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 (Purisima & 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).

references