A molecular fragment with an unsatisfied valency (by which it might later be attached to another such group) would have that feature represented by a 'vanishing virtual' atom which removes the need for any organizational distinction between such fragments and complete molecules. Fragments, such as amino-acid residues, may be assembled from atoms, and molecules may be assembled from atoms and/or from such fragments invoked by name, by the superposition and elimination of the relevant vanishing virtuals. The assembly process includes the development of a connectivity tree for the molecule and provision is made for the 'turning' or reconstruction of such trees if the combination of such fragments redefines the root atom of one or more of the fragments. The system also provides for ring closure. Model building initially uses fixed bond lengths and angles, varying only the dihedral angles in single bonds, but has a library of preformed rings which could not otherwise be modelled on the simple basis. The results of such modelling may then be subjected to an energy-minimization routine using a steepest-descent method in the space of the dihedral angles and referring to the Lennard–Jones potential for non-bonded atom pairs. Atoms are first sorted into contiguous cubes so that all neighbours of any atom may be found by searching not more than 27 cubes.

The system is also capable of modelling by reference to electron density either by the translation and rotation of molecular fragments and the rotation of rotatable bonds within them or by the automatic linking of peaks in an electron-density map which are separated by less than, say, 1.8 Å, which is an important aid to interpretation when the resolution is sufficiently high.

3.3.3.2.2. *GRIP*

This system, developed by Professor F. P. Brooks, Dr W. V. Wright and associates at the University of North Carolina, Chapel Hill, NC, USA, was designed for biopolymers and was the first to enable a protein electron-density map to be interpreted *ab initio* without the aid of mechanical models (Tsernoglou *et al.*, 1977). Girling *et al.* (1980) give a more recent example of its use.

In its 1975 version *GRIP* is a three-machine system. Centrally there is a minicomputer which receives inputs from the user and controls a vector display with high-speed matrix-multiplication capability. The third machine is a mainframe computer with high-speed communication with the minicomputer.

The system develops a polymer chain from a library of monomers and manipulates it through bond rotations or free rotations of fragments explicitly specified by the user, with the aid of dials which may be coupled to bonds for the purpose. Bond rotations in the main chain either rotate part of the molecule relative to the remainder, which may have undesirable long-range effects, or the scope of the rotation is artificially limited with consequential discontinuities arising in the chain. Such discontinuities are removed or alleviated by the mainframe computer using the method of Hermans & McQueen (1974), which treats atomic position vectors, rather than bond rotations, as independent variables.

The system made pioneering use of a two-axis joystick to control orientation and a three-translation joystick to control position.

3.3.3.2.3. *Barry, Denson & North's systems*

These systems (Barry & North, 1971; North *et al.*, 1981; North, 1982) are examples of pioneering work done with minicomputers before purpose-built graphics installations became widespread; examples of their use are given by Ford *et al.* (1974), Potterton *et al.* (1983) and Dodson *et al.* (1982). They have the ability to develop a polymer chain in sections of several residues, each of which may subsequently be adjusted to remove any misfit errors where the sections overlap. Manipulations are by rotation and translation of sections and by bond rotations within sections. These movements are directly controlled by the user, who may simultaneously observe on the screen the agreement with electron density, or calculated estimates of potential or interaction energy, or a volume integral of the product of observed and model densities, or predicted shifts of proton magnetic resonance spectra. Thus models which are optimal by various criteria may be constructed, but there is no optimizer directly controlling the rotational adjustments which are determined by the user.

One of the earliest applications of them (Beddell, 1970) was in the fitting of substrate molecules to the active site of lysozyme using difference electron densities; however, the systems also permitted the enzyme–substrate interaction to be studied simultaneously and to be taken into account in adjusting the model.

3.3.3.2.4. *MMS-X*

The Molecular Modelling System-X (*MMS-X*) is a system of purpose-built hardware developed by Barry, Marshall and others at Washington University, St Louis. Associated with it are several sets of software. The St Louis software consists of a suite of programs rather than one large one and provides for the construction of a polymer chain in helical segments which may be adjusted bodily to fit the electron density, and internally also if the map requires this too. Non-helical segments are built helically initially and unwound by user-controlled rotations in single bonds. The fitting is done to visual criteria. An example of the use of this system is given by Lederer *et al.* (1981).

Miller *et al.* (1981) have described an alternative software system for the same equipment. Functions invoked from a keyboard allow dials to be coupled to dihedral angles in the structure. Their system communicates with a mainframe computer which can deliver small blocks of electron density to be contoured and stored locally by the graphics system; this provides freedom of choice of contour level at run time. An example of the use of this system is given by Abad-Zapatero *et al.* (1980).

3.3.3.2.5. *Texas A&M University system*

This system (Morimoto & Meyer, 1976), a development of Meyer's earlier system (Section 3.3.3.1), uses vector-graphics technology and a minicomputer and is free of the timing restrictions of the earlier system. The system allows control dials to be dynamically coupled by software to rotations or translations of parts of the structure, thus permitting the re-shaping or re-positioning of the model to suit an electron-density map which may be contoured and managed by the minicomputer host. The system may be used to impose idealized geometry, such as planar peptides in proteins, or it may work with non-idealized coordinates.

The system was successfully applied to the structures of rubredoxin and the extracellular nuclease of *Staphylococcus aureus* (Collins *et al.*, 1975) and to binding studies of sulfonamides to carbonic anhydrase (Vedani & Meyer, 1984). In addition, two of the first proteins to be constructed without the aid of a 'Richards' Box' were modelled on this system: monoclinic lysozyme in 1976 (Hogle *et al.*, 1981) and arabinose binding protein in 1978 (Gilliland & Quiocho, 1981).

3.3.3.2.6. *Bilder*

This system (Diamond, 1980*a*,*c*, 1982*b*) runs on a minicomputer independent of any mainframe. It builds a polymer chain from a library of residues and adapts it by internal rotations and overall positioning in much the same way as previous systems described in this section. Like them, it can provide user-controlled bond rotations, but its distinctive feature is that it has an optimizer within the minicomputer which will determine optimal combinations of bond rotations needed to meet the user's declared

 references