Second Annual Report
Interactive Graphics for
Molecular Graphics System

TR76-04
April 1976

Frederick P. Brooks, Jr.

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Chapel Hill, NC 27599-3175

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NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH RESOURCES
BIOTECHNOLOGY RESOURCES BRANCH

SECTION I - RESOURCE IDENTIFICATION

Report Period:
From: June 30, 1975 To: June 29, 1976

Grant No.
5-P07-RR00898-02

Date of Report Preparation
April 1976

Name of Resource: Interactive Graphics for Molecular Graphics System

Resource Address: 273 Phillips Hall, UNC Chapel Hill, N.C. 27514

Principal Investigator: Dr. F. P. Brooks, Jr.
Title: Professor & Chairman

Grantee Institution: University of North Carolina at Chapel Hill
Type of Institution: State University

Name of Institution's Biotechnology Resource Advisory Committee:
Scientific Advisory Committee

Membership of Biotechnology Resource Advisory Committee: (* Committee Chairman)

<table>
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<tr>
<th>Name</th>
<th>Title</th>
<th>Department</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>Frederick P. Brooks, Jr. *</td>
<td>Professor &amp; Chairman</td>
<td>Computer Science</td>
<td>UNC</td>
</tr>
<tr>
<td>Ernest L. Eliel</td>
<td>Professor</td>
<td>Chemistry</td>
<td>UNC</td>
</tr>
<tr>
<td>Jan Hermans</td>
<td>Professor</td>
<td>Biochemistry</td>
<td>UNC</td>
</tr>
<tr>
<td>Sung Hou Kim</td>
<td>Associate Professor</td>
<td>Biochemistry</td>
<td>Duke</td>
</tr>
<tr>
<td>Edward Perl</td>
<td>Professor &amp; Chairman</td>
<td>Physiology</td>
<td>UNC</td>
</tr>
<tr>
<td>David Richardson</td>
<td>Assistant Professor</td>
<td>Biochemistry</td>
<td>Duke</td>
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</tbody>
</table>

Typed Name & Title of Principal Investigator: Frederick P. Brooks, Jr., Professor & Chairman
Signature: [Signature]
Date: May 5, 1976

Typed Name & Title of Grantee Institution Official: John F. Leonard, Contract Administration
Signature: [Signature]
Date: [Date]
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II.A. DESCRIPTION OF RESOURCE OPERATIONS AND PROGRESS.

Our research resource aims to make the power of interactive computer graphics available to biochemists and crystallographers studying the conformation and function of proteins and nucleic acids. During the past year we have developed our prototype system to the level of functional completeness, convenience of use, and reliability necessary for productive use by chemists in original research. Since July 1975 we have operated on regular schedule and have served five groups of chemists, who have used a total of 545 hours of graphics system time.

II.A.1. ADMINISTRATIVE STRUCTURE.

Our resource is based in the Department of Computer Science at the University of North Carolina. The attached chart shows the division of labor and relationships among those contributing to the resource this year.

Resource Facility Administration and Development

The Department of Computer Science's Computer Graphics Laboratory, the facility we use, was managed as a service facility by Mr. James Robb, the department's associate chairman. Under his supervision was Mr. Peter Nichols, an electrical engineer in charge of the equipment. Because funding for 75-76 was not as much as in 74-75, Mr. Robb resigned in December; Mr. Nichols was laid off. The facility is currently managed by Dr. J. D. Foley.

Software support for our graphic facility includes several locally developed programs: a S/360-PDP11 cross-compiler for a substantial subset of the PL/1 language, routines for communication between the PDP11 and its host S/360 computer, routines enabling the PDP11 to access disk files attached to its host, and graphics subroutine packages. This software has been developed and maintained by a group of research assistants under the direction of Dr. Foley.
The diagram represents the organizational structure of the UNC Molecular Graphics Research Lab. The labels indicate various roles and departments within the lab. Each role is connected by lines, indicating a hierarchy or reporting structure. The specific roles and titles are not clearly visible in the image due to handwriting or printing quality.
Service Support

The facility is made available to our client chemists on a regular schedule of fifteen hours per week. Additional time is available for both production use by chemists and for system development, in competition with the other users of the facility. Allocation of the available graphics time among the client chemists is managed by Dr. W. V. Wright.

Dr. Wright directs a team of computer science research assistants who help chemists prepare data for the system, tutor them in its use as needed, and accompany production sessions as needed. A typical production session has a chemist at the controls as pilot, a collaborator by his side as copilot, and when necessary, a computer science research assistant handy as flight engineer.

Development of Molecular Graphics System

The original GRIP system for displaying molecules was developed by Dr. Wright as a dissertation project under Dr. Brooks. That system has been converted to the current equipment and later developments have been integrated into it.

The team under Dr. Wright continues to do enhancements to the GRIP-GRAB System, and maintains the official current version used for service and for a development base. Dr. Wright himself not only coordinates development of GRIP-GRAB enhancements but also coordinates the design of GRIP-II. Dr. Wright is working 4/5 time as an investigator on our resource project through a joint study agreement between UNC and his employer, IBM. This agreement was renewed for the two-year period 1 Jan. 1976 - 31 Dec. 1977.

Mr. Edward Britton, a Ph.D. student under Dr. Brooks' direction, working with research assistants M. Pique and J. Lipscomb under Dr. Wright's direction, converted GRIP to the Vector-General, converted its molecular manipulation from character-string commands to real-time analog commands, and added electron density maps and their contouring. This major package called GRAB gave us the first production system usable for crystallography. It went into service in July 1975, and has been the basis for all further work. This year Mr. Britton has been documenting GRAB as his doctoral dissertation.

Drs. Wright, Brooks, and Wallace have been working as the design team for GRIP-II. In addition, Drs. Wallace and Foley serve as consultants on human factors aspects and on many questions concerning interactive computer graphics.
Exploratory Development.

Mr. Michael Pique, who worked on GRAB under Dr. Wright in 1974-75, has this year been developing a facility for twisting a substructure about multiple rotatable bonds. This is his M.S. thesis work, advised by Dr. Wallace. His facility is about to be integrated into the standard system. Mr. James Lipscomb, who also worked on GRAB under Dr. Wright in 74-75, is completing a M.S. thesis under Dr. Wallace on 3-D Visualization. His developments have now been integrated into the standard system.

Mr. Jon Bentley worked under Dr. Wright on improved near-neighbor algorithms based on trees. He showed that these do not achieve full power for (1) dense structures such as molecules, and/or (2) those of the size of the molecules we have used.

Dr. John McQueen, a post-doctoral researcher working under Dr. Jan Hermans, prepared a scaled-down version of REFINE for the on-line (45-60 seconds) idealization of molecular structures. This has been integrated into the standard system.

Users and Collaborators:

All of the system users also serve as consultants in the development of the system, suggesting new functions and needed improvements in convenience. They also help assign priorities to these items. Of these Dr. J.L. Sussman of Duke University has been particularly helpful.

Our client users at Duke University also use a Tektronix 4014 display unit furnished under this grant. This terminal has been used primarily for access to the NIH CHRYST system. Software for this terminal has been adapted from available programs by Dr. Sussman in collaboration with Dr. Richard Feldman of NIH. We plan to develop software enabling this terminal to access the UNC molecular graphics system.

Drs. Hermans and McQueen have continued the development of the full-scaled batch version of REFINE. This program is now being distributed to other chemists.
II.A.2. Scientific Achievements

Core Research and Development.

This is an enumeration of the more important additions that our resource personnel have made to the system during the past year. A brief description of each of these enhancements is given in section IV.A. These enhancements fall into two classes.

1) Interactive Functions

- Calculation of contour maps from given electron density data and their display.
- Real-time manual manipulation of selected parts of a molecule and posting of the final conformation to the model.
- Many aids for visualizing the models and maps in three dimensions.
- Idealization of molecular geometry in selected parts of the model
- Recording of the picture being displayed at any moment.

2) Bridges to other programs and off-line storage

- Routines for transmitting atom coordinates and density data between our system and the S/370 model 165 located at TCCC. (Our users execute most large programs from building and refining molecular data on the TCCC machine.)
- Routines to save molecular models and density data on tape and off-line disk packs at the UNC Computing Center and to recover their data.
- A routine to construct hard-copy plots of any picture displayed during an interactive session.

Support Software Development.

Work continued on application-independent facility software, as described above under II.A.1.
Collaborative Research:

1) **REFINE**. The programs used in our system to idealize molecular geometry on-line were derived from the REFINE package, a set of FORTRAN programs developed by Dr. Jan Hermans and his group supported by a grant from the National Science Foundation. Dr. Hermans has been collaborating with Drs. Jensen and Waterpaugh at the University of Washington and has made his programs available to a number of other groups including Dr. Feldman at NIH.

2) **Storage-Tube Graphics**. A Tektronix 4014 Storage-tube Display was installed in the biochemistry laboratory at Duke. Dr. Sussman has collaborated with Dr. Richard Feldman of NIH to implement access to the CRYST system from this terminal. They have added to CRYST some functions needed for analysis of molecular structures by X-ray crystallography. The resulting facility has been useful for making pictures of electron density maps and molecular structures for study and publication.

Service

Since July 1975 we have made our system available to five groups of biochemists for the purpose of carrying out original research. Their use falls into two general classes: (1) use as an electronic Richards Box, and (2) the comparison of two or more similar molecular structures. The use of our system as a substitute for a Richards Box has ranged from an attempt at an *ab initio* fit (the map was not good enough), to refinement of a structure for which an initial fit was available, to the fitting of a complex of a well-understood structure. Detailed descriptions of these applications of the system are given in Sections IV.A. We facilitate comparison of molecules by giving the user real-time control of the relative intensities of their superimposed displayed structures.

Training

No significant use was made of the system for education of biochemistry students during the year.

II.A.3. Plans and Objectives:

Our short and long-range plans are set forth in gory detail (80 pages of technical description plus appendicies,
etc.) in our continuation proposal dated August 26, 1975, and numbered 2-P41-ER-00898-03. These plans have been slipped a year, but not changed substantially. We shall briefly review them here.

GRIP works; REFINER works; GRAB works surprisingly well. GRAB and REFINER are in routine productive use and have assisted in the production of substantial published chemical results.

Our plans fall into two parts.

1. We want to establish a lab, a display system, a dedicated small crew, and a stable software system as a Regional Production Resource, for collaborative use by biochemists and crystallographers from the whole Southeast (and anywhere else as capacity allows).

2. We have begun a ground-up redesign of a GRIP-II system combining GRIP and GRAB functions and using the lessons learned from actual use of the existing systems.

GRIP and GRAB are both prototype systems. GRIP was built for the 11/45-Vector General using most of the code from Wright's earlier IBM 360/50 IBM 2250 system; GRAB is superimposed on GRIP. As a result, the organization of much of GRIP, and hence of GRAB, is based on design decisions made 6 years ago, for a system configuration quite dissimilar to our own. Despite this, in the summer of 1974, when our resource was first funded, we concluded that we should build onto GRIP to learn more quickly about the needs of biochemists and crystallographers.

This strategy has been quite productive for us. The clear consequence, however, is that we at some point had to say "We have gone as far as is reasonable with GRIP and GRAB; now is the time to use what we have learned in designing a new system." Hence the GRIP-II design.

It is organized to meet the objectives delineated in our original proposal:

- It will be product-quality software, well-documented, exportable, and usable by strangers.

- It will be usable from a variety of graphics display terminals, from a variety of minicomputers, and from a variety of main computers.
Where a configuration includes a powerful satellite (mini) computer, it will process all user actions not requiring extensive computations. If powerful enough, it will be able to execute the whole system stand-alone.

For less-powerful satellites, some or all of the application program function will be easily movable to the main host computer. If there is no satellite computer, all functions will be performed by the host.

Human factors (usability) considerations will be of paramount importance.

While the new system is being built, we will continue to expose biochemists to GRIP and GRAB, to add functions, and to simplify using procedures.

The REFINER program is an integral and important part of GRIP and GRAB. Our collaborative work in this area is aimed at enhancing its function, decreasing the space and time needed for execution, and making it available to other users. Improvements of REFINER will be continue to be integrated into GRAB.

We will undertake to implement a scaled-down version of GRAB for use with the Tektronix display in Dr. Kim's lab.

Our facility work will continue. In particular, we plan to investigate still more methods for enhancing three-dimensional perception.

II.A.4. Implications for future NIH Support.

NIH's BRB originally stressed to us the importance of getting a usable, useful, and used system as quickly as possible and demonstrating chemically significant results. This has been done. The natural next steps are the construction of a product-quality, second-generation system and the establishment of a service-oriented multi-user facility. Each of these will take a lot of money. Both together will take upwards of $1 million over a three-year period. The real, tangible and usable results to biochemistry may exceed, however, those from any of the millions heretofore spent on molecular graphics. The planned systems are not flashy or esoteric; they will, however be carefully designed, user-oriented, and constructed to professional standards of quality. The probability of success is very high.
II. B. SUMMARY OF COMPUTER RESOURCE USAGE

Since we share the UNC Computer Graphics Laboratory, rather than having an NIH-furnished resource, a description of its use seems more appropriate than the conventional form.

UNC Graphics Laboratory Usage 1975-76
15 July 1975-30 April 1976

1. Molecular Graphics (all under NIH 5-P07 RR00898-02)

<table>
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<th>Production Use</th>
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<td>D. &amp; J. Richardson</td>
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<td>Carter</td>
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<td>Ferro</td>
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<td>Lipscomb</td>
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</table>

| Development          | 342       |
| Demonstration        | 51        |
|                      | 938       |

2. Other Research Projects (non health-related) 170

3. Education (non health-related) 453

4. Facility and Software Development 151

5. Maintenance of hardware 68

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II.C. THE RESOURCE FACILITY AND EQUIPMENT LIST

Figure 2 depicts the entire complement of equipment available to our resource. Only the Tektronix 4014 at Duke has been acquired with NIH funds and is solely used as part of the resource. The display console and most of the interaction devices are clustered around a work station. The work station design is our second complete design. It has proved to be much more convenient than that reported last year. We do not contemplate any changes.

The various interaction devices in the drawing and photograph have been assembled to give us the widest latitude in designing the man-machine interface to suit the user. The various knobs and joysticks are useful for indicating positions, angles, sizes, or rates of rotation or translation. The manipulator arm, furnished by the ABC, will at some time in the future be used for positioning molecules or portions thereof.
## RESOURCE EQUIPMENT LIST

<table>
<thead>
<tr>
<th>Description/Identification</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Model</th>
<th>Date Installed</th>
<th>Date Accepted</th>
<th>Purchase Price</th>
<th>Annual Rent</th>
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<tr>
<td>Graphics Display System</td>
<td>Vector General</td>
<td>2DR</td>
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<td>5/20/73</td>
<td>8/27/74</td>
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<td>DX11-</td>
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<td>Translation, Scaling,</td>
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<td>Programmable Desk Calculator</td>
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<td>HP-65</td>
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<td>1974</td>
<td>854</td>
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<td>32K Memory Unit</td>
<td>Cambridge Memory, Inc.</td>
<td>1974</td>
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<td>Disk Controller</td>
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<td>5,200</td>
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<td>1969</td>
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<td>Master/Slave Manipulator</td>
<td>Argonne Laboratories</td>
<td>E3</td>
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<td>1972</td>
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<td>Supplies, etc.</td>
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RESOURCE EQUIPMENT LIST

Equipment Located Outside the Main Resource Area

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<th>Type</th>
<th>Model</th>
<th>Date Installed</th>
<th>Date Accepted</th>
<th>Cost</th>
<th>Annual Rent</th>
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<tbody>
<tr>
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<td>4014</td>
<td></td>
<td></td>
<td>4/30/75</td>
<td>4/30/75</td>
<td>13,000</td>
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<td>NIH</td>
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LOCATION: Duke University, Durham, North Carolina
II.D. SUMMARY OF PUBLICATIONS


Richardson, J. S.; Richardson, D. C.; Thomas, K. A.; Silverton, E. W.; and Davies, D. F. "Similarity of Three Dimensional Structure Between the Immuno-Globulin Domain and the Cu, Zn Superoxide Dismutase Subunit, *Journal Mol. Biol.**, In Press.


III.A. SUMMARY OF RESOURCE EXPENDITURES

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<thead>
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<td>Current</td>
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<td>Budget</td>
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<td>Period</td>
<td>Period</td>
</tr>
<tr>
<td>1. Personnel</td>
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</tr>
<tr>
<td>a. Salaries &amp; Wages</td>
<td>46,321.00 55,192.00</td>
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<tr>
<td>b. Fringe Benefits</td>
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<tr>
<td>Subtotal</td>
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<td>2. Consultant Services</td>
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<td>3. Equipment</td>
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<td>a. Main Resource - Rented</td>
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<tr>
<td>b. Main Resource - Purchased</td>
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<td>c. Supporting Equipment</td>
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<td>d. Equipment Maintenance</td>
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<td>4. Supplies</td>
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<tr>
<td>5. Travel</td>
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<tr>
<td>6. Alterations &amp; Renovations</td>
<td>397.00 213.00</td>
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<td>7. Publication Costs</td>
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<tr>
<td>8. Other</td>
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## III.B. EXPENDITURE DETAILS
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<th>% of Effort</th>
<th>(Hours)</th>
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<tr>
<td>% of Salary from BR Grant</td>
<td>Amount</td>
<td>Effort</td>
<td>Amount</td>
</tr>
</tbody>
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### 1. PERSONNEL

#### 1. Professors

- **F.P. Brooks, Jr.**
  - 12%
  - 3,600.00
  - 7%
  - 145
- **J. Hermans**
  - 10%
  - 208

#### 2. Associate Professor

- **V.L. Wallace**
  - 31%
  - 6,715.00
  - 25%
  - 519

#### 3. Assistant Professor

- **J.N. Foley**
  - 8%
  - 1,889.00
  - 8%
  - 166

#### 4. Research Associate

- **P. Nichols**
  - 83%
  - 5,872.00
  - 50%
  - 1038
- **J. McQueen**
  - 100%
  - 6,996.00
  - 100%
  - 2076

#### 5. Secretary

- **P. Cisneros**
  - 100%
  - 7,080.00
  - 100%
  - 40

#### 6. Research Assistants

- **E. Britton**
  - 29%
  - 427.00
  - 100%
  - 20
- **J. Crawford**
  - 17%
  - 670.00
  - 50%
  - 10
- **T. Dineen**
  - 94%
  - 3,626.00
  - 100%
  - 20
- **R. Hogan**
  - 68%
  - 1,920.00
  - 68%
  - 13
- **M. Ling**
  - 100%
  - 1,920.00
  - 100%
  - 20
- **R. Motley**
  - 100%
  - 3,849.00
  - 100%
  - 20
- **M. Pique**
  - 100%
  - 1,920.00
  - 100%
  - 20
- **J. Walker**
  - 50%
  - 1,920.00
  - 100%
  - 20
- **J. Warner**
  - 42%
  - 1,242.00
  - 100%
  - 20
- **Fringe Benefits**
  - 4,947.00

**Total**

- 54,597.00
### 2. Consultant Services

### 3. Permanent Equipment

*Main Resource - Rented*
1. IBM Copier 1  
   - 1,087.00  
2. IBM Copier 1  
   - 720.00  
3. 2314 Disk Pack  
   - 1,500.00  
4. Other  
   - 12.50  
   **Subtotal**  
   1,100.00 3,320.00

*Main Resource - Purchased*
1. Vector General FCO (and other parts for a modification of the VG system).  
   - 985.00  
2. Estimated to be spent by 6/29/76  
   - 498.00  
3. Other  
   - 985.00  
   **Subtotal**  
   985.00 1,734.00

*Equipment Maintenance*
1. Repair of Interface Control  
   - 124.00  
2. Digital Equipment Corp. Maintenance Contract  
   - 2,481.00  
3. Other  
   - 18.20  
   **Subtotal**  
   2,500.00 2,624.00

### 4. Consumable Supplies

1. Electronic parts  
   - 15.30  
2. Electronic parts  
   - 791.00  
3. Film  
   - 142.00  
4. Paper  
   - 60.00  
5. Paper  
   - 575.00  
6. Printed Information  
   - 59.00  
7. Printed Information  
   - 22.00  
8. Computer Cards  
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9. Other  
   - 512.70  
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EXPENDITURE DETAILS (continued)

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### III.C SUMMARY OF RESOURCE FUNDING

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<tr>
<td><strong>Total</strong></td>
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</table>

New Air Force grant is not in support of resource.
IV.A.1. The Interactive System.

Our current interactive computer graphics system for molecular studies is primarily the work of Messrs. Britton, Lipscomb, and Pique all of whom are presently completing the requirements for degrees in computer science at UNC. These three, working under Drs. Wright and Brooks, based their design on and converted programs from the pilot system for molecular graphics built by Dr. Wright in 1970. This work has been continued during the past year by three first-year graduate students, Mrs. Motley and Messrs. Dineen and Tolle. The most important interactive functions of this system are:

a. Display of Kendrew-type stick-figure models of proteins and nucleic-acid structures.

b. Real-time joystick control of the direction from which the molecule is viewed. The user can smoothly turn the picture. This gives an imitation of head-motion parallax, an important depth cue.

c. Stereoscopic display of molecules using an Evans & Sutherland lorgnette, depth cueing by intensity, depth cueing by a Z-axis clipping plane, depth cueing by steady rotation or oscillation, and stereoscopic display by half-silvered mirror and polarized filters (over-under stereo). These techniques can be applied in various combinations. We have observed that an intensity depth-cued, z-axis clipped, joystick controlled, lorgnette stereo picture is perceived much better than a picture presented using only one of the 3-D techniques. This work has been done by J. Lipscomb under Dr. Wallace's direction. Mr. Lipscomb has not been supported by grant funds.

d. Selective display of individual residues in a molecule, and control of the detail displayed. Because a picture showing all bonds of the entire molecule is confusing for interesting macromolecules, a facility has been added for displaying three levels of detail: (1) a set of lines not corresponding to
valence bonds but connecting the principal atoms of each residue (e.g. the alpha carbon atoms of a protein); (2) all bonds of the main chain, or (3) all bonds. These levels of detail are illustrated by pictures of the phenylalanine transfer tRNA (tRNA) molecule in Figures 3 through 6. The level of detail displayed can be controlled independently for each residue. This can be seen in Figure 5 in which all bonds in a selected region of the tRNA molecule are shown and in Figure 6 which shows part of this same region expanded (and rotated) so that it fills the display screen.

e. Manual analog specification of a point in the model space. A joystick with three rectilinear degrees of freedom is used to move a cursor about in the display screen. This enables the user to specify a point in the model space more quickly and more easily than with the keyboard entry and light-button commands of the original GRIP system. Such input is useful for moving a molecule to an approximate position. The directions of cursor movement are those of laboratory space.

f. Interactive contouring and display of electron density maps. These density maps are displayed as contours of equal density drawn on a set of parallel planes evenly spaced through the visible portion of the model space. Figure 7 shows the portion of the tRNA model illustrated in the previous figure embedded in the corresponding electron density map. The fitting of this model to its density map as shown in this figure has not been completed, and a number of discrepancies are apparent in this picture. The user specifies the density levels to be shown, and several selected densities can be shown simultaneously. The contour planes are always perpendicular to one of the coordinate axes of the model space. The user can choose any one, two, or all three of the possible sets of orthogonal planes for simultaneous display. Figure 8 shows the region of the previous figure with two sets of contour planes displayed. Another feature allows the user to suppress the display of any individual contour and, if desired, to reinstate it later without recalculation.
Figure 3  Backbone of tRNA—the C1 atoms of adjacent residues in the molecular sequence are connected by line segments.
Main chain of tRNA— each valence bond in the main chain is represented by a line segment.
Figure 5

Selected detail of tRNA— all valence bonds of residues 28 through 42 are shown with the backbone of the remainder of the molecule.
Figure 6  Enlarged detail of tRNA— a portion of the previous figure enlarged six times and rotated.
Figure 7  tRNA model and electron density map— the portion of tRNA shown in the previous figure embedded in its electron density map which is shown as a set of contour maps on parallel planes.
q. Manual fitting of a model and electron density map in real time. The user can select a part of his model (e.g., a residue) and can manipulate its position and orientation by means of two separate manual input devices with three degrees of freedom each. He can also twist up to eight selected bonds in the selected substructure by turning one knob at the workstation for each bond. The new position, orientation and conformation of the selected substructure are dynamically shown and can be recorded in the molecular data structure upon command. This is an essential facility for fitting a model to an electron density map or any other visually determined conformation. This facility was developed by Mr. Pique working under Dr. Wallace's direction.

h. Plotter output. The user can record the picture he sees on the graphic screen at any time. A complete description of this current picture is stored on disk where it can be used to generate a permanent copy via a plotter or a line printer. This facility was used to generate Figures 3 through 8 of this report. It also provides a means for making large reproductions of an electron density map or a molecular model.

i. Real-time control of the relative brightness of the map and model on the display screen (or of two models if so map is displayed). This helps the user distinguish his map and model when fitting and is useful for comparing.

j. Interactive computational refinement of a selected part of the model to minimize deviations from the ideal bond lengths and angles. This function, built by Dr. McQueen, uses an on-line version of the REFINE program developed by Dr. Hermans and his group.

k. Library management. The GRIP system now includes several libraries of molecular models recorded on disk. Commands are provided for displaying a list of the models in any selected library, for loading a model from a library into the core memory of the system, for saving the current model in a library, and for deleting a model from a library. It is intended that each user should have his own library of models. Models can also be entered into the sys-
tem from punched cards or magnetic tapes. The current version of this facility was built by Mrs. Notley.

1. Recovery from a system failure. A facility is provided which records the current molecular model on a disk library after every user command which modifies this model. Thus, the most recent molecular model is always available on disk. When the system is restarted after a normal or abnormal termination, this model can be reloaded into core memory. These backup models are recorded alternately in two separate libraries to give some protection against a system failure during the recording process. In the near future we plan to add facilities for recording the system control information which specifies the current view of the molecules in addition to the model data.

Human Factors. We have devoted a considerable part of our effort to building a system with smooth human factors. For example, we have selected manual input devices whose degrees of freedom are intuitively related to the model parameter control. Also, all manual controls except bond-twisting work in laboratory space instead of model space.

Releases. As we began to use the systems for productive research it became obvious that evolving experimental systems are not suitable for productive work. Therefore, we have constructed a sequence of stable, consolidated releases of our system for production use. Each of these incorporates all of the facilities proven workable by the chosen cut-off date. The most recent release represents our status as of February, 1976.

IV. A. 2. Bridges to Batch Programs.

We have begun to build bridge programs between GRIP and a number of existing batch programs for building molecular models from residue sequence data, for refining structures, and for calculating electron density maps.
Two sets of orthogonal contour maps--the previous figure with another set of contour maps added which are drawn on planes perpendicular to those used for the first set of contour maps.
We intend several basically different modes of operation: closely coupled, nearly stand-alone, and stand-alone. There are also many modes in between the extremes. Our objective is to produce software which can be very easily adapted to any of the modes. We now have in hand the basic tools needed to do this: the first tool is compatible compilers for the 360/75 and 11/45. Our first such was developed before this grant started; a second-generation PLCD compiler is now under development. The second has been completed and documented this year, a system called CAGES - Configurable Applications for Graphics Employing Satellites, written as part of G. Hamlin's dissertation work.

CAGES is a programming system which substantially simplifies the process of writing interactive graphics application programs for use in a distributed processing, satellite-host configuration. It allows programs written in a PL/I subset to be configurable; program modules and data can be easily reassigned from the host to the satellite, or vice versa. That is, the division of labor between the two computers is readily modified.

The CAGES system supplements the operating system services normally provided on the host and satellite computers by providing the illusion that the application is executing in a single computer memory with dual CPU's. In reality the application is distributed between the memories of the host and satellite computers. To maintain this illusion CAGES provides three types of services:

a. Inter-computer subroutine CALLs and RETURNS. A subroutine call executed on one computer and targeted to a subroutine resident on the other computer is known as a remote procedure call. A message containing the subroutine's name and parameters is sent to the computer where the subroutine is to be executed. Following its execution, a message containing results is sent back, and the calling routine continues its execution.

b. Inter-computer signals. A SIGNAL statement or interrupt on one computer can raise a CONDITION for which there is an enabled ON-BLOCK in the other computer.
c. GLOBAL data references. Variables with EXTERNAL scope which may be referenced from subroutines in both computers are known as GLOBAL variables. The CAGES system handles such references by obtaining the needed data from the remote computer and placing a local copy of it in the memory of the referencing computer. The program is then allowed to access this copy.

Beyond the mere capability of configuring an application to a particular host-satellite system, CAGES allows the application program designer to view his program as a whole, as if it were to be executed on just one computer, without knowing its ultimate configuration. This is very helpful in producing a conceptually integrated design. On the other hand, ultimate efficiency of operation demands that the designer recognize that the program will in fact be distributed. To aid in designing optimally for distributed configurations, Haalin has set forth a series of design and programming guidelines. They are concerned with how the application is modularized, how data is accessed, and inter-module and intra-module patterns of reference to data files, GLOBAL variables, and procedures. The guidelines have been proven sound, both experimentally and theoretically. We will use them.

Another advantage of CAGES is that it allows the division of processing and data between the host and satellite to be fine-tuned to maximize responsiveness. In this regard, we will draw on the tools and insights developed by Foley's and Wallace's Air Force-sponsored work on modelling of graphics systems. Their goal has been to develop models and guidelines to be used in dividing processing and data between the host and satellite.

IV.A.4. Portability__DIGS

Many existing interactive graphics application programs (including ours) are written using a graphics subroutine package which in one way or another mirrors both the exact capabilities and peculiarities of the display terminal with which it is used. This has very detrimental implications to our project's goal of making our programs usable from a variety of display terminals, ranging from low-cost, low-performance systems such as storage tube terminals up to the high-cost, high-performance Vector General display which is the current heart of our resource.
Such a goal is a necessary one, because it is not reasonable to assume that all biochemists who want to use our programs will have Vector General displays with the exact set of options we have. A display-independent graphics package, DIGS, addresses this problem. Its design hides the details of any particular real display terminal behind the mask of a virtual display terminal, each generic characteristic of which can be realized either in the hardware of the more powerful displays, or in the software support of other displays. The point is that this mechanism hides display terminal details from the application programmer.

Display-independent packages are not new; several already exist, such as OMNIGRAPH [Sproull73], GPGS [Caruthers72], and GINO [Sanchez73]. We have examined these, and others, in detail. Unfortunately, none of them meets the demanding needs imposed by our applications. Therefore we are undertaking the design and implementation of DIGS.

DIGS has a number of salient features. A full 2-D or 3-D scale-rotate-translate and window-to-viewport transformation is applied at the time the display code is generated. Extents (boxes) can be applied to portions of a picture to speed up the clipping process. Portions of the displayed image can be named, using a full block-structured naming capability.

The basis for picture modifications is the named segment, which is a collection of picture primitives such as lines, text, and points. The segment can be deleted, augmented, or dynamically transformed. A viewport is a collection of segments. It too can be deleted, augmented (by adding segments), and dynamically transformed. Thus a two-level picture modification capability is provided.

Input is also device-independent, being handled through the mechanism of virtual devices. These include entity indicators (typified by the lightpen), position indicators (typified by a joystick-cursor), text string inputs (as from a keyboard), and value inputs (as from knobs and dials).

The structure of DIGS makes it usable by displays ranging from storage tubes to Vector Generals. Our plans call for three implementations (each implementation includes substantial portions of common code) of DIGS; one for the 11/45-Vector General, one for a Tektronix 4014 coupled via communications link to a S/360 or S/370, the third for a 4014 coupled to a 11/45 and that in turn to a S/360 or S/370. The DIGS architecture has been completed [Foley75], and much of the internal organization has been designed. Some coding
for the 11/45-VG version has been completed. We intend to use DIGS in GRIP-II.


Mr. J. Bentley, a fellowship student in the Department of Computer Science, has been investigating algorithms suitable for finding all atoms in a specified neighborhood of a molecular model. These algorithms have excellent asymptotic performance as the number of atoms in the structure increases. Bentley has concluded, however, that for dense molecules of less than 2000 atoms, the partitioning-type algorithms are superior to tree algorithms.
IV. E. 1. The REFINE Program

REFINE is a program package developed by Hermans in collaboration with McQueen, Wei and Ferro under support by a grant from the National Science Foundation. It is a batch FORTRAN program which can be used with sets of experimental coordinates to:

- test the stereochemistry of the coordinates.
- build a model best fitting the coordinates.
- build a model of low packing (nonbonded) energy.
- find a structure of lowest energy, considering not only the packing energy, but also the energy required for deformation of the structure from ideal geometry.

The version of this program which performs the first two of these options was put into use in 1973 by Jensen and Watenpaugh at the University of Washington and by Sussman and Kim at Duke. In January 1975, a second version (REFINE2) was made available to the groups already using the first release, to Feldman at N.I.H., to Meyer at Texas A & M, and Koetzle at Brookhaven. A third version has been completed and is being used by Hermans at U.W.C. A publication describing results obtained with model building calculations has appeared. [Hermans75].

We prepared a CDC version of REFINE2 and this has been installed at Brookhaven. The staff at Brookhaven has made the program accessible on the CRYSNET system (June 1975).

The CDC version of REFINE2 has also been installed at the University of Groningen (July 1975). It will soon replace the old version in use at the University of Washington. Feldman and Sussman have integrated REFINE2 into the molecular graphics system at N.I.H.; this system is accessible via telephone lines. Sussman uses it at Duke with the Tektronix terminal. Program and manual are available to other groups on request.

Use of REFINE3. REFINE3 is the most recent version of our refinement program. This version minimizes not only the nonbonded energy of the model, but models deformations of
the structure (such as bond angle bending) and distributes these properly over the molecule.

The program is being used in a series of calculations. The first of these, on cyclo-triproline, showed that excellent geometry is obtained with energy minimization of a strained ring structure. The second, on antamanide, a cyclic sodium binding decapptide, showed that energy minimization of a preliminary X-ray structure gives improvement towards the structure obtained with classical crystallographic refinement. These studies have been completed and the results are available. [Hermans et al 1975]

In the third project we have almost completed a study of the refinement of a much larger structure, that of the protein rubredorin. (This work is being carried out in collaboration with Jensen’s group, which determined and refined this structure). As a fourth project, we have begun a study of the activated state of the enzyme-substrate complex of the cystine protease papain, using X-ray crystallographic data obtained by Drenth’s group in Groningen. The mechanism of catalysis by papain is similar to that by the serine proteases subtilisin, chymotrypsin, trypsin, thrombin, etc.

**IV.B.2. Storage-Tube Graphics at Duke**

There is a need for at least a primitive computer graphics facility in the hands, i.e. the laboratory, of molecular biologists to perform routinely the following functions:

- a. to visualize in detail and in three-dimensions macromolecular structures.
- b. to alter the conformations of these structures.
- c. to attempt to fit a three-dimensional model of a macromolecule to an electron density map derived from X-ray diffraction data.

As part of our initial grant, we acquired a Tektronix 4016 direct-view storage tube and installed it in Dr. Kim’s laboratory. Drs. Kim and Sussman have been exploring its uses of the above purposes.

As several laboratories have developed programs to do many of these operations already, we have worked with other groups in extending and adapting their systems. So far the bulk of our collaboration has been with Richard Feldmann of
the NIH in extending the CRYST system for our particular needs.

The facility to display macromolecular structures (or for that matter any structure in the Cambridge Crystal File) in up/down polarized-filter stereo on a storage tube terminal has been implemented for about two years on the NIH CRYST system.

The CRYST system for molecular display has been a pleasure to use, as it is almost transparent to even a novice user although extremely powerful. It is extremely well documented and everyone in our laboratory who has tried to use the system has become more or less expert in less than an hour of real time use.

In our laboratory we have used the visualization features of the CRYST system for two specific applications:

1) **Comparison of different macromolecular structures**

Jane Richardson compared in detail the three-dimensional structure of Superoxide Dismutase (SOD) whose crystal structure was recently determined in our laboratory [Richardson, et al, 1975] with several different immunoglobulin structures (solved in other laboratories) that appeared to have similar structure although quite different function. The coordinates for these structures were already on the CRYST system.

Figure 9 was prepared by redrawing the hand tracing of the SOD and two other portions of a protein (V & C) from two different points of view.
Figure 9
Redrawn hand-tracings
21. **Examination of the tRNA structure detail**

Joel Sussman has used the CRYS[T] system to display the three-dimensional structure of yeast-tRNA which was recently solved in our laboratory in order to scrutinize our current model.

So as to minimize telephone and computer costs we have used the audio cassette recorder option of our terminal in order to store various views and fragments of the tRNA structure on cassettes. In this way we have begun to build up a library of cassettes which can be used stand-alone on our terminal to view the tRNA structure.

31. **Manipulation of macromolecular structures**

In the course of a macromolecular structure refinement it is essential to know if one's model has reasonable stereochemistry and, if not, to have the facility to correct any shortcomings. The REFINER program performs just such a function. **Over the past year**, Sussman in our laboratory has modified this program to make it more suitable for nucleic acid structures and has used it on the TUCC computer without graphics capability in a batch mode.

41. **Fitting a three-dimensional model to an electron density map**

Sussman and Feldmann have adapted an electron density contour map drawing program (which Feldmann had written several years ago) to run with the storage tube as an output device. In addition they have "married" the molecular model to the map with all the molecular manipulation features of the CRYS[T] system. Both the map and the molecule can be drawn in stereo. Generally one examines a portion of the map/model space of one to three residues, with the computer keeping track of all the bookkeeping such as what part of the map to include, scale, center, etc. Thus they have developed a prototype Electronic Richards' Box which runs on a time-shared computer with a storage tube as its display vehicle.

The contour drawing program can also be used by itself to draw the entire map plane by plane. These sections can be copied onto transparent sheets of acetate (via an inexpensive thermal copier) and a mini map of the entire structure can be assembled quite quickly.
The system has been used on five biochemical research projects. Each of these projects represents a different stage in the investigation of a molecular structure.

A group working under Dr. W. Lipscomb at Harvard used GRIP to sketch a model of ACTase. This investigation is at a very early stage, with a low-resolution map.

Dr. David Richardson and Jane Richardson of Duke used GRIP to construct a model of Superoxide Dismutase. The Richardsons had preliminary coordinates for their alpha carbon atoms and are thus somewhat farther along than the Harvard group. This is the first instance we know of in which a graphics model was constructed without a Kendrew model being built beforehand or simultaneously.

Drs. Kim and Sussman of Duke are currently using the system to improve an existing model of tRNA. Their investigation has advanced considerably further than the two mentioned above. Refined coordinates have been published.

Dr. Ferro, in Dr. Hermans' laboratory at UNC, used the system to compare several alternative models of Rubredoxin which are already quite refined. His work thus represents the farthest advanced investigation for which GRIP has been used.

Dr. Carter of UNC used the system to compare the oxidized and reduced states of HIPIP.

Duke Users' Experience

We (Sung-Hou Kim and Joel Sussman) have used the UNC graphic display system in production as an "electronic Richards' box" for the purpose of fitting the crystal structure of yeast-tRNA to its electron density map.

We have found it to be far superior to a conventional Richards' Box in visualization of both the model and the map, as well as in the actual fitting by interactive manipulation of the model to the map. In addition we have found it much easier for two people to work together in trying to fit the model to the map than ever was possible with the conventional Richards' box.
Visualization. The visualization is better in that it is possible to get an optimal view of a particular region of the map/model space in order to do the fitting. This generally involves:

(1) Selecting a small part, a few residues, of the model and map space.

(2) Rotating the fragment of the model/map space until one sees just the right viewpoint to begin fitting. Generally this has been done with one-dimensional (planar) contours, since the lognate stereo limits the number of vectors that can be drawn. At present, one can have stereo plus one-dimensional contouring or monocular viewing plus two- or three-dimensional contours. If more drawing speed were available, we would routinely view density contours in two orthogonal planes (the basket-weave contours developed by Barry). This effect greatly enhances our ability to understand how a residue should fit into the map.

(3) Changing the contouring level(s) for the particular fragment of map/model space until the right contours are present to do the fitting without cluttering the picture with too many contours. We usually use one contour level at a time.

Fitting. The actual fitting generally proceeds in three steps:

a) FITRES - a residue (one nucleotide) is 'detached' from the structure, giving it 6 degrees of freedom, 3 rotations and 3 translations. We then attempt to fit the sugar and base portion of the residue to the electron density map. Once they fit we reconnect the residue to the rest of the structure (freeze it).

b) FITPHOS - next the phosphate group for the same residue is 'detached' from the structure and again with 6 degrees of freedom it is fitted to the map, and frozen.

c) BONDTWIST - finally when a particular residue is involved in hydrogen bonding base pairing with another residue in the structure, both residues are displayed, and by means of FITRES and BONDTWIST around the sugar base bond, the bases are fitted to
the map as well as to each other in a reasonable hydrogen bonding configuration.

The above process introduces some unacceptable stereochemistry, i.e., when the residues are detached and moved and then reconnected, some bond lengths, bond angles and dihedral angles become absurd. Also unusually close contacts between atoms are sometimes introduced. In order to correct these distortions the coordinates are sent to TOCC where the nucleic acid version of the REFINER program is used to idealize the stereochemistry. This is generally done after a session lasting 4-5 hours at the graphic display terminal. These coordinates are then sent back to UNC for reexamination and minor adjustments to ensure a proper fit to the electron density map.
REFERENCES


