Use of Mathematical Programming Techniques for Phase Determination

By Arthur M. Lesk

*Department of Biochemical Sciences, Frick Chemical Laboratories, Princeton University,
Princeton, New Jersey 08540, U.S.A.*

The phase problem can be cast into a form equivalent to that of certain optimization problems arising in operations research. Computational techniques of mathematical programming developed for these problems are thereby made applicable to phase determination. This reformulation of the phase problem is derivable by combining the nonnegativity property of electron-density distributions with molecular model building. If a structural model is available, the algorithms select phases for the nonnegative electron-density distribution, consistent with the measured intensities, that best matches the model. If no model is introduced, the algorithms produce some (or all) of the nonnegative distributions consistent with the data. The approach to the phase-problem presented here is similar to that of R. J. Dakin (*Acta Cryst.* 1970, B**26**, 2112). However, practical computational tests also are reported: an example, the 0*kl* projection of dihydrouracil demonstrates that algorithms based on mathematical programming techniques can solve a real structure using real data. The coupling of phase determination with molecular model building should be particularly useful in crystallographic studies of biological macromolecules. The algorithms are well-adapted to the introduction of low-resolution models inferred from hydrodynamic measurements, or detailed structures suggested by model building or computed by energy minimization.

Introduction

By combining the general principle of direct methods – the nonnegativity of electron-density distributions – with molecular model building, the phase problem can be cast into a form mathematically equivalent to certain problems of operations research (*cf.* Freeman, Sime, Bennet, Dakin & Green, 1963; Dakin, 1970). Many algorithms, and experience in their use, are thus made applicable to problems of X-ray crystallography.

The purpose of this report is to describe and derive this equivalence, and to present computational tests for the centrosymmetric case. In succeeding sections, we show how the nonnegativity principle may be expressed as a set of simultaneous inequalities; also we derive the mathematical programming formulation of the phase problem for centrosymmetric and general noncentrosymmetric cases, and present illustrative examples. The solution of the 0*kl* projection of dihydrouracil, using structure factors reported in a recent paper (Rohrer & Sundaralingam, 1970), but *without* introducing any structural model, demonstrates that the mathematical programming approach to phase determination works using real data, at least in a simple case, and that a model is not required.

Expression of the nonnegativity principle as a set of simultaneous inequalities

The appearance of numerous inequality constraints is characteristic of mathematical programming problems. To express the nonnegativity property of electron-density distributions in this form, let the unit cell be divided into nonoverlapping subsets, and let ϱ_k be the average value of the electron-density distribution in the kth subset. Then if ϱ_k can be expressed as a linear function of the structure factors, the conditions $\varrho_k \geq 0$, $k=1$, ... M, express an approximation to the nonnegativity principle as a set of simultaneous inequalities. The accuracy of the approximation increases with the fineness of the partition of the unit cell into subsets.

For the purpose of computing the coefficients in these inequalities, it is convenient to think of two expansions of the electron-density distribution, using different sets of expansion functions. The precise form of the inequalities can then be derived from the standard equations of transformation between two basis sets.

First, consider the conventional Fourier expansion in trigonometric functions. Let this basis set be denoted by $\chi_\mathbf{h} = V_c^{-1/2} \exp(-2\pi i \mathbf{h} . \mathbf{r})$, in which V_c is the volume of the entire unit cell, and the vector subscript $\mathbf{h}$ specifies a triple of Miller indices. The functions $\chi_\mathbf{h}$ are

normalized so that $(\chi_\mathbf{h}, \chi_{\mathbf{h}'}) = \int_{\text{unit cell}} \chi_\mathbf{h}^*(\mathbf{r}) \chi_{\mathbf{h}'}(\mathbf{r}) d\mathbf{r} = 1$.

In centrosymmetric cases it is appropriate to choose the basis set $\chi_{000} = V_c^{-1/2}$; $\chi_\mathbf{h} = (2V_c)^{-1/2} \cos(2\pi \mathbf{h} . \mathbf{r})$, $\mathbf{h} \neq (0, 0, 0)$.

The second expression for the electron-density distribution is an expansion in terms of the set of characteristic functions of a partition of the unit cell. (The characteristic function of a set is the function that takes the value 1 at points in the set and 0 at points outside.) Thus, the second expansion is a step function whose value at any point is the average value of the electron density in that subset of the unit cell containing

the point in question. Note that these characteristic functions are themselves real and nonnegative; *i.e.*, these desired properties of the computed electron density are built directly into the expansion functions.

Let $\{X_k\}$ denote such a partition, *i.e.*, $\cup X_k = C$ (the unit cell), and $X_k \cap X_{k'} = \varnothing$, (the null set) if $k \neq k'$. V_k is the fractional volume of X_k, relative to the entire unit cell. The number, sizes, and shapes of the sets X_k are arbitrary, but it is convenient to choose them with the symmetry of the unit cell. Also, it is convenient to index these functions by a vector k, since this is a natural way to specify members of a three-dimensional array.

The set $\{\psi_k\}$ of normalized characteristic functions of the sets X_k, defined by: $\psi_k(r) = V_k^{-1/2}, r \in X_k$; $\psi_k(r) = 0, r \notin Xk$; is orthonormal. The electron-density distribution in the unit cell, $\varrho(r)$, can be approximated by an expansion of the form $\varrho(r) = \sum_k c_k \psi_k(r)$.

A transformation matrix $\mathbf{A}$ relates the expansion coefficients c_k to the structure factors F_h (the coefficients of the original Fourier expansion):

$$c_k = \sum {}_h A_{kh} F_h = \sum_h \hat{A}_{kh} \exp(i\alpha_h),$$

in which $\hat{A}_{kh} = A_{kh} |F_h|$ and α_h is the amplitude or phase angle of F_h. The matrix element A_{kh} is simply the scalar product $(\psi_k, \chi_h) = V_k^{-1/2} \int_{X_k} \chi_h(r) dr$. c_k is propor-

Fig. 1. Electron-density distributions for two atoms in a one-dimensional centrosymmetric unit cell. Abscissa: fractional coordinate x/a; ordinates: arbitrary linear scales. (*a*) Basis functions distributed equally throughout the unit cell. (*b*) Basis functions concentrated under peaks of (*a*).

tional to the average value of the electron density distribution in X_k.

The nonnegativity constraint is then expressed, approximately, by the simultaneous inequalities:

$$c_k = \sum_h \hat{A}_{kh} \exp(i\alpha_h) \geq 0,$$

which, in this form, are linear in trigonometric functions of the phase angles. Substitution of a new set of variables equal to cosines and sines of the phase angles linearizes these inequalities, at the expense of certain additional constraints whose particular form depends on the symmetry group of the crystal.

Mathematical programming formulation of the phase problem

The computational task of determining the nonnegative distribution consistent with measured structure-factor magnitudes, which best resembles a model, is equivalent to one of several types of mathematical programming problems.

If the unit cell is centrosymmetric, all structure factors are real. It is convenient to make the substitution $x_h = 1/2[1 + \exp(i\alpha_h)]$; x_h is then a Boolean variable, taking on the value 1 if $\alpha_h = 0$ and 0 if $\alpha_h = \pi$. Define $b_k = -\sum_h \hat{A}_{kh}$.

The average value in the set X_k of the computed electron density for some choice of phases is then $c_k = \sum_h (2\hat{A}_{kh} x_h) + b_k$. If a structural model has analogous expansion coefficients $(c_m)_k$, then to find the best match between the model and the computed electron-density distribution, the quantity to be maximized is:

$$\sum_k (c_m)_k c_k = \sum_k (c_m)_k [\sum_h (2\hat{A}_{kh} x_h + b_k]$$

$$= 2 \sum_h [\sum_k (c_m)_k \hat{A}_{kh}] x_h + \sum_k (c_m)_k b_k.$$

Defining $(c'_m)_h = \sum_k (c_m)_k \hat{A}_{kh}$, and dropping the second term since it is independent of the choice of phases, the quantity to be optimized by suitable choice of the variables x_h reduces to $\sum_h (c'_m)_h x_h$.

The nonnegative electron-density distribution, consistent with the experimental data, that best matches a model, is then the solution of a Boolean programming problem:

Maximize $\mathbf{c}'_m \cdot \mathbf{x}$ subject to the constraints:

$$2\hat{\mathbf{A}} \cdot \mathbf{x} + \mathbf{b} \geq 0,$$

$$x_h = 0 \text{ or } 1.$$

If no model is introduced, it is still possible to apply the nonnegativity constraints alone: solutions of the simultaneous linear Boolean inequalities $2\hat{\mathbf{A}} \cdot \mathbf{x} + \mathbf{b} \geq 0$, $x_h = 0$ or 1, produce phases for some nonnegative electron-density distribution consistent with the measured intensities. An example, the $0kl$ projection of dihydrouracil (presented in a subsequent section), shows that it is possible to solve structures in this way, without introducing a model. The conclusion is that a model can be useful for preselecting the correct member of a set of homometric structures and for speeding the
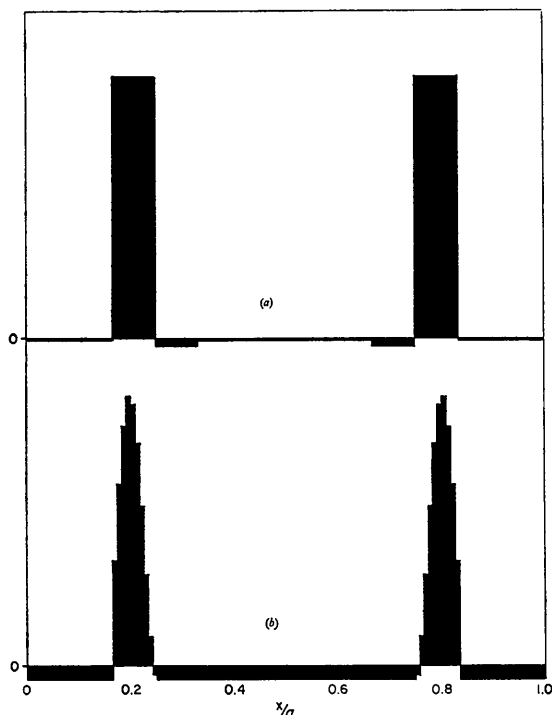
computation, but it is not an absolute requirement of this approach.*

In noncentrosymmetric space groups, phases may, in general, take on any value in the interval $[0, 2\pi]$. As before, let c_m be the vector of expansion coefficients of a model on the basis set $\{\psi_k\}$. Let $c'_m = c_m^{tr} \cdot \hat{A}'$, and $c''_m = c_m^{tr} \cdot \hat{A}''$, in which $\hat{A}'$ and $\hat{A}''$ are the real and imaginary parts of $\hat{A}$. Defining $x_h = \cos \alpha_h$, and $y_h = -\sin \alpha_h$, the programming problem takes the form:

maximize $\sum_h [(c'_m)_h x_h + (c''_m)_h y_h]$,

subject to the constraints:

$$c_k = \sum [\hat{A}'_{kh} x_h + \hat{A}''_{kh} y_h] \geq 0$$
$$-1 \leq x_h \leq 1, \ -1 \leq y_h \leq 1$$
$$x_h^2 + y_h^2 = 1.$$

In most space groups, the symmetry restricts certain phases to a discrete set of values; these phases can be described by Boolean variables as in the centrosymmetric case. For these space groups, the programming formulation of the phase problem is of the mixed integer-continuous type.

Computational tests

Two examples illustrate the application of mathematical programming techniques to the phase problem in centrosymmetric cases. The first is a model problem, consisting of two point atoms in a one-dimensional centrosymmetric unit cell. The second, the $0kl$ projection of dihydrouracil, represents a test of the method on actual experimental data, taken from a recently published paper (Rohrer & Sundaralingam, 1970).

Model problem

Consider a one-dimensional centrosymmetric unit cell, $a = 10$ Å, containing two |nonvibrating point atoms, at $X = 1 \cdot 941$ and $8 \cdot 059$ Å. Thirteen structure factors (the entire copper sphere) were computed. The constraint $\varrho \geq 0$ was relaxed to $\varrho \geq -F/10$, because of the artificial sharpness of the atoms.

Two different basis sets were studied. First, the unit cell was divided into 12 equal intervals. The basis set consisted of the six characteristic functions of centrosymmetric combinations of pairs of intervals.

In this example, the Fourier basis set is $\chi_0 = 1$; $\chi_h = 2^{-1/2} \cos (2\pi hx)$, $h > 0$. Here x is a fractional coordinate. The characteristic function basis set is defined by

$$\psi_k(x) = (12)^{1/2}, \quad \text{if} \quad (k-1)/12 \leq x \leq k/12$$

or

$$1 - (k/12) \leq x \leq 1 - [(k-1)/12],$$

and 0 otherwise; for $k = 1, \ldots 6$. Both sets of functions are centrosymmetric, i.e., $\chi_h(x) = \chi_h(1-x)$ and $\psi_k(x) =$

$\psi_k(1-x)$. Therefore, the matrix elements $A_{kh} = (\psi_k, \chi_h)$ are equal to $2\sqrt{12} \int_{(k-1)/12}^{k/12} \cos 2\pi hx dx = 2\sqrt{12}$ $[\sin (2\pi k/12) - \sin (2\pi (k+1)/12)]$.

The structural model introduced was a broad peak extending over the outer thirds of the unit cell: it took on the values 8, 10, 10, 8, 1, 1, 1, 1, 8, 10, 10, 8 on successive twelfths of the unit cell.

The Boolean programming algorithm applied was the implicit enumeration technique of Balas (1965), as described by Geoffrion (1967).† A single iteration of the algorithm produced the distribution shown in Fig. 1(a), localizing the solution to the proper sixth of the unit cell.

The second basis set shows how a low-resolution structure such as that in Fig. 1(a) can be parlayed into a higher-resolution structure. It illustrates the versatility available through a more general choice of basis set.

The two intervals under the peaks in Fig. 1(a) were each divided into 10 equal subintervals. Ten basis functions were characteristic functions of centrosymmetric unions of pairs of these subintervals; the last was the characteristic function of the rest of the unit cell. Thus, by partitioning the unit cell into subsets of different sizes, regions of high interest can be studied at high resolution, and regions of low interest can be studied at low resolution.

The sharply peaked distribution shown in Fig. 1(b) was computed with the second basis set, using phases derived from the low-resolution structure.

Dihydrouracil, 0kl projection

The second example, the $0kl$ projection of dihydrouracil, serves to demonstrate that the method works with real data, and that a model is not essential. Cell dimensions are $a = 4 \cdot 201$, $b = 5 \cdot 816$, $c = 19 \cdot 777$ Å, $\beta = 95 \cdot 15°$; there are four molecules in each unit cell. The $0kl$ projection has pgg symmetry.

The measured magnitudes of 66 structure factors, $h = 0$, $0 \leq k \leq 4$, $0 \leq l \leq 14$, were introduced, and two signs were fixed to define the origin. No model was used. A basis set of the proper symmetry was constructed by division of b into 8 equal intervals and c into 30, to produce a grid of almost square rectangles. The 60 basis functions were the characteristic functions of unions of symmetry-related tetrads of rectangles.

Non-negativity constraints (relaxed to $\varrho \geq -0 \cdot 01$ F_{000}) take the form of simultaneous linear inequalities in Boolean variables. A program coded directly from the algorithm of Hammer & Rudeanu (1968) fixed

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* This formulation in terms of Boolean variables could be applied to noncentrosymmetric problems also, if structure-factor magnitudes from a single isomorphous derivative are also measured. In that case too, experimental data determine the structure factors up to a choice between two possible phases.

† Programs were coded for the IBM 360/91 to effect the basis transformation, to solve simultaneous linear Boolean inequalities (Hammer & Rudeanu, 1968), and to solve Boolean programming problems (Balas, 1965; Geoffrion, 1967). These were coded by the author, making use of standard IBM-supplied FORTRAN library subroutines and a sorting program distributed by the Quantum Chemistry Program Exchange (Rochkind, 1970). Programs were executed under OS release 18·

the signs of 44 structure factors.‡ A Fourier transform showed enough of the molecule to permit the positioning of an atomic model in the unit cell. Fig. 2 shows the original Fourier transform and a partially refined structure.

Relation to other work

During the preparation of this article, the earlier work of Dakin (1970), presenting much the same basic idea, came to the author's attention. The formulation presented here differs from Dakin's primarily in that the quantities to which the nonnegativity constraint is applied are not a sampling of the computed electron-density distribution at points of a mesh; instead, they are the average of the computed electron density over a region in space. This may be preferable, since truncation errors can cause the computed distribution to dip negative.

The practical application of mathematical programming algorithms to the phase problem has been initiated by the demonstration that such an approach can work successfully with real data.

Discussion and conclusions

The mathematical programming formulation of the phase problem combines the powers of direct methods based on the nonnegativity principle and molecular

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‡ See footnote marked elsewhere with †.

model building. The equivalence of the phase problem to problems of operations research makes possible the application of previously developed algorithms and computational experience.

Computational tests reported here demonstrate the feasibility of using Boolean programming algorithms for centrosymmetric problems. Computational experiments currently in progress are designed to apply the more powerful algorithms available (Balinski & Spielberg, 1969; Byrne & Proll, 1969; Geoffrion, 1969; Gue, Liggett & Cain, 1968; Roth, 1970) to larger examples of the centrosymmetric case, and to test the method in a noncentrosymmetric case. In a preliminary, but nevertheless encouraging, trial the Boolean programming code of Geoffrion & Nelson (1968) determined phases for the $0kl$ projection of dihydrouracil with sufficient accuracy to position an atomic model in less than 0·5 seconds on an IBM 360/91.

It is hoped that these techniques will prove useful in solving the structures of biological macromolecules, for which structural models are often available. Hydrodynamic and low-angle X-ray scattering experiments that determine rough molecular dimensions are sources of low-resolution models for biological macromolecules. Prof. R. Langridge has suggested that electron microscopy might also provide models. *A priori* predictions of the conformations of proteins of known amino acid sequence, or nucleic acids of known base sequence, could, if successful, produce detailed high-resolution models.
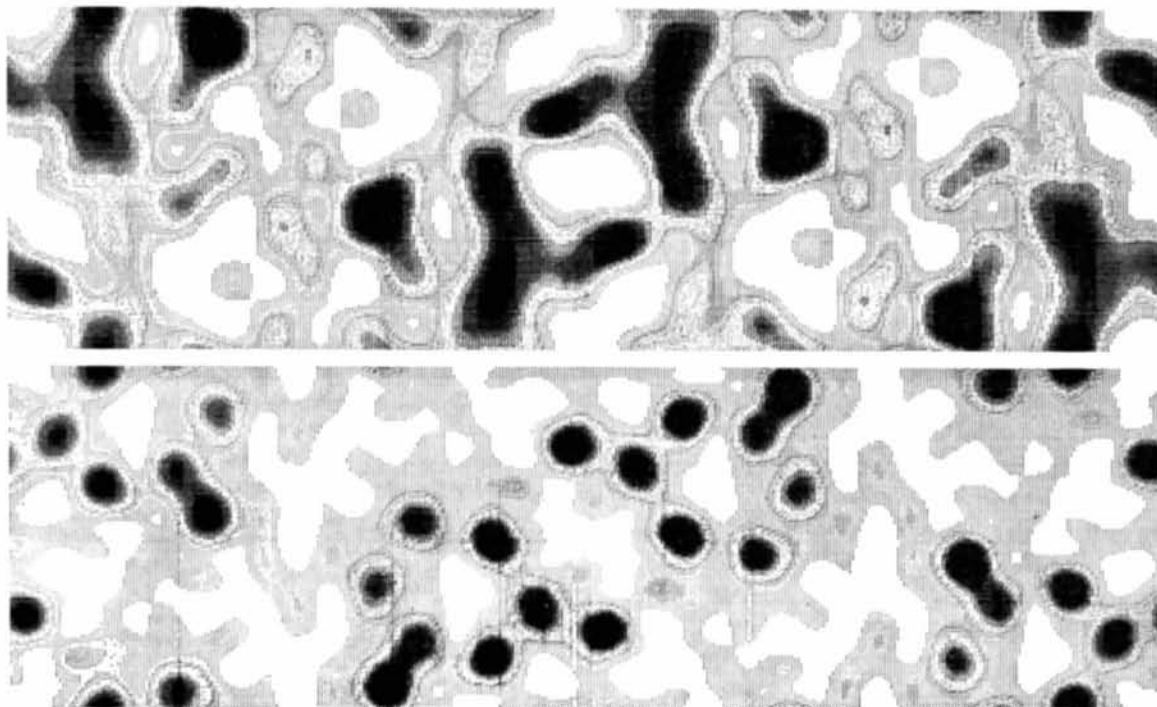

Fig. 2. Electron-density distributions for the $0kl$ projection of dihydrouracil. Top: preliminary electron density from phasing program. Bottom: partially refined structure. Half-tone drawings of the projected electron density were produced by a program that differed only in minor details from one written by MacLeod (1970).

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Bestimmung der Änderung der Gitterkonstanten und des Anisotropen Debye–Waller-Faktors von Graphit mittels Neutronenbeugung im Temperaturbereich von 25°C bis 1850°C*

VON A. LUDSTECK†

Physik-Department der Technischen Hochschule, München, Deutschland (BRD)

With a double-axis spectrometer the neutron-scattering cross section $d\sigma/d\Omega$ of polycrystalline graphite has been measured as a function of temperature. The elastic coherent scattering yielded the variations of the lattice constants for the directions parallel and perpendicular to the *c* axis of the hexagonal graphite lattice. For these lattice directions also the Debye–Waller factors have been determined and from them the mean-square vibration amplitudes of the atoms and the effective Debye temperatures have been calculated.

Einleitung und theoretische Grundlagen

Die Dynamik des Kristallgitters von Graphit wurde bisher meist nur theoretisch untersucht, da viele Experimente, z.B. die Messung von Dispersionskurven, durch das Fehlen von Graphit-Einkristallen erschwert oder unmöglich sind. Auch die Debye–Waller-Faktoren von Graphit wurden fast ausschliesslich indirekt aus der Temperaturabhängigkeit der spezifischen Wärme bestimmt. Berechnungen der Debye–Waller-Faktoren aus der Änderung der Intensität der elastisch kohärenten Streuung über einen grossen Temperaturbereich wurden bisher nicht durchgeführt. Für diese Methode ist ein präzises Neutronen-Pulverspektrometer besonders gut geeignet, da mit dieser Apparatur auch am Polykristall die Intensitäten der elastischen Streuung für Impulsüberträge in den beiden ausgezeichneten Richtungen des Graphitgitters getrennt gemessen werden können. Ausserdem kann man mit Neutronenspektrometern höhere Probentemperaturen erreichen als bei Messung mit Röntgenstrahlen.

Graphit kristallisiert in einem nach ihm benannten hexagonalen Gitter (Bernal, 1924; Wyckoff, 1963) mit 4 Atomen je Elementarzelle, deren Koordinaten (000), $(\frac{1}{3}\frac{1}{3}0)$, $(00\frac{1}{2})$ und $(\frac{2}{3}\frac{1}{3}\frac{1}{2})$ sind.

Die primitiven Translationsvektoren des Gitters