

The SAS Maximal Principle: a New Approach to the Phase Problem

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Dedicated to my friend and colleague, Hendrik Krabbendam

Abstract

The phase problem, when single-wavelength anomalous scattering (SAS) diffraction data are available, is formulated as a problem in global optimization. Although the objective function has a myriad of local maxima, its global maxima, never more than two, are readily accessible and easily identified by virtue of their isolation. The ability to determine the global maxima of the objective function represents the latest and most successful attempt to go directly from the known probabilistic estimates of the three-phase structure invariants to the values of the individual phases. The relationship between the maxima of the objective function and the solutions of the newly formulated system of SAS tangent equations plays a key role in this development.

1. Introduction

The techniques of modern probability theory lead to the joint probability distributions of arbitrary collections of diffraction intensities and their corresponding phases. These distributions constitute the foundation on which direct methods are based. They have provided the unifying thread from the beginning, *ca* 1950, until the present time. They have led, in particular, to the (first) minimal principle (Hauptman, 1991; Hauptman, Velmurugan & Han, 1991; DeTitta, Weeks, Thuman, Miller & Hauptman, 1994) which has found expression in the *Shake-and-Bake* formalism (Weeks, DeTitta, Hauptman, Thuman & Miller, 1994; Miller, Gallo, Khalak & Weeks, 1994), a computer program that provides a completely automatic solution to the phase problem, *ab initio*, provided that diffraction data to at least 1.2 Å are available. Our experience shows that structures having as many as 600 independent non-H atoms are routinely accessible to this approach and suggests that its ultimate potential is greater still.

It should perhaps be pointed out that the minimal principle, the theoretical basis of *Shake-and-Bake*, replaces the phase problem by one of *constrained*

global minimization, in sharp contrast to an earlier formulation by Debaerdemaeker & Woolfson [1983, equation (16)], in which the (unconstrained) global minimum was sought. The distinction is crucial, not only on the theoretical level but in the applications as well: Not only does the constrained global minimum yield accurate values of the individual phases *ab initio* but this formulation suggests how the minimum is to be reached (*via* the *Shake-and-Bake* program) and how to identify it. The failure to impose the constraints, as is done in the earlier work, greatly limits the usefulness of that approach, especially since it is not at all clear how to reach or identify the unconstrained global minimum.

One naturally anticipates that, with the availability of single-wavelength anomalous-scattering data, the ability to determine phases *ab initio* will be strengthened. This expectation is in fact realized here. Specifically, a SAS maximal principle is formulated which, even though unconstrained, nevertheless strengthens the earlier minimal principle by incorporating SAS estimates of the cosines and sines of the three-phase structure invariants. The initial applications show that, in this way, the phase problem is solvable *ab initio*, even for macromolecules, when SAS diffraction data alone are available at a resolution of about 2.5 Å.

This work represents the latest attempt to go directly from known estimates of the three-phase structure invariants to the values of the individual phases (*cf.*, for example, Han, DeTitta & Hauptman, 1991; Hauptman & Han, 1993). However, instead of attempting to solve by least squares a redundant system of linear equations, as was done in the earlier work, the formulation presented here transforms the problem into one of global optimization, a problem with a surprisingly easy solution. Furthermore, as shown by the initial applications, briefly described here and in further detail in a forthcoming publication, the results derived here represent a substantial improvement over the earlier work.

Although other phasing methods employing SAS data have been devised (*e.g.* Fan, Hao, Gu, Qian &

Zheng, 1990), with the exception of the two references cited in the previous paragraph, none of these exploits the information contained in the SAS estimates of the three-phase structure invariants. Thus, this work marks a radical departure from the earlier approaches.

Once again, the probabilistic theory of the (three-phase) structure invariants, initiated in the SAS case in 1982 (Hauptman), plays the central role. It should perhaps be stressed at the outset that, owing now to the breakdown of Friedel's law and contrary to all earlier belief, unique values for all the structure invariants in the whole interval from 0 to 2π are determined since the enantiomorph is fixed by the observed magnitudes $|E|$. It is believed that the ability to fix the enantiomorph *ab initio* accounts for the unexpected result described here (§9).

The approach adopted here is similar to that used in the derivation of the minimal principle but is suitably modified in order to take into account the availability of the SAS diffraction data. Not only is one led in this way to the SAS maximal principle but an important connection with the SAS tangent formula, the analogue of the traditional tangent formula, is established. Two remarkable properties of the SAS maximal function emerge: (a) the easy accessibility and ready identification of its global maxima and (b) the isolated character of these maxima.

2. The probabilistic background

With the assumption that SAS diffraction data are available, the conditional probability distribution $P(\Phi)$ of the triplet

$$\varphi_{\mathbf{HK}} = \varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}, \quad (1)$$

given the six magnitudes

$$|E_{\mathbf{H}}|, |E_{-\mathbf{H}}|, |E_{\mathbf{K}}|, |E_{-\mathbf{K}}|, |E_{\mathbf{H}+\mathbf{K}}|, |E_{-\mathbf{H}-\mathbf{K}}|, \quad (2)$$

is known to be (Hauptman, 1982)

$$P(\Phi) = [2\pi I_0(A_{\mathbf{HK}})]^{-1} \exp\{A_{\mathbf{HK}} \cos(\Phi - \omega_{\mathbf{HK}})\}, \quad (3)$$

in which I_0 is the modified Bessel function and $A_{\mathbf{HK}}$ and $\omega_{\mathbf{HK}}$ are expressed in terms of the six magnitudes (2) and the (presumed known) complex-valued atomic scattering factors f . Hence, $A_{\mathbf{HK}} (> 0)$ and $\omega_{\mathbf{HK}}$ are here assumed to be known for every pair (\mathbf{H}, \mathbf{K}) . Note that, owing to the breakdown of Friedel's law, the six magnitudes (2) are, in general, distinct.

In view of (3), the most probable value of $\varphi_{\mathbf{HK}}$ is $\omega_{\mathbf{HK}}$, and the larger the value of $A_{\mathbf{HK}}$ the better is this estimate of $\varphi_{\mathbf{HK}}$:

$$\varphi_{\mathbf{HK}} = \varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} \approx \omega_{\mathbf{HK}}. \quad (4)$$

3. The expected values of $\cos \varphi_{\mathbf{HK}}$ and $\sin \varphi_{\mathbf{HK}}$

Refer to Appendix A to conclude that the expected values of $\cos \varphi_{\mathbf{HK}}$ and $\sin \varphi_{\mathbf{HK}}$ are given by

$$\varepsilon(\cos \varphi_{\mathbf{HK}}) = [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \cos \omega_{\mathbf{HK}} \quad (5)$$

and

$$\varepsilon(\sin \varphi_{\mathbf{HK}}) = [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \sin \omega_{\mathbf{HK}}, \quad (6)$$

respectively.

4. The SAS minimal principle

In view of (5) and (6), one defines the SAS minimal function $m(\varphi)$, a function of the phases φ , by means of

$$m(\varphi) = \left[1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \right] \left[\sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \left(\{\cos \varphi_{\mathbf{HK}} - [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \cos \omega_{\mathbf{HK}}\}^2 + \{\sin \varphi_{\mathbf{HK}} - [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \sin \omega_{\mathbf{HK}}\}^2 \right) \right], \quad (7)$$

where $\varphi_{\mathbf{HK}}$ is given by (1), and conjectures that the global minimum of $m(\varphi)$ yields the true values of the phases for some choice of origin (the SAS minimal principle). Recall that, owing to the breakdown of Friedel's law, the enantiomorph is fixed by the observed magnitudes $|E|$ (Hauptman, 1982).

5. The SAS maximal principle

In view of Appendix B, one replaces the SAS minimal function $m(\varphi)$ by the much simpler SAS maximal function $M(\varphi)$:

$$M(\varphi) = \left(1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \times \cos(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} - \omega_{\mathbf{HK}}), \quad (8)$$

and infers that the global maximum of $M(\varphi)$ yields the true values of the phases for some choice of origin (the SAS maximal principle). There remains the problem of finding the global maximum of $M(\varphi)$, a problem presumed to be difficult by virtue of the existence of a myriad of local maxima of $M(\varphi)$. The solution, however, turns out to be unexpectedly straightforward. How the problem is solved *via* the system of SAS tangent equations is described in the next section.

It is instructive to compare the SAS maximal principle, as formulated here, with equation (18) of Debaerdemaeker & Woolfson (1983), of which our $M(\varphi)$ may be regarded as the SAS counterpart. Whereas the global maximum of $M(\varphi)$ solves the phase problem, the global maximum of Debaerde-

maeker & Woolfson's equation (18) yields the value zero for every phase, clearly a non-solution.

6. The system of SAS tangent equations

Refer to Appendix C to deduce the system of SAS tangent equations.

For each fixed value of the reciprocal-lattice vector \mathbf{H} ,

$$\begin{aligned} \tan \varphi_{\mathbf{H}} = & \left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \right. \\ & \times \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \left. \right\} \\ & \times \left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \right. \\ & \times \cos(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \left. \right\}^{-1}, \quad (9) \end{aligned}$$

where

$$\begin{aligned} \sin \varphi_{\mathbf{H}} = & (1/C) \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \\ & \times \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \quad (10) \end{aligned}$$

$$\begin{aligned} \cos \varphi_{\mathbf{H}} = & (1/C) \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \\ & \times \cos(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \quad (11) \end{aligned}$$

and

$$\begin{aligned} C = & \left(\left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \right. \right. \\ & \times \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \left. \right\}^2 \\ & + \left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}})/I_0(A_{\mathbf{HK}})] \right. \\ & \times \cos(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \left. \right\}^2 \left. \right)^{1/2} > 0. \quad (12) \end{aligned}$$

Thus, (9) determines two possible values for $\varphi_{\mathbf{H}}$, differing by π , while (10) to (12) resolve the ambiguity. Hence, (9)–(12) determine $\varphi_{\mathbf{H}}$ uniquely when all other phases are assumed to be known.

Although (9) differs from the standard tangent formula only in the presence of the non-zero estimates $\omega_{\mathbf{HK}}$ of the three-phase structure invariants $\varphi_{\mathbf{HK}}$, as well as the completely different set of weights $A_{\mathbf{HK}}$ (the presence of the ratio of Bessel functions I_1/I_0 being of negligible significance), these differences are of fundamental importance in the applications. As described in §14, the present formulation solves the phase problem for macromolecules in the SAS case with diffraction data to 2.5 Å resolution; not surprisingly, the same claim cannot be made for the standard tangent formula

when used in the same way. Nevertheless, it should be stressed that use of the standard tangent formula in the way described here (§8) is a very effective technique for phase determination for smaller structures when atomic resolution data are available (Yao, 1981). Our method may be regarded as the SAS counterpart of this earlier work.

7. The maximal property of the system of SAS tangent equations

Refer to Appendix D for the proof of the following.

Fundamental maximal property. Fix \mathbf{H} . Assume that the values of all phases other than $\varphi_{\mathbf{H}}$ are specified arbitrarily. Then the maximal function $M(\varphi)$ becomes a function, $M(\varphi_{\mathbf{H}}/\varphi)$, of the single phase $\varphi_{\mathbf{H}}$. As a function of $\varphi_{\mathbf{H}}$, $M(\varphi_{\mathbf{H}}/\varphi)$ has a unique maximum in the whole interval $(0, 2\pi)$ and the value of $\varphi_{\mathbf{H}}$ that maximizes $M(\varphi_{\mathbf{H}}/\varphi)$ is given by the SAS tangent equations (9) to (12). In short, every plane section of $M(\varphi)$ parallel to a coordinate plane has a unique maximum in the interval $(0, 2\pi)$ given by the SAS tangent equations (9) to (12).

It has long been known that the standard tangent formula may be derived by maximization of $\sum A_{\mathbf{HK}} \cos \varphi_{\mathbf{HK}}$, essentially the result described here when all the $\omega_{\mathbf{HK}}$ s are equal to zero. The significance of our generalization of this earlier work is that the maximal property of the system of SAS tangent equations leads to a practical method of phase determination whereas the earlier result does not (§§6–9).

8. How to climb a mountain using the SAS tangent trail

Specify arbitrarily initial values for all the phases φ . Fix \mathbf{H} . Calculate a new value for the phase $\varphi_{\mathbf{H}}$ by means of the SAS tangent equations (9) to (12), in this way, in view of §7, increasing the initial value of the maximal function $M(\varphi)$. Fix $\mathbf{H}' \neq \mathbf{H}$. Calculate a new value for $\varphi_{\mathbf{H}'}$, again using (9)–(12), the new value for $\varphi_{\mathbf{H}}$, and initial values for the remaining phases, thus increasing still further the value of $M(\varphi)$. Continue in this way to obtain new values for all the phases, thus completing the first iteration and, in the process, continuously increasing the value of $M(\varphi)$. Complete as many iterations as necessary in order to secure convergence. Convergence is assured since the iterative process yields a monotonically increasing sequence of numbers, the values of $M(\varphi)$, bounded above by unity. Evidently also, the process leads to a local maximum of $M(\varphi)$, the top of the mountain, and a corresponding set of values for all the phases φ .

The applications show that only rarely does convergence require more than 30 iterations, and usually fewer than 20 suffice.

9. The tallest peak, totally isolated, smooth and ripple free, rests on the broadest base

The process described in §8 always leads to a local maximum of $M(\varphi)$, the number of which is legion. It is natural therefore to ask: Will the process ever lead to the global maximum? Preliminary calculations, based on three structures ranging in complexity from 1000 to 4000 independent atoms and in resolution from 3.0 to 2.5 Å, show unequivocally that the answer is yes, frequently! Quite unexpectedly, the success rate is high, usually in the range of 10 to 15%, so that 1000 trials, which is readily computable, yield, as it turns out, at most two distinct global maxima having, however, almost identical values, at least 100 times in typical cases.

A remarkable additional feature of the SAS maximal function is the total isolation of its global maxima. Thus, while the values of the local maxima are continuously distributed in a rather narrow range, the values of the global maxima exceed these by far. This remarkable property of $M(\varphi)$ not only makes it easy to identify its global maxima and the associated sets of values for the phases but no doubt accounts as well (in some way not understood at present) for the unexpectedly large circle of convergence surrounding each global maximum.

If the anomalous signal is weak (as is usually the case), the breakdown of Friedel's law is not severe and, in implementing §§5–9, it may be assumed, to a sufficiently good approximation, that Friedel's law holds. If, on the other hand, the anomalous signal is strong, a more general approach may be called for, as described next.

10. The generalized SAS maximal principle

The work described here has been based on the triplet φ_{HK} [(1)] and its conditional probability distribution $P(\Phi)$ [(3)]. One may instead base a completely analogous theory on the triplet $\bar{\varphi}_{\text{HK}}$ defined by means of

$$\bar{\varphi}_{\text{HK}} = \varphi_{\text{H}} + \varphi_{\text{K}} - \varphi_{\text{H+K}}, \quad (13)$$

which, because of the breakdown of Friedel's law, is not equal to φ_{HK} , and its conditional probability distribution (Hauptman, 1982)

$$\bar{P}(\bar{\Phi}) = [1/2\pi I_0(\bar{A}_{\text{HK}})] \exp\{\bar{A}_{\text{HK}} \cos(\bar{\Phi} - \bar{\omega}_{\text{HK}})\}, \quad (14)$$

where, once again, the parameters \bar{A}_{HK} and $\bar{\omega}_{\text{HK}}$ are expressible in terms of the six magnitudes (2) and the complex-valued atomic scattering factors f . The details are so similar to those already described that they are not explicitly given here. Only the final combined

results are briefly summarized. Thus, the generalized SAS maximal function $M(\varphi)$ is defined by

$$M(\varphi) = \left[\sum_{\text{H,K}} A_{\text{HK}} + \sum_{\text{H,K}} \bar{A}_{\text{HK}} \right]^{-1} \\ \times \left\{ \sum_{\text{H,K}} A_{\text{HK}} [I_1(A_{\text{HK}})/I_0(A_{\text{HK}})] \right. \\ \times \cos(\varphi_{\text{H}} + \varphi_{\text{K}} + \varphi_{-\text{H-K}} - \omega_{\text{HK}}) \\ \left. + \sum_{\text{H,K}} \bar{A}_{\text{HK}} [I_1(\bar{A}_{\text{HK}})/I_0(\bar{A}_{\text{HK}})] \right. \\ \left. \times \cos(\varphi_{\text{H}} + \varphi_{\text{K}} - \varphi_{\text{H+K}} - \bar{\omega}_{\text{HK}}) \right\} \quad (15)$$

and has the property that its global maximum yields the true values of all the phases. Again, the generalized SAS tangent equations become

$$\tan \varphi_{\text{H}} = \left\{ \sum_{\text{K}} A_{\text{HK}} [I_1(A_{\text{HK}})/I_0(A_{\text{HK}})] \right. \\ \times \sin(\omega_{\text{HK}} - \varphi_{\text{K}} - \varphi_{-\text{H-K}}) \\ \left. + \sum_{\text{K}} \bar{A}_{\text{HK}} [I_1(\bar{A}_{\text{HK}})/I_0(\bar{A}_{\text{HK}})] \right. \\ \left. \times \sin(\bar{\omega}_{\text{HK}} - \varphi_{\text{K}} + \varphi_{\text{H+K}}) \right\} \\ \times \left\{ \sum_{\text{K}} A_{\text{HK}} [I_1(A_{\text{HK}})/I_0(A_{\text{HK}})] \right. \\ \times \cos(\omega_{\text{HK}} - \varphi_{\text{K}} - \varphi_{-\text{H-K}}) \\ \left. + \sum_{\text{K}} \bar{A}_{\text{HK}} [I_1(\bar{A}_{\text{HK}})/I_0(\bar{A}_{\text{HK}})] \right. \\ \left. \times \cos(\bar{\omega}_{\text{HK}} - \varphi_{\text{K}} + \varphi_{\text{H+K}}) \right\}^{-1}, \quad (16)$$

where

$$\sin \varphi_{\text{H}} = (1/C') \left\{ \sum_{\text{K}} A_{\text{HK}} [I_1(A_{\text{HK}})/I_0(A_{\text{HK}})] \right. \\ \times \sin(\omega_{\text{HK}} - \varphi_{\text{K}} - \varphi_{-\text{H-K}}) \\ \left. + \sum_{\text{K}} \bar{A}_{\text{HK}} [I_1(\bar{A}_{\text{HK}})/I_0(\bar{A}_{\text{HK}})] \right. \\ \left. \times \sin(\bar{\omega}_{\text{HK}} - \varphi_{\text{K}} + \varphi_{\text{H+K}}) \right\} \quad (17)$$

$$\cos \varphi_{\text{H}} = (1/C') \left\{ \sum_{\text{K}} A_{\text{HK}} [I_1(A_{\text{HK}})/I_0(A_{\text{HK}})] \right. \\ \times \cos(\omega_{\text{HK}} - \varphi_{\text{K}} - \varphi_{-\text{H-K}}) \\ \left. + \sum_{\text{K}} \bar{A}_{\text{HK}} [I_1(\bar{A}_{\text{HK}})/I_0(\bar{A}_{\text{HK}})] \right. \\ \left. \times \cos(\bar{\omega}_{\text{HK}} - \varphi_{\text{K}} + \varphi_{\text{H+K}}) \right\} \quad (18)$$

and C' is a positive coefficient chosen in such a way as to ensure that the identity, (33), holds. Finally, §§7-9 again hold, without change.

It is anticipated that the more general formulation described here will usually not be needed unless the anomalous signal is so strong that the breakdown of Friedel's law is severe and necessitates the use of this somewhat more accurate formalism.

11. The global maximum of $M(\varphi)$

If the true values φ_T of the phases φ are substituted into the SAS maximal function, one obtains the value of its (presumed) global maximum, $M(\varphi_T)$, which, in view of Appendix E, is simply

$$M(\varphi_T) = \left(1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{H}\mathbf{K}}\right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{H}\mathbf{K}} [I_1^2(A_{\mathbf{H}\mathbf{K}}) / I_0^2(A_{\mathbf{H}\mathbf{K}})] < 1. \quad (19)$$

If, on the other hand, one chooses the values of the phases at random, then, since the average value of the cosine in (8) is zero, one obtains $M(\varphi_R)$:

$$M(\varphi_R) = 0. \quad (20)$$

Hence,

$$0 = M(\varphi_R) < M(\varphi_T) < 1. \quad (21)$$

12. The SAS correspondence principle

It is clear from §§7 and 8 and Appendix D that there corresponds to every solution of the system of SAS tangent equations (9)–(12) a local maximum of $M(\varphi)$, and conversely (the SAS correspondence principle).

13. The linear congruence connection

The problem of going from the estimated values $\omega_{\mathbf{H}\mathbf{K}}$ of the three-phase structure invariants $\varphi_{\mathbf{H}\mathbf{K}}$ [(4)] to the values of the individual phases φ may be formulated as the problem of solving the redundant system of linear congruences

$$\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} \equiv \omega_{\mathbf{H}\mathbf{K}} \pmod{2\pi} \quad (22)$$

each with weight $A_{\mathbf{H}\mathbf{K}}$. This was the point of view adopted in the earlier work of Han *et al.* (1991) and Hauptman & Han (1993) in which the system (22) was transformed into a redundant system of linear equations

$$\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} = \omega_{\mathbf{H}\mathbf{K}} + 2\pi n_{\mathbf{H}\mathbf{K}} \quad (23)$$

and the attempt was made, with limited success, to determine the integers $n_{\mathbf{H}\mathbf{K}}$ in such a way as to make the system (23) self-consistent. The resulting redundant system of linear equations (23) was then solved by least squares.

The SAS maximal principle may thus be re-interpreted as yielding the solution of the redundant system of linear congruences (22). Somewhat unexpectedly, in those cases where the SAS maximal function has two global maxima, the system of redundant linear congruences (22) has two solutions, only one of which is the proper solution of the phase problem.

14. The initial application

The method described here was applied, with experimentally determined diffraction data, to the *ab initio* solution of the phase problem for the platinum derivative of the previously known macromycin structure (Van Roey & Beerman, 1989) consisting of approximately 750 protein atoms and 150 solvent molecules and crystallizing in the space group $P2_1$. With diffraction data to 2.5 Å resolution, 150 000 three-phase structure invariants with largest A values were estimated. These involved 2710 phases whose values were to be determined.

100 solutions of the system of SAS tangent equations (9)–(12) were obtained using initial values of the phases chosen at random. Each of these trials converged to solution in five to eight cycles. Of the 100 trials, 17 yielded the same global maximum of the SAS maximal function $M(\varphi)$ [(8)], which, in this case, turned out to be unique. Since the macromycin structure had been previously determined, it was possible to calculate the average initial phase error using the known phases from the refined structure. This turned out to be 49° for all 2710 phases. It should be stressed that this solution of the phase problem for macromycin was strictly *ab initio* in the sense that the only information needed was the observed SAS diffraction intensities at 2.5 Å resolution; and the resulting map was interpretable.

With error-free diffraction intensities, the same calculation, again using SAS estimates for 150 000 three-phase structure invariants, yielded the values of 2120 phases with an initial average phase error of 30°. Details will be described in a forthcoming publication.

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APPENDIX A

The expected values of $\cos \varphi_{\mathbf{H}\mathbf{K}}$ and $\sin \varphi_{\mathbf{H}\mathbf{K}}$

From the distribution (3),

$$\begin{aligned} \varepsilon(\cos \varphi_{\mathbf{H}\mathbf{K}}) &= [2\pi I_0(A_{\mathbf{H}\mathbf{K}})]^{-1} \int_0^{2\pi} (\cos \Phi) \\ &\times \exp\{A_{\mathbf{H}\mathbf{K}} \cos(\Phi - \omega_{\mathbf{H}\mathbf{K}})\} d\Phi \quad (24) \end{aligned}$$

$$\begin{aligned}
&= [2\pi I_0(A_{\mathbf{HK}})]^{-1} \int_0^{2\pi} \{ \cos(\Phi - \omega_{\mathbf{HK}}) \\
&\quad \times \cos \omega_{\mathbf{HK}} - \sin(\Phi - \omega_{\mathbf{HK}}) \sin \omega_{\mathbf{HK}} \} \\
&\quad \times \exp\{A_{\mathbf{HK}} \cos(\Phi - \omega_{\mathbf{HK}})\} d\Phi \quad (25)
\end{aligned}$$

$$\begin{aligned}
&= [2\pi I_0(A_{\mathbf{HK}})]^{-1} \int_0^{2\pi} (\cos \omega_{\mathbf{HK}} \cos \Phi \\
&\quad - \sin \omega_{\mathbf{HK}} \sin \Phi) \exp(A_{\mathbf{HK}} \cos \Phi) d\Phi \quad (26)
\end{aligned}$$

from which (5) follows.

The derivation of (6) is similar.

APPENDIX B The SAS maximal function

The SAS minimal function $m(\varphi)$ [(7)] may be re-written

$$\begin{aligned}
m(\varphi) &= 1 + \left(1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}}\right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} [I_1^2(A_{\mathbf{HK}}) / I_0^2(A_{\mathbf{HK}})] \\
&\quad - \left(2 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}}\right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\varphi_{\mathbf{HK}} - \omega_{\mathbf{HK}}), \quad (27)
\end{aligned}$$

only the last term of which depends on the phases φ . Reversing the sign of the last term and dividing by 2, one then defines the SAS maximal function $M(\varphi)$ by means of

$$\begin{aligned}
M(\varphi) &= \left(1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}}\right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\varphi_{\mathbf{HK}} - \omega_{\mathbf{HK}}) \quad (28)
\end{aligned}$$

and concludes that the maxima of $M(\varphi)$ coincide with the minima of $m(\varphi)$, and conversely.

APPENDIX C The system of SAS tangent equations

Fix \mathbf{H} . From (4),

$$\varphi_{\mathbf{H}} \simeq \omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}, \quad (29)$$

$$\sin \varphi_{\mathbf{H}} \simeq \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}), \quad (30)$$

which has approximate validity for each fixed value of \mathbf{K} . Averaging the right-hand side of (30) over \mathbf{K} , naturally using weights $A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})]$, one obtains

$$\begin{aligned}
\sin \varphi_{\mathbf{H}} &\simeq \left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \right\}^{-1} \\
&\quad \times \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}). \quad (31)
\end{aligned}$$

Similarly,

$$\begin{aligned}
\cos \varphi_{\mathbf{H}} &\simeq \left\{ \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \right\}^{-1} \\
&\quad \times \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}). \quad (32)
\end{aligned}$$

Least-squares adjustment of $\sin \varphi_{\mathbf{H}}$ and $\cos \varphi_{\mathbf{H}}$ as given by (31) and (32), constrained to satisfy

$$\sin^2 \varphi_{\mathbf{H}} + \cos^2 \varphi_{\mathbf{H}} = 1, \quad (33)$$

leads directly to (10)–(12) and thence to the SAS tangent equations (9)–(12).

APPENDIX D

The maximal property of the system of SAS tangent equations

Refer to §7 for the definition of $M(\varphi_{\mathbf{H}}/\varphi)$, a function of the single phase $\varphi_{\mathbf{H}}$ whose maximum we seek. Therefore, from (8), we find, for fixed \mathbf{H} ,

$$\begin{aligned}
dM(\varphi_{\mathbf{H}}/\varphi)/d\varphi_{\mathbf{H}} &= - \left(1 / \sum_{\mathbf{K}} A_{\mathbf{HK}}\right) \\
&\quad \times \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \sin(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} - \omega_{\mathbf{HK}}) \\
&= 0, \quad (34)
\end{aligned}$$

in which, for strict validity, the terms with $\mathbf{K} = \mathbf{H}$ and $\mathbf{K} = -2\mathbf{H}$ are to be deleted. Equation (34) leads directly to

$$\begin{aligned}
&\sin \varphi_{\mathbf{H}} \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} - \omega_{\mathbf{HK}}) \\
&\quad + \cos \varphi_{\mathbf{H}} \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \sin(\varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} - \omega_{\mathbf{HK}}) = 0, \quad (35)
\end{aligned}$$

from which the SAS tangent formula (9) follows immediately. Equation (9) permits two possible values for $\varphi_{\mathbf{H}}$ differing by π , only one of which satisfies (10)–(12). Taking for $\varphi_{\mathbf{H}}$ the unique value determined by (10)–(12), one finds

$$\begin{aligned}
d^2M(\varphi_{\mathbf{H}}/\varphi)/d\varphi_{\mathbf{H}}^2 &= - \left(1 / \sum_{\mathbf{K}} A_{\mathbf{HK}}\right) \\
&\quad \times \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}} - \omega_{\mathbf{HK}}) \quad (36)
\end{aligned}$$

$$\begin{aligned}
&= -\left(1 / \sum_{\mathbf{K}} A_{\mathbf{HK}}\right) \left\{ \cos \varphi_{\mathbf{H}} \right. \\
&\quad \times \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \cos(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \\
&\quad + \sin \varphi_{\mathbf{H}} \sum_{\mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \left. \times \sin(\omega_{\mathbf{HK}} - \varphi_{\mathbf{K}} - \varphi_{-\mathbf{H}-\mathbf{K}}) \right\} \quad (37)
\end{aligned}$$

$$\begin{aligned}
&= -\left(C / \sum_{\mathbf{K}} A_{\mathbf{HK}}\right) \\
&\quad \times (\cos^2 \varphi_{\mathbf{H}} + \sin^2 \varphi_{\mathbf{H}}) \\
&= -\left(C / \sum_{\mathbf{K}} A_{\mathbf{HK}}\right) \\
&< 0. \quad (38)
\end{aligned}$$

In short, $M(\varphi_{\mathbf{H}}/\varphi)$, as a function of the single phase $\varphi_{\mathbf{H}}$, has a unique maximum in the whole interval $(0, 2\pi)$, which is reached by the value of $\varphi_{\mathbf{H}}$ defined by the tangent equations (9)–(12).

APPENDIX E

The global maximum of $M(\varphi)$

If the true values φ_T of the phases φ are substituted into the SAS maximal function, the right-hand side of (8) becomes

$$\begin{aligned}
&\left(1 / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}}\right) \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} [I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \\
&\quad \times \{ \cos(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}) \cos \omega_{\mathbf{HK}} \\
&\quad + \sin(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}) \sin \omega_{\mathbf{HK}} \}, \quad (39)
\end{aligned}$$

which becomes, if the double summations are restricted to those pairs (\mathbf{H}, \mathbf{K}) for which $A_{\mathbf{HK}}$ and $\omega_{\mathbf{HK}}$ have fixed specified values,

$$\begin{aligned}
&[I_1(A_{\mathbf{HK}}) / I_0(A_{\mathbf{HK}})] \left\{ \left(\cos \omega_{\mathbf{HK}} / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \right) \right. \\
&\quad \times \sum_{\mathbf{H}, \mathbf{K}} \cos(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}) \\
&\quad + \left(\sin \omega_{\mathbf{HK}} / \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \right) \\
&\quad \left. \times \sum_{\mathbf{H}, \mathbf{K}} A_{\mathbf{HK}} \sin(\varphi_{\mathbf{H}} + \varphi_{\mathbf{K}} + \varphi_{-\mathbf{H}-\mathbf{K}}) \right\}. \quad (40)
\end{aligned}$$

In view of (5) and (6), this reduces simply to

$$\begin{aligned}
&[I_1^2(A_{\mathbf{HK}}) / I_0^2(A_{\mathbf{HK}})] (\cos^2 \omega_{\mathbf{HK}} + \sin^2 \omega_{\mathbf{HK}}) \\
&= I_1^2(A_{\mathbf{HK}}) / I_0^2(A_{\mathbf{HK}}), \quad (41)
\end{aligned}$$

which is seen to be independent of $\omega_{\mathbf{HK}}$. Dropping the restriction on the double summation, one obtains (19).

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