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On the Maximum-Entropy Estimate of the Electron Density Function

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Abstract

The principle of maximum entropy, considered as a form of statistical inference, is used to obtain an estimate of the electron density function on the basis of partial information. First a maximum-entropy probability distribution of maps, which explicitly takes into account the available information, is obtained, its functional form being a strict consequence of the type of constraint used. Next the electron density function is estimated using this probability distribution. For the particular type of constraint considered here the formulation presented is shown to correspond exactly to a maximum-entropy algorithm using a new form of the configurational entropy of maps.

1. Introduction

Entropy maximization methods have been used in connection with the problem of image reconstruction (Gull & Daniell, 1978). Similar techniques have been used by crystallographers to produce electron density maps (Collins, 1982; Wilkins, Varghese & Lehmann, 1983). The main goal of these methods is to construct maps that use all the available information (e.g. diffraction data, positivity of the map) while being maximally noncommittal to any other information. Different expressions for the entropy have been used (see e.g. Frieden, 1972; Abels, 1974), which were associated, sometimes in a non-explicit way, with different assumptions.

In this paper we use a statistical approach and information theory to produce a maximum-entropy estimate of the electron density function. A maximum-entropy probability distribution of maps that explicitly takes into account the available information will be obtained starting from first principles. The statistical entropy of this probability distribution will then be calculated, its functional form being a strict consequence of the constraint imposed on the sought map. In particular, if the constraints are functionals of the estimated map, the statistical entropy is itself a functional of it and is called the configurational entropy of the map. For certain types of constraints we find the forms used by other authors

(Khachaturyan, Semenovskaya & Vainshtein, 1981; Collins, 1982; Narayan & Nityananda, 1982; Bricogne, 1982), but our entropy formula, which only uses positivity and boundedness of the map, differs from those already proposed in the literature. The basis of the theory presented here is provided by the fundamental work of Jaynes (1957).

Our formulation is not limited to the usual crystallographic case of positive maps and other situations where the sought map is not everywhere positive (e.g. scattering-length densities in neutron diffraction) are also considered.

The conceptual difference between the use of entropy values to select a particular map and the use of a probability distribution of maps from which estimates are calculated is made particularly clear if we assume that no information is available. In the first case the uniform map will be the selected one whereas in the second case we will obtain a uniform distribution of maps. The connection between the procedures is that the uniform map is also the expected value of the random map computed with the uniform distribution.

Formulations in terms of an underlying probability distribution have been used in reciprocal space by Britten & Collins (1982) and Piro (1983). In real space it has been used by Lajzerowicz & Lajzerowicz (1960) and Wilkins et al. (1983). Our formulation uses a functional formalism developed by Feynman & Hibbs (1965) whose value is the assistance it gives in bringing together physical insight and mathematical analysis. Similar results can be obtained using more standard techniques.

A brief discussion of the theoretical limitations of entropy maximization methods based on configurational entropies expressed as functionals of the estimated map is presented.

Numerical methods of solution of the fundamental equations are developed. Even if the formulation is essentially a real-space one the methods involve as many variables as structure factors are experimentally available. Numerical tests are presented to illustrate the predictions of the theory.

2. Maximum-entropy probability distribution of maps

The construction of the electron density map using diffraction data is a problem conditioned by lack of information such as limited resolution, missing phase values, and errors. Owing to the lack of information many different maps can be built consistent with the available data, so that a criterion is needed to select that map that will be considered as an appropriate estimate of the electron density function. A safe criterion should allow us to select a map incorporating all the available information about the electron density function and being maximally noncommital with respect to missing information.

Information theory gives one answer to this problem in the following way. We can imagine a machine that produces random maps while taking into account whatever information is given. We can interpret the frequency of occurrence of a given map as the probability that such a map be produced if we asked the machine to produce one. Information theory tells us what the results would be if the machine were the ideal one, the one that produces random maps while taking into account *nothing but the available information.*

From a subjectivist point of view this probabilistic description is merely an expression of our ignorance of the complete information required to lead us to definite conclusions. We may consider that each probability distribution has inherently associated some amount of lack of information or uncertainty about the experiment it describes. To make inferences on the basis of partial information we should then use that probability distribution that has the greatest amount of uncertainty while agreeing with whatever information is given.

Information theory tells us that a measure of the amount of lack of information exists and is the unique one that satisfies the following properties:

(a) Continuity with respect to the probabilities.

(b) Independence with respect to the events of zero probability.

(c) Maximum value for the uniform distribution.

(d) Additivity: the uncertainty of a compound experiment is obtained by adding the uncertainty of one component to the uncertainty of the other component conditioned by the first one.

This measure is given by Shannon's statistical entropy H associated with the probability distribution p (Shannon & Weaver, 1949),

$$p = \{p_1, \ldots, p_n\}, \quad p_i \geq 0, \quad \sum_{i=1}^{n} p_i = 1$$

$$H(p) = -\sum_{i=1}^{n} p_i \ln (p_i). \tag{1}$$

We will use the probability distribution that has maximum entropy while agreeing with whatever information is given, as, in keeping with the above theory, it is the only unbiased assignment we can make. This is the working rule of what has been called the principle of maximum entropy (PME). Since we are looking for a statistical estimation of the electron density function we will identify it with *the maximum-entropy estimate of the map, i.e. the mean value of the random map computed with a probability distribution that has maximum entropy.*

In view of the mathematical treatment we will arrange the available information into two different classes. The information of the first class is taken into account by properly defining the set of admissible maps, these being the properties of positivity,

boundedness and periodicity of the electron density function. The other class is incorporated as constraints to be fulfilled by the probability distribution, thus giving different weights to different maps. Information of this latter class will also be called constraint.

A distinction will be made between the type and the form of a constraint. To illustrate this point let us assume that our information is the measured amplitude of a particular reflection, say $|F^{ob}(H)|^2$. The observed structure factors will be measured in units of $F^{ob}(0)$ so that they will be adimensional quantities related to an adimensional electron density function through

$$F^{ob}_{(h)} = \frac{1}{V} \int \rho(r) \exp(+2\pi i h r) \, d^3 r \qquad (2)$$

and its inverse relationship

$$\rho(r) = \sum_h F^{ob}_{(h)} \exp(-2\pi i h r). \qquad (3)$$

With this normalization one possible choice of the type of constraint is

$$\left| \frac{1}{V} \int \bar{m}(r) \exp(+2\pi i H r) \, d^3 r \right|^2 - |F^{ob}(H)|^2 = 0, \qquad (4)$$

where $\bar{m}(r)$ is the mean value of the adimensional random map $m(r)$.

The different choice of type of constraint

$$\frac{1}{V^2} \int \langle m(r) m(r') \rangle \exp[2\pi i H(r - r')] \, d^3 r \, d^3 r'$$
$$- |F^{ob}_{(H)}|^2 = 0 \qquad (5)$$

is an alternative way of taking into account the same experimental information.

We will say that two constraints are of different type if they are expressed as functionals of different moments of the random map $m(r)$. Within a given type different forms of constraints will denote different analytical expressions.

We will now derive the probability distribution $P[m]$ of observing the map $m(r)$ using the PME. Such a functional has a meaning only if we define its domain, it means the set of admissible functions $m(r)$. In the crystallographic case it will be those maps that are bounded between two values, zero and ρ_{max}, and have the periodicity of the crystal. This is the largest domain we can consider but it can be significantly reduced if some other a priori information is introduced, as for example in the case where it is possible to distinguish the molecule from the solvent region in a protein. $P[m]$ will also satisfy the normalizing condition

$$\int P[m] \mathscr{D} m = 1 \qquad (6)$$

and a certain number of constraints. In this paper, we will assume that all constraints are functionals of the average map $\bar{m}(r)$, which has been identified with the estimate of the electron density function.

The definition (1) of entropy can be extended to denumerably infinite probability distributions and the continuous case can be obtained either by a limiting process or by considering entropy variations. This expression is then extended to denumerably infinite continuous distributions, called stochastic processes, and to its limiting case of an infinite number of continuous distributions called random functions, the latter being the case considered in this paper. In our case the usual extension of Shannon's entropy grows linearly with the number of random variables, also called number of degrees of freedom. The pertinent quantity is then the entropy rate defined as the limit of the entropy per degree of freedom when the number of degrees of freedom, denoted by μ, goes to infinity (Papoulis, 1981).

The entropy rate associated with the probability distribution $P_\mu[m]$ is proportional to

$$S_\mu = -\frac{1}{\mu} \int P_\mu[m] \ln(P_\mu[m]) \mathscr{D}^\mu_m$$
$$= -\frac{1}{\mu} \langle \ln(P_\mu[m]) \rangle, \qquad (7)$$

where the continuous integral extends over all functions belonging to the domain of $P_\mu[m]$. μ is here given a finite value, the limit as $\mu \to \infty$ will be taken at the end of the calculations.

We introduce the Lagrange multipliers λ_p and $\ln(Z_\mu/e)/\mu$ to take account of the constraints, which we formulate as $C_p = 0$, and the normalizing condition (6). The maximization of

$$S_\mu - \sum_p \lambda_p C_p - \ln(Z_\mu/e)/\mu \left(\int P_\mu[m] \mathscr{D}^\mu_m - 1 \right) \qquad (8)$$

with respect to $P_\mu[m]$ gives the maximum-entropy probability distribution of the random map $m(r)$:

$$P^M_\mu[m] = \frac{1}{Z_\mu} \exp\left[-\frac{\mu}{V} \int \chi(r) m(r) \, d^3 r \right], \qquad (9)$$

$\chi(r)$ being defined as

$$\chi(r) = \sum_p \lambda_p \delta C_p[\bar{m}] / \delta \bar{m}(r). \qquad (10)$$

$\delta C_p[\bar{m}]/\delta \bar{m}(r)$, the functional derivative of C_p with respect to $\bar{m}(r)$, is defined as the function of r, which to each variation of the map $\delta \bar{m}(r)$ associates the variation of C_p in the following way:

$$\delta C_p = (1/V) \int [\delta C_p / \delta \bar{m}(r)] \delta \bar{m}(r) \, d^3 r. \qquad (11)$$

$\chi(r)$ plays an important role in the following analysis because *the main results are independent of the specific form of the constraints*. The condition (6) implies

$$Z_\mu = \int \exp\left[-\frac{\mu}{V} \int \chi(r) m(r) \, d^3 r \right] \mathscr{D}^\mu_m, \qquad (12)$$

so that Z_μ, the partition function, can be considered as a functional of $\chi(r)$. All the quantities of interest will be expressed in terms of $\Phi_\mu = \ln(Z_\mu)/\mu$. In order to compute it we divide the unit cell into N equal cells of volume v, centered at points r_j. Each map is represented by the values of $m(r)$ at these points. A sum over all the maps so constructed reduces then to a multiple integral over all values of $m(r_j)$ between zero and $\rho_{\max}$, for all r_j,

$$\Phi_\mu = \frac{1}{\mu} \ln \left\{ \int \exp\left[-\frac{\mu}{V} \sum_{j=1}^{N} \chi(r_j) m(r_j) v \right] d^N m \right\}$$

$$= \frac{1}{\mu} \ln \left\{ \prod_{j=1}^{N} \int_0^{\rho_{\max}} \exp\left[-\frac{\mu v}{V} \chi(r_j) m(r_j) \right] dm(r_j) \right\}$$

$$= \frac{1}{\mu} \sum_{j=1}^{N} \ln \left(\left\{ 1 - \exp\left[-\frac{\mu v}{V} \chi(r_j) \rho_{\max} \right] \right\} \right.$$

$$\left. \times \left[\frac{\mu v}{V} \chi(r_j) \right]^{-1} \right), \tag{13}$$

and we have to take the limit of this expression when the number N of equal cells and the number μ of degrees of freedom go to infinity. For this subdivision of the total volume of the unit cell V, N equals μ so that

$$\mu = N = V/v, \qquad \mu v/V = 1. \tag{14}$$

Then

$$\Phi[\chi] = \lim_{\mu \to \infty} \Phi_\mu[x]$$

$$= \lim_{N \to \infty} \frac{1}{V} \sum_{j=1}^{N} \ln \left\{ \frac{1 - \exp[-\chi(r_j)\rho_{\max}]}{\chi(r_j)} \right\}$$

$$= \frac{1}{V} \int \ln\{1 - \exp[-\chi(r)\rho_{\max}]/\chi(r)\} d^3 r$$

$$= \frac{1}{V} \int \left(\ln \left\{ \frac{\sinh[\chi(r)\rho_{\max}/2]}{\chi(r)\rho_{\max}/2} \right\} \right.$$

$$\left. - \chi(r)\rho_{\max}/2 \right) d^3 r + \ln(\rho_{\max}). \tag{15}$$

3. Maximum-entropy estimates

The maximum-entropy estimate of the electron density function is the mean value of the random map, and can be calculated as a functional derivative of Φ

$$\bar{m}_M(r) = \int P^M[m] m(r) \mathcal{D}m = -\delta\Phi/\delta\chi(r)$$

$$= \rho_{\max}/2 + (\rho_{\max}/2)$$

$$\times \{1/\chi(r)\rho_{\max}/2 - 1/\tanh[\chi(r)\rho_{\max}/2]\}. \tag{16}$$

This, together with (10) [with $\bar{m}(r)$ substituted by $\bar{m}_M(r)$],

$$\chi(r) = \sum_p \lambda_p \, \delta C_p[\bar{m}_M]/\delta\bar{m}_M(r), \tag{17}$$

defines the maximum-entropy estimate of the map as an implicit function of the Lagrangian multipliers λ_p.

We show in Fig. 1 $\bar{m}_M$ as a function of χ.

Fluctuations of the random map around its average value can be studied within the present formalism. Let us call $\Delta m = m - \bar{m}_M$ and consider the mean value $\langle \Delta m(r) \Delta m(r') \rangle$. It can be used as a measure of the correlation of the statistical fluctuations of m at points r and r' and can be calculated as a functional second derivative

$$\langle \Delta m(r) \Delta m(r') \rangle = \frac{1}{\mu} \frac{\delta^2 \Phi_\mu}{\delta\chi(r)\,\delta\chi(r')}. \tag{18}$$

Taking the limit as $\mu \to \infty$, we obtain a finite value when $r = r'$, zero otherwise. We write this result in the formal way

$$\langle \Delta m(r) \Delta m(r') \rangle = \langle \Delta m^2(r) \rangle \{ \lim_{\mu \to \infty} \delta(r - r')/\mu \}, \tag{19}$$

where the term between the braces is unity for $r = r'$, and the mean-square value of the fluctuation of the map is

$$\langle \Delta m^2(r) \rangle = -d\bar{m}_M[\chi(r)]/d\chi(r)$$

$$= (\rho_{\max}/2)^2 \{[\chi(r)\rho_{\max}/2]^{-2}$$

$$- \sinh^{-2}[\chi(r)\rho_{\max}/2]\}. \tag{20}$$

Fig. 2 shows $\langle \Delta m^2 \rangle / \rho_{\max}^2$ and the relative fluctuation $(\langle \Delta m^2 \rangle)^{1/2}/\bar{m}_M$ as functions of $\bar{m}_M/\rho_{\max}$.

The lack of correlation among the fluctuations of the map manifests itself in reciprocal space in a particular way. Let us call

$$F(h) = \frac{1}{V} \int m(r) \exp(+2\pi i h r) \, d^3 r \tag{21}$$

the random Fourier coefficient of the random map $m(r)$, with mean value $\bar{F}_M(h)$, and $\Delta F(h) = F(h) - \bar{F}_M(h)$. Then

$$\langle \Delta F(h) \Delta F^*(h') \rangle$$

$$= \frac{1}{V^2} \int \langle \Delta m(r) \Delta m(r') \rangle \exp[2\pi i(hr - h'r')] \, d^3 r \, d^3 r'$$

$$= \frac{1}{\mu} \frac{1}{V} \int \langle \Delta m^2(r) \rangle \exp[2\pi i(h - h')r] \, d^3 r \tag{22}$$
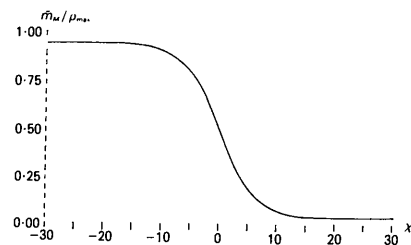

Fig. 1. Maximum-entropy estimate $\bar{m}_M$ as a function of χ (equation 16 with $\rho_{\max} = 1$).

and setting $h = h'$, we see that $\langle |\Delta F(h)|^2 \rangle$ is independent of the reciprocal vector h. This implies that the integrated mean-square fluctuation of the map is uniformly distributed in reciprocal space,

$$\frac{1}{V} \int \langle \Delta m^2(r) \rangle \, d^3r = \sum_h \langle |\Delta F(h)|^2 \rangle, \qquad (23)$$

in accordance with Parseval's theorem.

The right side of (23) is a finite quantity so that the mean-square fluctuation of any particular Fourier coefficient of $m(r)$ is vanishingly small. We arrive thus at the conclusion that the theory gives definite predictions of the structure factors. It turns out that this is a point of discrepancy between the theory and experience. Since the domain or set of admissible maps is a reasonable one, the bias comes either from the identification of the estimated map with the mean value of a random map or from the assumption concerning the *type* of constraint used. We will not discuss here the possible solutions to this problem. We will simply cite (5) as a type of constraint that automatically leads to correlated fluctuations of the map. Such a type of constraint tends to emphasize the Patterson or autocorrelation function.

4. Use of diffraction data

We shall now consider some explicit expressions of the constraints that correspond to the type of information available in X-ray crystallography. Exact fitting of the data implies using one constraint equation for each structure factor. Most of the reflections have unknown associated phases. We will call $\mathscr{K}$ the set

Fig. 2. (a) Mean-square fluctuation of the map as a function of $\bar{m}_M/\rho_{max}$. (b) Relative fluctuation of the map as a function of $\bar{m}_M/\rho_{max}$.

of the corresponding reciprocal vectors and $\mathscr{H}$ the set whose associated structure factors are known in modulus and phase. We will have one complex equation of the form

$$C_H[\bar{m}_M] = \frac{1}{V} \int \bar{m}_M(r) \exp(+2\pi i H r) \, d^3r$$
$$- F^{ob}(H) = 0 \qquad (24)$$

for each H in $\mathscr{H}$ and one real constraint equation

$$C_K[\bar{m}_M] = \left| \frac{1}{V} \int \bar{m}_M(r) \exp(+2\pi i K r) \, d^3r \right|$$
$$- |F^{ob}(K)| = 0 \qquad (25)$$

for each K in $\mathscr{K}$. If both H and $-H$ are in $\mathscr{H}$, the constraints (24) can be used in complex form and the corresponding Lagrange multipliers will be complex numbers satisfying $\lambda_{-H} = \lambda_H^*$, because of Friedel's law. It will also be assumed that K and $-K$ belong to $\mathscr{K}$.

The function $\chi(r)$ given by (17) is now

$$\chi(r) = \sum_{H \in \mathscr{H}} \mu_H^* \frac{\delta C_H}{\delta \bar{m}_M(r)} + \sum_{K \in \mathscr{K}} \nu_K \frac{\delta C_K}{\delta \bar{m}_M(r)}$$

$$= \sum_{H \in \mathscr{H}} \mu_H \exp(-2\pi i H r)$$

$$+ \sum_{K \in \mathscr{K}} \nu_K \exp(i\varphi_K) \exp(-2\pi i K r), \qquad (26)$$

where φ_K is the phase of $\bar{F}_M(K)$ and ν_K is a real number, positive or negative. The function $\chi(r)$ depends on $\bar{m}_M(r)$ through the phases φ_K.

Summarizing, the maximum-entropy estimate of the electron density function is $\bar{m}_M$ given by (16), where $\chi(r)$ is a trigonometrical polynomial

$$\chi(r) = \sum_{L \in \mathscr{H} \cup \mathscr{K}} \lambda_L \exp(-2\pi i L r) \qquad (27)$$

having as many terms as observed structure factors are available. The λ's are complex numbers determined so that the Fourier coefficients of $\bar{m}_M(r)$ satisfy

$$\bar{F}_M(H) - F^{ob}(H) = 0 \qquad (28)$$

for each H in $\mathscr{H}$,

$$|\bar{F}_M(K)| - |F^{ob}(K)| = 0 \qquad (29)$$

and

$$\lambda_K^* \bar{F}_M(K) - \lambda_K \bar{F}_M^*(K) = 0 \qquad (30)$$

for each K in $\mathscr{K}$. The latter equation is simply another way of writing the equality, modulo π, of the phases of λ_K and $\bar{F}_M(K)$.

The determination of the Lagrangian multipliers requires the solution of the system (28)–(30) of as many equations as unknowns. In principle the estimate of the electron density function $\bar{m}_M(r)$ is now completely determined.
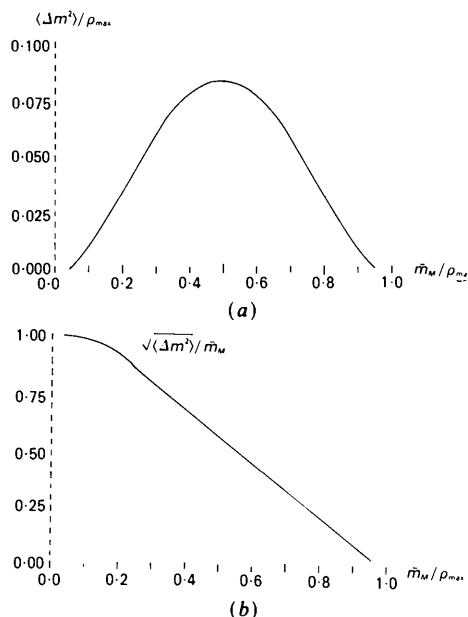
5. Expression of the entropy of the maximum-entropy probability distribution of maps as a functional of the average map

We will now show how the estimated map can be obtained starting from the entropy rate expressed in terms of $\bar{m}_M$. This will lead us to a maximum-entropy algorithm in which the estimated map is the solution of the constrained maximization of the entropy rate.

Substituting (9) into (7) and taking the limit as $\mu \to \infty$, we obtain an explicit expression for the entropy rate as a functional of $\chi(r)$

$$S_M = \lim_{\mu \to \infty} -\langle \ln(P_\mu^M[m])/\mu \rangle$$

$$= \Phi[\chi] + \frac{1}{V} \int \chi(r)\bar{m}_M(r)\, d^3r$$

$$= \Phi[\chi] - \frac{1}{V} \int \chi(r)\frac{\delta\Phi}{\delta\chi(r)}\, d^3r$$

$$= \frac{1}{V} \int \left(\ln \left\{ \frac{\sinh[\chi(r)\rho_{max}/2]}{\chi(r)\rho_{max}/2} \right\} \right.$$

$$\left. - \frac{\chi(r)\rho_{max}/2}{\tanh[\chi(r)\rho_{max}/2]} \right) d^3r + \ln(e\rho_{max}). \quad (31)$$

Here χ is considered as a function related to $\bar{m}_M$ by (16), so that S_M is defined parametrically as a functional of $\bar{m}_M$. Moreover, owing to the local relationship between $\bar{m}_M$ and χ it is in fact the integral of a function of $\bar{m}_M$,

$$S_M = \frac{1}{V} \int h[\bar{m}_M(r)]\, d^3r. \quad (32)$$

Fig. 3 shows h as a function of $\bar{m}_M/\rho_{max}$.

Using the definition (31) of the entropy rate we can easily compute the variational derivative of S_M with respect to $\bar{m}_M(r)$. It turns out to be

$$\delta S_M/\delta\bar{m}_M(r) = \chi(r) \quad (33)$$
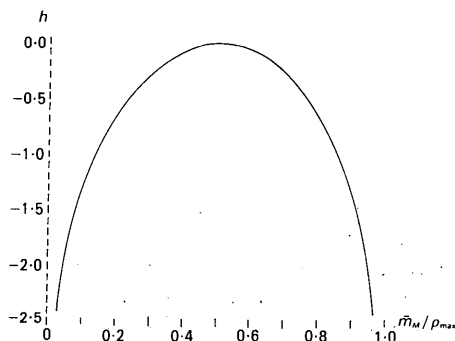
so that the constrained maximization of S_M under

Fig. 3. Entropy density h as a function of $\bar{m}_M/\rho_{max}$ (equation 32).

the same constraints $C_p = 0$ implies

$$\frac{\delta}{\delta\bar{m}_M(r)} \left\{ S_M[\bar{m}_M] - \sum_p \lambda_p C_p[\bar{m}_M] \right\}$$

$$= \chi(r) - \sum_p \lambda_p\, \delta C_p/\delta\bar{m}_M(r) = 0, \quad (34)$$

which is the same relationship between χ and the constraints as in (17).

The problem of construction of the electron density function can thus be solved in two steps. We first use a maximum-entropy probabilistic description as a device to obtain an entropy expression in terms of the estimated map. Next we use this entropy expression to determine the estimated map by means of a maximization procedure under the same constraints used in the previous step.

The latter step constitutes the MEM and can be seen as a procedure to discriminate between possible maps (Gull & Daniell, 1978; Bricogne, 1982).

6. Other entropy expressions

The entropy expression (31) depends only on the set of admissible maps and on the *type* of constraints employed but not on their specific form. It is valid for constraints that are expressed as functionals of the estimated map $\bar{m}_M$. Keeping this same type of constraint we may try to vary the domain of $P[m]$ to deal with more general situations. For example, we may have some *a priori* knowledge about the solvent region in a protein structure or about the disordered region in the final steps of a structure determination. We may also be interested in neutron diffraction maps that have negative as well as positive scattering-length densities.

All these cases can be dealt with by simply restricting the domain of $P[m]$ to the set of maps that are bounded between two functions, ρ_{max} and ρ_{min}, with $\rho_{max}(r) \geq \rho_{min}(r)$ for all r.

The resulting expressions are very similar to those already deduced when expressed in terms of the two functions

$$\rho_m(r) = \tfrac{1}{2}[\rho_{max}(r) + \rho_{min}(r)]$$

$$\Delta\rho(r) = \tfrac{1}{2}[\rho_{max}(r) - \rho_{min}(r)], \quad (35)$$

which represent the mid-point between the two bounds and one half of the amplitude respectively. The logarithm of the partition function is now

$$\Phi = \frac{1}{V} \int \left(\ln \left\{ \frac{\sinh[\chi(r)\Delta\rho(r)]}{\chi(r)\Delta\rho(r)} \right\} - \chi(r)\rho_m(r) \right) d^3r$$

$$+ \frac{1}{V} \int \ln[2\Delta\rho(r)]\, d^3r, \quad (36)$$

from which the maximum-entropy estimate of the

map and the entropy rate can be calculated,

$$\bar{m}_M(r) = \rho_m(r) + \Delta\rho(r)$$

$$\times \left\{ \frac{1}{\chi(r)\Delta\rho(r)} - \frac{1}{\tanh[\chi(r)\Delta\rho(r)]} \right\}, \quad (37)$$

$$S_M = \frac{1}{V} \int \left(\ln \left\{ \frac{\sinh[\chi(r)\Delta\rho(r)]}{\chi(r)\Delta\rho(r)} \right\} \right.$$

$$\left. - \frac{\chi(r)\Delta\rho(r)}{\tanh[\chi(r)\Delta\rho(r)]} \right) d^3r + \frac{1}{V} \int \ln[2e\Delta\rho(r)] d^3r.$$

Equations (37) define, parametrically, the entropy rate as a functional of the estimated map.

When the upper limit ρ_{max} of the admissible maps goes to infinity, the entropy rate is simply

$$S_M = \frac{1}{V} \int \ln[\bar{m}_M(r)] d^3r \quad (38)$$

and the estimated map

$$\bar{m}_M(r) = 1/\chi(r). \quad (39)$$

It has been demonstrated that (38) is proportional to the logarithm of a Karle–Hauptman determinant of infinite order (see e.g. Narayan & Nityananda, 1982). The positivity of such a determinant is a consequence of the sole positivity of the estimated map, a result consistent with the information we have used to derive (38), $0 \le m(r) < \infty$.

7. Use of atomicity

In the crystallographic case the problem of construction of the electron density function can be formulated in a still different way by explicitly using the notion of atomicity. The hypothesis of atomicity allows us to write the observed structure factors as explicit functions of the atomic positions. In the case of a structure consisting of A identical atoms they are

$$F^{ob}_{(H)} = f(H) \sum_{a=1}^{A} \exp(+2\pi iHr_a), \quad (40)$$

where the $f(H)$'s are the Fourier coefficients of an isolated atom. We proceed along the same lines of §2 and look for the less biased distribution of A atoms in the unit cell. Any distribution of the A atoms will be completely characterized by a sequence of numbers that take the values zero or one, such that the sum of these numbers equals A. We will discretize the unit cell by choosing N points in it. The limit as N tends to ∞ will be taken at the end of the calculations. A particular sequence n will then be

$$n = \{n_1, \ldots, n_N\}, \quad n_j = 0, 1, \quad \sum_{j=1}^{N} n_j = A. \quad (41)$$

The subindex j denotes the position r_j in the unit cell. The n_j's will be called the occupation numbers.

The sequence n plays now the role of the random event and, as in (21), it will be associated with a random 'Fourier coefficient'

$$F(h) = f(h) \sum_{j=1}^{N} n_j \exp(+2\pi ihr_j). \quad (42)$$

To deduce the probability distribution $P[n]$ of sequences, we have also to make a choice of the type of constraint to be employed. The analog to the one used so far is, for example,

$$f(H) \sum_{j=1}^{N} \bar{n}_j \exp(+2\pi iHr_j) - F^{ob}(H) = 0, \quad (43)$$

i.e. the constraints are expressed as functions of the mean value of the sequences, $\bar{n} = \{\bar{n}_j\}$.

Maximization of Shannon's entropy (1), subject to a certain number of constraints $C_p = 0$ and the normalizing condition

$$\sum_n P[n] = 1 \quad (44)$$

gives

$$P[n] = (1/Z) \exp\left(-\sum_{j=1}^{N} x_j n_j \right), \quad (45)$$

where

$$x_j = \sum_p \lambda_p \, \partial C_p[\bar{n}]/\partial\bar{n}_j. \quad (46)$$

The evaluation of Z is rather complicated because of the condition (41). The expression is recognized as the one leading to the Fermi–Dirac distribution if the x_j's are replaced by the energy values ε_j's. It is well known that, if A and N are large numbers, the strict condition (41) can be replaced by

$$\sum_{j=1}^{N} \bar{n}_j - A = 0 \quad (47)$$

and the summation is now performed over all possible values of the independent occupation numbers (Landau & Lifshitz, 1959). Moreover, (47) is a constraint of the same type as the C_p's and can be incorporated into (46).

The results are

$$\Phi = \sum_{j=1}^{N} \ln[1 + \exp(-x_j)]$$

$$\bar{n}_j^M = 1/[1 + \exp(x_j)] \quad (48)$$

$$S_M = -\sum_{j=1}^{N} \{\bar{n}_j^M \ln(\bar{n}_j^M) + (1 - \bar{n}_j^M) \ln(1 - \bar{n}_j^M)\}.$$

To obtain the limit of these expressions when N tends to infinity we will assume that the r_j's are the centers of small cubes of volume $v = V/N$. Then a limiting argument is used: The $\bar{n}_j^M$'s are written in terms of a density $\bar{\rho}_M(r)$ as

$$\bar{n}_j^M = \bar{\rho}_M(r_j)v/V = \bar{\rho}_M(r_j)/N \quad (49)$$

so that any summation involving the $\bar{n}_j^M$'s will tend to an integral involving $\bar{p}_M$. If no $\bar{n}_j^M$ is strictly equal to unity, the density function will be, in general, well-behaved. Each unitary $\bar{n}_j^M$ gives rise to a δ distribution centered at the position r_j. If such contributions are assumed not to exist (although they can be easily taken into account by a subtraction procedure), (49) gives the asymptotic behavior of the $\bar{n}_j^M$'s for large N. This together with the inverse of the second equation in (48) gives

$$x_j = \ln N - \ln [\bar{p}_M(r_j)], \qquad (50)$$

which shows a logarithmic divergence for large N. We can then write

$$x_j = \ln N + \chi(r_j), \qquad (51)$$

where $\chi(r)$ is in general a well behaved function.

Substituting from (51) into (48) and taking the limit $N \to \infty$, we obtain

$$\Phi = (1/V) \int \exp[-\chi(r)] \, d^3r$$

$$\bar{p}_M(r) = \exp[-\chi(r)]$$

$$S_M[\chi] = \Phi - (1/V) \int \chi(r)[\delta\Phi/\delta\chi(r)] \, d^3r \qquad (52)$$

$$= (1/V) \int \exp[-\chi(r)](1 + \chi(r)) \, d^3r$$

$$S_M[\bar{p}_M] = (-1/V) \int \bar{p}_M(r) \ln(\bar{p}_M(r)/e) \, d^3r.$$

The entropy expression in (48) also gives rise to an additional term

$$\ln(N)(1/V) \int \bar{p}_M(r) \, d^3r. \qquad (53)$$

For fixed but large N this contribution is absorbed by the Lagrangian multiplier associated with the constraint (47). Besides, this term behaves as an additive constant because of this same constraint (47) and can hence be eliminated from the entropy.

The meaning of (53) is that the greater the number of cells accessible to the A atoms, the greater the uncertainty about their positions. It can also be interpreted as an expression of the fact that, in practice, two very close positions cannot be considered as distinct (Papoulis, 1981). This entropy expression has been extensively used in the literature. Although our derivation uses the explicit hypothesis of atomicity it can also be obtained using the formalism of the preceeding sections under an additional assumption concerning the measure of integration $\mathcal{D}m$ (see e.g. Levine, 1980, for a derivation in a discrete case).

8. Numerical methods

The estimate of the electron density function $\bar{m}_M(r)$ is determined by the set of λ's that satisfy the system of equations (28)–(30). When the phases of the observed structure factors are available, the Newton–Raphson procedure applied to (28) gives, if it exists, the unique solution. This method consists in correcting the current estimate of the λ's by an amount $\Delta\lambda$

that cancels the first-order expansion of (28) (Hildebrand, 1956). This expansion is

$$\bar{F}_M(H) - F^{ob}(H) + \sum_{L \in \mathcal{H}} \frac{\partial \bar{F}_M(H)}{\partial \lambda_L} \delta\lambda_L$$

$$= \bar{F}_M(H) - F^{ob}(H) + \sum_{L \in \mathcal{H}} H_{H,L} \delta\lambda_L. \qquad (54)$$

The matrix H is easily calculated from the expression

$$\delta\bar{F}_M(H) = (1/V) \int (d\bar{m}_M/d\chi) \, \delta\chi(r) \, d^3r$$

$$= -\sum_{L \in \mathcal{H}} (1/V) \int \langle \Delta m^2 \rangle$$

$$\times \exp[+2\pi i(H - L)r \, d^3r \delta\lambda_L$$

$$= -\sum_{L \in \mathcal{H}} D(H - L)\delta\lambda_L, \qquad (55)$$

getting $H = -D$. The matrix D is positive definite and not singular for all finite values of the λ's because it is the Karle–Hauptman matrix of the positive-definite function $\langle \Delta m^2 \rangle$ given by (20). So the correction $\Delta\lambda$ equals the inverse of D times the differences $(\bar{F}_M - F^{ob})$.

Even if this procedure can be readily generalized to the treatment of problems where some phases are not known, the convergence of the Newton–Raphson method becomes very uncertain when applied to (28)–(30).

If the unknown phases φ_K are considered as fixed parameters, the problem of the determination of the λ's is reduced to the previous one except that now a solution exists only for φ_K's inside a restricted domain of admissible phases. Moreover, as will be seen later, (30) is only a condition of stationarity, so that a solution of (28)–(30) does not necessarily correspond to a maximum of the entropy.

To obtain a maximum the following iterative procedure can be adopted. First a particular solution of the restricted system of equations (28)–(29) is obtained, without taking into account the constraints on the phases, by minimization of the function

$$R = \frac{1}{2} \sum_{H \in \mathcal{H}} |\bar{F}_M(H) - F^{ob}(H)|^2$$

$$+ \frac{1}{2} \sum_{K \in \mathcal{K}} (|\bar{F}_M(K)| - |F^{ob}(K)|)^2 \qquad (56)$$

with respect to the complex λ's. Using the notation

$$\Delta F_L = \bar{F}_M(L) - F^{ob}(L) \qquad \text{for } L \in \mathcal{H}$$

$$\Delta F_L = \bar{F}_M(L) - |F^{ob}(L)| \exp(i\varphi_L) \quad \text{for } L \in \mathcal{K} \qquad (57)$$

and (55), the gradient of R can be expressed as

$$\frac{\partial R}{\partial \lambda_L^*} = -\sum_{L' \in \mathcal{H} \cup \mathcal{K}} D(L - L') \Delta F_{L'}. \qquad (58)$$

The vanishing of the gradient implies the vanishing of each one of the differences ΔF, provided that the

λ's take finite values. It turns out that the Newton-Raphson method, when applied to $\Delta F = 0$, gives the same corrections $\Delta\lambda$ as in the case of known phases, under the condition that no $\bar{F}_M(K)$ be zero (otherwise the derivatives of $|\bar{F}_M(K)|$ are not defined). This condition is certainly satisfied in the neighborhood of any of the many possible sets of λ's that make R a minimum. The particular solution so obtained corresponds to a particular set of phases $\varphi_K^{(0)}$ belonging to the restricted domain of admissible phases.

In a second step the equilibrium entropy rate is expanded in powers of the differences $\delta\varphi_K = \varphi_K - \varphi_K^{(0)}$,

$$S_M \simeq S_M^{(0)} + \sum_{K \in \mathcal{H}} \frac{\partial S_M}{\partial \varphi_K} \delta\varphi_K$$
$$+ \tfrac{1}{2} \sum_{K, K' \in \mathcal{H}} \frac{\partial^2 S_M}{\partial \varphi_K \partial \varphi_{K'}} \delta\varphi_K \, \delta\varphi_{K'}. \qquad (59)$$

and a new set of phases, corresponding to the maximum of (59), is determined (this amounts to applying the Newton-Raphson procedure to $\partial S_M / \partial \varphi_K = 0$). New λ's are then calculated to fit the new phases and the observed moduli as well as the observed complex structure factors. This second step is repeated until the vanishing or the first derivative of S_M is obtained.

The procedure converges very rapidly if all the eigenvalues of the Hessian matrix in (59) are negative, which correspond to a local concave domain in the space of phases. Otherwise several iterations are needed to move the phases into a concave domain.

The derivatives entering in (59) are calculated using (33), which gives

$$\delta S_M = \frac{1}{V} \int \frac{\delta S_M}{\delta \bar{m}_M(r)} \delta\bar{m}(r) \, d^3r$$
$$= \frac{1}{V} \int \chi(r) \, \delta\bar{m}_M(r) \, d^3r$$
$$= \sum_{K \in \mathcal{H}} \lambda_K^* \, \delta\bar{F}_M(K) \qquad (60)$$

and recalling that K and $-K$ are in $\mathcal{H}$ and also that $\delta\varphi_K = -\delta\varphi_{-K}$,

$$\frac{\partial S_M}{\partial \varphi_K} = i[\lambda_K^* \bar{F}_M(K) - \lambda_K \bar{F}_M^*(K)]. \qquad (61)$$

The second derivatives are calculated using the inverse of the relationship (55)

$$\partial^2 S_M / \partial \varphi_K \, \partial \varphi_{K'}$$
$$= -[\lambda_K^* \bar{F}_M(K) + \lambda_K \bar{F}_M^*(K)] \delta_{KK'}$$
$$+ i[\bar{F}_M(K) \partial \lambda_K^* / \partial \varphi_{K'} - \bar{F}_M^*(K) \partial \lambda_K / \partial \varphi_{K'}]$$
$$= \text{real} \, [-\lambda_K^* \bar{F}_M(K) \delta_{KK'} + \bar{F}_M(K) D_{-K,K}^{-1} \cdot \bar{F}_M(K')$$
$$- \bar{F}_M^*(K) D_{K,-K}^{-1} \cdot \bar{F}_M(K')] \times 2, \qquad (62)$$

where D^{-1} is the inverse of the matrix D.

The condition of local maximum of S_M with respect to the unknown phases is that the matrix (62) be negative definite. In the case where the set consists of the only reflection $H = 0$, the translational invariance of the problem manifests itself in a threefold degenerate eigenvalue of (62) corresponding to three linearly independent translations. At a local maximum all the other eigenvalues must be less than zero.

When a great number of λ's have to be determined, the Newton-Raphson procedure cannot be used because it needs the inversion of matrices of high dimensionality. In such cases other techniques should be applied.

The procedures described above are not exempt of possible divergences owing to inconsistencies in the data as, for example, if no positive map could reproduce the observed F^{ob}'s.

A different method can still be used to obtain a solution in all practical cases. The procedure involves the minimization of the function

$$G = R - tS \qquad (63)$$

with respect to the λ's, t being a positive parameter. From (55), (58) and (60), the gradient of G can be calculated, giving

$$\frac{\partial G}{\partial \lambda_L^*} = - \sum_{L' \in \mathcal{H} \cup \mathcal{H}} D(L - L')(\Delta F_{L'} - t\lambda_{L'}). \qquad (64)$$

The parameter t forces the λ's to take finite values so that the matrix D is not singular. Thus, the condition of stationarity of G can be written either as the vanishing of its gradient or, equivalently, as

$$\Delta F_L - t\lambda_L = 0. \qquad (65)$$

A solution of (65) will also satisfy (30). Thus, the stationarity of G with respect to infinitesimal variations of the λ's implies the stationarity of S_M with respect to infinitesimal variations of the unknown phases.

The minimization of G can be accomplished by a modified gradient method based on (65). We have seen that the left side of this equation equals the negative of a positive-definite matrix times the gradient of G. It defines then a direction of descent of G. The correction $\Delta\lambda$ to the current λ's can then be taken along this direction

$$\Delta\lambda_L = \alpha(\Delta F_L - t\lambda_L) \qquad (66)$$

where the step α can be given a fixed value or can be calculated by linear search along the direction defined by (65) (see e.g. Agarwal, 1978; Le Marechal, 1981). Two Fourier transforms are needed to calculate the function G and the direction of descent. If we now call λ' a stationary solution of G for a given fixed value of t, it is obvious that the limit, if it exists, of λ' as t goes to zero is a solution of the system (28)–(30). This limit may not exist because some of

the λ''s can diverge as $1/t$ as t tends to zero [the product t times λ' being finite as implied by (65)].

In practical applications the parameter t can be given a value so as to obtain a reasonable R factor. However, qualitatively new results (e.g. super-resolution) can be obtained if the data are known to high accuracy so that the limit $t \rightarrow 0$ can be safely taken.

Functions similar to G but with different entropy expressions and R factors, and involving the electron density values as variables, were considered by several authors (Gull & Daniell, 1978; Khachaturyan et al., 1981; Wilkins et al., 1983; Collins, 1982). One of these functions was based on statistical thermodynamic analogies (Khachaturyan et al., 1981, equation 6) and consists of a Fermi-Dirac entropy expression plus an R factor involving the intensities instead of the structure factors. It can easily be proved that the condition of stationarity for this function can be written as

$$[|\bar{F}_M(K)|^2 - |F^{ob}(K)|^2]\bar{F}_M(K) - t\lambda_K = 0. \quad (67)$$

Equation (67) admits $\lambda_K = 0$, $\bar{F}_M(K) = 0$ for some K in $\mathscr{H}$ as solutions. However, such particular solutions cannot be present if sufficiently small values of t are used because they give rise to important contributions to the R factor. For solutions with non-zero $\bar{F}_M$'s, (65) and (67) give the same phase relationship between λ_K and $\bar{F}_M(K)$.

Other authors use a weighted R factor as a constraint in order to avoid spurious detail in the map arising solely from noise in the data, and also to reduce the dimensionality of the minimization problem (Gull & Daniell, 1978; Wilkins et al., 1983). A closer examination of the problem shows that the amount of calculation they need is the same as in our case. In fact, (65) is the analog of that given by Gull & Daniell to determine the map, whose evaluation implies essentially two Fourier transforms, but now the successive iterations are computed in reciprocal space (the space of the λ's) of smaller dimensionality.

There is, however, a practical difference between our approach and those that use density values as variables. In fact, the minimization procedure defined by (66), or yet the method of successive substitutions defined by (65), need only the values of the Fourier coefficients $\bar{F}_M$ corresponding to observed reflections. These coefficients are functions of the current λ's and are obtained essentially by two Fourier transforms computed by numerical methods, which impose a discretization of the unit cell. We will speak of grid resolution when referring to discretization to differentiate it from the experimental resolution. If the relationship between $\bar{m}_M$ and χ were linear a grid resolution corresponding to the experimental resolution could be taken because of Shannon's criterion of sampling (Brillouin, 1962), but considering the particular form of this relationship a greater grid is expected to be needed. The only requisite to be fulfilled by the grid resolution is to supply accurate values of the needed $\bar{F}_M$'s.

Such a grid may correspond to non-interpretable auxiliary maps, i.e. maps from which the $\bar{F}_M$'s are calculated by a numerical Fourier transformation, even if the final λ's give rise to interpretable ones. This remark can help in reducing the dimensionality of the minimization problem.

Several authors have studied the minimum grid spacing that allows a good evaluation of phases and amplitudes of structure factors (Barret & Zwick, 1971; Collins, Cotton, Hazen, Meyer & Morimoto, 1975; Ten Eyck, 1977). The number of points at which the
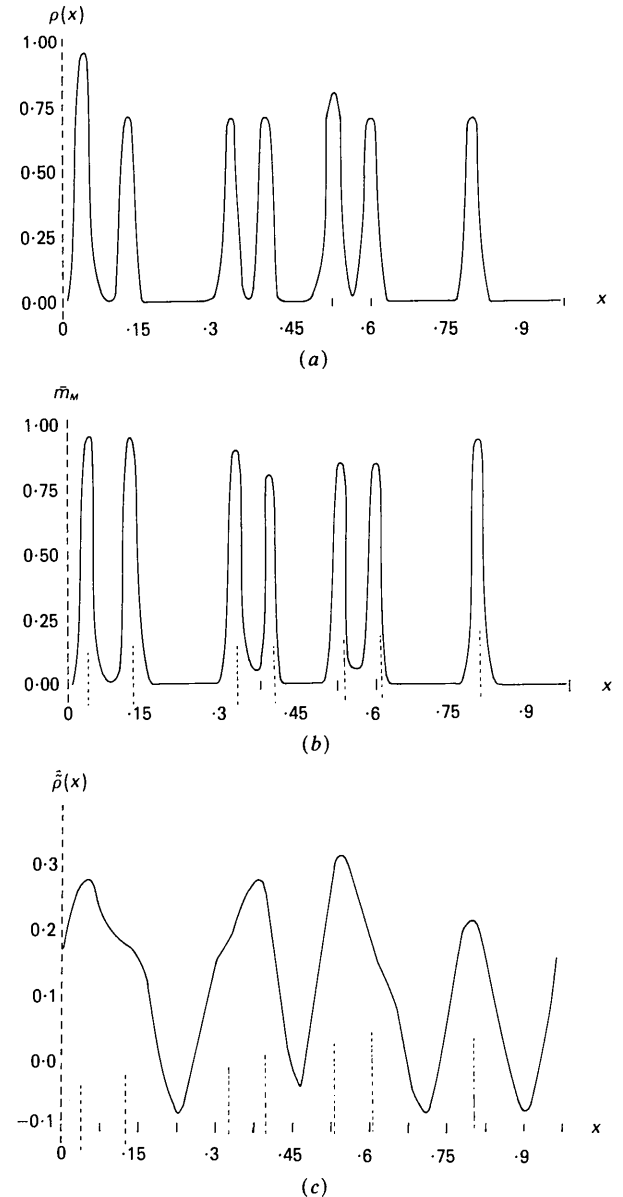

Fig. 4. (a) Test-case electron density function. (b) Estimated map based on nine observed complex structure factors $F^{ob}(H)$, $H = 0-8$. (c) Inverse Fourier transform computed with the same nine observed structure factors ($\tilde{\rho}$).

electron density should be sampled in any direction should be at least three times the highest index in that direction.

Calculations can be started with a great grid spacing, switching to a smaller spacing to improve the accuracy of the λ's only at the final steps of the procedure. This switching does not involve in our case any interpolation at all.

9. Numerical results

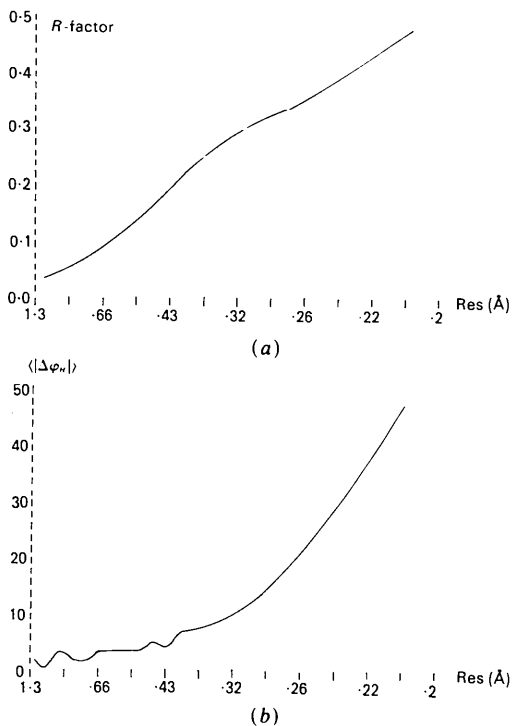The most interesting results were obtained when the estimate of the electron density function fitted exactly

the available data. Equations (28)-(30) were applied to different sets of data corresponding to a hypothetical one-dimensional $P1$ seven-atom structure.

(a)

(b)

Fig. 5. (a) Crystallographic R factor corresponding to extrapolated data as a function of resolution. (b) Mean phase deviation $\langle|\Delta\varphi_h|\rangle$ as a function of resolution (in degrees).
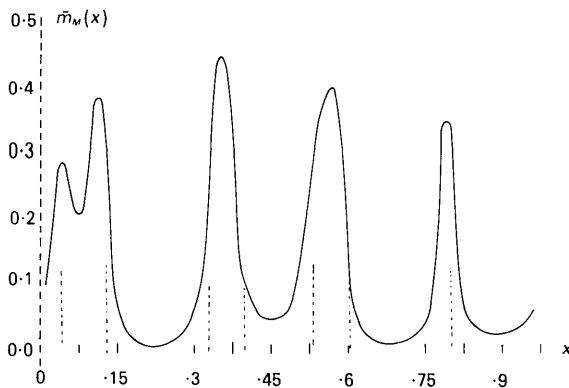
Fig. 6. Estimated map based on five complex observed structure factors $F^{ob}(H)$, $H = 0$-4, and four observed moduli $F^{ob}(K)$, $K = 5$-8.
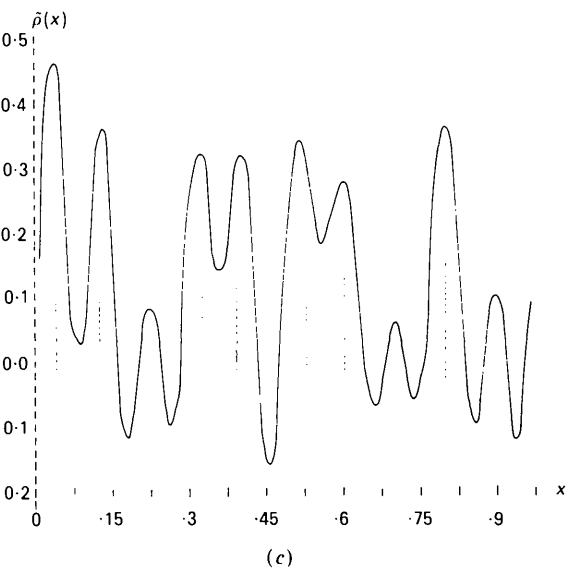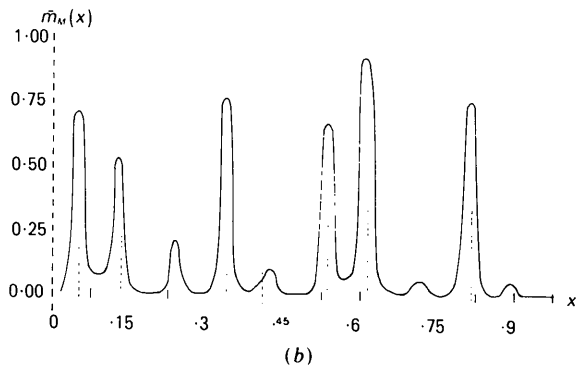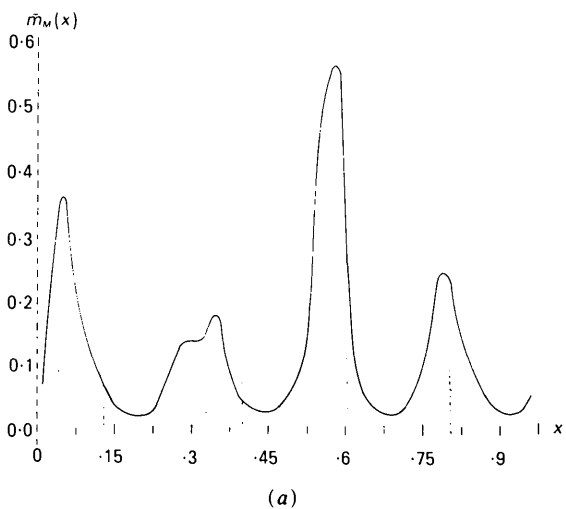
(a)

(b)

(c)

Fig. 7. (a) Maximum entropy map based on nine observed moduli $F^{ob}(K)$, $K = 0$-8. (b) Estimated map based on twelve observed moduli $F^{ob}(K)$, $K = 0$-11. (c) Inverse Fourier transform computed with the twelve coefficients $F^{ob}(H)$, $H = 0$-11 $(\tilde{\rho})$.

Three cases were considered ($\emptyset$ denotes the empty set):

   (a) $\mathscr{H} \neq \emptyset$ and $\mathscr{K} \neq \emptyset$

   (b) $\mathscr{H} \neq \emptyset$ and $\mathscr{K} \neq \emptyset$

   (c) $\mathscr{H} = \emptyset$ and $\mathscr{K} \neq \emptyset$.

In case (a) the system (28) was solved by the Newton-Raphson method starting with all λ's equal to zero, which corresponds to a uniform map.

The resulting electron density estimate is shown in Fig. 4. It is undoubtedly more realistic than the corresponding inverse Fourier transform and it exhibits super-resolution.

The statistics of the deviation of the estimated structure factors from the true values are displayed in Fig. 5. This figure shows the crystallographic R factor and the mean value of the phase deviation $\langle |\varphi_M(H) - \varphi^{ob}(H)| \rangle$ corresponding to extrapolated data as a function of resolution.

In case (b) a particular solution of the restricted system (28)-(29) was obtained with the Newton-Raphson procedure. The phases corresponding to this solution were then modified so as to maximize the entropy (59), and new λ's were calculated as in case (a). This was repeated until the vanishing of the derivatives (61) was obtained.
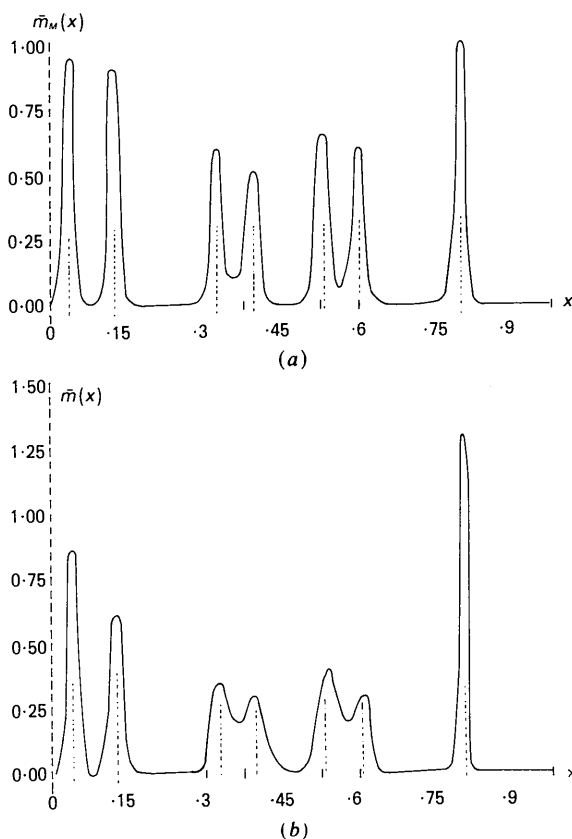

Fig. 8. (a) Estimated map based on eight complex structure factors $F^{ob}(H)$, $H = 0$-7, obtained by maximization of S_M (equation 32). (b) Estimated map based on the same structure factors obtained by maximization of $(-1/V) \int \bar{m} \ln(\bar{m}) \, d^3 r(\bar{m})$.

The resulting estimated map is shown in Fig. 6.

In case (c) the same procedure as in (b) was adopted. A starting set of random complex λ's was used to avoid centrosymmetric solutions. The results obtained were always the same, after a possible enantiomorph reversal and origin shift, irrespective of the starting point, when a maximum was looked for. Stationary solutions were also obtained, corresponding to smaller values of the entropy. The estimated phases computed with one of these stationary solutions were close to the true ones.

The resulting estimated maps, for different numbers of unknown phases, are shown in Fig. 7. It is interesting to compare the eigenvalues and the diagonal terms of the matrix (62) corresponding to different sets of phases. For the phases that make the entropy a maximum these quantities are small negative values, ranging from zero to -13 in the case of 12 unknown phases. For the true phases the eigenvalues range from 16 to $-14\,800$ and the diagonal terms from -34 to -8700. This means that the true phases are, individually, near the top of a very sharp maximum whereas, as a whole, they are not even placed in a concave region. The mean phase deviation between the sets of phases is 53°.

Tests were performed using the expression $(-1/V) \int \bar{m} \ln(\bar{m}) \, d^3 r$ for the configurational entropy. In most cases the results were qualitatively similar, although some situations were found where our formulation gave better results, as illustrated in Fig. 8.

The algorithms were programmed in the APL computing language. The programs are at the disposal of any interested reader.

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Internal Molecular Vibrations from Crystal Diffraction Data by Quasinormal Mode Analysis

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Abstract

The established procedure for analyzing molecular vibrations in terms of normal modes has been adapted so that experimental anisotropic thermal parameters can be used to study low-frequency internal vibrations of simple molecules in crystals. This involves quasinormal modes, which are linear combinations of selected low-frequency internal modes such as the torsional librations about individual bonds. Higher-frequency modes are neglected, since their contribution to the atomic mean-square displacements should be small. The force constants for selected low-frequency internal modes, together with the tensor components $(\mathbf{T}, \mathbf{L}, \mathbf{S})$ that describe the overall molecular vibration, become the variables in an iterative least-squares refinement in which the observations are the atomic U_{ij} values. As a result, the concerted motion of the atoms for each quasinormal mode is defined and also its vibrational frequency. Corrections to bond lengths and angles due to internal vibrations can be calculated. In tests involving two different lipid crystal structures, the internal motions were introduced as torsions about two or three bonds occurring near the junction of an extended hydrocarbon chain with a relatively rigid massive atomic grouping. Compared with the simple rigid-body model, there were highly significant improvements in agreement between experimental and calculated U_{ij} values. Force constants for torsion about three C–S bonds were also in agreement [26 (5), 23 (6) and 22 (6) J mol^{-1} deg^{-2}]. In one of the crystal structures (determined at 123 K), the six C–C bonds of a paraffin chain have average lengths 1·526 (2) Å before correction, 1·527 (3) Å after correction for simple rigid-body libration and 1·536 (4) Å after corrections including the quasinormal vibrations. The latter agrees with the electron diffraction value 1·542 (4) Å for *n*-hexadecane.

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Introduction

In the analysis of molecular vibrations in terms of atomic anisotropic thermal parameters, a model must be introduced in order to define how the individual atomic motions are correlated with each other. The most widely used is the rigid-body model (Cruickshank, 1956; Schomaker & Trueblood, 1968). When internal modes of vibration are appreciable, they may be taken into account by assuming that the molecule consists of rigid segments with the segments in relative motion (Johnson, 1970; Dunitz & White, 1973). Usually, they are assumed to ride on each other (Busing & Levy, 1964), but otherwise to move in an uncorrelated way.

There are certain kinds of molecules that are not well suited to analysis with these models. They include molecules with semi-rigid fused-ring systems, such as cholesterol and other steroids, and lipids in which a lengthy hydrocarbon chain is attached to a bulky more rigid segment, such as the fatty-acid esters of cholesterol. Thus, it would be desirable to treat the vibrations of atoms along the lipid chain as being correlated in various ways that can be readily defined and tested against the diffraction results. With this aim, we have developed a general procedure based on the normal coordinate analysis of molecular vibrations (Wilson, Decius & Cross, 1955). It is assumed that molecules in the crystal are vibrating independently of each other. The internal motion of each molecule is described in terms of quasinormal modes. A quasinormal mode is defined as some linear combination of a small number of internal modes of vibration. A particular internal mode would typically be the torsional motion of the molecule about a selected covalent bond. The major simplifying approximation is the neglect of high-frequency internal modes such as framework bond stretching and bond-angle bending. These modes have large force constants and thus make only a small contribution to the mean-square (m.s.) atomic displacements. As a result of such simplification, the internal motion of the molecule can