Eleventh Annual Report
Interactive Graphics for
Molecular Graphics System

TR85-025

February 1985

Frederick P. Brooks, Jr.
Michael Pique
James S. Lipscomb

The University of North Carolina at Chapel Hill
Department of Computer Science
CB#3175, Sitterson Hall
Chapel Hill, NC 27599-3175

This research was sponsored in part by NIH Grant #RR-02170-02.

Goals

1. The scientific goals are those in the original proposal – to develop successively more powerful computer graphics techniques and systems for molecular structure studies. This work has had seven subprojects.

2. **Progress and results.**

   2.1 **MOLIX - Low-cost molecular graphics system.** We entered into a collaboration with Massachusetts Computer Corp. (Masscomp), installed two Masscomp 500 systems (one free), and began porting our GRINCH software. A surprising and useful intermediate result was a port from our VAX11/780 - PS300 configuration to the radically cheaper Masscomp - PS300 configuration. We conceived this as merely a transition step to an all-Masscomp configuration. But GRINCH ran well on it, so Profs. D. & J. Richardson, our biochemist collaborators at Duke, installed the configuration and are running it in productive use.

   We also built a first prototype of the all-Masscomp GRINCH. It runs but is not yet good enough for user test.

   2.2 **GRINCH system.** The big accomplishment of the year was M. Pique's port of the system to an IBM 3081 -PS300 configuration running the VM operating system! This was done at U. of Conn. in collaboration with Prof. Judith Kelly and colleagues there. It has produced useful results for Belgian biochemists visiting Connecticut.

   Pique also ported the system to a VAX VMS system at the University of Chicago. It is in productive use. VAX Unix versions were exported to other sites – we do not know of use.

   D. Schiff produced our first product-quality user manual for GRINCH.

   We ran many GRINCH users at Chapel Hill and acquired experience on quite a few new maps and molecules.

   2.3 **Visualization Techniques.** M. Pique and J.S. Lipscomb produced an 8-second (some 2000 frames) fly-through of the Superoxide Dismutase molecule for the first Omnimax (2-pi steradian) film ever made by computer graphics (see Publications List). This required computing 19 reels of tape giving color values for over 2 billion pixels. A new technique was developed by Pique and Lipscomb to compute motion-blurring (temporal anti-aliasing) to compensate for the sampling done inherently in motion picture. They also devised a meta-graphics system to enable camera flight paths to be interactively planned on a graphics system.

2.4 **Enzyme-Substrate Docking.** D. Schiff developed novel techniques for reticulating a molecular surface with triangles so that it can be readily perceived and moved in real-time. Most recently, he incorporated a grid technique developed by Pattabiraman of UCSF for real-time approximate computation of binding energy.

2.5 **Trailblazer Graphics System.** Our 1974 GRIP system was ported completely from the IBM 360 - 75 - PDP11 configuration to our VAX11/780 - Vector-General 3300 configuration and put into productive use. (See the User List).

We are installing a high-speed parallel interface between our VAX and the E&S PS300.

H. Thorvaldsdottir, working under the guidance of Prof. T. Whitted, developed and installed software for the convenient and automatic production of videotape recordings. S. Black installed the new videotape hardware.

A second Adage-Ikonas 3000 raster-scan display system was acquired (in a swap for software) and installed in the Graphics Laboratory.

2.6 **Smooth motion of shaded spheres.** Relatively less work this year. We entered into a collaboration with Tektronix on the development of a new stereo shutter that avoids wires to the user. We are the field test site. It gives the best illusions effects of any stereo device we have seen, with good transmissivity. In stereo, updates per second is approximately halved, however.

2.7 **Advanced Graphics Technology.** We developed a prototype system using a Votan instrument to recognize spoken commands during GRINCH operation, hoping to aid visual continuity and speed up work. Technical problems forced postponement of the user test planned for November.

We installed and began testing a Masscomp array processor for rapid computation of binding energies.

We closed our collaboration with the IBM UK Scientific Centre in Winchester England. They are ending their molecular graphics project and will be doing molecular work in a more general solids-modeling context. It was a very useful collaboration to us.

We entered into a collaboration with a group under Prof. G. Blaauw at the Twente Technical University in Enschede, Netherlands. They will design for us a custom VLSI chip for computing inter-atomic distances between two molecules. We are aiming for an add-on board for Multibus workstations such as the Masscomp that will do rapid binding-force, torque, and energy calculations for molecules.

3. Objectives for the Coming Year.

We plan to continue pushing on all seven subprojects, in roughly the same priority shown below.

3.1 **Docking.** Our major push for 1985-86 will be to build a subsystem for our GRINCH system to facilitate studies of enzyme-substrate docking. This will include new capabilities for displaying molecule surfaces, dynamic real-time user-driven motion, and real-time calculation and display of binding forces, binding energies, and collisions, with user-specifiable force and energy models.

3.2 **Molix.** In 1985-86 we plan to user test and field a ridge-line map interpreting graphics system for a Masscomp workstation costing $50,000, or less.

3.3 **Advanced Graphics Technology.** We plan to chemist-test voice recognition of commands to speed up the use of graphics systems. We will install a screen-size prototype stereo viewing shutter. We expect to build a prototype force-feedback system for docking studies. We will collaborate on the design of a special purpose microelectronic chip for inter-atomic force calculation.

3.4 **Trailblazer system.** We plan to add model-building, fitting, and energy-computing capabilities to the GRINCH system.

3.5 **Ridge lines.** We hope to start a collaborative study with a biochemist on the relative scientific effectiveness of the ridge-line display of electron density.

3.6 **Moving shaded spheres.** We will study new hardware possibilities, including array processors.

3.7 **Visualisations.** We will study new ways of representing density clouds and contour surfaces.

PS300 GRINCH users:

Bud Suddath
Howard Einspur
Kaza Seguna
University of Alabama in Birmingham
Title: high resolution structure of pisum sativum lectin

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

Jane & David Richardson
Duncan McRee
Duke University
Title: structure of SIR sulphite reductase
Title: structure of ACP

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

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

Chang Park
Richard Blevins
(PI Allen Tulinsky)
Michigan State University
Title: structure of prothrombin fragment 1

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

John Rosenberg
Christine Frederick
University of Pittsburgh
Title: structure of DNA-EcoRI Endonuclease complex

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

Rufus Burlingame
Brad Brandon
Johns Hopkins
Title: structure of Eukaryote DNA binding histone octomer

The histone octomer to be interpreted consisted of three regions.

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

Judith Kelly
University of Connecticut
Title: structure of d-alanyl-carboxypeptidase-transpeptidase from stretomyces R61

Judy Kelly returned to UNC to see how her algorithmic idealization of her molecule to her map had moved the molecule since her last visit. Note that she did not interpret her map this time, since she finished that job on her last visit.

Roger Fenna
Roger Egen
University of Miami
Title: structure of bacteria chlorophyll protein

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

PS300 non-GRINCH users:

Mike Cory
Burroughs-Wellcome
Title: dihydrofolate reductase and trimethoprim

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

Stuart Solin
Michigan State University
Title: structure of ammonia-graphite complex

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

Margaret Eastman
University of North Carolina, Chapel Hill
Title: energy minimization of bovine prothrombin

Mike Pique and Doris Knechet at this NIH resource produced

stick-figure stereo pictures and raster CPK pictures of the many molecular configurations resulting from Margaret Eastman's energy minimizations of the 18-23 residue loop region of bovine prothrombin. The energy calculations investigated calcium binding and proline trans/cis isomerization.

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

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

Ramalingam Veerappapillai
Roger Engen
University of Miami
Title: crystal packing of human alpha-lactalbumin

The structure of human alpha-lactalbumin is believed to be similar to that of hen egg white lysozyme. Preliminary data suggests how the lactalbumin molecules are oriented when crystallized. The similar lysozyme molecule was oriented that way and the chemists explored possible packing confgurations possible when the molecule is moved about without further rotation.

GRIP-75 VAX-VG3303 users:

Susan Lord
UNC Chapel Hill
Title: structure of fibrinogin

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

Christine Wright
Medical College of Virginia
Title: structure of plant lectin

This year's visit was not successful for Christine Wright. She had refined the molecule and the map to each other algorithmically, and she came to UNC to manually touch up the positions of a few problem amino acids in loops on the outside of the molecule. The lack of stereo display and color caused perceptual problems, though, and she was able to do her work only later on a Richards box and a FRODO molecular graphics system elsewhere.

5. Publications by NIH Facility Users

•Chang, C.H., Short, M.T., Westholme, F.A., Stevens, F.J., Wang, B.C., Furey, W., Soloman, A., and Schiffer, M. A novel arrangement of immunogolbulin VBL domains: x-ray crystallograpic analysis of the lambda chain dimer bence-jones protein LOC. *Biochemistry*, (accepted).

•Corey, M., McKee, D.D., Kagan, J., Henry, D.W., and Miller J.A. Design systhesis and DNA binding properties of bi-functional intercalators. Comparison of polymethyline and diphenylether chains connecting phenanthridine. *Journal of the American Chemical Society*, (in press).

Eastman, M.A., Pedersen, L.G., Hiskey, R.G., Pique, M., Koehler, K.A., Gottschalk, K.E., Nemethy, G., and Scheraga, H.A. The Conformation of the 18-23 loop region of bovine prothrombin: an energy minimization study. *International Journal of Peptide and Protein Research*, (submitted).

•Einspahr, H., Parks, E., Suguna, K., Subramanian, E., and Suddath, F.L. The 3Å structure of p-lectin. (in preparation).

•Kelly, J.A., Knox, J.R., Moews, P.C., Hite, G.J., Bartolone, J.B., Zhao, H., Joris, B., Frere, JM., and Ghuysen, JM. 2.8A structure of penicillin-sensitive d-alanyl-carboxypeptidase-transpeptidase from *streptomyces R61* and complexes with beta-lactams. *Journal of Biological Chemistry*, (in press for June 1985).

•Yoshioka, N. and Atassi, M.Z. Hemogolbin binding with haptoglobin: localization of the haptoglobin binding sites on the beta chain of human hemoglobin by synthetic overlapping peptides encompassing the entire chain. *Biochemical Journal*, (submitted).

Publications by Builders

•Abram, G.D., Pique, M.E., Lipscomb, J.S., and Hern, T.A. *UNC 1983 Computer Graphics Sampler.* Video tape, color, sound, 5 minutes. Shown at ACM SIGGRAPH'83 Conf., Detroit, Michigan, (August 1983). Published in *ACM SIGGRAPH Video Review*, #10 (27 October 1983).

•Pique, M.E., Lipscomb, J.S., and Andersen, A.C. Trip Through Molecule of Superoxide Dismutase. Part of the movie, *The Magic Egg*. Produced by Garrickfilms and ACM SIGGRAPH. Omnimax-Imax film, color, 15 minutes. UNC segment 1.3 minutes, (1984).

• Acknowledges facility.

Research Highlights

Research Completed

1. Porting GRINCH to other systems.

The GRINCH molecular graphics system has been successfully used by scientists to determine the structure of protein molecules from their electron-density maps. This system was developed on a VAX11/780 computer with a PS-300 display system, under the Unix operating system.

A major accomplishment this year was our making GRINCH more widely accessible by revising it to operate on other hardware and software. This work was led by Michael Pique.

GRINCH was successfully ported to a VAX configuration with the (non-Unix) VMS software, at the University of Chicago.

It was also, and this is more difficult, successfully ported to an IBM 3081 operating VM at the University of Connecticut.

Both systems are in productive use.

2. First lower-cost version developed.

Existing molecular graphics systems run on fairly expensive hardware configurations, frequently costing $150K - $250K. We broke the $100K barrier this year by developing a version of GRINCH that operates on a PS-300 system using a Masscomp 500 as host.

The first system of this configuration is installed in the Richardsons' laboratory at Duke University, where it is in regular use.

Research in Progress

1. Molecular docking studies.

A major effort is under way to enhance both the visual and the mathematical modeling of enzyme-substrate docking. The perception of allowable and forbidden dockings is crucial to analytic drug design and very important for understanding the action of toxins and carcinogens.

2. Still-lower-cost systems

We expect this year to have a running version of our Molix system, a GRINCH-like system that runs effectively on a hardware configuration costing under $50,000. Our strategy is to use off-the-shelf color