Thirteenth Annual Report
Interactive Graphics for
Molecular Graphics System

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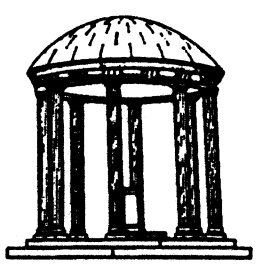

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Summary of Research Progress

1. Objectives and Operation

We have built, and operate as a service resource, an effective interactive computer graphics facility for seeing, manually manipulating, and computationally modifying mathematical models of complex molecules.

We have two objectives. We provide powerful graphics and expert assistance to chemists, both in our laboratory and by building software for export. We also advance the art of interactive computation and interactive three-dimensional graphics. Our chemist collaborators provide a real, complex, and interesting driving problem for our computer science research; our computer science research in turn provides them better insight into complex structures.

Fundamental to our approach are the following principles:

- The GRIP Resource is designed to help chemists get results from their research, and its success is measured only by theirs.
- Our systems are designed to help the chemists visualize their molecules and density maps, so that they can use their knowledge to guide computational processes. That is, they are an aid to, not a surrogate for, human thinking and manipulation. Hence we emphasize the human engineering of our tools.
- Our system is designed to serve many users, not one or two, so it includes an armory of alternative tools and techniques.

We depend on feedback from real users attempting to solve real problems. Our users are almost exclusively working on the structures of molecules of considerable biomedical interest: proteins and nucleic acids. We advance health-oriented biochemical research by enhancing the productivity of individual researchers through better tools.

The facilities are displays, computers, interactive devices, recorders, and quite elaborate software, grown over some seventeen years.

2. Project Progress and Computer Science Results

In last year's proposal we stated six objectives, quoted as stated then:

"1. **Docking Studies.** Our major push will be to complete the ARM's force-feedback subsystem, including software, and test it with real molecule force models. We have as a special objective to get this running by October, 1986, when we will host a SIGGRAPH-sponsored workshop on interactive 3-D computer graphics.

"2. **Molix.** We plan to user-test and field the Masscomp-only version of GRINCH, in a configuration costing less than $50,000.

"3. **Space-Filling Models on Pixel-Planes.** We plan to demonstrate real-time user-directed motion of protein-sized molecules on the Pixel-Planes machine, once again in time for the October workshop.

"4. **Advanced Graphics Technology.** We plan to demonstrate a restricted-volume head-mounted display working with real molecular data.

"5. **GRINCH Field Support.** We plan to support GRINCH users, whether visitors to our laboratory or users of GRINCH systems installed elsewhere, with consultation, bug fixes, feature enhancements, and documentation enhancements.

"6. **Building Move.** We will move our laboratory into the new Computer Science building. This will slow other work."

Progress against these objectives, as of now, is as follows:

1. **Docking Studies.** The ARM force-feedback system, including software, was built for first public showing in October, as planned.

2. **Molix.** Molix did not get debugged in time for a user test this year. It did get sped up and improved. We imported Frodo and ported it to Unix for the VAX-PS300 and Masscomp-PS300 configurations, and exported the VAX version to the US Naval Academy.

3. **Space-Filling Models on Pixel-Planes.** We beat our objective, and demonstrated real-time user-directed molecule motion at the SIGGRAPH annual conference in August!

4. **Advanced Graphics Technology.** We demonstrated a prototype head-mounted display with test images in October, but it is not yet good enough for real molecular images.

5. **GRINCH Field Support.** We not only supported GRINCH users, GRINCH was enhanced in performance by switching to new GSR's in the PS300. Copies of GRINCH were shipped to:

Donald Voet, Dept. of Chemistry, University of Pennsylvania

Otto Dideburg, Institut de Physique, Universite de Liege, Belgium

Dulio Cassio, Molecular Biology Institute, UCLA

Jim Bentley, Burroughs-Wellcome, Research Triangle Park

6. **Building Move.** The building slipped almost a year, so we didn't get our laboratory moved.

We now give more detail:

Docking Studies. The whole team worked on getting the Argonne Remote Manipulator operating as a force-feedback display. Ming, Hughes, and Pique completed the interfacing to the Masscomp 5500, revision of the grip and thumb switches, and the substitution of Masscomp programs for some of the analog filtering, etc. electronics. A team under Schiff prepared the Pattabiraman rapid intermolecular force evaluation program. Another group prepared suitable visual displays, and test cases consisting of point charge fields and probes.

By the time of the workshop, we could demonstrate manual exploration of simple force fields. Later work has been devoted to calibration.

Meanwhile, Tom Palmer has been building another docking visualization system to run on the Ikonas and generate simpler, but we hope, adequate views.

We negotiated with Michael Connolly to become a beta test site for his new PPMS (Piecewise Polynomial Molecular Surface) and TRB (Triangulation by Recursive Bisection) programs.

The visual model, generated on the PS300, was rear-projected onto a 4' $\times$ 6' screen behind the manipulator, so that the scale of motion and seeing is the same as that of the ARM — a region of about three-foot radius.

Molix. The Masscomp-PS300 version of GRINCH has been exported and supported in the field this year.

The Masscomp-only version, designed to be fieldable on a hardware configuration costing less that $50,000, made a lot of progress. Our first model required a costly 10-bit-plane graphics card in the Masscomp. Wang devised a way to run it on the more-widely-used 6-plane version. Substantial interface usability and speed improvements, especially in rotations, were made during the year. The system is now ready for field test.

Michael Carson of the University of Alabama at Birmingham has ported GRINCH to the Silicon Graphics Iris display. He has shipped copies to:

Stuart Oatley, University of California, San Diego

F. Scott Matthews, Washington University, St. Louis

J. Fontecilla, Centre National de Research, Marseille, France

Besides GRINCH, our team worked on preparing a version of the popular FRODO model-fitting program for low-cost configurations. We started with the Fortran 77 version ported by a group at of Rice University. This Srinivasan and Boughton ported to the Unix-Vax-PS300 configuration, which required extensive PS300 work. This is finished and has been exported to the US Naval Academy.

The FRODO for the Masscomp-PS300 configuration is almost ready.

Pixel-Planes. A major triumph in this area. A team under Thorvaldsdottir prepared a shaded spherical model of dihydrofolate-reductase (1300 atoms) and trimethoprim and a shaded polygonal ribbon model of superoxide dismutase for the new Pixel-Planes display engine, and debugged these models while the machine itself was being debugged. We showed all this live at SIGGRAPH in August. The user manipulates two 3-D joysticks to rotate the objects in real-time or to dock the drug in the proteins cavity in real-time, working in the three translations and three rotations simultaneously, at will.

Advanced Graphics Technology — Head-Mounted Display. Ming, Hughes, and Pique fabricated a prototype using two Casio tiny TV's, half-silvered mirrors, the Polhemus sensor, and the PS300 as an image-generator. Pique and Thorvaldsdottir took the head unit prototype to the May meeting of the Molecular Graphics Society in France.

Work the rest of the year concentrated on calibration and on speeding up the Polhemus sensing loop. We are getting 4-10 updates/second and must achieve 20 updates/second to achieve steady, realistic virtual objects. Getting to 20 updates/second requires meticulous, detail-by-detail engineering of the whole system. We are getting closer month by month by switching from ASCII to binary transmission, moving calculation of matrices downstream to the faster machine, using faster PS300 GSR subroutines, etc. The next effort is to get 19,200 baud transmission working.

Meanwhile we have started fabricating a second-generation display, using Seiko color TV's with about 2× the former resolution.

Advanced Graphics Technology-Stereoscopic Display. We installed several of the new 19" shutters, for which we were the collaborating user and first field-test site for Tektronix.

During Alwyn Jones's June visit, the last month of Pique's stay, Lynn Ten Eyck also visited our project. That team tested the new Tektronix shutter on the Barcodata projector, mounting it diagonally across the three lenses, and rear-projecting the image on a ground-glass type plastic screen. Circular polarization is preserved! Hence big-screen images can be projected and viewed with cheap glasses by all the people in the room.

Responding to that news, Tektronix undertook to make us three 5" plates, each

tuned for the color of one of the Barcodata guns. These have been installed.

The persistence of the Barcodata green phosphor is a little too long for stereo to be perfect. Since all our images have arbitrary coloring, we just lower the fraction of green in the output colors.

We demonstrated this stereo projection at the October NSF-SIGGRAPH Workshop.

Trailblazer System. We did not get our Trailblazer system moved from Phillips Hall to Sitterson Hall, the new Computer Science building, because the building schedule slipped by a year.

We did, however, make extensive improvements to our Trailblazer hardware configuration. The most important was the installation of a Barcodata video projector and a 4' × 6' rear-projection screen. This is mounted behind the ARM, so that one sees, in one-to-one scale, a computer image in a projection of the space swept by the ARM. With the stereo windows we put on the projector, the image can be hung in the actual 3-space swept by the ARM.

The operation of this in Phillips Hall with Pixel-Planes, which is in New West Hall, required connecting the two via inter-building coaxial cable. To get a high-fidelity image from Pixel-Planes and through the coax, we first borrowed, then bought, a high fidelity Faroudja NTSC video encoder.

In software, we built a C interface on the Blox interface management system, and created pop-up windows on the Blox facility on the Masscomp.

Another enhancement included an upgrade on the data acquisition attachment of the Masscomp, and two more workstations in the Graphics Laboratory.

Douglas Schiff undertook, together with the Richardsons of Duke, a comparative evaluation of two commercial molecular graphics systems, Biosym's Insight and Tripos's Mendyl. We expect to select one of these as the base for our next generation of the Trailblazer system.

People. 1986 was marked by major personnel changes. A big event was the departure of Michael Pique, our project Director, for the Scripps Research Institute, where he established his own molecular graphics laboratory. He had been the key person for ten years, so this departure was a major change. He continues as a member of our 1987 Advisory Council, and a collaborator who visits several times a year.

Helga Thorvaldsdottir, formerly a graduate Research Assistant on the project, completed her M.S. and succeeded Pique as Director of the project. A major effort in the spring and summer was the technology transfer from Pique to Thorvaldsdottir.

Mark Harris, Ph.D., came to us from York University, for a two-year appointment as Project Biochemist. He started January 31, 1987.

Key chemists who visited as consultants and advisors were Dr. Michael Connolly,

whose visit is described above, and Dr. Alwyn Jones of Uppsala, author of the Frodo system.

3. Objectives for the Next Project Year

1. **Visualizations.** We shall specify and prototype a general "visualization workbench" system for molecular structures, density functions, molecular and atomic properties, etc. With this the user will have a flexible way to generate impromptu ways of assigning geometric and other properties to graphics representors.
2. **Docking Studies.** We shall refine the ARM force-feedback system and test it in a real docking problem, in collaboration with Professors David and Jane Richardson of Duke.
3. **Molix.** We plan to user-test and field the Masscomp-only version of GRINCH, in a configuration costing less than $50,000.
4. **Trailblazer-Mendyl.** We expect to port the commercial Mendyl molecular software to Unix, install the PHACT database system, and use these as the base for our enhancements and new systems.
5. **Advanced Graphics Technology.** We expect to demonstrate a higher-resolution, color head-mounted display prototype working with real molecular data.
6. **Building Move.** This year, surely, the new Computer Science building will be finished and we shall move ourselves and our laboratory into it.

4. Collaborative Research and (Biochemical) Results

Al Clark

North Carolina Central University

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.

Michael Cory

Burroughs-Wellcome
DNA intercalators

Michael Cory requested images of a variety of DNA intercalators bound to DNA. He provided the coordinates, we worked together to select appropriate views, and we generated and photographed spacefilling images.

Judy Kelly

University of Connecticut

The group at the University of Connecticut continues to use GRINCH in their studies of antibiotics. They have added features to GRINCH, and they also use it for data reduction for their own packing program. There have not been any visiting GRINCH users at the University of Connecticut this year, but many visitors to the lab are shown GRINCH as part of the general facilities of the lab.

Alex McPherson

University of California, Riverside

Alex McPherson requested a number of appropriate images to accompany an article for *Scientific American* concerning the role of crystallography in drug design. Seven images were prepared, all of which were selected for publication. 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 Sterptomyces R61 (data from Judith A. Kelly, University of Connecticut).

David and Jane Richardson

Duke University

We collaborated with the Richardsons on the comparative evaluation of Biosym's Insight versus Tripos's Mendyl as a base on which to build next-generation molecular graphics tools, especially those for protein design.

Jan Richardson

Burgess Publishing
ATP

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

Steve Satterfield

US Naval Academy

We provided Steve Satterfield our UNIX version of the protein fitting program FRODO and our software to control the Lyon Lamb VAS IV video sequencer.

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 xenon was inserted.
We have also supported Dr. Hermans's own new PS-300 installation, with various system-programming assistances.

Craig Smith

University of Alabama, Birmingham
axl sea anemone toxin

Craig Smith used GRINCH on a Silicon Graphics Iris to continue his study of the map of the sea anemone toxin axl. The data from the current crystals proved to be not good enough for interpretation, and further derivatives are being sought.

Duncan McRee

Research Institute of Scripps Clinic
Bacterial yellow photoactive protein

Duncan McRee has been using GRINCH on the Vax/MPS configuration at Scripps to interpret the map of Bacterial yellow photoactive protein, a globular protein that contains the same chromophore as rhodopsin.

Neela Srinivasan

University of North Carolina, Chapel Hill
DNA

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.

Ed Westbrook

Argonne National Labs.
Ketosteroid isomerase

Ed Westbrook continued his work on the structure of ketosteroid isomerase using GRINCH at the University of Chicago. The structure has now been refined to an R-factor of 31%, and a manuscript is in preparation.

Peter Wolfenden
Jan Hermans

University of North Carolina, Chapel Hill

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 has lab and was expecting delivery of a graphics processor.

We had a number of requests for videotapes of our molecular graphics work.

Donna Cohen
Cohen Computer graphics

Donna Cohen requested samples of our molecular graphics work on videotape for 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.

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

J.D. Andrade is involved with protein molecular graphics at the University of Utah. He requested a copy of *What Does a Protein Look Like, 1982.*

4.1 Advisory Council

Our Advisory Council during 1986 has consisted of the following persons, with their affiliations and principal interests:

Professor David Blow, Imperial College, energy modeling for molecular interaction

Dr. Michael Cory, Burroughs-Wellcome, analytic drug design

Professor Jan Hermans, UNC Dept. of Biochemistry, molecular dynamics and modeling

Mr. Michael Pique, Scripps Research Institute, molecular graphics (from July 1)

Professor David Richardson, Duke Dept. of Biochemistry, protein structure and the design of new proteins

Professor Jane Richardson, Duke Dept. of Biochemistry, protein structure and the design of new proteins

Dr. William V. Wright, IBM Corporation, molecular graphics

The group met with project members in all-evening formal discussions on about four occasions during 1986 with subgroups meeting more often.

Professor Robert Langridge, University of California at San Francisco, Principal In-

vestigator of the other NIH Research Resource for Molecular Graphics joined the Council in 1986, but there has not yet been a meeting with him as a member. Dr. Brooks met with Professor Blow once (in London) during 1986.

Dr. Mark Harris, our new project biochemist whom we recruited in the summer, was unable to join the team until January 30, 1987. We therefore engaged Dr. Michael Connolly, formerly of Scripps Research Institute and then in private consulting practice, to visit us for nine days in 1986, bringing us his biochemists' expertise for our work in docking and in surface description.

5. Publications

Publications by Users

* acknowledges Resource

* 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*, (submitted).

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

* 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.

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

* 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 *Eschericia coli* Sulfite Reductase. *J Biol Chem, 261*, 10277-10281, 1986.

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

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

Conference Presentations by Users

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

Kelly, J.A., Modelling a Beta-lactam Antibiotic Bound to its Enzymatic Target *Computational Methods in Chemical Design: Molecular Modelling and Computer Graphics*, Oct. 20-24 1986, Garmisch-Partenkirchen, Federal Republic of Germany

J.A. Kelly, J.A., Crystallographic Comparisons of Penicillin Binding Enzymes and Studies of Antibiotic Binding *Takeda Science Foundation Symposium on Biological Science, Frontiers of Antibiotic Research*, Nov. 25-27, 1986, Kyoto, Japan.

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

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

Publications by Builders

Brooks, F.P., "No Silver Bullet: Esssence and Accidents of Software Engineering", *Information Processing 86*, H.J. Kugler, ed. Amsterdam: Elsevier Science Publishers B.V. (North Holland), pp. 1069-1076.

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 it 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.

Conference Presentations by Builders

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.

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

Henry Fuchs and Helga Thorvaldsdottir presented user-directed real-time motion of a space-filling model of trimethoprim docking into dihydrofolate-reductase at the SIGGRAPH '86 Conference.

The whole GRIP team demonstrated all our recent work over a series of sessions at the NSF-SIGGRAPH Workshop on Interactive 3-D Graphics in Chapel Hill in October.

Research Highlights

Research Completed

1. Space-Filling Visual Models of Molecules Movable in Real Time Demonstrated

At the SIGGRAPH annual meeting in August, 1986, we demonstrated real-time motion of spherical space-filling computer-graphics models of trimethoprim docking in dihydrofolate-reductase. The whole scene can be rotated smoothly by the user, for better seeing. The drug can be independently moved smoothly in real time.

No other graphic system has ever been able to do this. This was the first public demonstration of the UNC-developed Pixel-Planes rapid 3-D display, invented by Fuchs and implemented by a team under Poulton.

2. Frodo Ported to Vax-PS300-Unix Configuration

We have taken Rice University's Fortran 77 version of Alwyn Jones's molecule-fitting system, Frodo and converted it to run on a Vax-PS300 configuration under Unix. This powerful tool has already been exported to molecular structure scientists at the US Naval Academy.

The availability of the popular Frodo on this common configuration will enable Unix sites to use it for molecular structure determination. This capability should substantially aid the chemist's perception of the detailed steric structure and charge distribution of drug binding sites.

Research in Progress

1. Trailblazer System to be Converted to Commercial Software

We are in negotiation and technical evaluation for conversion of one of the off-the-shelf molecular software packages to our Unix-based system.

New tools, systems, and advanced technology prototypes built at our Resource will then build on this base, saving a great deal of effort. Moreover, fielding them on a standard application software base will make their widespread adoption easier.

2. Force Display Prototype Demonstrated

At the NSF-SIGGRAPH workshop on Interactive 3-D Graphics in October, 1986, we demonstrated user-directed probing of force fields with the Argonne Remote Manipulator. This promises to let the drug designer feel as well as see the forces acting in molecular docking. It should aid in the design of new drugs and analogs to known drugs. We expect it to substantially enhance our usefulness to the molecular research community.