

over a dense three-dimensional grid in the direct space.

To perform this task directly in the reciprocal space, two procedures have been proposed in this paper. The first is based on calculations of the DMSD using triplet invariants (6), where the arguments of goniometric functions have to be calculated by solving the set of linear equations (5). The second is based on minimizing the right-hand side of (7) [or (8) for centrosymmetrical structures]. It has been shown that the second procedure is preferable because of its simplicity.

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## On the Role of Atomicity in Direct Methods: a New Criterion for *Ab Initio* Phase Determination

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### Abstract

A formulation of the phase problem in terms of the phases of all the experimentally available structure factors is presented, based on exact algebraic relations between Fourier coefficients, which express atomicity. A criterion is constructed whose minimum is attained by the true phases. All the observed data are used to minimize the sum of the squared residuals of an overdetermined system of equations, thereby minimizing the influence of errors upon the estimated phases. The approach brings together the theoretical power of matrix methods and the stability of overdetermined equations. The hypothesis of positivity of the electron density is not used.

### Notation

$N$  number of atoms in the unit cell  
 $z_a$  number of electrons of the  $a$ th atom  
 $s_a$  scattering length of the  $a$ th nucleus

$$n_a = \begin{cases} z_a / \left( \sum_{a=1}^N z_a^2 \right)^{1/2} & \text{(X-ray case)} \\ s_a / \left( \sum_{a=1}^N s_a^2 \right)^{1/2} & \text{(neutron case)} \end{cases}$$

$V$  volume of the unit cell  
 $\mathbf{k}, \mathbf{h}, \mathbf{h}_p$  reciprocal vectors  
 $\mathbf{r}_a$  vector of coordinates of the  $a$ th atom  
 $E(\mathbf{h}) = \sum_{a=1}^N n_a \exp(2\pi i \mathbf{h} \cdot \mathbf{r}_a)$  normalized structure factor

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### References

- HAŠEK, J. (1989). *X-ray and Neutron Structure Analysis in Materials Science*, pp. 293-306. New York, London: Plenum Press.  
 HAŠEK, J., HUML, K., SCHENK, H. & SCHAGEN, J. D. (1983). Proc. 8th ECM, Abstr. 4-04.  
 HAUPTMAN, H. & KARLE, J. (1956). *Acta Cryst.* **9**, 45-55.  
 HAUPTMAN, H. & KARLE, J. (1959). *Acta Cryst.* **12**, 93-97.  
 ROGERS, D. (1980). In *Theory and Practice of Direct Methods in Crystallography*, edited by M. F. C. Ladd & R. A. Palmer, pp. 23-32. New York, London: Plenum Press.

$E(\mathbf{h})^*$  complex conjugate of  $E(\mathbf{h})$   
 $\delta_{ab}$  Kronecker delta  
 $\otimes$  convolution  
 $\mathbf{F}, \mathbf{F}^{-1}$  direct and inverse Fourier transforms, respectively  
 $\mathbf{M}_s | \mathbf{t}_s, s = 1, \dots, g$  transformation matrix  $\mathbf{M}_s$  and translation  $\mathbf{t}_s$  corresponding to the  $s$ th symmetry operation

### Introduction

The property of positivity of the electron density has played such an important role in the mathematical foundations of direct methods that it is now generally accepted that non-negativity is sufficient *a priori* information to determine a unique atomic structure. The practical success of these methods in producing atomic maps, *i.e.* maps that can be interpreted in terms of atomic distributions, has confirmed this point of view.

On the other hand, maximum-entropy techniques have shown that positive maps that satisfy a large number of experimental data, but which are not atomic, can routinely be obtained (Navaza, 1986; Decarreau, Hilhorst, Lemaréchal & Navaza, 1992). Since these techniques provide the statistically most unbiased estimates possible with the given information, we conclude that atomicity cannot be recovered if only information of positivity of the electron density and knowledge of the moduli of a subset of its Fourier coefficients are used. In other words, positivity is not a sufficient condition; we will also see that neither is it a necessary condition.

Atomicity is assumed directly or indirectly in current direct methods. For example, approximations of Sayre's equation (Sayre, 1952) are found in most formulations of the phase problem, although the conditions for its applicability are seldom fulfilled in practice: the hypothesis of equal atoms is often seriously violated and the number of normalized structure factors used in the summations is extremely small compared to that required theoretically.

Sayre's equation is not the only relation expressing atomicity. This property was in fact explicitly introduced by Goedkoop (1950) when showing that the determinants of Karle-Hauptman matrices of order greater than  $N$ , built with normalized structure factors, should vanish. The result is an extension of the theory of inequalities and, as such, the property is recovered only if a great number of determinants (in theory an infinite number) are considered (Karle & Hauptman, 1950). Later, it was shown that knowledge of the elements of a matrix of order  $N+3$  is sufficient in principle to determine the atomic positions (Navaza & Silva, 1979; [NS] hereafter). Unfortunately, matrix methods are so sensitive to errors that their potential merit is lost in most practical situations.

However, we found that atomicity may be recovered from Goedkoop's result, using a single matrix of order about the number of independent atoms in the crystal. The analysis is based on the theory developed in [NS]. We will briefly restate some results of this theory and show how the mathematical relations that express atomicity are alone sufficient to solve the phase problem. All the available experimental information is incorporated in a single matrix of rather small order, explicitly depending on the unknown phases, which is set up so as to express atomicity instead of merely positivity.

The present formulation is closely related to the matrix approach of direct methods, although the main shortcomings of the latter are avoided. Surprisingly, the assumption of positivity of the electron density is not required, which makes the theory still more attractive since matrix methods often conflict with the assumption of positivity due to errors. Methods of solution of the proposed equations will be discussed, as well as the connection with other procedures of direct methods.

### The mathematical foundations

In the first part of this section, we assume that the normalized structure factors are known for all vectors in reciprocal space; they will be interpreted as scalar products between particular elements of an  $N$ -dimensional complex vector space  $\mathbf{S}$ , with orthonormal basis  $\{\bar{\mathbf{e}}_a, a = 1, \dots, N\}$

$$\langle \bar{\mathbf{e}}_a | \bar{\mathbf{e}}_b \rangle = \delta_{ab}. \quad (1)$$

To each reciprocal vector  $\mathbf{h}$ , we associate in  $\mathbf{S}$  the

pair of vectors

$$\begin{aligned} \bar{\mathbf{v}}(\mathbf{h}) &= \sum_{a=1}^N \exp(-2\pi i \mathbf{h} \cdot \mathbf{r}_a) \bar{\mathbf{e}}_a, \\ \bar{\mathbf{w}}(\mathbf{h}) &= \sum_{a=1}^N n_a \exp(-2\pi i \mathbf{h} \cdot \mathbf{r}_a) \bar{\mathbf{e}}_a. \end{aligned} \quad (2)$$

It follows that the Hermitian scalar product

$$\langle \bar{\mathbf{w}}(\mathbf{k}) | \bar{\mathbf{v}}(\mathbf{h}) \rangle = E(\mathbf{k} - \mathbf{h}) \quad (3)$$

is a normalized structure factor. Since  $\mathbf{S}$  has dimension  $N$ , given a set  $\mathbf{B}_M = \{\mathbf{h}_p, p = 1, \dots, M\}$  of  $M > N$  reciprocal vectors, we can always construct a nontrivial linear combination

$$\sum_{p=1}^M \beta_p \bar{\mathbf{v}}(\mathbf{h}_p) = \mathbf{0}, \quad (4)$$

with coefficients  $\beta$  normalized to

$$\sum_{p=1}^M |\beta_p|^2 = 1. \quad (5)$$

Projecting (4) onto  $\bar{\mathbf{w}}(\mathbf{k})$  and using (3), we get

$$\sum_{p=1}^M E(\mathbf{k} - \mathbf{h}_p) \beta_p = 0, \quad (6)$$

for every vector  $\mathbf{k}$  in reciprocal space. Taking the squared moduli and summing over  $\mathbf{k}$ , a system of  $K \geq M$  equations like (6) is equivalent to

$$\sum_{q=1}^M \sum_{p=1}^M \beta_q^* Q_{qp} \beta_p = 0, \quad (7)$$

where

$$Q_{qp} = (1/K) \sum_{\mathbf{k}} E(\mathbf{h}_q - \mathbf{k}) E(\mathbf{k} - \mathbf{h}_p). \quad (8)$$

$Q$  is thus a positive semidefinite Hermitian matrix. According to some general results of linear algebra, its rank is less than or equal to  $N$  or, equivalently, it has  $[M - \text{rank}(Q)]$  zero eigenvalues. The components of any of their associated eigenvectors may be taken as the coefficients  $\beta$  entering in the above equations. The number of independent sets of coefficients  $\beta$  equals the multiplicity of the zero eigenvalue of  $Q$ .

If the sum over  $\mathbf{k}$  runs over the whole of the reciprocal space (we will denote this limit by  $K \rightarrow \infty$ ), the above equations take simple forms, in particular when written in direct space. Equation (6) is a convolution; its Fourier transform gives

$$\mathbf{F}^{-1}(E \otimes \beta) = \mathbf{F}^{-1}(E) \mathbf{F}^{-1}(\beta) = \rho(\mathbf{r}) \gamma(\mathbf{r}) = 0, \quad (9)$$

for every  $\mathbf{r}$  in the unit cell. An important result follows:  $\rho$  may take nonzero values only at the points where  $\gamma$  vanishes; therefore, the atomic positions are zeros of  $\gamma$ . Expression (8) also has a meaning in the limit as  $K \rightarrow \infty$ . It may be calculated as the Fourier transform of  $\rho^2$ . However, since  $\rho$  is a distribution, its

square is not correctly defined (Schwartz, 1966); as in the case of the Sayre-Hughes equation,  $\rho^2/K$  tends to a new distribution, denoted  $\rho^{sq}$ , with Fourier coefficients  $E^{sq}$ . Accordingly,  $Q$  is a Karle-Hauptman matrix with elements

$$Q_{qp} = E^{sq}(\mathbf{h}_q - \mathbf{h}_p), \quad (10)$$

and the quadratic expression (7) becomes

$$\int \rho^{sq}(\mathbf{r}) \gamma(\mathbf{r})^2 d\mathbf{r}. \quad (11)$$

We have so far presented the implications of atomicity. We will now investigate the converse problem and see which properties of  $Q$  imply atomicity. In the one-dimensional case we can demonstrate the following proposition: if for a conveniently chosen set  $\mathbf{B}_M$  the rank of  $Q$  is  $N$ , then the  $E$  values are the Fourier coefficients of a distribution consisting of  $N$  point atoms. In other words, we have necessary and sufficient conditions for atomicity. Here  $\mathbf{B}_M$  may be any set of  $M = N + 1$  consecutive Miller indices, for example  $\mathbf{B}_M \equiv \{\mathbf{h}_p = p - 1, p = 1, \dots, M\}$ . Therefore, there is a unique eigenvector, which determines  $\gamma$  up to a phase factor. But  $\gamma$  is a polynomial of order  $N$  in the complex variable  $z = \exp(-2\pi ix)$ ,

$$\gamma(x) = \sum_{p=1}^{N+1} \beta_p \exp(-2\pi ix)^{p-1} = \sum_{q=0}^N \beta_{q+1} z^q = P_N(z), \quad (12)$$

so that there are at most  $N$  values of  $x$  in  $[0, 1]$  ( $N$  zeros of  $P_N$  in the complex plane) such that  $\gamma(x) = 0$ . The number of such points cannot be less than  $N$ , and also  $\rho$  cannot vanish at them. Otherwise, (9) would imply that  $F^{-1}(E)$  is a sum of less than  $N$  distributions centered at the zeros of  $\gamma$ . Then, repeating the above construction of  $Q$  [(1) to (10)], we would have  $\text{rank}(Q) < N$ , contradicting our hypothesis.

The assumption that the  $E$  values are known for all vectors in reciprocal space, as required by (9), is not really needed. Indeed, for given  $\beta$  values, (6) may be used to extrapolate data by a sequential process:  $E(\mathbf{k})$  is given by a linear combination of the  $N$  preceding  $E$  values (Collins, 1978). The feasibility of the extrapolation process, together with the above proposition, implies that the atomic structure is uniquely determined by a limited number of  $E$  values.

In three dimensions, we see no rigorous way of demonstrating the above proposition without introducing assumptions concerning the distribution of atoms within the unit cell. However, the following simple argument indicates the way atomicity manifests itself. Let us denote by  $\gamma^{(n)}$ ,  $n = 1, \dots, M - N$ , the Fourier transforms of the different eigenvectors corresponding to the zero eigenvalues of the matrix  $Q$ . Each equation  $\gamma^{(n)}(\mathbf{r}) = 0$  defines a surface in the variables  $\mathbf{r} = (x, y, z)$ , so that (at least) three such (independent) surfaces intersect in a finite

number of points. The construction is similar to the one proposed in [NS] to determine the atomic positions using a small number of  $E$  values. Numerical experiments have shown that the number of intersections is  $N$  for sets  $\mathbf{B}_M$  involving small Miller indexes, but no conclusions can be drawn with respect to this number within this reasoning.

The important point here is that  $M \approx N$ . Otherwise, the above proposition reduces to a trivial result. Indeed, it is well known that the eigenvalues of the Karle-Hauptman matrix of infinite order are essentially the values of  $\rho$  ( $\rho^{sq}$  in our case). Accordingly, a necessary and sufficient condition for  $\rho$  to be a distribution of  $N$  point atoms is that the rank of this matrix be  $N$ . Since this result is based on the unitarity of the Fourier transformation, it also holds for the discrete case.

The smallest number of  $E$  values needed to build a matrix  $Q$  is generally obtained when the set of  $\mathbf{k}$  vectors used in (8) coincides with the set  $\mathbf{B}_M$ . In this case  $Q$  is proportional to the square of a traditional Karle-Hauptman matrix of order  $M \approx K$ . In three dimensions the resolution of a sphere containing  $M$  reciprocal vectors is  $(4\pi V/3M)^{1/3}$  Å. For  $M = N$  and a ratio  $V/N \approx 15$  Å<sup>3</sup>, which corresponds to a typical small structure (counting only non-hydrogen atoms), this gives resolution  $\approx 4$  Å. Therefore, the minimal resolution necessary to build  $Q$  is about 2 Å. For such structures, experimental data extend far beyond this limit.

Although we have, for simplicity, assumed  $P_1$  symmetry, the extension of the preceding discussion to any space group is very simple.  $N$  would then denote the number of atoms in the asymmetric unit and the Karle-Hauptman matrices would become Goedkoop matrices. Starting from definition (1) and

$$\bar{\mathbf{v}}(\mathbf{h}) = \sum_{a=1}^N \sum_{s=1}^g \exp[-2\pi i \mathbf{h} \cdot (\mathbf{M}_s \mathbf{r}_a + \mathbf{t}_s)] \bar{\mathbf{e}}_a, \quad (13)$$

$$\bar{\mathbf{w}}(\mathbf{h}) = \sum_{a=1}^N n_a \sum_{s=1}^g \exp[-2\pi i \mathbf{h} \cdot (\mathbf{M}_s \mathbf{r}_a + \mathbf{t}_s)] \bar{\mathbf{e}}_a,$$

which correspond to definitions (2), all the pertinent formulas may be easily derived.

### The phase determination

In practical applications the crystallographer is confronted with the problems of errors, lack of phases and limited resolution. The results of the preceding section provide the basis for a method of phase determination that overcomes these problems, if a reasonable amount of data is available. The method consists in driving the rank of the  $M \times M$  matrix  $Q$  to the value  $N$ . This may be formulated as an optimization problem where the sum of the  $M - N$  smallest eigenvalues of  $Q$  are minimized with respect to the unknown phases. Indeed, since  $Q$  is by construction

non-negative for any values of the phases,  $\text{rank}(Q) = N$  is strictly equivalent to the vanishing of the sum of  $M - N$  eigenvalues of  $Q$ . Assuming the eigenvalues  $\varepsilon^{(n)}$  are sorted in ascending order, this criterion takes the form

$$R = \sum_{n=1}^{M-N} \varepsilon^{(n)} = \sum_{n=1}^{M-N} \left( \sum_q \sum_{p=1}^M \beta_q^{(n)*} Q_{qp} \beta_p^{(n)} \right); \quad (14)$$

it measures the quadratic misfit of the set of equations (6) used in the construction of  $Q$ . The method may be regarded as a least-squares solution of (6) under the constraints (5). It is almost an atom-parameter refinement reformulated in terms of phases.

A typical minimization procedure involves the calculation of the  $M - N$  smallest eigenvalues  $\varepsilon^{(n)}$  and eigenvectors  $\beta^{(n)}$  of  $Q$ , a somewhat shorter problem than a matrix diagonalization. At each step, the solution of this limited eigenvalue problem allows one to calculate the criterion  $R$  and its gradient

$$\partial R / \partial \varphi = \sum_{n=1}^{M-N} \left( \sum_q \sum_{p=1}^M \beta_q^{(n)*} \partial Q_{qp} / \partial \varphi \beta_p^{(n)} \right), \quad (15)$$

from which new values of the phases  $\varphi$  are determined by the optimization algorithm. Note that the eigenvectors are not differentiated with respect to the phases (*cf.* first-order perturbation theory in any textbook of quantum mechanics). Unfortunately, continuous phase changes are not always possible because of space-group restrictions. In particular, the components of the gradient vanish for the symmetry-restricted phases.

Alternative optimization procedures may be envisaged. For example, (6) may be used to improve the values of the phases, from which new coefficients  $\beta$  are obtained by solving an eigenvalue problem. The first step is achieved by a technique of successive substitutions, which provides phase changes in all cases. Since  $\mathbf{B}_M$  is defined up to a translation, we can always assume  $\mathbf{h}_1 = \mathbf{0}$  and  $\beta_1 \neq 0$ , and write (6) in the form

$$E(\mathbf{k}) = \sum_{p=2}^M E(\mathbf{k} - \mathbf{h}_p) (-\beta_p / \beta_1) = \sum_{p=2}^M \alpha_p E(\mathbf{k} - \mathbf{h}_p). \quad (16)$$

The  $\alpha_p$  are then used to set up an iterative algorithm of the simple form

$$\varphi_{\mathbf{k}}^{(j+1)} = \text{phase} \left[ \sum_{p=2}^M \alpha_p |E(\mathbf{k} - \mathbf{h}_p)| \exp(i\varphi_{\mathbf{k} - \mathbf{h}_p}^{(j)}) \right], \quad (17)$$

where  $\varphi^{(j)}$  denote the  $j$ th iterate of the phases. After some iterations, new  $\alpha_p$  are calculated and a new cycle is started.

Although we have considered the unknown phases as the only variables of the optimization problem, complex  $E$ s may be incorporated as variables too. In this case we are simultaneously solving the problem of data extrapolation. In particular, when all the

unknown  $E$ s are included,  $Q$  is given by the Karle-Hauptman matrix corresponding to  $E^{\text{sq}}$ . Despite the fact that the number of variables is greatly increased, most computations are now performed by FFT techniques (with the exception of the limited eigenvalue problem).

Programing all this is not trivial, but we have realistic hopes of constructing algorithms useful even for macromolecules. Some experiments have still to be performed to assess the influence of resolution, errors and choice of  $\mathbf{B}_M$  upon the estimated phases. For the moment, we have checked that function (14) gives a minimum for the true phases, as compared either with random ones or with all phases set to zero. The tests were performed with experimental data corresponding to several structures,  $N$  ranging from 25 to 150. The development of suitable optimization techniques and the corresponding programs, in collaboration with J. C. Gilbert and C. Lemaréchal at INRIA, is part of our current research.

### Discussion

The criterion (14) and Sayre's equation are, for the moment, the only tractable exact functions of the phases that exist in crystallography. The latter assumes equal atoms (not necessarily positive) and needs all data, at atomic resolutions, to be satisfied. The former assumes point-atom structure factors, involving significant errors, but forcing the data to satisfy overdetermined relations.

Probabilistic reasoning has been bypassed entirely. Nevertheless, a link with other formulations of the phase problem, including probabilistic ones, is provided by (16). It was the starting point of the analysis presented in [NS], where the equivalence with the regression equation of the maximum determinant method of Tsoucaris (1970) and the generalized tangent formula of Karle (1971) was shown. Moreover, using a first-order expansion of the  $\alpha_p$  in terms of the normalized structure factors, (16) leads to a partial sum of Sayre's equation. Navaza & Silva (1979) emphasized the fact that, in their approach, the hypothesis of equal atoms was not necessary. We are now in a position to affirm that positivity is not necessary either. In our opinion, positivity is not an essential ingredient of direct methods, although it certainly strengthens some relations between structure factors. In summary, unexpected analogies appear at the level of relations to be satisfied rather than functions to be optimized.

However, a profound difference between the algebraic and the probabilistic approaches remains. This is illustrated, for example, by the fact that (16) minimizes the Karle-Hauptman determinant corresponding to the matrix in (10), whereas most probabilistic formulations would tend to maximize it. In terms of maps, Fig. 1 shows the catastrophic effect of estima-

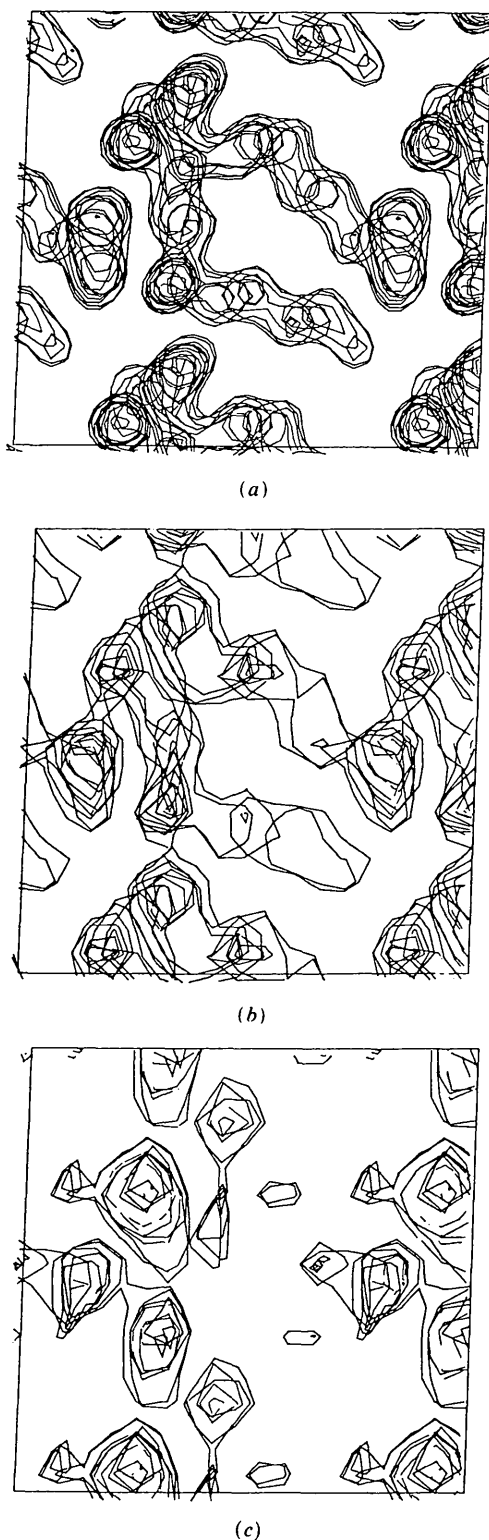


Fig. 1. (a) Projection of a 2 Å resolution Fourier map of prostaglandin PGE2 (De Titta, Langs, Edmonds & Duax, 1980). (b) Projection of a Fourier map computed with all the structure factors entering in an  $N \times N$  Karle-Hauptman matrix ( $N = 25$ , 64 independent reflections, true phases). (c) Same as (b), but with phases that maximize  $-\int \rho(\mathbf{r}) \ln [\rho(\mathbf{r})] d\mathbf{r}$ .

ting phases by probabilistic methods: the phases entering a matrix of order  $N$  were moved from their true values so as to maximize the Boltzmann entropy. This produced a rise of about 20 units in the logarithm of the corresponding determinant.

But perhaps the most important property made clear by the present analysis is that atomicity implies that each  $E$  can be expressed as a linear combination of a finite number of other  $E$ s (a sort of 'bootstrap'). Such relations are found in most of the existing programs for direct determination of structures. Therefore, by analogy with the equations derived in this paper, they may as well work on structures consisting of 'negative' atoms. This is effectively what happened when we applied *MULTAN80* (Main *et al.*, 1980) to the experimental neutron data of barium nitroprusside trihydrate,  $\text{Ba}[\text{Fe}(\text{CN})_5\text{NO}]\cdot 3\text{H}_2\text{O}$ , space group *Pbcm*,  $a = 7.620$ ,  $b = 19.394$ ,  $c = 8.631$  Å,  $Z = 4$  (Navaza, Schweiss, Alzari, Chevrier, Heger & Guida, 1989), treated as X-ray data. Incidentally, the program did not succeed with the true X-ray data. We also constructed the fictitious structure shown in Fig. 2, whose coordinates correspond to non-hydrogen atoms of diethylene glycol ditosylate  $\text{C}_{18}\text{H}_{22}\text{O}_7\text{S}_2$ , space group *C2/c*,  $a = 23.772$ ,  $b = 5.472$ ,  $c = 15.284$  Å,  $\beta = 89.61^\circ$  (Ferchaux, Villain & Navaza, 1990). The first set of phases showed the complete structure. To pick up the negative atoms we just took the absolute value of the map at the input of the peak-search subroutine. Other examples have already been reported in the literature (Sikka, 1969; Frey, Lehmann, Koetzle & Hamilton, 1973), with specification of the type of data (neutron radiation). We have no way to decide whether these results are

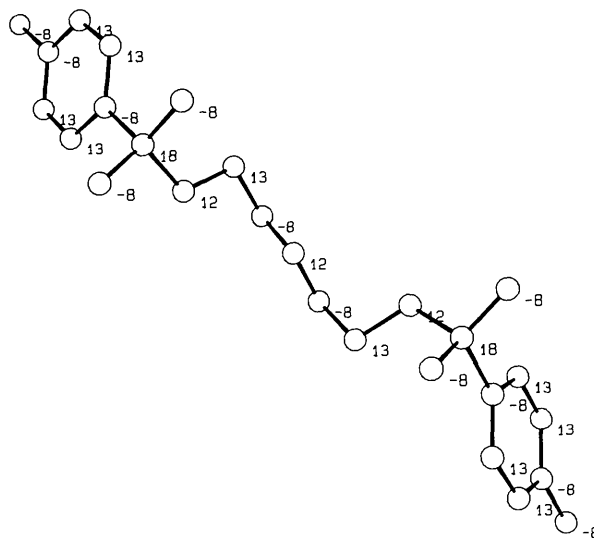


Fig. 2. Fictitious structure, with correct positions and arbitrary scatterers. The numbers in the drawing correspond to the atomic scattering factors used in the calculation of the diffraction intensities.

fortuitous or to be expected; obviously, they confirm the theory put forward in the present article. They suggest that the final strategy to optimize criterion (14) will certainly take advantage of the established algorithms used in current direct methods.

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#### References

- COLLINS, D. (1978). *Acta Cryst.* **A34**, 533–541.  
 DECARREAU, D., HILHORST, D., LEMARÉCHAL, C. & NAVAZA, J. (1992). *SIAM (Soc. Ind. Appl. Math.) J. Optim.* In the press.  
 DE TITTA, G. T., LANGS, D. A., EDMONDS, J. W. & DUAX, W. L. (1980). *Acta Cryst.* **B36**, 638–645.  
 FERCHAUX, Y., VILLAIN, F. & NAVAZA, A. H. (1990). *Acta Cryst.* **C46**, 346–348.  
 FREY, M., LEHMANN, M., KOETZLE, T. & HAMILTON, W. (1973). *Acta Cryst.* **B29**, 876–884.  
 GOEDKOOP, J. A. (1950). *Acta Cryst.* **3**, 374–378.  
 KARLE, J. (1971). *Acta Cryst.* **B27**, 2063–2065.  
 KARLE, J. & HAUPTMAN, H. (1950). *Acta Cryst.* **3**, 181–187.  
 MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.  
 NAVAZA, A. H., SCHWEISS, P., ALZARI, P., CHEVRIER, G., HEGER, G. & GUIDA, J. (1990). *J. Solid State Chem.* **89**, 23–30.  
 NAVAZA, J. (1986). *Acta Cryst.* **A42**, 212–223.  
 NAVAZA, J. & SILVA, A. M. (1979). *Acta Cryst.* **A35**, 266–275.  
 SAYRE, D. (1952). *Acta Cryst.* **5**, 60–65.  
 SCHWARTZ, L. (1966). *Théorie des Distributions*, p. 116 Paris: Hermann.  
 SIKKA, S. K. (1969). Thesis, Bombay Univ., India.  
 TSOUCARIS, G. (1970). *Acta Cryst.* **A26**, 492–499.

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### 3D Structure Determination from Electron-Microscope Images: Electron Crystallography of Staurolite

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#### Abstract

Resolution of better than 2 Å has been obtained in many crystals by high-resolution electron microscopy. Although this resolution is sufficient to resolve interatomic spacings, structures are traditionally interpreted by comparing experimental images with contrast calculations. A drawback of this method is that images are 2D projections in which information is invariably obscured by overlap of atoms. 3D electron crystallography, developed by biophysicists to study proteins, has been used to investigate the crystal structure of staurolite. Amplitudes and phases of structure factors are obtained experimentally from high-resolution images (JEOL ARM 1000 at the National

Center for Electron Microscopy at LBL), taken in different directions from thin regions where dynamic scattering is minimal. From images in five orientations (containing 59 independent reflections to a resolution of 1.38 Å), a 3D electron potential map is constructed which resolves clearly all cations (Al, Si, Fe, including those with partial occupancy) and all O atoms. This method has great potential in crystal structure determinations of small domains in heterogeneous crystals which are inaccessible to X-ray analysis. It is estimated that 3D structure determinations should be possible on regions only about ten unit cells wide and should resolve not only atom positions but also site occupancies. The method is also applicable to space-group determination.