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Combining Direct Methods with Isomorphous Replacement or Anomalous Scattering Data. III. The Incorporation of Partial Structure Information

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Abstract

The probability formulas given in Parts I and II of this series have been improved by incorporating the information contained in Sim's distribution. Possible applications to the discrimination of the phase ambiguities arising from the single isomorphous replacement technique, the one-wavelength anomalous scattering (OAS) technique or pseudo centrosymmetry in small structures are discussed. With a set of experimental protein OAS data, the efficiency of the improved formula has been shown to be better than that of the older one.

Notation

$\mathbf{H}$ the reciprocal vector, which corresponds to the diffraction index *hkl*

$\mathbf{F_H}$ the structure factor at the reciprocal-lattice point $\mathbf{H}$

$F_\mathbf{H}$ the modulus of $\mathbf{F_H}$

$\varphi_\mathbf{H}$ the phase of $\mathbf{F_H}$

$\mathbf{E_H}$ the normalized structure factor

$E_\mathbf{H}$ the modulus of $\mathbf{E_H}$

$\mathbf{F}_{\mathbf{H},A}$ the diffraction contribution calculated from the real-part scattering of the anomalous scatterers, *i.e.*

$$\mathbf{F}_{\mathbf{H},A}=\sum_{A=1}^{N_A}(f_A+\Delta f'_A)\exp[i2\pi\mathbf{H}\,.\,\mathbf{r}_A]$$

$\mathbf{F}''_{\mathbf{H},A}$ the diffraction contribution from the imaginary-part scattering of the anomalous scatterers, *i.e.*

$$\mathbf{F}''_{\mathbf{H},A}=\sum_{A=1}^{N_A} i\Delta f''_A\exp[i2\pi\mathbf{H}.\,\mathbf{r}_A]$$

$\sigma_n=$ $\sum_j Z_j^n$, Z_j is the atomic number of the jth atom in the unit cell, n is an integer equal to 2 or 3

$\sigma_u=$ $\sum_u Z_u^2/\sigma_2$, Z_u is the atomic number of the uth atom, which belongs to the unknown part of the structure

Subscripts:

A the anomalous scattering atoms

R the replacing atoms of an isomorphous pair

N the atoms in the native protein

D the atoms in the heavy-atom derivative of the native protein

p the atoms of the partial structure with known positions in the unit cell

u the atoms of the unknown part in the unit cell

Formulation

A phase doublet can be expressed in the generalized form

$$\varphi_\mathbf{H}=\varphi'_\mathbf{H}\pm|\Delta\varphi_\mathbf{H}|. \quad (1)$$

In the case of single isomorphous replacement (SIR):

$$\varphi'_\mathbf{H}=\varphi_{\mathbf{H},R},$$

where $\varphi_{\mathbf{H},R}$ is the phase calculated from the replacing atoms. If $\varphi_\mathbf{H}$ denotes the phase of a reflection from the native protein, then

$$\Delta\varphi_\mathbf{H}\equiv\Delta\varphi_{\mathbf{H},N}$$
$$=\pm\cos^{-1}[(F^2_{\mathbf{H},D}-F^2_{\mathbf{H},R}-F^2_{\mathbf{H},N})/2F_{\mathbf{H},R}F_{\mathbf{H},N}]. \quad (2)$$

If $\varphi_\mathbf{H}$ denotes that from the heavy-atom derivative, then

$$\Delta\varphi_\mathbf{H}\equiv\Delta\varphi_{\mathbf{H},D}$$
$$=\pm\cos^{-1}[(F^2_{\mathbf{H},D}+F^2_{\mathbf{H},R}-F^2_{\mathbf{H},N})/2F_{\mathbf{H},R}F_{\mathbf{H},D}]. \quad (3)$$

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In the case of one-wavelength anomalous scattering (OAS):

$$\varphi'_{\mathbf{H}} = \varphi''_{\mathbf{H},A},$$

where $\varphi''_{\mathbf{H},A}$ is the phase of $\mathbf{F}''_{\mathbf{H},A}$. We can also write

$$\varphi'_{\mathbf{H}} = \varphi_{\mathbf{H},A} + \omega_{\mathbf{H}},$$

where $\varphi_{\mathbf{H},A}$ is the phase of $\mathbf{F}_{\mathbf{H},A}$, while $\omega_{\mathbf{H}}$ is the phase difference between $\mathbf{F}''_{\mathbf{H},A}$ and $\mathbf{F}_{\mathbf{H},A}$. If there is only one kind of anomalous scatterer in the unit cell, then $\omega_{\mathbf{H}} = \pi/2$. We have for the OAS case (see Blundell & Johnson, 1976)

$$\Delta\varphi_{\mathbf{H}} = \pm\cos^{-1}[(F^+_{\mathbf{H}} - F^-_{\mathbf{H}})/2F''_{\mathbf{H},A}]. \tag{4}$$

Notice that $\varphi_{\mathbf{H}}$ in this case is defined as the phase of

$$\mathbf{F}_{\mathbf{H}} = (\mathbf{F}^+_{\mathbf{H}} + \mathbf{F}^{-*}_{\mathbf{H}})/2,$$

where $\mathbf{F}^{-*}_{\mathbf{H}}$ is the conjugate of $\mathbf{F}^-_{\mathbf{H}}$.

In the case that the phase doublets are caused by a centrosymmetric partial structure (CPS) in a non-centrosymmetric unit cell,

$$\varphi'_{\mathbf{H}} = 2\pi\mathbf{H} \cdot \mathbf{r}_0,$$

where $\mathbf{r}_0$ is the positional vector of the pseudo inverse centre with respect to the origin of the unit cell. According to Fan Hai-fu & Zheng Qi-tai (1978) we have in this case

$$\tan\Delta\varphi_{\mathbf{H}} = \pm(F^2_{\mathbf{H}} - C^2_{\mathbf{H}})^{1/2}/C_{\mathbf{H}}, \tag{5}$$

where

$$C_{\mathbf{H}} = \sum_j f_j \cos 2\pi\mathbf{H} \cdot (\mathbf{r}_j - \mathbf{r}_0),$$

$\mathbf{r}_j$ denotes the positional vector of any one of the two possible positions associated with the jth atom in the unit cell.

According to Cochran (1955), for a set of triplet structure invariants of the form $\varphi_{\mathbf{H}} - \varphi_{\mathbf{H}'} - \varphi_{\mathbf{H}-\mathbf{H}'}$, the conditional probability distribution of $\varphi_{\mathbf{H}}$ given $E_{\mathbf{H}}$, $E_{\mathbf{H}'}$, $E_{\mathbf{H}-\mathbf{H}'}$, $\varphi_{\mathbf{H}'}$ and $\varphi_{\mathbf{H}-\mathbf{H}'}$ is as follows:

$$P_{\text{Cochran}}(\varphi_{\mathbf{H}}) = N \exp\left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos(\varphi_{\mathbf{H}} - \varphi_{\mathbf{H}'} - \varphi_{\mathbf{H}-\mathbf{H}'})\right], \tag{6}$$

where N is a normalized factor and

$$K_{\mathbf{H}\mathbf{H}'} = 2\sigma_3\sigma_2^{-3/2} E_{\mathbf{H}} E_{\mathbf{H}'} E_{\mathbf{H}-\mathbf{H}'}.$$

With the expression $\varphi_{\mathbf{H}} = \varphi'_{\mathbf{H}} + \Delta\varphi_{\mathbf{H}}$, the triplet phase becomes

$$\begin{aligned}\varphi_{\mathbf{H}} - \varphi_{\mathbf{H}'} - \varphi_{\mathbf{H}-\mathbf{H}'} &= \Delta\varphi_{\mathbf{H}} - [\Phi'_3 + \Delta\varphi_{\mathbf{H}'} + \Delta\varphi_{\mathbf{H}-\mathbf{H}'}] \\ &\equiv \Delta\varphi_{\mathbf{H}} - \beta'',\end{aligned} \tag{7}$$

where $\Phi'_3 = -\varphi'_{\mathbf{H}} + \varphi'_{\mathbf{H}'} + \varphi'_{\mathbf{H}-\mathbf{H}'}$.

Substitution of (7) into (6) gives

$$P_{\text{Cochran}}(\Delta\varphi_{\mathbf{H}}) = N \exp\left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos(\Delta\varphi_{\mathbf{H}} - \beta'')\right]. \tag{8}$$

Let

$$\alpha' \cos\beta' = \sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos\beta'' \tag{9}$$

and

$$\alpha' \sin\beta' = \sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \sin\beta'', \tag{10}$$

(8) becomes

$$P_{\text{Cochran}}(\Delta\varphi_{\mathbf{H}}) = [2\pi I_0(\alpha')]^{-1} \exp[\alpha' \cos(\Delta\varphi_{\mathbf{H}} - \beta')], \tag{11}$$

where $I_0(\alpha')$ is the zero-order modified Bessel function of the first kind with α' as argument,

$$\alpha' = \left\{\left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos\beta''\right]^2 + \left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \sin\beta''\right]^2\right\}^{1/2},$$

$$\tan\beta' = \sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \sin\beta'' \Big/ \sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos\beta''.$$

On the other hand, according to Sim (1959), if partial structure information is available, we have

$$P_{\text{Sim}}(\theta) = [2\pi I_0(x)]^{-1} \exp[x \cos\theta], \tag{12}$$

where

$$x = 2E_{\mathbf{H}} E_{\mathbf{H},p}/\sigma_u,$$

$$\theta = \varphi_{\mathbf{H}} - \varphi_{\mathbf{H},p},$$

$E_{\mathbf{H},p}$ and $\varphi_{\mathbf{H},p}$ are the modulus and phase of $\mathbf{E}_{\mathbf{H},p}$ respectively, $\mathbf{E}_{\mathbf{H},p}$ is the partial structure contribution to $\mathbf{E}_{\mathbf{H}}$. With the expression $\varphi_{\mathbf{H}} = \varphi'_{\mathbf{H}} + \Delta\varphi_{\mathbf{H}}$, (12) becomes

$$P_{\text{Sim}}(\Delta\varphi_{\mathbf{H}}) = [2\pi I_0(x)]^{-1} \exp[x \cos(\Delta\varphi_{\mathbf{H}} - \delta_{\mathbf{H}})], \tag{13}$$

where

$$\delta_{\mathbf{H}} = \varphi_{\mathbf{H},p} - \varphi'_{\mathbf{H}}.$$

Combination of (11) and (13) gives the total probability distribution of $\Delta\varphi_{\mathbf{H}}$ as

$$\begin{aligned}P(\Delta\varphi_{\mathbf{H}}) &= P_{\text{Cochran}} P_{\text{Sim}} \\ &= [2\pi I_0(\alpha)]^{-1} \exp[\alpha \cos(\Delta\varphi_{\mathbf{H}} - \beta)],\end{aligned} \tag{14}$$

where

$$\alpha = \left\{\left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \sin\beta'' + x \sin\delta_{\mathbf{H}}\right]^2 + \left[\sum_{\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \cos\beta'' + x \cos\delta_{\mathbf{H}}\right]^2\right\}^{1/2}$$

and

$$\tan\beta=\left[\sum_{\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\sin\beta''+x\sin\delta_{\mathbf{H}}\right]\times\left[\sum_{\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\cos\beta''+x\cos\delta_{\mathbf{H}}\right]^{-1}.$$

Since $|\Delta\varphi_{\mathbf{H}}|$ is a known quantity when phase-doublet information is available, the probability that $\Delta\varphi_{\mathbf{H}}$ has a positive sign can be derived from (14):

$$P_+(\Delta\varphi_{\mathbf{H}})=\tfrac{1}{2}+\tfrac{1}{2}\tanh\left\{\sin|\Delta\varphi_{\mathbf{H}}|\times\left[\sum_{\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\sin(\Phi_3'+\Delta\varphi_{\mathbf{H}'}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'})+x\sin\delta_{\mathbf{H}}\right]\right\}. \quad (15)$$

On the other hand, by maximizing (14) we have $\Delta\varphi_{\mathbf{H}}=\beta$. Hence

$$\tan(\Delta\varphi_{\mathbf{H}})=\left[\sum_{\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\sin(\Phi_3'+\Delta\varphi_{\mathbf{H}'}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'})+x\sin\delta_{\mathbf{H}}\right]\times\left[\sum_{\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\cos(\Phi_3'+\Delta\varphi_{\mathbf{H}'}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'})+x\cos\delta_{\mathbf{H}}\right]^{-1}. \quad (16)$$

With the concept of 'best phase relationship' [Fan Hai-fu Han Fu-son & Qian Jin-zi (1984), hereafter referred to as paper II], (15) and (16) can be modified to give

$$P_+(\Delta\varphi_{\mathbf{H}})=\tfrac{1}{2}+\tfrac{1}{2}\tanh\left\{\sin|\Delta\varphi_{\mathbf{H}}|\times\left[\sum_{\mathbf{H}'}m_{\mathbf{H}'}m_{\mathbf{H}-\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\sin(\Phi_3'+\Delta\varphi_{\mathbf{H}'\text{best}}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'\text{best}})+x\sin\delta_{\mathbf{H}}\right]\right\} \quad (17)$$

and

$$\tan(\Delta\varphi_{\mathbf{H}})=\left[\sum_{\mathbf{H}'}m_{\mathbf{H}'}m_{\mathbf{H}-\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\sin(\Phi_3'+\Delta\varphi_{\mathbf{H}'\text{best}}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'\text{best}})+x\sin\delta_{\mathbf{H}}\right]\times\left[\sum_{\mathbf{H}'}m_{\mathbf{H}'}m_{\mathbf{H}-\mathbf{H}'}K_{\mathbf{H}\mathbf{H}'}\cos(\Phi_3'+\Delta\varphi_{\mathbf{H}'\text{best}}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'\text{best}})+x\cos\delta_{\mathbf{H}}\right]^{-1}, \quad (18)$$

where

$$m_{\mathbf{H}}=\exp(-\sigma_{\mathbf{H}}^2/2)\{[2(P_+-\tfrac{1}{2})^2+\tfrac{1}{2}]\times(1-\cos2\Delta\varphi_{\mathbf{H}})+\cos2\Delta\varphi_{\mathbf{H}}\}^{1/2} \quad (19)$$

and

$$\tan(\Delta\varphi_{\mathbf{H}\text{best}})=2(P_+-\tfrac{1}{2})\sin|\Delta\varphi_{\mathbf{H}}|/\cos\Delta\varphi_{\mathbf{H}}. \quad (20)$$

The value of $\sigma_{\mathbf{H}}^2$ in (19) is related to the experimental error and can be calculated from the mean square of the 'lack of closure error' (Blow & Crick, 1959). Equations (17) and (18) differ from (21) and (24) of II in only the terms containing x and $\delta_{\mathbf{H}}$, which carry the partial structure information.

Application to SIR case

1. *With the replacing atoms in a noncentrosymmetric arrangement*

Substitute $P_+(\Delta\varphi_{\mathbf{H}})=\frac{1}{2}$ into (19) and (20), the initial $m_{\mathbf{H}}$ and $\Delta\varphi_{\mathbf{H}\text{best}}$ can be obtained for all reflections. Then, by using (17), new values of $P_+(\Delta\varphi_{\mathbf{H}})$ can be calculated, most of which will differ from $\frac{1}{2}$ considerably. Thus the phase ambiguities can be automatically resolved. Iterative calculations using (19), (20) and (17) can further improve the result. If the refinement of $|\Delta\varphi_{\mathbf{H}}|$ is also desired, then (18) should be involved.

2. *With the replacing atoms in a centrosymmetric arrangement*

In this case, since $\Phi_3=0$ or π, the term $\sin(\Phi_3'+\Delta\varphi_{\mathbf{H}'\text{best}}+\Delta\varphi_{\mathbf{H}-\mathbf{H}'\text{best}})$ at the beginning will always be zero if $P_+(\Delta\varphi_{\mathbf{H}})=\frac{1}{2}$ is used for all reflections.

If, in addition to the replacing atoms, some part of the structure is known, this gives rise to non-zero values of $\delta_{\mathbf{H}}$, which is now the phase difference between the contribution from the total partial structure and that from the replacing atoms. Consequently, $P_+(\Delta\varphi_{\mathbf{H}})$ calculated from (17) will be biased to differ from $\frac{1}{2}$ by the term $x\sin\delta_{\mathbf{H}}$. Hence the procedure mentioned in 1 will still be applicable.

If, on the other hand, there is no partial structure information other than that of the replacing atoms, $\delta_{\mathbf{H}}$ will be always zero. Thus, starting from $P_+(\Delta\varphi_{\mathbf{H}})=\frac{1}{2}$, the same $P_+(\Delta\varphi_{\mathbf{H}})$ will be obtained from the calculation using (19), (20) and (17). Hence the problem of phase ambiguity cannot be solved as above. This difficulty can be overcome by a multi-solution procedure using random starting sign sets. Assign randomly to every $|\Delta\varphi_{\mathbf{H}}|$ a positive or negative sign associated with $P_+=0{\cdot}6$ or $P_+=0{\cdot}4$, respectively. Iterative calculations using (19), (20) and (17) are then used to refine the signs. A figure of merit defined as the following is used to select the best solution.

$$\text{FOM}=\left(\sum_{\mathbf{H}}m_{\mathbf{H}}E_{\mathbf{H}}\Big/\sum_{\mathbf{H}}m_{1/2}E_{\mathbf{H}}\right)-1,$$

where $m_{1/2}$ is the m_H calculated with $P_+ = \frac{1}{2}$, *i.e.*

$$m_{1/2} = \exp(-\sigma_H^2/2)|\cos \Delta\varphi_H|.$$

Hence

$$\text{FOM} = \left[\sum_H m_H E_H / \sum_H \exp(-\sigma_H^2/2)|\cos \Delta\varphi_H| E_H\right] - 1.$$

Application to OAS case

In this case, neither $\sin(\Phi'_3 + \Delta\varphi_{H'best} + \Delta\varphi_{H-H'best})$ nor $x \sin \delta_H$ will be identical to zero at the beginning. Using (19), (20) and (17), the phase ambiguities can be broken easily by starting with $P_+ = \frac{1}{2}$. The procedure is equivalent in principle to combining the direct method with the 'resolved anomalous scattering method' proposed by Hendrickson & Teeter (1981). The latter method has proved to be efficient in solving some unknown small protein structures. It is reasonable to expect that this method can be strengthened by the incorporation of a direct method.

Application to the CPS case in the absence of SIR and OAS data

This subject is in fact beyond the scope of the present paper. However, the treatment in this case is closely related to that in the SIR case. Hence a brief description is given here.

In the determination of small noncentrosymmetric structures containing heavy atoms, it often happens that the heavy atoms are in a centrosymmetric arrangement leading to the enantiomorphous phase ambiguity and resulting in a pseudo centrosymmetric image, which contains both enantiomorphs. On the other hand, direct-method determination of light-atom structures belonging to polar space groups, such as $P2_1$, leads sometimes to the instability of the enantiomorph fixation resulting also in a pseudo centrosymmetric image. This is a well known difficulty in the determination of small structures. However, the problem can be solved easily by making use of (17) and (18). Starting from the pseudo centrosymmetric image we can calculate C_H and then obtain a set of $|\Delta\varphi_H|$ using (5). If the structure contains heavy atoms in known positions, then let the partial structure consist of the heavy atoms and one of the light atoms, whose position can be fixed by picking up any one of the two possible positions on the pseudo centrosymmetric image. Then the phase ambiguity can be resolved by a procedure like that of 1 in the SIR case. Alternatively, we can use the multi-solution procedure like that described in the SIR case to derive the signs of $\Delta\varphi_H$.

Procedures similar to those described in this paragraph have already been tested on solving the enantiomorphous ambiguities in a number of small structures and were verified to be very efficient (Fan Hai-fu & Zheng Qi-tai, 1978; Fan Hai-fu & Qian Jin-zi, 1981; Fan Hai-fu & Zheng Qi-tai, 1981; Fan Hai-fu & Gu Yuan-xin, 1982).

Table 1. *Test results with APP data using* 1000 *E's and* 60 000 $\sum_2$ *relationships*

I Results calculated with (17).
II Results calculated with (21) of paper II.
% Percentage of reflections with the signs of $\Delta\varphi_H$ correctly determined in the test.
ER Average error of phases (in degrees).

	I		II	
Cycle	%	ER	%	ER
1	86·3	36	63·5	61
2	86·0	37	76·0	47
3	86·0	37	86·0	37
4	86·0	37	86·0	37

Test for the effect of the incorporation of partial structure information

A comparison of the efficiency of the two probability formulas, (17) of the present paper and (21) of paper II, was made by test calculations with the experimental OAS data from the Hg derivative of APP (avian pancreatic polypeptide), which crystallized in space group $C2$ with unit-cell dimensions $a = 34{\cdot}18$, $b = 32{\cdot}92$, $c = 28{\cdot}44$ Å and $\beta = 105{\cdot}30°$. There are about 2100 independent reflections at 2 Å resolution. 1000 largest E's were included in the calculation. They yielded about 130 000 $\sum_2$ relationships, only 60 000 of them were reserved and used for deriving the probability $P_+(\Delta\varphi_H)$. The calculation was done on an IBM 4341 computer. 20 min CPU time was used for setting up the $\sum_2$ relationships and 1 min CPU time per cycle was required for the iterative calculation of $P_+(\Delta\varphi_H)$. The results are listed in Table 1. It shows that, with the incorporation of the partial structure information, only one cycle of iteration led to a good and stable result while, without the incorporation of the partial structure information, for obtaining a similar result three cycles were needed. It also shows that the difference between the two sets of results is significant at the beginning of the iteration process but becomes negligible at the final stage. This can be interpreted as follows:

Equation (17) differs from (21) of paper II only in the term $x \sin \delta_H$. At the beginning, since m_H are all small, $x \sin \delta_H$ plays an important role. As the iteration goes on, the effect of $x \sin \delta_H$ will reduce with the increase of the values of m_H. For a protein crystal the diffraction contribution from the whole structure will be much greater than that from the heavy atoms, hence the effect of $x \sin \delta_H$ will be small at the final stage. However, this will not be the case for small structures.

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Combining Direct Methods with Isomorphous Replacement or Anomalous Scattering Data. IV. Test in the SIR Case with the Replacing Atoms in the Centrosymmetric Arrangement

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Abstract

The method described in the preceding papers has been applied to the single isomorphous replacement (SIR) case with the replacing atoms in a centrosymmetric arrangement. Two kinds of phase ambiguities simultaneously occurred in this example. One is inherent in the SIR method and was resolved by calculating the probabilities $P_+(\Delta\varphi_{\mathbf{H}})$. The other comes from the special arrangement of the replacing atoms and was treated by a multi-solution procedure with random starting sign sets. A new figure of merit was used to predict the quality of the solutions. The method has been verified using a set of error-free data from the model structures of a protein and its heavy-atom derivative.

Introduction

Many attempts have been made since Blow & Rossmann (1961) to resolve the phase ambiguity of the SIR method in the determination of protein structures. The ambiguity can in principle be resolved in either the real or the reciprocal space. Up to now the real-space methods have been more successful in practice. With the so-called ISIR method, a dozen unknown protein structures have been solved (Wang Bi-Cheng, 1981, 1984). However, in spite of its high phasing power, this method is subject to the limitation that it will not be applicable if the replacing atoms are in a centrosymmetric arrangement. This paper describes the application of a reciprocal-space method to treat this problem.

Method

In the SIR case, each reflection not belonging to a centric zone has two equally possible phases, *i.e.*

$$\varphi_{\mathbf{H}} = \varphi_{\mathbf{H},R} \pm |\Delta\varphi_{\mathbf{H}}|,$$

where $\varphi_{\mathbf{H}}$ denotes the phase of the structure factor $\mathbf{F}_{\mathbf{H}}$, $\varphi_{\mathbf{H},R}$ is the phase contribution from the replacing atoms and $\Delta\varphi_{\mathbf{H}}$ is the difference between $\varphi_{\mathbf{H}}$ and $\varphi_{\mathbf{H},R}$. According to our preceding papers (Fan Hai-fu, Han Fu-son, Qian Jin-zi & Yao Jia-xing, 1984; Fan Hai-fu, Han Fu-son & Qian Jin-zi, 1984; Fan Hai-fu & Gu Yuan-xin, 1985; hereafter referred to as papers I, II and III respectively), this phase ambiguity can be resolved by calculating the probability for $\Delta\varphi_{\mathbf{H}}$ to have a positive sign:

$$P_+(\Delta\varphi_{\mathbf{H}}) = \tfrac{1}{2} + \tfrac{1}{2}\tanh\{\sin|\Delta\varphi_{\mathbf{H}}| \times \left[\sum_{\mathbf{H}'} m_{\mathbf{H}'} m_{\mathbf{H}-\mathbf{H}'} K_{\mathbf{H}\mathbf{H}'} \sin(\Phi'_3 + \Delta\varphi_{\mathbf{H}'\text{best}} + \Delta\varphi_{\mathbf{H}-\mathbf{H}'\text{best}})\right]\}, \quad (1)$$

where

$$m_{\mathbf{H}} = \exp(-\sigma_{\mathbf{H}}^2/2)\{[2(P_+ - \tfrac{1}{2})^2 + \tfrac{1}{2}] \times (1 - \cos 2\Delta\varphi_{\mathbf{H}}) + \cos 2\Delta\varphi_{\mathbf{H}}\}^{1/2} \quad (2)$$

and

$$\tan(\Delta\varphi_{\mathbf{H}\text{best}}) = 2(P_+ - \tfrac{1}{2})\sin|\Delta\varphi_{\mathbf{H}}|/\cos\Delta\varphi_{\mathbf{H}}. \quad (3)$$

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