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Looking Ahead

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Abstract

It is now almost 200 years since Gauss, a teenager at the time, formulated his famous principle of least-squares and used it to determine, for the first time, the orbit of one of the asteroids, a problem which had defeated astronomers for years. When applied to the crystallographic phase problem, least-squares leads directly to the formulation of the minimal principle, which effectively replaces the phase problem by one of constrained global minimization. *Shake-and-Bake*, the computer software package which implements this formulation of the phase problem, provides a completely automatic solution of this problem. The program has solved *ca* two dozen structures, of which five or six had been previously unknown, with no failure. Three of these structures – gramicidin A, crambin and rubredoxin – in the 300–500 atom range, and six or seven others, in the 100–200 atom range, were all routinely solved. With this background it now appears likely that, provided data to atomic resolution is available, structures having as many as 1000 atoms or more will prove to be solvable by this technique. What if only diffraction data to less than atomic resolution is available? Here the crystal ball becomes murky and the evidence less than compelling. Nevertheless, in view of recent experience, it is again conjectured that, building on existing techniques, complex structures will eventually prove to be routinely solvable, even with data to only 1.5 Å resolution.

1. Introduction

1.1. *The normalized structure factors E*

In the equal atom case (space group $P1$) the normalized structure factors are defined by

$$E_{\mathbf{H}} = |E_{\mathbf{H}}|\exp(i\varphi_{\mathbf{H}}) = (1/N^{1/2})\sum_{j=1}^{N}\exp(2\pi i\mathbf{H}.\mathbf{r}_j), \quad (1)$$

where $\mathbf{H}$ is an arbitrary reciprocal lattice vector, N is the number of atoms in the unit cell and $\mathbf{r}_j$ is the position vector of the atom labeled j. The magnitudes $|E|$ are directly obtainable from the diffraction intensities, but the phases φ are lost in the diffraction experiment.

1.2. *The structure invariants*

Although the values of the individual phases are known to depend on the structure and the choice of origin, certain linear combinations exist of the phases whose values are determined by the structure alone and are independent of the choice of origin. These linear combinations of the phases are called the structure invariants. The most important class of structure invariants, and the only one to be considered here, consists of the three-phase structure invariants (triplets)

$$\varphi_{\mathbf{HK}} = \varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}. \quad (2)$$

1.3. *The probabilistic background*

It is assumed that (a) a crystal structure is specified, (b) three non-negative numbers R_1, R_2 and R_3 are also specified and (c) the reciprocal lattice vectors $\mathbf{H}$ and $\mathbf{K}$ are the primitive random variables which are assumed to be uniformly and independently distributed in the subset of reciprocal space defined by

$$|E_{\mathbf{H}}| = R_1, |E_{\mathbf{K}}| = R_2, |E_{\mathbf{H}+\mathbf{K}}| = R_3, \quad (3)$$

where the magnitudes $|E|$ are defined by (1). Then the structure invariant $\varphi_{\mathbf{HK}}$ (2), as a function of the primitive random variables $\mathbf{H}$ and $\mathbf{K}$ (1), is itself a random variable.

1.4. *The conditional probability distribution of $\varphi_{\mathbf{HK}}$, given $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$ and $|E_{\mathbf{H}+\mathbf{K}}|$*

Under the three assumptions of §1.3 the conditional probability distribution of the triplet $\varphi_{\mathbf{HK}}$ (2), where $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$ and $|E_{\mathbf{H}+\mathbf{K}}|$ are given by (3), is known to be

$$P(\Phi/R_1, R_2, R_3) = \{1/[2\pi I_0(A_{\mathbf{HK}})]\}\exp(A_{\mathbf{HK}}\cos\Phi), \quad (4)$$

where

$$A_{\mathbf{HK}} = (2/N^{1/2})R_1R_2R_3 = (2/N^{1/2})|E_{\mathbf{H}}E_{\mathbf{K}}E_{\mathbf{H}+\mathbf{K}}| \quad (5)$$

and I_0 is the modified Bessel function. Equation (4) implies that the mode of $\varphi_{\mathbf{HK}}$ is zero, and the conditional expectation value (or average) of $\cos\varphi_{\mathbf{HK}}$, given $A_{\mathbf{HK}}$, is

$$E(\cos\varphi_{\mathbf{HK}}/A_{\mathbf{HK}}) = [I_1(A_{\mathbf{HK}})]/[I_0(A_{\mathbf{HK}})] > 0. \quad (6)$$

It is also readily confirmed that the larger the value of $A_{\mathbf{HK}}$, the smaller is the conditional variance of $\cos\varphi_{\mathbf{HK}}$, given $A_{\mathbf{HK}}$. It is to be stressed that the conditional expected value of the cosine (6) is always positive since $A_{\mathbf{HK}} > 0$.

2. The minimal principle

2.1. *The heuristic background*

It is assumed that a crystal structure consisting of N identical atoms in the unit cell is fixed, but unknown, that the magnitudes $|E|$ of the normalized structure factors E are known, and that a sufficiently large base of phases, corresponding to the largest magnitudes $|E|$, is specified.

The mode of the triplet distribution (4) is zero and the variance of the cosine is small if $A_{\mathbf{HK}}$ (5) is large. In this way one obtains the estimate for the triplet $\varphi_{\mathbf{HK}}$ (2)

$$\varphi_{\mathbf{HK}} = \varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} \approx 0, \qquad (7)$$

which is particularly good in the favorable case when $A_{\mathbf{HK}}$ (5) is large, *i.e.* when $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$ and $|E_{\mathbf{H+K}}|$ are all large. The estimate given by (7) is one of the corner stones of the traditional techniques of direct methods. It is surprising how useful (7) has proven to be in the applications, especially since it yields only the zero estimate of the triplet and only those estimates are reliable for which $|E_{\mathbf{H}}|$, $|E_{\mathbf{K}}|$ and $|E_{\mathbf{H+K}}|$ are all large. Clearly the coefficient $2/N^{1/2}$ in (5), and therefore also $A_{\mathbf{HK}}$, both decrease with increasing N, *i.e.* with increasing structural complexity. Hence, the relationship (7) becomes increasingly unreliable for larger structures, and the traditional step-by-step sequential direct methods procedures based on (7) eventually fail. However, the phase-annealing approach of Sheldrick (1990) and the program *SAYTAN*, devised by Woolfson & Yao (1990), have to some extent overcome this limitation. Here a different approach is described.

In view of (6) and the previous discussion, one now replaces the zero estimate (7) of the triplet $\varphi_{\mathbf{HK}}$ by the estimate

$$\cos\varphi_{\mathbf{HK}} \approx [I_1(A_{\mathbf{HK}})]/[I_0(A_{\mathbf{HK}})] \qquad (8)$$

and expects that the smaller the variance, that is the larger the $A_{\mathbf{HK}}$, the more reliable this estimate will be. Hence, one is led to construct the function, determined by the known magnitudes $|E|$

$$R = R(\varphi) = \left(1/\sum_{\mathbf{H,K}} A_{\mathbf{HK}}\right)\sum_{\mathbf{H,K}} A_{\mathbf{HK}} \times \{\cos\varphi_{\mathbf{HK}} - [I_1(A_{\mathbf{HK}})]/[I_0(A_{\mathbf{HK}})]\}^2, \qquad (9)$$

which is seen to be a function of all those triplets $\varphi_{\mathbf{HK}}$ which are generated by a prescribed set of phases $\{\varphi\}$. Recall that if the basis set of $\{\varphi\}$ is sufficiently large then there are many more structure invariants $\varphi_{\mathbf{HK}}$ than individual phases φ, and a myriad of identities among these structure invariants must, of necessity, then be satisfied. In accordance with the principle of least-squares, it is natural to suppose that the set of values for the structure invariants $\varphi_{\mathbf{HK}}$ is best which minimizes the weighted sum of squares of residuals R (9), subject to the constraint that all identities among the structure invariants are in fact satisfied.

Since the triplets $\varphi_{\mathbf{HK}}$ are defined by (2) as functions of the individual phases φ (9) defines R implicitly as a function of the individual phases. One therefore naturally anticipates that the set of values for the individual phases is best which minimizes the residual R (9), now regarded as a function of the individual phases φ. The advantage of this formulation is that all identities among the structure invariants will then automatically be satisfied, and it is unnecessary to define in further detail what the nature of these identities must be.

2.2. *The minimal principle*

In order to derive the conditions under which the formulation of the minimal principle given in the previous paragraph is valid, one first defines R_T as the value of R (9) obtained when the phases are equal to their true values for some choice of origin and enantiomorph. One then defines R_R as the value of R when the phases are assigned values at random so that in this case

$$\langle\cos\varphi_{\mathbf{HK}}\rangle_{\mathbf{H,K}} = \langle\cos 2\varphi_{\mathbf{HK}}\rangle_{\mathbf{H,K}} = 0. \qquad (10)$$

With these definitions for R_T and R_R it may then be shown that (De Titta, Weeks, Thuman, Miller & Hauptman, 1994)

$$R_T < \tfrac{1}{2} < R_R. \qquad (11)$$

While the inequalities (11) tend to confirm the conjecture that the true values of the phases minimize R, the conjecture itself is in fact not true. As it turns out, special values exist for the phases which yield values for R even less than R_T, so that R_T is not the global minimum of R. It is for this reason that one must further constrain the phases to satisfy certain identities among them which are known to exist because their number generally exceeds by far the number of unknown parameters needed to specify the crystal structure. In short, it is the constrained global minimum of R which yields the desired phases (the minimal principle). The next section describes how this minimum is reached in practice.

3. The computer program *shake-and-bake*

The six-part *shake-and-bake* (Weeks, DeTitta, Hauptman, Thuman & Miller, 1994) phase-determination procedure, shown by the flow diagram in Fig. 1, combines minimal-function phase refinement and real-space filtering. It is an iterative process that is repeated until a solution is achieved or a designated number of cycles have been performed. With reference to Fig. 1, the major steps of the algorithm are described next and typical values of the various parameters used in this procedure are given and summarized in Table 1, in which N' denotes the number of non-H atoms, assumed identical, in the asymmetric unit.

3.1. *Generate invariants*

Normalized structure-factor magnitudes ($|E|$'s) are generated by standard scaling methods such as a Wilson plot, and the triplet invariants that involve the largest corresponding $|E|$'s are generated. Parameter choices that must be made at this stage include the number of phases and triplets to be used. The total number of invariants is ordinarily chosen to be at least 100 times the number of atoms.

3.2. *Generate trial structure*

A trial structure or model is generated that is comprised of a number of randomly positioned atoms and their symmetry-related mates sufficient to specify the origin and enantiomorph for the space group in question. The starting coordinate sets are subject to the restrictions that no two atoms are closer than a specified distance (normally 1.2 Å) and that no atom is within bonding distance of more than four other atoms.

3.3. *Structure-factor calculation*

A normalized structure-factor calculation based on the trial coordinates is used to compute initial values for all the desired phases simultaneously. In subsequent cycles, peaks selected from the most recent Fourier series are used as atoms to generate new phase values. In the applications reported here, all non-H atoms were considered to be equal unless stated otherwise.

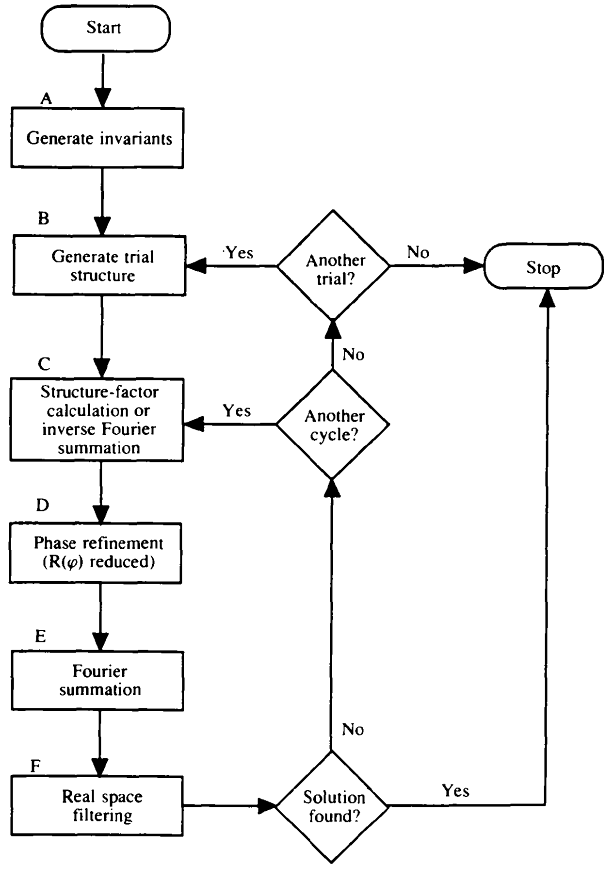

Fig. 1. Flow chart for *shake-and-bake*, the minimal-function phase refinement and real-space filtering procedure.

Table 1. *Shake-and-bake variables with typical values*

Independent non-H atoms	N'
Invariant generation:	
Phases per atom	10
Triplets per atom	100
Initial phasing model	1, 2 or 4 atoms
Parameter shift	
Step size	16
Number of steps	±5
Real space:	
Grid size (Å)	0.33
Peaks selected	$\sim N'$
Number of cycles	$\sim N'$

3.4. *Phase refinement*

The values of the phases are perturbed by a *parameter-shift* method in which $R(\varphi)$, which measures the mean-square difference between estimated and calculated structure invariants, is reduced in value. $R(\varphi)$ is initially computed on the basis of the set of phase values obtained from the structure-factor calculation in §3.3. The phase set is ordered in decreasing magnitude of the associated $|E|$'s. The value of the first phase is incremented by a preset amount and $R(\varphi)$ is recalculated. If the new calculated value of $R(\varphi)$ is lower than the previous one, the value of the first phase is incremented again by the preset amount. This is continued until $R(\varphi)$ no longer decreases or until a predetermined number of increments has been applied to the first phase. A completely analogous course is taken if, on the initial incrementation, $R(\varphi)$ increases, except that the value of the first phase is decremented until $R(\varphi)$ no longer decreases or until the predetermined number of decrements has been applied. The remaining phase values are varied in sequence as just described. Note that when the ith phase value is varied, the new values determined for the previous $i-1$ phases are used immediately in the calculation of $R(\varphi)$. This process, when convergent, yields the constrained global minimum of $R(\varphi)$. The step size and number of steps are variables whose values must be chosen. In centrosymmetric space groups, each phase takes on the values 0 and 180°, and the value yielding the smaller $R(\varphi)$ is chosen.

3.5. *Fourier summation*

Fourier summation is used to transform phase information into an electron-density map. Normalized structure-factor amplitudes $|E|$'s have been used at this stage (rather than F's) because phases are available for the largest E's but not for all the largest F's. The grid size must be specified.

Table 2. *Test data sets re-solved using the minimal function*

Structure	Atoms	Formula	Space group	Reference
Prostaglandin E_2	25	$C_{20}H_{32}O_5$	$P1$	Edmonds & Duax (1974)
Prostaglandin $F_1\beta$	25	$C_{20}H_{35}O_5$	$C2$	G. T. DeTitta (unpublished)
Aldosterone	27	$C_{21}H_{28}O_5H_2O$	$P2_1$	Duax & Hauptman (1972)
9α-Methoxycortisol	28	$C_{22}H_{32}O_6$	$P2_12_12_1$	Weeks, Duax & Wolff (1976)
AZET	48	$(C_{21}H_{16}ClNO)_2$	$Pca2_1$	Colens, Declercq, Germain, Putzeys & Van Meersche (1974)
Tetrahymanol	63	$(C_{30}H_{52}O)_2.H_2O$	$P2_1$	Langs, Duax, Carrell, Berman & Caspi (1977)
APAPA	69	$C_{30}H_{37}N_{15}O_{16}P_2.6H_2O$	$P4_12_12$	Suck, Manor & Saenger (1976)
Antibiotic A204A	71	$C_{49}H_{84}O_{17}H_2O.C_3H_6O$	$C2$	Smith, Strong & Duax (1978)
Isoleucinomycin	84	$C_{60}H_{102}N_6O_{18}$	$P2_12_12_1$	Pletnev, Galitskii, Smith, Weeks & Duax (1980)
meso-Valinomycin	84	$C_{60}H_{108}N_6O_{18}$	$P\bar{1}$	D. A. Langs (unpublished)
Nonpeptidic enkephalin analog	96	$(C_{24}H_{30}N_2O_6)_3$	$P1$	D. A. Langs (unpublished)
Hexaisoleucinomycin	127	$C_{81}H_{110}N_8O_{24}.14H_2O$	$P2_12_12_1$	Pletnev, Ivanov, Langs, Strong & Duax (1992)
Gramicidin A	317	$(C_{99}H_{140}N_{20}O_{17})_2.15C_2H_5OH$	$P2_12_12_1$	Langs (1988)

3.6. *Real-space filtering (identities among phases imposed)*

Image enhancement has been accomplished by a discrete electron-density modification consisting of the selection of a specified number of the largest peaks on the Fourier map for use in the next structure-factor calculation. The simple choice, in each cycle, of a number of the largest peaks corresponding to the number of expected atoms has given satisfactory results. No minimum interpeak-distance criterion is applied at this stage.

The *shake-and-bake* procedure has been tested successfully using the experimentally measured atomic resolution intensities for the known structures (among others) listed in Table 2. These structures range in size from 25 to 317 independent non-H atoms in the asymmetric unit and crystallize in seven different space groups. Two structures contain moderately heavy P or Cl atoms. Some of these structures (*e.g.* 9α-methoxycortisol) were easily solved by conventional direct methods, while at least one (gramicidin A) required years of painstaking nonroutine effort. Several presented some challenge and three (prostaglandin E_2, AZET and APAPA) were included in a suite of difficult structures supplied by the crystallographic group at the University of York, England. In all cases those trials which led to solutions were readily identified by the behavior of the minimal function $R(\varphi)$ (9) during successive cycles (Weeks *et al.*, 1994). Thus, the fact that these structures had been known was not used in these applications.

4. Three notable applications

4.1. *Gramicidin A*

After years of back-breaking work, this 317 atom structure (cited in Table 2) was finally solved by Langs (1988), who used the full power of direct methods then available in combination with molecular replacement. In sharp contrast, *shake-and-bake* solved this structure automatically with a success rate of 0.3%. More precisely, 14 solutions were obtained in 4728 trials. The initial models consisted of 300 randomly positioned atoms per asymmetric unit, and in each of the prescribed 160 cycles of *shake-and-bake* the strongest 250 peaks in the Fourier were chosen. The basis set consisted of 2500 phases with the largest $|E|$ values, and the 25 000 triplets having the largest A values were used in defining R (9).

4.2. *Crambin*

The crystal structure of crambin (space group $P2_1$), a 46-residue protein consisting of approximately 400 non-H atoms, was first solved at 1.5 Å by exploiting the anomalous scattering of its six S atoms at a single wavelength far removed from the absorption edge of sulfur (Hendrickson & Teeter, 1981). All previous attempts to solve crambin *ab initio* by conventional direct methods have been unsuccessful (Sheldrick, Dauter, Wilson, Hope & Siekes, 1993). In this application, data were collected to a resolution of 0.83 Å, equivalent reflections were averaged, and differences due to the anomalous dispersion of the S atoms were ignored. The 4000 reflections with the largest $|E|$ values were used to generate the 40 000 triplets having the largest $A_{\mathbf{HK}}$ values in order to define the minimal function $R(\varphi)$ (9). One thousand trial structures, each consisting of two randomly positioned atoms per asymmetric unit, were subjected to 200 cycles of the *shake-and-bake* procedure. In the first cycle the structure-factor calculations were based on these random two-atom structures. Since a total of approximately 400 atoms was expected, the 400 largest peaks in each Fourier map were used in subsequent structure-factor calculations with the six largest peaks being treated as S atoms and the remainder as C atoms. After 200 or fewer *shake-and-bake* cycles, 36 of the 1000 trial structures yielded solutions, for a success rate of 3.6%. Final values for the minimal function $R(\varphi)$ were in the range 0.412–0.423 for the 36 solutions, but were in the range 0.450–0.499 for the 964 nonsolutions. Thus, the minimal function served to separate the solutions from the nonsolutions and to identify the solutions unambiguously. It is of some interest to observe that R_T, the value of the constrained global minimum of $R(\varphi)$ when all phases are equal to their true values for any choice of origin and enantiomorphs, is predicted on theoretical grounds to be 0.422, well within the range (0.412–0.423) actually reached by *shake-and-bake*. It is of even greater interest to observe that even if the six S atoms are replaced by C atoms and diffraction intensities modified so as to simulate real data for this fictional all light-atom structure, *shake-and-bake* still works in eight out of 1000 trials or at the reduced success rate of 0.8%.

4.3. *Rubredoxin* (*space group* $P2_1$)

This 494-atom structure ($C_{243}H_{504}N_{57}O_{187}S_6Fe_1$) was readily solved by *shake-and-bake* with a success rate of 2.7% (25 solutions in 918 trials) using data to 0.92 Å resolution. The initial trial structures consisted of two randomly positioned atoms; the 45 000 triplets with largest $A_{\mathbf{HK}}$ values generated by the 5000 phases having largest $|E|$ values were used in the definition of the minimal function $R(\varphi)$. 250 cycles per trial were run and the 494 largest peaks were selected in successive Fourier maps as successive approximations to the true structure in those cases when the process converged to solutions. It should be noted that this structure had been previously solved by conventional direct methods (Sheldrick *et al.*, 1993).

5. The second minimal principle

The probabilistic background on which the (first) minimal principle is based has been described in §1.3. With a different probabilistic background one arrives at a different minimal principle.

5.1. *The probabilistic background*

It is assumed that (*a*) a crystal structure (consisting of N identical atoms per unit cell in $P1$) is specified, (*b*) the reciprocal lattice vector $\mathbf{h}$ is also specified, (*c*) two non-negative numbers R_2 and R_3 are also specified, and (*d*) the reciprocal lattice vector $\mathbf{K}$ is the primitive random variable which is assumed to be uniformly distributed in the subset of reciprocal space defined by

$$|E_{\mathbf{K}}| = R_2, |E_{\mathbf{h+K}}| = R_3, \tag{12}$$

where the magnitudes $|E|$ are defined by (1). Then, the structure invariant

$$\varphi_{\mathbf{hK}} = \varphi_{\mathbf{h}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{h}-\mathbf{K}}, \tag{13}$$

as a function of the primitive random variable K (1), is itself a random variable.

5.2. *The conditional probability distribution of* $\varphi_{\mathbf{hK}}$, *given* $\mathbf{h}$, $|E_{\mathbf{K}}|$ *and* $|E_{\mathbf{h+K}}|$

Under the four assumptions of §5.1, the conditional probability distribution of the triplet $\varphi_{\mathbf{hK}}$ (13), given $\mathbf{h}$, $|E_{\mathbf{K}}|$, $|E_{\mathbf{h+K}}|$, is known to be

$$P_{\mathbf{h}}(\Phi/\mathbf{h}, R_2, R_3) = [1/2\pi I_0(A_{\mathbf{hK}})]\exp(A_{\mathbf{hK}} \cos \Phi), \tag{14}$$

where

$$A_{\mathbf{hk}} = (2/N^{1/2})|E_{\mathbf{h}}|R_2R_3, \tag{15}$$

which should be compared with (4) and (5). The distribution (14) leads directly to the following relationship among the (complex) normalized structure factors E

$$\langle\{[I_1(A_{\mathbf{hK}})]/[I_0(A_{\mathbf{hK}})]\}|E_{\mathbf{K}}E_{\mathbf{h-K}}|\rangle_{\mathbf{K}}E_{\mathbf{h}} = |E_{\mathbf{h}}|\langle E_{\mathbf{K}}E_{\mathbf{h-K}}\rangle_{\mathbf{K}}, \tag{16}$$

where $\mathbf{h}$ is fixed, $A_{\mathbf{hK}}$ is defined by (15) and the averages are taken over the same arbitrary set of reciprocal lattice vectors $\mathbf{K}$, for example, those for which $|E_{\mathbf{K}}|$ and $|E_{\mathbf{h-K}}|$ are both large.

5.3. *The second-minimal principle*

Referring once again to the principle of least-squares, (16) leads directly to the second-minimal function, a function of the phases dependent on presumed known magnitudes $|E|$

$$\begin{aligned} R' = R'(\varphi) = \left(1/\sum_{\mathbf{h}}|E_{\mathbf{h}}|\right)\sum_{\mathbf{h}}\left[|E_{\mathbf{h}}|/\left(\sum_{\mathbf{k}}|E_{\mathbf{K}}E_{\mathbf{h+K}}|\right)^2\right] \\ \times\left\{\left[\sum_{\mathbf{K}}|E_{\mathbf{K}}E_{\mathbf{h+K}}|(\cos\varphi_{\mathbf{hK}} - [I_1(A_{\mathbf{hK}})]/[I_0(A_{\mathbf{hK}})])\right]^2\right. \\ \left.+\left[\sum_{\mathbf{K}}|E_{\mathbf{K}}E_{\mathbf{h+K}}|\sin\varphi_{\mathbf{hK}}\right]^2\right\}, \end{aligned} \tag{17}$$

in which the sums are taken over arbitrary sets of reciprocal lattice vectors $\mathbf{h}$ and $\mathbf{K}$. Equation (17) should be compared with (9), the first-minimal function. Denoting by R'_T the value of $R'(\varphi)$ when the phases are equal to their true values, no matter what the choice of origin and enantiomorph, and by R'_R the value of $R'(\varphi)$ when the phases are chosen at random, it is readily verified that

$$R'_T < R'_R, \tag{18}$$

in analogy with the inequalities (11). Hence, one anticipates, as before, that the constrained global minimum of $R'(\varphi)$ yields the true values of the phases for some choice of origin and enantiomorph (the second-minimal principle).

A computer program analogous to *shake-and-bake*, which would implement the second-minimal principle has not yet been written. Once this is complete and the program tested extensively, it will be possible to compare these two related, but different, approaches to the phase problem.

6. A fundamental minimal principle (looking ahead)

Since (16) is a relationship among the complex normalized structure factors E, it leads, again *via* least-squares, not only to (17), a function of phases only in which the magnitudes $|E|$ appear as parameters, but also to the function $R(\varphi, |E|)$ of phases φ and magnitudes $|E|$ defined by

$$R(\varphi, |E|) = \Big(1/\sum_{\mathbf{H}} |E_{\mathbf{H}}|\Big) \sum_{\mathbf{H}} \Big[|E_{\mathbf{H}}|/\Big(\sum_{\mathbf{k}} |E_{\mathbf{K}}E_{\mathbf{H+K}}|\Big)^2\Big] \times \Big\{\Big[\sum_{\mathbf{K}} |E_{\mathbf{K}}E_{\mathbf{H+K}}|(\cos\varphi_{\mathbf{HK}} - [I_1(A_{\mathbf{HK}})]/[I_0(A_{\mathbf{HK}})])\Big]^2 + \Big[\sum_{\mathbf{K}} |E_{\mathbf{K}}E_{\mathbf{H+K}}| \sin\varphi_{\mathbf{HK}}\Big]^2\Big\}, \quad (19)$$

where $\varphi_{\mathbf{HK}}$ and $A_{\mathbf{HK}}$ are defined by (2) and (5). $R(\varphi, |E|)$ is expected to be minimal, in some sense, when the phases φ and magnitudes $|E|$ correspond to one and the same crystal structure. $R(\varphi, |E|)$ will be named the minimal function. The sense in which $R(\varphi, |E|)$ is minimal is made precise by the following.

6.1. *Fundamental minimal principle*

A crystal structure is presumed to be given. $R(\varphi, |E|)$ is a function of phases φ and magnitudes $|E|$. If some (possibly no) phases φ_l are presumed to be known and/or some (possibly no) magnitudes $|E_{\mathrm{L}}|$ are presumed to be known, then $R(\varphi, |E|)$ becomes a function of the remaining phases φ_{h} and the remaining magnitudes $|E_{\mathrm{H}}|$ in which the known phases and/or magnitudes appear as parameters

$$R(\varphi, |E|) \to R(\varphi_{\mathrm{h}}, |E_{\mathrm{H}}|/\varphi_l, |E_{\mathrm{L}}|). \quad (20)$$

If the known φ_l's and/or the known $|E_{\mathrm{L}}|$'s are sufficient to determine the crystal structure, then the φ_{h}'s and the $|E_{\mathrm{H}}|$'s are also determined and their values minimize the function

$$R(\varphi_{\mathrm{h}}, |E_{\mathrm{H}}|/\varphi_l, |E_{\mathrm{L}}|). \quad (21)$$

Corollary 1. *Magnitudes $|E|$ determine phases φ.* If a set of magnitudes $\{|E|\}$ (sufficient to determine a crystal structure) is presumed to be known, the minimal function $R(\varphi, |E|)$ becomes a function of phases only

$$R(\varphi, |E|) \to R(\varphi/|E|), \quad (22)$$

with the property that the true values of the phases minimize.

$$R(\varphi/|E|). \quad (23)$$

Thus, magnitudes $|E|$ determine phases φ.

Corollary 2. *Phases φ determine magnitudes $|E|$.* If a set of phases $\{\varphi\}$ (sufficient to determine a crystal structure) is presumed to be known, the minimal function $R(\varphi, |E|)$ becomes a function of magnitudes $|E|$ only

$$R(\varphi, |E|) \to R(|E|/\varphi), \quad (24)$$

with the property that the true values of the magnitudes minimize

$$R(|E|/\varphi). \quad (25)$$

Thus, phases φ determine magnitudes $|E|$.

Corollary 3. *Magnitudes $|E|$ and low-resolution phases φ_l determine high-resolution phases φ_{h}.* If a set of magnitudes $\{|E|\}$ and a set of low-resolution phases $\{\varphi_l\}$ (sufficient to determine a crystal structure) are presumed to be known, the minimal function $R(\varphi, |E|)$ becomes a function of high-resolution phases φ_{h} alone

$$R(\varphi, |E|) \to R(\varphi_{\mathrm{h}}/\varphi_l, |E|), \quad (26)$$

with the property that the true values of the high resolution phases φ_{h} minimize

$$R(\varphi_{\mathrm{h}}/\varphi_{\mathrm{l}}, |E|). \quad (27)$$

Thus, magnitudes $|E|$ and low-resolution phases φ_l determine high-resolution phases φ_{h}.

Corollary 4. *Low-resolution magnitudes $|E_{\mathrm{L}}|$ determine high-resolution magnitudes $|E_{\mathrm{H}}|$ and phases φ.* If a set of low-resolution magnitudes $\{|E_{\mathrm{L}}|\}$ (sufficient to determine a crystal structure) is presumed to be known, the minimal function $R(\varphi, |E|)$ becomes a function of phases φ and high-resolution magnitudes $|E_{\mathrm{H}}|$

$$R(\varphi, |E|) \to R(\varphi, |E_{\mathrm{H}}|/|E_{\mathrm{L}}|), \quad (28)$$

with the property that the true values of the phases φ and the true values of the high-resolution magnitudes $|E_{\mathrm{H}}|$ minimize

$$R(\varphi, |E_{\mathrm{H}}|/|E_{\mathrm{L}}|).$$

Thus, low-resolution magnitudes $|E_{\mathrm{L}}|$ determine high-resolution magnitudes $|E_{\mathrm{H}}|$ and phases φ. Preliminary calculations using known structures have confirmed the validity of Corollaries 1–4.

The fundamental minimal principle and its corollaries, in particular Corollary 4, must not be construed to imply that a resolution higher than inheres in the known (or observable) data is attainable, only that the higher resolution information is determined with an uncertainty commensurate with the resolution of the given data. Of course, there still remains the problem, at present not resolved, of finding the required minima in the several cases. Since *shake-and-bake* has solved this problem in the special case that magnitudes $|E|$ alone are known to atomic resolution, one may perhaps be forgiven for looking ahead to the day when the problems formulated here, and known to have solutions in principle, are finally resolved.

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