won intuition, usually by experienced crystallographers.

Our approach has been to provide crystallographers with an interactive graphical model of the diffractometer and to allow them to try out various collection strategies while graphically indicating the volume of the reciprocal space swept. The Biochemistry department at UNC has been using the program for several months and is now processing data collected with strategies planned with it. Use of the program has improved the efficiency of collection, reduced the chance of erroneous scanning and enabled inexperienced users to plan their own collections.

During a session, the user is prompted for information about his detector system and his particular crystal, and the program uses this information to draw an Ewald-like construction depicting the real and reciprocal cell axes, the laboratory axes, the goniometer, and the area detector, along with a sphere representing the chosen resolution limit and the boundary of a volume of unique data characteristic of the crystal's space group. The goniometer model can then be manipulated interactively, and the volume of reciprocal space swept is displayed at the end of each scan. Gaps and redundant collections in the strategy can be identified readily from the display.

For practical reasons, such as mechanical limits on the movement of the goniometer, it is sometimes impossible to collect a complete data set in a continuous region of reciprocal space, and collections from symmetry-equivalent positions have to be made. To address the difficulty in judging how such noncontiguous volumes complement each other, RSpace can optionally map all swept volumes to equivalent regions of a single unique volume.

The current version is a C-language program that runs under UNIX or VMS on Masscomp or VAX processors, driving Evans and Sutherland PS300 series displays.

RSpace can model any data collection based on rotation methods, including those using the Xuong-Hamlin, Centronics and FAST detector systems. It can be used for teaching or as a research tool.

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Force Display in Molecular Docking

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We have developed a real-time system that uses the master station of a remote manipulator system as a force and torque display in interactive modeling. The force system is integrated with interactive computer graphics and a high-speed calculation of the interaction forces between a drug and its receptor site to form a tool for molecular docking. When the drug molecule is maneuvered by the user's hand, the manipulator serves both as an input device for six-dimensional manipulation and as an output device for displaying forces.

The GROPE-III molecular modeling system consists of the Argonne E-3 Remote Manipulator (ARM) for force and torque presentation to the user, a graphic system (Evans and Sutherland's PS300 or Fuchs's Pixel-Planes, a very fast raster graphics engine developed at UNC-Chapel Hill) for displaying proteins and drugs, a Tektronix alternating polarization plate for stereo images and software for energy and force calculations. The system operates under Unix, with Ethernet connections between the graphic systems and a Masscomp 5500 workstation, whose digital-to-analog (D/A) and analog-to-digital (A/D) converters control the ARM. At present we achieve 4.5 updates/second.

Real-time force and torque evaluation is achieved by precalculating electrostatic and van der Waals forces on a grid, using the technique of Pattabiraman.[1] Most of the update time is spent doing image generation and the A/D, D/A sampling.

Considered as descendants of force-feedback remote manipulators, GROPE-III and a conventional robot are opposites. A conventional robot is a master-slave remote manipulator with a computer model assuming the role of the master station and its user. Grope-III is a remote manipulator with a computer model assuming the role of the slave station and its task-world.

We have simulated the interaction forces between dihydrofolate reductase enzyme (DHFR) and the inhibitor trimethoprim, which contain 1500 and 21 atoms, respectively. Even at the present slow update rate, we have found that chemists can reliably dock the drug into the crystallographically determined docking position, starting from arbitrary undocked positions and guided by their chemical intuition and a combination of visual and force feedback. Experienced chemists can dock trimethoprim into DHFR accurately in about 20 minutes. Docking with visual feedback alone is much more difficult, and we conclude that force feedback can be a useful tool.

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References

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CHAIN — A Crystallographic Modeling Program

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The program CHAIN is the result of our laboratory's long experience in the use of molecular graphics for fitting atomic models to electron density. The program is used to display atomic coordinates and electron density maps on a graphics system and then fits the atomic model to the electron density.

The user first prepares data files containing the desired coordinate and density information. CHAIN then allows one to display up to eight different electron density contour levels, superimposed with atomic coordinates on the screen. One can then interactively modify the coordinates.

A number of additional features are included with the program; they initiate various routines to automatically regularize or refine the coordinates and to display them in a variety of ways. The program also provides a number of interfaces to read in and write out the atomic coordinate information so it can use data from and be used by non-CHAIN programs.

CHAIN is actually a series of tightly and logically coupled subroutines connected via a main parser. As keyword commands are given to the program, the parser interprets the command and invokes the required subprogram to perform the desired function. Because of this type of organization, new subprograms can be added easily to CHAIN, provided that they are able to uiltize the CHAIN file formats. Additional entries can be added to the keyword list along with the appropriate calling routines.

The program also contains an on-line utility to allow the user to obtain immediate assistance with any command. A 200-page manual accompanies the distribution.

The program is designed, at present, to run on an Evans & Sutherland PS300 graphics unit.

Chemical Graphics Input/Output Package for the Cambridge Structural Database

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The Cambridge Structural Database (CSD) is the world's leading database of molecular structure. It is a unique collection of chemical, numeric and bibliographic information for all published organocarbon compounds analyzed by X-ray or neutron diffraction. It is thus an invaluable tool in computer-aided drug design and in the analysis of geometrical parameters to obtain new insights into structure and bonding.

A core program, QUEST88, lets users search bibliographic, chemical connectivity and selected numerical data within a single query. Tests of individual fields are combined via logical operators to form a complete question.

A graphical input/output package has now been developed for inclusion in QUEST89, which will replace the current alphanumeric coding of the search question. Queries may be input via a fully interactive, menu-driven interface. Substructure, textual and numeric searches may all be specified from within this integrated package.

Six menus provide the ability to generate a substructure, which may be edited, saved for future use or combined with further bibliographic or numerical questions using the logical operators AND, OR and NOT. The complete query is then passed to the database search software.

Special features of the input package include

- over 60 system templates, including hydrocarbons, steroids, and porphyrins
- the ability to save and reread user-defined templates
- Feldmann ring notation: e.g., 66U6D5 specifies the steroid skeleton
- full UNDO facility, with journaling, to rerun a previous session
- a powerful editing facility, for generating production-quality chemical diagrams
- symmetry operations, and a "copy" facility, which may be applied to complete structures of fragments, for efficient generation of high-quality diagrams
- a full on-line HELP facility

Output from QUEST88 is enhanced by the generation of two-dimensional (2D) chemical diagrams. These publication-quality diagrams use x,y atomic coordinates, generated via CCDC in-house software, which are now incorporated within the chemical connectivity records. They will form part of future database releases. Substructures located by QUEST88 can be highlighted on these diagrams. 3D crystallographic (molecular) diagrams can also be selected for the display of hits.

The interface program, like QUEST88, is written in standard FORTRAN77 and sends Tektronix escape codes to the terminal. Tektronix 4010/4014 (monochrome), 4100 Series (color) and 4200 Series (color) terminals and emulators are supported. For the 4010/4014 and 4105 standards, software emulation of the 4200-style "dialog area" facility is provided.

Menu operation is controlled by a graphical input (GIN) device, such as a mouse or tablet, or simply via cursor keys. At all times, however, the menus may be suppressed by typing commands manually, thus providing greater flexibility for experienced users. (The Tektronix 4200F4M three-button mouse and Tektronix 4957 tablet are supported, although the program requires only a one-button device for operation.) In addition, HP–GL plotters are supported, for generating hard copy.

The complete graphical input/output system has been developed to provide easier access to CSD's already extremely powerful search software. It will be released to academic and industrial users in 1989.