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Direct methods: a paradox with regard to the convergence of random phase trials toward solutions

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A frustrating observation, based on an $R_{\min}$ variance analysis within the 'shake and bake' framework of direct methods phasing, is described. The variance of $R_{\min}$ can on occasion identify large subsets of phases that have a significantly lower mean phase error than the entire direct methods phase set of otherwise unsuccessful phasing trials for which the overall phase error occasionally dips below 75 or 80°. This is the first time, other than for a handful of Σ1 phase indications in optimal situations, that *a priori* phase estimates have been attained for large numbers of E values, prior to solving the structure. Although the *a priori* variance of $R_{\min}$ is a useful tool for identifying such phases, the *a posteriori* phase refinement shifts indicated by its minimum often prevent a successful convergence to the solution. Similar efforts to encourage solution convergences in the realm of real space have also been discouraging.

1. Introduction

> 'How wonderful that we have met with a paradox. Now we have some hope of making progress.' (Niels Bohr)

The shake-and-bake (SnB) direct methods phasing procedure (Hauptman, 1988; DeTitta *et al.*, 1994; Weeks *et al.*, 1994) has provided a significant improvement over older direct methods phasing procedures based on the tangent formula (Karle & Hauptman, 1956). In this regard the SnB program can more or less routinely solve crystal structures that are five to ten times larger than those previously solved by tangent formula methods. Given this success, there is a great temptation to conclude that the SnB algorithm cannot be significantly improved over what has already been demonstrated. New findings now raise the intriguing possibility that there may be more to be learned and gained with regard to increasing the success rate and range of convergence of the SnB phasing algorithm.

2. Background

All direct methods program applications have generally been viewed as 'all or nothing' calculations that will either produce a recognizable solution, as indicated by reliable figures of merit, or will not, given the particular number of phase trials examined. A direct methods failure is often addressed by increasing the number of trials in a renewed attempt to find a different starting set of phases with the potential to converge to the correct solution. Changing the number of E values used to generate the triples phase relations, and the number of accepted triples based on the magnitude of the A values, can also sometimes be effective. Cosine invariant analysis (Hauptman, 1972) has also been occasionally used on difficult structures (Langs, 1993) to avoid suspected aberrant phase relationships and help ensure a more successful outcome, but they have not been accepted as a general method of choice.

If direct methods have been used unsuccessfully, usually nothing is to be gained by further examining those phase sets that have failed to produce a solution. An exception to this is the situation where a chemically meaningful fragment of the expected structure has been recognized from a non-solution E map (Karle, 1968) and, if need be, repositioned in the cell by translation function methods (Rossmann, 1990). Tangent formula or SnB recycling methods can then be used to solve the structure from the phases of the partial structure if that fragment has been correctly placed.

SnB is different from tangent formula methods in that it refines phases in both real and reciprocal space, whereas the tangent formula operates completely in reciprocal space. Moreover, the phase refinement target function for SnB in reciprocal space is $R(\varphi_{\mathbf{h}})$, the triples cosine invariant residual that is defined as

$$R(\varphi_{\mathbf{h}}) = \sum_{\mathbf{k}} A_{\mathbf{h},\mathbf{k}}[\cos(\varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{-\mathbf{h}-\mathbf{k}}) - I_1(A_{\mathbf{h},\mathbf{k}})/I_0(A_{\mathbf{h},\mathbf{k}})]^2 / \sum_{\mathbf{k}} A_{\mathbf{h},\mathbf{k}},$$

where $A_{\mathbf{h},\mathbf{k}} = 2\sigma_3|E_{\mathbf{h}}E_{\mathbf{k}}E_{-\mathbf{h}-\mathbf{k}}|/\sigma_2^{3/2}$, $\sigma_n = \sum_{j=1,N} f_j^n$, f_j are the N atomic form factors representing the contents of the primitive unit cell, and I_n are the nth-order Bessel functions of the real argument. Here the ratio $I_1(A_{\mathbf{h},\mathbf{k}})/I_0(A_{\mathbf{h},\mathbf{k}})$ represents the direct

Table 1
Unrefined one-atom phase sets.

Phase errors, $\delta\varphi = \langle|\varphi_{cal} - \varphi_{true}|\rangle$, were computed from the N one-atom sites for four light-atom structures containing no atom larger than oxygen. The number of phases used in the SnB analysis and the percentage of N trials that proceeded to solutions are given. The range, mean and standard deviations of the N sets are cited. Also listed is the percentage of phase sets, each undergoing 100 SnB cycles of random N-atom refinement, *excluding solutions*, that attain $\delta\varphi$ less than 80 and 75°.

Structure	No. of atoms N	No. of φ's	No. of triples	% Solutions	$\delta\varphi$ range (°)	$\delta\varphi \pm$ standard deviation (°)	$< 80°$ (%)	$< 75°$ (%)	Reference
ILED	84	840	8000	34	68 → 87	78 ± 4	30	9	(*a*)
FILE4	95	800	9000	15	66 → 88	79 ± 5	28	5	(*b*)
TERN	110	700	7000	3	70 → 87	79 ± 4	31	3	(*c*)
FILE5	117	900	10000	9	68 → 89	82 ± 5	23	4	(*d*)

References: (*a*) Pletnev *et al.* (1980); (*b*) Pletnev *et al.* (1991); (*c*) Miller *et al.* (1993); (*d*) Pletnev *et al.* (1992).

methods expectation value of $\cos(\varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{-\mathbf{h}-\mathbf{k}})$ derived by Hauptman (1966) based on its A value. For an N-atom structure determination, one usually selects *ca* $10N$ E values and $100N$ triple phase invariants as the basis of phase refinement by the $R(\varphi_{\mathbf{h}})$ function.

An SnB phasing trial begins with randomly generating coordinates for an N-atom structure and using those positions to compute the initial phase values. Those phases are next refined by minimizing $R(\varphi_{\mathbf{h}})$, for each phase $\varphi_{\mathbf{h}}$, while all others, $\varphi_{\mathbf{k}}$ and $\varphi_{-\mathbf{h}-\mathbf{k}}$, are temporarily held fixed until it is their turn to be refined. One of the simplest refinement schemes simply increments the value of $\varphi_{\mathbf{h}}$ by 0, ±90 and 180°, and accepts the value that produces the lowest value of $R(\varphi_{\mathbf{h}})$. Once all the phases have been adequately refined in this manner, an E map is computed and the N largest peaks are then chosen as the starting point for the next cycle of refinement. A sufficient number of cycles of refinement are performed to ensure convergence, at which time R_{min}, the overall value of $R(\varphi)$ for all the phases, will approach its global minimum. The value of R_{min} is generally significantly less than 0.5 for the correct solution, and greater than 0.5 for all the various non-solutions. A solution is usually not obtained in those instances where there is no clear separation in R_{min} values. Fig. 1 compares the progress of a typical SnB solution *versus* a non-solution with regard to the computed value of R_{min} and its associated average mean phase error, $\langle|\delta\varphi|\rangle = \langle|\varphi_{true} - \varphi_{cal}|\rangle$, as a function of the SnB phase refinement cycle number.

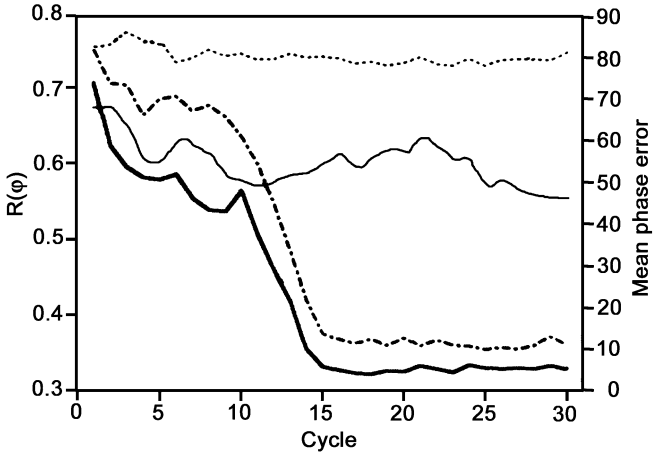

Figure 1
Example of the SnB progress of a solution *versus* a non-solution. The heavy line marks the value of R_{min} as a function of SnB cycle number for a solution, the value for R_{min} drops significanly below 0.5 at about cycle 10. The $\langle|\delta\varphi|\rangle$ associated with this trial (dot-dashed line) rapidly decreases to ∼10° once this is achieved. R_{min} for a typical non-solution (fine line) seldom reaches as low as 0.5, while its associated $\langle|\delta\varphi|\rangle$ (dotted line) hovers near that for randomly generated phases in the vicinity of 85 to 90°.

Once a solution has been obtained, one characteristic of well determined phases is that the values of $R(\varphi_{\mathbf{h}})$ for the individual phases should increase dramatically upon perturbing the value of $\varphi_{\mathbf{h}}$ by 0, ±90, 180° from their solution values. Conversely, if there should be little difference among the four R values, then there would be no particular reason to believe that any one of the four permuted values would be any better than the other three. Having made this conjecture, one might also ask the same question with regard to SnB phase sets that have not fully converged to a recognizable solution. That is, might a large variance indicator for any $R(\varphi_{\mathbf{h}})$ still be correlated with how well that phase has converged toward its true value? We decided to examine this possibility.

3. Numerical tests

Four moderately large $P2_12_12_1$ structures each having about 100 non-H atoms in the primitive unit cell were selected. Firstly, it will be necessary to be able to evaluate $\langle|\delta\varphi|\rangle$ for any SnB trial with the known structure relative to some unknown choice of origin and enantiomorph. It is a fairly trivial matter to do this in the space group $P2_12_12_1$ by simply examining the 16 permissible choices of origin and enantiomorph and selecting the choice with the smallest phase error. Secondly, it is well known as a point of interest that single-atom search models often generate initial trial sets with a significantly lower $\langle|\delta\varphi|\rangle$ than N-atom models (Weeks *et al.*, 1994). Table 1 lists the one-atom phase errors for the starting sets of phases corresponding to each of the N atoms of the four known structures chosen. For the purpose of the following study we temporarily ignored all those single-atom starting sets that subsequently produced SnB solutions upon further refinement, or between 3 and 34% of all sets depending on the

accuracy, resolution and completeness of the data and the structural complexity, as indicated in Table 1. In this way we can focus our attention on just those phase sets that are on the edge of refining to a solution but fail to converge upon further SnB cycling. Structures containing considerably more than 100 atoms were excluded from this analysis because their one-atom phase sets seldom have $\langle|\delta\varphi|\rangle$ less than 80° and cannot be considered to be on the edge of convergence to a solution.

We initially performed our variance analysis of $R(\varphi_{\mathbf{h}})$ using the standard four-point SnB parameter shift protocol, but later adopted an eight-point scheme since those results appeared more convincing. Thus, given each one-atom starting set meeting the criteria above, the individual variance of each phase was computed from each of eight permuted values of $R(\varphi_{\mathbf{h}})$ representing progressive 45° shifts in the original value of $\varphi_{\mathbf{h}}$. The standard deviation of $R(\varphi_{\mathbf{h}})$ is $\sigma(R) = [\langle R_j^2\rangle - \langle R_j\rangle^2]^{1/2}$, where R_j is the value of $R(\varphi_{\mathbf{h}} + j \times 45)$, and $\langle R_j\rangle$ indicates the average value computed from these eight points. The phases were next sorted on their values of $\sigma(R)$, and $\langle|\delta\varphi|\rangle$ was determined for groups of ∼50 phases as a function of $\sigma(R)$. The result of a typical analysis having an overall $\langle|\delta\varphi|\rangle$ of 78.5° is shown in Fig. 2.

Let $n_{\min}$ be the particular value of j for the minimum value among the eight R_j values cited above and, similarly, $n_{\max}$ for its maxima. Next we investigated how this error compared for subgroups of phases based on the values of $n_{\min}$ and $n_{\text{del}} = |n_{\max} - n_{\min}|$, the number of shift increments observed between the minimum and maximum values of R_j. Moreover, since there are eight shift intervals spanning the range from 0 to 360°, we shall treat a shift of $n \times 45°$ as being Friedel equivalent to a shift of $(8 - n) \times 45°$ should the value of n exceed 4. In this way the values of $n_{\min}$ and n_{del} can both be expressed as values from 0 to 4, or from 0 to 180° in increments of 45°. Given these rules the data presented in Fig. 2 can be re-sorted into groups based on the values of $n_{\min}$ and n_{del}, where a new pattern emerges (Fig. 3). We now see that the groups (0, 4), (1, 3) and (2, 2), which represent about half of the total number of phases, are similar in that they produce a slanted line that is much steeper than that indicated in Fig. 2. Conversely, all the remaining sets excluding those previously mentioned produce a line that is significantly flatter than that shown in Fig. 2. Thus, it appears that when $\sigma(R)$ is large it is more likely that the true phase value is 180° from the maximum of $R(\varphi_{\mathbf{h}})$, rather than being closer to its minimum.

We next wanted to determine whether N-atom SnB phase sets having $\langle|\delta\varphi|\rangle$ in the range of 75 or 80° behaved similar to the one-atom sets described above. To test this a large number of random N-atom phase sets for the four known test structures were refined by the SnB program and non-solution phase sets for which $\langle|\delta\varphi|\rangle$ dipped below the 75 and 80° thresholds were collected. These phase sets were subjected to a $\sigma(R)$ analysis and shown to produce a slanted line similar to that indicated in Fig. 2, which indicates that $\langle|\delta\varphi|\rangle$ is smaller for those phases having larger $\sigma(R)$ values. Re-plotting the data according to their ($n_{\min}$, n_{del}) values, however, does not indicate that the (0, 4), (1, 3) and (2, 2) groups are any better than any of the rest, *i.e.* all groups appear to behave the same.

To follow up on this, 1000 random N-atom trials were generated and subjected to 200 cycles of SnB refinement for each of the four test structures. The percentage of those trials that produced SnB solutions for each of the four test structures is noted in column 2 of Table 2. However, particular attention was now paid to those trials that had $\langle|\delta\varphi|\rangle$ less than 80 or 75° at some time during their refinements, but failed to converge to a solution, which are reported in columns 3 and 6, respectively. The fraction of those trials which converged (Cng%) to a solution after crossing the 80 or 75° thresholds are noted in columns 4 and 7, as are the average number of cycles ($\langle\#\rangle$) for which $\langle|\delta\varphi|\rangle$ remained less than the 80 and 75° thresholds.

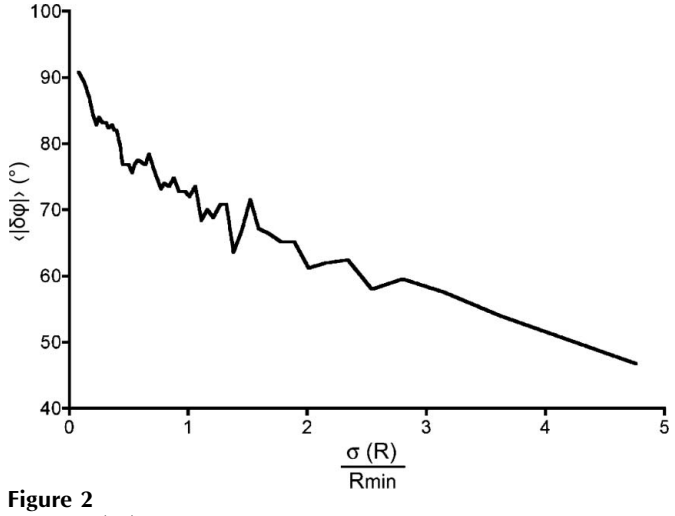

Figure 2
A plot of $\langle|\delta\varphi|\rangle$ as a function of the value of $\sigma(R)/R(\varphi_{\mathbf{h}})_{\min}$ for the 84-atom ILED structure. The overall average $\langle|\delta\varphi|\rangle$ for the 84 one-atom phase sets was 78.5°. The data were sorted in descending order on the value of $\sigma(R)/R(\varphi_{\mathbf{h}})_{\min}$ for each phase and averaged in groups of 50 phases. This plot was made using the program *Prism*.

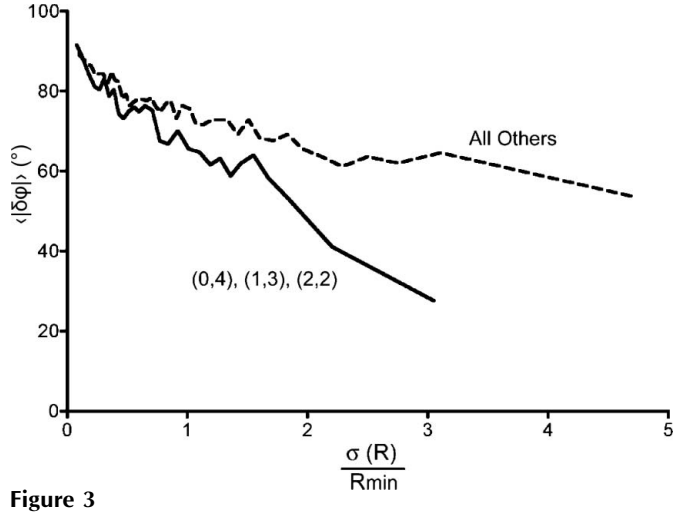

Figure 3
A re-plot of the data presented in Fig. 2. The data were first sorted into groups based on the values of ($n_{\min}$, n_{del}), as explained in the text. The data represented by groups (0, 4), (1, 3) and (2, 2) were then plotted together as is shown by the lower solid line. All the remaining groups were then merged and plotted as the upper dashed line in the figure.

Table 2
Results for a total of 1000 random *N*-atom phase sets each refined for 200 SnB cycles.

The percentage of solutions that were observed is noted in column 2. The percentage of all *non-solution* sets for which $\langle|\delta\varphi|\rangle$ is less than 80 and 75° are given in columns 3 and 6, respectively. The percentage of the total number of sets, solutions and non-solutions that converged to the solution (Cng%) after crossing the 80 and 75° thresholds is noted in columns 4 and 7. The average number of times $\langle\#\rangle$ during the 200 cycles of refinement that $\langle|\delta\varphi|\rangle$ dips below those thresholds are noted in columns 5 and 8. In general it may be stated that whenever $\langle|\delta\varphi|\rangle$ dips below these thresholds, the phase error could well remain beneath those thresholds for the next 5 to 20 consecutive refinement cycles.

Structure	% Solutions	< 80° (%)	Cng% (%)	⟨#⟩	< 75° (%)	Cng% (%)	⟨#⟩
ILED	18	31	37	18	9	66	13
FILE4	4.6	27	15	27	8	36	10
TERN	0.3	38	0.8	17	7.5	4	11
FILE5	4.5	38	10	22	9	33	10

Several ideas were pursued with regard to exploiting the information provided by the subsets of phases having a lower $\langle|\delta\varphi|\rangle$ value that were identified. Firstly, several *ad hoc* weighting schemes were devised in an effort to take advantage of the observed $\sigma(R)$ phase error distribution shown in Fig. 2. The weights for the phases can be determined in the first SnB pass through the phases to compute $\sigma(R)$, in which case the phases are not refined. The list of $\sigma(R)$ values was sorted in descending order and weights for the individual phases were assigned by various schemes to increase from 0 to 1 as $\sigma(R)$ approached is maximum value. These weights were then temporarily applied to $A_{\mathbf{h},\mathbf{h}}$ as $\mathrm{wt}(\mathbf{h})\mathrm{wt}(\mathbf{k})\mathrm{wt}(-\mathbf{h}-\mathbf{k})\,A_{\mathbf{h},\mathbf{k}}$ in the second pass in which the phases are refined. A second scheme simply involved holding the better-determined phases, say the top 25% based on $\sigma(R)$, fixed for a limited number of cycles while the remaining phases were refined by the SnB procedure in the hope that they would converge toward their solution values. Thirdly, a variant of this latter procedure (Langs *et al.*, 1995) allowed the set of better phases to be tested against a small number of sets of random values for the remaining phases. In this regard the SnB program was run *ab initio* for each of the four test structures and the $\sigma(R)$ analysis was performed on the non-convergent phase sets for which $\langle|\delta\varphi|\rangle$ was in the range 75– 80°. The better-phased subsets that were identified were used as the basis for testing the effectiveness of the three refinement schemes described in this paragraph.

4. Discussion

The data presented in Table 1 indicate that the range of $|\delta\varphi|$ values, $\langle|\delta\varphi|\rangle$ and standard deviations are all very similar for each of the four $N \simeq 100$-atom structures. The SnB success rates vary, however, based on the accuracy, completeness and resolution of the data and other less well defined structural peculiarities. As a point of information it is cited that although 34% of the 84 one-atom trials for the ILED structure will actually converge to an SnB solution (column 4, Table 1), none of these same phase sets will converge if subjected to standard tangent formula refinement. However, somewhat constant for all four structures are the percentages of SnB trials that encounter phase sets that have $\langle|\delta\varphi|\rangle$ less than 75° (3 → 9%) or 80° (23 → 31%), without converging to a solution, as is shown in the last two columns of Table 1. Thus, even though a solution was not found in these particular cases, there was the expectation that many of these phase sets might have converged if subjected to a $\sigma(R)$ analysis to identify subsets of phases with $\langle|\delta\varphi|\rangle$ in the vicinity of 60° or less.

The results presented in Fig. 3 for the one-atom phase analysis sorted on $n_{\min}$ and n_{del} are both surprising, and a bit puzzling. Whereas $\langle|\delta\varphi|\rangle$ ranged between 45 and 90° as a function of $\sigma(R)$ for unsorted results as shown in Fig. 2, we see they now range between 25 and 90° for groups (0, 4), (1, 3) and (2, 2) and 55 to 90° for all the other groups. Moreover, what is not shown is that if one were to apply the $n_{\min}$ shift to those phases in groups (1, 3) and (2, 2), which is to follow the SnB convention, the $\langle|\delta\varphi|\rangle$ becomes larger. Thus, although large $\sigma(R)$ values help identify the better-determined phase values, the shifts suggested by $R(\varphi_{\mathbf{h}})_{\min}$ can actually lead away from the solution! At least for unrefined one-atom phases, it is actually better to accept those phase shifts that are 180° away from $R(\varphi_{\mathbf{h}})_{\max}$, rather than those that are closest to $R(\varphi_{\mathbf{h}})_{\min}$.

A slightly different pattern arises for the non-convergent *N*-atom phase sets for which $\langle|\delta\varphi|\rangle$ occasionally dipped below 75 or 80°. Although the larger $\sigma(R)$ values also indicate groups of phases with a lower $\langle|\delta\varphi|\rangle$, as indicated in Fig. 1, there is nothing to be gained by re-sorting the phases into groups based on the values of $n_{\min}$ and n_{del} as the patterns for these groups all have the same general shape. One obvious difference between the one-atom and *N*-atom phase sets having the same relative phase errors is that the one-atom sets correspond to actual atomic positions, but the vast majority of the *N*-atom sites most probably do not.

The question may arise as to how frequently one may expect to encounter random atom phase sets which have $\langle|\delta\varphi|\rangle$ less than 75 or 80° in the course of an SnB refinement. Table 2 indicates that between 7.5 and 9.0% of the random trials will experience a phase set with $\langle|\delta\varphi|\rangle$ less than 75°, and that this will occur between 10 or 13 times during the phase refinement for those particular trials for the four test structures examined. In most instances, these occur as a string of consecutive refinement cycles for which $\langle|\delta\varphi|\rangle$ remains low, until it eventually diverges. Likewise, if the $\langle|\delta\varphi|\rangle$ threshold is raised to 80°, the fraction of random trials that encounter phase sets lower than this threshold logically increases to between 27 and 38%. Likewise, the average number of times this will occur during the refinement also increases to between 17 and 27 times. Thus, if a $\sigma(R)$ analysis was perfomed every ten or so cycles, there is a good likelihood that one would not miss catching the refinement at some low point in $\langle|\delta\varphi|\rangle$ before it diverged to become larger.

The results from comparing the three weighted SnB refinement schemes based on an initial SnB subset of better-determined phases were not as encouraging as initially hoped. The weighted SnB formulation only moderately increased the

random-atom success rates of the ILED, FIL4 and FIL5 structures by a factor of 10% at most (*i.e.* from 18 to 20% for ILED and about 4.5 to 5% for FIL4 and FIL5), but the success rate for the TERN structure increased from 0.3% to as much as 2.5% depending on the mean phase error and relative size of the fixed basis set selected. This most certainly should be viewed as an eightfold increase in the success rate rather than a mere 2% improvement. Simply holding the basis set phases fixed for a number of cycles without the benefit of weights for refining the remaining phases (scheme 2) usually did not move them in the direction toward the solution. It was far more effective to replace the remaining phases with random-atom values and explore a small number of such random sets in the hopes of producing a solution that the overall $R_{\min}$ figure of merit can decisively identify, or continue the standard SnB refinement to resume this multi-solution stance again 10 or 15 cycles later. It is rather disappointing that a much larger fraction of sub-80° phase sets could not be induced to produce convergent solutions in spite of successfully identifying significant subsets of phases with $\langle|\delta\varphi|\rangle$ in the vicinity of 60°. Thus, although the variance of $R(\varphi_{\mathbf{h}})$ appears to be a powerful tool to identify such subsets, its simple minimization is not so effective as to determine the remaining phases accurately. This is a strange observation since it runs contrary to our experience and expectations from using relatively small blocks of similarly well determined phases computed from molecular fragments or inferred from crystal derivative data. Similar efforts to encourage these sets to converge to solutions in the realm of real space, through maps whose E values were appropriately weighted by their expected phase accuracy based on the variance of $R(\varphi_{\mathbf{h}})$, only marginally improved the success rates. Also, random peak omission (Sheldrick *et al.*, 2001), which often produces a marked 40–50% improvement in the normal random SnB success rate, was surprisingly much less effective when applied to these reluctant-to-converge phase sets.

5. Summary

A method for identifying better subsets of phases from SnB trials that have not fully converged to solutions has been outlined based on the variance of the $R(\varphi)$ value for the individual phases. The method appears to work as long as the overall $\langle|\delta\varphi|\rangle$ is less than 80°, which is considerably larger than what may have initially been conjectured. Although phase sets meeting this criterion are fairly common in SnB analyses of structures containing 100 or more atoms in the asymmetric unit, perhaps affecting one in every three random SnB trials, it remains to be demonstrated whether a more robust solution convergence scheme can be devised to take advantage of this unexpectedly frequent situation.

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References

DeTitta, G. T., Weeks, C. M., Thuman, P., Miller, R. & Hauptman, H. A. (1994). *Acta Cryst.* A**50**, 203–210.
Hauptman, H. A. (1966). *A Relationship Among Large Structure Factors*, Abstract 1.5. VIIth Congress and General Assembly of the IUCr, 12–21 July, Moscow, USSR.
Hauptman, H. A. (1972). *Crystal Structure Determination: The Role of the Cosine Seminvariants*. New York: Plenum Press.
Hauptman, H. A. (1988). *Proceedings of the American Crystallographic Association Meeting*, Abstract R4, p. 53. Philadelphia, USA.
Karle, J. (1968). *Acta Cryst.* B**24**, 182–186.
Karle, J. & Hauptman, H. (1956). *Acta Cryst.* **9**, 635–651.
Langs, D. A. (1993). *Acta Cryst.* A**49**, 545–557.
Langs, D. A., Miller, R., Hauptman, H. A. & Han, G. W. (1995). *Acta Cryst.* A**51**, 81–87.
Miller, R., Galitsky, N. M., Duax, W. L., Langs, D. A., Pletnev, V. Z. & Ivanov, V. T. (1993). *Int. J. Pept. Protein Res.* **42**, 539–549.
Pletnev, V. Z., Galitskii, N., Smith, G. D., Weeks, C. M. & Duax, W. L. (1980). *Biopolymers*, **19**, 1517–1534.
Pletnev, V. Z., Ivanov, V. T., Langs, D. A., Strong, P. & Duax, W. L. (1992). *Biopolymers*, **32**, 819–827.
Pletnev, V. Z., Mikhailova, I. Yu., Ivanova, V. T., Langs, D. A., Grochulski, P. & Duax, W. L. (1991). *Biopolymers*, **31**, 409–415.
Rossmann, M. G. (1990). *Acta Cryst.* A**46**, 73–82.
Sheldrick, G. M., Hauptman, H. A., Weeks, C. M., Miller, R. & Usón, I. (2001). *International Tables for Crystallography*, Vol. F, edited by M. G. Rossman & E. Arnold, ch. 16.1, pp. 333–351. Dordrecht: Kluwer Academic Publishers.
Weeks, C. M., DeTitta, G. T., Hauptman, H. A., Thuman, P. & Miller, R. (1994). *Acta Cryst.* A**50**, 210–220.