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A New Approach to Structure Determination of Large Molecules by Multi-dimensional Search Methods

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Abstract

A new multi-dimensional search approach, incorporating packing criteria with *R*-factor calculations for low-resolution X-ray data, proved to be extremely efficient for the solution of large molecular structures. A computer program, *ULTIMA*, based on this approach solved *ab initio* the structure of a double-helical DNA octamer and also reproduced the correct solutions of a double-helical DNA dodecamer and of a tRNA molecule (322, 486 and 1652 non-hydrogen atoms, respectively). The efficiency of the procedure is enhanced by using group scatterers in lieu of individual atoms. The method allows, for more complex structures, the separation of parameters in the multi-dimensional space, either by using one-dimensional reflection data or by approximating the entire molecule to a 'super-atom' scatterer.

Introduction

We have shown (Rabinovich & Schmidt, 1966) that small molecular structures can directly and effi-

ciently be solved by a systematic search procedure (*SEARCH*) using geometrical criteria such as global molecular packing considerations and hard-sphere atom-atom contacts. The method owes its efficiency to a set of multi-level sieving operations, by means of which only a limited number of accepted trial structures are left for further examination by structure-factor calculations.

This procedure proved, however, to be inefficient for large molecular structures since it was time consuming as a result of the large number of atoms. It also yielded too many accepted trial structures because of the rather small number of intermolecular atom-atom contacts resulting from the fact that a large fraction of the unit-cell volume consists of solvent molecules. We have, therefore, developed a new multi-dimensional search approach, incorporating global packing criteria with structure-factor calculations for very-low-resolution X-ray data, which proved to be extremely efficient for the solution of large molecules. A computer program, *ULTIMA*, based on this approach, solved *ab initio* the structure

of the DNA double-helical octamer $d(\text{GGTATACC})_2$ (Shakked *et al.*, 1981) and also reproduced the correct solutions of the DNA double-helical dodecamer $d(\text{CGCGAATTCGCG})_2$ (Wing *et al.*, 1980) and of tRNA^{Phe} (Kim *et al.*, 1973; Robertus *et al.*, 1974).

Methods

Generation of trial structures

The first stage in our method is the systematic generation of trial structures. This is achieved by defining the model of the generating unit (which, as, for example, in cases where the models occupy special positions, need not be identical with the asymmetric unit of the unit cell) by specifying its atomic coordinates, m_i ($i = 1, 2, 3$), in an orthogonal system defined by the three principal axes of inertia, \mathbf{M}_i , of the model. The inertial system allows the definition of the global dimensions of the generating unit, *i.e.* we approximate it to an ellipsoid where the lengths of the major, mean and minor axes, m_1^0 , m_2^0 , and m_3^0 are the maximum extensions of the model along the three principal axes of inertia.

A trial structure may now be generated by specifying (a) the orientation of the \mathbf{M}_i system with respect to the unit-cell axes; (b) the position of the origin of \mathbf{M}_i in the unit cell; and (c) the operation of the space-group symmetry elements on the generating unit.

It is convenient to define the orientation of \mathbf{M}_i in the unit cell by using the three Eulerian angles (φ, ψ, θ) specifying the rotation of \mathbf{M}_i with respect to an orthogonal system, \mathbf{L}_i , embedded in the unit cell. \mathbf{L}_i is defined by the matrix T .

$$\mathbf{L}_i = \sum_j T_{ij} \mathbf{a}_j \quad (\mathbf{a}_1 = \mathbf{a}, \mathbf{a}_2 = \mathbf{b}, \mathbf{a}_3 = \mathbf{c}). \quad (1)$$

We can now express the fractional coordinates, r , of the atoms in the generating unit, when its origin coincides with that of the unit cell by the following transformation:

$$r = mRT, \quad (2)$$

where R , the Eulerian angle matrix (Goldstein, 1959), is

$$R = \begin{bmatrix} \cos \varphi \cos \psi & \sin \varphi \cos \psi & \sin \psi \sin \theta \\ -\sin \varphi \sin \psi \cos \theta & +\cos \varphi \sin \psi \cos \theta & \\ -\cos \varphi \sin \psi & -\sin \varphi \sin \psi & \cos \psi \sin \theta \\ -\sin \varphi \cos \psi \cos \theta & +\cos \varphi \cos \psi \cos \theta & \\ \sin \varphi \sin \theta & -\cos \varphi \sin \theta & \cos \theta \end{bmatrix}. \quad (3)$$

The relative orientation of \mathbf{M}_i and \mathbf{L}_i and the definition of the Eulerian angles φ, ψ, θ are shown in Fig. 1.

The position of the origin of \mathbf{M}_i in the unit cell is defined by a vector \mathbf{u} ($u_1 = u, u_2 = v, u_3 = w$). For given

unit cell and space group and given generating unit, any possible trial structure may be defined by specifying the six parameters $\varphi, \psi, \theta, u, v, w$. A systematic generation of a set of trial structures is accomplished by constructing a six-dimensional grid in this parameter space.

The asymmetric volume of the space that needs to be searched is defined by the Cheshire group and the symmetry of the generating unit (Hirshfeld, 1968).

Elimination of grid points by packing considerations

The number of trial structures thus generated is large even for a coarse grid. A considerable fraction of this number can be eliminated by global-packing considerations. The elimination process is performed separately for the rotational and translational grids. In the former, for any orientation $R(\varphi, \psi, \theta)$ the ellipsoid-to-ellipsoid contacts (Fig. 2) are computed between the generating unit and its translation-related neighbours up to a preset radial distance. These contacts, which depend solely on the orientation of the generating unit and not on the position of its origin \mathbf{u} , are evaluated by the quadratic form

$$Q = \tilde{\mathbf{I}} \tilde{\mathbf{R}} \mathbf{A} \mathbf{R} \mathbf{I}, \quad (4)$$

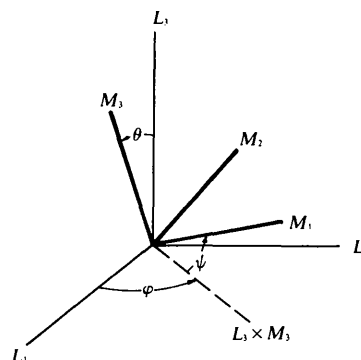


Fig. 1. Relative orientation of \mathbf{M}_i and \mathbf{L}_i and the definition of the Eulerian angles φ, ψ, θ .

Angle	from	to	range (°)
φ	\mathbf{L}_1	$\mathbf{L}_3 \times \mathbf{M}_3$	0–360
ψ	$\mathbf{L}_3 \times \mathbf{M}_3$	\mathbf{M}_1	0–360
θ	\mathbf{L}_3	\mathbf{M}_3	0–180

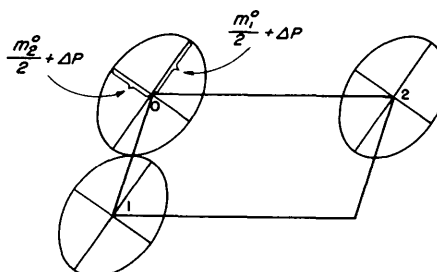


Fig. 2. Ellipsoid-to-ellipsoid contacts. $Q = 4$ and $Q > 4$ for ellipsoids 1 and 2, respectively. The generating unit ellipsoid is at 0.

where \mathbf{l} is the vector from the origin of the generating unit to one of its translation-related neighbours, R is the corresponding Eulerian-angle matrix for that rotational grid point and Λ is a diagonal matrix related to the canonical representation of the ellipsoid of the generating unit:

$$\Lambda_{ii} = (m_i^0/2 + \Delta p)^{-2}. \quad (5)$$

For contacting ellipsoids $Q = 4$, so that a rotational grid point is eliminated when $Q \leq 4$ for any lattice vector \mathbf{l} . If we wish, however, to allow some interpenetration of the ellipsoids a scalar $P < 4$ is chosen such that the elimination criterion is $Q < P$. The test is performed for all

$$|\mathbf{l}| \leq m_1^0 + 2\Delta p.$$

Analogously, a large fraction of the translational grid points can be rejected by virtue of their proximity to the several elements of symmetry of the unit cell which may lead to 'bumping' (see, e.g., Fig. 3). A grid point \mathbf{u} is rejected when the following condition (6) is fulfilled for any one of the \mathbf{u}_s , symmetry-related points

$$|\mathbf{u} - \mathbf{u}_s| \leq m_3^0 + 2\Delta b, \quad (6)$$

where Δb , like Δp , allows for more flexibility in the presetting of the bumping distance.

Each of these two tests is very fast as it is performed, independently of the other, in its own subspace and depends solely on the global molecular parameters and not on the detailed structure of the generating unit. This strategy usually results in a considerable decrease in the number of trial structures that need to be further examined.

Sifting trial structures by structure-factor calculations

The remaining trial structures are subjected to structure-factor calculations serving as an ultimate criterion for acceptability. The use of the transforms of the atoms of the generating unit, $G_s^r(\mathbf{H})$, and the fringe functions of the translations of its origin $G_s^u(\mathbf{H})$ allows extremely fast calculations (Lipson & Cochran, 1957; Rae, 1977). The structure factor $F_c(\mathbf{H})$ is

given by

$$F_c(\mathbf{H}) = \sum_s G_s^u(\mathbf{H}) \cdot G_s^r(\mathbf{H}) \quad (7)$$

$$G_s^u(\mathbf{H}) = \exp(2\pi i \mathbf{H} \cdot \mathbf{u}_s) \quad (8)$$

$$G_s^r(\mathbf{H}) = \sum_j f_j \exp(2\pi i \mathbf{H}_s \cdot \mathbf{r}_j), \quad (9)$$

where the first summation is over all the s symmetry operations, \mathbf{r}_j are the atomic radius vectors, evaluated by (2), and f_j are the atomic scattering factors. Expression (9), which involves summation over all atoms in the asymmetric unit, is computed only once for each accepted orientation. The set of $G_s^u(\mathbf{H})$ is computed only once for each accepted translation.

A great improvement in the performance of the method is achieved by using group scatterers g_j instead of the individual atomic scatterers f_j . For example, in nucleic-acid structures each of the three basic components, the phosphate, sugar or base, is treated as a single scatterer positioned at the center of mass with a spherically averaged group scattering factor, given by

$$g_i^2 = \sum_p f_p^2 + 2 \sum_{p>q} f_p f_q \sin(\mu R_{pq}) / \mu R_{pq}, \quad (10)$$

where $\mu = 4\pi \sin \theta / \lambda$. The first summation extends over all atoms in the group and the second over every pair of different atoms in the group, R_{pq} being the distance between atoms p and q with scattering factors f_p, f_q (Zernicke & Prins, 1927; Debye & Mencke, 1931).

Several criteria for testing the agreement between the observed and calculated structure factors were considered, e.g. product functions, correlation functions and the discrepancy R . The R factor, which is more indicative for further refinement, was also found to be more discriminative. Accordingly, the final sifting was performed by selecting the set of trial structures (typically 20) with the lowest R and then subjecting them further to a rigid-body least-squares-refinement procedure to yield the correct structure.

Results and discussion

The *ULTIMA* program was first applied during our attempts to solve the structure of the octamer $d(\text{GGTATACC})_2$. This structure (I) appeared to be an ideal candidate for search methods, since, firstly, reliable models for the various types of DNA structures are available from X-ray diffraction analysis of DNA fibers (Arnott & Hukins, 1972) and, secondly, as the space group is polar, the parameter space to be searched is only five-dimensional and thus reasonable computing time might be anticipated.

Two possible models were considered, the A and B forms of DNA. An attempt to obtain the orientation of the models by means of the rotation functions (Argos & Rossmann, 1980) failed as no unambiguous

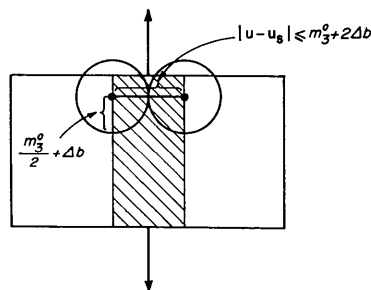


Fig. 3. Rejection of translational grid points by twofold rotation axes. All points within the hatched volume are rejected.

Table 1. Results of computer experiments

	$d(\text{GGTATACC})_2$ (I)	$d(\text{CGCGAATTCGCG})_2$ (II)	tRNA ^{Phe} (III)
a, b, c (Å)	45 45 42	25 40 66	33 56 161
m_1^0, m_2^0, m_3^0 (Å)	30 21 18	39 19 19	85 63 29
$P, \Delta p$ (Å), Δb (Å)	4 0 1.5	3.5 1.5 1.5	2 -1 0
Space group	$P6_1$	$P2_12_12_1$	$P2_12_1$
Cheshire group	$Z'622$	$Pm m m$	$Pm m m$
Molecular symmetry	2	2	1
Number of atoms	322	486	1652
Number of groups	46	70	228
Asymmetric volume (°)	$60 \times 360 \times 90$	$180 \times 180 \times 90$	$180 \times 180 \times 180$
(Å)	$a \times b \times c$	$\frac{1}{2}a \times \frac{1}{2}b \times \frac{1}{2}c$	$\frac{1}{2}a \times \frac{1}{2}b \times \frac{1}{2}c$
Grid steps $\Delta\theta$ (°)	$30/\sin \theta, 30, 30$	$22.5/\sin \theta, 22.5, 22.5$	$15/\sin \theta, 15, 15$
ΔU (Å)	3 3 0	3 3 3	4 4 4
Number of calculated grid points	72×225	200×308	1092×560
Number of searched grid points	72×24	128×162	303×294
Resolution range (Å)	25-10	25-10	50-16.5
Number of reflections	28	49	47
R	42	42	40
R_b	23	28	20
Maximum parameter shifts	$12^\circ, 1.4 \text{ \AA}$	$6^\circ, 1.6 \text{ \AA}$	$10^\circ, 3 \text{ \AA}$
CPU time (s)	13	74	315

peaks were discernible. An attempt to solve the structure by the multi-dimensional *SEARCH* method (Rabinovich & Schmidt, 1966) was time consuming and ended in too many acceptable structures for further examination.

The structures of both (I) and its 5-bromouracil analog were eventually solved by the first-version *ULTIMA* program, using individual atomic scatterers (Shakked *et al.*, 1981).

In order to find the optimal working conditions and to study the several input variables for this method, two additional known structures were analyzed (Table 1). The DNA dodecimer (II) (Wing *et al.*, 1980) was chosen since it represents another large structure, but this time with six degrees of freedom, whereas the tRNA molecule (III) (Kim *et al.*, 1973; Robertus *et al.*, 1974) served as an example of a considerably larger structure with a less-regular shape.

Table 1 lists the constants and input variables, as well as the results of the computer experiments. Of utmost importance for an optimal use of the method is the resolution limit d_{lim} . A low resolution entails fewer reflections and coarser grid, and thus shorter runs as well as relative insensitivity to differences between the model and the real structure. On the other hand, too low a resolution would jeopardize the discriminative power of the method. The optimal value of d_{lim} may be obtained by considering the transform $G(s)$ of a distribution of a spherical shell of diffracting matter of uniform density unity and radius $R = m_3^0/2$.

$$G(s) = 4\pi R^2 (\sin 2\pi R s) / 2\pi R s, \quad (11)$$

where the reciprocal vector s is related to the resolution d by $d = s^{-1}$. The nodal spheres of zero value are at reciprocal radii $s = n/m_3^0$. If the limiting sphere of the radius s_{lim} includes the first two of the nodal spheres ($n=2$), enough information about $G(s)$ is

available to give a fairly accurate idea of the distribution (James, 1962). Accordingly, a fair estimate of d_{lim} is

$$d_{\text{lim}} \sim m_3^0/2. \quad (12)$$

A lower cut-off value can also be applied to eliminate the lowest-order reflections which are mostly affected by the solvent.

Again, the size of the grid steps must be chosen judiciously. Small intervals result in excessive computing time, while too large ones might miss the correct structure.

A rough estimate of the rotational grid step, $\Delta\theta$, is obtained by calculating the angle necessary to move the end of the s_{lim} vector by one reciprocal geometric mean diameter of the generating unit, $(m_1^0 m_2^0 m_3^0)^{-1/3}$, *i.e.*

$$\Delta\theta = d_{\text{lim}} (m_1^0 m_2^0 m_3^0)^{-1/3}. \quad (13)$$

An estimate of ΔU , the translational grid step (Å), is obtained by considering the fringe function $G_s^u(\mathbf{H})$ (8), and setting $\mathbf{H} \cdot \mathbf{u} = s_{\text{lim}} \Delta U = \frac{1}{4}$, thus allowing a quarter-cycle phase shift in the fringe function at the extremity of the resolution limit. This equality yields

$$\Delta U \sim m_3^0/8. \quad (14)$$

The three other variables, P , Δp and Δb , which are functions of the unit-cell dimensions and the generating unit axes, determine the number of rotational and translational grid points that are eliminated. Hence, P , which allows for ellipsoidal interpenetration, is irrelevant when the largest molecular axis $m_1^0 + 2\Delta P$ is smaller than the shortest lattice vector, as is the case in (I).

In (II), which is a rod-shaped molecule, the ellipsoidal approximation is quite realistic, as may be judged either by drawing the molecule and the ellipsoid or by calculating the volume packing ratio

$$V_r = [n\pi m_1^0 m_2^0 m_3^0 / 6V] = 0.45,$$

where V is the unit-cell volume containing n ellipsoids. Here we use $\Delta p = 1.5$ to account for the fact that the ellipsoid axis lengths were determined by the group-scatterer positions, rather than by the individual atoms, thus yielding a somewhat contracted model. P was set to 3.5 to allow for some interpenetration in order to minimize the risk of missing the correct solution.

In (III), an L -shaped molecule, the ellipsoidal approximation is poorer, resulting in too large a generating unit, $V = 1.09$. Here we use $\Delta p = -1$ (perhaps too pedantic, $\Delta p = 0$ would do as well) and $P = 2$, to allow for deep interpenetration.

An estimate of Δb can be derived by comparing m_3^0 and the shortest lattice translation. In (II) and (III), where the two differ by little, we set $m_3^0 + 2\Delta b$ somewhat smaller than the shortest translation; in (I) we use $\Delta b = 1.5$. The use of these variables has reduced the number of grid points to be searched by factors 9, 3 and 7 for (I), (II) and (III), respectively.

Table 1 also lists the Cheshire group (Hirshfeld, 1968), the molecular symmetry and the dimensions of the asymmetric multi-dimensional volume to be searched, and also shows the large economy achieved through the use of group scatterers. The validity of this approximation was tested independently by comparing structure factors calculated by this approximation, and by individual atom scatterers. It was found that the differences were negligible to a resolution of about 6 Å, well below the working range of our method.

The R factor of the correct structures, and the rigid-body refined values R_b are listed together with the maximum shifts in Θ and U accompanying the refinement procedure. It is noteworthy that more than one of the twenty lowest- R -factor structures refined to the correct one; the entries in Table 1 are those related to the maximum shifts.

The idealized models of (I) and (II) were taken from Arnott & Hukins (1972). For (III) the refined structure of the monoclinic form (Hingerty, Brown & Jack, 1978) was taken as the model. The r.m.s. deviations of the groups, for the best molecular fit between the model used in *ULTIMA* and the finally refined structures, are 1.0, 1.5 and 1.0 Å for (I), (II) and (III), respectively.

In view of the space group ($P6_1$ or $P6_3$) and the model (A or B form) ambiguities in (I), four combinations were tried with the same run variables, and while the values of the lowest R factors differ by no more than a few percent, only the correct combination (A- $P6_1$) refined to a significantly lower R_b value. The refinement of (I) and its 5-bromouracil analog was continued with a constrained-restrained least-squares program, *CORELS* (Sussman, Holbrook, Church & Kim, 1977), yielding R factors of 20 and 14% at a resolution of 1.8 and 2.25 Å, respectively (Shakked *et al.*, 1983).

The last entry in Table 1 gives the CPU time consumed on an IBM 370/165 computer using an extended H compiler. For (I) and (II) the times are almost ridiculously small, for (III) it is still comfortable. It is obvious, however, that in the case of considerably larger structures the multi-dimensional approach, notwithstanding its merits, may become inefficient as far as computing time is concerned. A way out of this difficulty is the partitioning of the multi-dimensional space into independent subspaces, *i.e.* to apply an appropriate separation of the space parameters. Here we offer two distinct procedures to accomplish this separation.

Use of one-dimensional diffraction data

Examination of the Eulerian matrix (3) reveals that its third column is a function of two parameters, ψ and θ , only. By proper choice of the L_i system, through the T matrix (2), a translational parameter can be defined in such a way that the structure factors of a set of axial reflections can be a function of three parameters only. For example, the set of structure factors for the $00l$ reflections would be a function of ψ , θ and w only when $L_3 = c$. The best trial structures obtained by this fast three-dimensional search are used as the starting points for a second three-dimensional search involving φ , u and v , using a set of general reflections hkl . This procedure is very fast and reduces computing time by more than an order of magnitude in both (II) and (III). However, it is not general enough, and may be completely inapplicable when the number of axial reflections is very small, *e.g.* in (I), the number of $00l$ reflections precludes the possibility of using this approach.

The 'superatom' approach

In this approach, which is quite general, a separation between the rotational and translational parameters is achieved by going one step further in the scattering-factor approximation. The whole generating unit is treated as a single spherical 'superatom'. The space to be searched now consists of the three-dimensional translational grid only. Again, a set of the best solutions consisting of the first ten lowest R -factor grid points is then searched in the rotational space. This apparently naive approximation proved to be successful and time-saving as it reduced the number of translational grid points by a factor of ten.

To conclude, we have shown that the use of low-resolution X-ray diffraction data, which permits a rather coarse multi-dimensional grid, combined with rejection criteria based on global molecular packing considerations, results in an efficient method for generating a reasonably small number of trial structures which may further be tested by R -factor calculation of higher-order data. The use of spherically averaged

group scatterers in lieu of individual atomic ones improves the efficiency by almost an order of magnitude. We are currently testing the method on oligonucleotide and protein structures.

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An Analytical Method for Studying the Variation of the Interfacial Symmetry Due to Relative Displacements of the Bicrystal Components

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Abstract

This paper investigates changes of the bicrystal symmetry caused by rigid-body relaxation. Analytical expressions are derived for the determination of the symmetry of a bicrystal, or, more generally, of a binary composite, corresponding to a particular relative displacement of its components. Such displacements can change the point and/or space symmetry of the composite either by compressing symmetry operations or by transforming symmorphic symmetry operations to their nonsymmorphic counterparts, or *vice versa*. In the latter case the relative displacements have a well defined magnitude and direction and it is shown that the composite space groups associated with these displacements correspond to a new type of subgroups of space groups. These subgroups, although having the same unit cell as the original space group, are

similar to the *klassengleiche* subgroups in the sense that the descent in symmetry has affected the translations in the unit cell of the original group. Furthermore, it is pointed out that the reduction of symmetry due to relative displacements is accomplished by a multiplicity of crystallographically equivalent ways and that their number and interrelation depends on the space symmetry of the original composite.

1. Introduction

The crystallographic framework of planar grain boundaries was recently discussed by Pond & Bollmann (1979). Their considerations, enabling the description of the interfacial symmetry, were based on the introduction of the bicrystal which is defined as the system of the two adjacent crystals containing the planar interface. The starting point of the methodology of Pond & Bollmann, which was subsequently extended by Vlachavas (1980) and Pond &

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