

## 3.3. MOLECULAR MODELLING AND GRAPHICS

It may happen that  $B_1^T M_2 B_1$  is itself singular because there are insufficient data in the vector  $t_2$  to control the structure and the parametric shifts contained in  $\theta_2$  fully. In this event the same process may be applied again, basing the solution for  $\theta_2$  on

$$\begin{pmatrix} A_2^T \\ B_2^T \end{pmatrix} B_1^T M_2 B_1 (A_2 B_2)$$

so that the vectors in  $B_2$  represent the degrees of freedom which remain uncommitted. This method of application of constraints by subspace sectioning may be nested to any depth and is completely general.

A valid matrix  $A_1$  may be found from  $M_1$  by using the fact that the columns of  $M_1$  are all linear combinations of the columns of  $E_\lambda$  and are void of any contribution from  $E_0$ . It follows that  $A_1$  may be found by using the columns of  $M_1$  as priming vectors in the Gram–Schmidt process [Section 3.3.1.2.3 (i)] until the normalizing step involves division by zero.  $A_1$  is then complete if all the columns of  $M_1$  have been tried.  $(A_1 B_1)$  may then be completed by using arbitrary vectors as primers.

Manipulation of a ring of  $n$  atoms may be achieved by treating it as a chain of  $(n + 2)$  atoms [having  $(n + 1)$  bond lengths,  $n$  bond angles and  $(n - 1)$  dihedral angles] in which atom 1 is required to coincide with atom  $(n + 1)$  and atom 2 with  $(n + 2)$ .  $t_1$  then contains two vectors, namely the lack-of-closure vectors at these points, and is typically zero.  $A_1$  is then found to have five columns corresponding to the five degrees of freedom of two points of fixed separation;  $\theta_1$  contains only zeros if the ring is initially closed, and contains ring-closure corrections if, through non-linearity or otherwise, the ring has opened.  $B_1$  contains  $(p - 5)$  columns if the chain of  $(n + 2)$  points has  $p$  variable parameters. It follows, if bond lengths and bond angles are treated as constants, that the seven-membered ring is the smallest ring which is flexible, that the six-membered ring (if it can be closed with the given bond angles) has no flexibility (though it may have discrete alternatives) and that it may be impossible to close a five-membered ring. Therefore some variation of bond angles and/or bond lengths is essential for the modelling of flexible five- and six-membered rings. Treating the ring as a chain of  $(n + 1)$  atoms is less satisfactory as there is then no control over the bond angle at the point of ring closure.

A useful concept for the modelling of flexible five-membered rings with near-constant bond angles is the concept of the pseudorotation angle  $P$ , and amplitude  $\theta_m$ , for which the  $j$ th dihedral angle is given by

$$\theta_j = \theta_m \cos \left( P + \frac{4\pi j}{5} \right).$$

This formulation has the property  $\sum_{j=0}^4 \theta_j = 0$ , which is not exactly true; nevertheless,  $\theta_j$  values measured from observed conformations comply with this formulation within a degree or so (Altona & Sundaralingam, 1972).

Software specialized to the handling of condensed ring systems has been developed by van der Lieth *et al.* (1984) (Section 3.3.3.3.1) and by Cohen *et al.* (1981) (Section 3.3.3.3.2).

## 3.3.2.2.2. Methods based on positional coordinates

Modelling methods in which atomic coordinates are the independent variables are mathematically simpler than those using angular variables especially if the function to be minimized is a quadratic function of interatomic distances or of distances between atoms and fixed points. The method of Dodson *et al.* (1976) is representative of this class and it may be outlined as follows. If  $\mathbf{d}$  is a column vector containing ideal values of the scalar distances from atoms to fixed target points or to other atoms, and if  $\mathbf{l}$

is a column vector containing the prevailing values of these quantities obtained from the model, then

$$\mathbf{d} = \mathbf{l} + D\delta\mathbf{x} + \boldsymbol{\varepsilon}$$

in which the column matrix  $\delta\mathbf{x}$  contains alterations to the atomic coordinates,  $\boldsymbol{\varepsilon}$  contains residual discrepancies and  $D$  is a large sparse rectangular matrix containing values of  $\partial l / \partial x$ , of which there are not more than six non-zero values on any row, consisting of direction cosines of the line of which  $\mathbf{l}$  is the length.  $\boldsymbol{\varepsilon}^T W \boldsymbol{\varepsilon}$  is then minimized by setting

$$D^T W (\mathbf{d} - \mathbf{l}) = D^T W D \delta\mathbf{x},$$

which they solve by the method of conjugate gradients without searches. This places reliance on the linearity of the observational equations (Diamond, 1984*b*). It also works entirely with the sparse matrix  $W^{1/2} D$ , the dense matrix  $D^T W D$ , and its inverse, being never calculated.

The method is extremely efficient in annealing a model structure for which an initial position for every atom is available, especially if the required shifts are within the quasi-linear region, but is less effective when large dihedral-angle changes are involved or when many atoms are to be placed purely by interpolation between a few others for which target positions are available. Interbond angles are controlled by assigning  $d$  values to second-nearest-neighbour distances; this is effective except for bond angles near  $180^\circ$  so that, in particular, planar groups require an out-of-plane dummy atom to be included which has no target position of its own but does have target values of distances between itself and atoms in the planar group. The method requires a  $d$  value to be supplied for every type of nearest- and next-nearest-neighbour distance in the structure, of which there are many, together with  $W$  values which are the inverse variances of the distances concerned as assessed by surveys of the corresponding distances in small-molecule structures, or from estimates of their accuracy, or from estimates of accuracy of the target positions.

Hermans & McQueen (1974) published a similar method which differs in that it moves only one atom at a time, in the environment of its neighbours, these being considered fixed while the central atom is under consideration. This is inefficient in the sense that in any one cycle one atom moves only a small fraction ( $\sim 3\%$ ) of the distance it will ultimately be required to move, but individual atom cycles are so cheap and simple that many cycles can be afforded. The method was selected for inclusion in *Frodo* by Jones (1978) (Section 3.3.3.2.7) and is an integral part of the *GRIP* system (Tsernoglou *et al.*, 1977; Girling *et al.*, 1980) (Section 3.3.3.2.2) for which it was designed.

## 3.3.2.2.3. Approaches to the problem of multiple minima

Modelling methods which operate by minimizing an objective function of the coordinates (whether conformational or positional) suffer from the fact that any realistic objective function representing the potential energy of the structure is likely to have many minima in the space of the variables for any but the simplest problems. No general system has yet been devised that can ensure that the global minimum is always found in such cases, but we indicate here two approaches to this problem.

The first approach uses dynamics to escape from potential-energy minima. Molecular-mechanics simulations allow each atom to possess momentum as well as position and integrate the equations of motion, conserving the total energy. By progressively removing energy from the simulation by scaling down the momentum vectors some potential-energy minimum may be found. Conversely, a minimization of potential energy which has led to a minimum thought not to be the global minimum may be continued by introducing atomic momenta sufficient to overcome potential-

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energy barriers between minima, and subsequently attenuate the momenta again. In this way a number of minima may be found (Levitt & Warshel, 1975). It is equivalent to initializing a potential-energy minimization from a number of different conformations but it has the property that the minima so found are separated by energy barriers for which an upper limit is known so that the possibility exists of exploring transition pathways.

A second approach (Purísima & Scheraga, 1986) is relatively new. If the objective function to be minimized can be expressed in terms of interatomic distances, and if each atom is given coordinates in a space of  $n - 1$  dimensions for  $n$  atoms, then a starting structure may be postulated for which the interatomic distances *all* take their ideal values and the objective function is then necessarily at an absolute minimum. This multidimensional structure is then projected into a space of fewer dimensions, within which it is again optimized with respect to the objective function. The dimensionality of the model is thus progressively reduced until a three-dimensional model is attained at a low energy. This means that the minimum so attained in three dimensions is approached *from beneath*, having previously possessed a lower value in a higher-dimensional space. This, in itself, does not guarantee that the three-dimensional minimum-energy structure so found is at the global minimum, but it is not affected by energy barriers between minima in the same way, and it does appear to reach very low minima, and frequently the global one. Because it is formulated entirely in terms of interatomic distances it offers great promise for modelling molecules on the basis of data from nuclear magnetic resonance.

#### 3.3.3. Implementations

In this section the salient characteristics of a number of systems are described. Regrettably, it cannot claim to be a complete guide to all existing systems, but it probably describes a fairly representative sample. Some of these systems have arisen in academia and these are freely described. Some have arisen in or been adopted by companies which now market them, and these are described by reference to the original publications. Other marketed systems for which originators' published descriptions have not been found are not described. Yet other systems have been developed, for example, by companies within the chemical and pharmaceutical industries for their own use, and these have generally not been described in what follows since it is assumed that they are not generally available, even where published descriptions exist.

Software concerned especially with molecular dynamics has not been included unless it also provides static modelling capability, since this is a rapidly growing field and it has been considered to be beyond the intended scope of this chapter. Systems for which outline descriptions have already been given (Levitt & Lifson, 1969; Levitt, 1974; Diamond, 1966; Warme *et al.*, 1972; Dodson *et al.*, 1976; Hermans & McQueen, 1974) are not discussed further.

For some of the earliest work Levinthal (1966) still makes interesting reading and Feldmann (1976) is still an excellent review of the technical issues involved. The issues have not changed, the algorithms there described are still valuable, only the manner of their implementation has moved on as hardware has developed. A further review of the computer generation of illustrations has been given by Johnson (1980). Excellent bibliographies relating to these sections have been given by Morffew (1983, 1984), which together contain over 250 references including their titles.

The following material is divided into three sections. The first is concerned primarily with display rather than modelling though some of these systems can modify a model, the second is concerned with molecular modelling with reference to electron density and can develop a model *ab initio*, and the third is concerned with modelling with reference to other criteria.

Where software names are known to be acronyms constructed from initial letters, or where the original authors have used capitals, the names are capitalized here. Otherwise names are lower case with an initial capital.

While it is recognised that many of the systems here described are now of mainly historical interest, most have been retained for the second edition, some have been updated and some new paragraphs have been added.

#### 3.3.3.1. Systems for the display and modification of retrieved data

One of the earliest systems designed for information retrieval and display was that described by Meyer (1970, 1971) which used television raster technology and enabled the contents of the Brookhaven Protein Data Bank (Meyer, 1974; Bernstein *et al.*, 1977) to be studied visually by remote users. It also enabled a rigid two-ring molecule to be solved from packing considerations alone (Hass *et al.*, 1975; Willoughby *et al.*, 1974). Frames for display were written digitally on a disk and the display rate was synchronized to the disk rotation. With the reduction in the cost of core storage, contemporary systems use large frame buffer memories thus avoiding synchronization problems and permitting much richer detail than was possible in 1970. A majority of the systems in this section use raster techniques which preclude real-time rotation except for relatively simple drawings, though *GRAMPS* is an exception (O'Donnell & Olson, 1981; Olson, 1982) (Section 3.3.3.1.4).

##### 3.3.3.1.1. ORTEP

This program, the Oak Ridge Thermal Ellipsoid Program, due to Johnson (1970, 1976) was developed originally for the preparation of line drawings on paper though versions have since been developed to suit raster devices with interactive capability.

The program draws molecules in correct perspective with each atom represented by an ellipsoid which is the equi-probability surface for the atomic centre, as determined by anisotropic temperature factor refinement, the principal axes of which are displayed. Bonds are represented by cylindrical rods connecting the atoms which in the drawing are tapered by the perspective.

In line-drawing versions the problem of hidden-line suppression is solved analytically, whereas the later versions for raster devices draw the furthest elements of the picture first and either overwrite these with nearer features of the scene if area painting is being done or use the nearer features as erase templates if line drawings are being made.

##### 3.3.3.1.2. Feldmann's system

R. J. Feldmann and co-workers (Feldmann, 1983) at the National Institutes of Health, Bethesda, Maryland, USA, were among the first to develop a suite of programs to display molecular structure using colour raster-graphics techniques. Their system draws with coloured shaded spheres, usually with one sphere to represent each atom, but alternatively the spheres may represent larger moieties like amino acids or whole proteins if lower-resolution representations are required. These workers have made very effective use of colour. Conventionally, oxygens have been modelled in red, but this system allows charged oxygens to be red and uncharged ones to be pink, with a similar treatment in blue for charged and uncharged nitrogens. By such means they have been able to give immediacy to the hydrophobic and electrostatic properties of molecular surfaces, and have used these characteristics effectively in studies of the binding possibilities of benzamidine derivatives to trypsin (Feldmann *et al.*, 1978).