Progress 1978-83
Proposal 1984-89
Interactive Graphics for Molecular Graphics System

TR83-06

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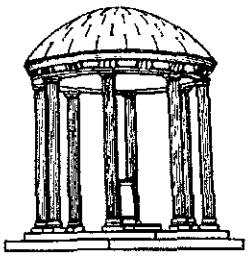

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Section 2. Research Plan

A. Summary–Specific Aims

Since 1969 our team of computer scientists at UNC-Chapel Hill has been applying interactive graphics technology in collaboration with and support of biochemists studying macromolecular structure. We have both adapted known graphics technology and invented new.

During 1974-84, we have developed and operated an NIH-funded Research Resource, including the GRIP-75 crystallographic fitting system. Accomplishments include:

- collaboration with some 27 teams of biochemists from 27 institutions in 14 states and three foreign countries. Fifteen teams have been users over several years.
- published results crediting our Resource in at least 34 biochemistry papers.
- published results on new graphics techniques in 15 computer science papers.

Our most recent contribution has been the development of a totally new interactive graphics system, GRINCH, for *ab initio* interpretations of maps. This system pioneers in the practical exploitation of Carroll Johnson's ridge-line representation of electron density distributions.

Among the several groups developing molecular graphics, we have been characterized by our openness to scientific collaborators, our support of them, and our emphasis on the human factors of our systems.

The sweep of computer and graphics technology, however, now makes it unnecessary for users to travel to central Research Resources for the use of high-powered graphics systems. Within three years it should be possible to put such systems within economic and intellectual reach of most molecular structure laboratories. Decentralization is the glory of the new technology.

We plan therefore to cease operating a Research Resource as such in 1984. We instead propose a program of Resource-Related Research projects:

1. Continually develop a **trailblazer molecular graphics system**, a facility with state-of-the-art hardware, and advanced and varied software, where biochemists will continue to come for pioneering work and collaboration on technique development.
2. Exploit and evaluate the scientific potential of Johnson's **ridge-line** representation of electron density through use and extension of the GRINCH system.
3. Develop a **modest-cost molecular graphics configuration, MOLIX**, for the working biochemist to have in his laboratory. We will use and develop application software for a commercially available computer and operating system.
4. Develop economical **real-time manipulation** capability for **space-filling models.**
5. Evaluate the scientific potential of **multiple visualizations** of molecules.
6. Develop real-time techniques for modeling **molecular docking.**
7. Explore **advanced technology** for all aspects of the above.

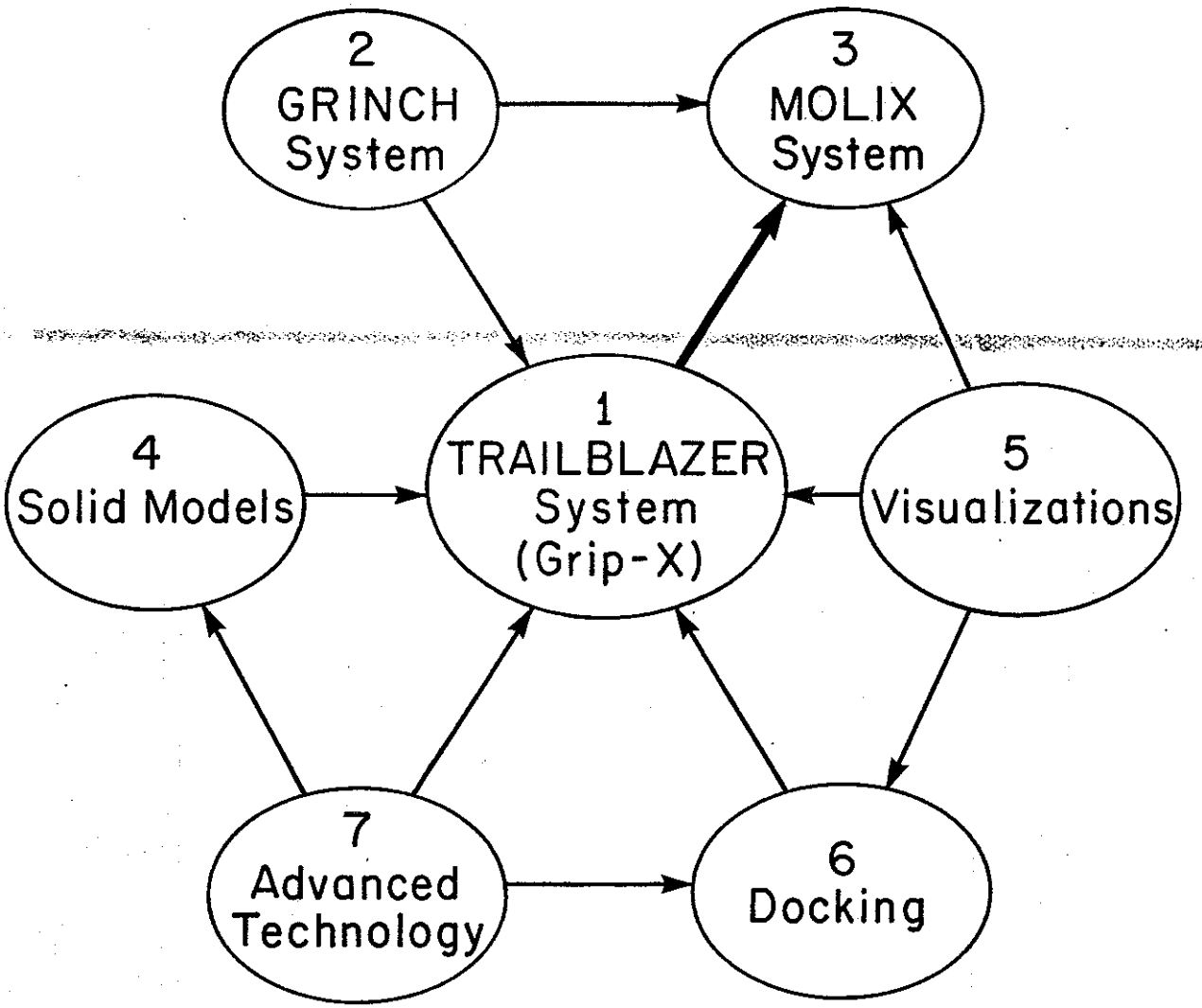

Figure 1. The Seven Projects - Relationships

C. The Research Program—Projects and Methods

Net. Our seven projects, shown in Figure 1, devote a proven team of computer graphics researchers to toolbuilding for studies of biologically interesting molecular structures. We are not biochemists; we cannot contribute to the biochemistry proper. We do, however, have a record of fruitful collaboration with many teams of biochemists. We propose to continue this collaboration.

Our driving-problem research strategy. We believe that computer science advances fastest when work has purpose, focus, some time-urgency, and is disciplined by extrinsic measurement of results.

A strategy we have therefore followed is to develop computer-science ideas at any level by choosing a *driving problem* for each idea, and then:

- **aiming** research at the real concrete needs of that problem instead of vague, hypothetical ones.
- **focusing** the mainline research at the needs of that problem, instead of at all conceivable uses. This strategy does not preclude exploration of side alleys. It does insist that such exploration be identified as such, unless and until an alley proves promising enough to become the main street.
- **driving and ordering** research subgoals by the timing and ordering of the driving problem's needs.
- **testing and measuring** research results against the extrinsic criteria of the driving problem. "The proof of the pudding is in the eating."
- **generalizing** to a larger problem set after a solution is shown to work for the initial problem.

In 1969, molecular study appeared to be the most promising driving problem for research in interactive three-dimensional real-time computer graphics, because of the local availability of excellent collaborators, because of the scientific importance of the application, because of its inherent three-dimensional nature, and because the field would not be saturated with commercial competitors (as would, for example, computer-aided design of metal parts.) In 1982 we surveyed our work of the decade and looked again at possible graphics application areas. Molecular structure study is still the area of greatest scientific opportunity.

Why five years? First, some of the projects will take that long. Second, for productivity. During 1974-1979 we were supported by one- and two-year grants as a Research Resource. For the period 1979-1984 we have had a five-year grant. We perceive the difference in scientific productivity to be great. In the latter period we've been able to put our attention on the science to be accomplished rather than on the continual writing and prosecution of competitive proposals. Therefore we propose a five-year program of research for the period 1984-1989.

C.1 TRAILBLAZER System

Computer and graphics costs keep dropping, about 25% per year. This trend shows no sign of stopping.

The molecular graphics discipline needs a state-of-the-art hardware facility where there can be developed now the molecular graphics software for deployment on low-cost hardware a few years hence.

Our central research project, therefore, is to continue the steady evolution and operation of our present TRAILBLAZER molecular graphics system. As Figure 1 shows, this builds on a VAX-UNIX-C implementation of our successful GRIP-75 crystallographic fitting system. The capabilities of our prototype GRINCH ridgeline system will be added to this base, along with the results of our other research projects.

We foresee now the deployment of very powerful interactive computer graphics hardware to the biochemists' laboratories at affordable prices in 1985 - 1989. So it is important to begin even now the development, debugging, and human-factors tuning of the molecular studies software necessary to capitalize on that hardware .

The trailblazing function requires:

- forecasting trends in computer and graphics technology.
- maintaining an experimental graphics hardware facility continually at the state of the art.
- continual importation of good new programs and techniques.
- collaboration with real users in solving molecular problems too hard for less powerful systems.
- publication of results and techniques.
- incorporation of techniques into laboratory-deployable packages.

Computer and Graphics Trend Forecasting. Toward this end we regularly attend professional conferences on computer hardware, on graphics hardware, on graphics techniques, and on software engineering. We regularly study the journals in all these areas. We have approximately twenty visiting speakers a year on our campus in these areas, and members of our team or department visit approximately 12 - 20 manufacturers and software suppliers per year.

Facilities for the TRAILBLAZER System. As the Resources and Environment Section above details, we have available for this research program a substantial hardware and software facility, with expertise in the use of many software-building and graphics tools. We have been awarded a 5-year, $3 million NSF grant under the Coordinated Experimental Research program. The purpose of this grant is to enhance the department's equipment and technical support for experimental work in computer graphics and VLSI machine design. The molecular graphics research proposed here will benefit from this enhanced facility and research environment.

a unified Agent screen and menu management approach.

Extended Capabilities. Ever since the productive use of the GRIP-75 system began, our team has continually used it as a test bed on which to experiment with advanced techniques in computer graphics, improved human factors, or added graphics, and new chemistry capabilities. Our first-year graduate curriculum includes a Software Engineering Laboratory. Students in teams of four undertake to build, demonstrate, and document a nontrivial working software product. The most common single way for doing the original prototyping of GRIP enhancements has been as such projects.

We make a *playpen copy* of the then current production version of GRIP for the developers of the new features. From it, they may remove features as necessary to get the memory space for experimental features. A prototype is built and demonstrated, and if possible it is used by our scientific collaborators.

If the feature proves its worth, then a second round of development is begun , frequently as an M.S. thesis or research project. After the new capability has been developed to product quality, it is installed in the next production version of the GRIP system.

During 1984-89 we expect to add in a unified way to this system many different capabilities which have already been prototyped one at a time on experimental versions of our system. These include:

- Incorporation of three-dimensional joysticks and/or trackball for viewing controls.
- Incorporation of all manipulation controls into a data tablet and into the two-dimensional display of the plane of the screen in order to give tactile continuity to the system user. Comparative human factors studies of this against the multiple-joystick approach of GRIP-75.
- Incorporation of internal energy calculations. An early version of the GRIP system could calculate molecular potential energy using the Scheraga model, as well as to calculate the force and torque exerted on one molecular fragment by another. This made it possible to do interactive relaxation studies. At each push of the button the users would watch the free molecular fragment move an incremental distance toward the direction and orientation dictated by the forces and torques upon it. The energy model used in this early version did not make provision for solvent. Hermans and his group are now working with a simple energy model that takes solvent water into account.
- Incorporation of multiple representations of molecules, including especially dynamic Ramachandran plots - plots that change as residues are moved.
- Incorporation of user-changeable interactive definition of new menu items from adjunct language primitives and new menu groupings of predefined menu items.
- Incorporation of molecule editing facilities of PROPHET, including interactive access to the PROPHET database, with smooth automatic translation (both ways) between PROPHET data formats and GRIP data formats.
- Incorporation of the ability to set up and invoke batch molecular software including Lynn F. Ten Eyck's Fast Fourier Transform, various contourers, geometric idealizers, and refining programs.

Human Factors of Alternative Forms of Manual Input. In using the GRIP-75 system one really needs three hands. The left hand translates the residue being fit with a three-

C.2 The GRINCH System For Semi-Automatic Density Map Interpretation

Williams's Work. As detailed in the next section and Appendix D, Thomas V. Williams for his Ph.D. dissertation developed a new interactive man-machine computer graphics system designed to help biochemists do *ab initio* interpretation of electron density maps. This GRINCH system pioneered the use of Carroll Johnson's ridge-line representation of electron density rather than contours of density on planes in 1, 2, or 3 dimensions, as has been customary in most molecular graphics systems.

Ridge-line representation uses many fewer lines to show an electron density map than do contour representations. As a consequence of this representational economy:

- It is possible for the user to zoom back and view the whole map at once with some hope of comprehending what one is seeing.
- The user can dynamically, in real-time, change the density level threshold below which lines are invisible.
- The ability to move dynamically up and down the density scale makes it easy to see the relationships among density peaks, ridges between peaks, and structural features such as α-helices and β-sheets.
- The representation can be adapted to limited line-drawing powers of the raster scan color display technology, which is radically cheaper than vector-drawing color display technology.

Williams, working in collaboration with Duke biochemists Jane Richardson, John Tainer,and Elizabeth Getzoff, was able to show that *ab initio* interpretation of density maps, never heretofore done on computer graphics systems (so far as the literature shows), can be successfully done with much higher productivity than with the customary plastic mini-maps.

Crystallographic fitting today requires three steps once the data has been taken. (1) *Interpretation* of the density map to determine which clump of density corresponds to which residue. The usual result of this step is locations of the alpha carbons. (2) *Manual fitting* of the remainder of the peptide unit and of the side chain so as to account for almost all the density by the placement of the specific atoms of each residue. (3) *Algorithmic refinement* , e.g. by least squares, to establish each atom's location in a position that optimally accounts for the density or measured diffraction amplitudes and satisfies bond length, bond angle and dihedral angle constraints.

We will use the terms *interpretation*, *fitting*, and *refinement* in these narrow senses.

Hypotheses. Even our limited testing of Williams's prototype system suggests several exciting hypotheses for further investigation:

Successful interpretation of poorer quality maps? J. Richardson believes it is possible that the use of the GRINCH system will enable biochemists to interpret maps of a resolution or noise quality heretofore too poor to be interpreted by classical mini-map methods. She believes the zooming and multi-directional viewing may enable the biochemist to perceive structure that could not be perceived with the mini-map methods. This possibility is very exciting. An ability to get an initial interpretation earlier in the cycle of map refinement and data taking could substantially speed up the whole crystallographic structure determination process.

To investigate it, we plan to create from known structures artificial maps at several different degrees of resolution, and, working with biochemistry graduate students unfamiliar with the molecules in question, to see what quality of interpretations can be derived. In addition we will do exploratory interpretation with our collaborators on maps that have never been interpreted because the quality appears to be too poor. A third kind of experiment is to take maps whose original published interpretation was wrong, and, working with appropriately ignorant biochemist subjects, see if they are able to derive the right interpretation using Williams's system and the original poor-quality map.

Skip manual fitting? The second step, manual fitting with human judgement as to the placement of atom centers, is necessary because the algorithmic least squares processes require initial conditions quite close to the true value. Unless each atom is relatively close to its final position, the algorithmic process is apt to converge to an incorrect placement. Early work with the GRINCH prototype suggests that it might often be possible to locate not only alpha carbons but also other peptide atoms and side chains during the initial interpretation process. In other words, that manual fitting can be done with the ridge-line representation and that it will not be necessary to go to the conventional contour representation and do the more precise fitting. If this is true it means that a step in the process can be skipped entirely.

We propose to test this by finding a collaborator who is willing to attempt manual fitting using the GRINCH system for the whole process.

Complete Crystallographic System on Raster Scan Display? A perfect ridge-line representation of a perfect density map would in fact be a Kendrew model, showing the atoms at the density peaks and the ridge-lines connecting density peaks. For this reason an interpretation tends to lie on top of the density structure being fit. It is important to distinguish them by color, line quality, et cetera. Color is much the best way, and the GRINCH system therefore has greater need for color display than contour-line based systems such as GRIP-75.

At the same time the GRINCH system may make it possible to take advantage of raster-scan color display technology because far fewer lines are needed to represent electron density. The raster-scan technology is the main line of graphics technology, deriving as it does directly from color television . Each new advance in color television technology directly benefits and supports the raster scan display technology. If graphics for molecular studies can be so organized as to fit on raster scan displays, molecular studies can move to the main line of display development rather than being in the expensive, small-market, sideline area of vector graphics. The third hypothesis raised by the GRINCH system, therefore, is that by the use of ridge-line representations of electron density maps a complete molecular studies system can be built using raster-scan color technology at radically less cost than would be possible for vector technology.

We propose to test this hypothesis by constructing a prototype complete molecular studies system on a low-cost raster-scan color display. We call this project the MOLIX system. It is discussed in the next section.

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C.3 MOLIX Project - Molecular Interactive Conformational System

We propose to build an integrated hardware-software molecular studies system to be used for viewing, crystallographic interpretation, crystallographic fitting, computation, docking, and multiple representations of molecules. The MOLIX workstation will have a 1984 system target price of $40,000. Fundamentally our approach is to use off-the-shelf computer hardware, graphics hardware, and operating systems software. We would equip it with molecular application studies software. Characteristics of the system as we envision it are

- built around a professional workstation using one or more Motorola 68010 processor chips with memory management.
- one megabyte internal memory with expandability to two or more.
- attached disk capacity of approximately 75 megabytes.
- RS 232, Ethernet, and perhaps other standard networking communications.
- color raster-scan graphics with approximately 512 x 512 resolution.
- mouse, viewpointer joystick, and other analog interactive devices.
- processor speed of approximately 1 million operations per second, with hardware floating-point optional.
- UNIX operating system.
- initially GRINCH software with follow-on GRIP-X (extended) software. All software product-quality, tested, documented, supported from Chapel Hill with updates, revisions, phone-answering service.
- hardware service by established service network from the hardware manufacturer.

We expect the cost of this system to decline by a factor of 2 over four years and be enhanceable over that time with off-the-shelf array processors. We are currently experimenting with a system with roughly these properties built by SUN Microsystems, Inc. Our collaborators at Duke, the Richardsons, are also acquiring one of these. We will work together on software development and use.

We are familiar with Kent Wilson's proposal of February 1983, to build a similar system around array processors. Our MOLIX project goals are much less ambitious. MOLIX will have much less compute power. We do not propose to do hardware development, integration, or field maintenance. We plan to build only such molecular studies software as can be done for commercially available, vendor-integrated, vendor-maintained systems.

The relationship of MOLIX to Wilson's project will then be of one of three forms, depending upon events:

If Wilson's project is funded and succeeds as planned, we will adapt all our software to his system and field-support it on his system.

If NIH is unable to fund Wilson's project, MOLIX will provide a lower-cost, much less powerful fall-back system for biochemists' laboratories.

If Wilson's project is funded but runs into delays or technical problems, MOLIX will provide a lower-cost, lower-power, lower-risk backup or interim system for his intending users.

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C.4 Dynamic Rotation of Solid Models.

Need. Today the biochemists can choose in computer graphics between Kendrew (stick figure) models of molecules which can be rotated dynamically as an aid to depth perception and structure scrutiny, or CPK (space-filling) models in which each atom is represented by a sphere. The space filling models cannot today be rotated dynamically for protein-sized molecules except with expensive processors. Molecular studies, including viewing and docking, will need the ability for dynamic rotation and rocking of space-filling models. We believe this can be accomplished economically during the next five years; we believe our laboratory is an excellent position to do it first.

We propose therefore to achieve dynamic rotation of protein sized molecules in space-filling model form first on our TRAILBLAZER system with a target of the end of the 1985-86 project year, and then on the MOLIX workstation with a target of the end of the 1988-89 project year.

Poker Chips. We have demonstrated two ways of approaching this goal. In the first, demonstrated by Zeeberg, et al in 1982, a "poker-chip" representation devised by Pique was used. Each atom's sphere is represented by a disk continually parallel to the screen, painted to look like a sphere. These disks can then be manipulated very rapidly. We have demonstrated real-time dynamic rotation of molecules of several dozen atoms by this technique.

This technique shows one artifact: spheres do not intersect. Each appears to lie entirely in front of or entirely behind its neighbor with whom it really shares some space. This artifact is observable as a popping of a "poker-chip" disk from behind to before a neighboring atom as the molecule is rotated. The effect is not especially bothersome and the view of the molecule as a whole is rather good. We do not intend at present to explore this technique further except in conjunction with the Pixel-Planes display hardware.

True Spheres. In an alternative approach Mike Pique has demonstrated the dynamic rotations of molecules of up to 50 atoms represented properly by intersecting spheres. The accompanying video tape shows this work in true real time. This approach embodies the approach of a very fast graphics processor, an AMD 2901 bit-slice microprocessor contained in the Ikonas 3000 graphics display device. Special programming by Pique was used to accomplish the rotation. We shall explore this technique further to squeeze out more speed and perhaps get the representable molecule up to protein size.

Pixel-Planes. H. Fuchs has invented a modified graphics buffer memory which is capable of calculating at each pixel simultaneously (1) enclosure of a pixel in a set of broadcast polygons, (2) the hidden surface problem, and (3) the interpolated color of a pixel in a shaded, smoothed polygon. Essentially each pixel circuit contains one bit of multiplier, a one-bit adder, the normal pixel buffer, a few extra bits of pixel memory and the controls that enable expressions of the form $Ax+By+C$ to be evaluated simultaneously at every pixel location (X,Y) as the coefficients A, B, and C are broadcast to all the pixels . Fuchs has shown how each of the above tasks can be accomplished by the evaluations of the form $Ax+By+C$.

Brooks has shown how with the addition of memory for one quantity for each pixel circle definition can be accomplished. That is, coefficients A, B, and C defining a circle

are broadcast to each pixel and each pixel calculates whether it is inside or outside that circle. Circle definition is accomplished with the same computational work as is required for one edge for polygon definition.

Consider the circle n, with radius r_n and center at x_n, y_n. A pixel at x,y is on or inside the circle n if

$$(x-x_n)^2 + (y-y_n)^2 \leq r_n^2$$

Expanding:

$$x^2 - 2x_n x + x_n^2 + y^2 - 2y_n y + y_n^2 - r_n^2 \leq 0$$

Collecting:

$$-2x_n x - 2y_n y + (x_n^2+y_n^2-r_n^2) + (x^2+y^2) \leq 0$$

which is of the form $Ax+By+C+(x^2+y^2)$. The last term depends only on the pixel location, not the broadcast circle, so it can be built in as ROM or pre-stored.

We plan to incorporate a Pixel-Planes processor within our TRAILBLAZER system and initially expect to use it in conjunction with the poker-chip algorithm to accomplish real-time display of solid models of molecules of up to a thousand atoms. Our plan is to accomplish this by the end of the 1985-86 project year.

Investigations are underway to see if the Pixel-Planes evaluator can be used to evaluate conic sections other than circles. If so, this might enable the same buffer memory to be used for the intersecting sphere algorithm. This is a long shot.

C.5 Multiple Molecular Visualizations. "The purpose of computing is insight not numbers"-(Hamming). A fundamental thesis of much of our work is that insight in molecular studies can be enhanced by the concurrent, or rapidly selectable, use of many different ways of visualizing a molecule, each chosen to display some particular aspect of the molecular properties.

The enclosed videotape, Appendix E, *What does a Protein Look Like?*, by Mike Pique, was first shown at *Science* magazine's Conference on Computers in Science, in December, 1982. For this videotape we have assembled almost all the visualization techniques for molecules that we have seen. We have applied them to a single molecule, Bovine (Cu,Zn) Superoxide Dismutase (SOD), in order to demonstrate the differences among the techniques (listed in Appendix C) and to demonstrate the cumulative power of seeing the molecule from many different conceptual viewpoints.

For most of the representations we have successfully imported to our TRAILBLAZER system programs from the original author of the representation. In one case, because of the lack of a color vector display, we imported film clips instead, from Robert Langridge's laboratory at the University of California in San Francisco showing Connolly dot surfaces.

In this part of this project we expect to continue to import programs for new visualizations as they are developed anywhere in the research community, as well as to continue to develop new visualizations here.

Raster Analytic Molecular Surfaces. Dr. Michael Connolly of Scripp's Clinic Research Institute in La Jolla visited our facility for 10 days in February and August 1982 to collaborate with Pique in developing Connolly's shaded-surface display of molecular surfaces. Like his well-known dot surfaces, these show the molecular surface accessible to a probe sphere of a given radius. Unlike the dots, or tiled surfaces

derived from the dots, the surfaces generated by his RAMS program are continuous, analytically smooth, and cover the molecule with no gaps or cracks. The program runs on our VAX computer and generates images for the Ikonas color raster display. Each view of a typical protein requires about two hours to calculate. About 60 such images were included in Pique's videotape, described above.

C.6 Docking.

Molecular graphics systems were first used for viewing molecules, then for crystallographic fitting of molecules, and now to study molecule-molecule interactions. This extension to docking is of central importance for the analytic design of new drug molecules.

In collaboration with biochemists from the Burroughs Wellcome Company we have been studying the docking problem on our TRAILBLAZER system. A systematic investigation of ways of doing docking by joy-stick manipulation and ways of perceiving the docking task will be a major project in our research program.

The real molecule docking problem is not the same as the docking problem for two rigid objects. Part of what happens during molecular docking is changing conformation of one or more of the dockers. Moreover, Karplus has shown that it is necessary to consider the thermal and other statistical behaviors of the molecule, which may allow docking under low-probability circumstances which nevertheless occur frequently in the world's real-time scale. We will start with rigid-body docking and proceed from there.

The hardest part of the rigid-body docking problem appears to be the simultaneous perception of the two surfaces which are to be docked and the detection of contact by eye or by algorithm. Our approaches to this problem are given below.

Negative volume display. As two space-filling models of molecules approach each other, perhaps the most useful visualization of docking progress and the docking task is to display the space between the molecules as if it were a solid object which can be viewed from all directions and which dynamically changes shape as one molecule is brought up against the other with a 6-degree-of-freedom joy-stick control.

Colored dot-surfaces. Langridge and collaborators have shown how Connolly dot surfaces calculated for the surface of a receptor and the surface of an enzyme can be used to help dock the enzyme. With color display equipment due for delivery this summer we will have this capability. We expect to investigate it in direct comparison with other docking display techniques.

Mathematical surface description. Lee R. Nackman of this department has shown in his Ph.D. dissertation how Blum's algorithm for the description of contours in two dimensions can be extended for the description of surfaces in three dimensions. This algorithm may be especially appropriate for describing solvent-accessible surfaces of molecules or their inverses, the negative space between two such. Recent work by Gerry Radack, University of Pennsylvania, has shown how docking can be described in terms of critical points of the two surfaces. We plan to continue investigation of such algorithmic methods.

Voxel-Planes bump checker. Brooks has shown how Fuchs's Pixel-Planes graphics buffer can be programmed to describe regions of space cut into volume elements. Given a Pixel-Planes buffer of 512 by 512 pixels at 64 bits per pixel, Brooks's algorithm can be used to detect attempted multiple occupancy of 512 by 512 by 63 voxels.

The volume is layered to 63 layers. The circular intersection of each atomic sphere with each layer is calculated. These circle definitions are broadcast to all the pixels for a given layer, and each pixel identifies which circles it is within, by the method described in C.4, above. After the atom circles for the one molecule have been broadcast, those for the docking molecule are broadcast. If any pixel lies within circles for both molecules, a bump between the two has occurred and the location of the collision is reported.

When the prototype Pixel-Planes device is available to us, we plan to program it as a bump checker. We expect to be able to use it for prototype docking studies by the 1986-87 project year.

Force Feedback. In docking real solid models, the best fit is usually known by the tactile sense: after a bump occurs between the two models being docked, one continues to push, allowing the models to orient and to translate in such a way as to snuggle into the best fit. This seems a natural and powerful mode of working; it would be desirable to achieve it in a molecular graphics system.

J. Kilpatrick in a Ph.D. dissertation in this department investigated the use of kinesthetic feedback as an aid to simple manipulation tasks in 1976. His results showed that kinesthetic feedback improved user perception of the world-model under manipulation, more even than did three-dimensional stereo viewing. We have a computer-interfaced, seven-degree-of-freedom, force-feedback manipulator pair which can be used for such studies. A possible project is to use these force-feedback manipulators together with the Voxel-Planes bump checker to give visual and kinesthetic docking capabilities for computer models of molecules.

C.7 Advanced Technology.

We plan to continue exploring and prototyping new graphics technology for molecular studies, things not yet reducible to routine use. These investigations will mostly be done as student class or dissertation projects.

The Varifocal mirror. H. Sands Hobgood in 1970 investigated here the computer-graphics use of Traub's varifocal mirror. The technology at that point was insufficiently advanced to make this feasible. S. M. Pizer and H. Fuchs of this department have developed a way of accomplishing display with relatively modest added cost (the mirror and its driver are the only new electronics) from a ordinary visual raster scan display buffer such as the Ikonas 3000. The very fast internal processing speeds of the Ikonas 3000 and its 2901 microprocessor permit objects not only to be displayed in three dimensions but also to be rotated and windowed in real time. We have successfully done prototype line-drawing displays of proteins using this technique. We plan to continue comparative studies of this technique versus other three-dimensional techniques for the visualization of molecules and of electron densities.

Three-Dimensional Viewing Techniques. We have in the past prototyped a variety of three-dimensional viewing illusions and done some comparative studies on them. They include:

- time-division multiplexing of left and right eye images with synchronized eye shutters. We are today using this technique on the production GRIP-75 system, using a Bausch and Lomb mechanical shutter and will shortly be attaching a Kerr-cell electrical shutter to the TRAILBLAZER system for this technique.
- Side-by-side stereo for photography.
- Up-down dual-display stereo using a half-silvered mirror and polarizing filters (Ortony system).
- Head-position sensing using a CCD detector of a head-mounted light's angular position.

We plan to continue investigating every aid to three-dimensional viewing that the technology offers.

Color vector graphics. Larry Sinclair, engineer and proprietor of a firm called Anti-Gravitational Systems, Inc., has devised a low cost scheme for providing a color monitor attached to the Vector General display. The Vector General display unit is capable of having multiple display heads. He uses one of these drivers each for the red, green, and blue guns in a color monitor tube.

We entered into a collaboration with him, allowing him to use our Vector-General system and providing test programs. Sinclair and his display spent two weeks here during 1982. His system, while sound in concept, did not have big enough power supplies to maintain full picture size. He has gone back to the drawing board. We expect to work with him again when he has a new version of the display ready.

Head-mounted display. The view of an imaginary world offered by an ordinary graphics screen is a view through a porthole with the user on one side and the imaginary world on the other side. Ivan Sutherland in 1965 proposed a construction of a display that would make the viewer a participant in the imaginary world; i.e. it would superimpose the imaginary world on top of the real world about the viewer. He constructed such a display using a mechanical linkage to detect head position and orientation. It was unsatisfactory because of the cumbersomeness of the linkage.

Fifteen years later the technological possibilities are entirely new. A team in our laboratory under the direction of Prof. H. Fuchs is constructing a new head-mounted display. Separate images are displayed to each eye through small television monitors, reflected off half-silvered mirrors that superimpose the displayed universe on the real one. The hard problem is sensing the position and orientation of the viewer's head, and of his hand if he is to manipulate the abstract objects in the imaginary universe. G. Bishop for his Ph.D. dissertation is designing an integrated VLSI (very-large-scale-integration) chip that integrates optical sensing and pattern processing logic. He plans to mount these in a dodecahedral configuration. All parts of the room about the viewer will be continually scanned at 500 images per second, with comparisons made of the position of any distinguishable object from its position in the previous sample. From the integration of this information he expects to derive translation and orientation information. Such a device will be mounted on the head as a crown or held in the hand as a scepter. The first two test chips have been fabricated, the second achieving

almost fifty times the light sensitivity, and hence sampling speed, of the first.

The GRIP team is collaborating with the head-mounted display team in furnishing the data and display programs for a room-filling molecule which the viewer will move and whose conformation he will manipulate by bond twisting. A prototype viewing system is currently in operation, although it does not operate with real-time speeds.

The present sensing scheme is the third that has been conceived in our laboratory for this application. It appears to be the most promising so far. The first used wall-mounted sensors of a head-mounted light, with a cone of polarizing material around the light and a polarizing detector on the sensors to give orientation information. The second scheme used wall-mounted tracking lasers and a head-mounted retro reflector.

We plan to determine if the effective illusion of presence in the superimposed worlds can be accomplished, and if it enhances the chemist's ability to perceive and to manipulate molecular structure.

D. Resource Accomplishments of the Past Five Years.

Much of what we have done is described above as the technical base for our proposed work. Here we will discuss the other major accomplishments.

D.1 GRIP-75 Use.

Propagation of Systems–Demonstrations. At the start of our 1979-84 grant, interactive computer graphics systems were a rarity in molecular laboratories. Now the list which we maintain for the community shows some 75 systems worldwide. In 1977, Dr. David Barry, then of Washington University of St. Louis, could say at the American Crystallographic Society meeting, "More chemistry has been done on the GRIP system at Chapel Hill than on all other graphic systems in the world combined." Today molecules are routinely fit by graphical methods.

We have played a role in this spreading of the graphical technique. The first demonstration of its complete feasibility for solving protein molecules was done here by Petsko and Tsernoglou in 1976. Our openness to visitors and our frequent demonstrations for visitors in the last five years has helped spread the word. Because our system uses a peculiar hardware and supporting software configuration, it itself has not been exported, but thirteen of our users operate their own systems after having acquired the technique and seen its power in our laboratory.

The tables in the Progress Report attached as Appendix C show the hours of use of the GRIP-75 system, 1975-1982 and the names, institutions, and use by each user.

The Sea-snake Neurotoxin. In 1976, Professor D. Tsernoglou of Wayne State University and Dr. J. McQueen of UNC fit a 2.2Å map of a sea snake neurotoxin using GRIP-75. Knowledge of the structure of this neurotoxin is important to understanding the nature of the neural connections it blocks.

In 1976 and 1977, Dr. G. Petsko of Wayne State University did further work on this neurotoxin using GRIP-75.

During 1981, Prof. Barbara Low of Columbia University and Dr. Steve Ginnell, a research associate of hers, spent about 150 hours fitting the structure of the neurotoxin to a greatly improved 1.4Å resolution electron density map phased by the density modification procedures of Dr. Douglas Collins, Texas A&M University.

Yeast Phenylalanine tRNA. Drs. Joel Sussman, Stephen Holbrook, and Wade Warrant, and Mr. George Church, working under the direction of Professor Sung-Hou Kim, used GRIP-75 in combination with their constrained-restrained least squares method to refine the 3-dimensional structure of Yeast Phenylalanine Transfer RNA.

Professor Kim's group also investigated three RNA-ligand interactions associated with this molecule:

- Metal binding sites in Yeast Phenylalanine tRNA - Drs. Sussman, Holbrook, and Warrant discovered why magnesium ions are essential to the activity of this tRNA molecule. By displaying a difference map on our molecular graphics system, they were able to identify the number and the coordination geometry of the essential magnesium ions and study their specific stereochemical environments.

- Protamine -- double helix interaction - Dr. Warrant investigated how Protamine becomes alpha-helical upon interaction with the tRNA and how it stabilizes the packaging of two adjacent double helical segments of tRNA's.
- Aromatic mutagen -- tRNA interaction - Dr. Warrant identified tentative binding sites for several aromatic mutagens on the tRNA molecule.

Copper,Zinc, Superoxide Dismutase (Bovine). Recently, the most active scientific collaborators of our Resource have been the team of David Richardson, Jane Richardson, John Tainer, and Elizabeth Getzoff, who have solved the structure and elucidated the function of Superoxide Dismutase.

The Richardson team used GRIP-75 to fit a model of SOD to an experimentally determined electron density map. GRIP-75 enabled them to fit the entire crystal structure of four subunits, totaling about 5000 atoms, to superimpose these four subunits, and then to arbitrate apparent differences among them.

On-line idealization, on-line checking of bond lengths and angles, on-line display of Ramachandran plots all aided the work considerably.

The quality of the map was then improved by refinement at Wayne Hendrickson's lab, using a process that is highly sensitive to the quality of the initial fit. The resulting map is good enough to resolve long-standing questions about how groups of atoms in the active site are associated.

D.2 Molecular Mechanics. Our first collaborator on molecular graphics, starting in 1969, was Professor Jan Hermans of the UNC Department of Biochemistry. In recent years, Hermans has turned to molecular mechanics including Monte Carlo simulations of thermal ensembles and molecular-dynamics simulations of molecular motion. In the year just finished, Professor Hermans and his associates used hours of VAX 11/780 time in molecular modeling work, molecular dynamics work, and in molecular refinement work, and made frequent use of the graphics facilities.

A number of programs have been brought into a unified format using the UNIX preprocessors "macro" and "rat" and the F77 compiler:

- PREDATOR - prepares the data describing a system to be simulated in a form usable by the other programs and by GRIP-75, from easy-to-understand input.
- CEDAR - performs molecular dynamics or energy minimization; the program allows for the presence of any number of molecules in the system, has special features for rapid calculation of water-water interactions, and maintains crystal symmetry.
- MONTE - performs Monte Carlo calculations on the same sort of systems, moving and rotating water molecules.
- ANALYSIS - Various features within Cedar, and several stand alone programs perform calculations of structural parameters, of average and RMS values, of simulated density maps, and of time correlation functions.
- GRAPHICS - performs playback of short-time sequences of a molecular-dynamics run, as images of stick models with dotted hydrogen bonds, on the Evans and Sutherland PS 300. Another program shows a stick model with thermal parallelopipeds at each atom location.

Current work focuses on comparison of the dynamics of simple molecules (e.g., poly-alanine in alpha-helical conformation) in absence and presense of solvent, and on

solvent structure as influenced by the presense of the solvent molecule.

D.3 GRINCH.

Thomas V. Williams completed construction and testing of a prototype man-machine system for initial interpretation of density maps of proteins, a feat not heretofore accomplished by computer graphics. The breakthrough was the choice of Carroll K. Johnson's ridgeline representation for electron density instead of the conventional contour representation. This allows the biochemist to zoom back and forth between global and local views and to dynamically change the level of density visible. The dissertation is attached as appendix D.

By *initial interpretation* we mean estimating from an electron density map the positions of the mainchain atoms and perhaps the carbonyl and C-beta atoms, using the amino acid sequence if it is available.

Man-machine System. Williams's system is a man-machine system. Earlier attempts to interpret a map by a computer alone have not been very successful. Humans are very good at pattern recognition. They can bring together diverse sources of specialized information. They can balance a feature's match to a local pattern with the feature's global context to make an overall decision. Computers are capable of accurate storage and recall of large amounts of information, pattern recognition for local, well-defined patterns, and numerical calculations.

The computer's task then is to remember the current state of interpretation and display it at all times. The ridge line graph and model are shown on a graphics screen with the edges color-coded as uninterpreted map, and map interpreted as mainchain, sidechain, carbonyl, disulfide bonds, and hydrogen bonds. This encoding helps the user to see at a glance the portion of the mainchain traced so far, which edges attached to the mainchain have not been accounted for yet, and many other useful pieces of information about the current interpretation. The current display implementation does color line drawing on the Ikonas raster graphics system and monochrome drawing on the VG 3303 and PS-300.

The user identifies features in the ridge lines and tells the computer which feature to associate with which part of the molecular model. The computer colors the features accordingly. The user adds edges as needed; the computer traces connected patterns. An extensive undoing capability permits easy backing out.

Ridge-Line Representation of the Electron Density Map. The most commonly used representation for electron density is contours drawn in sets of parallel planes. The contours show surfaces in the electron density function either at one or a small number of density values. The difficulty with using contours for initial fitting is that many lines are needed to accurately show the surface, and a global overview is often necessary to resolve ambiguities. There is a limit to the number of lines that can be comprehended at once. There is also a limit to the number that can be displayed flicker-free and dynamically rotated.

Ridge line representations of the electron density map were first suggested by Dr. Carroll K. Johnson of Oak Ridge National Laboratory. A ridge line representation shows the essential information about the location of high density and how it is connected, using many fewer lines than does a contour representation. Ridge lines, named by

analogy to geographic terrain, form a graph connecting peaks (local maxima) through passes. If there was one and only one peak for each atom in the molecule, then producing the ridge lines would completely solve the problem - each graph vertex would correspond to an atom and each edge to a bond. For molecules the size of proteins this never occurs because of insufficient map resolution, phase errors, noise in the data collection process, crystal imperfections, etc. The interpretation problem has been reduced to determining the correspondence between the actual ridge lines and the model. Some edges of the ridge line graph will lie along bonds, some edges are spurious, and some edges are missing, leaving bonds unaccounted for.

Color. The use of ridge-line density map representations so reduces the number of lines to be displayed that Williams was able to build his prototype on the raster-scan Ikonas. This gave him color, which radically simplified the user interface.

Density Changes. A key capability is the ability to show or hide ridgelines according to the mean density they represent. A slider control allows the user to change this threshold dynamically. We observe that users zoom in and out in their viewing, moving from local to global views and back. They also move often between high and low density visibility thresholds.

Results. Three different maps of differing qualities were interpreted by three user groups of different expertise in initial tests of the system.

Williams, not a biochemist, interpreted a 2.5Å Staphylococcal nuclease map with a sequence of 142 residues. He required 26 working hours and placed all but the last few residues at either end without significant error. Mainchain atoms were positioned with a mean distance of 0.86Å from published coordinates.

Jane Richardson, a seasoned crystallographer, interpreted a good quality 3.0Å map of cytochrome b5, 93 residues. Residues 4 through 82 were located and fit in 9 hours with a mean mainchain error of 0.66Å. The disordered ends were not interpreted, either by Richardson nor in the published interpretation.

E. Getzoff, J. Tainer, and D. McRee, biochemists and students of the Richardsons, interpreted a 2.8Å map of cytochrome c550. The work, covering 121 residues, took 22 hours and had mean mainchain errors of 1.04Å. In all three cases, sidechains were also located; mean errors for all atoms were 1.5 to 2 times those for mainchain atoms.

An unexpected result is that molecular boundaries show up clearly in the ridge-line representation.

D.4 Depth Cues for Molecular Graphics.

A major component of our research has been the systematic investigation of three dimensional depth cues for molecular graphics. This work culminated in the Ph.D. dissertation of James S. Lipscomb in 1981.

Depth perception of molecular models and density maps is a task quite different from depth perception of natural scenes of landscapes, etc., and from depth perception of visible man-made objects, such as mechanical parts. In the last case, geometrical regularities abound; in each of the latter two cases the hiding of one surface by another is the most potent depth cue. In the molecular modeling case, any

surface which one defines is at best a visualization of an abstraction.

A second important depth cue is the kinetic depth effect achieved whenever the scene moves or the head moves: objects which are nearer the eye have a greater angular displacement. This is powerfully and intuitively interpreted by the brain.

A third important depth cue is perspective. Our observations indicate perspective to be radically less important in the molecular environment. The observer is much more often concerned with trying to discern parallelism among bonds, as in beta sheet structures, than he is in trying to interpret known parallelisms and their distortion as a cue to depth.

In the molecular environment, Lipscomb's studies show the kinetic depth effect to be the strongest available depth cue. Besides user-driven, kinetic motion of the model space by means of a two-axis viewpointer joystick, our present GRIP-75 system includes other aids devised by Lipscomb: spinning, torsion-pendulum-type rocking, smooth 90 degree turns with controlled acceleration.

Stereopsis. One thinks first of stereoscopic perception as an important 3-D illusion. It is, but it is less important than hiding and the kinetic depth effect. We have extensively explored stereo perception in the GRIP system. Three different forms of stereoscopic display have been provided: side-by-side stereo, space-division polarized-fitter stereo, and time-division stereo.

Lipscomb showed that although in real life stereoscopic perception is viewing from two slightly different angles, a better stereo effect is produced when a shear transformation instead of rotation is used to produce left and right eye images. This avoids artifacts due to view-clipping planes parallel to the plane of the screen.

Head-Motion Parallax. A powerful form of the kinetic depth effect is head motion parallax, in which small motions of the head create small distance-dependent changes in the angular position of objects in the scene. Thomas V. Williams and David Holmes did this using a small head-mounted light and a lateral angular sensor consisting of a 1728-photodetector charge-coupled device (CCD) and a razor blade which cast a shadow across the linear array of the detector.

Head-position sensing was reliable, rapid, and smooth. Images could be updated smoothly in accordance with head position. But it did not make as much difference in depth perception as we had expected. Perhaps this is due to the unfamiliarity of the molecular structures; perhaps it is due to the lack of hiding. In any event, the result was disappointing.

Then we used a prototype head-motion parallax system together with rotating shutter stereopsis. To our great surprise the effect of the two together was much more than one would expect from looking at either one separately.

All stereoscopic illusions which consist of only two images have the disadvantage that the structural relationships among objects are fixed. If one moves the head, the scene distorts in such a way as to maintain its relationships. The head-motion parallax system removes this artifact and hence gives the stereo a naturalness that one had not previously realized was missing.

representation, both showing skeletal structures and suggesting space-filling properties in one representation.

Multiple Visualizations. We and our scientific collaborators have developed and have imported programs for producing many different geometric and parametric visualizations of molecular structure. This year we brought this work together in a focussed effort to apply all available techniques to a single molecule, Superoxide Dismutase. In this way the various graphics techniques can be compared for their insight-inducing power and their costs. Moreover, combining all techniques on one molecule offers maximum insight into its structure and function.

Michael Pique produced a 17-minute videotape, "What Does a Protein Look Like?", that embodies some 40 visualizations of the SOD molecule, found at Appendix E, enclosed only with the original proposal. Color photos from this videptape are attached at Appendix A. The videotape, together with a companion paper by F.P. Brooks, "Views of Unseen Worlds," was one of two invited keynote addresses at *Science* Magazine's Conference on Computers in Science, in December. These works have been submitted for publication to *ACM SIGGRAPH Video Review*, a videotape journal. John Tainer and Elizabeth Getzoff of Duke University were the biochemist consultants for the work.

June 30, 1983 F.P. Brooks, Jr.

G. Advisory Councils

UNC Advisory Council

Although we will no longer be operating a Research Resource proper, we will still need the advice and counsel of biochemists, both as to our research strategy and directions and as to which potential collaborators appear to have highest potential yield for our effort.

Name	Degree	Title	Department	Institution
F.P. Brooks	Ph.D.	Kenan Professor & Chairman	Computer Science	UNC-CH
J. Hermans	Ph.D	Professor	Biochemistry	UNC-CH
D. Richardson	Ph.D.	Professor	Biochemistry	Duke U.
J. Richardson	M.S.	Assistant Professor	Anatomy	Duke
W.V. Wright	Ph.D.	Senior	Research Systems Architect	IBM Triangle Park Laboratory

'MolecularGraphics

NIH has recently supported three Research Resources engaged in molecular graphics, Langridges, Wison's and ours. NIH also has a distinguished in-house researcher in this area, Richard Feldman.

We would propose to organize these four investigators into a Molecular Graphics Advisory Council. We envision this meeting annually or semiannually to advise each other and BTR as to trends, directions, and future opportunities in molecular graphics.

June 30, 1983 F.P. Brooks, Jr.

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