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Seventeenth Annual Progress Report and 1992-97 Renewal Proposal Interactive Graphics for Molecular Studies

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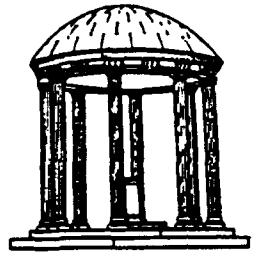

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UNC-CH Research Resource in Interactive Graphics for Molecular Studies

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Description

The UNC Resource develops **forefront molecular graphics techniques** and harnesses them into prototype research tools designed for biochemists studying macromolecules. The end objective is understanding the structure and function of proteins and nucleic acids, crucial to understanding disease and to designing drugs.

Our Resource is the only molecular graphics group composed chiefly of computer scientists, not chemists. As such, we have special capabilities and facilities. We **collaborate** closely with biochemists and serve as **bridge-builders** between the disciplines.

We maintain a **trailblazer** molecular graphics facility, a top-performance hardware-software configuration, continually advancing the state of the art and testing the trailblazer against real users We welcome visiting chemists from everywhere and *help* them use the facility.

We **wildcat** radical new molecular graphics ideas to the **prototype** stage. Winning ideas are spun off to the thriving commercial industry or into autonomous research projects. Although we cannot develop and support commercial products, we test each prototype on users who come here; then we distribute it to interested users, document it, help them install it, fix bugs, and provide telephone support.

For the next five years, our main technical vision is to build **graphics molecular models** that the biochemist can **interactively** fold, twist, dock, etc., **in real-time** with the model **maintaining** visual **and physics fidelity**, holding all constrained lengths and angles, and continually minimizing free energy. This includes models that simultaneously work in real space and Fourier space.

A second main project will be exploring new techniques for visualizing volumes, such as electron density maps and the electric fields around molecules. A whole new class of real-time **direct volume visualization** techniques offers new power.

Other major activities will be building tools with **collaborators** doing drug design and *de novo* protein design, evaluating the suitability of **new graphics engines** for molecular laboratories, exploring new ways to address the molecular **docking** problem, continuing work on representing molecular **surfaces**, and adapting our high-function software to **low-cost workstations.**

A. Aims

We aim to harness the rapidly increasing power of computer and graphics technology to help biochemists understand the structure and function of like molecules. Understanding protein and nucleic acid is crucial for understanding disease and for designing drugs. Molecular function follows from molecular structure, which uses 3-space in wonderful ways, subject to complex forces.

Computer graphics and indeed real-time interactive computer graphing has become an indispensable tool for the molecular structure scientist, a development we have helped pioneer since 1970. Over the years, the increasing power of computer graphics has been in turn used to give

- real-time motion to stick-figure models
- stereo viewing by one device or another
- a variety of richer visual models, beginning with CPK spheres, and preserving real-time motion.

The increasing performance/price of computer graphics now enables the next step – real-time force modeling.

Our Vision

We foresee, in this decade, the technical capability to give biochemists molecular graphics tools of totally new power: macroscopic 3-D virtual molecules that

- **act real**, obeying in real-time scaled up versions of molecular forces,
- **look "real"**, that is, like physical models,
- **change appearance** to show selected chemical or physical properties,
- **feel real**, like plastic or brass models subject to invisible forces.
- **can be simultaneously viewed** in real space and Fourier, Ramachandran or other spaces.

Physical models of plastic or brass look "real". They really exist in 3-space. They feel real— the fingers comprehend and manipulate the shape and experience the constraints of bond lengths, bond angles, peptide planarities. Molecular scientists need these properties.

Computer models, on the other hand, can model real force fields, bonded and non-bonded. They also are accurate, escape gravity, and go away when one doesn't need them. Moreover, they can , at the touch of a button change in geometric representation, color, transparency, etc. to emphasize particular chemical, physical, or biological properties. One can view them from inside, or sliced, or superimposed. Computer models can show real-space properties, and those in reciprocal space, Ramachandran space or i-j chain sequence space.

What powerful conceptual aids would be models that unite all of the above capabilities! This is now in sight, though yet distant. The conceptual power depends upon **real-time interactivity**, just as does that of WYSIWYG word processing or spread sheets. What is coming is workstation power to give real-time force modeling and continual energy minimization to protein and nucleic acid models.

We propose to explore the individual pieces of advanced technology and algorithms needed for specific features of such "real-physics" models, and to trailblaze their assembly into complete prototype systems.

B. 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.

From 1974-84 our Molecular Graphics research program was operated as a regular NIH 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. 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 continued to operate essentially as a Resource, with technological R&D, collaborative research, service, training, and dissemination. In 1988 NIH felt it appropriate for us to become a Research Resource again. We have been funded at $ 300K-$ 400K per year for 1989-92.

The Case for our Resource is Simple

1. The molecular structures discipline, and the country need a **trailblazer**, who is constantly exploring the molecular graphics usefulness of new computer and graphics technological developments.

2. The molecular graphics discipline needs a **wildcatter**, exploring radical new ideas to the running prototype. Winning ideas will be developed into, or incorporated into, products by the now-thriving molecular-graphics industry, but the industry can't afford to do the pre-competitive exploratory research. It is an industry in which the United States has a dominating lead (with the British next) which the US should maintain.

3. Both disciplines needs a **bridge-builder**, who shows biochemists the significance of new computer/graphics developments and who shows hardware and software vendors what molecular graphics needs.

4. **We fit this role.** Our Resource is especially well fitted to meet these needs for trailblazer, wildcatter, and bridge-builder, because of:
   - its roots in computer graphics,
   - its highly leveraged environment, and
   - its program of active collaboration with molecular structures scientists.

5. **This role fits us.** Of all conceivable roles for our experienced cadre of molecular graphicists, the three-part role of one trailblazer, wildcatter and bridge-builder fits us best. We should not be competing with the molecular graphics industry in product development, for reasons of propriety for a publicly funded enterprise, of probable lack of success due to our small staff, and of inappropriateness to the education of our students.

6. **Our track record is strong.** We built the interactive graphics system on which a protein was first solved without a physical model. Ideas from our prototypes have influenced commercial software. We have explored advanced display technologies, spinning off winners into separate projects. We have influenced vendors, e.g.,

to adapt liquid-crystal technology to stereo viewing devices for molecular graphics. We have populated vendors. with students trained on molecular problems.

Our Capabilities

The GRIP Molecular Graphics 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, generally a faculty visitor. 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:

- Our GRIP Resource is part of one of the strongest university computer graphics clusters in the world, consisting of five faculty teams ("chairs") working on different aspects of the graphics technology, all emphasizing real-time user interaction and 3-D modeling.

- UNC is one of the five sites of the new NSF Science and Technology Center in Computer Graphics and Scientific Visualization. With our partners at Brown, CalTech, Cornell, and Utah, we cover all subfields of modern computer graphics research and are committed to pushing the state of the art.

- 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.

- Our team has been committed to molecular structure studies as our driving application since 1970. This has enabled *sustained thrusts* along several different axes, set forth below.

- Within computer science the UNC team is 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.

Leveraging

NIH support for the GRIP Research Resource is highly leveraged:

- **volume visualization technology**, heavily supported by GRIP during its initiation phase, is now mostly supported by another NIH grant and an NSF-DARPA grant. GRIP only supports its exploitation for density maps, about one-sixth of the total effort.

- the **head-mounted display project**, supported entirely by GRIP during three years of initiation, doubled in 1988 by picking up ONR support. In 1990 a separate HMD project grant, some $ 561 K/year, was funded by DARPA. GRIP now finances none of the HMD project. The HMD project continues to address molecular applications, among others.
- the **equipment shared** among all UNC graphics projects provides both variety and capacity that NIH doesn't pay for:

- construction of the PxPl4 and PxPl5 super-display-engines graphics was financed by NSF and DARPA.
- the 4000-processor MasPar (massively parallel) computer that we have used to such advantage this year was bought with state and ONR funds.
- the Pixar was a vendor gift.
- the Argonne Remote Manipulator (ARM) used in our GROPE system, a $120 K piece of equipment, was given to us by Argonne Laboratory under an AEC grant.
- the IBM Risc System/6000 Model 730, a high-performance graphics workstation, was a vendor gift explicitly for GRIP Resource work.
- the Cray YMP, which we can use, was entirely financed by legislative appropriation.
- the high-speed interim fiber optics link, and the eventual gigabit link, between our laboratory and the Cray, are paid for by NSF networking funds.
- three-quarters of the Sun and DEC workstations in the graphics cluster were vendor gifts or bought by other projects or the NSF departmental CER grant.
- GRIP only paid for some 15% of our extensive video editing and publication facilities.

- a **shared support staff** provides both capacity and skill mix at low cost to each project:
  - GRIP supports only one of the three technicians in the graphics cluster.
  - the 7-person departmental workstation hardware-software support staff is paid by state, NSF and ONR funds.

- Brooks's 1991 **research leave**, which will be 80% devoted to molecular graphics, will be only 30% funded by GRIP. State funds will pay the other 70%.

A key part of our mode of operation is to initiate and support start-up projects that can spin off with their own funding.

If we have substantial support for UNC's computer graphics enterprise from other sources, why should NIH put any of its money here? Because by supporting a small part of the total UNC graphics effort as a molecular graphics Research Resource, NIH causes a disproportionate fraction of the ideas and innovations to be focussed on and adapted to molecular structures.

Objectives: Our ambitious goal for the decade has many technical components. Our strategy is to pursue independent subprojects, which will come together to compose our goal molecular system, and will be separately useful along the way. Each subproject has one or two graduate students. Figure 1 summarizes our research plan for the coming five years

The central Trailblazer system will continue to be supported by ongoing research in six technical areas:
- real time molecule-molecule **docking, folding, and other interactions.**
- better ways to visualize electron density maps and other 3-D **volume-density** functions.
- better ways to visualize solvent-accessible and other **surface** representations of molecules,
- totally new molecular **visualizations**, and comparative studies of known ones.
- packaging Trailblazer functions for fielding on **low-cost** workstations.
- experiments with **advanced graphics technology**, to adapt it to molecular problems.

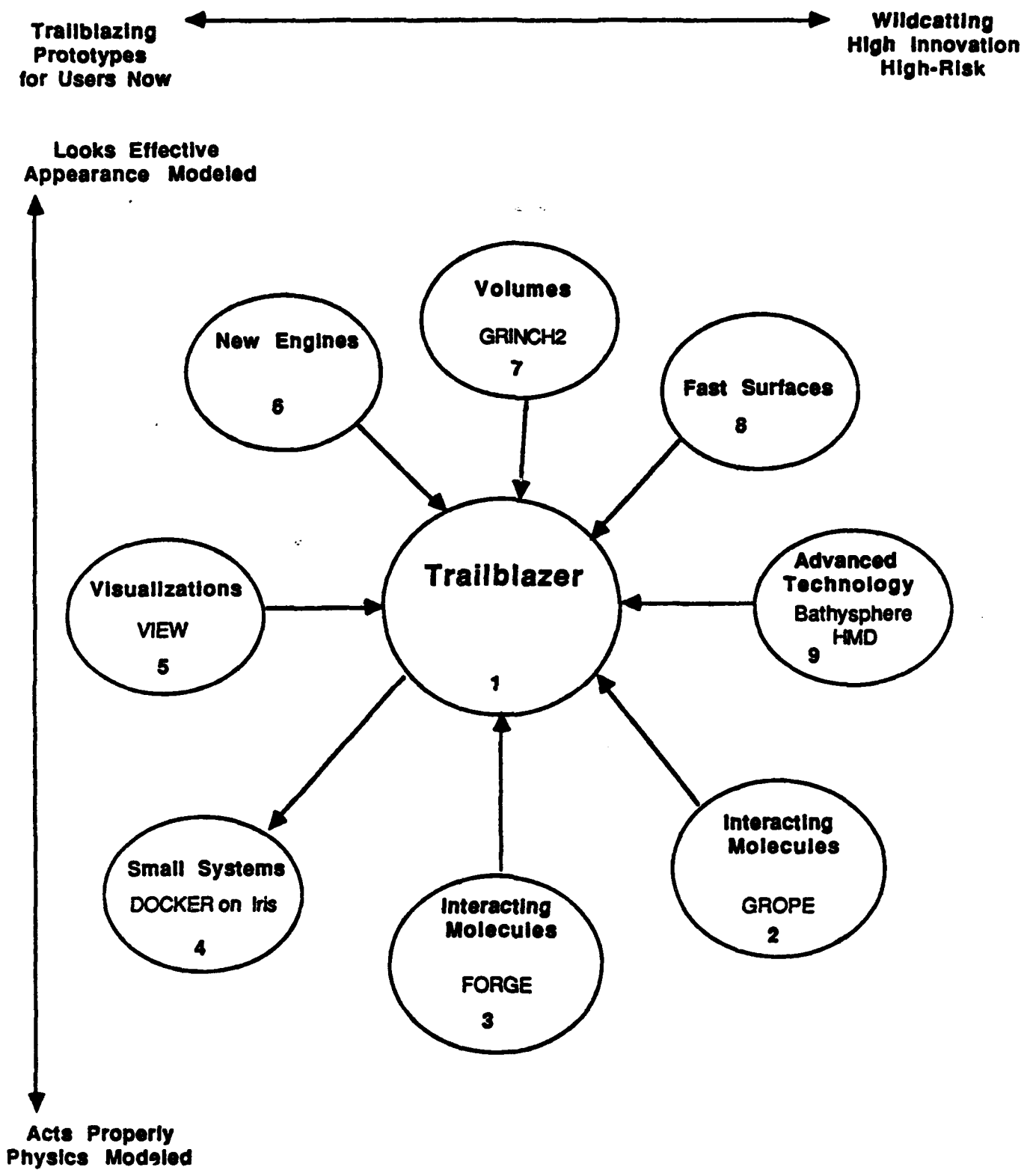


Figure 1. The Research Plan Proposed for 1992-97

C. Summary Progress Report

Activity Under Present Grant. This project was last reviewed competitively in 1988, and funded for May 1, 1989 - April 30, 1992. We discuss progress since the date of our last proposal, June, 1988.

The key personnel have been:

F. P. Brooks, Jr., P.I. – May 1, 1984 - present; 25%
William V. Wright, Project Director – April, 1990 - present; 100%
Mark R. Harris, Research Associate (Biochemist) – February 1, 1987 - present; 100%
Marc Levoy, Research Assistant Professor, September, 1989-June, 1990, 25%
David C. Richardson Project Biochemist – September, 1989-June, 1990; 100%
Jane S. Richardson, Project Biochemist – September, 1990 - June, 1991; 100%
Warren Robinett, Research Associate - September, 1989 - March 1, 1990; 100%

Organization of These Sections. Much of what we propose to do in 1992-97 is a direct continuation of what we are now doing. Therefore, instead of having separate sections on Progress and Proposed Work, this section will summarize the progress, with both wins and disappointments. Section D will combine a detailed treatment of progress with the proposed future work, organized by scientific area.

C.1. Summary of Wins

1. The **GROPE Project**, using remote manipulator technology to enable users to feel molecular forces, reached a major milestone. Graduate student Ming Ouh-Young as his dissertation project built a molecular docking system and by controlled experiments showed that force display enhances biochemist docking performance—significantly, but less than a factor of two. Perception is also substantially enhanced.

A major paper reviewing the whole 20-year project and the GROPE-I, GROPE-II, and GROPE-III experimental results was published at SIGGRAPH '90, the premier outlet for computer graphics work.

2. Real-time, user-steered **volume visualization** of an **electron density map** was accomplished on the new UNC Pixel-Planes5 graphics superengine. Graduate student Steven Hench adapted software built by graduate student John Rhoades. Users can see medium-resolution volumes and surfaces contoured at any density level with a wait time of about one second.

3. The GRIP-incubated **head-mounted display project** was in 1990 spun off with $561 K/year (direct costs) independent funding from DARPA. Resource Director Warren Robinett became the Project Manager of the new HMD project. The enlarged project includes a subproject developing an outward-looking optical head tracker, a subproject developing a new display and optical system, a subproject developing a complete software library, and a subproject developing applications, including molecular applications. Visiting Project Biochemist Dave Richardson, working with NRL collaborators, used the head-mounted display to model clathrate molecules of especial interest to the Navy.

4. Major **new equipment** came on line in our laboratory:
   - a Silicon Graphics 4D/240 GTX
   - the UNC-built Pixel-Planes5
   - an IBM Risc System/6000 Model 730
   - a MasPar MP-1, a 4000 processor massively-parallel computer
   - a Cray YMP supercomputer was installed at the North Carolina Supercomputer Center.

Of these, only the Silicon Graphics machine required Resource funds.

5. UNC's computer graphics team, together with collaborating teams at Brown, Caltech, Cornell, and Utah, has just been selected and funded by NSF and DARPA to establish a **Science and Technology Center for Computer Graphics and Scientific Visualization**, at some $2.6M/year (total costs – all five schools). The competition for second-round NSF S & T centers was very fierce. We proposed a new kind of center—distributed over five sites, linked by communications, prolonged visits, and many pairwise collaborations. Industry partners also pledged considerable support for the Center

6. UNC Computer Science's team, together with other Triangle-area collaborators was selected as one of five national testbed sites for the NSF **gigabit fiber optics network.** This will give very high-speed access to the Cray from our laboratory.

7. **Dr. William V. Wright,** a 20-year colleague and collaborator, retired from IBM and joined the project as Project Director. This resolved the 1988 Study Section's concern about stable senior staff.

8. **Prof. George Rose,** already a member of our Advisory Committee, accepted an offer to join the UNC Department of Biochemistry. We look forward to having another local collaborator.

9. The Resource substantially enhanced **dissemination,** including organizing and hosting **three national/ international workshops and conferences.**

Summary of Disappointments

1. **The VIEW System** for extemporaneous visualizations of molecules, on which we have invested considerable effort since 1987, failed the usability test when we asked real biochemists to try it for real work. During 1989-90 we made a major redesign with the guidance of visiting Project Biochemist David Richardson. We changed VIEW from a rich-function closed package to a set of independently-usable modules. A sharply reduced team is completing modifications and will have a package ready this spring, some 18 months behind our original schedule. It will be usable by relatively sophisticated users this spring, but a new user interface needs to be designed and built before it will be accessible by novices.

2. Our **graphics systems evaluation** effort was overtaken by events, so that the results of a year's work in doing careful performance measurements of competitive systems yielded no publishable results. Our policy was to publish results only when the manufacturers had agreed to their accuracy. Manufacturers didn't object to our

measurements, but they moved very slowly in certifying them. Meanwhile, Stellar and Ardent, whose first-generation machines we were comparing against each other, put out new machines, merged, and mooted much of our work.

We still hope to publish the careful collaborative work done by Matt Fitzpatrick and Mike Pique in defining benchmarks to use in measuring graphics engines' performance on molecular problems. We shall try to get them incorporated into industry standard graphics benchmarks.

3. GRIP project member **Prof. Marc Levoy** accepted an offer to start a program in computer graphics at Stanford. For the country and for the discipline, this is hardly a loss, since it starts another well-supported program at a truly excellent school that hasn't heretofore been in computer graphics at all. We will feel his loss locally, however.

4. Collaborator **Prof. Phil Bowen** left the UNC Department of Medicinal Chemistry to go to Georgia.

D. Proposed Work and Detailed Progress Report

D.1. Technological Research and Development

We divide into subsections by scientific area, with **Progress** and **Proposed Work** as subheads under each. We treat the topics in clockwise order on Figure 1, beginning at the center and proceeding according to the numbers.

D.1.1 Trailblazer Facility – Progress

The hardware facilities have been significantly upgraded.

Silicon Graphics Iris 4D/240 GTX Installed. The Resource purchased and installed this commercial graphics super-engine. It has four MIPS 3000 processors and an SGI rendering engine that was the fastest commercial graphics machine available when we bought in 1989.

For our task of dissemination, it is important that we have and use a commercially available machine, in addition to any special machines available to us. The SGI provides us very high performance, yet programs written for it run on even desk-top Personal Iris machines.

FORGE (SCULPT) and DOCKER have been built on the SGI. GROPE has ported its image-generation to the SGI. We will move ARM control in the coming year.

IBM Risc System/6000 Model 730 Installed. IBM has donated one of its top-of-line graphics workstations for the work of the Resource. It is being installed this week. The machine has a fast processor, 32MB of memory, and an 800 MB disk.

Workstation Upgrades. The Resource installed a Sun/4 and a DEC 3200, replacing Sun 2's that were beyond repair.

MasPar's 4000 Processors Harnessed. The department bought, at no cost to the Resource, a 4000-processor MasPar MP-1 computer. Graduate research assistant Russell Taylor programmed it to do real-time intermolecular force, torque, energy calculations using the Amber force model.

Software Engineering. 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, if not towards C. Our Resource has recently moved to a much more controlled approach to the building of software systems – object-oriented programming, using the C++ language. VIEW and FORGE (SCULPT) are built in C++.

Trailblazer - Proposed Work

Molecule Modeling Workbench. During 1992-97 we will build an integrated system combining ideas and software from our several subprojects. The chemist, seated, will work in a half-meter-cubed workspace using his/her hands to manipulate virtual models of macro molecules. The hands will be sheathed in Datagloves that report their positions and shapes. Pushbutton controls will choose among various geometric representations and property visualizations for the molecule and the fields around it. Stereo glasses will enable the chemist to see the molecule hanging in the workspace, properly placed in front of, or behind, the hands. As the biochemist works, continuous constrained energy minimization allows the display of energies, and force and torque vectors, and keeps the molecule from being manipulated into impossible conformations.

If suitable technology becomes available to us at reasonable cost, we would hope the chemist could also feel these forces as part of the total workbench integrated capability. But we can't promise that.

D.1.2 Docking – GROPE Progress

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 [1976] 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 the arm.

During 1988-91, Ming Ouh-Young took as his Ph.D. project the construction and evaluation of a prototype molecular docking system, GROPE-III. In Ming's system, the forces and torques to be applied to the user's hand were approximately calculated in real time by the grid method of Pattabiriman and Langridge [Pattabiraman et al, 1985]. Bumps were marked visually by flashing yellow arrows.

Trial users found it effective, so Ming did a controlled experiment. He found that chemists could dock drugs into dihydrofolate reductase (DHFR) at rates significantly faster, but not twice as fast, with force display turned on as with it off. The stereo visual displays on the E & S PS-330 were exactly identical. Appendix A is the SIGGRAPH '90 paper describing the whole 20-year project [Brooks, 1990].

In June, 1990, Dr. Vivian Cody of Roswell Memorial Institute came and studied the docking of some adamantines in DHFR. Using GROPE-III, she found two previously unknown additional stable docking positions. An abstract covering this work has been submitted to the 1991 Molecular Graphics Society meeting.

Exact Force and Torque Calculations. As described above, Taylor as a class project undertook and in December 1990 achieved dynamic real-time evaluation of intra- and inter-molecular forces exactly according to the Amber model. This has now been integrated into the GROPE-III system, eliminating the grid approximations.

Docking – Proposed work

GROPE Consolidation and Calibration. Dr. Cody's visit showed us many system needs. Ming undertook to answer only two questions with his prototype GROPE-III system—"Can one build a usable real-time force-displaying molecular docker?" and "Will it demonstrably help chemists?" Now we are consolidating on Ming's experience, and re-engineering the GROPE-III system on a strong scientific base.

Measurement and Calibration. Graduate research assistant Russell Taylor and Prof. Wright are measuring arm distances, force, and the impedances and other parameters used in the control theory. This has already resulted in improvements in the isotropy of the virtual space. The calculation of optimum damping is being redone, and velocity data from ARM joint sensors will be used to improve stability, and sensitivity.

Test Cases. The team is designing a set of simple peg-in-the-hole test cases that will enable us to judge hard-surface collision fidelity and sliding friction more precisely.

Consolidation onto SGI Iris. Ming's system controlled the ARM and evaluated forces and energies with a dedicated Sun4. Images were generated and displayed with a concurrent program on the PS-330, ethernet-coupled. We will consolidate ARM control and image generation on the faster four-processor SGI Iris. This may give an improved update rate; it will surely make the system simpler to maintain.

New Force Device. The Argonne Remote Manipulator is 1960's technology. We are engaged in a world-wide search for a new, 1990's technology 6-degree of freedom force display device. We want something that works hand-and-finger scale instead of arm-and-hand scale. We are currently studying devices made at the mechanical engineering laboratories of Dr. Iwata in Tsukuba and of Prof. S. Jacobson at Utah.

Sound. The voice-input for menu command selection is complete and must be user-tested. Kilpatrick's 1975 GROPE-II system also had sound output. We think sound will be useful for bump indication and for the energy thermometers, and plan to add it to GROPE-III.

User Evaluation. We plan extensive user evaluation over the next year, with outside users such as Dr. Cody and Dr. Mike Cory of Burroughs-Wellcome, who works with intercalations into DNA.

D.1.3 Physics-Constrained Folding—FORGE (SCULPT)—Progress

Graduate research assistant Mark Surles is building as his Ph.D. project a first prototype of the FORGE (SCULPT) interactive molecular model, working to desiderata and specifications devised by our collaborators, the Richardsons. There is still some debate as to what this system shall be called.

FORGE (SCULPT) Concept. The ideal is to allow the chemist to fold, deform, or dock molecular models while the models continuously maintain all constrained lengths and angles, and adjust free torsion angles within the "molten zone" to continually minimize free energy.

Implementation. Modern computer speeds move this ideal to the edge of feasibility. Surles is building his system on the SGI 4D/240 Iris, using one processor for display, one for the minimization calculation, and one to maintain the near-neighbors list.

In Surles's system today, one gets constrained minimization at better than one update/second, without the handling of non-bonded forces. The chemist can tack down atoms, or frozen regions, and apply spring forces at various other points in the model. It responds faithfully, if sluggishly, on small proteins such as the Richardsons's designed protein, Felix, which has four substantial alpha-helices.

Physics-Constrained Folding—FORGE (SCULPT)—Proposed Work

Completion of the Prototype FORGE (SCULPT) I. Our first goal is to have the FORGE (SCULPT) I prototype working, including non-bonded forces, before May, 1992.

User-Testing in Protein Design. Prof. David Richardson believes the tool will be especially useful for those designing proteins, so they can test how strands fit against, conform to, and bond with, each other, as a function of the exact amino acid sequence chosen.

Minimization Algorithms. Surles is devoting his principal efforts to the real-time constrained minimization. His system, with several hundred variables, is larger than seem to have been addressed with a real-time, continuous minimization objective. Prof. Robert Cohen of the Department of Mathematics, a specialist in optimization, is guiding him in this work. After the FORGE (SCULPT) I prototype is completed (and Surles graduated), we shall explore other minimization mathematics. Prof. Al Barr, our Caltech collaborator in the S & T Center, is the world's specialist in physically-based modeling in computer graphics. Our first visit there will be this month [Barzel & Barr, 1988; Platt & Barr, 1988].

Variable Reduction. It is important to characterize secondary structure chunks with appropriate parameters, such as helix length and pitch, and then to use these parameters instead of individual atomic coordinates in the minimization process. In the first place, that seems to correspond to nature. In the second place, it radically reduces the mathematical work of minimization. In the third place, it allows the chemist to manipulate the objects and variables he thinks about. At the moment we are following a bottom-up strategy in which the minimization is phrased in terms of atomic coordinates and then these are aggregated into rigid subunits, until stresses become too great. An alternative strategy we want to explore is to start with secondary structure subunits, descending to atomic coordinates as required. The work of the laboratory of Prof. Mornon in Paris is especially exciting in this connection [Lavery, 1989; Tufféry, 1990].

Interface. A highly interactive system such as FORGE (SCULPT) demands a natural graphical and manipulation interface. Graduate research assistant Rob Katz has worked on this problem. Jim Begley, a new graduate research assistant with SGI experience, has now picked it up.

Second FORGE (SCULPT) System. During 1992-97 we expect to see FORGE (SCULPT) I user-tested and then re-design and construct a second system, FORGE (SCULPT) II, incorporating the lessons.

D.1.4 Small Systems and DOCKER – Progress

The important happening in molecular graphics in the past five years has been the advent of workstations at $10K to $25K. Many biochemists now have their own dedicated workstations. We develop new techniques on very powerful systems—big SGI machines, Pixel-planes, 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.

DOCKER. As part of Ming's GROPE-III force-displaying docker, Ming devised new and powerful visual representations of docking molecules and their energies. Undergraduate research assistant Andrew Certain is currently building a visual-only drug-enzyme docking tool on the SGI Iris. The user controls the drug in three dimensional translation and rotation, using a mouse and some effective conventions. Bump arrows, force arrows, torque arrows, and energy thermometers help one see what is happening.

MOLIX – GRINCH on Workstations. The ordinary workstation with raster graphics cannot yet do smooth motion of complicated molecules, as the E&S Picture System-300's can. We therefore adapted GRINCH for Sun workstations, a system we call MOLIX.

Small Systems and DOCKER—Proposed Work

We plan to complete DOCKER, test it on the Personal Iris, and put some copies out for β-test. Assuming that it proves effective and usable, we will either make it available to the community at distribution cost, or offer it to commercial vendors who can fully support it.

Two other current efforts of our Resource that we hope to port to smaller machines are the VIEW system and the volume visualization work. Assuming both researches fulfill their present promise, we will first incorporate each, in full-function form, into 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 1992-97 work, prepare fieldable versions on the workstations and graphics devices the user community then has.

D.1.5 Visualizations – Progress

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 [Richardson et al, 1975]. 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 you their visualizations, you see at most what they saw in the data. If they share data and computational results with you, and you have a VIEW system, you 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. Our first prototype runs on the Sun 3, producing pictures on the Adage Ikonas, the PS-300, Pixel-Planes 4, and the Macintosh.

Testing of the 1988 prototype by biochemists showed we needed:

- much more flexibility in the order in which component modules are used—the visualization pipeline.
- the ability to superimpose and compare entirely separate molecules from the PDB database, that is, to handle multiple databases and geometry lists.
- many detailed capabilities we did not have.
- a much more intuitive interface.

We scaled the project team back and undertook a major redesign with the on-site assistance of Professor Dave Richardson, visiting 1989-90. Professor Richardson has built CHAOS, a system of visualization modules for the E&S PS-300 family. Our new system incorporates many CHAOS ideas. The new VIEW system is now much more loosely connected, and the crucial new functions have been added. We decided to go for the functional integrity and usefulness of the system in the hands of a knowledgeable user, and have not yet put any effort on a new interface.

R-Space. During the previous grant period, Project Biochemist Mark Harris, working with Dr. Frank Hague and Prof. C. Carter of the UNC Biochemistry Department, built R-Space, an interactive system designed to help crystallographers plan data-collection strategies for diffractometers with area detectors. 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.

For the past two years, R-Space has been distributed and supported by the department's SoftLab, a departmental infrastructure for the purpose of supporting software distributed by any project. Some 55 copies have been purchased, 35 academic and 20 commercial. Dr. Lynn Ten Eyck, a former GRIP Project Director now at the San Diego Supercomputer Center, is taking over updates and support. SoftLab will continue distribution.

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

Visualizations – Proposed Work

VIEW. 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 1992. In 1992-93 we presently expect our emphasis on VIEW will be on improving the interface. Then we shall integrate these capabilities into the Trailblazer system.

During the entire 1991-92 academic year, Dr. Brooks will be on leave, and will spend four days per week at Duke in the Richardsons' laboratory, refreshing himself technically by solving visualization problems with his

own hands. In particular, he plans to exercise VIEW extensively, both to improve the tool and to improve his vision of what a tool should be. So this will be part of our prototype user testing, and we expect to reflect the results into the shippable system.

D.1.6 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. 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 as gifts or loans because of the concentration of graphics investigators and projects in our laboratory, and its high visibility. This enables us to do long-term evaluations with minimum equipment cost to the Resource.

Molecular Benchmark. During 1988, Graduate research assistant Matt Fitzgibbon and Mike Pique developed a five-part benchmark to be used for measuring the performance of graphics machines in molecular applications.

Stellar-Ardent Evaluation. Pique and Fitzgibbon ran the benchmark on comparable configurations of the first-generation Stellar and the first-generation Ardent Titan. Our Resource was at the time planning to acquire a new system, so this measurement was in dead earnest. We aimed to publish the results, and for fairness submitted them to the vendors to see if we had exploited each machine fully and measured fairly. Meanwhile, we planned a measurement of SGI's forthcoming 4D graphics system.

Three things happened during 1989-90:

- The vendors dragged their feet in responding.
- Both Stellar and Ardent brought out new models, thereby rendering the comparative results on the old ones largely academic.
- Stellar and Ardent merged and began restructuring their product line.

As a result we abandoned publishing our results.

New Engines – Proposed Work

Molecular Benchmark. The Fitzgibbon-Pique benchmark is a good representation of the kinds of tasks that characterize molecular graphics, as opposed to other graphics applications. It is our objective to get it into use.

Two possibilities exist. The best would be to get it adopted by the graphics industry's new Systems Performance Evaluation Cooperative, as part of their standard suite. Else we can offer it for publication in the *Journal of Molecular Graphics*.

MasPar MP-1. We plan to continue learning how to exploit massively parallel machines such as the MasPar and the Connection Machine. Such machines only work well for applications with special properties, but we and others have shown that some molecular problems fall in that set. Now the issues are:

- What problems to tackle this way?
- What new algorithms are appropriate?

We will invest effort in documenting our experience (with some numbers), but not in large-scale measurement activities.

Pixel-Planes5. As this machine comes up to speed, we shall see how this unique machine, with 16 general processors and dozens of massively parallel renderers, fits molecular problems. This is of research interest; since one configuration provides both kinds of parallelism, it is well suited for discovering where the bottlenecks inherent in the applications lie.

New Workstations. Besides the above, we will continue to work on forefront conventional workstations ($50,000 - $100,000 class), the Sun 4, the Digital 5000, and the IBM RS/6000 Model 730. Here too we will document our comparisons, but not undertake a formal measurement program.

D.1.7 Volumes–Electron Density Maps – Progress

There are many fruitful ways to visualize electron density, conventionally represented by contour maps. Our GRINCH system uses Carroll Johnson's ridge-line representation to reduce scene complexity by a factor of about 100 compared to contour maps [Johnson, 1976; Richardson, 1985]. Since 1987 we have been exploring direct rendering methods, in which the voxels of data are themselves rendered.

Direct Rendering – Westover. Contour lines 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. Starting as a Resource graduate research assistant, Lee Westover has shown the filtering methods necessary for rendering volume data directly visible, by treating each volume element (voxel) as luminous and projecting them onto the view screen. His work came to publication during this period. [Westover, 1989; Westover, 1990] He is continuiing his dissertation while working full-time for Sun Microsystems.

Westover's approach has the attraction that one sees the raw density data barely interpreted. His visualizations look fuzzy because the data itself is of low resolution, a fact contouring conceals.

Direct Rendering – Levoy. As a Resource graduate research assistant Marc Levoy devised 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. Levoy's method is compute-intensive. His first pictures took hours of Sun-4 time per frame, but he has steadily brought this time down.

During 1988-91, Levoy completed his Ph.D. dissertation (in 1989) and continued developing his techniques. For 1989-90, he was a visiting Research Assistant Professor, supported in part by the Resource. He has since been recruited to Stanford to start a new academic program in computer graphics.

Real-Time Volume Rendering. Levoy's new developments include adaptive refinement, in which a low resolution image is produced quickly, and then the resolution is progressively improved while the user watches.John Rhoades, a graduate research assistant on the Pixel-Planes project, has built software to realize adaptive volume rendering on PxPl5.

Stephen Hench has modified the software, and built the interface, to make it work for electron density maps. The user can change viewpoint, clipping planes, etc. interactively and get a new rendering in about a second [?]. After a few more seconds the image sweetens—its resolution improves.

Volume Visualization Workshop. During this period Resource people and our colleagues on other projects organized and hosted the first meeting for the emerging volume visualization discipline. More is reported below under D.5, Dissemination.

Volume Studies – Proposed Work

Develpment and Testing. Our Advisory Committee believes the volume visualization work to have great promise, since it shows electron density, or any other volume-based variable, in quite new ways.

We propose high-priority development and testing of real-time volume visualization techniques. First, we shall exploit PxPl5's capabilities using and adapting Levoy methods until we have something good enough for real users who have an uninterpreted map. For 1992, we know we need to work on interpolation methods, lighting models, and user interface.

Then we shall test it on real users, and find where the shoe pinches. Then another round of work on the most serious shortcomings. Meanwhile, as interested graduate students appear, we shall initiate a parallel exploration of Westover's radically different techniques, and get some biochemist feedback.

Real-Time Map Working in Transform Spaces. As we have studied interpolation in electron density data, it has occurred to us that interpolants can be calculated by Fourier-transforming known or postulated higher-order crystallographic reflections. These interpolants may have more physical validity than purely numerical manipulations in real space.

Crystallographers have often improved phasing of local parts of large maps by suppressing the local atoms completely, calculating phases from the atom coordinates remaining, using these phases to recalculate density in the local region, and then re-locating atoms in the new density. The process seems to converge when in good hands.

New computer power makes a real-time system for such manipulations feasible before 1997. We envision a multiple-view system in which one sees on one screen the density volume-rendered, perhaps with atoms and bonds superimposed. On another window one would see crystallographic reflection amplitudes. On another, phases. Perhaps on another, a reciprocal-space 3-D representation of the density map. The chemist would manipulate objects or values in one window and immediately see the effects in the others.

Our hypothesis is that

(1) manipulations of amplitudes or phases of reflections will usually tend to make densities less molecule like,

(2) when a density map does change to look more molecule-like, the odds are good that it looks like the true molecule, not a spurious one

(3) biochemists are far more able to recognize molecule-like densities than algorithms are or will be.

We propose a long-term effort over the whole 1992-97 period to develop such a real-time multiple-view map study system. Homologous sequences are today's hot topic re crystallographic fitting. We believe a map manipulation system ties right into this trend. Such a system lends itself to the study of homologous molecules and their relationships in Fourier space.

GRINCH II - Direct Map Interpretation. Levoy's work, in particular, suggests that volume visualizations might be better than ridge-lines in a GRINCH-like direct map interpretation system. During later years we propose to build such a GRINCH II system.

D.1.8 Surface Studies - Progress

Real-Time CPK Models. 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, on protein-sized models. This objective was completely achieved.

How it was achieved is a good example of why it is important to have bridgebuilders between the molecular studies world and the computer graphics world. Fuchs, Poulton, and team were building Pixel-Planes4, in 1986 the world's fastest general-purpose graphics engine. The Resource team studied the planned machine and saw that it did polygons swiftly, curved surfaces poorly. We said, "That won't do for molecular work." Brooks devised a fast-spheres algorithm for PxPl4, and the builders put it into the microcode. [Fuchs, 1985]

Prodded by our example commercial graphics vendors have recognized the importance of spheres. The Ardent Titan and its successors include them as primitives.

Surface Studies - Proposed Work

Objective for 1992-97: Dynamic Motion of Solvent-Accessible Surfaces. We find solvent-accessible surface depictions of molecules to be much easier to understand than CPK models, particularly as to the structure of active sites. We believe that a solvent-accessible transparent surfaces superimposed on opaque ribbon models might be an especially powerful visual representation [Lee & Richards, 1971].

To achieve this potential usefulness, such models must be displayed in stereo and moved and rotated in real time, so the kinetic depth effect can aid perception. This is not possible for proteins with today's hardware.

Our objective is to demonstrate such user-steered dynamic motion of solvent-accessible surface models early in the 1992-97 period, and to help them make their way to the chemist's workstation by the end of the period.

Trailblazer System on PXPL-5. Our goal requires us to go beyond the dynamic display of spheres to achieve the dynamic display of transparent toroidal (fourth-degree) patches and spherical patches. Pixel-Planes5 will render quadratic patches as a graphics primitive. We shall start by approximating toroidal patches by hyperboloidal ones. Meanwhile we shall see if special algorithms for toroids can be devised for the machine.

Faster Richards Surface Algorithms. Doug Schiff while a Resource graduate assistant explored the use of plane-sweep algorithms from computational geometry as a way of calculating solvent-accessible surfaces in real-time, which Connolly's algorithm cannot yet do [Connolly, 1981]. So far this approach has not worked; there are other algorithmic approaches to be tried.

D.1.9 Advanced Technology – Progress

Head-Mounted Display Separately Funded. For some years we have envisioned an 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 our Resource team began to build such a display as soon a miniature liquid-crystal television sets came on the market. We generate right- and left-eye images on the SGI Iris or Pixel-Planes4. 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.

When this work was entirely in the Resource, we could invest only one graduate student, plus technician time, in it. When in 1988 it attracted favor with our ONR sponsors, we tripled the team. In 1990, Brooks and Fuchs proposed, and were awarded, a separate 5-year grant from DARPA to develop head-mounted display technology. So we have successfully incubated and hatched this as a separate research project.

We shall invest no Resource in the HMD technology effort during the 1992-97 period. We shall commit part or all of one graduate research assistant's time to working with the HMD team, furnishing them appropriate molecular models and testing their advances against molecular applications.

Toward the end of the period we propose to build a user-manipulable room-filling protein, to see how that scale compares for insight against tabletop molecular models .

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 application we have seen. 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 some years ago. 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.

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. Some years ago the Resource acquired and tested a Votan speech recognition system, which does speaker-dependent recognition for disconnected speech, with a vocabulary of up to 256 phrases.

In our limited tests to date it seemed to work fine. Recognition was fast, faster than mouse motion. Accuracy ran well above 95%, and it rarely missed in a catastrophic way. We have included the exploitation of speech recognition technology in the spun-off Head-Mounted Display project.

Advanced Technology – Proposed work

Stereoscopic Large-Screen 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 work with Tektronix to have fabricated a special-sized set of windows to fit our video projector, and a tube with a fast green phosphor is on order..

Bathysphere - High-Resolution Surround with Tracking. Our earlier work on head-motion parallax, and the severe resolution and field-of-view limits on head-mounted displays have led the head-mounted display team to start work on a separate attack using a different display paradigm, the *Bathysphere*. The user will be half-surrounded by 19" display monitors, head-motion will be tracked, and the image will change to compensate for head translations. Viewing will be in stereo. Pixel-Planes5 will maintain coherent images on all the monitors.

The Resource will work with this exactly as with the rest of the HMD project—furnish molecular models and participate in testing the system with molecular applications. We will devote no Resource effort to building the Bathysphere system.

Summary of Proposed Work and Priorities

Priorities. So many things to do, and few hands to do them. The reader may ask, Which ones are you **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, in declining order:

- FORGE (SCULPT) completion, first user test
- Docking studies, especially GROPE-III
  - Real use
  - Consolidation of scientific base
  - Move onto SGI machine
  - Visual docker on Personal Iris
- Volume visualization in real time
- New engines – exploitation and evaluation
- VIEW user testing, including Brooks's work at Duke
- Use head-mounted display, bathysphere.

D.2 Collaborative Research

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 D.3.

We estimate that some 30% of all of our effort over the past 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.

At this time we are engaged in two formal collaborative research projects, documented here. The biographies of our collaborators and their letters are in the appropriate sections. Besides these collaborations with molecular graphics users, we will continue to maintain our several collaborations with other computer graphics groups, at UNC and at the other four Science and Technology Center Universities.

David C. and Jane S. Richardson – Molecule Sculpturing and the FORGE System. The Richardsons are engaged in the design of proteins *de novo*. They need tools with which they can twist alpha helices, dock them (with side chains conforming properly), warp beta sheet, etc.

The specific objective is to design a graphics tool which enables the biochemist to do and view 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, powerful hardware, and strong experience with manipulative interfaces. We and the Richardsons will, of course, continue our long-standing collaboration on other projects.

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, 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. Our students, Matt Fitzgibbon and Larry Bergman have each spent a summer at Scripps. Getzoff and Tainer have a history of inventing good ways of looking at molecules.

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.

Technical Support for Local Collaborators' Facilities. Our local collaborators have installed configurations like ours. 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.

What We Aren't Going To Do – QC, MD, 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 five years. These include quantum chemistry, molecular dynamics, 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.

D.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.

GRIP USERS since 1 May 1988

Alexander Claiborne
Bowman Gray School of Medicine
Department of Biochemistry
(919) 748-3914

Used Mendyl to study the accessibility of the reactive cysteine in glutathione reductase in order to interpret his experimental data. Used VIEW to illustrate results. His experience with our systems helped him justify the acquisition of a graphics system for his laboratory. They bought an ESV.

Holly Miller and A. Claiborne, Peroxide modification of monoalkylated glutathione reductase: evidence for stabilization of an active-site cysteine-sulfenic acid intermediate. A short paper in the proceedings of the conference Flavins and Flavoproteins - 1990, ed. Bruno Curti, S. Ronchi and G. Zanetti, in press.

Holly Miller and A. Claiborne, Peroxide modification of monoalkylated glutathione reductase. stabilization of an active-site cysteine-sulfenic acid intermediate. A full paper to be submitted to Jour. of Biological Chemistry about 1 March 1991.

Holly Miller and A. Claiborne, Yeast glutathione reductase as a model for investigating protein thiol reactivity. Abstract submitted for a presentation at the FASEB meeting for April 1991.

Laurie Betts
UNC-CH
Department of Biochemistry
(919) 966-3263

Is currently using our GRINCH system to derive an initial structural model for cytidine deaminase from a new map she has calculated. She uses our system both at our site and on a PS300 display in her own laboratory running on our processor via ethernet.

Frank C. Church
UNC School of Medicine
Department of Pathology
(919) 966-3311

Used Mendyl to study the published structure of alpha-1-antitrypsin and to predict the folding and binding site of the homologous heparin cofactor II and protein-C inhibitor. Has graduate student who might want to use our docking system.

Herbert C. Whinna, Morey A. Blinder, Mark Szewczyk, Douglas M. Tollefsen, and Frank C. Church, Role of lysine 173 in heparin binding to heparin cofactor II. Jour. of Biological Chemistry, in press, 1991.

Acknowledges Mark Harris, Phillip Bowen and the UNC Laboratory for Molecular Modeling.

Charlotte W. Pratt and Frank C. Church, Antithrombin: Structure and Function. Seminars in Hematology, Vol. 28, No. 1 (January 1991), pp 3-9. Acknowledges two NIH grants but not ours.

Frank C. Church, Herbert C. Whinna, Rebecca L. Brown, Mark R. Harris and Charlotte W. Pratt, an abstract, Structure and function relationships of the heparin binding sites of antithrombin III, heparin cofactor II and protein C inhibitor. UCLA Symposium entitled "Protein and Pharmaceutical Engineering." Published in Jour. of Cell. Biochem. suppl. 13A, p.51 (1989).

Vivian Cody
Medical Foundation of Buffalo
(716) 856-9600

Used our docking system to study the binding of DAMP, DAPT and TMP with chicken liver dihydrofolate reductase and the binding of thyroxine and bromoflavone with a prealbumin.

Presented slides and a ten-minute video made with our facilities at the Medicinal Chemistry Symposium in June 1990.

Michael Dobres
N. C. State University
Department of Botany, now located at
Drexel University
Department of Bioscience
(215) 895-1972

Used Mendyl to look at the published structure of concanavalin A which is homologous to a protein whose cDNA he has isolated.

David and Jane Richardson
Duke University
Department of Biochemistry

Ion Channels as 3-D Protein Structures. Presented at Gordon Conference on Ion Channels, July 1990. Showed slides and results calculated with our facilities.

Molecular Structure in Biology, a CD ROM. Oxford University Press, to appear summer 1991. Used our VIEW system and Penny Rheingans' software.

James N. Siedow
Duke University
Department of Botany

(919) 684-6573/3715

Used Mendyl to investigate possible folding patterns for his membrane protein ORF32 which has no obvious relationship to any other protein.

Francine Smith
UNC-CH
Department of Biochemistry
(919) 966-3263

Used VIEW to display a backbone ribbon for the ypsilanti mutant of human hemoglobin. The picture was not suitable for her purposes, so she used FRODO in her own lab to get a

D.4 Training

The GRIP Resource carries out its education and training role in five 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 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 and scientific visualization:

Joseph Capowski	UNC Dept. of Physiology
Matt Fitzgibbon	Thinking Machines
John Gauch	Boston University
Griffin Hamlin	Dept. of Energy
Brad Hemminger	UNC Dept. of Radiology
Jeffrey Hultquist	NASA Ames Lab
Marc Levoy	Stanford University
James Lipscomb	IBM Watson Lab
Thomas Palmer	Cray Research
Michael Pique	Scripps Research Institute
Douglas Schiff	SUN Microsystems
Lee Westover	SUN Microsystems
William Wright	UNC – GRIP Resource
John Zimmerman	Washington Univ., St.Louis

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

Organic Chemistry Course Aids. Graduate research assistant Pan Johnson has been collaborating with the UNC Department of Chemistry in updating the teaching of the introductory organic chemistry course. Chemistry has just installed an undergraduate molecular graphics teaching laboratory equipped with Macintoshes and the ALCHEMY software.

Johnson, who came to UNC after several years of building molecular graphics software in a government laboratory, has prepared introductory interactive tutorials for ALCHEMY. It is being class-tested now. We expect to continue this effort on a 10-hour-per-week basis.

Faculty and Staff. Over the past 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 more about molecular graphics.

Molecular Modeling Course. Dr. Brooks participates as a lecturer in the graduate course, Medicinal Chemistry 275, Molecular Modelling, offered in the School of Pharmacy. We have formally agreed to continue this collaboration as part of the Resource's training function.

D.5 Dissemination

Following the admonitions of our 1988 Study Section, we have stepped up efforts on dissemination. Our major dissemination accomplishment during this period has been hosting national and international meetings. We have also supported and distributed our previously produced software, and we have been much more active in publishing research papers.

Chapel Hill Workshop on Volume Visualization, May, 1989. The Resource hosted, in collaboration with UNC's NIH-fund Med 3-D Project, the first scientific meeting on volume visualization techniques. Dr. Craig Upson of Stellar Computer chaired the Program Committee, Dr. Brooks was Workshop Chairman. The Resource staff organized local arrangements. The university and the Molecular Graphics Society provided subsidies. Some 165 people came, from North America, Europe, and Asia. Resource editor David Lines, working with the authors and Dr. Upson, edited, typeset, and laid out the *Conference Proceedings*, which were distributed to attendees at registration [Upson, 1989]. The volume included 49 color plates. The Association for Computing Machinery, upon recommendation of the SIGGRAPH Executive Committee, took over the post-conference sale and distribution of the *Proceedings*. The Table of Contents is attached as Appendix B. An exhibit of hardware, software, and books for molecular graphics was part of the meeting, as well as demonstrations of our Resource's work.

The Workshop is generally considered to have been quite successful, so much so that it has become a series. The second workshop was held in San Diego in December, 1990.

Chapel Hill Workshop on Geometry for Molecular Visualization and Characterization, March 1990. The Resource, mostly through the efforts of graduate research assistant Larry Bergman, sponsored this

one-day workshop, with some 40 attendees. The university, NSF, and the North Carolina Biotechnology Center provided funding. Abstracts, including 38 color images, were edited by Bergman into a notebook for registrants. A copy of the Table of Contents is attached as Appendix C.

Molecular Graphics Society, Tenth International Meeting, May 1991. The Resource will host on campus the second of the annual International Meetings of MGS to be held in the United States. Mike Pique of Scripps is chairing the Program Committee, Dr. Brooks is general chairman, and Mary Ducker is organizing local arrangements. Program abstracts will be pre-published for registrants and later published in the *Journal of Molecular Graphics*. This meeting will also have an exhibit.

Software. We continue to distribute RSpace and to support users of GRINCH around the country.

Demonstrations to Visitors

An important means of dissemination continues to be visits here, and demonstrations to visitors from industry, universities, the media, and government agencies, and to local groups from schools, colleges, and professional societies. The following is a selected list of the people we have demonstrated our molecular graphics facilities to since our last proposal. The most distinguished was Senator Al Gore from Tennessee, who made a trip to Chapel Hill just to see UNC's Computer Graphics lab. Media coverage included *Scientific American* [Stix, 1991], *Smithsonian Magazine* [Stewart, 1991].

1989
Mark Cutter, Apple Computer
Eric Jansen, Delft Institute of Technology, The Netherlands
Tomoyuki Nishita, Fukuyama University, Japan
Michel Rua, Philips Medical Systems, France
J. Covert, D. Hager, and C. Reynolds, Wright-Patterson AFB
University of North Carolina Board of Governors
Jean-Daniel Nicoud, Swiss Federal Institute of Technology
Undergraduate engineering students, Duke University
Bell Northern Research
Kadi Bouatouch, University of Rennes, France
Branko Gerovac, Digital Equipment Corp., Marlboro, Mass.
Arya, Gupta, Haumann, Norton and Rossignac, IBM T.J. Watson Lab.
E. MacCormac and two delegations of West German scientists
Penny Bauersfeld, Apple Computer
Robin McLeod, Annette Smith, and Glenn MacDougall, Tektronix
Justin Rattner, et al, Intel
John Brockway, Davidson College
Naval Research Lab.
National Computer Graphics Association
Andrew Woo, SAS Institute, Canada
Jaron Lanier, VPL Research
Judy Bunch, Duke University
Food and Drug Administration
Ben Davis, Discover Magazine
Nathan Myhrvold and Diane Hargrove, Microsoft Corp.
Kicha Ganapathy, AT&T Bell Labs
Ferran Sanz, Universitat Autonoma de Barcelona, Spain

Martin Duerst, Kunii Lab., Japan
Mark Finlay and Gary Diver, IVEX Corp.

1990

Stephen Westin, Ford Motor Corp., West Germany
Lauren Seeley, WGBH-TV (Nova), Boston
Graduate students in computer science, psychology and engineering,
North Carolina State University
Thomas Furness, University of Washington
Kathy Haight, Charlotte Observer
Claudio Gatti, Europeo, Italy
Participants (biochemists) in Molecular Geometry Workshop
Alexander Stoyenko, faculty candidate
Michael Coffin, faculty candidate
Texas Instruments
Niklaus Wirth, ETH, Zurich, Switzerland
Michael Taylor, Matsushita Electric Works, Japan
Phil Amburn, Wright-Patterson AFB

1990 (continued)

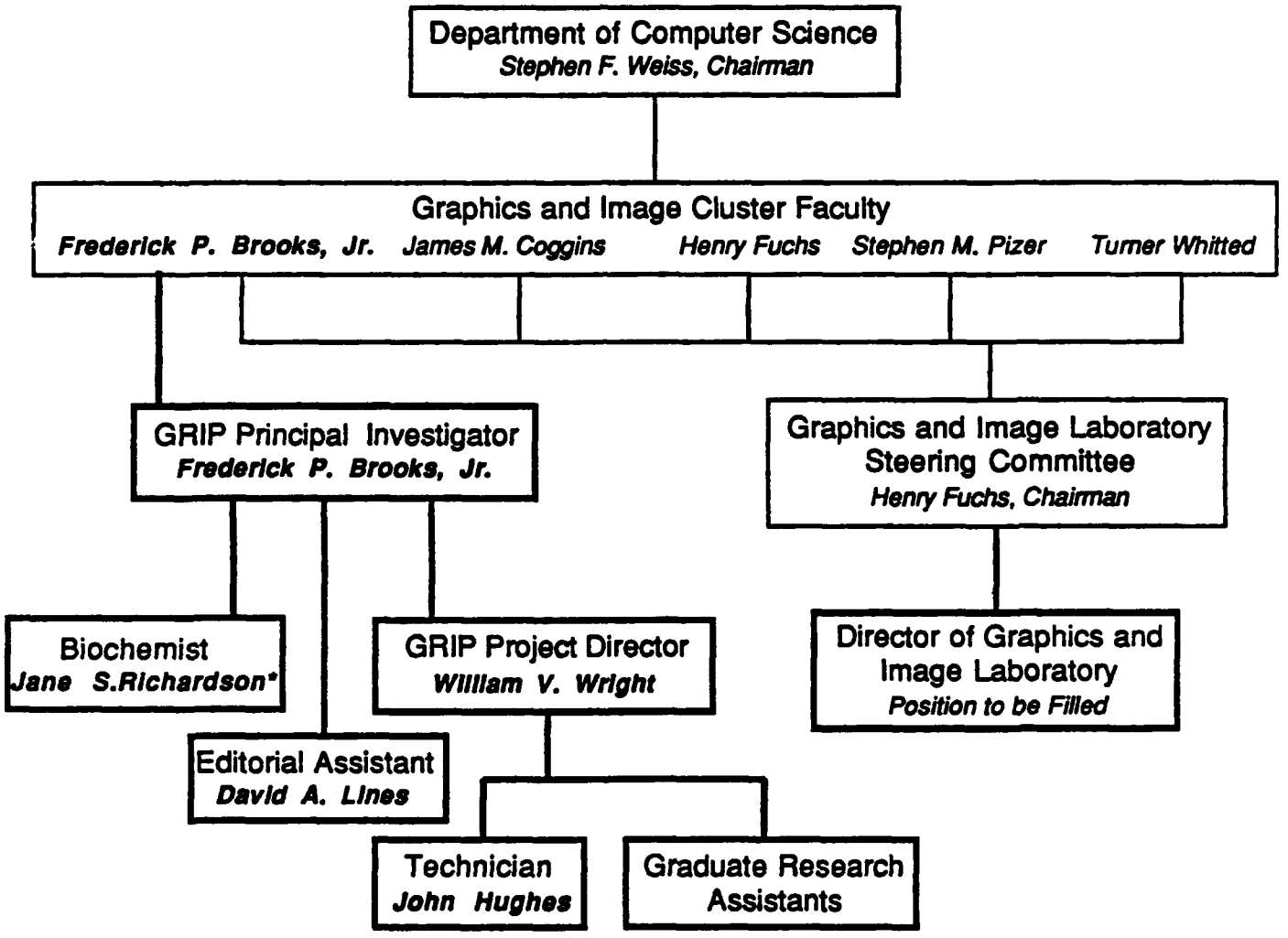
Peter Shirley, faculty candidate
Junior Science & Humanities Symposium, high school students
Peter Menzel, Smithsonian Magazine
Students from UNC School of Information and Library Science
Bob Liang and Mario Schkolnick, IBM T.J.Watson Lab.
Nat Durlach, Massachusetts Institute of Technology
Charles Gupton, Newsweek Magazine
David Hill, et al, Virtus Corp.
Swami Manohar and computer science students, UNC-Charlotte
American Institute of Chemical Engineers, local chapter
Russ Eberhart, APL Biomedical Program, Office of Naval Research
Doug Stetson, U.S. Navy
IEEE Symposium on Computer-based Medical Systems
Charlie Brooks, Biochemistry, Carnegie Mellon University
Hirofumi Ishida, NEC, Kawasaki, Japan
Owen Jacobs and Ed Johnson, Army Research Institute
Antoine Collet-Billon, Philips, Paris
High school chemistry teachers attending conference in
UNC School of Education
Doug Schiff, et al, Sun Microsystems
Mechanical engineering students from North Carolina State University
G. Kossoff and G. Devy, Australia
Tom Kominski, Astronautics
Office of Naval Research, site visitors
Industrial sponsors of Duke University Engineering Research Center
DARPA Contractors' Meeting
Steve Squires, et al, DARPA
Albert Gore, U.S. Senator
IBM Science Advisory Committee
Students from East Rowan High School, Salisbury, NC
Edouard Launet, Les Echos, Paris, France

Class of gifted and talented sixth graders, Glenwood School, Chapel Hill, NC
Japanese Public TV
Josh Scully, biochemist, Wayne State University, Ohio
T. Miyazawa, IBM Tokyo Research Lab.
Kikinis and Jolesz, Brigham and Women's Hospitals, Boston

1991 (through January 31)
Art Chin, et al, General Electric Research, Schenectady, NY
Michael Shneier, Mehran Moshseghia and Benjamin Zhu,
Philips, Briarcliff, NY
Armed Forces Institute of Pathology
Glen Emory, Insight Magazine
Charles Brownstein, National Science Foundation
Larry Yaeger, Vivarium project, Apple Computer
GRIP Advisory Committee

H. Resource Organizational Structure

a. Organizational Structure. The Resource is operated as part of the Department of Computer Science in the Faculty of Arts and Sciences. Resource organization and the relationships of all the persons supported in part by it are shown in the chart. The bold lines and names are Resource-related:



* 1990-91 only.

GRIP Research Resource Organization

b. Resource Staff Responsibilities. They are almost self-evident from the chart, except that the Project Biochemist, currently Prof. Richardson, has a special responsibility for relationships with our collaborators and users. All members of the staff are involved in all aspects of the work. The expertise of the professionals is covered in the biographies. Dr. Wright did his dissertation research on molecular graphics in the '70's, and has worked in the field for many years since. Mr. Lines is an expert editor of text and pictures, having edited and published one magazine while in college, and a second since entering graduate school. Mr. Hughes is a master mechanic and has also had training and experience in computer repair.

c. **Operating Procedures.** We pick projects according to our judgement, as advised by our Advisory Council. Scheduling is not a problem.

e. Resource Advisory Committee. The current membership is:

Jeff Blaney, Protos
Vivian Cody, Medical Foundation of Buffalo
Michael Cory, Burroughs-Wellcome
Richard DuBois (ex officio), National Institutes of Health
David DuChamp, The Upjohn Company
Elizabeth Getzoff, Research Institute of Scripps Clinic
Arthur Olson, Research Institute of Scripps Clinic
Michael Pique, Research Institute of Scripps Clinic
David Richardson, Duke Medical Center
Jane Richardson, Duke Medical Center
George Rose, Penn State College of Medicine

All of the above are biochemists except Mr. Pique, who is a computer scientist.

The committee meets annually, with local members meeting over dinner from time to time. The committee will advise on service and collaboration policies, as needed. More important, it will identify new opportunities and needs of the molecular scientists and help us choose among them.

I. Literature and Resource Publications

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