds. The limit of resolution discussed in § 2 is independent of the accuracy of the observations, and can only be reduced by going to shorter wavelengths, and so enlarging the reciprocal-space 'window' through which the density is viewed. For Cu *Kα* radiation, for example, the limit is of the same order of magnitude as the size of the features interpreted as bonding electrons.

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Note: Since this paper was written the principal papers given at the Bat-Sheva Seminar on Electron Density Mapping, 1977, have appeared (Hirshfeld, 1977). Many of the points made in the present paper were touched on in the seminar, but not treated as fully. A few references to the seminar papers or the original sources have been added at the 'referee's report' stage.

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