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'The display of electrostatic fields on raster graphics devices' **Morffew, A J, Quarendon, P, Rogers, N K* and Sternberg, M J E†** IBM UK Scientific Centre, St Clement Street, Winchester, Hampshire. *Laboratory of Molecular Biophysics, South Parks Road, Oxford. †Department of Crystallography, Birkbeck College, Malet Street, London.

Electrostatic interactions in globular proteins play an important role in their folding and function. Charges of the side chains are distributed asymmetrically over the surface of the molecule giving a large molecular dipole. Secondary structure elements such as the alpha-helix also possess appreciable dipole moments[1]. Warwicker and Watson's[2] finite difference algorithm is used to calculate the potentials in and around enzymes. The power of the algorithm is that it models the markedly different dielectric responses of the protein ($\epsilon = 3.5$) and the solvent ($\epsilon = 80$) together with a detailed consideration of the shape and charge distribution of the protein. Potential values are calculated on the points of a 3D cartesian grid of 1A spacing in a box of side 60A. The examples here were calculated on the Cray IS at ULCC.

It is difficult to analyse the results of these calculations without a graphics device. The Winchester Graphics System is being used to explore various representations.

- WINSOM[3] is used to produce CPK and secondary structure raster pictures of the molecule, on which the potentials are mapped in colour.
- A half-plane may be passed through the centre of the molecule parallel to the screen, potentials surrounding the molecule may be displayed.
- The potentials around the molecule may also be displayed by drawing spheres of increasing radius and colour contouring the potential over the surface. The set of pictures may be animated giving the viewer the impression of a growing sphere sampling the potential field.
- Isopotential surfaces may be calculated and displayed in colour on the raster device.
- The most successful method investigated so far, is to calculate lines of force by plotting trajectories of 'inertialess' charged particles. These can be displayed on a vector refresh device allowing realtime interactive manipulation. Alternatively, they may be displayed as arrows surrounding the CPK or secondary structure representations on the raster device. The arrows may also be animated to aid clarity.

REFERENCES

1 **Rogers, N K and Sternberg, M J E** *J. Mol. Biol.* (in press)
2 **Warwicker, J and Watson, H C** *J. Mol. Biol.* (1982) Vol 157, pp 671–679
3 **Quarendon, P** (see abstract 18)

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'Computer-assisted modelling and examination of protein-molecule complexes' **Müller, K** Central Research Units, F Hoffmann-La Roche & Co Ltd, CH-4002 Basel, Switzerland

Some features and applications of the Roche Interactive Molecular Graphics (RIMG) system are discussed. This software package is being developed at Hoffmann-La Roche, Basel, on a DEC VAX-11/780 computer equipped with an Evans & Sutherland Color Multi-Picture System.

RIMG provides various facilities for interactive examination of protein structures and cavity analyses, for modelling, superposition and comparison of small molecules, and for design and evaluation of protein-molecule complexes. Efficient algorithms for complete topological analyses of complex molecular structures enhance many features of molecular modelling and structure matching. An extended module for interactive and computer-assisted superposition of partially or fully flexible molecular structures with various optional constraints is a major asset of RIMG. Several graphic techniques are available for the examination of intermolecular packing, such as body/surface-differentiated raster representations, dotted-surface, space-filling, or chickenwire representations of molecular volumes.

RIMG is illustrated by some recent applications in the field of anti-folate drug design.

Comparison of model complexes of *L casei* and *E coli* dihydrofolate reductases (DHFR) with selected diaminopyrimidine inhibitors gives a rationale for differences in their binding properties. Examination of the (hypothetical) binding of dihydrofolate and tetrahydrofolate to *L casei* DHFR points to a potential hydride-transfer activating mechanism involving the remote arginine 57. Modelling of ternary DHFR-inhibitor-NADPH complexes provides clues to questions of DHFR conformational changes upon inhibitor and/or cofactor binding.

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'A model for the graphical display of pseudorotation in small rings' **Murray-Rust, P and Tonge, A P** Chemical Research Department, Glaxo Group Research, Greenford, Middlesex UB6 0HE, UK

Five-membered rings, such as the furanose ring in nucleic acids and the cyclopentane ring in prostaglandins, are frequently found in biological molecules. The conformational flexibility of these rings can have a marked effect on the spatial relationship of substituent groups and hence influence the biological activity of these compounds.

We have developed algorithms for describing the motion of the ring atoms and their substituents during the pseudorotational cycle of both carbocyclic and heterocyclic rings. These routines have been incorporated into a molecular modelling system to permit interactive manipulation of molecules through the pseudorotational pathway. Realtime display of associated molecular properties have been implemented, such as conformational energies derived from torsional and nonbonded potential functions and proton coupling constants calculated from a modified Karplus equation.

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'Real time energy calculation and minimization in interactive three dimensional computer graphics'

Pattabiraman, N, Levitt, M, Ferrin, T E and Langridge, R Computer Graphics Laboratory, University of California, San Francisco, CA 94143, USA

Realtime interactive computer graphic visualization of the interactions between molecules uses various geometric representations such as solvent-accessible and resulting van der Waals surfaces. In most molecular modelling methods, however, the main focus is on the 'lock and key' idea, ie is purely steric. We have developed a realtime docking method in which the energy of interaction between drug and receptor is displayed on a high performance 3D colour graphics system as the drug is moved in the receptor site. In our method, the atoms in the receptor are enclosed in a 3D cartesian grid and the electrostatic, repulsive and attractive potentials due to the receptor atoms are stored at the grid points. As the drug molecule is moved inside the receptor, the total energy of interaction is calculated from these grid points and updated on the screen in real time. A simplex method is used to minimize the energy of interaction while docking. Supported by research grant NIH RR-1081 and a Guggenheim Fellowship (RL).

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'Real time rotation of space-filled molecular models' **Pearson, J E** Ciba/Geigy, Switzerland

With the development of advanced raster-scan terminals which have more and more local computing capabilities it is now possible to do realtime rotation of true 3D space-filled molecular models.

After a brief review of some of the methods already in use for the display of static space-filled models, the new method will be described in detail. The method relies on an extension to polygon filling known as 'Back face testing'. Polygons described by lines drawn clockwise are shown on the screen whereas polygons drawn anticlockwise are not displayed. When a solid , each of whose faces have been drawn clockwise in turn, is viewed from the front, the back face will be described in a counter-clockwise fashion and will not be displayed.

Although the initial generation of the picture is fairly time-consuming (about 45 s for 100 atoms) the outstanding advantage of this method is that once the picture has been drawn, the host computer is no longer required for picture drawing and is merely required to amend the rotation matrix, if the solid is to be rotated. This means that the movement of a solid can be extremely fast and in practice it has been found necessary to up-date the rotation matrix every third of a degree in order to slow the rotation down to a useable speed.

The new method readily lends itself to software clipping of the surface so that it can be used to describe just part of a larger molecule. This means that the surface can be cut away to reveal a skeletal model inside.

With the latest generation of intelligent raster-scan displays it is possible to request that a surface be displayed as transparent. This would mean that it is possible to see an enclosed skeletal model and be able to differentiate readily between these and skeletal models which are outside the surface. Such models would be moveable in relation to each other in realtime.

Although the method uses a lot of display memory (~1/4 Mbyte/60 atoms) it can still be used to simplify complex pictures such as drugs in the active sites of enzymes, since only a limited number of atoms on the enzyme need be enveloped by a surface at any one time.

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'Work in progress at UNC Chapel Hill NIH Research Resource' **Pique, M** University of North Carolina, Chapel Hill, NC, USA

The University of North Carolina at Chapel Hill operates a research resource supported by the United States government's National Institutes of Health.

Three current computer graphics projects for molecular studies are:

- Evaluating and exploiting the scientific potential of our GRINCH system, which combines Carroll Johnson's ridge line representation of electron density maps with appropriate interactive tools. GRINCH users may trace the main chain, register the sequence, and roughly place side-chain atoms. GRINCH thus bridges mini-map interpretation and the contour-based, atomic-level fitting systems such as GRIP-75, FRODO, and BILDER.
- Developing multiple visual representations of molecules, including skeletal, surface, volume, and non-geometric views.
- Producing smoothly rotating CPK molecular models. We can now draw eight shaded raster images/s of a 50 atom molecule using our coupled DEC VAX-11/780 and Adage Ikonas RDS-3000.

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'The use of constructive solid geometry for molecular graphics' **Quarendon, P** IBM UK Scientific Centre, St Clement Street, Winchester, Hampshire, UK

A method of producing realistic representations of objects on a raster graphic terminal is described as is its application to molecular graphics. The basis is a general program which draws simple geometric primitives, such as spheres, cylinders and planes. These can be combined by Boolean operations to build more complex shapes. This method is becoming popular in CAD.

The program input consists of a text file which describes the objects to be drawn as an expression in this Constructive Solid Geometry. It can also specify the colour and surface appearance of the objects and the position and characteristics of the sources of light to be assumed.

The algorithm used to construct pictures is developed from one by Woodwark and Quinlan. It continually subdivides the space in which the objects lie until it finds regions which are either empty, uniformly filled, or are too small to subdivide further.

Relatively simple application programs are then used to generate a variety of representations from molecular data held in a relational database. Examples of the type of pictures which can be produced are: