

Progress 1983-88
Proposal 1989-94
Interactive Graphics for Molecular Studies

TR88-028

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Division of Research Resources
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Section 2—Research Plan

2A. Aims

Our Resource aims continually to develop state-of-the-art computer-graphics techniques into reliable, working research tools especially designed for chemists and biochemists studying macromolecules. The end objective is to advance studies of the structure and function of proteins and nucleic acids.

Understanding macromolecules, the keys to life processes, is crucial for designing new drugs. These molecules have intricate 3-D geometric and electrical structures. The geometries alone are hard to visualize without models, and only computer graphics can enable the scientist to visualize charge distribution, electric fields, hydrophobicity, and dynamic ensemble behavior. Computer graphics has become an indispensable tool for such studies.

Our Resource is the only molecular graphics group in the world composed chiefly of computer scientists, not chemists. We stay informed about biochemistry and its needs by continual close collaboration with biochemists, and by employing one. We also stay in touch with the molecular graphics groups composed mainly of biochemists. They have special capabilities we can never expect to have.

We bring, for our part, the following special capabilities to the task:

- We are part of one of the strongest university computer graphics groups in the world, consisting of five faculty-led teams working on different aspects of the graphics technology, all emphasizing real-time user interaction and 3-D modeling.
- As part of the larger UNC graphics and image cluster, we share an unparalleled collection of leading-edge hardware, software, interface devices, and graphics know-how, substantially beyond that of any one project.
- We have been committed to molecular structure studies as our driving application since 1970. This has enabled *sustained thrusts* along several different axes, set forth below.
- We have been pioneers in applying computer graphics to *scientific visualization*, just now becoming fashionable.
- Within computer science we are also known for special competence in
 - computer architecture, relevant to understanding and evaluating new hardware, and
 - software engineering, relevant to building robust, documented software tools.

Our central, unifying effort is to maintain a Trailblazer molecular graphics facility, continually advancing the state of the art and testing it with real users. At any time, the computer graphics industry offers new but costly high-performance computers and display engines which have important new capabilities for molecular studies. We help chemists capitalize on these advances by maintaining a high-performance hardware-software configuration, which we *help* visitors use.

As a second mode of service, we continually develop molecular graphics software to exploit the new hardware capabilities. Since building a software system takes about three years, we have it ready about the time the new high-powered hardware comes down to lab-affordable cost. We distribute this software to interested users, document it, help them install it, fix bugs, issue new releases, and provide telephone support.

2B. Background and Significance

Molecular Graphics was pioneered by Levinthal [Levinthal, 1966], followed by Langridge, Diamond, Barry, et al. After starting with protein folding studies with Hermans in 1970, our project built GRIP, the first molecular graphics system on which a protein was solved without a physical model – Superoxide Dismutase, by D. and J. Richardson [Richardson, 1975]. Our work was funded by NIH DRR through several short grants before 1974.

Research Resource vs. Resource-Related Research. From 1974-84 our Molecular Graphics research program was operated as a regular NIH DRR Research Resource (#RR 00898). At that time, we were among the first of the computer-based Resources to experience the mode-shift that has now become universal. Instead of users coming to our laboratory, we began shipping unique software we had developed to users around the country. Our contract officer in DRR therefore recommended that we apply as Resource-Related Research, instead of a Resource proper.

We did so, and were funded at \$300K-\$400K per year for 1984-89. (#RR 02170). In spite of the formal change of status, we have continued to operate essentially as a Resource, with technological R&D, collaborative research, service, training, and dissemination activities. Now our DRR sponsors believe it appropriate for us to apply under the Resource rubric again. So, although this is technically a new application, it is *de facto* a competing renewal.

Objectives: 1984-89. Figure 1 summarizes our research plan for the present five years, as set forth and diagrammed in our 1983 proposal, and indeed, executed:

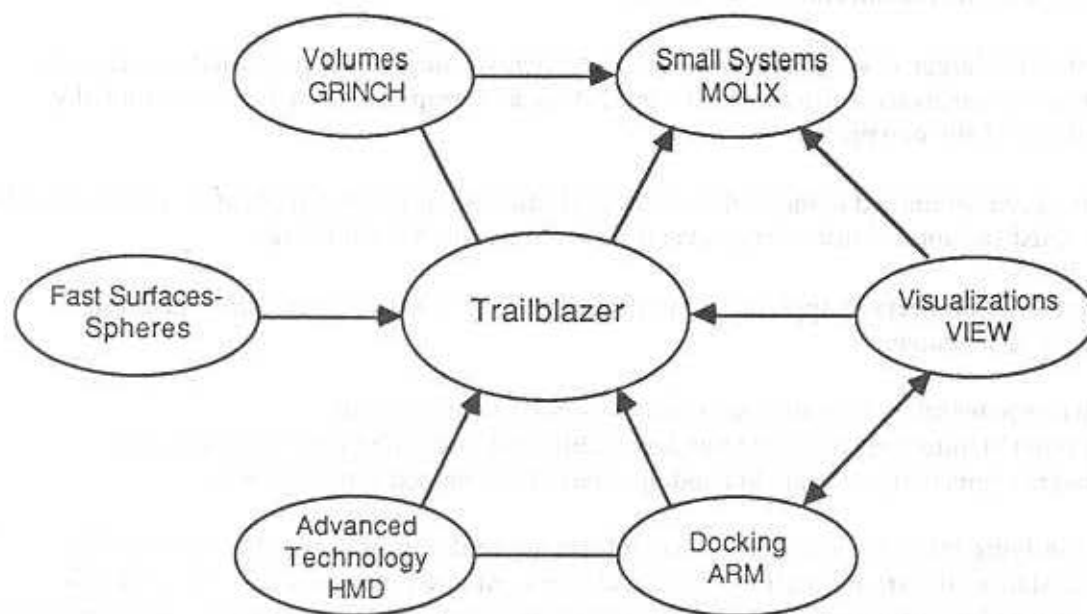


Figure 1. The Research Plan Proposed in 1983

The central Trailblazer system is supported by ongoing research in six areas:

- better ways to visualize electron density maps and other 3-D volume-based functions.
- packaging Trailblazer functions into systems suitable for fielding on low-cost workstations.
- totally new molecular visualizations, and comparative studies of known ones.
- studies of molecule-molecule geometric and electrical docking.

- experiments with advanced graphics technology, some far-out, some close-in, to see how it can be adapted to molecular structures problems.
- better ways to visualize spherical and other surface representations of molecules, as opposed to stick-figure bond-atom drawings.

Objectives: 1989-94

We propose a modestly enlarged effort (15% real growth), centered on the same Trailblazer thrust. Figure 2 diagrams the entire plan. This central thrust is built by four principal research efforts, shown at the cardinal compass points, and four smaller efforts shown at the diagonal points. For each category, we sketch what we have done up to now, and both short-term and long-term goals. In each category, we see both the past fruit and the future potential of long-term sustained thrusts.

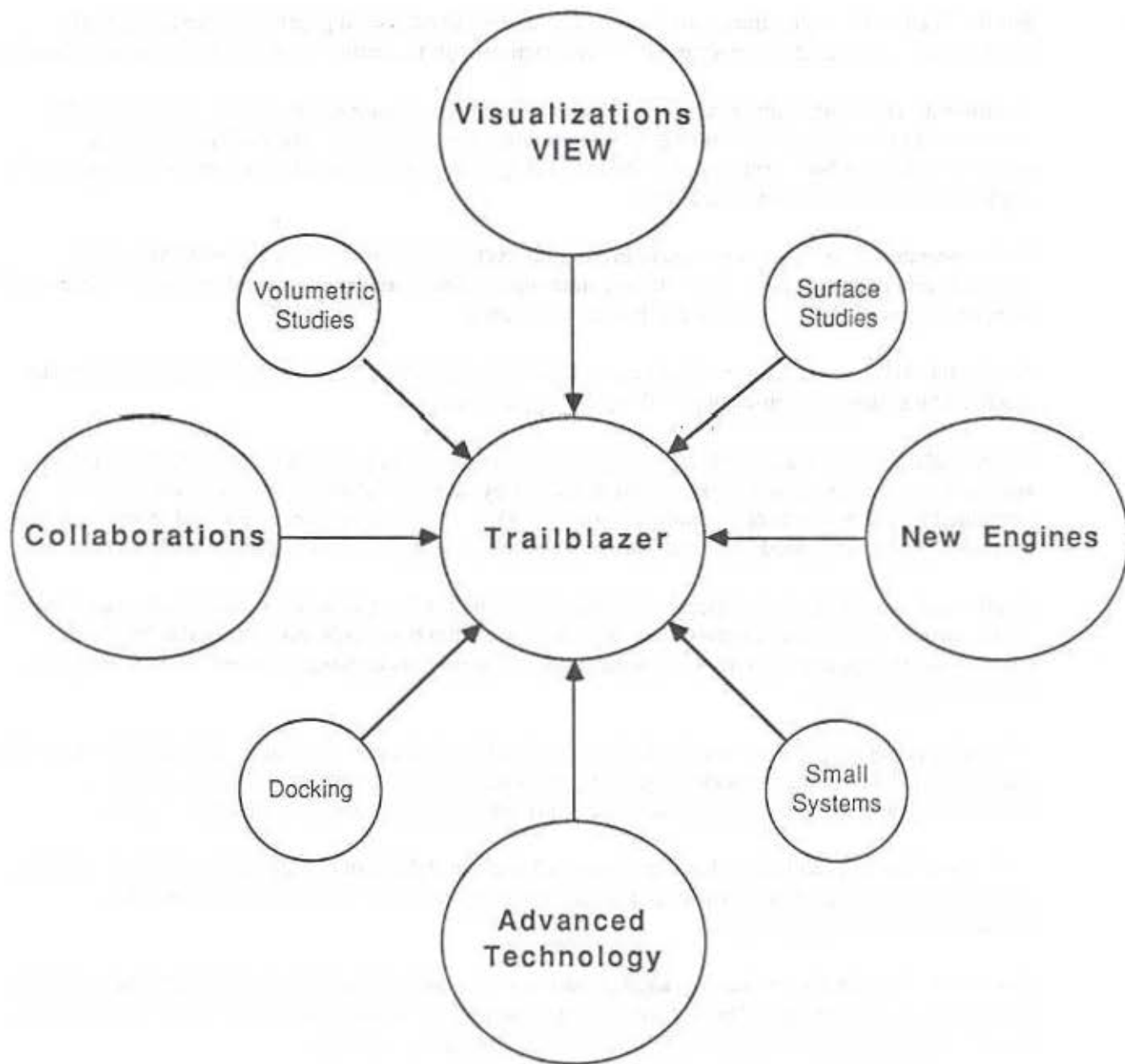


Figure 2. Research Plan for 1989-94

North. Compared to 1983, we now see the Visualization effort as much enlarged, resulting in a major distributable software system in 1989, to be enhanced thereafter. This is an area where our peculiar capabilities and experiences can especially contribute to the field at large.

East. Newly recognized, but not at all new, is our function as exploiters and evaluators of new graphics engines. Our shared laboratory, its facilities, and its people with their specialized knowledge give us a special opportunity here.

West. Also newly recognized but not new is our effort at doing things that our collaborators need, but which we probably would not do otherwise. Over the past 15 years, we estimate that some 30% of our efforts have been thus spent. Many useful systems and ideas, and much science have resulted. Moreover, our willingness to be helpful has provided us with brilliant and cooperative collaborators.

South. The fourth major effort is an ongoing exploration of advanced graphics technology, both displays for output and devices for natural interaction with the virtual world of room-sized molecules.

Northwest. The most exciting current work at our Resource is a pair of totally new ways to render volume data directly, without fitting approximating lines or surfaces. We shall pursue these vigorously, hoping both for better density-map interpreting systems and for new techniques generally applicable to many scientific problems.

Volume-rendering techniques are costly in compute cycles and memory. They would have been inconceivable five years ago; they will be commonplace five years from now. They probably came from computer scientists because of our ray-tracing experience.

Northeast. Five years ago our objective was to accomplish dynamic, real-time viewing of molecules modeled by spheres, not just bonds. That we have achieved.

The next challenge is to accomplish dynamic viewing of more complex and more interesting surfaces, such as the solvent-accessible surface first described by Lee and Richards [Lee, 1971] and usually calculated by the methods of Connolly [Connolly, 1981]. Such surfaces can be painted in many insight-producing ways. One needs dynamic viewpoint change and stereo for their proper study.

Southwest. Understanding molecule-molecule interaction is the goal of all molecular structure studies. As the structures of more complexes are solved, we want to have tools that will enable biochemists to perceive what happens when molecules dock, and what inhibits docking for some near-isomorphs of things that dock well.

Many degrees of freedom are involved. A hierarchy of models can be invoked: static geometric docking, static electric and geometric docking, docking with side-chain twisting, docking with grosser deformation, and statistical docking modeled only with molecular dynamics [Karplus, 1983].

The problem of perceiving what is going on, what computations of energy models predict, is at once very difficult and absolutely crucial to the refinement of models. We will not exhaust that visualization task in five years.

Southeast. We plan to continue packaging Trailblazer functions for affordable workstations. For the near term, we are betting on Unix-based workstations such as SUNs and Micro-VAXes. For the longer term, we are beginning to explore fitting such functions onto Macintoshes.

2. (C. and) D. Progress Report and Proposed Work

Activity Under Present Grant. This project was last reviewed competitively in 1983, and funded for May 1, 1984 - May 1, 1989. We shall discuss progress since the date of our last 5-year proposal, June 30, 1983.

The key personnel have been:

F. P. Brooks, Jr., P.I. - May 1 1984 - present; 25%

Michael Pique, Project Director - May 1, 1984 - August 31, 1986; 100%

Helga Thorvaldsdottir, Project Director - September 1, 1986 - present; 100%

Mark R. Harris, Research Associate (Biochemist) - February 1, 1987 - present; 100%

2D.1. Technological Research and Development

Progress Report Videotape. Interactive graphics systems are hard to capture in prose. Therefore we attach, as Appendix A, a 20-minute VHS videotape that reviews our 5-year progress against each of the 1983 aims in Figure 1. We urge the reader to view the videotape before proceeding.

Organization of This Section. Much of what we propose to do in 1989-94 is a direct continuation of what we are now doing. Therefore, instead of having separate sections on Progress and Proposed Work, we divide into sections by scientific area, with Progress and Proposed Work as subheads under each. Since each of the areas of Figure 1 is also present in Figure 2, we shall treat the topics in clockwise order on Figure 2, beginning at the northwest and designating topics by compass point.

2D.1.NW Volumes-Electron Density Maps - Progress

Ridge Lines and GRINCH. In 1983 we were just discovering the power of the ridge-line representation of an electron density map, as opposed to the conventional contour map. The ridge lines, proposed by Carroll Johnson [Johnson, 1976], require about 100x fewer line segments, permitting the display of the density map of an entire protein without overwhelming either hardware or viewer.

We built a software system, GRINCH, for *ab initio* interpretation of electron density maps, the only graphical tool designed for this part of the crystallographic task. It has been built in Unix, VMS, and IBM MVS versions, for a variety of host computers and graphics displays:

Adage Ikonas

Vector-General 3303

Evans and Sutherland PS-300

Evans and Sutherland MPS

Silicon Graphics Iris

IBM System/370 and compatibles

DEC VAX11/780 and compatibles

Masscomp 500

Appendix F is a copy of the general GRINCH manual.

GRINCH has been installed and used at a variety of sites. The User List in Section 2D.3 lists chemistry that has been done with it. We are still shipping copies and assisting with installations. Mike Carson while at the University of Alabama at Birmingham, ported GRINCH to VAX VMS with the Silicon Graphics Iris. He distributes that version and supports it. We do not attempt to track those users.

Direct Rendering – Westover. Contour line and ridge lines both fit discontinuous artifacts to the continuous density function. How the density volume looks is a strong function of how these artifacts are fit.

Lee Westover has been exploring the possibility of rendering volume data directly visible, by treating each volume element (voxel) as luminous. The videotape shows both his early efforts, in monochrome, and more recent work, a slab rendered in glowing colors which encode density gradient in hue, density itself in intensity.

We do not yet know whether Westover's approach will prove fruitful. It has the attraction that one sees the raw density data barely interpreted.

Direct Rendering – Levoy. Marc Levoy has been pursuing a different approach, in which one or two threshold surfaces in the density are defined and then rendered as shells of specified opacity. Light from one or more external directions is traced through the volume. Levoy has applied his method both to density maps and to CT-scan medical images. The videotape shows the results. Appendix B contains his first published paper, with a molecule picture. A separate paper for *Molecular Graphics* is planned.

Figure 7 of Appendix B emphasizes that one can see quite different aspects of the *same* volume data set by changing the rendering parameters.

Levoy's method is compute-intensive. His first pictures took hours of Sun-4 time per frame. Since the end of 1987 he has improved his algorithm's speed 40-fold, and he can now make pictures in minutes. Exploration by a viewer requires a large image memory to hold a loop of frames; we use a Pixar. Intermediate results require vast storage spaces – the skull study took 140 MB

Volume Studies – Proposed Work

Westover and Levoy Work. Both techniques will be pursued to the Ph.D. dissertation level during 1988-89. Levoy has won an IBM Graduate Fellowship in national competition. He has accepted a research faculty appointment here, to start after his Ph.D. completion. A medical-imaging grant will fund that.

We will try both Westover's and Levoy's representations on our biochemist collaborators to see what yields any new insight, then pursue that farther.

The Levoy feasibility studies thus far have used very good quality ($R=0.17-0.19$) maps of 1.8-1.9 Å resolution. Spectacular pictures result. An acid test, for which we are just now preparing, is to see how robust these techniques are on low-resolution or noise-degraded maps.

Direct Map Interpretation. Levoy's work, in particular, suggests that volume visualizations might be better than ridge-lines in a GRINCH-like direct interpretation system.

2D.1.N Visualizations – Progress

Omnimax Film – *The Magic Egg*. We were invited to participate in the first Omnimax (and Imax) film made by computer graphics, which premiered at SIGGRAPH 84 and is still shown in planetariums and science museums. Mike Pique and James Lipscomb made some 80 seconds of a fly-through of the

Superoxide Dismutase molecule, with different representations used for the protein backbone ribbon, the Cu and Zn, the surface of the active site, and the electric field near the active site. When the film is projected on a planetarium dome, covering a full hemisphere, the effect is absorbing. Pique and Lipscomb devised new techniques for calculating the proper intensities of motion-blurred objects (compensating for the time-sampling inherent in film frames). The formulas postulated in the literature turned out to be wrong when actually applied.

R-Space. Mark Harris, working with Prof. C. Carter of the UNC Biochemistry Department, has built R-Space, an interactive system designed to help crystallographers plan data-collection strategies for diffractometers with area detectors. The system has been extensively tested by Carter's team, his letter is enclosed with other user letters. It is about ready for β -testing by more users.

X-ray crystallographic data is visualized as nested spherical shells in 3-D reciprocal space. The useful limits of experimental data are contained within the "sphere of resolution", and the area detector is represented by a patch on the surface of a second sphere (*Ewald's sphere*), whose surface touches the center of the sphere of resolution.

The data points collected during a scan are contained in the volume of reciprocal space swept by the area-detector patch, as the crystal, and hence the sphere of resolution, are rotated. The crystallographer chooses his rotational scans to optimize coverage of the unique asymmetric volume.

Ad Hoc Pictures for Users. A steady stream of requests for the construction of particular visualizations of particular molecules came to our Resource; we were able to fill most of them. Each one requires iteration to get an insight-communicating view; the first conception is rarely adequate.

Scientific Visualization. Fred Brooks of our project and Turner Whitted of our cluster participated in the work of the National Science Foundation's Panel on Graphics, Image Processing, and Workstations. The Panel produced the report "Visualization in Scientific Computing" [McCormick, 1987].

As the only computer scientist on the National Science Board, Brooks has been especially concerned with the operation of the National Supercomputer Centers and their efforts at incorporating visualization in their work. We are concerned that the emphasis on scientific visualization so far has been on the communication of insights already grasped by the investigator. As we argue at length in [Brooks 1988], included as Appendix C, the much more promising use of scientific visualization is in the production of new insights from data.

VIEW - The Visualization Impromptu Evaluation Workbench. Our 1982 videotape, *What Does a Protein Look Like?*, applied some 40 different visualizations to one dataset, that for Superoxide Dismutase. It convinced us that different visualizations yield different kinds of insight.

Hence one wants a "workbench" on which an investigator can explore data by fashioning new visualizations as fast as the imagination conceives them. If colleagues show me their visualizations, I see at most what they saw in the data. If they share data and computational results with me, and I have a VIEW system, I can hope to see insights never before seen by anyone.

We began sketching such a tool in 1986, assigned three-persons to it in 1987, and increased the team to six in 1988. It now gets more than half of the project's effort. Doubling the team demanded, and provided the manpower for, adopting a better software engineering environment, more formal version control, and better documentation procedures.

Our first prototype is running on the Sun 3, producing pictures on the Adage Ikonas, the PS-300, the VG 3303, and on Pixel-Planes 4. The videotape shows samples of its use.

Visualizations – Proposed Work

VIEW. We are in full-scale production of a major new software system. We plan to begin user-testing of our prototype this fall, and plan to have a product-quality system ready for field testing by the end of 1989. In 1988-89, our emphasis on VIEW will be in improving the interface, by iterating on prototype after prototype. Ease of visualization specification is crucial.

2D.1 NE Surface Studies – Progress

Fast Spheres on the Ikonas. In 1983, one had the choice of dynamic manipulation of stick-figure (Kendrew) models of molecules, or static renderings of colored, shaded spherical models (CPK). Depth perception is important for structural understanding, and dynamic motion a very powerful depth cue. We set as a 5-year objective to achieve and user test smooth dynamic motion of CPK models, with proper sphere interpenetration. This objective was completely achieved.

First, a student team simulated spheres by flat disks painted to look spherical. They did not interpenetrate, and the disks disconcertingly popped in front of each other as the molecule rotated.

Then Mike Pique exploited the 10 MIPS specialized processor in the Ikonas display engine to produce images of real, interpenetrating spheres. These pictures were at 256 x 256 resolution, which turned out to be quite acceptable. Seven levels of shading were used, three z-depth levels for interpenetration. The videotape shows the result. Molecules of up to several hundred could be moved smoothly enough to give good depth perception.

This program was first provided to interested biochemists and later traded to Ikonas for more equipment. It was commercialized with full field support by Intermetrics Incorporated.

Flashlight. Before we could do large proteins with smooth motion, David Holmes developed a technique for enhancing depth perception of multi-sphere surfaces by changing the surface lighting in real time. The videotape shows the effect. The method uses color-table animation. The image buffer stores a combination of color and the direction of the surface normal of the surface at that pixel. As the light source is moved, the color table can be updated in real time, whereas the image buffer could not.

The method assumes parallel light rays. When we provided a flashlight interface (detected by a television camera on top of the display) we found that users nevertheless tried to illuminate cavities in the protein surface by moving the flashlight closer, instinctively trying to harness beam divergence.

PXPL-4. Henry Fuchs of our faculty invented a graphics processor which uses 250,000 bit-serial processors, one per pixel on a 512 x 512 screen, to generate real-time displays of scenes modeled with colored, shaded polygons, properly hiding each other. Various early, small prototypes were built, and in 1985 work was started on a full-scale product-quality VLSI implementation. It was completed in time to be demonstrated at SIGGRAPH in August, 1986. In the summer of 1987, it was turned over to the Graphics and Image Laboratory for routine use. It has been our workhorse ever since.

We are always eager to seize new graphics technology for molecular applications, so we studied Pixel-Planes intently from the start. Brooks devised an algorithm that displays circles at the same time-cost

as one polygon edge by storing x^2+y^2 for that pixel's location on the screen [Fuchs, 1985]. Spheres are represented as several concentric circles at different depths. This enables proteins of almost any size to be dynamically manipulated. Since Pixel-Planes 4 provides standard NTSC video output as an option, it can drive ordinary video projectors and recorders.

Connolly Host. Michael Connolly, who developed the popular MS, AMS and RAMS programs for computing solvent-accessible surfaces, had more ideas he wanted to develop as a free-lancer. We hosted him for a month, making our laboratory, our equipment, our software, and our support services available.

Connolly β -Test. We later beta-tested Connolly's new PPMS (Piecewise Polynomial Molecular Surface) and TRB (Triangulation by Recursive Bisection) programs. We displayed the surfaces on the Vector-General, PS-330, Sun 3, and Pixel-Planes.

Surface Studies – Proposed Work

Objective for 1989-94: Dynamic Motion of Solvent-Accessible Surfaces. Whereas today's engines let us move CPK models dynamically, we cannot yet do that for solvent-accessible surfaces unless they are approximated by polygons or spheres. We intend to accomplish dynamic motion for such surfaces. To do this we must handle toroidal patches and spherical patches, not just interpenetrating spheres.

Faster Richards Surface Algorithms. Doug Schiff explored the use of plane-sweep algorithms from computational geometry as a way of generating solvent-accessible surfaces in real-time. So far this approach has not worked; there are other algorithmic approaches to be tried.

Faster Hardware. The commercial graphics engines just coming to market in 1988 are about the same speed as Pixel-Planes 4. Without new algorithmic invention, they will not handle dynamic motion of Richards surfaces. Fuchs' team is, however, designing Pixel-Planes 5, to be finished by 1990. It will render certain higher-order curved patches as primitives. We will work with the team to make sure it can support our application.

Levoy Technique Extended for Solvent-Accessible Surfaces. Levoy's technique involves independent classification and shading procedures, as Appendix B shows. Instead of doing threshold classification in a density function, one can calculate a solvent-accessible surface by any technique whatever, and then use Levoy's shading method to render the surface as semi-transparent. This may be just what is needed as a visual aid to docking.

2D.1.E Evaluating and Exploiting New Engines – Progress

Collaboration with Scripps Research Institute. Since Mike Pique left our project to join the Scripps Research Institute, we have maintained an active collaboration, treated in more detail below. A major part of our effort has been the evaluation of new computers, especially those specialized for graphics applications.

Pixel-Planes 4. This machine, described above, was constructed with funds from NSF and DARPA. It is made fully available to us as part of the equipment of our shared Graphics and Image Laboratory. As the videotape shows, we have evaluated it intensively in molecular applications, and the computer architecture concepts it embodies seem very well suited to such.

Pixar Image Computer. This machine is on free loan to our laboratory, from Philips Electronics Medical Imaging Division. It is a powerful four-processor system designed especially for making high-quality graphics images, originally those used in film animation. Pixar has also invented volume-rendering techniques similar to those of Levoy (whose publication is prior).

Our evaluation of the Pixar for molecular applications shows it to be ill-designed for real-time interactive use, so we are not now building applications on it. The Pixar has a massive image memory; we are using it to store sets of pre-computed images. They can then be displayed as rotating. The videotape shows this for Levoy's images.

Sun TAAC. We have on indefinite loan in our laboratory a Trancept Application Accelerator Card for the Sun 3 workstation. This machine, whose performance on suitable problems is over 10 MIPS, has been extensively evaluated by Mike Pique at Scripps. Lee Westover here is using it to do his volume rendering work. It appears to be very cost/performance effective for molecular graphics.

Masscomp Dual Processor. Masscomp loaned us, free, a dual-processor system which we use for controlling the GROPE arm. The Masscomp has a very good interface for A/D and D/A connections.

Masscomp Array Processor. Also loaned was a Masscomp array processor auxiliary board, installed in our 1-MIPS Masscomp 500 system. By arduous hand-coding, Pique was able to do molecular energy-model evaluation on the array processor about 25 times faster than on a VAX11/780. A student team in the Software Engineering Laboratory course built a high-level language macro compiler for the array processor. The energy evaluation problem ran 8 times faster than on the VAX.

Sun 4. The VLSI Design cluster in our department has installed a Sun 4, a desk-top supermini with 8-10 MIPS performance. Since it has been available to us, Levoy has been evaluating it in the compute-intensive work he has been doing. It is powerful and compatible with our other Suns; the Graphics cluster is using it more today than the VLSI cluster is. We shall need one of our own for floating-point computation.

Cray XMP. Pique has evaluated the Cray XMP at the San Diego National Supercomputer Center against the Sun 3 on his work. Because the Cray is time-shared and because of the access rubrics, he gets about the same elapsed-time performance on the Sun as on the Cray.

New Engines – Planned Work

Explosion and Comparative Advantage. Custom VLSI chips enable many manufacturers to offer specialized computers, and many are aimed especially at high-performance graphics. The market in 1988 is seeing a veritable explosion of new entries; the pace will not slacken soon.

We therefore believe we can be of service to the molecular graphics community by performing and publishing qualitative and quantitative evaluations of new machines as applied to the molecular field. This work will be part of our collaboration with Scripps.

The two places are especially well suited for this work, because of the large variety of graphics engines we have installed, and because of the extensive experience we have had with such variety. UNC has the additional advantage, demonstrated above, that we have been able to get machines on loan because of the concentration of graphics investigators and projects in our laboratory. This enables us to do long-term evaluations with minimum equipment cost to the Resource. Moreover, we naturally get comparative evaluations over four applications: medical imaging, building architecture, constructive

solid geometry, and molecular modeling.

Stellar/Ardent Evaluation and Acquisition. Pique at Scripps has been benchmarking the new Stellar and the Ardent Titan. Scripps is installing one of each. We will be installing one or the other. We are out for bids now and plan some benchmarking as part of our purchase decision. Goodness in a graphics processor depends upon many parameters, so brand superiority may vary sharply from application to application.

Pixel-Planes 5. We expect to install this in the Graphics and Image Laboratory in due course, and to use and evaluate it as we have Pixel-Planes 4.

N.C. Supercomputer. The North Carolina General Assembly has voted \$ 18 million for the purchase of a Cray-class machine to be installed in the Research Triangle Park. It will be available to us, initially at no cost. We and our local collaborators will see what it can do on our problems.

Macintosh II. This "personal" computer has a 68020 chip, is faster than the first-generation workstations, and has a Unix just now being delivered. It has an immense supply of third-party software. We suspect it will be widely used by the biochemist community. So we have installed a big color screen, ethernet, and shortly, Unix on it. We shall evaluate it for molecular applications.

2D.1.SE Small Systems and MOLIX – Progress

The important happening in computers in the past five years has been the advent of workstations at \$10K to \$25K. These have passed the VAX 11/780 in performance. Many biochemists now have Evans and Sutherland PS-300's installed, and their own dedicated computers.

We develop new techniques on very powerful systems – dedicated VAX'es, Pixel-planes, PIXAR, etc. A continuing part of our Resource service, therefore, is to adapt these techniques to the machines our user community has. Today that is workstations.

MOLIX–GRINCH on Workstations. The workstation with raster graphics cannot yet do smooth motion of complicated molecules, as the E&S Picture System-300's can. On the other hand, colored spherical models are easier, though slow, on raster systems.

We have therefore adapted GRINCH for workstations, a system we call MOLIX. In the early days of workstations, we and our collaborators picked Masscomps, because of their speed and their superior interface to laboratory instruments. So the first version of MOLIX was for the Masscomp. Mike Pique also built ZBS, a molecule display program for the Masscomp. We are just now distributing. The market chose SUN's however, and indeed, our department now has over 70 of them installed. So we have ported MOLIX and ZBS to the SUN, and will start distribution shortly.

The videotape shows GRINCH on the Masscomp 500, with Cytochrome B5. To make up for the lack of smooth motion and the depth perception it yields, MOLIX rocks molecules by the rapid alternate display of two views. It also allows stereoscopic viewing with the inexpensive Tektronix plate.

Small Systems – Proposed Work

The two major current efforts of our whole project are the VIEW system and the exciting volume visualization work. Assuming both researches fulfill their present promise, we will first incorporate

each, in full-function form, in our Trailblazer system, using all the graphics power available.

We will test with collaborators. Then as systems are proven useful, we will, as part of our proposed 1989-94 work, prepare fieldable versions on the workstations and graphics devices the user community then has.

2D.1.S Advanced Technology – Progress

Virtual-Worlds Research. Computer graphics work at UNC concentrates on 3-D model worlds, and on real-time interaction. Appendix C sketches the virtual-worlds systems our teams have built over the years. The problem of the manipulation interface for virtual worlds is especially challenging – how shall one most naturally push, pull, twist, and connect virtual objects?

In the molecular graphics Resource, our virtual world is that of molecular structure. We see it as our mission not only to adapt state-of-the art graphics technology but also to invent totally new graphics technology for this problem.

Stereoscopic Viewing. A technology area we have worked in through the years is stereoscopic viewing. Buildings, and other models with parallel lines and right angles, give strong perspective depth cues. Molecules do not. Perspective can even hurt perception when one is trying to discover parallelism in structures. For this reason, perhaps, stereoscopic viewing makes more difference in the molecular application than any other we have seen.

During this five years we worked with three stereo technologies: PLZT glasses, liquid-crystal glasses, and liquid-crystal windows. Both of the glasses had several disadvantages: entangling wires to the viewer, substantial voltages on the user's head, limited number of viewers at once, and viewer synchronization to only one display at a time. The liquid-crystal window has none of these problems. The glasses cost less than five dollars; a roomful of people can watch at once.

PLZT glasses had the additional problem of very low transmissivity, less than 10%. The Milgram liquid-crystal glasses have high transmissivity and good extinction, but slightly slow response.

Tektronix invented a liquid-crystal window, originally for the purpose of getting colors on monochrome oscilloscope displays. We worked with them to adapt the technology to stereo viewing and to define a market for it in the molecular community. Our prototype testing led them to the improved product now offered, which incorporates circular polarization rather than linear, so that head tilt does not affect extinction. Of the eight stereoscopic techniques we have tested over the past 15 years, the Tektronix window is by far the most satisfactory.

Head-Motion Parallax. We hypothesized that making a display respond to the head motion of the viewer would be a powerful depth cue. Using a 1728-position CCD optical detector and a head-mounted flashlight bulb, we tested this. A razor-blade mounted in front of the detector gave a sharp-edged shadow that moved across the detector as the head moved from side to side.

Surprisingly, the effect didn't help much. But when it was combined with stereoscopic viewing, the two together were much more powerful than either separately.

Varifocal Mirror. In 1970 we built a varifocal mirror that creates a true 3-D display. A decade later, Fuchs and Pizer of our department showed how the costly display electronics needed for most such systems could be replaced by a standard video frame buffer, in our case that of the Ikonas. We have

experimented with molecules on this system. For our applications, it seems to have little relative advantage over stereo, although for medical applications of surfaces it shows real promise.

Head-Mounted Display. For some years we have envisioned the ultimate macro-molecule display to be a head-mounted one, with which one could move about inside a room-filling molecule, twisting bonds and testing docking. So we began to build one as soon as a miniature liquid-crystal television sets came on the market. The videotape shows both the device itself and its use. We generate right- and left-eye images on the PS-300 or Pixel-Planes. The virtual objects are superimposed on the real world by half-silvered mirrors. Our hypothesis is that the familiar objects in the room will help one become spatially familiar with the molecule.

At present the illusion suffers from a perceptible lag between when the head is moved and when the image is updated. This makes virtual objects swim about in space when they should appear to stay still. Even in this condition, the display appears to be useful.

Voice Input for Commands. All menu-driven graphics systems suffer from a need for two cursors, one indicating a point in the data, and another controlling menu picking. Many possible solutions can be imagined. The one we have tried is the use of spoken commands for menu selection.

We acquired a Votan speech recognition system, which does speaker-dependent recognition for disconnected speech, with a vocabulary of up to 256 phrases. The menu-selection task in GRINCH is ideally suited to this set of capabilities. Users work for hours at a time, so the 20-minute training session is not burdensome, especially since user voice profiles can be stored from session to session.

In our limited tests to date it seems to work fine. Recognition is fast, faster than mouse motion. Accuracy seems to run well above 95%, and it rarely misses in a catastrophic way. We have recently adapted the Votan system to work with the ARM in the GROPE system, where there is a pressing need to avoid manual menu selection of commands.

Advanced Technology – Proposed work

Stereoscopic Projection. In the summer of 1987 we lashed up a test of the Tektronix windows by putting three of them in front of the lenses of the Barcodata video projector. We discovered that our plastic rear-projection screen does indeed preserve circular polarization. We also found that the red and blue phosphors on the Barcodata are fast enough, but the green one decays rather too slowly to give good extinction. Since we can color molecules arbitrarily, this should prove no problem. We are currently working with Tektronix to have fabricated a special-sized set of windows to fit our Barcodata.

Head-Mounted Display. When this work was entirely in the Resource, we could invest only one graduate student plus technician time in it. It has attracted favor with our department's ONR contract sponsors, so we have been able to triple the size of the team in 1988 – three half-time graduate students.

Future work will concentrate on the update lag problem until that is solved. At the moment we are doing careful timing experiments to measure the component lags in each part of the image pipeline. We are also entering a collaboration with Major Phil Amburn of the Air Force Institute of Technology in Dayton. He and colleagues will be developing Kalman-filter algorithms for predictive tracking, so that we can compensate for residual lag. We will give them our present hardware designs and software, so they can make copies of our HMD system.

The tracking problem is by far the most serious of our technical problems. We will initiate work on optical trackers, and perhaps accelerometers, as alternates or supplements to the magnetic tracking used today.

Image resolution is poor, 256×256 , but it will get better as the tiny television technology matures. We will invest no effort there. The narrow angle of view is a more serious image problem. We see no way to improve it while preserving superposition of virtual objects on the real world. We have ordered some wide-angle optics. We will test these against our present ones, to see whether superposition or wide visual angle is the more valuable attribute for molecular images.

2D.1.SW Docking – Progress

Docktool. Tom Palmer's Docktool, built for the Adage Ikonas, allows a user to explore drug docking on a slow raster display, where space-filling models cannot be updated in real time as the user moves the objects. Following an idea of David Barry's, the large enzyme's many spheres are represented as stationary, but with double the van der Waal's radius. The drug being docked is represented as a stick figure of zero radius. The drug image therefore touches a sphere when the two would in fact bump. The small stick figure can easily be displayed and manipulated in real time.

Seeing what is happening is nevertheless difficult. The very surfaces that show the space-filling property conceal the inner structure. Palmer uses dynamic front-to-back clipping to help the viewer.

GROPE – Force Display. Even if one had magical technology, it is hard to imagine what one would like to see in order to perceive docking. One really wants to feel the hard-surface and the subtler electrostatic forces.

GROPE uses the master station of an Argonne Remote Manipulator, (ARM), which Argonne gave us. Kilpatrick [1977] built a force feedback system with it and tested it with users, using as his world model a table and seven toy blocks. He found force feedback to be an effective cue in enabling the viewer to form an accurate mental world model – more effective than stereoscopic vision, in fact.

At that time we concluded we would need 100 x our available compute power in order to model molecular docking, so we mothballed the ARM. After a decade, we had the 100 x compute speed, so we reactivated it and attached it to the Masscomp.

The forces and torques to be applied to the user's hand are calculated in real time, using the grid method of Pattabiraman and Langridge. The force image is only a supplement to a visual image projected on a 4' x 6' screen using a video projector. This makes the visual image the proper scale for the ARM's motions. Bumps are marked visually by flashing yellow arrows.

We have just now got the system to perform well enough that it might now be useful to a chemist. Last month Dave and Jane Richardson did an hour-and-a-half test run. It is ready for more serious testing.

Blow's Energy Modeling. Prof. David R. Blow, F.R.S., of the Biophysics Department, Imperial College, London, spent a sabbatical semester with our Resource in 1986. He studies the effects of solvent on macromolecule energy models. He reckons that the hydrophobic forces may account for a third of the total energy in a docking situation. These are essentially thermodynamic forces, occasioned by solvent displacement as two hydrophobic surfaces approach each other. The conventional potential function does not take them into account at all. We worked with Prof. Blow in his rewriting of his programs that model such forces more accurately. He also learned the fundamentals of molecular graphics.

Docking – Proposed work

GROPE Calibration. Our next substantial effort will be calibration. The only non-linear forces that are familiar to human experience are magnetic. We have acquired two strong 6-inch magnets. We plan to mount one in the working region of the ARM and the other on the ARM handgrip. With motors off, but all the inertia and backlash at work, one can experience how the real magnetic field feels as one approaches one magnet to the other. Then we will substitute a block of wood for the magnet on the ARM and activate the motors, force model, and programs and see how nearly it behaves and feels the same. Force measurements can be taken with spring balances.

Sound. The voice-input for menu command selection is just complete and must be user-tested. Kilpatrick's early GROPE system also had sound output, which is technically easy and was useful. We think it will be a useful auxiliary for bump indication.

User Evaluation. We plan extensive user evaluation over the next year, with the Richardsons and with Mike Cory of Burroughs-Wellcome, who works with intercalations into DNA.

2D.1.W Collaborations – Progress

Necessity. We are collaborators. We have to be, since we aren't biochemists and don't know the craft we are attempting to serve. Over the past five years we have had several active collaborations, in addition to the service our Resource has given users. User service is documented in Section 2D.3.

We estimate that some 30% of all of our effort over the past five years has been devoted to user service and to doing things for our collaborators that we would not have done on our own. Many useful system ideas, and we think some useful chemistry, has resulted.

All of our collaborations have been on a no-money-changes-hands basis, except that with IBM UKSC, described below, where they covered the cost of our travel to them as well as of their travel to us, and the phone bills; and that with Prof. Blow, where we assisted with his travel and living expenses here.

Recap. The discussion above has covered many collaborative efforts:

- with Scripps on equipment evaluation,
- with Richardsons on visualization,
- with Blow on energy programs,
- with Carter on R-Space,
- with Tektronix on the stereo window,
- with Connolly,
- with the Pixel-Planes team.

Technical Support for Local Collaborators' Facilities. Our local collaborators have installed configurations like ours: Masscomp 500 with E.&S. Picture System-300. We have helped them get their facilities up, installing ethernet connections between the workstation and the display, porting our software to them, building electronic controllers for their Tektronix windows, etc. The installations thus supported include, to one degree or another, the UNC Department of Biochemistry, the Richardsons' lab at Duke, and the computer graphics facility at Burroughs-Wellcome.

IBM United Kingdom Scientific Centre. In most of our previous grant period and the early years of this one, we had a very active collaboration with the IBM UK Scientific Centre at Winchester. Their molecular graphics group and ours jointly defined a new total graphics Trailblazer system, with

emphasis on a cleaner system organization and a user interface that was easier and more comprehensive. The system was especially designed to allow new software tools to be readily incorporated in a standard way, using a standard database. During this period we exchanged visits annually and had a telephone conference between our two groups every week. This ended when IBM decided not to proceed with building the system, and redirected their graphics efforts.

E.&S. Tripos Division. This past year we and our local collaborators together entered into a joint agreement with Tripos, which subsequently became a division of Evans and Sutherland. Under this agreement our Resource is the central point of contact between the whole community and Tripos. Their standard products, Sybyl and Mendyl are made available to our whole community. For our part, we adopted Mendyl as the base system on which we plan to build all future Trailblazer functions, and we started several ports of Tripos' software to our configurations.

Prof. William Switzer. Prof. Switzer, of the Department of Chemistry at North Carolina State University, Raleigh, has been spending this sabbatical semester at our Resource. He has been working on a large problem in simulating gas chromatography, doing the programming and preliminary calculations before putting it on the Cray at the Pittsburgh National Supercomputer Center. We have been working with him to get experience in the kinds of problems demanding supercomputers, and to explore scientific visualization.

Collaborations – Proposed Work

See Section 2D.2. The prescribed format for this proposal treats this there.

What We Aren't Going To Do – QC, MM, QSAR. Although we are interested in the application of computers and graphics to molecular structures, and we tend to move into areas of opportunity as defined by the technology and our collaborator's interests, we have ruled out certain large areas for the coming 5-years. These include quantum chemistry, molecular mechanics, and quantitative structure-action relationships. We may well indeed work with Prof. Jan Hermans on ways to visualize molecular dynamics, but not on ways to do the calculations.

2D.1.CENTER Trailblazer Facility – Progress

New Building, Laboratory, and Communications Plant. The major progress affecting our entire Resource during the past five years came about as a result of the totally unexpected 1983 decision by the governor and the General Assembly to fund a new Computer Science building at UNC, 74,000 square feet, \$ 10.25 million.

In 1983-84 we programmed the building and worked with the architects on the design. In 1985-87, we specified and monitored every conceivable sort of technical detail, especially the peculiar communications, electrical, floor, lightning-protection, and air-conditioning systems.

In August, 1987 we moved in, consolidating the department from some seven buildings. This put the Resource's offices and laboratory in the same building, and indeed, the P.I. into the same building with the rest of the Resource staff and students. A mundane thing, but a real accelerator of Resource progress.

Of necessity, all our graphics research groups had been compressed into one small Graphics laboratory in the old buildings. We learned so much from each other, however, that we elected to have one large

Graphics and Image Laboratory continuing to be shared among us, rather than individual laboratories. The new laboratory proper is about five times as big as the old one, plus shops, conference areas, video editing facilities, and offices.

The new building has a state-of-the art communications plant that gives us great flexibility in connecting our machines, displays, cameras, video facilities, etc.

Software Engineering and Standards. Our department long ago adopted Unix and C as house standards for all our machines. The workstation community has made the same selection of Unix, as has the supercomputer community. So the chemists' community is moving towards Unix.

Our Resource has recently adopted a much more controlled approach to the building of software systems, adopting modern software methods. We decided to move to object-oriented programming, using the C++ language, which is compiled into C by a pre-processor. VIEW is being built in C++, our first system to be done this way. It also adopts and follows the X-Windows and PHIGS+ graphics standards.

Trailblazer - Planned Work

Priorities. So many things to do, and few to do them. The reader may ask, Which ones are they really going to do?

Over the five years we expect to address all the areas. New opportunities and ideas will have to compete against the plan set forth here. Indeed, one of the joys of having collaborators is that they keep coming up with new needs and ideas.

Nevertheless, we have some fixed priorities for the initial period:

- VIEW
- Volume visualization, especially exploiting Levoy's work
- GROPE and its use in docking
- the Head-Mounted Display, at least made to work
- installing and exploring the new Stellar-Ardent class machine
- working with the Richardsons on protein sculpting, of which more below.

2D.2 Collaborative Research

At this time we plan two formal collaborative research projects, documented here. The biographies of our collaborators and their letters are in the appropriate sections.

David C. and Jane Richardson – Molecule Sculpturing. The Richardsons are engaged in the design of proteins *de novo*. They need tools with which they can twist alpha helices, dock them, warp beta sheet, etc. We have been exploring the mathematics behind such graphics tools. Doug Schiff worked on the problem for a semester, John Rohlf another semester. The new constraint-based modeling techniques appear to be directly applicable. We plan to seek one or two appropriate graduate research assistants, send them to the Richardsons' lab to work for a while, and then build a tool prototype.

The specific objective is to design a graphics tool which shows the biochemist what he is doing as it allows him to do naturally specified and chemically valid gross manipulations of secondary structures. The object is to think and operate in terms of the helices and sheets, rather than upon atom positions, or even backbone ribbon positions.

The Richardsons bring the need, some pilot studies, and very clear ideas as what they want the tool to do. We bring some exposure to constraint-based modeling, a good base of software primitives out of which to build such tools, and strong experience with manipulative interfaces. We and the Richardsons will, of course, continue our long-standing collaboration on other projects. We will continue to help with their facility, in particular, with the installation of Mendyl. They will be our users for first evaluation of VIEW, GROPE, the Head-Mounted Display, etc.

The Richardsons are located at Duke University. Their laboratory receives its principal funding from NIH GMS, with other funding from private foundations and the NCI. We do not anticipate any money changing hands on this collaboration.

Scripps Research Institute – Equipment Evaluation and Visualization Ideas. Mike Pique, Art Olson, Libby Getzoff, and John Tainer at Scripps will be working with us both on the evaluation of new hardware and software for molecular graphics, and on ideas for new molecule visualizations. This is a continuation and formalization of our present collaboration, where we exchange substantial visits, communicate frequently by electronic mail, and encourage our research assistants to spend the summer there. Matt Fitzgibbon is at Scripps this summer. He is already bringing Mendyl up on their system.

Getzoff and Tainer have a history of inventing good ways of looking at molecules. Olson and Pique are senior investigators in molecular graphics. We believe close ties will benefit us both.

Scripps receives some \$ 36 million in NIH grants, from many divisions. None of our collaborators are funded by DRR at all. We do not anticipate any money changing hands in our collaboration.

2D.3 Service

We expect our modes of service in the future to be essentially the same as in the past: people will come to us with hard problems that require the most powerful equipment and technique, and we will export software to users around the country to run on their systems.

Users, 1983-1988

Bud Suddath, Howard Einspur, Kaza Seguna

University of Alabama in Birmingham

High resolution structure of *pisum sativum* lectin

This team used GRINCH to revise the mainchain trace that they had already tried on a minimap. There are two monomers, both of which were traced in the 3 Angstrom map. The new GRINCH alpha carbon coordinates were used later to start fitting on the FRODO molecular graphics system in Alabama.

Jane & David Richardson, Duncan McRee

Duke University

Structure of SIR sulphite reductase

Structure of ACP

The iron-sulphur and heme groups of the SIR sulphite reductase molecule were fit on the UNC GRINCH system and on the GRINCH system running at Duke University on a Masscomp computer and an E&S PS-300 display. Detailed fitting was not possible because of the low resolution of the electron density map (3 Angstroms).

The ACP *e-coli* map was observed on GRINCH, but no interpretation was attempted, because of its low resolution (2.5 Angstroms with poor phases).

Chang Park, Richard Blevins

(PI Allen Tulinsky)

Michigan State University

Structure of prothrombin fragment 1

This is the prothrombin amino-terminal fragment 3/4 of whose alpha-carbon chain was traced on GRINCH. The remaining 1/4 was too disordered to see in the 3.5 angstrom electron density map. The disorder is caused by a 5,000 molecular weight carbohydrate whose disorder is inflicted on the nearby prothrombin.

John Rosenberg, Christine Frederick

University of Pittsburgh

Structure of DNA-EcoRI Endonuclease complex

This team came with a sequence for the endonuclease protein, preliminary coordinates for the 13 base-pair DNA fragment, and a 3 Angstrom map. Much of the 277 residues in the protein were interpreted over two visits to UNC.

Rufus Burlingame, Brad Brandon

Johns Hopkins

Structure of Eukaryote DNA binding histone octamer

The histone octamer to be interpreted consisted of three regions. Four subunits at the center are flanked by two subunits on one side, and two more subunits on the other, forming a prolate spheroid that the DNA wraps around. The 8 subunits have about 100-130 residues each. The map had such low resolution (3.3 Angstroms) that no useful work could be done on GRINCH.

Roger Fenna, Roger Egen

University of Miami

Structure of bacteria chlorophyll protein

Bacteria chlorophyll protein had recently been sequenced, but the structure was unknown. This team had produced a 2.8 Angstrom electron density map that they were able to interpret. They interpreted about 360 of the 365 residues of the protein using GRINCH on one visit, and returned to touch-up the coordinates on GRIP-75, which was modified to display ridge lines in addition to the usual contour lines. The 365 residue chlorophyll protein forms hydrogen bonds to seven chlorophylls.

Mike Cory
Burroughs-Wellcome
Dihydrofolate reductase and trimethoprim

Mike Cory has been working with Doug Schiff, a Ph.D. student on the UNC team, on building tools for drug design. The molecules listed above are employed as driving problems that serve to focus this effort along fruitful lines. Doug has programmed the display of drug and receptor surfaces. He has also prototyped a system for manually pushing the drug into the receptor site, aided by display of total system energy continuously recalculated using an orthogonal grid of electron density.

Stuart Solin
Michigan State University
Structure of ammonia-graphite complex

The complex consists of an ammonia molecule constrained between graphite planes in a graphite intercalation compound. During his visit, Dr. Solin was able to determine the possible tilt angles between the ammonia threefold axis and the graphite c-axis.

Michael Carson, Dan Carter
University of Alabama in Birmingham
Structure of human erythrocyte purine nucleoside phosphorylase (PNP)

The major interest in solving the structure of PNP is to enable the rational design of PNP inhibitors, which would allow nucleoside analog anti-cancer drugs to reach their target without degradation. This team had already used the FRODO molecular graphics system elsewhere to partly determine the structure, but the going was rather slow. They wished to try alternate chain tracings on GRINCH, which is hard to do on FRODO. In 3 days they fit 35 residues and determined about 150 additional alpha-carbon positions.

Susan Lord
UNC Chapel Hill
Structure of fibrinogen

The structure of fibrinogen is unknown, but Susan Lord tried to get some clues to the structure by comparing the sequence of fibrinogen, which is known, to the sequence of proteins whose structures are known. Specifically, she looked for beta turns. When she found a run of the fibrinogen sequence similar to that of a known beta turn in another protein, she modeled the fibrinogen fragment on GRIP-75 and attempted to twist it into a beta turn to see if that might be possible in nature.

Margaret Eastman
University of North Carolina at Chapel Hill
Bovine prothrombin

Margaret Eastman used the facility frequently to examine energy-minimized conformations of a cyclic hexapeptide from bovine prothrombin. She made stick-figure and shaded-surface CPK views of the model for study and publication. This dissertation research is under the direction of UNC Professor L. G. Pedersen.

Margaret C. Etter **
University of Minnesota
Cyclohexadione-benzene

We prepared computer graphics visualizations of a model structure of an unusual organic cryptand structure with six cyclohexanedione molecule intermolecularly hydrogen bonded into a macrocyclic hexameric ring, termed a cyclohexamer, with a benzene molecule trapped in the center. Etter suggests to us that this might be a useful model for neutral molecule guest binding at receptor sites. We hope to use this as a test case for the force-feedback docking project.

Francis Jurnak
University of California, Riverside
Elongation Factor Tu

Dr. Jurnak visited our facilities a number of times in 1985. She used both GRINCH and GRIP-75 to interpret the electron density map of the Elongation Factor - Tu. There are three domains in the protein, but Dr. Jurnak worked mainly on the DGP domain, which is the largest and functionally the most important.

Judith Kelly *
University of Connecticut
Beta-lactamase

GRINCH running on the IBM 3804/PS300 configuration at the University of Connecticut was used for the preliminary fitting of beta-lactamase. The resulting backbone tracing was then taken and compared to a penicillin target. Dr. Kelly's collaborators from Belgium did some of the GRINCH work.

Patrick Mize
Becton-Dickenson
c1-s

The amino acid sequence is known for c1-s, a component of complement, but the structure has not been solved. The structure of the active site is of special interest. The facilities were used to study the shape of the active site, in the hope of then being able to predict the structure of the substrates.

Jane Richardson **
Burgess Publishing
Aspirin

We prepared illustrations of the molecular structure of aspirin for a chemistry textbook.

R. Sarma
State University of NY at Stony Brook
Protein S

GRINCH was used to fit a model to an electron density map of Protein - S, a bacterial protein from *myxococcus xanthus*. The map was calculated to 2.8A resolution.

Paul Sigler, Richard Schevitz
University of Chicago
TRP repressor

GRINCH running on the VAX 750/PS300 configuration at the University of Chicago was used to begin interpretation of the electron density map.

Craig Smith *
University of Alabama at Birmingham
ax1 sea anemone toxin

GRINCH running on the VAX 750/PS300 configuration at the University of Alabama at Birmingham is being used for the main-chain tracing of 65-residue disulphide-rich sea anemone toxin. This has not had much success because the map connectivity is unclear but he continues to use GRINCH.

Hope Taylor
Duke University
Ribonuclease - S'

Hope Taylor came on many short visits to use GRIP to refine her model of semi-synthetic ribonuclease - S'. She hopes to finish that work by the middle of 1986.

Ramalingam Veerappapillai, Robert Egan
University of Miami
Human alpha-lactalbumin

The amino acid sequence of the human alpha-lactalbumin protein has been known for a number of years. Both GRINCH and GRIP-75 were used to build a model of this protein.

Ed Westbrook *

Argonne National Labs

Delta5-3 ketosteroid isomerase

GRINCH running on the VAX 750/PS300 configuration at the University of Chicago was used to fit a model to an electron density map of Delta5-3 ketosteroid isomerase. All 125 residues were traced and built into the map using GRINCH.

Al Clark

North Carolina Central University

Shape description

Al Clark is working on a protein shape description method using ellipsoids. He used our graphics facility to display and study his ellipsoid representation for a number of protein structures.

Alex McPherson

University of California, Riverside

DHFR and cephalosporin C

Alex McPherson requested a number of appropriate images to accompany an article for Scientific American concerning the role of crystallography in drug. They include various representations of trimethoprim and three analogs, bound to the active site of dihydrofolate-reductase (data from Burroughs Wellcome, RTP), and cephalosporin C as bound to D-alanyl-D-alanine Carboxypeptidase/Transpeptidase from *Streptomyces* R61 (data from Judith A. Kelly, University of Connecticut).

S. Shankar , Jan Hermans

University of North Carolina, Chapel Hill

Myoglobin

Shankar and Jan Hermans used the graphics facility to study the results of a molecular dynamics study of interactions of xenon atoms with the interior of the myoglobin molecule. We generated and photographed vector images and spacefilling images for the study. We also made a videotape of spacefilling images in an attempt to show the changing of the internal cavities as the was inserted.

Neela Srinivasan

University of North Carolina, Chapel Hill

Alkylating mutagens

Neela Srinivasan used our graphics facilities to study the conformational changes on a 5 basepair DNA sequence. This was part of a study to determine the effect of alkylating mutagens.

Peter Wolfenden, Jan Hermans

University of North Carolina, Chapel Hill

Masscomp graphics

Peter Wolfenden, a summer assistant in Jan Hermans' lab, used our Masscomp and our help to learn about and program the Masscomp graphics processor. Jan Hermans has a Masscomp in his lab and was expecting delivery of a graphics processor.

Donna Cohen

Cohen Computer graphics

Video review

Donna Cohen requested samples of our molecular graphics work on videotape or a documentary on computer graphics she was putting together. Ms. Cohen hopes the documentary will be shown on network television.

Nelson L. Max

Lawrence Livermore National Lab.

Protein video

We sent Nelson Max a videotape with a copy of *What Does a Protein Look Like, 1982* and some of the UNC graphics samplers. He showed parts of it with a presentation in Japan, and he also uses it in a computer graphics class he teaches.

Dr. Johnson
University of Illinois, Chicago.

Dr. Johnson requested a copy of *What Does a Protein Look Like, 1982*.

J.D. Andrade
University of Utah, Salt Lake City, Utah.

Dr. Andrade requested a copy of *What Does a Protein Look Like, 1982*.

Charlie Carter UNC
Biochemistry dept.

Workers in the UNC biochemistry department test site have been prolific users of RSPACE, using it to plan data collections for the following structures over the last 6 months :

Dr. Charles Carter (in collaboration with Dr. Charles Zelwer of LURE) :

Met. tRNA synthetase, 4 datasets to 3 Å.

Dr. Francine Smith : Ysplitanti mutant haemoglobin, 2 datasets to 2.5 Å .

Laurie Betts : Cytidine deaminase E. Coli, 1 dataset to 2.7 Å .

Eric Baldwin : Pseudo catalase, 1 dataset to 3.5 Å .

Katherine Crumley : Complexed Trp tRNA synthetase, 1 dataset to 5 Å .

David Coleman : Trp tRNA synthetase, type 4 heavy atom screening.

Frank Starmer
Duke University

Dr. Starmer used the program SECSTR to search for correlations between the sequences of proteins involved in various biological channels, including Acetyl CoA, Calcium, and Sodium channels, but was unable to find any significant similarity.

F. Scott Matthews
University of Washington

F. Scott Matthews used GRINCH in an attempt to interpret a 3 Angstrom map of Para-cresol methyl hydroxylase, but the quality of the data has proved to be intractably poor.

* Work done in investigator's own lab using UNC-developed software.

** Investigator did not visit UNC; we made pictures to order.

2D.4 Training

The GRIP Resource carries out its education and training role in four ways: we train computer science graduate students in molecular graphics, we help train chemistry graduate students in molecular graphics through their work in our laboratories, we host chemists on sabbatical, and we collaborate in the new Laboratory for Molecular Modelling in the UNC School of Pharmacy, and in their course, Medicinal Chemistry 275.

Computer Science Students. Over the past five years, many computer science M.S. and Ph.D. students have participated in the work of the GRIP Resource as Research Assistants. Several of these are today employed in molecular graphics:

Helga Thorvaldsdottir	GRIP Project
Thomas Palmer	National Cancer Institute
Douglas Schiff	SUN Microsystems
Neela Srinivasan	Biogen

Many others are employed in the computer graphics industry, where their awareness of molecular graphics requirements influences products.

Faculty and Staff. In the past five years, we have welcomed a half-dozen chemists who wanted to spend significant periods with us, either as project members or as visiting scholars on sabbatical, to learn molecular graphics.

Laboratory for Molecular Modelling and Medicinal Chemistry Course. This year the UNC School of Pharmacy established, with major industry support, a Laboratory for Molecular Modelling. This is believed to be the first such laboratory established principally for education, rather than research. Professor J. Phillip Bowen is the Director. Dr. Brooks is a Co-Principal Investigator.

Dr. Brooks also participates as a lecturer in the new graduate course, Medicinal Chemistry 275, Molecular Modelling, offered in the School of Pharmacy. About 20 students we enrolled for the first offering in Spring 1988.

Continuing Collaboration. We have formally agreed to continue this collaboration as part of the Resource's training function. Prof. Bowen's biography and his letter are in the appropriate sections.

2D.5 Dissemination

We expect to carry out the dissemination function in much the same way we have. In the past two years we have increasingly emphasized publication and the preparation of videotapes for conference presentations. We continue to contribute to the ACM SIGGRAPH *Video Review*, a videotape journal.

We were co-hosts, in 1987, of a NSF-SIGGRAPH workshop on 3-D interactive graphics, attended by 125 leaders in the field. We are planning to hold a similar workshop on visualizing functions of volumes in the fall of 1989.

An extremely important means of dissemination continues to be visits here, and demonstrations to visitors and to local chapters of school, college, and professional societies. We average two to three demonstrations per week. The new building and larger laboratory makes this much simpler. Even so, it is a significant component of Resource effort.

2I. Literature and Resource Publications

References

Barry, C.D., Bosshard, R.A., Ellis, R.A., Marshall, G.R. (1974) Evolving macromolecular modelling system, *Fed. Am. Soc. Expt. Biol., Fed. Proc.*, 33, 12, 2368-2374

Brooks, F.P., (1988) Grasping reality through illusion – Interactive graphics serving science. (Fifth Computer-Human Interface Conference, keynote address). *Proc. CHI 88*, 1-11, Addison-Wesley 1988

Connolly, M.L., (1981) Ph.D. Dissertation, University of California, Berkeley

* Fuchs, H., J. Goldfeather, J.P. Hulquist, S. Spach, J.D. Austin, F.P. Brooks, Jr., J.G. Eyles, and J. Poulton, (1985), Fast Spheres, Shadows, Textures, Transparencies, and Image Enhancement in Pixel-Planes, *Computer Graphics* 19, 3, 111-120.

Johnson, C.K., Groose, E., (1976) Interpolation polynomials, minimal spanning trees, and ridge-line analysis in density-map interpretation. *American Crystallographic Association Program and Abstracts*, 48.

Karplus, M., McCammon, J.A., (1983) *Ann. Rev. Biochem.*, 15, 263-300.

Kilpatrick, P.J., (1976), The use of kinesthetic supplement in an interactive system, Ph.D. dissertation, Univ. of N.C. at Chapel Hill.

Lee, B., Richards, F.M., (1971) The interpretation of protein structures: Estimation of static accessibility. *J. Mol. Biol.*, 55, 379-400

Levinthal, C., (1966) Molecular modelling by computer. *Sci. Am.*, 214, 6, 42-52.

McCormick, B.H. et al, ed., (1987) Visualization in Scientific Computing, *Computer Graphics*, 21, 6.

Pattabiraman et al (1985), Real-time docking, energy calculation, and minimization, *J. Computational Chemistry*, 6, 432-436.

Richardson, Thomas, Rubin, and Richardson, (1975) Crystal structure of bovine Cu, Zn Superoxide Dismutase at 3 Å resolution: Chain tracing and metal ligands, *Proc. Nat. Acad. Sci. USA* 72, 1349-1353.

Tsernoglou, D., Petsko, G.A., (1977) Three-dimensional structure of Neurotoxin a from venom of the Phillipines sea snake. *Proc. Natl. Acad. Sci. USA*, 74, 3, 971-974

Publications by Resource Builders and Users 1984-88

1984

* Pique, M.E. and Lipscomb, J.S. How the UNC Segment of the SIGGRAPH'84 Omnimax Movie was Made. Evans and Sutherland Users Group Meeting, ACM SIGGRAPH'84 Conf., Minneapolis, Minnesota, July 1984

1985

- * Cory, M., McKee, D.D., Kagan, J., Henry, D.W., Miller, A.J. Design Synthesis and DNA Binding Properties of Bifunctional Intercalators - Comparison of Polymethylene and Diphenyl Ether Chains Connecting Phenanthridine, *Journal of the American Chemical Society*, 107, 2528, 1985
- * Fuchs, H., J. Goldfeather, J.P. Hulquist, S. Spach, J.D. Austin, F.P. Brooks, Jr., J.G. Eyles, and J.P.oulton, Fast Spheres, Shadows, Textures, Transparencies, and Image Enhancement in Pixel-Planes, *Computer Graphics* 19, 3, 111-120.
- * Jurnak, F. The structure of the DGP domain at EF-Tu in the location of the amino homologous to ras oncogene proteins. *Science*, 230, 32-36, Oct 1985
- * Lipscomb, J.S., Brooks, F.P., Jr., Pique, M.E., and Smith, D. UNC 1985 Computer Graphics Sampler. Video tape, color, sound, 4 minutes. Shown at ACM SIGGRAPH'85 Conf., San Francisco, California, July 1985. Published in *ACM SIGGRAPH Video Review*, 20, November 1985.
- * Lipscomb, J.S. Comparison of stereo display devices. Fourth International Meeting of the Molecular Graphics Society, Oxford, England (15-17 April 1985). Abstract published in: *Journal of Molecular Graphics*, 3, 122, September 1985.
- McCormick D.J. and Atassi M.Z. Antigenic Structure of Human Hemoglobin: Delineation of the Antigenic Site (Site 2) Within Region 41-65 of the Alpha Chain by Immunochemistry of Synthetic Peptides. *Journal of Protein Chemistry* 4,3, 171-184, 1985.
- * Pique, M.E., Lipscomb, J.S., and Andersen, A.C. Trip Through Molecule of Superoxide Dismutase. Slide of one frame from the UNC segment of the movie, *The Magic Egg*. Produced by Garrickfilms and ACM SIGGRAPH. Published in *ACM SIGGRAPH'85 Technical Slide Set*, slide no.60 July 1985.
- * Pique, M.E. and Lipscomb, J.S. What to Look for in Color Raster Graphics. Video tape, color, sound, 14 minutes. Shown at Atlantic City conference on Scientific Computing and Automation, March 1985.
- * Pique, M.E. Research resource: computer graphics for molecular studies. Fourth International Meeting of the Molecular Graphics Society, Oxford, England (15-17 April 1985). Abstract published in: *Journal of Molecular Graphics*, 3, 122-123, September 1985
- * Pique, M.E. Drug Information Association, February 1985 Chicago (invited speaker)
- * Pique, M.E. American Crystallographic Association, August 1985 Palo Alto (invited speaker)
- Richardson, D.C, Richardson, J.S. Interpretation of Electron Density Maps, Chapter 14 of *Diffraction Methods for Biological Macro-Molecules*, vol.115b in *Methods in Entymology*, 189-206. Editors Wyckoff, Hirs and Timasheff. Academic Press. NY 1985
- *Schevitz, R. et al. TRP Repressor. *Nature*, 317, 782-786, Oct 1985
- * Taylor, H.C., Komoriya, A., Chaiken, I.M. Crystallographic structure of an active, sequence-engineered ribonuclease. *Proc. Natl. Acad. Sci. USA, Biochemistry*, 82, 6423-6426, Oct 1985
- Tulinsky, A., Park, C., Rydel, T.R. The structure of prothrombin fragment 1 at 3.5A resolution. *Journal of Biological Chemistry*, 260, 10771-10778, 1985.

1986

- Cory M. Studies of DNA Intercalating Anti-Tumor Agents. Poster. Nat. Medicinal Chemistry Meeting, Chapel Hill, NC, June 1986.

Eastman M.A., Pedersen L.G., Hiskey R.G., Pique M.E., Koehler K.A., Gottschalk K.E., Nemethy G. and Scherega H.A. Conformation of the 18-23 loop region of bovine prothrombin in the absence and presence of a model Ca^{2+} ion. *Int. J. Peptide Protein Res.* 27, 1986.

Etter C.M., Lipkowska Z., Jahn D. and Frye J. The solid state structural characterization of 1,3-cyclohexadione and of a 6:1 cyclohexadione-benzene cyclomer, a novel-host guest species. *JACS* 108, 58-71, 1986.

Hermans J. and Shankar S. The free energy of xenon binding to myoglobin from molecular dynamics simulation. *Isr. J. Chem.* 27,225-227,1986.

* Kelly, J.A. et al. On the origin of bacterial resistance to penicillin : a comparison of a beta-lactamase and a penicillin target. *Science*, (in press March 1986)

Knox J. Comparison of Penicillin Target Enzyme with Penicillinase, Mid-Atlantic Protein Crystallography Workshop, Gaithersburg, MD, May 1986.

Luther D., Fisher R.G. and Swanson E. Molecular Modeling for Chemical Design. *Computer Graphics World* 9, 11, 32, Nov 1986.

McPherson A. Protein Crystals : Keystones of Biotechnology. *Scientific American*, (accepted 1986).

McRee D.E., Richardson D.C., Richardson J.S. and Siegel L.M. The heme and Fe_4S_4 Cluster in the Crystallographic Structure of *Escherichia coli* Sulfite Reductase. *J Biol Chem*, 261, 10277-10281, 1986.

Pique M.E. Technical Trends in Molecular Graphics, Computer Graphics and Molecular Modeling. Editors Fletterick F. and Zoller M. Cold Spring Harbor Laboratory, 1986.

Pique M.E. Computer graphics model of an aspirin molecule and its exterior surface. Cover picture. *General Organic Biological Chemistry*, 2nd edition. Burgess Publishing, 1986.

Pique M.E. and Lipscomb J.S. Segment of How the UNC Segment of the SIGGRAPH '84 Omnimax Movie was Made. *Computer Graphics Special* (videotape). Produced by Cohen Computer Graphics and Geoffrey de Valois Assoc. for One Pass Productions.

Pique M.E. Force Feedback for Molecular Graphics: March 1986 Progress Report, 5th International Meeting of the Molecular Graphics Society, Cap d'Agde, France, April 1986.

Pique M.E. et al. UNC sampler April '86. Videotape, sound. 5th International Meeting of the Molecular Graphics Society, Cap d'Agde, France, April 1986.

Ramalingam V. Determination of the 3-D structure of human alpha-lactalbumin. PhD thesis, University of Miami, 1986.

Shankar S. Molecular Dynamics Study of Xenon-myoglobin Interactions, Mid-Atlantic Protein Crystallography Workshop, Gaithersburg, MD, May 1986.

Thorvaldsdottir H. Molecular Graphics on a Masscomp Workstation, 5th International Meeting of the Molecular Graphics Society, Cap d'Agde, France, April 1986.

Yoshioka N. and Atassi M.Z. Haemoglobin binding with haptoglobin. *Biochem J.* 234, 453-456, 1986.

1987

Brooks F.P., No Silver Bullet. *IEEE Computer*, 20(4), April 1987.

Brooks F.P., Report of the Defense Science Board Task Force on Military Software. (Chairman). Office of the Under Secretary of Defense for Acquisition, Washington D.C. 1987.

Glassner A.S., Supporting Animation in Rendering Systems. CHI+GI '87 Workshop on Rendering Algorithms and Systems., Toronto, April 1987. Workshop participation was by invitation only. Workshop proceedings to be published by Canadian Information Processing Society, Toronto.

Holloway R.L., Head-Mounted Display Technical Report. UNC Dept of Computer Science Technical Report TR87-015. June 1987.

Levoy M., Rendering Surfaces from Volumetric Data. UNC Dept of Computer Science Technical Report TR87-016. June 1987. Also accepted for publication by IEEE Computer Graphics and applications.

Palmer T.C., Docktool: A Dynamically Interactive Raster Graphics Visualization for the Molecular Docking Problem., Master's thesis. UNC Dept of Computer Science Technical Report TR87-013. May 1987.

Thorvaldsdottir H., Computer graphics model of an ATP molecule. Cover picture. Chemistry and Life by Hill J.W. and Feigl D.M, 3rd edition. Macmillan Publishing Company, 1987.

Lipscomb J.S., Comparison of Stereoscopic Display Devices at the University of North Carolina at Chapel Hill. Chemical Design Automation News, Vol. 2, No. 5, May 1987, pp. 3-6. Invited paper.

Levoy M., Direct Visualization of Surfaces from Computed Tomography Data. SPIE/Medical Imaging II. Newport Beach, Feb 1987.

Thorvaldsdottir H. and Pique M.E., Scouting Expeditions in Molecular Graphics. Invited talk. Shell Conference on Computer Aided Molecular Modelling. Hoenderloo, Netherlands, October 1987.

Wright, C. The crystal structure of wheatgerm agglutinin isolectin 2 refined at a nominal resolution 1.8A. Journal of Molecular Biology, 194,501-529,1987

1988

Brooks, F.P. Grasping reality through illusion - Interactive graphics serving science. (Fifth Computer-Human Interface Conference, keynote address). Proc. CHI 88, 1-11, Addison-Wesley 1988

Ouh-young, M., Pique M.E., Hughes J. and Brooks F.P., Using a Manipulator for Force Display in Molecular Docking. International Robotics and Automation Conference, 1988.