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'GUIDE: Groningen University interactive display of enzymes and other biological macromolecules' **Hol, W G J and Postma, J** Laboratory of Chemical Physics, University of Groningen, The Netherlands.

GUIDE is a program which runs on a PDP-11/34 which is the controller of an Evans and Sutherland Picture System 2. The PDP is connected by DECNET to a PDP-11/45, which in its turn is connected to a Cyber 170/760 and to a PDP-11/70. The PDP has access to one 205 Mbyte RA 80 disc. It is intensively used by the Groningen protein crystallography group for a variety of purposes. The capabilities of the program will be illustrated by examples taken from the research projects going on in the laboratory. Topics are:

- refinement of protein structures
- simultaneous investigation of several electron density maps plus a molecular model
- simultaneous display and manipulation of up to 4 different molecular models
- creating 'new' proteins by altering the amino acid side chains according to a new sequence

The striking similarity of dinucleotide-binding $\beta\alpha\beta$-units in six different proteins will be described. The prediction of the 3D structure of a crucial part of an oncogenic protein will be highlighted.

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'Application of a parallel processor to molecular graphics' **Hubbard, R, Fincham, D and Quinn, J E*** University of York. * Queen Mary College.

A disadvantage of many interactive molecular modelling packages is their inability to produce interactive space filling representations of the CPK type. These representations would allow a fuller appreciation of the spatial relationships present than the 'dot surface' types used on vector machines (making, for example, the interaction of enzymatic active sites with model substrates much clearer). In this paper an algorithm for drawing such models using a truly parallel processor (the ICL DAP (digital array processor) at Queen Mary College in London) is discussed along with its implementation using DAP Fortran to produce an image for display on a raster graphics device.

In general terms the algorithm is an application of the '*Z* buffer' method but makes use of the very powerful masking techniques available on the DAP to calculate blocks of 64 × 64 pixels simultaneously. Although no formal optimization of the program has been carried out, use has been made of the variable word lengths (standard features on the DAP) wherever arithmetic is required, to provide substantial decreases in execution time. (Already we can create these pictures in times of about half a millisecond/atom).

A combination of the power of the parallelism of the DAP allied with any suitable graphical output device, will enable interactive computation of space filling models, including whole and part rotations of the molecule, thereby providing a significant increase in the ability of computers to present adequate descriptions of molecular species.

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'The future of molecular graphics: invited lecture' **Langridge, R and Ferrin, T E** Computer Graphics Laboratory, University of California, CA 94143, USA

Application of the tools of such an explosively growing field, computer science, to equally rapidly developing areas such as genetic and protein engineering and drug design, make prediction unwise. We will therefore first describe the developments about which we are fairly certain, ie the direction of the UCSF Computer Graphics Laboratory over the next year or two, and devote only a little time at the end to speculation beyond that. The overall strategy of the laboratory is to combine the methods of numerical analysis, artificial intelligence and computer graphics into a system which is transparent to the user and with easily exportable software. Building on our present software (based on the Bell Laboratories UNIX operating system, which we adopted in 1976 and is now available on hosts from micros to main frames) we will install several workstations of differing levels of complexity communicating over a 10M bit/s local area network. The graphics will range from simple bitmapped black and white displays to high-performance colour vector systems. Numeric calculations for interaction geometries and energies will be done at all levels, aided by special purpose attached scientific processors. The artificial intelligence aspects will be concentrated on special-purpose LISP machines devoted to both general symbolic manipulation (eg protein chain folding) and the development of heuristics and expert systems. Supported by research grants NIH RR-1081, DOD DAAG29-83-G-0080 and a Guggenheim Fellowship.

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'A low cost, high resolution colour raster graphics workstation for molecular modelling' **Lindley, M R, White, D N J and Tyler, K** Chemistry Department, The University, Glasgow G12 8QQ, Scotland

A 16-bit microcomputer using the Intel 8086 microprocessor, with 1/2 megabyte of memory and a graphics processor was used to develop a program for molecular modelling. The graphics processor is based on the Thomson EF9365 graphic processor chip, which has a resolution of 512 × 512 and writes 1.5 million pixels/s. A standard RGB monitor was used for the display. The system cost approximately £7500.

The programn known as CHEMMOD (chemical molecular modelling system) displays molecules as colour-coded stick models. The program is user friendly, is menu driven using a lightpen and permits realtime rotation, translation, scaling and other standard manipulations of the molecules in space filling and stick formats. Space filling representations and red/green stereo views of molecules are also available for the display. Comparison of structures is provided for with a least-squares superimposition procedure. Structure building routines are included which enable

molecules to be built or modified. Alteration of torsion angles allows realtime changes in conformation. A set of I/O routines enable files of cartesian coordinates and connection tables of individual molecules to be used as the input for structural displays. The program has been written in Fortran 77 with a set of graphic driver routines written in 8086 assembly language.

Chemmod provides an extremely useful tool to study chemical structures and interactions using high resolution raster graphics with a 16-bit microcomputer at a low cost. Raster graphics are ideally suited for the display of space filling representations of the molecules, which can also be manipulated in realtime.

The program is being transferred to a Motorola MC68000-based Sage II microcomputer which has considerably better performance than the 8086 system described above. A version of the graphics processor board previously mentioned, using the Thomson EF9365 chip, is commercially available from Digisolve Ltd. After minor modifications to provide double buffering and a light pen, this unit has been connected to the Sage II. This system costs approximately £9500.

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'Exploration of known and unknown active sites of proteolytic enzymes' **Marshall, G R, Naruto, S*, Schneider, C† and Labanowski, J** Department of Physiology and Biophysics, Washington University School of Medicine, St Louis, MO 63110, USA. *Guest investigator, Sankyo Pharmaceuticals, Tokyo, Japan. †Guest investigator, Boehringer-Ingelheim, West Germany.

Problems facing molecular modelling can be divided into those with detailed information regarding the binding site of the drug, and those in which only structure-activity data exists. In order to evaluate various approaches, we have explored current techniques with both classes of problem in studies of proteolytic enzymes. The serine proteases have been characterized by *X*-ray crystallography, and chymotrypsin studied by molecular modelling by Pincus and Scheraga and by DeTar. Mechanism-based inhibitors for proteolytic enzymes have been developed by the groups of Abeles and Katzenellenbogen. Detailed studies of the interaction of these inhibitors with chymotrypsin have been conducted in collaboration with Professor Katzenellenbogen of the University of Illinois. A limited active site was excised from the enzyme and the severed backbone segments anchored for subsequent minimizations. Systematic search of possible productive binding modes with the active site serine were performed, and representative examples minimized. In addition, alternative binding modes for the transition state, acyl intermediate and affinity-labelling compounds were all examined. Several predictions regarding stereospecificity have resulted which are in the process of being experimentally verified. The minimization procedure used was MAXIMIN which allows the flexibility necessary for a problem of this sort. Examination of the results on the PS 330 colour graphics system confirms the interactions, and the appropriate course of minimization. Entropic terms could best be approached by molecular dynamics beginning with those coordinates and alternate modes of interaction.

Angiotensin converting enzyme (ACE) and enkephalinase are two zinc proteases of considerable pharmaceutical interest. Roques and coworkers have recently described an analogue of thiorphan in which the amide bond has been reversed which inhibits enkephalinase, but not ACE. Examination of possible geometrical arrangements of the three groups postulated for ACE interaction with inhibitors (ie the C-terminal carboxylate, the central amide carbonyl and the active site zinc ligand) has led to a single geometrical arrangement consistent with the set of ACE inhibitors in the literature. The retroamide bond analogue of enkephalinase cannot assume an appropriate conformation while thiorphan binds to this hypothetical site in agreement with the data. The methodology used to deduce the site geometry will be illustrated, including orientation and vector maps.

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'Display of the course of α-carbon chains of large proteins in 3-dimensional space without utilising stereopsis' **Milner-White, E J** Department of Biochemistry, University of Glasgow, Glasgow G12 8QQ, Scotland

Previous work[1–3] in this Laboratory has concentrated on methods of displaying features of the surfaces at the subunit–subunit interactions of large proteins. In the present work new methods are being developed for visualizing the course of their α-carbon chains without recourse to stereo pairs. It is a relatively easy matter to make drawings of polypeptide chains of proteins that show the spatial folding unambiguously. I and colleagues have written new software that achieves the same effect by computer.

The initial processing of the coordinates is carried out on an ICL 2988 mainframe computer. Colour displays are produced on a Sigma T5680 terminal attached to the mainframe, with the help of the GINO graphics package. Hardcopy is generated in two ways, either by direct photography of the screen, or by means of a Trilog colour plotter associated with the graphics terminal.

An averaging procedure is used to produce a pleasing representation of the course of the chain. Zigzags and acute angles are largely smoothed out which means that the course of the chain is much easier to follow. The lines joining the averaged α-carbon positions are thickened so that they are clearly visible in the final picture. Shading, together with hidden-line elimination, is used to show the course of the α-carbon chains of each of the six subunits (three regulatory and three catalytic) in one half of the 12-subunit aspartate transcarbamoylase molecule. The *X*-ray crystallography was carried out by others[4].

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