objectives. Such objectives are normally target positions for atoms set by the user by visual reference to the density, using the method of Section 3.3.1.3.9, but they may include target values for angles. These latter may either declare a required shape that is to take precedence over positional requirements, which are then achieved as closely as the declared shape allows, or they may be in least-squares competition with the positional requests. The optimizer also recognizes the constraints imposed by chain continuity and enables an internal section of the main chain to be modified without breaking its connection to the rest of the molecule. Similar techniques also allow ring systems to adopt various conformations, by bond rotation, without breaking the ring, simultaneously permitting the ring to have target positions. The optimizer is unperturbed by under-determined situations, providing a minimum-disturbance result in such cases. All these properties of the optimizer are generated without recourse to any 'special cases' by a generalization of the subspace section technique which was used to maintain chain continuity in a 'real-space-refinement' program (Diamond, 1971). This is based entirely on the rank of the normal matrix that arises during optimization, which may serve to satisfy a constraint such as chain continuity or ring closure and simultaneously to establish what degrees of freedom remain to be controlled by other criteria. In *Bilder* this is achieved without establishing eigenvalues or eigenvectors. The method is described in outline in Section 3.3.2.2.1 and in detail by Diamond (1980*a*,*b*).

The angular variables used normally comprise all single bonds but may include others, such as the peptide bond with or without a target of 180°. Thus this bond may be completely rigid, elastic, or completely free. Any interbond angles may also be parameterized but at some cost in storage. The normal mode of working is to develop a single chain for the entire length of the molecule, but if cumulative error makes fitting difficult a fresh chain may be started at any stage. *Bilder* may itself reconnect such chains at a later stage.

Construction and manipulation operates on a few residues at a time within the context of a polymer chain, but any or all of the rest of the molecule, or other molecules, may be displayed simultaneously.

Contouring is done in advance to produce a directoried file of contoured bricks of space, each brick containing up to 20 independently switchable elements which need not all be from the same map. Choice of contour level and displayed volume is thus instantaneous within the choices prepared.

The system is menu driven from a tablet, only file assignments and the like requiring the keyboard, and it offers dynamic parallax as an aid to 3D perception (Diamond *et al.*, 1982). Bloomer *et al.* (1978), Phillips (1980), and Evans *et al.* (1981) give examples of its use.

3.3.3.2.7. *Frodo*

This system, due to Jones (Jones, 1978, 1982, 1985; Jones & Liljas, 1984), in its original implementation was a three-machine system comprising graphics display, minicomputer and mainframe, though more recent implementations combine the last two functions in a 'midi'. Its capabilities are similar to those of *Bilder* described above, but its approach to stereochemical questions is very different. Where *Bilder* does not allow an atom to be moved out of context (unless it comprises a 'chain' of one atom) *Frodo* will permit an atom or group belonging to a chain to be moved independently of the other members of the chain and then offers regularization procedures based on the method of Hermans & McQueen (1974) to regain good stereochemistry. During this regularization, selected atoms may be fixed, remaining atoms then adjusting to these. A peptide, for example, may be inverted by moving the carbonyl oxygen across the peptide and fixing it, relying on the remaining atoms to rearrange themselves. (*Bilder* would do the equivalent operation by cutting the chain nearby, turning the peptide explicitly, reconnecting the chain and optimizing to regain chain continuity.) The *Frodo* approach is easy to use especially when large displacements of an existing structure are called for, but requires that ideal values be specified for all bond lengths, angles and fixed dihedrals since the system may need to regain such values in a distorted situation. *Bilder*, in contrast, never changes such features and so need not know their ideal values.

Frodo may work either with consecutive residues of a polymer chain, useful for initial building, or with a volume centred on a chosen position, which is ideal for adjusting interacting side chains which are close in space but remote in sequence.

In recent implementations *Frodo* can handle maps both in density grid form and in contour form and permits on-line contouring. It has also been developed (Jones & Liljas, 1984) to allow the automatic adjustment of the position and orientation of small rigid groupings by direct reference to electron density in the manner of Diamond (1971) but without the maintenance of chain continuity, which is subsequently reintroduced by regularization.

Horjales and Cambillau (Cambillau & Horjales, 1987; Cambillau *et al.*, 1984) have also provided a development of *Frodo* which allows the optimization of the interaction of a ligand and a substrate with both molecules being treated as flexible.

3.3.3.2.8. *Guide*

Brandenburg *et al.* (1981) have described a system which enables representations of macromolecules to be modified with reference to electron density. Such modifications include rotation about single bonds under manual control, or the movement with six degrees of freedom, also under manual control, of any part or parts of the molecule relative to the remainder. The latter operation may necessitate subsequent regularization of the structure if the moved and unmoved parts are chemically connected, and this is done as a separate operation on a different machine. The system also has the capability of displaying several molecules and of manually superimposing these on each other for comparison purposes.

3.3.3.2.9. *HYDRA*

This program, due to Hubbard (1985) (and, more recently, to Molecular Simulations) has several functional parts, referred to as 'heads', which all use the same data structure. The addition of further heads may be accomplished, knowing the data structure, without the need to know anything of the internal workings of existing heads.

The program contains extensive features for the display, analysis and modelling of molecular structure with particular emphasis on proteins. Display options include dotted surfaces, molecular skeletons, protein cartoons and a variety of van der Waals, ball-and-stick, and other raster-graphics display techniques such as ray tracing and shaded molecular surfaces. Protein analysis features include the analysis of hydrogen bonding, and of secondary and domain structure, as well as computational assessment of deviations from accepted protein structural characteristics such as abnormal main-chain or side-chain conformations and solvent exposure of hydrophobic amino acids. A full set of protein modelling facilities are provided including homology modelling and the 'docking' of substrate molecules. The program contains extensive tools for interactive modelling of structures from NMR or X-ray crystallographic data, and provides interfaces to molecular-mechanics and dynamics calculations. There are also database searching facilities to analyse and compare features of protein structure, and it is well suited to the making of cine films.

references