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# A Maximum Entropy Derivation of the Integrated Direct Methods–Isomorphous Replacement or Integrated Direct Methods–Anomalous Scattering Probability Distributions

BY R. K. BRYAN

*European Molecular Biology Laboratory, Meyerhofstrasse* 1, 6900 *Heidelberg, Federal Republic of Germany*

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## Abstract

It is shown that taking the appropriate terms from a series expansion of the Shannon–Jaynes entropy of a density map subject to intensity constraints gives the standard direct methods structure factor probability distribution functions. The use of two maps, one to represent a native structure, the other to represent either heavy atoms or the number density of anomalous scatterers, and the application of a similar expansion to the total entropy of both maps rapidly gives either the integrated direct methods-single isomorphous replacement or the integrated direct methods-anomalous scattering probability densities.

## 1. Introduction

The techniques of probabilistic direct methods have been applied to pairs of isomorphous structures (single isomorphous replacement, SIR) (Hauptman, 1982*a*; Karle, 1983, 1984*b*; Giacovazzo, Cascarano & Zeng Chao-de, 1988), and to structures containing anomalous scatterers (single-wavelength anomalous scattering, SAS) (Hauptman, 1982*b*; Giacovazzo, 1983; Karle, 1984*a*, *b*, *c*), and give rise to probability distribution functions (p.d.f.s) for combinations of the two sets of structure factors involved, *i.e.* those of the native and derivative, or of the Bijvoet pairs, respectively. Such distributions have been obtained both for two structure factors, which are trivial in the native-only case, but now relate the native and derivative structure factors with the same index, or the two members of a Bijvoet pair, and for the six structure factors dependent on a given triplet of reciprocal space indices, from which conditional distributions of eight kinds of three-phase invariants may be found as functions of the six amplitudes. The implications of these relations have been examined in several contexts, and Karle (1986) and Fortier, Moore & Fraser (1985) give further references to these developments.

These results were obtained from the standard direct methods hypothesis of atoms randomly independently and *a priori* uniformly distributed throughout the unit cell, and follow in a similar way to the calculation of p.d.f.s of invariants for the native-only case. Extensive calculations were needed to combine the contributions of each atom towards the overall p.d.f. of the structure factors. The p.d.f. of a particular phase invariant was found by fixing the amplitudes at the measured values, and possibly also integrating out phases not involved in the invariant of interest.

Much discussion of the theory of applying maximum entropy to the phase problem has taken place in recent years (*e.g.* Collins, 1982; Wilkins,

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Varghese & Lehmann, 1983; Bricogne, 1984; Livesey & Skilling, 1985; Navaza, 1985). One aspect of these developments has been to interpret the entropy of a density map as the logarithm of the probability of the distribution of the atoms within the unit cell, and thus show the equivalence to direct methods when intensity constraints are applied (Bricogne, 1984). Arguments have, however, been made against such a literal interpretation (Gull & Skilling, 1984; Livesey & Skilling, 1985). Taking the appropriate marginals of this p.d.f. (Bricogne, 1984) gives p.d.f.s of phase invariants similar to direct methods (Hauptman, 1975*a*; Fortier & Hauptman, 1977*a*, *b*; Giacovazzo, 1980). Moreover, there have also been several computational demonstrations of the use of Maxent [this term will be used here in the specific context of the maximization of the Shannon–Jaynes entropy (Jaynes, 1968, 1982) of the spatial distribution of density within a map, subject to data constraints] with *structure factor* constraints, although its successful practical use in crystallography with *intensity* constraints seems to have been limited to centrosymmetric space groups (Gull, Livesey & Sivia, 1987), or with SIR data using known heavy-atom positions (Bryan & Banner, 1987), where in both cases the problem is simplified to making a choice between alternative phases. SIR fibre data (Bryan, Bansal, Folkhard, Nave & Marvin, 1983; Marvin, Bryan & Nave, 1987) give the additional constraint of continuity in reciprocal space, and have enabled a previously unknown structure to be solved by Maxent.

In a further calculation with SIR data (Bryan, 1988), the assumption of known heavy-atom positions was not made. Instead, two independent maps were used to represent the native density and heavy-atom densities respectively, and their total entropy maximized subject to the constraints imposed by the intensities of both the native and derivative structures. This method appears to bear the same relation to the integrated direct methods–SIR method as single-map Maxent does to conventional direct methods, so a formal proof of this is presented here, and additionally it is shown that the integrated direct methods–SAS result can be found in a very similar way. As a preliminary, the methodology of Bricogne (1984) for the derivation of phase-invariant distributions from Maxent is examined, and it is shown that similar results can be achieved by taking the appropriate terms from a series expansion of the entropy. This method is then used for the derivations of the 'integrated' distributions.

## 2. Structure factor distributions by series expansion of entropy

Bricogne (1984) has given a very complete discussion of the relation between probabilistic direct methods and particular approximations of the Shannon–Jaynes entropy of a map, subject to constraints on its Fourier intensities. This method involves the two-stage process of (i) obtaining the map $q$ which maximizes the entropy subject to some structure factor constraints; followed by (ii) calculating the relative entropy between the final map $p$ (subject to further intensity constraints) and $q$, and interpreting this relative entropy as being proportional to the logarithm of the probability of the map $p$. Appropriate choice of the two constraint sets and of the terms taken from series expansions of both $q$ as a function of the given structure factors, and of $p$ about $q$, then gives the phase invariant p.d.f.s.

For the purposes of this paper, a simpler treatment, that of a series expansion of the entropy around a uniform map, allows the required structure factor distributions to be obtained in a single step. When applied to the SIR or SAS problems, the expansion to third order may be compared directly with the expressions of Hauptman (1982*a*, *b*) and of Giacovazzo (1983). The initial work of Hauptman (1982*a*) calculated the distributions in terms of zero-angle atomic scattering factors, but recently Giacovazzo *et al.* (1988) have extended these results to allow for the wavelength dependence. Here, as the main purpose is to show that the distribution of invariants may be derived *via* the maximum entropy principle, the simplifying assumption of equal point atoms will be made. Unfortunately, the entropies, phase probabilities and relationships between isomorphous structures are most conveniently written in terms of unitary ($U$), normalized ($E$) and ordinary structure factors ($F$) respectively, so the scalings, with $N$ equal atoms of scattering factor $f$, $F=(Nf^2)^{1/2}E=NfU$ will often be needed. The inclusion of wavelength dependent atomic scattering factors, instead of the assumption of point atoms, would of course also make these relations depend on wavelength.

If $p(\mathbf{x})$, $\int p(\mathbf{x})\,\mathrm{d}^3\mathbf{x}=1$, represents a normalized density map in a unit cell of volume $\mathcal{V}$, so that $Np(\mathbf{x})$ is the number density of atoms at $\mathbf{x}$, the Shannon–Jaynes entropy of $p$ relative to a given prior map $m(\mathbf{x})$ is (Jaynes, 1968)

$$S(p;\,m)=-\int p(\mathbf{x})\log\left[p(\mathbf{x})/m(\mathbf{x})\right]\mathrm{d}^3\mathbf{x}. \tag{1}$$

Assuming a uniform prior $m(\mathbf{x})$ and expanding $p(\mathbf{x})$ about the uniform map, with $p(\mathbf{x})=(1/\mathcal{V})[1+u(\mathbf{x})]$, gives

$$\begin{aligned}S&=(1/\mathcal{V})\int[1+u(\mathbf{x})]\log[1+u(\mathbf{x})]\,\mathrm{d}^3\mathbf{x},\\&=-(1/\mathcal{V})\int\{\tfrac{1}{2}u(\mathbf{x})^2-\tfrac{1}{6}u(\mathbf{x})^3+\cdots\\&\qquad+[(-)^r/r(r-1)]u(\mathbf{x})^r\}\,\mathrm{d}^3\mathbf{x}.\end{aligned} \tag{2}$$

If we write $u(\mathbf{x})$ in terms of its Fourier transform, $u(\mathbf{x})=\sum_{\mathbf{k}} U_{\mathbf{k}} \exp(2\pi i\mathbf{x}\,.\,\mathbf{k})$, this becomes

$$-\frac{1}{2\mathscr{V}}\int \sum_{\mathbf{kl}} U_{\mathbf{k}}U_{\mathbf{l}} \exp\left[2\pi i\mathbf{x}\,.\,(\mathbf{k}+\mathbf{l})\right] \mathrm{d}^3\mathbf{x}$$
$$+\frac{1}{6\mathscr{V}}\int \sum_{\mathbf{klm}} U_{\mathbf{k}}U_{\mathbf{l}}U_{\mathbf{m}} \exp\left[2\pi i\mathbf{x}\,.\,(\mathbf{k}+\mathbf{l}+\mathbf{m})\right] \mathrm{d}^3\mathbf{x}+\cdots$$
$$+\frac{(-)^{r-1}}{r(r-1)\mathscr{V}}\int \sum_{\mathbf{h}_j, j=1,\ldots,r} \prod_j U_{\mathbf{h}_j} \exp\left(2\pi i\mathbf{x}\,.\,\sum_j \mathbf{h}_j\right) \mathrm{d}^3\mathbf{x}. \tag{3}$$

The integrations give $\mathscr{V}\times\delta$ functions, so, if we change to amplitude and phase, with $U=V\exp i\varphi$,

$$S=-\tfrac{1}{2}\sum_{\mathbf{k}} V_{\mathbf{k}}^2+\tfrac{1}{6}\sum_{\substack{\mathbf{klm}\\ \mathbf{k}+\mathbf{l}+\mathbf{m}=0}} V_{\mathbf{k}}V_{\mathbf{l}}V_{\mathbf{m}} \exp i(\varphi_{\mathbf{k}}+\varphi_{\mathbf{l}}+\varphi_{\mathbf{m}})$$
$$+\ldots+\frac{(-)^{r-1}}{r(r-1)}\sum_{\substack{\mathbf{h}_j, j=1,\ldots,r\\ \sum_j \mathbf{h}_j=0}} \prod_j V_{\mathbf{h}_j} \exp\left(i\sum_j \varphi_{\mathbf{h}_j}\right). \tag{4}$$

Since $N^{1/2}U\sim E=O(1)$, the sizes of the terms in this series decrease as $N^{-r/2}$.

The standard combinatorial argument (Gull & Daniell, 1978; Bricogne, 1984) for the derivation of the entropy uses Stirling's approximation to obtain $NS$ as an asymptotic approximation to the logarithm of the probability of $N$ atoms being so distributed as to give the normalized density $p$. Thus $\exp(NS)$ gives an asymptotic approximation to the probability of the density $p$, which by (4) may be expressed as a function of the structure factors corresponding to $p$.

From this result, we wish to obtain the marginal distributions of specific $r$-tuplets of structure factors, which in principle is performed by integrating out all the other structure factors, a rather complicated task. However, by taking the expansion only as far as the $N^{-1/2}$ term, we obtain, with $|E|=R$,

$$P\sim\exp\left[-\tfrac{1}{2}\sum_{\mathbf{k}} R_{\mathbf{k}}^2+(1/6N^{1/2})\right.$$
$$\left.\times\sum_{\substack{\mathbf{klm}\\ \mathbf{k}+\mathbf{l}+\mathbf{m}=0}} R_{\mathbf{k}}R_{\mathbf{l}}R_{\mathbf{m}} \exp i(\varphi_{\mathbf{k}}+\varphi_{\mathbf{l}}+\varphi_{\mathbf{m}})\right]. \tag{5}$$

The integration to give the marginal distribution of a single triplet invariant can be performed to $O(N^{-1/2})$ by the usual method (*e.g.* Hauptman, 1975*a*, *b*, 1982*a*) of expansion of the exponential containing the $N^{-1/2}$ term, integration, and the expansion of the logarithm in the equality $x=\exp(\log x)$. Since a given **klm** triplet, with $\mathbf{k}+\mathbf{l}+\mathbf{m}=0$, has six contributions from the summation in the third order term plus a Friedel symmetric term, the result is

$$P(E_{\mathbf{k}}, E_{\mathbf{l}}, E_{\mathbf{m}})\propto\exp\left[-(R_{\mathbf{k}}^2+R_{\mathbf{l}}^2+R_{\mathbf{m}}^2)\right.$$
$$\left.+2N^{-1/2}R_{\mathbf{k}}R_{\mathbf{l}}R_{\mathbf{m}}\cos(\varphi_{\mathbf{k}}+\varphi_{\mathbf{l}}+\varphi_{\mathbf{m}})\right]. \tag{6}$$

Changing from $\mathrm{d}^2E$ to $R\mathrm{d}R\mathrm{d}\varphi$ then gives the familiar structure factor triplet p.d.f. The result that, to third order, a triplet marginal of $S$ is maximized for fixed amplitudes if $\varphi_{\mathbf{k}}+\varphi_{\mathbf{l}}+\varphi_{\mathbf{m}}=0$, $\mathbf{k}+\mathbf{l}+\mathbf{m}=0$, was noticed by Bryan (1980), although its significance in crystallography was not.

Further terms in (4) should yield distributions of higher invariants, with the selection of terms being guided by the neighbourhood principle (Hauptman, 1977), or phasing shells (Giacovazzo, 1980, pp. 303-304). An $r$th order term ($r>2$), with indices $\{\mathbf{h}_i, i=1,\ldots,r;\ \sum_i \mathbf{h}_i=0\}$, will appear $r!$ times in the summation in (4), so the product of $r$ structure factors will have a net coefficient of $(-)^{r-1}2(r-2)!$ For $r=4, 5, 6$ these coefficients are seen to agree with those of the first neighbourhood for the quartet, quintet and sextet structure factor distributions (Hauptman, 1975*a*; Fortier & Hauptman, 1977*a*, *b*), evaluated for the particular case of equal atoms. There are some discrepancies, for reasons yet to be clarified, in the coefficients for some of the second neighbourhood terms, although these particular terms disappear when the conditional p.d.f. of the phase invariant is evaluated (Hauptman, 1975*b*; Giacovazzo, 1980, pp. 307-310; Hauptman & Fortier, 1977*a*, *b*).

### 3. Phase invariants by Maxent with SIR or SAS data

Hauptman (1982*a*, *b*), Karle (1983, 1984*a*, *b*, *c*) and Giacovazzo (1983) have shown that doublet and triplet phase invariant p.d.f.s can be derived when intensity data are available either for an isomorphous pair, or when anomalous scatterers are present. Eight such triplet invariants exist, where each structure factor may be either a native or a derivative (in SIR), or either of the Bijvoet pair (SAS). These calculations rely on the usual strategy for the derivation of distributions of structure factors: the combination of the contributions to the structure factors from a number of independently distributed atoms. The added complication for the SIR/SAS case is that the structure factors now have contributions from two species of atoms. Although Hauptman's results are for structures which are isomorphous in a rather general sense, the numerical results presented (Hauptman, Potter & Weeks, 1982; Fortier, Weeks, & Hauptman, 1984*a*) pertain to the more usual case of straightforward heavy atom addition, which will therefore be dealt with here.

To apply Maxent to these problems, a separate map is used to define the distribution of each species of atoms, so the p.d.f. of an invariant depends on the total entropy of both maps, subject to the data constraints. It is important, though, to represent the correct quantities by the density maps. There have been many criticisms of Maxent in the sense that it can only reconstruct real positive densities, whereas in some applications the physical quantity of interest may be negative or complex, for a reconstructed wave front, say, or, as here, complex scattering coefficients. The correct way to use Maxent (Skilling & Gull, 1984) in such problems is to have the map represent the *number density* of objects, necessarily positive, which may be imaged *via* physical quantities that may themselves also be real and positive, but may be complex, quaternion, or whatever. Thus, for the anomalous case one map represents the number density of anomalous scatterers, and the complex scattering factor is applied to the Fourier transform of this number density to give the correct contribution to the total structure factors. The same approximations as in § 2 will then give the marginal p.d.f.s of the structure factors of interest.

To demonstrate this process, the relations for the SIR doublet and triplet and for the SAS doublet will be derived for the case of identical native atoms and a single type of replacement atom. Higher order invariants may be found by the same methods, as indicated in § 2 for the native case.

### 3.1. *Preliminary definitions*

To preserve notation in the two applications, the total structure will be defined as the sum of two parts, one representing the native structure, and the second an 'additional' structure, representing the heavy atoms for SIR or the anomalous scatterers for SAS. Quantities for the native structure will be unsubscripted, those for the additional structure subscripted with $a$, and those for the total structure with $t$, so the native structure is composed of $N$ identical atoms of scattering factor $f$, the additional structure $N_a$ atoms of scattering factor $f_a$, with $N_t = N + N_a$. The structures are represented by maps of the number density of atoms, $Np(\mathbf{x})$ and $N_a p_a(\mathbf{x})$, where $p$ and $p_a$ are each normalized to unity. The total entropy of both maps can be written as the weighted sum of the entropies of the individual maps, using the usual laws (Shannon & Weaver, 1949). Thus

$$S(p; p_a) = (N/N_t)S(p) + (N_a/N_t)S(p_a) + S(N, N_a). \tag{7}$$

The third term in (7), given by

$$\begin{aligned} S(N, N_a) = &-(N/N_t)\log(N/N_t) \\ &-(N_a/N_t)\log(N_a/N_t), \end{aligned}$$

is the entropy of the distribution of the numbers of atoms between the two maps, and is constant if the numbers of atoms of each type are known, which is the case here, as the native and replacement atoms do not transmute. With $P = \exp(N_t S)$, to third order, using (4) and (5), one finds

$$\begin{aligned} \log P = &-\tfrac{1}{2}\sum_{\mathbf{k}} N|U_{\mathbf{k}}|^2 + N_a|U_{a\mathbf{k}}|^2 \\ &+\tfrac{1}{6}\sum_{\mathbf{k}+\mathbf{l}+\mathbf{m}=0} NU_{\mathbf{k}}U_{\mathbf{l}}U_{\mathbf{m}} + N_a U_{a\mathbf{k}}U_{a\mathbf{l}}U_{a\mathbf{m}}. \end{aligned} \tag{8}$$

In the following, reciprocal space indices will be omitted except where necessary.

### 3.2. *Doublet and triplet phase invariants with SIR data*

Isomorphism is imposed by setting $F_t = F + F_a$, where $F = NfU$, $F_a = N_a f_a U_a$. Let $\psi$ be the phase of $F_t$, so the second order term in (8) for one Friedel pair becomes

$$\begin{aligned} &-\frac{N}{(Nf)^2}|F|^2 - \frac{N_a}{(N_a f_a)^2}|F_t - F|^2 \\ &= -\frac{1}{N_a f_a^2}\left[\frac{Nf^2 + N_a f_a^2}{Nf^2}|F|^2 + |F_t|^2 \right. \\ &\qquad \left. -2|F||F_t|\cos(\varphi - \psi)\right] \\ &= -\frac{1}{1-\alpha^2}[|E|^2 + |E_t|^2 - 2\alpha|E||E_t|\cos(\varphi - \psi)], \end{aligned} \tag{9}$$

which is seen to be the exponent in equation (2.4) of Hauptman (1982*a*), with $\alpha_{20} = \alpha_{11} = Nf^2$, $\alpha_{02} = Nf^2 + N_a f_a^2$, $\alpha = (\alpha_{20}/\alpha_{02})^{1/2}$, $F = \alpha_{20}^{1/2}E$ and $F_t = \alpha_{02}^{1/2}E_t$.

The third order term for one **klm** combination from (8), upon substitution for $F_a$ and application of the ×6 multiplicity for permutations of the summation indices, is

$$\begin{aligned} &\left(\frac{1}{N^2 f^3} - \frac{1}{N_a^2 f_a^3}\right)F_{\mathbf{k}}F_{\mathbf{l}}F_{\mathbf{m}} \\ &\quad + \frac{1}{N_a^2 f_a^3}[F_{t\mathbf{k}}F_{\mathbf{l}}F_{\mathbf{m}} + \text{perms} \\ &\quad - (F_{t\mathbf{k}}F_{t\mathbf{l}}F_{\mathbf{m}} + \text{perms}) + F_{t\mathbf{k}}F_{t\mathbf{l}}F_{t\mathbf{m}}], \end{aligned} \tag{10}$$

where 'perms' denotes the three combinations of the indices with the native or the derivative structure factors. The change to normalized structure factors gives coefficients for the four types of terms of

$$\begin{aligned} \beta_0 &= \left(\frac{1}{N^2 f^3} - \frac{1}{N_a^2 f_a^2}\right)(Nf^2)^{3/2} = \frac{(N_a^2 f_a^3 - N^2 f^3)}{N^{1/2} N_a^2 f_a^3}, \\ \beta_1 &= \frac{Nf^2(Nf^2 + N_a f_a^2)^{1/2}}{N_a^2 f_a^3}, \\ \beta_2 &= -\frac{N^{1/2} f(Nf^2 + N_a f_a^2)}{N_a^2 f_a^3}, \\ \beta_2 &= \frac{(Nf^2 + N_a f_a^2)^{3/2}}{N_a^2 f_a^3}. \end{aligned} \tag{11}$$

The phases of the various terms are Hauptman's phase invariants, and changes of variable from $d^2F$ to $|F|d\varphi\, d|F|$ give, together with the doublet terms, equation (3.4) of Hauptman (1982*a*), with the $\beta_i$ coefficients evaluated for equal atoms. Clearly there is no obstacle to deriving quartet/second neighbourhood relations, except that 16 quartet and $8\times 3=24$ triplet terms will be involved.

### 3.3. *Doublet phase invariants with SAS data*

The SAS result follows in a similar way. The structure factors of the maps are rewritten in terms of the Bijvoet pair for the total density. If the anomalous scatterers have a scattering factor $f_a\, e^{i\delta}$, $f_a$ real, the Bijvoet pair is

$$\begin{aligned} F^+ &= NfU + N_af_aU_a\, e^{i\delta},\\ F^- &= NfU^* + N_af_aU_a^*\, e^{i\delta}, \end{aligned} \tag{12}$$

and hence

$$\begin{aligned} U &= \frac{F^+\, e^{-i\delta} - F^{-*}\, e^{i\delta}}{Nf(e^{-i\delta}-e^{i\delta})},\\ U_a &= \frac{F^+ - F^{-*}}{N_af_a(e^{i\delta}-e^{-i\delta})}. \end{aligned} \tag{13}$$

Writing $F^+ = A\, e^{i\varphi}$, $F^- = B\, e^{i\psi}$ and substituting in the second order term of (8), we obtain

$$\begin{aligned} \log P = {} & \{-(A^2+B^2)(N_af_a^2+Nf^2)\\ & +2AB[N_af_a^2\cos(\varphi+\psi-2\delta)\\ & +Nf^2\cos(\varphi+\psi)]\}\\ & \times\{4NN_af^2f_a^2\sin^2\delta\}^{-1}\\ = {} & \frac{-R^2-S^2+2XRS\cos(\varphi+\psi+\xi)}{1-X^2}, \end{aligned} \tag{14}$$

where

$$\begin{aligned} \tan\xi &= -N_af_a^2\sin 2\delta/(Nf^2+N_af_a^2\cos 2\delta),\\ \alpha &= Nf^2+N_af_a^2,\\ X &= (N^2f^4+N_a^2f_a^4+2NN_af^2f_a^2\cos\delta)^{1/2}/\alpha, \end{aligned}$$

and $R=A/\alpha^{1/2}$ and $S=B/\alpha^{1/2}$ are the normalized amplitudes. Equation (14) may be compared with the exponent of equation (2.10) of Hauptman (1982*b*), or equation (4) of Giacovazzo (1983). In exactly the same way, the p.d.f. of the triplet pairs can be found, but the very extensive coefficients are omitted here. Note that (12) implicitly selects the enantiomorph by relating the sign of the anomalous phase change to the +/− choice. It is for this reason that a non-zero estimate of the $\varphi+\psi$ invariant is produced, and not that a poor estimate of $\xi$ is used, as has been stated by Fortier, Fraser & Moore (1986). There is thus only a twofold ambiguity in the solution, not an eightfold, which explains why the results of Fortier, Fraser & Moore (1986) are clustered in two groups if the distribution of invariants is sharp. Indeed, their Fig. 2 is misleading, as the interpretation depends on the particular (positional) phase of the anomalous substructure compared with the normal.

## 4. Discussion

It has been shown that the integrated direct methods-SIR and direct methods-SAS structure factor distributions result also from an approximation of the entropy of the two-map density. The derivations here have assumed equal atoms within each set. In principle, the extension to the general case would be as follows, although the details have yet to be worked out. A separate ensemble is introduced for each atomic species, and the total entropy evaluated as the sum of the entropies of the individual ensembles, by the appropriate extension of (7). Consider first the native-only case, and suppose the $i$th ensemble contains $N_i$ atoms of scattering factor $f_i$, with unitary structure factor $U_i$. The marginal probability of the native structure factors $F_{\mathbf{h}}$ is evaluated by integration of $\exp(N_iS)$ over all the $U_i$, subject to the condition $F=\sum_i N_if_iU_i$, which could be performed by the usual methods of characteristic functions (*e.g.* Klug, 1958). The application to the isomorphous case is clear; there will be two linear combinations of the $U$'s that give observables, so integration over the $U_i$'s subject to two constraints gives the joint probability of both the native and derivative structure factors.

Hauptman (1982*a*, *b*) and Giacovazzo (1983) suggest that the two and six structure factor p.d.f.s should be exploited by fixing the amplitudes at the measured values and integrating out all but one of the invariants, thus giving the marginal distributions for each phase invariant. These would then be exploited in a phasing step to deduce all the phases from some starting set, in a similar way to the usual native-only methods. The Maxent approach allows the two maps to be calculated directly, and automatically takes into account the relations between phases to all orders. Bricogne (1984) gives a more complete discussion of these points in the native-only context, most of which is applicable here. The question as to whether the underlying assumption behind both probabilistic direct methods and this formulation of Maxent is the best criterion has, however, not yet been answered; *i.e.* whether the *a priori* assumption of uniformity and independence of the distribution of atoms is indeed appropriate, or whether it is an inadequate description of the complexity of molecular, and particularly macromolecular, structures, and further assumptions, perhaps involving density correlations (Bryan, 1986), are needed.

Analysis of both native and heavy atom maps from the point of view of *a priori* uniformity means that the very important knowledge that the heavy atom distribution consists of a few distinct atoms is ignored. Indeed, if the data are of sufficient quality for these procedures to be applicable, it is very likely that the difference Patterson function can be solved for the heavy atom positions anyway, making the full two-map treatment unnecessarily complicated. Not surprisingly, it has been noted (Fortier, Moore & Fraser, 1985; Karle, 1986) that introducing information on heavy atom positions improves the accuracy of the calculated phase invariants. The corresponding Maxent calculation has been recently reported (Bryan & Banner, 1987), and leads directly to a solution for the electron density, whereas a direct methods approach gives the phase invariants, to which a further procedure must be applied to give the phases themselves.

The Maxent approach has several further advantages over that of direct methods. In practical calculations, uncertainties in the data can be allowed for at the outset by suitable weighting in the $\chi^2$ statistic (Bryan & Banner, 1987), although the formulation in § 3 deals with exact intensity constraints. If the major heavy atom sites have been found by difference Patterson methods, these may be used to give a prior for the heavy atom map, and hence possible minor sites may be found during the Maxent calculation. As many data sets as are available, perhaps of varying quality and resolution ranges, can all be incorporated into a $\chi^2$ statistic, whereas the direct methods approach would require the distributions of the invariant to be derived for each combination of data individually (Fortier, Weeks, & Hauptman, 1984*b*). Moreover, space group effects are taken into account simply by defining the entropy on the asymmetric unit of the map and using a space group specific Fourier transform to give the unique structure factors for use in the $\chi^2$ test. A successful demonstration of the full double-map procedure using Maxent directly has also been performed (Bryan, 1988), using simulated native and SIR data. It remains to be seen whether the same method can be applied to experimental data sets, with attendant problems of noise, scaling or possible non-isomorphism.

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