

## The reliability index $R_2$ as a versatile tool in structure analysis of inorganic and small molecular compounds

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# The reliability index $R_2$ as a versatile tool in structure analysis of inorganic and small molecular compounds

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Applications of  $R_2$  in small-molecule crystallography are described. Ways of using  $R_2$  to evaluate initial models of a structure are discussed. These models, obtained from Patterson methods, are usually small. They may include one or more heavy atoms and pseudosymmetry is sometimes present in the model. The  $R_2$  criterion is used also to identify misplaced atoms prior to the start of the expansion process. Finally,  $R_2$  is used during structure expansion by the application of phase refinement or Fourier methods. Details of the procedures of extension, as well as the role of  $R_2$  therein, are presented and evaluated. Results obtained with various test structures are discussed.

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## 1. Introduction

Modern techniques for solving small or medium-sized crystal structures are based almost exclusively on direct methods or the Patterson function. For the evaluation of the results obtained, various proprietary figures of merit are in use, together with agreement factors based on  $F(\mathbf{h})$ ,  $E(\mathbf{h})$ ,  $I(\mathbf{h})$  and  $|E(\mathbf{h})^2|$ . In the past, Lenstra and coworkers have stressed the effectiveness and discriminatory power of  $R_2$  (Van Havere & Lenstra, 1983). These authors also derived expected values of  $R_2$  based on the size of the model and the contents of the unit cell. This paper describes the implementation of  $R_2$  at various stages of routine structure determinations.

*Ab initio* direct methods rarely lead to a complete structure; usually, some recycling procedure is needed to find all atoms. For large or difficult structures, sometimes only a small and/or partly erroneous fragment is obtained or recognized. In this case,  $R_2$  may be used to filter incorrectly placed atoms from the initial model.

Methods aimed at deconvoluting the Patterson function often lead to many plausible solutions. In a significant number of cases, the most probable solution does not correspond to a reasonable model of (part of) the structure. As the  $R_2$  function is not used in generating the solutions, we have investigated the use of  $R_2$  for the selection of the correct solution. The resulting model will fit the Patterson as well as having a relatively low  $R_2$  value.

Generally, consecutive phase refinement and Fourier recycling are used to find a complete structure. As is described in this paper, the  $R_2$  function is a powerful tool, increasing the effectiveness of the recycling procedures and widening the range of convergence in routine crystal structure analysis.

The limited size of the starting model used, pseudosymmetry, partially misplaced fragments, chicken-mesh structures, known (heavy) atoms lying on special or pseudospecial positions *etc.* may cause conventional Fourier recycling techniques to fail. Then, the use of the  $R_2$  function can be crucial in solving the structure. In practice, therefore, both automatic selection from multiple solutions and the automation of powerful recycling techniques are of great importance for both routine as well as difficult structure analyses. It is not surprising that this topic is the subject of many publications. Of particular interest is a paper by Sheldrick & Gould (1995).

In this paper, we present the results of our research in this area. The emphasis is on implementation and the results obtained in practice. In §3, a few essential formulae are recalled. The contribution of one atom to  $R_2$  is discussed. In §4, various uses of  $R_2$  are described:

- (i)  $R_2$  as a selection criterion for starting sets;
- (ii) improving starting models using  $R_2$ ;
- (iii) the role of  $R_2$  in the expansion strategy.

A function,  $Q_2$ , is proposed that may be used in the calculation of combined figures of merit. §5 deals with the results obtained. All implementations are discussed referring to results obtained using the programs *DIRDIF* (Beurskens & Smykalla, 1991; Beurskens *et al.*, 1999) and *CRUNCH* (de Gelder *et al.*, 1993).

## 2. Notation

Key symbols and notation used in this paper are shown in Table 1.

**Table 1**  
Symbols and notation.

$\Sigma_{\mathbf{h}}$	Summation over a selected set of reflections $\mathbf{h}$
$\mathbf{h}$	Reflection $h, k, l$
$F$	$F(\mathbf{h})$
$ F_o $	Observed structure factor on an absolute scale
$F_o$	Observed structure factor with a given (estimated or calculated) phase
$F_p$	Partial structure factor (calculated for the given model)
$ E_o $	Observed normalized structure factor
$E_p$	Normalized partial structure factor (calculated for the model)
$Z_j$	Number of electrons of atom $j$
$N$	Number of atoms in the unit cell
$N_p$	Number of atoms in the current model, in the unit cell
$p^2$	Scattering fraction represented by the current model: $p^2 = \sum_{j=1}^{N_p} Z_j^2 / \sum_{j=1}^N Z_j^2$
$s$	$\sin \theta / \lambda$
$f_j(s)$	Scattering factor of atom $j$
$\varepsilon$	Symmetry-enhancement factor
$\eta_0(s)$	Normalizing factor in $E_0 = F_0 / \eta_0(s)$ , $\eta_0^2(s) = \varepsilon \sum_{j=1}^N f_j^2 \exp(-2B_{ov} s^2)$
$\eta_p(s)$	As $\eta_0(s)$ ; summation over the atoms in the model only
$p_s^2$	Scattering fraction represented by the model, $p_s^2 = \eta_p(s) / \eta_0(s)$
$N_{\text{at}}$	Number of symmetry-independent atoms of the model
$N_{\text{h.at}}$	Number of symmetry-independent heavy atoms of the model

### 3. The $R_2$ criterion

The disagreement factor  $R_2$  is defined conventionally using either structure factors  $F$  or normalized structure factors  $E$ . Where this distinction is of importance in the discussion, we use a superscript explicitly [( $F$ ) or ( $E$ )]. Thus,  $R_2$  is defined as

$$R_2^{(F)} = \frac{\sum_{\mathbf{h}} (|F_0|^2 - |F_p|^2)^2}{\sum_{\mathbf{h}} |F_o|^4} \quad (1)$$

and

$$R_2^{(E)} = \frac{\sum_{\mathbf{h}} (|E_0|^2 - p_s^2 |E_p|^2)^2}{\sum_{\mathbf{h}} |E_o|^4}. \quad (2)$$

The presence of  $p_s^2$  in (2) is a consequence of normalization. Note that (2) is strictly valid for triclinic symmetry only; in other space groups, changes in the weights of special reflections should be used. In the case of  $\mathbf{h}$ , including all reflections within the sphere of measurement, an *a priori* estimate of  $R_2^{(E)}$  as a function of  $E_o$  and the scattering power of the current model may be obtained from

$$R_{2,\text{est.}}^{(E)} = \frac{\sum_{\mathbf{h}} [ |E_o|^4 (1 - p_s^4)^2 - 2 |E_o|^2 (c - p_s^4) (p_s^2 - p_s^4) + c (p_s^2 - p_s^4)^2 ]}{\sum_{\mathbf{h}} |E_o|^4}, \quad (3)$$

where  $c = 3$  for centric and  $c = 2$  for acentric distributions (Van Havere & Lenstra, 1983*a,c*).

The relation of  $R_2$  with reciprocal-space correlation functions is clear when (2) is written as

$$R_2^{(E)} = \frac{(\langle |E_o|^4 \rangle_{\mathbf{h}} - 2 p_s^2 \langle |E_o|^2 |E_p|^2 \rangle_{\mathbf{h}} + p_s^4 \langle |E_p|^4 \rangle_{\mathbf{h}}) / \langle |E_o|^4 \rangle_{\mathbf{h}}}{\langle |E_o|^4 \rangle_{\mathbf{h}}}. \quad (4)$$

The second term in the numerator of (4) is a correlation term. It is the primary term of the function maximized in the translation-function program *TRACOR* (see below). Comparing (1) and (2), we see clearly that many different  $R_2$ -like functions may be defined, depending on the sharpening introduced, as well as on possible rejection criteria for, say, weak reflections. Our experience has shown that using all available reflections as  $|E_o|$  is the best choice.

Although  $p_s^2$  is introduced correctly in (2) and (4),  $p^2$  is often used in the literature. For heavy-atom structures,  $p_s^2$  is far from constant, while  $p^2$  is independent of  $\sin \theta$ . We have found that, when  $p_s^2$  is used,  $R_2$  values do not agree very well with their estimates. Therefore, in practice we use the following expressions for  $R_2$  and  $R_{2,\text{est.}}$ , substituting  $p^2$  for  $p_s^2$  in (2) and (3). Dropping the superscript ( $E$ ), we now write

$$R_2 = \frac{\sum_{\mathbf{h}} (|E_0|^2 - p^2 |E_p|^2)^2}{\sum_{\mathbf{h}} |E_o|^4} \quad (5)$$

and

$$R_{2,\text{est.}} = \frac{\sum_{\mathbf{h}} [ |E_0|^4 (1 - p^4)^2 - 2 |E_o|^2 (c - p^4) (p^2 - p^4) + c (p^2 - p^4)^2 ]}{\sum_{\mathbf{h}} |E_o|^4}. \quad (6)$$

For a structure consisting of randomly distributed atoms,  $R_{2,\text{est.}}$  for a correct model may be approximated by  $R_{2,\text{est.}} \simeq 1 - p^2$ . With the structural model approaching completeness,  $p^2$  goes to unity and  $R_{2,\text{est.}}$  converges to zero. Owing to errors in both the experiment and the model, the minimum  $R_2$  observed is usually greater than 0.10. Our recycling procedures take this into account. An example of the effect of using expressions (5) and (6) instead of (2) and (3) is given in §5.2.1.

#### 3.1. The contribution of one individual atom to $R_2$

Consider a partial model consisting of  $N_p$  independent atoms. Define  $\Delta R_2$  as  $R_2^{N_p} - R_2^{N_p-j}$ , where  $R_2^{N_p}$  is the  $R_2$  value for the partial structure and  $R_2^{N_p-j}$  is the  $R_2$  value for the model without atom  $j$ .

If atom  $j$  is correctly positioned,  $\Delta R_2$  is expected to be negative. If  $\Delta R_2$  is close to zero or positive, then atom  $j$  is probably misplaced. Therefore,  $R_2^{N_p-j}$  may be used as a measure of the quality of atom  $j$ .

Next, consider  $\Delta R_2^{jk}$ , the difference in  $R_2$  obtained by deleting both atoms  $j$  and  $k$  from the model. Because of the correlation between atomic positions through  $E_o$ , this value is not exactly equal to the sum of  $\Delta R_2^j$  and  $\Delta R_2^k$ . This means that calculating the effect of deleting more than one atom from a given model poses a problem. There are two methods of dealing with this:

(i) After removing one atom  $j$  permanently, recalculate all structure factors and proceed to the next deletion. This method is accurate but time consuming.

(ii) Neglect the correlation mentioned. Both *AUTOFOUR* and *DIRDIF* use this method of judging the quality of atomic positions during the process of extension.

In the case of heavy-atom structures, the relative contribution to  $R_2$  is useful:

$$\Delta_{\text{rel.}}^j = \Delta R_2^j / \left| R_{2,\text{est.}}^{N_p} - R_{2,\text{est.}}^{N_p-j} \right| \quad (7)$$

Atoms that increase the value of  $R_2$  (i.e.  $\Delta_{\text{rel.}}^j > 0$ ) should be removed from the model. Atoms that hardly lower the value of  $R_2$  may be considered suspect.

#### 4. Applications of $R_2$

Automatic recycling has been in use in the program system *DIRDIF* for many years. Often, strategies have been changed based on experience. Usually, the structural fragment to be completed is obtained by either heavy-atom Patterson interpretation techniques (subprogram *PATTY*; Admiraal *et al.*, 1992) or by vector-search methods (subprogram *ORIENT*; Beurskens, Beurskens *et al.*, 1987) followed by reciprocal-space correlation methods (subprogram *TRACOR*; Beurskens, Gould *et al.*, 1987). At the start of the cyclic expansion procedure, most atoms of the fragment (partial structure) are assumed to be in approximately correct positions. The program system *DIRDIF* is then keyed to resolve possibly existing pseudosymmetry problems and to expand the fragment to the complete structure in a fast and automatic way.

The *CRUNCH* system is aimed at the *ab initio* determination of 'difficult' structures. The models obtained from the direct-methods section, *DETER* (de Gelder *et al.*, 1993), usually contain a limited number of atoms only. In the program *AUTOFOUR* (Kinnegeing & de Graaff, 1984), which is the other main subprogram of *CRUNCH*, the models are expanded to the complete structure by repeated Fourier recycling.

In both *DIRDIF* and *AUTOFOUR*, the  $R_2$  function is used:

- (i) to select and evaluate a model;
- (ii) to reject wrong atoms from starting models;
- (iii) to monitor the quality (or correctness) of the model or partial structure during the expansion procedure.

##### 4.1. The $R_2$ function as a criterion for the selection of starting models

A Patterson-interpretation program assigns a figure of merit (FOM) on a relative scale to each generated set of (heavy) atom coordinates. Additionally, the  $R_2$  value is calculated for each set. As a rule, the first model (i.e. the set with the highest FOM) is the correct one. However, often in practice the correct model has a FOM that is about 80% of the maximum value found. The  $R_2$  criterion may help to identify the correct model. In the case of the first solution being correct, the corresponding  $R_2$  value is almost always also the lowest one of all.

The  $R_2$  values of different models of approximately equal size may vary by only a few percent. Comparing models of different sizes is impossible on the basis of  $R_2$ . Small variations in large  $R_2$  values are often as significant as relatively large

variations in small  $R_2$  values. Therefore, a new  $R_2$ -related function,  $Q_2$ , is introduced:

$$Q_2 = (x - R_2) / (1 - R_{2,\text{est.}}) \simeq (x - R_2) / p^2, \quad (8)$$

where  $x$  is a fixed, positive number, chosen to be large enough to ensure that  $Q_2$  is positive.  $Q_2$  is expected to reach a maximum for the correct model. Variations in  $Q_2$  are relative and  $Q_2$  is independent of the size of the model. The spread in  $Q_2$  for different models of comparable quality is governed by the value chosen for  $x$ .  $Q_2$  may be used as a multiplication factor in combined figures of merit. In the following examples, we have used  $x = [1 + R_2(\text{top})]/2$ , where  $R_2(\text{top})$  is the  $R_2$  value of the solution of the highest FOM. As a combined figure of merit (CFOM) for the ordering of possible solutions, we define  $\text{CFOM} = \text{FOM} \times Q_2$ .

##### 4.2. Improving the starting model using $R_2$

*AUTOFOUR* was developed to handle 'poor' models. In the program, special attention is given to the very first screening of the input model. In *CRUNCH*, the initial model generated by the direct-methods section *DETER* is checked in the most accurate way (§3.1) in order to obtain a starting model containing as few incorrect atoms as is possible.  $R_2$  of the initial model is calculated. If it is higher than  $R_{2,\text{est.}}$ , the model is always pared down until  $p$  equals approximately 0.08.

If *AUTOFOUR* is offered a large fragment, and unless the value of  $R_2$  indicates that the model is (almost) completely correct, then instead of the complete fragment only the  $M$  highest peaks are taken as the input model and screened.  $M = 20$  or 20% of the number of atoms in the structure, whichever is the highest.

To clean up the starting model, *DIRDIF* uses the cheaper method given in §3.1. Atoms corresponding to positive values of  $\Delta_{\text{rel.}}^j$  [(7)] are removed before the process of extension is started.

##### 4.3. Expansion strategy: peak interpretation; selection for next cycle; when to stop

Often, obtaining the complete structure from a small model is not trivial. By now it is well known that in expansion procedures it is advantageous to alternate between reciprocal-space and direct-space techniques, i.e. direct methods or correlation methods *versus* electron-density modifications or peak-list optimizations. Well known examples are described by DeTitta *et al.* (1994) (*Shake and Bake*) and Sheldrick & Gould (1995). Such alternating expansion procedures have been in use in *AUTOFOUR* and in *DIRDIF* since the early 1970's.

In most publications on (automatic) structure solution using Fourier recycling techniques, a clear description is missing of how to proceed from one cycle to another. Whether it is best to accept many new peaks between cycles or to accept just a few new peaks and make sure that the procedure does not diverge is not discussed in detail. Here, we present the relevant aspects of our strategies.

**4.3.1. Recycling in AUTOFOUR.** Between cycles, *AUTOFOUR* checks the current model by calculating  $R_2$  and comparing the value obtained to its estimate. This is performed at each cycle, after the model has been updated. No more than half the number of the atoms already present in the model is added in each cycle.

The atoms, old as well as new, are sorted on their individual contributions to  $R_2$  (§3.1). If  $R_2$  is still above 40%, the first step in each cycle is to remove geometrically suspect atoms. From the atoms generating a conflict, the one with the highest contribution to  $R_2$  is removed. The threshold of 40% takes care of problems that might otherwise arise with structures containing elements of unusual geometry. The resulting pruned model is checked against  $R_{2,est.}$ . If the value of  $R_2$  is deemed to be too high, all atoms with a positive contribution to  $R_2$  are removed from the model. This careful strategy is based on Lenstra's observation that  $R_2$  is most effective as a criterion in atomic models containing not too many wrongly placed atoms. In fact, if the ratio between correctly and wrongly placed atoms approaches one, the effectiveness of  $R_2$  approaches zero.

**4.3.2. Recycling in DIRDIF.** Although the recycling strategies for *AUTOFOUR* and *DIRDIF* differ in many details, the basic strategy is the same. In crystal space: get peaks from a Fourier synthesis; assign atoms; remove atoms on the basis of geometrical conflicts. Next, continue in reciprocal space: use the  $R_2$  criterion to remove spurious atoms. If the model is small, *DIRDIF* applies phase refinement (subprogram *PHASEX*). The cycle concludes by calculating the next Fourier map.

Currently, the  $R_2$  function is used in combination with chemical geometry considerations, which is a powerful improvement. During the expansion process, the number of atoms converges to the number of atoms of the complete structure. However, the complete structure is obtained only in cases where all atoms are well defined: disordered structures and structures with strongly vibrating side chains cannot be completed fully by testing the  $R_2$  contribution of a single atom with a very weak scattering power.

At each cycle, the atomic contributions to  $R_2$  are calculated and atoms are removed as required (§3.1). Since *DIRDIF* assumes that the starting model contains few wrong atoms, the number of wrong atoms in consecutive cycles is not expected to be very large. Moreover, the first few cycles include the direct-methods phase-refinement step, which also removes wrong atoms from the model. Therefore *DIRDIF* allows the model to increase in size much more quickly than *AUTOFOUR*.

Peaks obtained from a Fourier map are sorted on integrated peak values. Assignments of atomic types are based on:

- (i) the expected (*i.e.* user-supplied) contents of the unit cell;
- (ii) the *a priori* expected (calculated) peak value;
- (iii) the effect on  $R_2$  of a change of the assignment.

Parallel with the determination of the atomic type, geometrical (*i.e.* chemical) criteria are used to reject peaks; for instance, satellite peaks around heavy atoms and peaks that are involved in unusual geometry. A 'figure of badness' is used to eliminate the worst peaks in a cyclic process. A new cycle is

**Table 2**  
Test structures.

Compound code name	$N_{at.}$	$N_{h.at.}$	Molecular formula†	Space group
ACNORT‡	31	–	$C_{23}H_{23}NO_7$	$P4_12_12$
JOOST	101	–	$C_{80}H_{60}N_{10}O_6 \cdot C_4H_{10}O$	$P2_1/n$
KAP3	154	7 Au, 1 W	$Au_7W(CO)_3(PC_{18}H_{15})_7 \cdot PF_6$	$P2_1/n$
MONOS	20	1 S	$C_{15}H_{16}N_2O_2S$	$P2_12_12_1$
NGUY	8	4 Se	$KCr_3Se_8$ ( $Z = 2$ )	$B2/m$
PBAG‡	6	Pb, Sb, Ag	$SbPbAgS_3$	$P2_1/a$

† Defined per asymmetric unit (except for NGUY). ‡ Used with calculated  $|F_o|$ .

**Table 3**  
The effect of substituting  $p^2$  for  $p_s^2$  for MONOS.

The model consists of one S atom.  $p^2 = 0.253$ . Relevant equation numbers are shown in square brackets.

	$R_2^E$ [(2)]	$R_{2,est.}^{(E)}$ [(3)]	$R_2$ [(5)]	$R_{2,est.}$ [(6)]	$1 - p^2$
S atom correctly placed	0.672	0.600	0.767	0.763	0.747
S atom misplaced by 0.3 Å	0.741	0.600	0.810	0.763	0.747

started by calculating the individual atomic contributions to  $R_2$  again *etc.*

## 5. Results

### 5.1. Test structures

Table 2 gives crystallographic data and other relevant items for all test structures referred to in the present paper. Here follow, in alphabetical order of their compound code names, short descriptions of some characteristics of the test structures, including literature references.

ACNORT (Zabel *et al.*, 1997) is used for checking the performance of the vector search: part of the molecule is 'almost' planar.

JOOST (Reek *et al.*, 1997) is one of a series of supra-molecular complexes that have a basket-type moiety in common. The basket varies slightly in different compounds.

KAP3 (Kappen *et al.*, 1992) is a 'gold'-cluster compound: the cluster consists of seven Au atoms. In the center lies one W atom. The outer (stabilizing) shell consists of seven triphenylphosphine ligands.

MONOS (Noordik *et al.*, 1978) is a problem structure of the past: the position of the symmetry-independent S atom is close to  $x = 0.0$ , which implies a pseudocentrosymmetric sulfur structure.

NGUY (Dung *et al.*, 1987) is a superstructure with a pseudotranslation vector at  $a/3$ . When we solved the structure, the composition was unknown.

PBAG (Ito & Nowacki, 1974) is a superstructure with a substructure of the PbS-type.

### 5.2. Examples

**5.2.1. MONOS.** Table 3 illustrates the effect of using expressions (5) and (6) instead of (2) and (3) for the calcu-

**Table 4**

8 out of 15 possible solutions for the heavy-atom positions in KAP3 found by *PATTY*.

Set number 2 gives the highest CFOM.

Set	<i>PATTY</i> figure of merit	Atoms found by <i>PATTY</i>	$p^2$	$R_{2,est.}$	$R_2$	Standard deviation of atoms from correct positions (Å)	Maximum deviation of atoms from correct positions (Å)	$Q_2$
1	1000	8	0.864	0.197	0.407	0.24	0.45	0.343
2	982	8	0.864	0.197	0.304	0.19	0.35	0.462
3	903	7	0.765	0.305	0.339	0.15	0.29	0.467
4	886	7	0.765	0.305	0.328	0.17	0.35	0.491
5	881	7	0.765	0.305	0.478	0.25	0.45	0.295
8	761	7	0.765	0.305	0.506	0.26	0.45	0.258
11	696	6	0.656	0.424	0.433	0.16	0.29	0.412
15	652	6	0.656	0.424	0.432	0.18	0.35	0.414

**Table 5**

Atoms removed by the  $R_2$  test after the first Fourier synthesis of KAP3.

Atoms are listed in order of removal.

Atom sequence number	Atom	$\Delta_{rel.}^i$	Atom sequence number	Atom	$\Delta_{rel.}^i$	Atom sequence number	Atom	$\Delta_{rel.}^i$
57	C64	4.18	45	C50	1.86	53	C59	1.11
30	C30	3.37	41	C44	1.76	55	C62	1.09
33	C33	2.61	31	C31	1.65	48	C54	1.07
19	F19	2.34	34	C35	1.64	32	C32	1.01
35	C36	2.32	47	C52	1.40	56	C63	0.95
40	C43	2.27	17	P17	1.40	26	O26	0.95
36	C37	2.20	28	C28	1.19	10	P10	0.89
23	F23	2.06	22	F22	1.18			

**Table 6**

Test compound PBAG.

Heavy-atom Patterson interpretation with, for all resulting sets, assignments of atoms in the set, distance to literature positions (shown in parentheses after each atom),  $R_2$  values and results (success or failure). Set number 2 gives the highest CFOM.

Set	FOM	Atoms	$p^2$	$R_{2,est.}$	$R_2$	$Q_2$	Result
1	1000	Pb (0.16 Å), Ag (0.11 Å), Sb (0.30 Å)	0.931	0.114	0.390	0.328	Failure
2	942	Pb (0.16 Å), Sb (0.24 Å)	0.739	0.289	0.271	0.574	Success
3	768	Pb (0.16 Å), Sb (0.11 Å), Ag (0.49 Å)	0.931	0.114	0.364	0.356	Success
4	617	Pb (0.16 Å), Sb (0.11 Å)	0.739	0.289	0.281	0.560	Success

lation of  $R_2$  and its estimated value. The two models of MONOS tested consist of one with the S atom placed at its correct position and one with it misplaced by 0.3 Å. Clearly, the use of expressions (5) and (6) leads to values of  $R_{2,est.}$  that are much closer to the values of  $R_2$  in practice.

**5.2.2. KAP3.** For KAP3, a large number of plausible starting models were obtained by the heavy-atom Patterson interpretation program *PATTY*. The list of results is given in Table 4. The large number of partly overlapping Au–Au and W–Au vectors in the KAP3 Patterson gives rise to many combinations of possible Au and W positions, and thus to many different starting models. In this case, all possible solutions are basically correct and all will undoubtedly solve the structure; nevertheless, the table illustrates the power of the  $R_2$  criterion. Clearly, the solution with the highest FOM is not the most accurate set of atoms. The second, eight-atom solution, is the best one. In our experience, the positions of the atoms are sometimes more accurate if sets containing fewer atoms are considered. Of the seven-atom solutions, numbers 3 and 4 have  $R_2$  values that are much

closer to the expected value. The atomic positions are slightly more accurate. However, we tend to use the solutions with the largest number of heavy atoms: in this type of structure, the phasing power of additional heavy atoms appears to be more important than the accuracy of the positions of the atoms.

The  $R_2$  criterion is very useful when many light atoms are present in a very-heavy-atom structure, as in the case of KAP3 (150 light atoms, constituting only 14% of the total scattering power). From the first Fourier synthesis based on eight heavy atoms, 58 possible atomic positions were selected. These were subjected to the  $R_2$  test. The average value of  $\Delta_{rel.}^i$  and its standard deviation s.d. $\Delta_{rel.}^i$  are 0.649 and 1.105, respectively. These are rather large values. Using the rejection criterion  $\Delta_{rel.}^i > 0.80$ , 23 atoms were removed from the set (Table 5). All the atoms that were removed were indeed incorrect, except the last one, a correctly placed P atom. This is not just bad luck: in our experience, the  $R_2$  test is not completely reliable for heavy-atom structures in cases where the set shows a large value of s.d. $\Delta_{rel.}^i$ .

**Table 7**

ACNORT: positioning of a model by vector search.

The Patterson FOM and  $R_2$  are given for each shift vector or set of atomic positions. Input model: phenanthrene; 14 atoms;  $p^2 = 0.373$ .

Shift set	FOM	Applied $R_2$	$Q_2$	Problem before expansion	Structure after expansion
1	155	0.754	0.330	Collision	–
2	149	0.762	0.308	Collision	–
3	148	0.780	0.260	Collision	–
4	142	0.770	0.287	Collision	–
5	140	0.723	0.413	–	Solved
6	134	0.730	0.394	–	Failure
7	133	0.744	0.356	Collision	–
8	129	0.746	0.351	–	Failure

**Table 8**

ACNORT: values of  $\Delta_{rel}^j$ , its average ( $\langle \Delta_{rel}^j \rangle$ ) and its standard deviation (s.d.  $\Delta_{rel}^j$ ) for two atoms under different conditions.

	$N_{at.}$	$R_{2,est.}$	$R_2$	$\langle \Delta_{rel}^j \rangle$	s.d. $\Delta_{rel}^j$	C(3) $\Delta_{rel}^j$	C(8) $\Delta_{rel}^j$
1994							
Input model	14	0.661	0.738	–0.837	0.264	–0.483	–0.343
1999							
Input model	14	0.660	0.737	–0.423	0.208	–0.429	–0.107
Next cycle	30	0.103	0.265	–0.583	0.509	0.716	0.570

**5.2.3. PBAG.** This is a super-structure leading to rather different results (Table 6). In all models, the heaviest atom (Pb) is correct, but the positions of other atoms vary. The result with the highest FOM fails to solve the structure. The second solution has the lowest  $R_2$  and solves the structure, although during the extension procedure the Sb and Ag positions are interchanged several times.

**5.2.4. ACNORT.** The test compound ACNORT was used in a realistic situation where problems are to be expected: the planar input model (phenanthrene) used gives rise to large weights of the interatomic vectors (due to overlap of parallel vectors that are not present in the actual molecule of the structure). The top four results (Table 7) of *TRACOR* lead to heavy overlap of symmetry-dependent molecules; they are incorrect. The correct shift is number 5 in the list; the corresponding  $R_2$  value is the lowest of all.

The expansion procedure in *DIRDIF* is started with a poor model. Two atoms in the model, C(3) and C(8), do not correspond to any atomic position in the structure. The average error in the positions of the remaining 12 atoms is 0.25 Å. In the first cycle, no atoms are deleted from the list. However, after phase-refinement by the *PHASEX* program, in the next cycle an improved, larger set of atoms is found. Now a test clearly indicates that C(3) and C(8) should be removed. That C(3) and C(8) are not recognized immediately as incorrect is related to the planar geometry of the input model: the two atoms fit in the chicken-mesh pattern of the planar part of the molecule, therefore corresponding to relatively strong Patterson vectors. Later, with 16 more atoms found, the overall planarity of the model is less pronounced.

Some values relating to the process of elimination of C(3) and C(8) are given in Table 8. ‘1994’ and ‘1999’ refer to

**Table 9**

ACNORT: analysis of atoms in phase refinement and Fourier recycling via  $R_2$ .

The histories of individual peaks or atoms are shown in consecutive columns from left to right. The first column contains the input model, with distances larger than 0.20 Å from the true positions. ‘>’ indicates that there is no matching atom in the structure. The third column shows the rejection of four atoms using the  $R_2$  criterion. ‘Geo-rej.’ indicates rejection by geometrical test. ‘\*’ indicates an incorrectly assigned atomic type.

Input model	Output Fourier	Application of $R_2$ criterion	Output Fourier	Final output after several more cycles	
C1 0.52	C1 0.49	Reject	C27	C23	
C2 0.41	C2 0.21		C2	C2	
C3 >	C3 >	Reject			
C4	C4		C4	C4 * O	
C5	C5		C5	C5	
C6	C6		C6	C6	
C7	C7		C7	C7	
C8 >	C8 >	Reject			
C9 0.24	C9		C9	C9 * N	
C10 0.24	C10		C10 (Geo-rej.)	C20	
C11 0.24	C11		C11	C11	
C12	C12		C12	C12	
C13	C13		C13	C13	
C14	C14		C14	C14	
–	O15	Reject	C31	C24	
–	O16		O13	O15	
–	O17		N19	O17	
–	O18		O12	C11	
–	O19		C21	C28	
–	O20		O18	C26	
–	O21		O14	C18 * N	
–	N22		O15	O13	
–	C23		C20	C16 * O	
–	C25		C24	C29	
–	C26		O17	O14	
–	C27		C23	C25	
–	C29		C22	C22	
–	C30		O16	O12	
–	C31		C25	C27	
–	C32		C26	C30	
–	–		C28	C21	
–	–		C29	C19	
–	–		C27	C23	
–	–		C30	C31	
$N_{at.}$	14	30	26	30	31
$R_2$	0.737	0.265	0.235	0.071	0.025

**Table 10**

Progression of the expansion process by *AUTOFOUR*.

Cycle	Atoms in the model	$R_2$	$R_{2,est.}$	Removed
0	13	0.804	0.710	9
1	4	0.858	0.871	–
4	18	0.559	0.544	4
8	31	0.181	0.178	–
12	31	0.078	0.178	–

different versions of the program *DIRDIF*: slight modifications of the scaling procedures (Israël *et al.*, 1995) and the vector-search procedures (Israël *et al.*, 1996) lead to significant differences in the data; however, the general trend is the same. Table 9 illustrates the progress during the automatic expansion procedure in *DIRDIF*.

The structure ACNORT was used also as a test for *CRUNCH* solving the structure *ab initio*. Table 10 shows a

sequence similar to the one in Table 9. The model obtained using phases found by *DETER* is completed by *AUTOFOUR*. Again, the starting model is not very good. The process of extension is started with four atoms. After four cycles, when 18 atoms have been found, four atoms with the highest contribution to  $R_2$  are removed from the model. After this clean-up operation, extension to the full structure proceeds smoothly. The final four cycles are just improving the coordinates. It is interesting to note that, from the four atomic positions selected from the input model, three are correct. The fourth one is removed after cycle four. During the expansion, *AUTOFOUR* treats all atoms as C atoms, which explains the high residual value of  $R_{2,est.}$  in the final cycles.

Note that in both *DIRDIF* and *AUTOFOUR* the final  $R_2$  value obtained is artificially low because calculated data were used.

**5.2.5. JOOST.** In the case of a supramolecular structure, a large search model is often available. However, usually the precise geometry is uncertain. We used a 42-atom model (the BASKET of the *DIRDIF* fragment library) positioned by *ORIENT* and *TRACOR*. The best solution obtained for JOOST included many inaccurately positioned atoms. Inaccuracies in the input model may give rise to several partially correct orientations and positions of the model. If using a large model fails to solve the structure, a possible strategy is to remove parts of the model before trying the search again.

As an example of a fairly routine *DIRDIF* structure extension, we show in Table 11 a few typical numbers for the first two cycles of the process of extension for JOOST. However, the basket is slightly flexible and the starting model for the expansion of the structure is not particularly good. Table 11 gives all 42 atoms in the model, with, in the second column, the distances of the atoms from the correct positions. Four atoms are too far away from any true atomic position.

Immediately, nine atoms are rejected by the  $R_2$  test: mostly – but not all – poorly positioned atoms. After the first phase refinement and Fourier synthesis (based upon 33 atoms), all atoms in the basket were present in the list of Fourier peaks, at very much improved positions. Many more atoms were found, of course, but we limit our discussion to the 42 atoms put in. The geometrical test removed four correct atoms ('Geo-rej.'). Neighboring atoms are geometrically consistent; however, in an absolute sense they are not very well positioned, resulting in some good atoms having a high 'figure of badness'. Two atoms ('Pk-low') are rejected because the corresponding peaks in the map are too low. In the next cycle,  $R_2$  removes all badly positioned atoms, as well as some good ones. In subsequent cycles, the atomic positions of all atoms as well as the designations of some atoms are improved. The final result is the complete structure. An unexpectedly present solvent molecule (with larger temperature factors) was easily recognized by the peak-integration procedure.

**5.2.6. NGUY.** This is an example where uncertainty with respect to the composition of the structure played an important role in the structure determination (Table 12). NGUY is a superstructure, causing Patterson overlap and scaling problems; the composition has been established during the

**Table 11**

The history of the first two cycles of the input model of JOOST.

The input model had 42 atoms. '>' indicates that there is no matching atom in the structure. The last column gives the result: wrong type of atom or reason for rejection. 'Geo-rej.' indicates rejection by geometrical test. 'Pk-low' indicates rejection because the corresponding peaks in the map are too low.

Input atoms	Distance to correct position (Å)	Test $\Delta_{rel}^j$	Output distance to correct position (Å)	Result $\Delta_{rel}^j$
C1	0.11		0.08	
C2	0.23		0.08	
C3	0.44		0.36	–0.30
C4	>		0.07	Geo-rej.
C5	0.39		0.19	
C6	0.13		0.05	
O1	0.16		0.03	
O2	0.54	–0.10	0.06	N
C7	0.08		0.05	
C8	0.09		0.06	
N1	0.12	–0.07	0.04	C
C9	0.11	0.26	0.04	Geo-rej.
N2	0.16	0.03	0.09	
C10	0.12		0.09	
O4	0.12		0.05	
N3	0.07		0.05	
C11	0.06		0.05	
N4	0.06		0.02	
C12	0.11		0.08	
O3	0.08		0.06	
C15	0.27	0.32	0.04	
C16	0.57		0.41	–0.20
C17	>		0.06	Geo-rej.
C18	>		0.03	Geo-rej.
C19	0.35		0.25	
C20	0.24		0.16	
O5	>	0.02	0.11	
O6	0.39		0.19	
C13	0.10	0.07	0.08	Pk-low
C14	0.16	–0.08	0.05	Pk-low
C21	0.08		0.06	
C22	0.14		0.08	
C23	0.26		0.15	
C24	0.38	–0.04	0.06	
C25	0.34		0.17	
C26	0.20		0.05	
C27	0.12		0.04	
C28	0.16		0.07	
C29	0.42		0.40	–0.08
C30	0.21		0.16	0.03
C31	0.23		0.08	–0.13
C32	0.24		0.05	–0.29
$R_2$	0.778	0.785	0.315	

structure analysis by the study of peak heights during various trial runs of phase extension.

Potassium was found at a disordered position near a mirror plane. In this report, K is taken as a 'normal' atom with a somewhat higher temperature factor. Table 12 illustrates the situation where the correct composition is used in the control data file. The input atoms are obtained by automatic heavy-atom interpretation;  $R_2 = 0.32$ . Probably owing to correlation between the Patterson and  $R_2$ , the results given in Table 12 lack clarity. After several cycles, when the structure is almost solved, *DIRDIF* puts too many atoms in the model, whereupon  $R_2$  explodes.

*DIRDIF*, which handles the assignment of atomic types, allows for uncertainties in the composition. If some atoms



**Table 12**

NGUY: analysis of the atoms during recycling, showing  $R_2$  and choice of atom for all Fourier peaks.

Atoms rejected because of the  $R_2$  criterion are indicated. An  $R_2$  of 9.99+ signals an unstable refinement (see §5.2.6).

	Input atoms	Output atoms	Output atoms	Output atoms	Output atoms	Output atoms after several more cycles	Final output atoms	Correct atomic types	Multiplicity factor	
	Se	Se	Se	Se	Se	Se	Se	Se	0.5	
	Se	Se	Se	Se	Se	Se	Se	Se	0.5	
	Se	Se	Se	Se	Se	Se	Se	Se	0.5	
	–	Cr†	Se	Rejected	Se	Se	Se	Se	0.5	
	Se	Se	Rejected	Cr	Rejected	Se	Rejected	Se†	Cr†	0.25
	–	–	Cr	Cr	Cr	Cr	Cr	Cr	0.5	
	–	Cr†	Cr†	Cr†	Se†	Se†	Cr	Cr	0.5	
	Se†	Se†	Rejected	K†	Rejected	Se†	Rejected	Se†	K	0.25
	–	–	–	–	–	K	Se	–	–	
	–	–	–	–	–	–	K	–	–	
$R_2$	0.32	0.24	0.16	0.18	0.22	0.98	0.31	9.99+	0.09	
$N_{\text{at.}}$	5	7	5	8	5	9	7	10	8	

† Position at a distance of 0.2–0.3 Å.

have lower or higher peak integrals than is in accordance with user-supplied cell contents, the program may modify the cell contents for use in subsequent cycles. This is a useful feature indeed; however, increasing the number of atoms and simultaneously increasing the scale factor sometimes causes an ‘explosion’ of the unit-cell contents. When this happens, the program stops recycling and returns to the set of atoms corresponding to the lowest  $R_2$  so far. Using an overall  $B$  value, a new map is calculated. The peaks are interpreted based on the original contents of the unit cell. Here, this automatic procedure reveals the complete structure.

**5.2.7. A final example.** We have chosen to illustrate several exceptional situations, *e.g.* poor input models for vector searches, very-heavy-atom structures, pseudosymmetry and superstructures. To stress the rule rather than the exception, we present one final example, Solanoeclepin A (Schenk *et al.*, 1999), where a notoriously difficult structure has been solved effortlessly by the routine application of *CRUNCH*.

All attempts to solve this structure by, at the time, conventional direct-methods packages failed. This is partly due to the fact that there was no advance knowledge of the nature of the compound and its exact composition. Using an estimated number of non-H atoms in the cell of 160 (space group  $P2_1$ ), *CRUNCH* was used with default parameters. 20 trial starting sets were needed to obtain a molecular fragment of 33 peaks from which the *AUTOFOUR* program was able to complete the structure. The structure proved to contain 78 atoms in the asymmetric unit.

Examination of the fragment of 33 putative atoms showed that this fragment contained only five atoms at completely correct positions. This is another clear illustration of the importance and the effectiveness of  $R_2$  as a selection criterion.

## 6. Conclusions

In this paper, various strategies have been described aimed at the automatic extension of (small) partial models to the complete structure. The implementation of these strategies in both of the programs *DIRDIF* and *AUTOFOUR* is discussed.

In §5.2, three structures are discussed for which the solution with the highest Patterson FOM is incorrect or is not the best one available. In all three cases, the  $R_2$  value of the correct solution is the lowest and  $Q_2$  is maximal. Reducing the value of  $x$  in the expression for  $Q_2$ , (8), ultimately forces the lowest  $R_2$  to be selected by the CFOM. Note that this is not the best policy: the Patterson FOMs must not be ignored. A sensible value of  $x$  should be used (§4.1), striking a balance between the Patterson FOM and  $R_2$  in the resulting CFOM.

In the case of the model with the highest CFOM being incorrect, the model with the next highest CFOM should be tried. Programs should be coded to try automatically, until a satisfactory solution is found, all acceptable solutions coming from Patterson interpretation programs with CFOMs down to about 70% of the highest CFOM present.

Other examples presented in §5.2 illustrate the effectiveness of  $R_2$  for cleaning up the model, both before the start of the process of extension and during it. Currently, we are investigating the automatic generation of multiple molecular conformations followed by a vector search, selecting the most promising models for further expansion to the structure. This will allow automatic structure solution based upon Patterson techniques for larger, flexible molecules.

Many technical details have been discussed in a global fashion only. The reader who is interested in technicalities such as the exact optimal values of various parameters and cut-offs *etc.* is referred to the source code that has been made available on public-domain Internet sites by de Graaff (1997) and Beurskens (2000).

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