18.4-01 A LABORATORY CRYSTAL STRUCTURE COMPUTING SYSTEM. By C.J. Gilmore, P.R. Mallinson, K.W. Muir and D.N.J. White, Chemistry Department, University of Glasgow, Glasgow G12 8QQ, U.K.

Hitherto, 12 or 16-bit architecture has been normal in mini-computers dedicated to structure analysis (E.J. Gabe, Ch. 23 in "Computing in Crystallography", ed. R. Diamond, S. Ramaseshan, K. Venkatesan, 1980). Enlargements in the scale of circuit integration have recently made available micro-computers with 32-bit registers and 20-bit program counters at comparable cost; the resulting increase in speed and task virtual address space provides the power, scope and ease of programming of a mainframe while retaining the closely-interactive features of a mini.

We are designing and building a program package oriented to this new generation of micro-computers, incorporating advanced direct methods, raster graphics, real-time structure solution and refinement, and interactive evaluation of results, with applicability to a wide range of chemical problems. The software is being developed in FORTRAN on a SYSTEMS 32/27 running the MPX-32 multi-user operating system, with the objective that it be transportable to any computer having fully-interactive ("hands on") access via raster graphics v.d.u., 0.5 Mbytes task virtual address space, 10 Mbytes of disc storage, and 9-track magnetic tape.

MPX-32 has macro (command file) and batch facilities. The use of parameter-driven macros greatly expedites system development, but will not be essential in the production version of the package. The ability to run tasks at different priorities could be used instead of the batch feature.

The package will be completely self-contained, so that the entire structure-analysis process from data reduction to preparation of typescript, tables and figures may be carried out in the laboratory. Tables will be generated in raw form on the 32/27; typescript and final table layout will then be handled by a separate 8-bit word processor, communicating with the main system, and utilizing the commercially available WORDSTAR software.

Some of the programs being incorporated into the structure determination suite are: processing of CAD4 diffractometer output, a new direct methods package using higher invariants, block-diagonal and full-matrix least squares, ORTEP, molecular geometry, and thermal motion analysis. The proprietary SIMPLEPLOT package is used to provide intermediate results in graphical form on the user's terminal during computations. Structural van-der-Waals surface representations and empirical force field energy minimisation will also be available.

Typical run speeds for some programs implemented at the time of writing are: data reduction - 20 reflections/sec., NORMAL - 30 reflections/sec., block diagonal least squares with anomalous dispersion - 2.1 min./cycle for 140 parameters, ORTEP - 1 sec./atom (including display), intermolecular contact search - 11 sec. for asymmetric unit of 30 atoms in 4 equivalent positions.

18.5-01 EXAMPLES OF THE USE OF INTERACTIVE COMPUTER GRAPHICS WITH REAL-TIME ENERGY CALCULATIONS IN STUDIES OF PROTEIN-LIGAND INTERACTIONS AND IN DRUG DESIGN. By A.A.Chabot, A.J.Geddes, A.C.T.North and E.A.Potterton, Astbury Department of Biophysics, University of Leeds, Leeds LS2 9JT, U.K.

By using a computer graphics system to represent and manipulate molecular models we have immediate access to quantitative information about them. In addition to bond lengths, bond angles and torsion angles, we can calculate distances between non-bonded atoms and thus derive interactive energies. Such energies can be calculated for pairs of atoms within one molecule or for atoms in separate molecules. This enables us to explore the stereo-specificity of interactions between molecules such as a drug and its receptor site.

Our system allows independent real-time rotation and translation of several molecules, using simple analog input devices, and the interaction between molecules can be represented graphically (for example, by joining atoms in close contact with dashed lines), or numerically, with both intra- and intermolecular interaction energies displayed continuously. In practice, the operator manoeuvres the molecules close to a minimum energy position and then a more precise positioning can be made using a separate energy-minimisation program. Further details of our system have recently been reported (North et al. in *Biomolecular Structure, Conformation, Function and Evolution*, Vol I, (ed. Srinivasan, R.) 59-72, Pergamon, Oxford, 1980).

The system has been tested by using the known binding energies between 2,3-diphosphoglycerate and normal and a variety of mutant forms of deoxy-haemoglobin, and between several synthetic analogs of 2,3-diphospho-glycerate and normal adult deoxy-haemoglobin. There is good agreement between calculation and experimental measurement.

In another test, the different proportions of the four isomers formed by the auto-catalytic breakdown of the haem group in oxy-myoglobin and in the α and β chains of oxy-haemoglobin are accurately predicted by calculating the relative accessibilities of the four methene bridges to the attacking haem-bound oxygen molecule (Brown, Chabot, Enderby and North, *Nature*, (1980), 289, 93-95).

Current work is concerned with a study of the possible modes of binding of a variety of inhibitors to the enzyme dihydrofolate reductase. The initial structure of the enzyme is taken to be that which occurs in its complex with the anti-cancer agent methotrexate, for which crystallographic data are available. The predicted mode of binding of the bacteriocide trimethoprim agrees well with available NMR data and we have designed analogs of trimethoprim which are calculated to bind more tightly to the enzyme. Similar studies are in progress with the anti-malarial compounds pyrimethamine and cycloguanil which also act by inhibition of dihydrofolate reductase. These studies provide a rational 3-dimensional structural basis for the synthesis and testing of a number of compounds of potential clinical importance.