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I Narrative Description

This is an annual report for the Stanford University Medical Experimental computer resource for applications of Artificial Intelligence in Medicine (SUMEX-AIM). It covers the period between May 1, 1981 and April 30, 1982.

This is the first year of a 5-year renewal of the SUMEX resource grant. It begins an important and exciting new phase for SUMEX-AIM community research. Successes in developing expert systems, many of them stemming from projects in the SUMEX-AIM community, have stimulated very strong and growing interest in AI research from many popular and industrial fronts. At the same time, the on-going revolution in computational tools, made possible by larger and larger scale microelectronic integration, is making routine applications of AI systems more practical and effective and is providing tools for new avenues of research. Our approved project goals focus principally on a merging of state-of-the-art community research in biomedical AI applications with these new computing tools and on the challenges they will bring to the SUMEX-AIM community and resource. We expect that the integration and exploitation of these emerging computer technologies that will have a profound effect on the development and dissemination of practical biomedical AI systems.

The earlier phases of the SUMEX-AIM resource were characterized by the building of a national community of biomedical AI collaborators around a central resource located at Stanford University. Beginning with 5 projects in 1973, the AIM community grew to 11 major projects at our renewal in 1978 and currently numbers 15 fully authorized projects plus a group of 4 pilot efforts. Many of the computer programs under development by these groups are maturing into tools increasingly useful to the respective research communities. The demand for production-level use of these programs has surpassed the capacity of the present SUMEX facility and has raised important issues of how such software systems can be optimized for production environments, exported, and maintained.

We continue to seek interesting new AI applications in our community of biomedical and computer scientists interacting through electronic media. However, we expect the SUMEX-AIM community to develop a somewhat different character in the coming years. It will become more decentralized in terms of computing resources, more diverse in scope, and even more heavily dependent on network communication facilities for interactions, collaborations, and sharing.

The following sections report on the activities of the SUMEX-AIM resource this past year including brief summaries of the objectives of SUMEX-AIM, a characterization of biomedical AI research, resource organization and operating procedures, recent core progress in system development and basic AI research, and progress in the collaborative projects.

I.A Summary of Research Progress

I.A.1 Overview of Objectives and Rationale

SUMEX-AIM ("SUMEX") is a national computer resource with a dual mission: 1) promoting applications of computer science research in artificial intelligence (AI) to biological and medical problems and 2) demonstrating computer resource sharing within a national community of health research projects. The central SUMEX-AIM facility is located physically in the Stanford University Medical School and serves as a nucleus for a community of medical AI projects at universities around the country. SUMEX provides computing facilities tuned to the needs of AI research and communication tools to facilitate remote access, inter- and intra-group contacts, and the demonstration of developing computer programs to biomedical research collaborators.

I.A.1.1 What is Artificial Intelligence

Artificial Intelligence research is that part of Computer Science concerned with symbol manipulation processes that produce intelligent action [1 - 7]. By "intelligent action" is meant an act or decision that is goal-oriented, is arrived at by an understandable chain of symbolic analysis and reasoning steps, and utilizes knowledge of the world to inform and guide the reasoning.

Placing AI in Computer Science

A simplified view relates AI research with the rest of computer science. The ways in which people use computers to accomplish tasks can be "one-dimensionalized" into a spectrum representing the nature of the instructions that must be given the computer to do its job; call it the What-to-How spectrum. At the How extreme of the spectrum, the user supplies his intelligence to instruct the machine precisely how to do his job, step-by-step. Progress in computer science may be seen as steps away from that extreme How point on the spectrum: the familiar panoply of assembly languages, subroutine libraries, compilers, extensible languages, etc. illustrate this trend.

At the other extreme of the spectrum, the user describes What he wishes the computer to do for him to solve a problem. He wants to communicate what is to be done without having to lay out in detail all necessary subgoals for adequate performance. Still, he demands a reasonable assurance that he is addressing an intelligent agent that is using knowledge of his world to understand his intent, complain or fill in his vagueness, make specific his abstractions, correct his errors, discover appropriate subgoals, and ultimately translate What he wants done into detailed processing steps that define How it shall be done by a real computer. The user wants to provide this specification of What to do in a

language that is comfortable to him and the problem domain (perhaps English) and via communication modes that are convenient for him (including perhaps speech or pictures).

The research activity aimed at creating computer programs that act as "intelligent agents" near the What end of the What-to-How spectrum can be viewed as a long-range goal of AI research.

Expert Systems and Applications

The national SUMEX-AIM resource is an outgrowth of a long, interdisciplinary line of artificial intelligence research at Stanford concerned with the development of concepts and techniques for building "expert systems" [1]. An "expert system" is an intelligent computer program that uses knowledge and inference procedures to solve problems that are difficult enough to require significant human expertise for their solution. For some fields of work, the knowledge necessary to perform at such a level, plus the inference procedures used, can be thought of as a model of the expertise of the expert practitioners of that field.

The knowledge of an expert system consists of facts and heuristics. The "facts" constitute a body of information that is widely shared, publicly available, and generally agreed upon by experts in a field. The "heuristics" are the mostly-private, little-discussed rules of good judgment (rules of plausible reasoning, rules of good guessing) that characterize expert-level decision making in the field. The performance level of an expert system is primarily a function of the size and quality of the knowledge base that it possesses.

Currently authorized projects in the SUMEX community are concerned in some way with the application of AI to biomedical research(*). The tangible objective of this approach is the development of computer programs that will be more general and effective consultative tools for the clinician and medical scientist. There have already been promising results in areas such as chemical structure elucidation and synthesis, diagnostic consultation, molecular biology, and modeling of psychological processes.

Needless to say, much is yet to be learned in the process of fashioning a coherent scientific discipline out of the assemblage of personal intuitions, mathematical procedures, and emerging theoretical structure comprising artificial intelligence research. State-of-the-art programs are far more narrowly specialized and inflexible than the corresponding aspects of human intelligence they emulate; however, in special domains they may be of comparable or greater power, e.g., in the solution of formal problems in organic chemistry.

(*) Brief abstracts of the various projects can be found in Appendix C on page 277 and more detailed progress summaries in Section II on page 81.

I.A.1.2 Resource Sharing

Besides the biomedical AI research theme of SUMEX-AIM, another central goal is an exploration of the use of computer-based communications as a means for interactions and sharing between geographically remote research groups engaged in biomedical computer science research. This facet of scientific interaction is gaining importance with the explosion of complex information sources and the regional specialization of groups and facilities that might be shared by remote researchers [8]. We expect an even greater decentralization of computing resources in the coming years with the emerging VLSI(*) technology in microelectronics and a correspondingly greater role for digital communications.

Our community building effort is based upon the current state of computer communications technology. While far from perfected, these developing capabilities offer highly desirable latitude for collaborative linkages, both within a given research project and among them. A number of the active projects on SUMEX are based upon the collaboration of computer and medical scientists at geographically separate institutions; separate both from each other and from the computer resource. The network experiment also enables diverse projects to interact more directly and to facilitate selective demonstrations of available programs to physicians, scientists, and students.

We have actively encouraged the development of additional affiliated computing resources within the AIM community and expect such decentralization to become the "way of the 80's". Since 1977, the facility at Rutgers University has allocated a portion of its capacity for national AIM projects and our network connections to Rutgers and common facilities for user terminals have been indispensable for effective interchanges between community members, workshop coordinations, and software sharing. The "Caduceus" project (page 180) at the University of Pittsburgh has installed a VAX computer and is converting their software to run initial clinical tests at Pittsburgh. Since last year, the "Simulation of Cognitive Processes" project has been doing most of their work on their own VAX computer, and several more projects have proposed machines dedicated to their own use.

The proliferation of distributed machines will serve to increase the importance of electronic communications to facilitate interactions and sharing. Even in their current developing state, communication facilities enable effective access to the SUMEX community resources from a great many areas of the United States and to a more limited extent from Canada, Europe, Japan, Australia, and other international locations.

(*) Very Large Scale Integration

I.A.1.3 Impact of AI in Biomedicine

Artificial Intelligence is the computer science of symbolic representations of knowledge and symbolic inference. There is a certain inevitability to this branch of computer science and its applications, in particular, to medicine and biosciences. The cost of computers will continue to fall drastically during the coming two decades. As it does, many more of the practitioners of the world's professions will be persuaded to turn to economical automatic information processing for assistance in managing the increasing complexity of their daily tasks. They will find, from most of computer science, help only for those of their problems that have a mathematical or statistical core, or are of a routine data-processing nature. But such problems will be relatively rare, except in engineering and physical science. In medicine, biology, management -- indeed in most of the world's work -- the daily tasks are those requiring symbolic reasoning with detailed professional knowledge. The computers that will act as intelligent assistants for these professionals must be endowed with symbolic reasoning capabilities and knowledge.

The growth in medical knowledge has far surpassed the ability of a single practitioner to master it all, and the computer's superior information processing capacity thereby offers a natural appeal. Furthermore, the reasoning processes of medical experts are poorly understood; attempts to model expert decision making necessarily require a degree of introspection and a structured experimentation that may in turn improve the quality of the physician's own clinical decisions, making them more reproducible and defensible. New insights that result may also allow us more adequately to teach medical students and house staff the techniques for reaching good decisions, rather than merely to offer a collection of facts which they must independently learn to utilize coherently.

The knowledge that must be used is a combination of factual knowledge and heuristic knowledge. The latter is especially hard to obtain and represent since the experts providing it are mostly unaware of the heuristic knowledge they are using. Medical and scientific communities currently face many widely recognized problems relating to the rapid cumulation of knowledge, for example:

- codification of theoretical and heuristic knowledge
- effective use of the wealth of information implicitly available in textbooks, journal articles and from practitioners
- dissemination of that knowledge beyond the intellectual centers where it is collected
- customizing the presentation of that knowledge to individual practitioners as well as customizing the application of the information to individual cases

We believe that computers are the most hopeful technology to help overcome these problems. While recognizing the value of mathematical modeling, statistical classification, decision theory and other techniques, we believe that effective use of such methods depends on using them in conjunction with less formal knowledge, including contextual and strategic knowledge.

Artificial intelligence offers advantages for representing information and using it that will allow physicians and scientists to use computers as intelligent assistants. In this way we envision a significant extension to the decision making powers of individual practitioners without reducing the significance of the individuals.

Knowledge is power, in the profession and in the intelligent agent. As we proceed to model expertise in medicine and its related sciences, we find that the power of our programs derives mainly from the knowledge that we are able to obtain from our collaborating practitioners, not from the sophistication of the inference processes we observe them using. Crucially, the knowledge that gives power is not merely the knowledge of the textbook, the lecture and the journal but the knowledge of good practice -- the experiential knowledge of good judgment and good guessing, the knowledge of the practitioner's art that is often used in lieu of facts and rigor. This heuristic knowledge is mostly private, even in the very public practice of science. It is almost never taught explicitly; almost never discussed and critiqued among peers; and most often is not even in the moment-by-moment awareness of the practitioner.

Perhaps the the most expansive view of the significance of the work of the SUMEX-AIM community is that a methodology is emerging therefrom for the systematic explication, testing, dissemination, and teaching of the heuristic knowledge of medical practice and scientific performance. Perhaps it is less important that computer programs can be organized to use this knowledge than that the knowledge itself can be organized for the use of the human practitioners of today and tomorrow.

The researchers of the SUMEX-AIM community currently constitute a large fraction of all the computer scientists whose work is aimed at the development of symbolic computational methods and tools. SUMEX-AIM is laying the scientific base so that medicine will be able to take advantage of these technological opportunities for inexpensive computer power. Medical diagnostic aids and tools for the medical scientist that operate in an environment of a network of professional workstation computers have the practical possibility of large-scale and low-cost use because of anticipated near-term developments in the computing industry.

I.A.2 Synopsis of Recent Progress

We can report substantial further progress during year 09 of our grant toward the overall goals of the SUMEX-AIM resource. We have continued the refinement of an effective set of hardware and software tools to support the development of large, complex AI programs for medical research and to facilitate communications and interactions between user groups. We have worked to maintain high scientific standards and AI relevance for projects using the SUMEX-AIM resource and have actively sought new applications areas and projects for the community. Many projects are built around the communications network facilities we have assembled; bringing together medical and computer science collaborators from remote institutions and making their research programs available to still other remote users. As discussed in the sections describing the individual projects, a number of the computer programs under development by these groups have matured into tools increasingly useful to the respective research communities. The demand for production-level use of these programs has surpassed the capacity of the present SUMEX facility and we have been actively investigating the general issues of how such software systems can be moved from SUMEX and supported in production environments.

A number of significant events and accomplishments affecting the SUMEX-AIM resource occurred during the past year:

- 1) SUMEX has acquired and integrated 5 Xerox Dolphin InterLisp workstations into the computing environment at Stanford to begin research on the important software issues involved in using personal computing environments for AI systems. Substantial systems work was done to develop Ethernet services to make the Dolphins work smoothly and effectively in our existing facility. This has been shared widely with other research groups outside of Stanford in order to broaden and assist the growing user community. Research has begun on moving the ONCOCIN, MOLGEN, AGE, and GUIDON systems to run on the Dolphins with promising early results. Shortly, one of the SUMEX Dolphins will be moved to Rutgers to enable researchers there to begin exploring its potential for biomedical AI systems.
- 2) We took on development and support of a VAX 11/780 UNIX system purchased with ARPA funds for shared access by the Stanford Heuristic Programming and Network Graphics projects and members of the SUMEX-AIM community. We have carried out necessary systems work to integrate this machine well into the Stanford network system, install FranzLisp and the USC-ISI implementation of InterLisp-VAX for AI research, and expand the stable of available user software. Various Lisp performance measurements have been made this past year with disappointing results.
- 3) The AI Handbook core research project completed publication of a three-volume, 1500-page compendium of knowledge about the field of Artificial Intelligence. It has been edited by Avron Barr, Paul Cohen, and Edward Feigenbaum at Stanford University, with textual contributions from students and investigators at several other

research institutions across the nation. The work contains hundreds of articles covering most of the important ideas, techniques, and systems developed during 26 years of research in AI.

- 4) The SUMEX-AIM collaborator project community has continued vigorous development of their respective programs. Details are reported by the individual investigators in Section II. The VM and ONCOCIN projects have continued preliminary clinical testing/evaluation this past year using SUMEX network and computing resources. The CADUCEUS project has begun setting up its own local VAX computing resources which should help reduce the load on SUMEX for newer pilot efforts. We have continued to work hard to meet the needs of collaborating projects and are grateful for their expressed appreciation.
- 5) We continued to support the highly successful GENET experiment for the dissemination of the MOLGEN programs into the molecular biology community. "Advertised" through presentations and demonstrations by MOLGEN investigators at several professional conferences, several hundred molecular biologists from over 60 institutions have used the system and most have found it easy to learn and highly effective as a research tool for their investigations. A new GENET Executive Committee has been set up to manage this sub-community and to direct its efforts from production analysis of DNA sequences to new developments of computer science applications in molecular biology.
- 6) We have continued support of the existing SUMEX facility hardware, software, and network systems to enhance throughput and to assist user access to existing and planned resources. Over the past year, we have improved internetwork software and developed Ethernet services to provide a gateway to other campus networks and to expand general terminal access. We are also completing a more efficient Ethernet interface for the KI-10 system and have supported CSD efforts to develop a mass bus Ethernet interface.
- 7) We have continued to investigate long term options for SUMEX-AIM equipment plans including professional workstations and central machine development. For the next 5-10 years, it is clear that the "ideal" configuration must comprise a heterogeneous environment including Lisp workstations and a substantial central resource for time-shared use by groups unable to afford enough workstations to support their planned staff. Recent work has indicated that the VAX is not an advantageous machine for LISP applications. We are therefore developing plans to upgrade the aging KI-10 system to a DEC 2060 TOPS-20 system.

I.A.3 Details of Technical Progress

The following material covers SUMEX-AIM resource activities over the past year in greater detail. These sections outline accomplishments in the context of the resource staff and the resource management. Details of the progress and plans for our external collaborator projects are presented in Section II beginning on page 81.

I.A.3.1 Facility Hardware

Over the past year, the SUMEX facility hardware configuration, including the main KI-10 machine (Figure 1), the 2020 satellite machine (Figure 2), the new shared ARPA VAX/UNIX system (Figure 3), and system network interconnections (Figure 4), have continued to develop according to plan and to operate effectively within capacity limitations.

The primary facility hardware development efforts this year have been directed at:

- 1) Installation and integration of 5 Xerox Dolphin InterLisp workstations.
- 2) Development of the shared VAX 11/780 configuration.
- 3) Upgrade and expansion of Ethernet cable coverage, completion of Ethernet interface equipment for the KI-10 and development of other network server facilities.
- 4) Investigation and planning of hardware configuration alternatives for facility development.
- 5) Planning and purchase of initial file server configuration.
- 6) Follow-up on AMPEX memory expansion late in year 08.
- 7) Support of local project hardware needs.

Phasing of Hardware Acquisitions

In the SUMEX renewal, both an augmentation of the central resource in terms of address space and capacity and exploratory work with Lisp workstations were planned in the first few years. The Initial Review Group recognized in their special study section report the importance of optimizing the timing of our planned hardware acquisitions to coincide with the availability of desired technological developments and community needs. They recommended in their report that we be allowed considerable flexibility as to phasing of equipment purchases within the 5-year renewal period.

We had initially planned to purchase a VAX during year 09 and our first workstations during year 10. However, we judged that the order of these purchases should be reversed for several reasons:

- 1) The VAX implementation of the InterLisp language, the basis for much SUMEX-AIM community AI research, was behind schedule and a preliminary working system was not expected until 1982. A widely usable production version would take somewhat longer.
- 2) An evaluation of the prospects of InterLisp-VAX performance was being prepared by Dr. Masinter (see Appendix A) and would not be available until late summer. This and the actual measured performance of InterLisp-VAX would strongly affect the suitability of the VAX for AI research.
- 3) In order not to delay non-LISP SUMEX-AIM work involving VAX, we were able to arrange that SUMEX-AIM would have shared access during year 09 to a VAX 11/780 funded by ARPA to support Heuristic Programming Project research.
- 4) InterLisp Dolphin workstations were available for delivery in the summer of 1981 on which research toward adapting expert AI systems for the interactive workstation environment could begin.

Dolphin Workstation Installation

We ordered 5 Xerox Dolphin InterLisp machines for delivery early in grant year 09. The machines were delivered on time, 2 in August and the remaining 3 in October. The installation of these machines proceeded very smoothly, given the previously established Ethernet setup at Stanford. Experience with the physical Ethernet installation was important but the software support that had been derived from Xerox PARC under a university grant license and the extensions made to this software by our own personnel were more important still. Facilities to monitor network activities, move files around, and connect terminals between systems have proven especially useful.

The machines received were preproduction models and were fully configured but quite noisy. The hardware has in general proven reliable except for the Shugart model 4008 disk drives that are part of the package. We have had several failures of memory, processor, and other component boards as might be expected with new machines. We have had 7 disk drive failures, however, in the last 9 months -- far more than should occur. These failures have concentrated in two of the machines, both of which are housed in machine room environments. This suggests an interaction between the machine and the disk in some undiscovered way. In all cases, Xerox personnel have been responsive in repairing problems.

Performance of the Dolphin workstations has improved substantially since February 1982. Dolphin performance is based largely on microcoded implementation of frequently used primitives and facilities. The initial

optimizations of the Dolphin microcode were based on work at Xerox observing their own programs running. When the Dolphin was exposed to other AI systems, it became clear that additional improvements were necessary. Xerox responded promptly to this new information and produced the Con Brio version of InterLisp-D which enhanced performance for CONS operations, function calls, disk management, garbage collection, and other areas. Improvements in individual areas of performance ranged from factors of 2 to 10. The Con Brio release made the Dolphins much more comfortably usable as programming workstations. Still further improvements are needed and planned, especially in numeric computations and in the speed of compilation of Lisp functions.

We have agreed to share one of the 5 Dolphins purchased by SUMEX with the Rutgers resource, subject to two conditions. First, we must complete development work to integrate the machines in the Stanford Ethernet environment and second, Rutgers must allocate funds to purchase a second Dolphin of their own and establish a local Ethernet to connect them with other host machines. The first condition is now met with our work during the past year. The second is in process now and we expect to ship a Dolphin to Rutgers this summer.

Other aspects of the integration of the Dolphin workstations into the SUMEX computing environment are described in a following section on local network developments (see page 26).

Shared ARPA VAX 11/780

During year 09, as part of the plan to accelerate purchase of the Dolphin workstations, we gained shared access to a VAX 11/780 which was purchased by ARPA for HPP research as well as work in network graphics and VLSI design. The configuration of this machine is shown in Figure 3. This past year we augmented the machine by adding 2 Mbytes of memory and expanding the file system with a newly-announced DEC RPO7 disk drive (512 Mbytes). Both of these expansions were funded by ARPA. Approximately 30% of the machine is allocated for HPP and SUMEX use.

Over the past year, much experience has been gained with the VAX as an environment for AI work using various Lisp implementations. This experience has been disappointing for the most part because of either shortcomings in the Lisp system itself (FranzLisp) or in the performance of the system on the VAX (InterLisp-VAX). This is discussed in more detail until the rationale for future hardware developments (see page 14)

Local Network Systems

Over the past 2.5 years, we have been developing a local, high-speed Ethernet to provide a flexible basis for planned facility developments and the interconnection of a heterogeneous hardware environment. Our development of Ethernet facilities has been guided by the goals of providing the most effective range of services for SUMEX community needs while remaining compatible with and able to contribute to and draw upon network developments by other groups. Since the early 3 Mbit/sec Ethernet

was given to Stanford and several other universities by Xerox, an agreement has been reached between DEC, INTEL, and Xerox on the standards for an even higher performance network [13]. The new network runs at 10 Mbits/sec and supports a significantly larger packet address space. Xerox has started to market products for the new network but debugged interfaces, software, etc. for general use are just now becoming routinely available. Furthermore, even though three companies have agreed on a set of low level protocols and interface conventions, the rest of the world may not go along. There is already an alternative (but closely related) IEEE specification in preparation and alternative wideband network systems being delivered. Even among the three parties in the Ethernet specification, there is no agreement on higher level protocols.

All of this suggests that it is not time to jump to the newer and faster networks yet. We feel the 3 Mbit/sec network is adequate for our bandwidth needs in the near future and there is already a significant hardware and software investment in 3 Mbit/sec network equipment at Stanford related to SUMEX community interests. In the longer term, we will want to upgrade to whatever hardware and protocol standard is broadly adopted.

In the meantime we are continuing to develop our 3 Mbit/sec PUP network services. This places a heavier burden on us to develop and maintain our own equipment for Ethernet support. We have tried to minimize the "home-brew" nature of this work by sharing common hardware and software designs with other groups in the same situation

The current Stanford network configuration related to SUMEX-AIM work is sketched in Figure 4. Over the past year, we have made considerable progress in a number of areas of network development:

- 1) KI-10 DMA interface complete -- The initial KI-10 Ethernet interface was made via a PDP-11 connected to the I/O bus which is inefficient under heavy traffic. The extra demand made on the KI-10's for performing file server functions for the Dolphin workstations, high-speed terminals, printer traffic, and other file transfers underscore the need for a more efficient direct memory access interface. This interface is now debugged and uses a phase decoder (design borrowed from the SUN terminal project at Stanford) to detect the incoming serial Ethernet signal, an internal packet buffer to prevent overruns to and from the TENEX time-sharing system, and a memory bus interface to transfer data. The interface is not in operation yet because of problems with the phase decoder in handling low level signals which we receive from the very old cable being used to connect our gateway to the Computer Science building across campus. This cable will be replaced shortly and the new interface will go into full operation.
- 2) UNIBUS interface complete -- In our initial Ethernet connections of the KI-10, 2020, and VAX hosts, we used a UNIBUS interface board designed by E. Markowski at Xerox. Because of the limited availability of these boards for our future work, we designed a PDP-11 interface board that uses the serial phase decoder network front

end mentioned above. This design provides several features not available on the Xerox board including more explicit error information and a more sophisticated filter on source addresses for incoming packets. A printed circuit version of this board has also been produced and is being used in our PDP-11 TIP described below.

- 3) Network cabling upgraded and extended -- We have extended the coverage of our Ethernet this past year to cover the SUMEX and MYCIN office areas. This allows connection of Dolphin workstations in the offices to other network resources and also facilitates developmental work on Ethernet servers such as the gateway and TIP. Our gateway connection to other campus Ethernets has been made via an old cable dating back to the ACME facility. This cable is an RG-58 video cable and is very far from the standard Ethernet specification. Still, since it was the only cable available at the time, we installed special signal conditioning and detection electronics to make it work, however marginally. We are in the process of replacing this cable with true Ethernet cable. In the meantime, we have found a number of weaknesses in the current net interface designs. Because the old cable has a high loss (more than 100:1), problems with DC offsets, encoding skew, and bandwidth limitations have been common. The phase decoder serial detector has proven particularly sensitive to these problems. Were we to make the decision again, we would not choose this method to decode the Manchester coded network signals. Rather we would use a threshold trigger/delay detector such as was used in the original Xerox design. This approach can also be extended to run at 10 Mbits/sec for the newer network protocols whereas the phase decoder cannot.
- 4) Ethernet gateway -- We chose to isolate the SUMEX Ethernet from other networks on the Stanford campus in order to avoid electrical interactions during development and to facilitate different administrative conventions for the use of the various networks. We therefore developed a gateway to couple the networks together as shown in Figure 4. This gateway consists of a PDP-11/05 with Ethernet interfaces on the SUMEX and Computer Science networks. It is located in Pine Hall which is a convenient intersection point for the networks. The major gateway effort was not in configuring the hardware but rather in developing the necessary software described on page 27.
- 5) Ethernet TIP -- Both because of a shortage in terminal ports to some of the host systems and the desire to allow terminals to connect freely to various hosts instead of being directly connected to one or another, we developed an Ethernet Terminal Interface Processor (TIP). This server is similar in function to the familiar ARPANET TIP. It is basically a machine that has a number of terminal lines and a network interface and software to manage the establishment of connections for each line and the flow of characters between the terminal and host. We have built two versions of the TIP, one based on a PDP-11/05 processor and one based on the SUN MC-68000 processor. The PDP-11/05 can handle up to 8 lines without memory management

because of buffer space limitations in the 32K address space. The MC-68000 can handle many more (probably up to 32), limited by processor speed. The hardware configurations are straightforward and include a processor, network interface, and groups of line interfaces. Again the major effort has been in developing software as described later.

Future Hardware Configuration Planning

Over the past year we have continued to evaluate strategies and alternatives for planned system configuration development. In particular, we have had a chance to evaluate the Dolphin InterLisp machines and shared VAX, reassess the role of the dual KI-TENEX system, and reach a local consensus about what the long term configuration of the SUMEX-AIM facility should be. In summary, we feel that the best resource configuration for the coming decade is a shared central machine coupled through a high-performance network to growing clusters of personal workstations. The central machine should be an extended addressing TOPS-20 machine and the workstations will be chosen from the viable products now available and scheduled for announcement.

- 1) Lisp Workstations -- Since delivery of the Dolphin InterLisp machines about 6 months ago, considerable experience has been gained in their use as Stanford AI projects have begun adapting their systems to the workstations. The concept of an individual workstation, especially with the high-bandwidth graphics interface, has proven ideal. Both program development tools and facilities for expert system user interactions are substantially improved over what is possible with a central time-shared system. The main shortcomings of these systems at the present time are processing speed and cost. Benchmarks of Dolphin performance have varied widely depending on what program is being run. These have ranged from roughly half the speed of a KL-10 to an order of magnitude or more slower. The "average" experience with performance at Stanford has been comparable to KI-10 speed under a load average of 4-5. This is marginally acceptable in that human resources are still badly constrained by machine speed but the systems are usable in comparison to the heavy overload of the SUMEX resource. We expect other workstations to be available soon (Xerox, Symbolics, LMI, HP, etc.) that should improve performance and hopefully lower costs. Still, for machines costing in the range of \$50,000, it will be some time before we can afford to equip most of the SUMEX-AIM community with individual workstations.
- 2) VAX -- Several groups have experimented with using the shared ARPA VAX/UNIX machine for AI system development. One group has used the FranzLisp derivative of MacLisp and the other has used the USC InterLisp implementation for the VAX. Both of these groups have reported poor performance of the VAX environment for various reasons. Both FranzLisp and InterLisp have proven very expensive on the VAX with InterLisp turning the VAX essentially into a single user machine. FranzLisp is a fairly minimal system compared to other modern Lisp systems and the development group at Berkeley is not providing

energetic support in extending or maintaining the system. The InterLisp-VAX system is based on the "Byte Lisp" system used for the Dolphin InterLisp system at Xerox and so is nicely compatible with other InterLisp's. We undertook a separate study of the InterLisp-VAX prospects under contract with Dr. Larry Masinter of Xerox, one of the key developers of InterLisp 10/D (see Appendix A). This study pointed out the difficulties of adapting InterLisp to the VAX and predicted that because of the internal data structures of InterLisp, a VAX implementation would be quite slow. It is a tribute to the USC-ISI group under Dave Dyer that the VAX implementation has reached a usable state. However, even with the further improvements predicted by USC, it does not appear that the VAX will be a cost-effective Lisp development machine. Preliminary results of another study of Lisp systems running on a wide variety of machine environments being done by R. P. Gabriel of the Stanford AI Laboratory, confirm this conclusion.

- 3) Dual KI-TENEX Role -- The SUMEX KI-10 system has served the AIM community well but is becoming a growing liability in terms of maintenance, staff commitment, and divergence from the mainstream of outside developments. For years we contributed to and derived from the TENEX community a wide variety of system software. That community is dwindling as more and more TENEX sites (e.g., USC, BBN, and SRI) move toward increasingly TENEX-incompatible TOPS-20 systems. We are thus left with a growing set of problems. New software being developed by the TOPS-20 community must undergo major changes to run on TENEX because of JSYS differences and the use of user-mode extended addressing in TOPS-20 with the release 5 monitor this past year. Our own software contributions have become of minimal use to other sites because they are incompatible. We are dependent on specialized and isolated in-house systems expertise to keep these machines running. Should we lose this in the competitive market for systems programmers, we would have a very difficult time finding or more likely training a replacement since there is no incentive for a programmer to learn a dying system. Even within DEC, it is becoming increasingly hard to find knowledgeable engineers for the KI-10 hardware and we are taking on more and more of the system diagnostic and troubleshooting tasks. We are coming up against a major software change caused by ARPA moving to the new IP/TCP protocol. DEC is taking on the monitor changes for the TOPS-20 community and others in the community are adapting user level programs to the change. No similar upgrade effort is underway for TENEX and we will likely be faced with developing our own software changes or lose our ARPANET connection. It is time to retire the KI-TENEX system and upgrade it to a more modern system that will provide the needed larger address space and free our systems staff to concentrate on more productive development efforts for the community such as related to professional workstations and compatible Lisp support.
- 4) Planned Configuration -- The cost and performance of individual Lisp workstations projected for the next few years means that much useful research can be done in experimenting with their use for expert AI systems but that we will not be able to equip a substantial part of the

AIM community with such systems. Thus, in order to continue support for the SUMEX-AIM community at large and to provide facilities for new AI efforts, the best facility configuration will continue to be a central shared system surrounded with growing numbers of workstations coupled by network. It does not appear feasible to continue support for the KI-TENEX system for that period and the VAX does not appear to be a cost-effective alternative. An upgrade of the KI-10 system to a DEC 2060 TOPS-20 system is the best solution. The 2060 is in the mainstream of on-going systems work; it has an extended address space for which some Lisp systems are being adapted (perhaps even an InterLisp); it has a processing capacity of 2-3 times the KI-10 badly needed for our community; and it is more compact, reliable, and maintainable. We are therefore preparing a plan for review by the AIM Executive Committee, NIH, and council to begin implementation of such an upgrade.

Initial File Server Development

The initial development of an Ethernet file server has been an integral part of our council-approved year 09 equipment plan with further expansions approved for later years. We have recently been able to take advantage of an exceptional offer by Digital Equipment Corporation, through their corporate external research sponsorship program, to purchase a VAX 11/750 as the processor part of the file server. In exchange for a substantially reduced price for the machine, we (among several groups at Stanford) have agreed to share information with DEC on the use of such machines in our "personal computing" environment.

In the initial file server configuration, we are also planning to purchase two 600 Mbyte disk drives for main file storage, one 800/1600 BPI tape unit for long term archives, and one 300 Mbyte removable pack drive for cyclic backups. We will most likely buy non-DEC peripheral equipment as the most cost-effective approach. We will then complete the planned initial file server configuration in year 10.

For a file server with such large storage capacity, the old approach of periodic tape dumps for backup becomes impractical, especially in terms of operations time required. We are therefore implementing a system whereby specific user requests to archive files will cause the files to be copied to tape. Other backups for system reliability purposes will be written on a removable pack disk drive and a circular queue of packs maintained to give backup recovery for the most recent 1 month period. Such a system has been working successfully at Xerox and elsewhere on large file server systems.

AMPEX Memory Expansion

At the end of year 08, we reported the expansion of our KI-10 AMPEX memory from 256K to 512K, funded after council approval of our 5-year renewal. This increase has improved system efficiency as predicted. We observed an average reduction in page trap handling overhead from 10.7% to 6.7% and a reduction in system overhead from 36.1% to 28.3% thereby delivering more processing to user jobs.

In the past years, we have observed infrequent parity errors in the AMPEX memory. By examining systematic records of these errors, we found they typically involved a single bit and all occurred in locations that are loaded once at system reload time and then not referenced until a system dump, monitor DDT operation, or other rare event. These errors could not be correlated with memory module and would change location when the monitor was reassembled. No information about the problem was available from AMPEX Corp. Since the problem was so highly intermittent and suspected to involve some backplane interaction that induced loss of contents of a static memory cell bit, we tried writing a program that every so often scans all memory thereby rewriting all cells during the read/refresh cycle. No further occurrences of this problem have been seen and we have not expended further resources on it.

Other Hardware Development

We have undertaken other hardware efforts as appropriate during the past year. These have included:

- 1) Installation of a machine room temperature and power monitor coupled to the Stanford Medical Center security office.
- 2) Purchase and installation of a Canon laser printer with an interface from Imagen, Inc. This system is just now being integrated into the SUMEX facility and will be reported in more detail next year.
- 3) Installation of a Vadic 1200/1200 dial-up rotary for the system using previously surplus hardware from the NIH.
- 4) Assistance in the debugging of the Mass bus Ethernet Interface System being developed by Computer Science.

In addition we have provided broad support to users for terminal and communications connections and repairs.

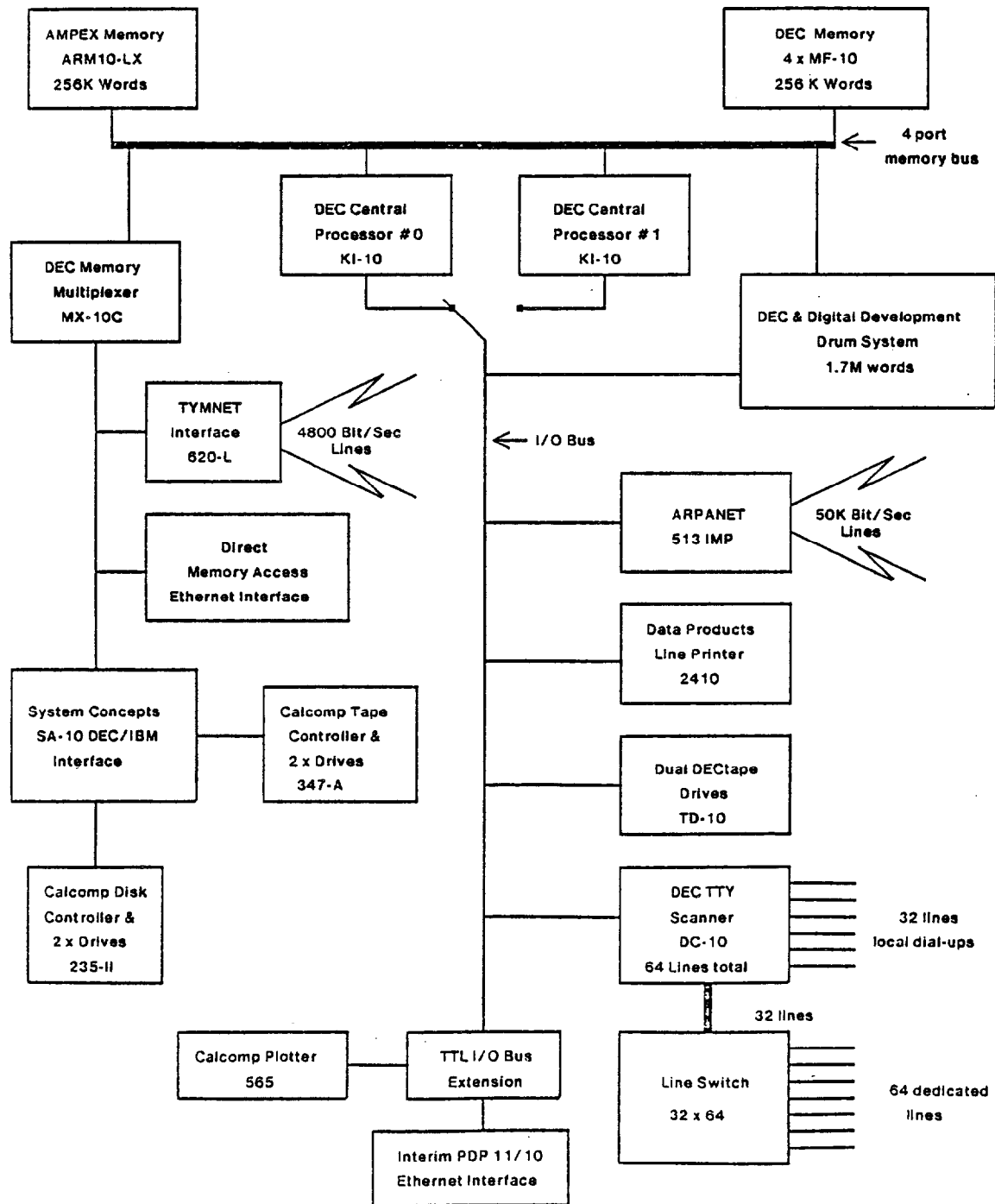


Figure 1. Current SUMEX-AIM KI-10 Computer Configuration

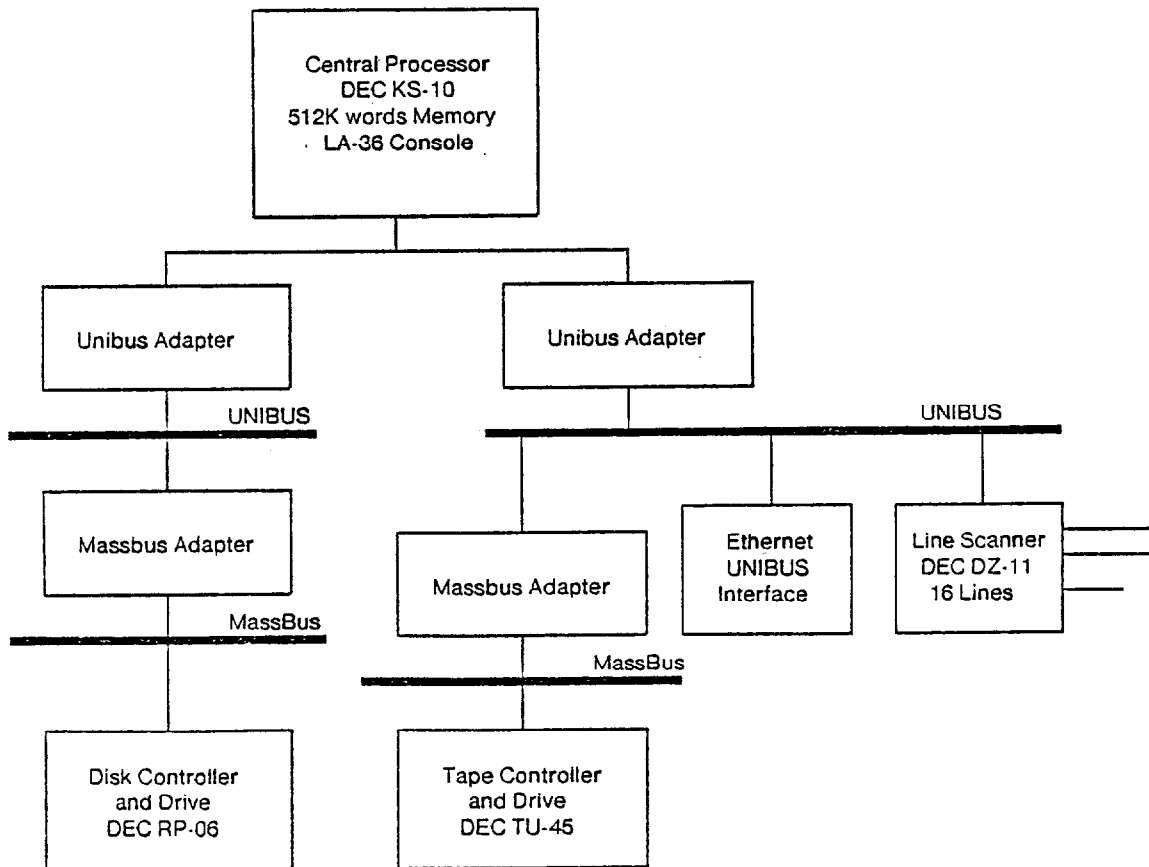


Figure 2. Current SUMEX-AIM 2020 Computer Configuration

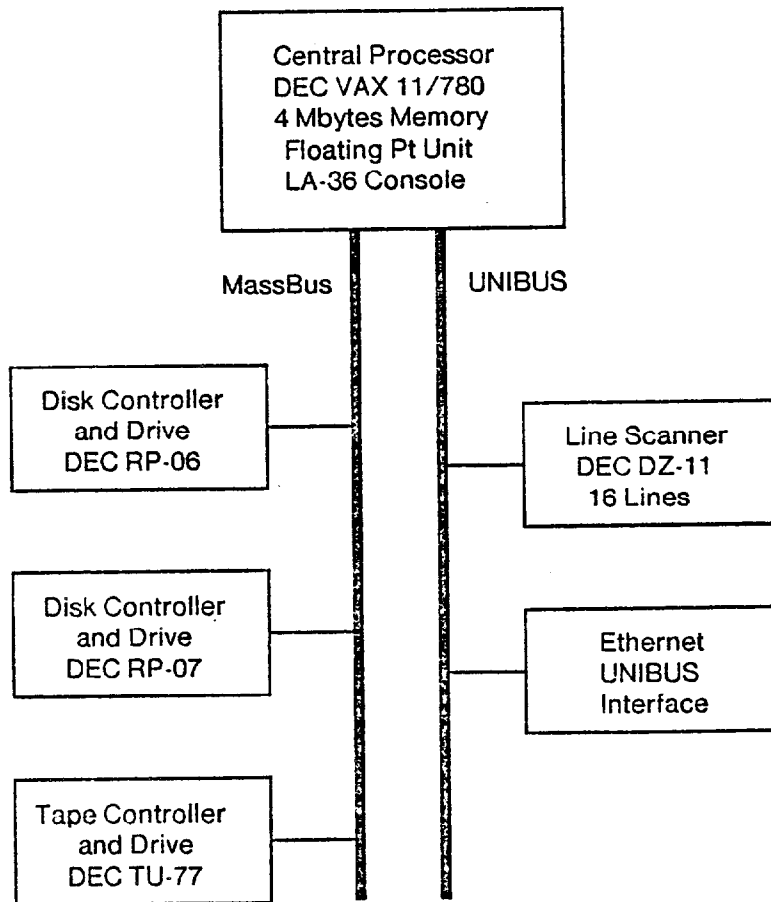


Figure 3. Current Shared VAX Computer Configuration

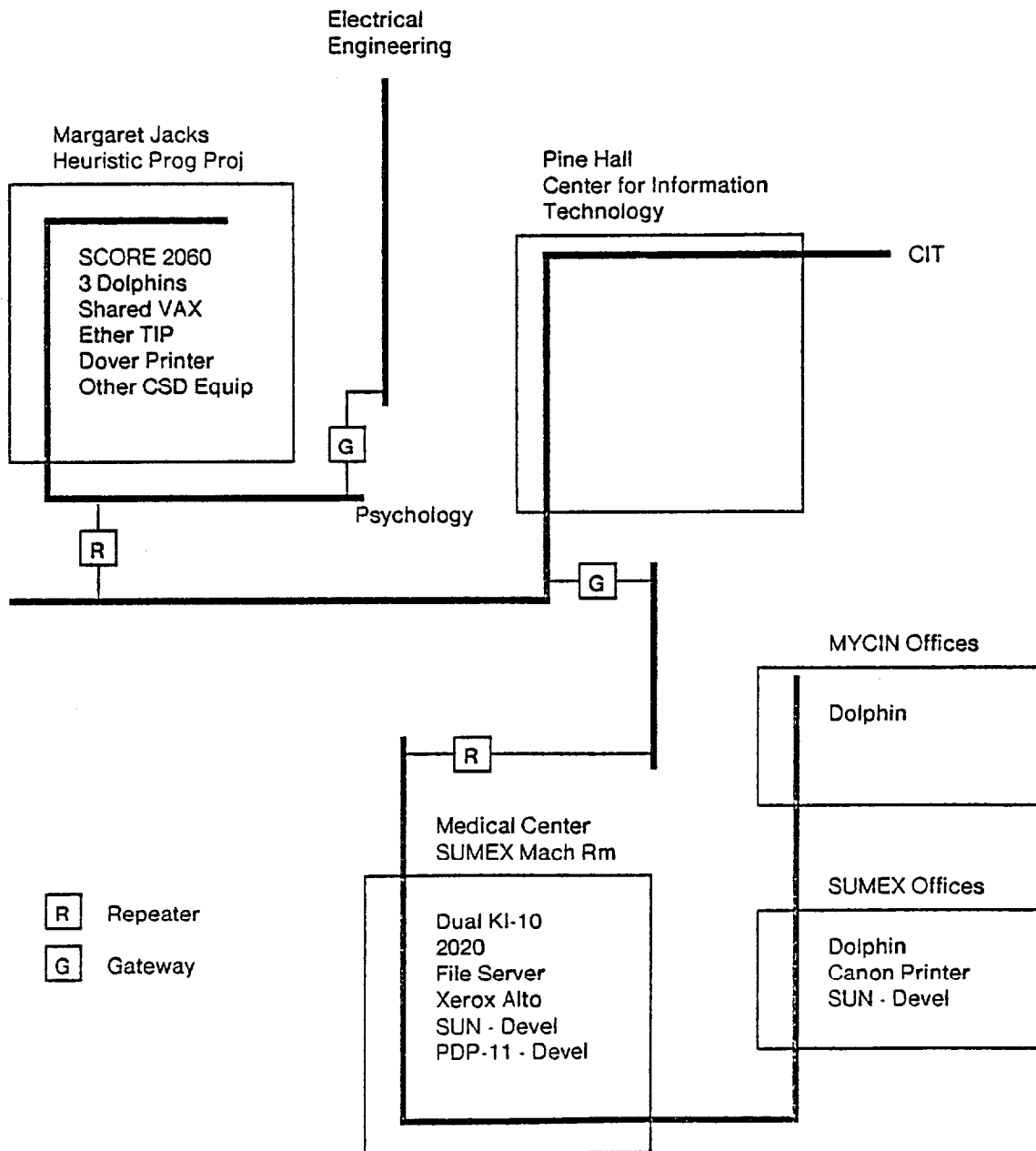


Figure 4. Intermachine Connections via ETHERNET

I.A.3.2 Host System Software

Our system software work this past year has concentrated on several areas including changes to support hardware development projects, upgrading and enhancing network interface service, correcting encountered system bugs, and implementing new features for better user community support. In addition we have invested substantial effort in becoming familiar with the VAX/UNIX system which has played a key role in our investigations this past year.

Dual KI/TENEX System

DMA Ethernet Interface -- In parallel with our hardware efforts this past year to extend and improve the KI-10 Ethernet connection, the necessary monitor changes were made to support the new hardware. Initial software work was begun earlier but the major part was completed this past year including a new interrupt driver module for the monitor and an extensive set of user-mode diagnostics. The dual processor system has proven extremely flexible in order to carry out hardware debugging while user time-sharing is in progress. Since most of the system hardware devices are on one CPU, developmental hardware can be connected to the other for debugging. That processor can be taken off-line temporarily for hardware changes without bringing down the rest of the system. Also, special diagnostics involving interrupt handling and other low level monitor functions such as mapping special memory pages used by the hardware under test can be performed on that machine without affecting other users. The interface and software are now checked out and are awaiting installation of the new gateway Ethernet cable so that reliable communications with the phase decoder packet interface will be possible.

File System Expansion -- In past years, we have reserved one disk drive as a backup in case of failure so that we could keep the system operational. Because of increasing pressures for more file space, we made the necessary monitor changes to bring this drive on-line, thereby expanding the file system by 76,760 pages. This has met user community needs at the expense of hardware backup.

ARPANET Protocols -- Effective January 1, 1983, the ARPANET is scheduled to change from the current NCP (Network Control Protocol) to IP/TCP (Internet Protocol/Transmission Control Protocol). This will require a major change in the monitor service that supports our ARPANET connection. In the past, changes of this type were funded for the community by ARPA or the hardware vendor so that individual sites would not have to redevelop such software. This is happening for the TOPS-20 implementation of IP/TCP with coordinated efforts between BBN and DEC. An old experimental system runs under TENEX but it does not integrate the network support into the standard file system calls as is the convention for TENEX/TOPS-20. These changes will have to be done by the local staff unless we can upgrade the KI-10's to a 2060 to take advantage of the community effort. At least 6 man-months of effort will likely be involved in such an effort.

System Loading Controls -- We previously reported on the system load controls we have implemented on the KI-10 system to allocate available system capacity effectively among projects and users according to Executive Committee guidelines. These continue to operate effectively and we have not made any substantial changes in this area.

Executive Program -- In order to better control the GENET community (see page 73) who share a single directory, we designed a subdirectory login facility in the EXEC that provides a two-step process for login. First the user must know the global account name and password for GENET. The subdirectory facility now requires an additional private user name and password for entry. We instituted this control in order to preserve the form of the GENET guest account but to screen out inappropriate users such as industrial people. Together with the limit of 2 simultaneous jobs, this mechanism has worked well.

Monitor Bug Fixes and Improvements -- We have continued to repair important bugs in our TENEX monitor. In general the system runs extremely reliably with most problems coming from explicit hardware malfunctions or periods of instability following significant monitor changes. We found several more subtle bugs in the system this past year that had been causing various problems. By now, all of the "obvious" bugs have been located and so those remaining are much more elusive, occurring infrequently or only after a long chain of rare events that is difficult to reconstruct.

One of these involved a problem with mapping temporary pages in the monitor in which the order of two instructions was inverted and the page was marked as free before the necessary reference to the page was complete. Another showed up during Ethernet interface debugging in the handling of processes forced to run on one processor or another. And finally we implemented an automatic recovery system for a bug that causes the ARPANET service to run out of buffers infrequently.

2020/TOPS-20 System

Monitor Upgrade -- Our 2020 system has continued to run very reliably this past year. We have upgraded the monitor to release 4 which required substantial work to remerge the Ethernet service changes in the new monitor code. At the same time we brought up the release 5 Executive program being run at SCORE which is a beta test site for monitor release 5. We also upgraded the COMND JSYS emulator package for TENEX to be compatible with release 4. There will likely be few further monitor releases for the 2020 since it does not support extended addressing and there are no plans to add this feature.

Demo Controls -- We previously instituted a mechanism for reserving the entire 2020 for demonstrations and developmental testing of various expert systems (e.g., DENDRAL, UNCOCIN, CADUCEUS, etc.). Because of the unpredictability of usage during these reserved times and the resulting waste of 2020 capacity, we changed this reservation policy by taking advantage of the pie-slice scheduler in the release 4 monitor. We now guarantee dedicated users a large fraction of the machine but also allow

others to do useful work when the demo demand is low. This system has nicely met the needs of both groups.

VAX/UNIX System

This past year we took on systems support for the ARPA VAX/UNIX system shared by the SUMEX-AIM community. Substantial effort was spent in becoming familiar with the UNIX monitor and in bringing up various user subsystems such as FranzLisp and InterLisp. The new Berkeley release 4.1 monitor was installed after merging local Ethernet software and the interprocess communication software from Carnegie-Mellon was imported and brought up. When the file system was expanded with the RP07 disk, the new device service and swapping off of both the RP06 and RP07 disks was added and appropriate file system partitioning instituted between the major user groups. A group protection facility was added to UNIX to facilitate more file privacy between disparate groups of users. Finally, a substantial effort was made to track down a serious bug in the multiplexed file code used extensively by FranzLisp programmers. This bug caused the file system to become corrupted when an "i-node" was erroneously written out twice. After isolating the cause of the problem, we were able to import a fix from CMU and the system has restablized nicely.

Dolphin System

Our system work on the Dolphins has centered mostly on the network services provided by the various host machines. Still a significant effort has gone into effective liaison with Xerox PARC and Electro-Optical Systems to coordinate bug and benchmark information, install new software releases and upgrades, and assure proper hardware maintenance. We actively supported the distribution of TENEX, TOPS-20, and UNIX file server software needed to interface the Dolphin to these host systems.

I.A.3.3 Network Systems

A highly important aspect of the SUMEX system is effective communication with remote users and between the growing number of machines available within the SUMEX resource. In addition to the economic arguments for terminal access, networking offers other advantages for shared computing including improved inter-user communications and more effective software sharing. We continue to base our local communications on the 3 Mbit/sec Ethernet and remote communications on TYMNET and ARPANET for reasons detailed in previous annual reports.

Users asked to accept a remote computer as if it were next door will use a local telephone call or hardline connection to the computer as a standard of comparison. Local networks stand up well in this comparison but remote network facilities do not. Data loss is not a problem in most network communications - in fact with the more extensive error checking schemes, data integrity is higher than for a long distance phone link. On

the other hand, remote networking relies upon shared use of communication lines for widespread geographical coverage at substantially reduced cost. However, unless enough total line capacity is provided to meet peak loads, substantial queueing and traffic jams result in the loss of terminal responsiveness. Limited responsiveness for character-oriented TENEX/TOPS-20 interactions continues to be a problem for network users.

TYMNET

TYMNET provides broad geographic coverage for terminal access to SUMEX, spanning the country and also increasingly accessible from foreign countries. Technical aspects of our connection to TYMNET have remained unchanged this past year and have continued to operate reasonably reliably. As noted earlier, however, users have complained periodically about having their connections dropped and we have implemented a data collection facility in the EXEC program to help document and classify these failures. There are definitely episodes in which all connections are lost and the jobs are detached. These occur about once every few days and we continue to analyze these data to try to separate out local from network causes.

TYMNET has made few technical changes to their network that affect us other than to broaden geographical coverage. The previous network delay problems are still apparent although better cross-country trunks into New York and New England are available improving service there. TYMNET is still primarily a terminal network designed to route users to an appropriate host and more general services such as outbound connections originated from a host or interhost connections are only done on an experimental basis. This presumably reflects the lack of current economic justification for these services among the predominantly commercial users of the network. Whereas TYMNET has interfaces meeting X.25 protocol standards, the internal workings of the network will likely remain the same, namely, constructing fixed logical circuits for the duration of a connection and multiplexing characters in packets over each link between network nodes from any users sharing that link as part of their logical circuit.

We have continued to purchase TYMNET services through the NLM contract with TYMNET, Inc. Because of current tariff provisions, there is no longer an economic advantage to this based on usage volume. SUMEX charges are computed on its usage volume alone and not the aggregate volume with NLM's contribution to achieve a lower rate. We have implemented the "dedicated port" charging system for SUMEX use and have realized a substantial reduction in monthly usage costs. We will continue to work closely with NIH-BRP and NLM to achieve the most cost-effective purchase of these services.

ARPANET

We retain our advantageous connection to the Department of Defense's ARPANET, now managed by the Defense Communications Agency (DCA). This connection has facilitated close collaboration with the Rutgers-AIM facility and many other computer science groups that are also on the net.

Consistent with our long-standing agreements with ARPA and DCA we are enforcing a policy that restricts the use of ARPANET to users who have affiliations with DoD-supported contractors and system/software interchange with cooperating network sites. We are somewhat unique in this policy among other network sites since NIH has not become a member of the "sponsor's group" for the network. We would strongly encourage this step so that biomedical users could have more uniform access to the superior facilities of the ARPANET. This will become increasingly important as more NIH-sponsored sites desire access to the net and each other.

We have maintained good working relationships with other sites on the ARPANET for system backup and software interchange. Such day-to-day working interactions with remote facilities would not be possible without the integrated file transfer, communication, and terminal handling capabilities unique to the ARPANET. The ARPANET is also key to maintaining on-going intellectual contacts between SUMEX projects such as the Stanford Heuristic Programming Project authorized to use the net and other active AI research groups in the ARPANET community.

As indicated in the discussion of monitor software development, we expect a significant change in ARPANET protocols to be instituted by January 1, 1983. Before then we also expect ARPA to upgrade our Honeywell 516 IMP to a new C-30 IMP and to add a connection between the C-30 and AI&DS, an ARPA contractor. We are also cooperating with the Network Graphics group in the Stanford EE department on the development of an ARPANET gateway that will operate over our local Ethernet.

ETHERNET

A substantial portion of our system effort this past year went into continued development of local Ethernet facilities which link SUMEX resource hardware with other parts of campus (especially to the Computer Science Department building where the Heuristic Programming Project is located). We have also developed a substantial set of software tools and diagnostics as a basis for implementing various kinds of Ethernet servers on both PDP-11 and SUN MC-68000 processors. These have been done in the language C, primarily for portability and because it is the language on which UNIX is based, has an active support community, and is being used for other network software that may be useful for our work. Specific areas of Ethernet development include:

- 1) Leaf server: We implemented the Sequin reliable packet protocol and Leaf byte-level file transfer protocol to enable the Dolphins to access files on the 2020 and KI-10. Code for the VAX/UNIX system was written by a EE student and is available as well. The Leaf protocol is built into the lowest levels of the Dolphin I/O system, and allows any file on a remote file server to be accessed as easily as a disk file in both paged or random access mode. The latest updates to the Sequin transport level have made marked improvements in efficiency. The 2020 now performs Leaf file transfers with a speed approaching that of Xerox's dedicated file server.

- 2) TENEX/TOPS-20 Ethernet Server: We implemented boot server software to enable Altos, PDP-11's, and SUN terminals to be booted by the KI-10s or the 2020 and also added the address lookup service so that all documented types of miscellaneous services are supported by TENEX and TOPS-20.
- 3) Ethernet Diagnostic Software: Many difficult situations arose in the past year involving the debugging of locally developed Ethernet interface boards or forcing the gateway link to work over very substandard cable. This necessitated the development of effective diagnostic tools to provide oscilloscope loops, loopback packet checks, local and remote echo checks, and other measures of hardware performance. Such programs were written for the KI-10, PDP-11, and SUN MC-68000 processors
- 4) Ethernet Gateway: We reported on the initial development of an Ethernet gateway last year. In order to make the gateway between the SUMEX network and other campus networks operate, we had to specially modify the transceivers and interface boards to work with the high-loss, 50 ohm cable currently available. Once working at the hardware level, much work has been done to develop an effective and supportable gateway. This includes a PROM EFTP memory dump and analysis capability to diagnose gateway failures and a miscellaneous services server program to record and analyze hourly event reports on the gateway hardware status. The gateway also now generates periodic Breath-of-Life(*) packets so that we can boot our Dolphins and Alto independently of their disk bootstraps in the event of a hardware failure. The gateway has been up continuously since the middle of December 1981, excepting power failures and outages.
- 5) Ethernet TIP: The PDP-11 Ethernet operating system and the byte sequential protocol implementation reported last year were combined with serial line handling software and a convenient user interface to create a terminal interface processor (TIP). In order to accommodate buffers for 8 lines in the 32K PDP-11, we wrote an optimizer for the MACRO-11 output from the PDP-11 C compiler. The optimizer provided about a 20% savings in core usage. The TIP code is now stable and the system is in use in Margaret Jacks Hall as the primary means for HPP access to the VAX. Work continues on a similar SUN MC-68000 version of the TIP which should have a substantially greater line capacity.

INTERNET SOFTWARE

One of the issues confronting the development of complex network-based systems, interconnected by gateway machines, is the support of internet communication of various kinds. For example, when a user at one of the Stanford Ethernet hosts wants to send a message to someone at MIT on a Chaosnet host, the mail handling programs have to know how to do the

(*) These are special non-PUP packets which cannot be generated or handled by the KI-10 or 2020 hosts currently.

routing and the mail server programs have to be prepared to receive such mail for forwarding. Similarly, when establishing terminal telnet connections between such sites, the path of the link should be established automatically with the intervening sites merely acting as relay stations.

In conjunction with groups at MIT and Stanford CSD, we have continued development of prototypical systems for internet mail handling and telnet connections. The mail system (XMAILR) is quite highly developed and currently knows how to route messages between hosts on the Stanford Ethernet, the ARPANET, the MIT Chaosnet, the MIT LCSnet, and the Dialnet. SUMEX has served as the major electronic mail gateway between the Stanford Ethernet community and other ARPANET hosts for the past year. We also brought up a new mail forwarding system (XMAILBOX) that incorporates list expansion, a more convenient syntax for forwarding entries, and allows indirect file references for expanding mail distribution lists.

I.A.3.4 User System Software

We have continued to assemble and maintain a broad range of utilities and user support software. These include operational aids, statistics packages, DEC-supplied programs, improvements to the TOPS-10 emulator, text editors, text search programs, file space management programs, graphics support, a batch program execution monitor, text formatting and justification assistance, magnetic tape conversion aids, and many more.

Over the past year we made a significant effort to improve the mail reading facilities available under TENEX. With the development of broad internet contacts, the old MSG program was unable to recognize host addresses on networks other than ARPANET. BBN refused to release the sources to MSG for further development, even though they were initially developed outside of BBN. We therefore decided to adapt the MM system developed for TOPS-20. Many changes were necessary to bridge the significant differences that have arisen between TENEX and TOPS-20, pointing up the impediments mentioned earlier to continued import of TOPS-20 community software. We also had to make substantial improvements to the TOPS-20 JSYS emulation software developed earlier. At the present time, MM is running in experimental mode with a subgroup of the SUMEX-AIM community and seems to work well. It provides a full internet capability and is in fact more efficient in terms of machine resources than MSG. We plan to finish adapting documentation for MM shortly and release it to the full community.

We also spent considerable additional effort improving the C compiler at SUMEX to be compatible with other UNIX compilers in terms of the syntax it understands. We also developed a postprocessing object code optimizer for the PDP-11 cross compiler to minimize the memory requirements in the generated code.

We worked on adding functions to Interlisp-10 to make it compatible with Dolphin Interlisp-D. This included adding a LOGIN() function which could be used by the Interlisp-10 FTP and PUPFTP packages, and an EMPRESS function so that Interlisp-10 could produce prettyprinted output with font changes similar to Interlisp-D's prettyprinted output. The LOGIN function has been sent to Xerox PARC. Completion of the EMPRESS function is awaiting some definitions from Xerox.

We also implemented extensions and maintenance updates to many other existing programs including, for example, BBD (the bulletin board system), OMNIGraph (the general graphics package from NIH), MSGFIX (a message file repair program), and FM (a locally developed fast mail reading program). We also participated with other sites at Stanford in a general license for access to the SCRIBE text formatting system from UNILOGIC including versions to run under TENEX, TOPS-20, and UNIX. SCRIBE is rapidly replacing PUB as the preferred tool for text preparation.

I.A.3.5 Documentation and Education

We have spent considerable effort to develop, maintain, and facilitate access to our documentation so as to accurately reflect available software. The HELP and Bulletin Board subsystems have been important in this effort. As subsystems are updated, we generally publish a bulletin or small document describing the changes. As more and more changes occur, it becomes harder and harder for users to track down all of the change pointers. Within manpower limits, we are in a continuous process of reviewing the existing documentation system for compatibility with the programs now on line and to integrate changes into the main documents. This will also be done with a view toward developing better tools for maintaining up-to-date documentation.

I.A.3.6 Software Compatibility and Sharing

At SUMEX-AIM we firmly believe in importing rather than reinventing software where possible. As noted above, a number of the packages we have brought up are from outside groups. Many avenues exist for sharing between the system staff, various user projects, other facilities, and vendors. The advent of fast and convenient communication facilities coupling communities of computer facilities has made possible effective intergroup cooperation and decentralized maintenance of software packages. The TENEX, TOPS-20, and UNIX sites on the ARPANET have been a good model for this kind of exchange based on a functional division of labor and expertise. The other major advantage is that as a by-product of the constant communication about particular software, personal connections between staff members of the various sites develop. These connections serve to pass general information about software tools and to encourage the exchange of ideas among the sites. Certain common problems are now regularly discussed on a multi-site level.

We continue to draw significant amounts of system software from other ARPANET sites, reciprocating with our own local developments. The TENEX community is on the decline, however, and we are becoming more and more isolated in our work for the KI-TENEX system. Still, significant sharing continues with the TOPS-20 and UNIX sites. Interactions have included mutual backup support, experience with various hardware configurations, experience with new types of computers and operating systems, designs for local networks, operating system enhancements, utility or language software, and user project collaborations. We have been able to import many new pieces of software and improvements to existing ones in this way. Examples of imported software include the message manipulation program MM, SAIL, PASCAL, SOS, INTERLISP, the C compiler, VAX Ethernet code, the RECORD program, ARPANET host tables, and many others. Reciprocally, we have exported our contributions such as the crash analysis program, drum page migration system, KI-10 page table efficiency improvements, GTJFN enhancements, PUB macro files, the bulletin board system, MAINSAIL, SPELL, SNDMSG enhancements, our BATCH monitor, and improved SA-10 software.

There are also several important examples of joint development efforts such as the internet mailer program (XMAILR). Because this program incorporates facilities for routing mail through many networks, it is important that the various sections of the program dealing with these specialized protocols be developed by the groups with expertise in the appropriate technology. Network connections have made a joint effort possible involving MIT, Stanford SCORE, and SUMEX. A growing number of network sites are now using this mailer program.

We have spent considerable effort developing a version of a TENEX/TOPS-20 compatibility package. The issue here is that as DEC develops TOPS-20, even though it is TENEX-like, it is not TENEX compatible and vice versa. Thus, a hope was to write a program that would resolve these compatibilities automatically rather than to force special adaptations for the two operating systems. The kinds of incompatibilities that exist include PDP-20 machine instructions that do not exist on earlier machines, new JSYS calls, incompatible changes to old JSYS calls, different syntax and facilities for device/file names, and different handling of error returns (types of return and error codes). It has proven very difficult to effectively handle all of these problems at the user level. Monitor changes are required to implement the widely used error return features (ERJMP/ERCAL) and make handling of other incompatibilities easier. We have not accomplished a complete compatibility package in any sense but have implemented requisite monitor changes and have developed several user packages that help emulate TOPS-20 JSYS calls for programs running on TENEX. We do not foresee being able to completely and effectively solve these problems and expect the differences to increase, especially with user access to extended addressing on the large TOPS-20 systems becoming more frequently used.

Finally, we have also assisted groups that have interacted with SUMEX user projects get access to software available in our community. The DENDRAL project has provided many examples of this kind of sharing -- (see page 96). The most voluminous guest user group is the GENET community started in collaboration with the MOLGEN project (see page 128).

I.A.3.7 Core Research

Over the past year we have supported several core research activities aimed at developing information resources, basic AI research, and tools of general interest to the SUMEX-AIM community. SUMEX is providing only partial support for these projects with complementary funding coming from ARPA, ONR, NLM, and NSF contracts and grants to the Stanford Heuristic Programming Project.

Principal areas of current effort include:

- 1) AI Handbook -- This is a compendium of knowledge about the field of Artificial Intelligence being compiled by Avron Barr, Paul Cohen, and Professor Feigenbaum. The handbook is broad in scope, covering most of the important ideas, techniques, and systems developed during 26 years of research in AI in a series of articles. Each is short and is a description written for non-AI specialists and students of AI. The handbook is now published in three volumes by William Kaufmann, Inc. The AI Handbook effort is described in more detail starting on page 92 and an outline of the contents of the handbook can be found in Appendix B.
- 2) AI Tools -- The objective of our core tool building research is to develop new tools and methods for representing knowledge in an attempt to generalize the methods explored in specific applications programs and to respond to problems encountered with existing methods. Several software packages are being developed, each of which has some degree of general applicability. Several have been applied to a variety of problems and thus provide experimental data on their strengths and limitations. These packages comprise what we term a Knowledge Engineer's Workbench. They are tools that facilitate the rapid construction, testing, modification, and explanation of knowledge-based expert systems.

Both EMYCIN and AGE-1 have reached maturity as vehicles of research. Each was completed and documented during the last year. Experiments with each system have also been performed and documented. Both programs are in use on medical and nonmedical problems at several institutions. These experiments, and their analysis, has led to an understanding of the strengths and limitations for each system and will provide valuable information for improved methods. More detailed descriptions of progress on these systems can be found on page 137 and on page 83.

Even though the Meta-knowledge Representation System (MRS) is still

under development, it has been exported to several sites and used experimentally on a variety of problems. A demonstration version of EMYCIN, implemented in MRS, has shown the power of the system's logic-based representation. MRS is implemented in a variety of Lisp's, including MacLisp and InterLisp on the DEC-20, InterLisp on the Xerox Dolphin, and FranzLisp on the VAX 11/780. The system is taught in Stanford's first graduate level AI courses.

In addition to the work on these major systems, improvements were made to the UNITS package, including its transfer to the Dolphin personal workstation.

- 3) Basic Research -- Building computer programs that reason with and about medical knowledge requires powerful methods for representing that knowledge and for reasoning with it. Basic core research efforts focus on understanding these issues. The three areas that we are addressing in this work are:

Knowledge Representation -- How can the knowledge necessary for complex problem solving be represented for its most effective use in automatic inference processes? In particular, how can knowledge of causal mechanisms be represented in programs that reason about medical problems?

Knowledge Acquisition -- How is this knowledge acquired most efficiently from human experts and from natural data gathered by instruments?

Knowledge Utilization -- By what inference methods can a variety of sources of knowledge of diverse types be made to contribute jointly and efficiently toward solutions?

Results of recent work are published in technical reports including experiments performed and documented on the power of production rules and of frame-based systems [Memos HPP-80-17, HPP-81-2, HPP-81-17]; and experiments with induction systems and with interactive programs for knowledge acquisition [Memos HPP-81-4, HPP-81-5, HPP-81-13, HPP-81-19]. In addition we have begun work on programs that explore fundamental questions in:

Causal Reasoning -- How do we represent and use causal mechanisms, e.g., about physiological processes, in knowledge-based computer programs?

Knowledge Acquisition -- How can we build an intelligent knowledge acquisition system that helps an expert construct a new knowledge base using old ones as models?

I.A.3.8 Resource Operations Statistics

The following data give an overview of various aspects of SUMEX-AIM resource usage. There are five sub-sections containing data respectively for:

- 1) Overall resource loading data (page 34).
- 2) Relative system loading by community (page 36).
- 3) Individual project and community usage (page 40).
- 4) Network usage data (page 48).
- 5) System reliability data (page 50).

1. Overall resource loading data

The following plots display several different aspects of system loading over the life of the project. These include total CPU time delivered per month, the peak number of jobs logged in, and the peak load average. The monthly "peak" value of a given variable is the average of the daily peak values for that variable during the month. Thus, these "peak" values are representative of average monthly loading maxima and do not reflect the largest excursions seen on individual days, which are much higher.

These data show well the continued growth of SUMEX use and the self-limiting saturation effect of system load average, especially after installation of our overload controls early in 1978. Since late 1976, when the dual processor capacity became fully used, the peak daily load average has remained between about 5.5 and 6. This is a measure of the user capacity of our current hardware configuration and the mix of AI programs.

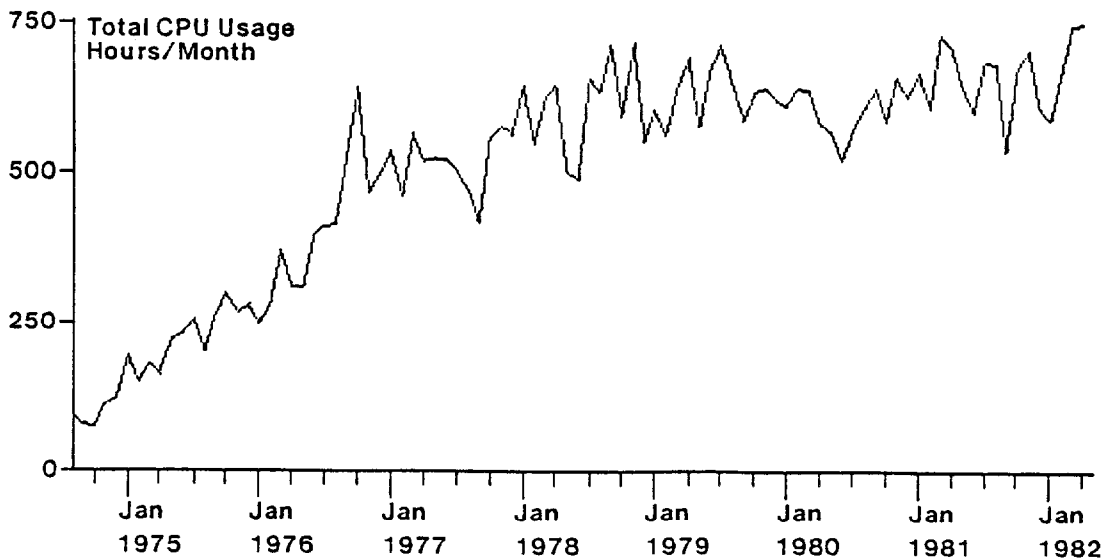


Figure 5. Total CPU Time Consumed by Month

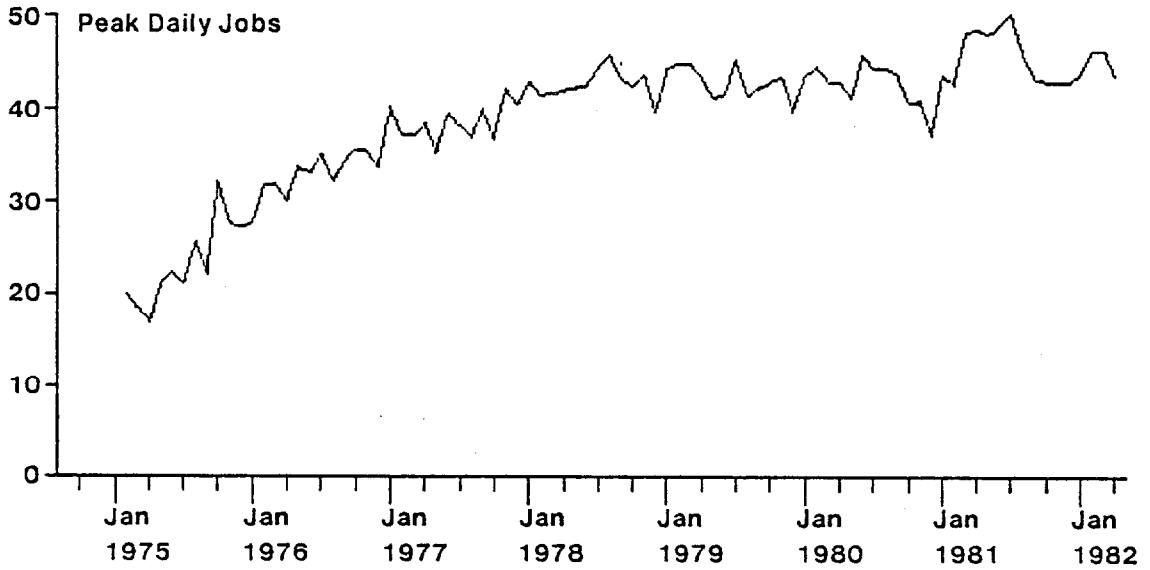


Figure 6. Peak Number of Jobs by Month

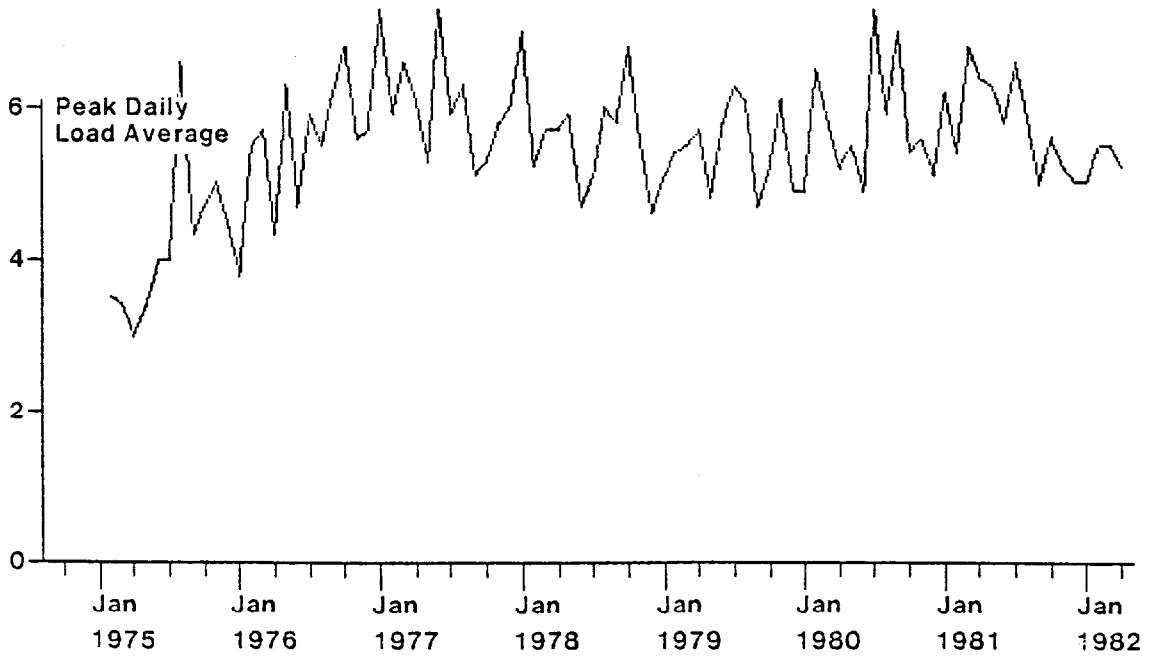


Figure 7. Peak Load Average by Month

2. Relative System Loading by Community

The SUMEX resource is divided, for administrative purposes, into 3 major communities: user projects based at the Stanford Medical School (Stanford Projects), user projects based outside of Stanford (National AIM Projects), and common system development efforts (System Staff). As defined in the resource management plan approved by BRP at the start of the project, the available system CPU capacity and file space resources are divided between these communities as follows:

Stanford	40%
AIM	40%
Staff	20%

The "available" resources to be divided up in this way are those remaining after various monitor and community-wide functions are accounted for. These include such things as job scheduling, overhead, network service, file space for subsystems, documentation, etc.

The monthly usage of CPU and file space resources for each of these three communities relative to their respective aliquots is shown in the plots in Figure 8 and Figure 9. Terminal connect time is shown in Figure 10. In the early years of the SUMEX resource, the Stanford projects held an edge in system usage despite our efforts at resource allocation and the substantial voluntary efforts by the Stanford community to utilize non-prime hours. This reflected the maturity of the Stanford group of projects relative to those getting started on the national side and has correspondingly accounted for much of the progress in AI program development to date. While the Stanford community has remained vigorous, national usage has grown to comparable levels in recent years, in part because of the popular GENET guest facility (see page 40 and page 73).

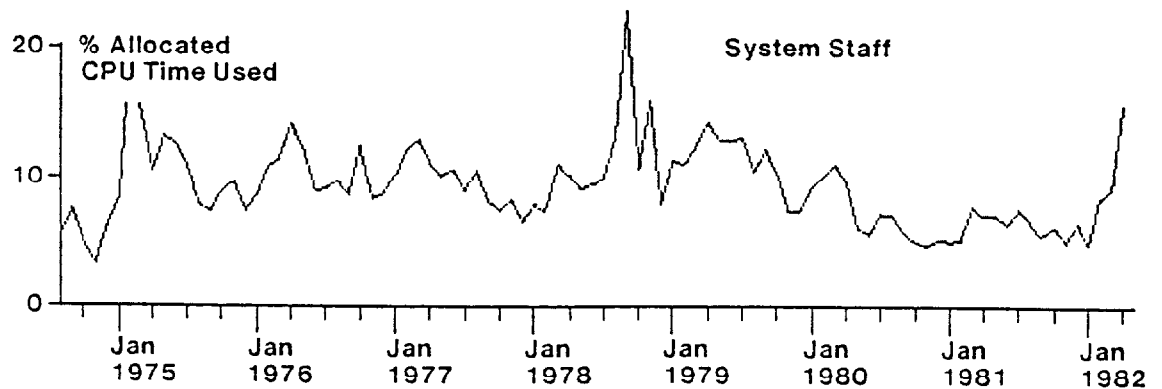
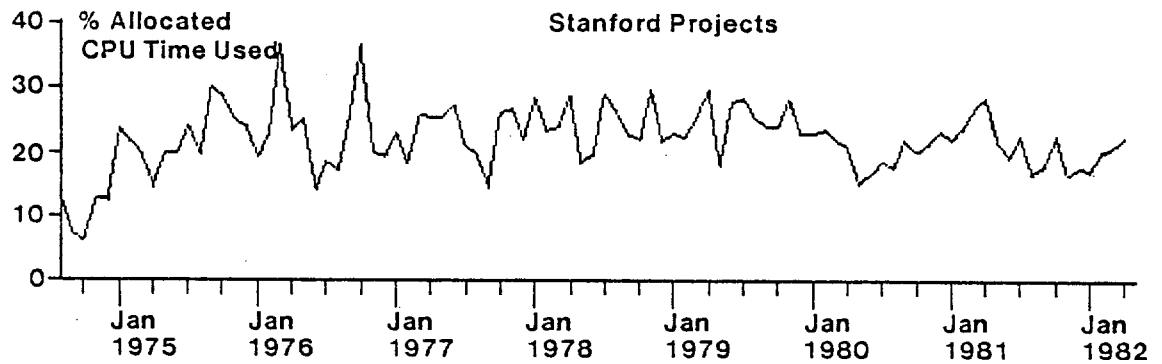
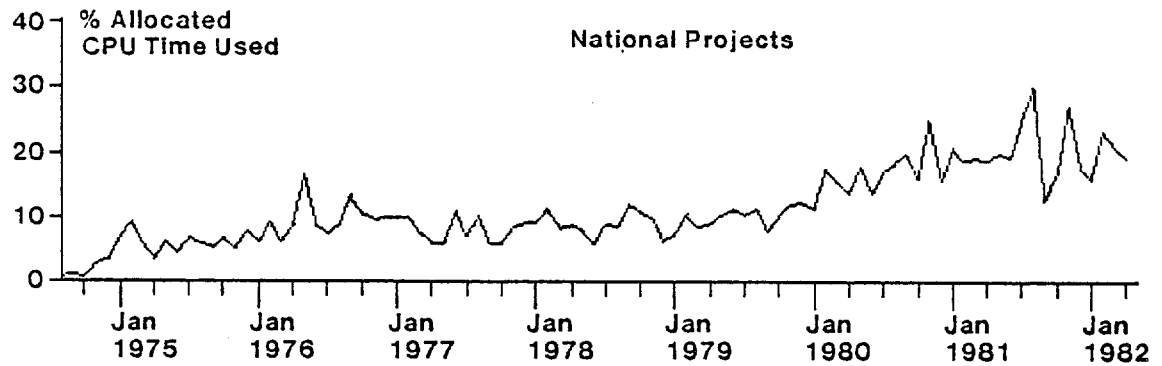


Figure 8. Monthly CPU Usage by Community

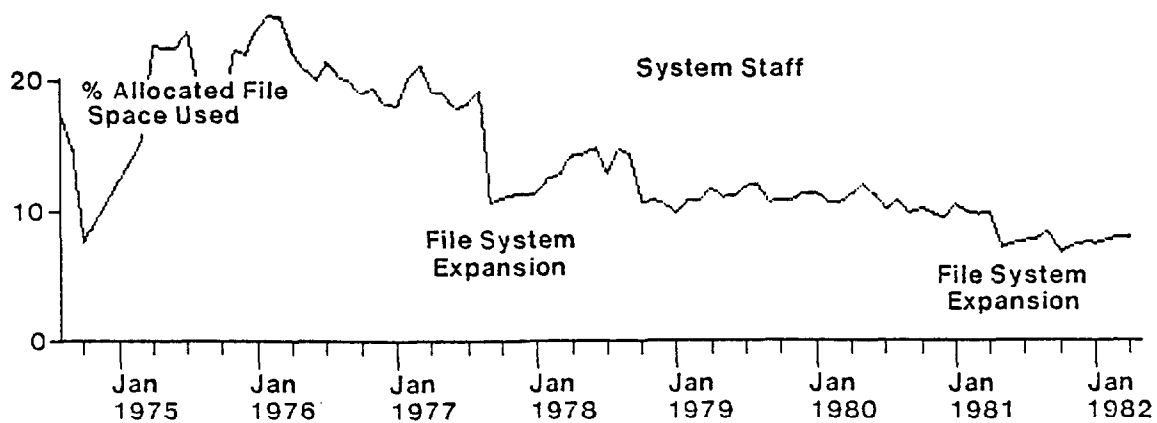
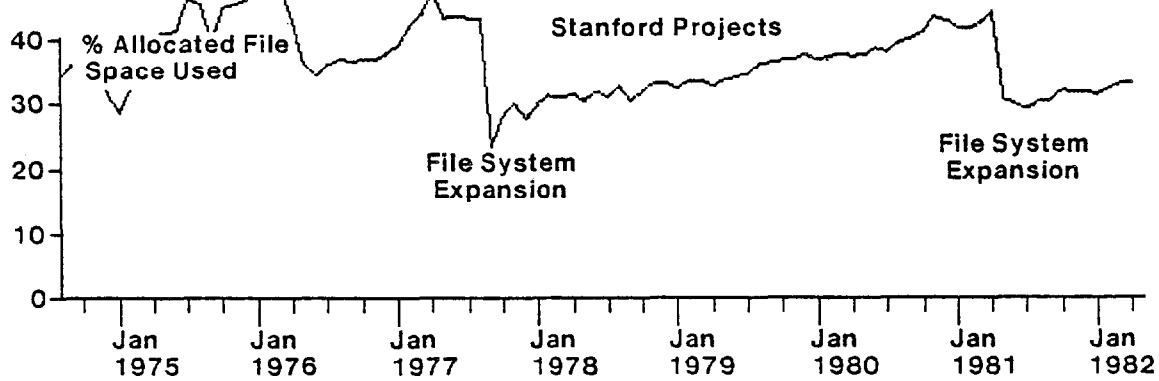
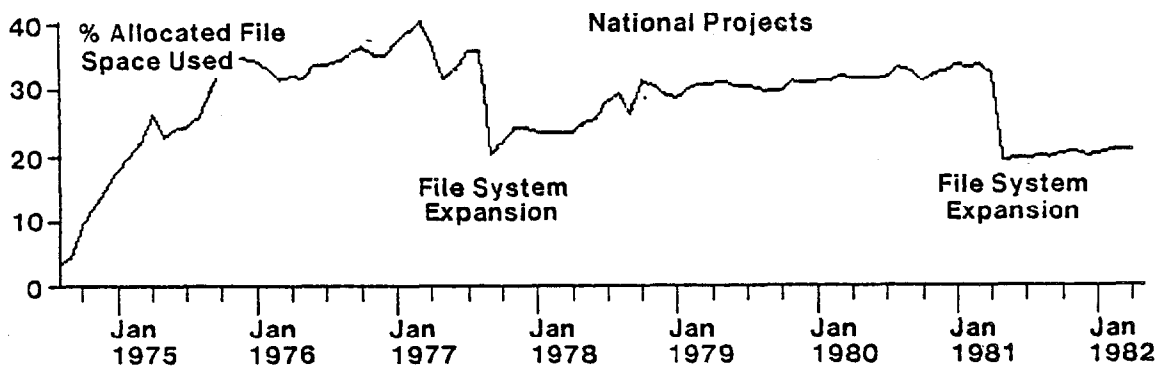


Figure 9. Monthly File Space Usage by Community

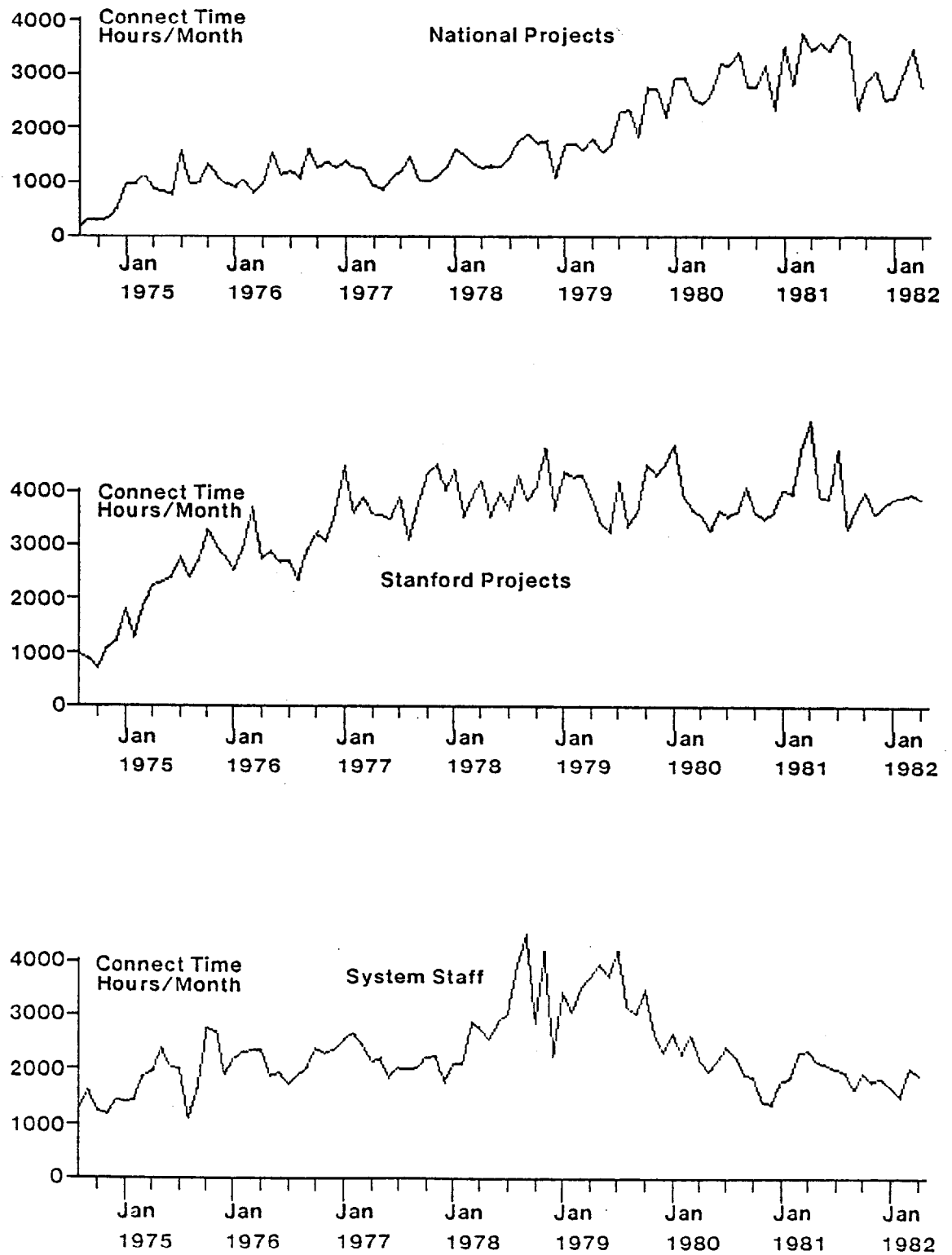


Figure 10. Monthly Terminal Connect Time by Community

3. Individual Project and Community Usage

The following histogram and table shows cumulative resource usage by collaborator project and community during the past grant year. The histogram displays the project distribution of the total CPU time consumed between May 1981 and April 1982. A key point to note is that the total national, Stanford, and Staff resource consumption is approximately in the mandated 40:40:20 ratio. Also note that the large consumption by AIM Users (21.3%) consists mostly of GENET community usage (18.3%), attesting to the great popularity of that facility in the molecular biology community (in spite of the severe access restrictions we have implemented!).

In the table following, entries include a text summary of the funding sources (outside of SUMEX-supplied computing resources) for currently active projects, total CPU consumption by project (Hours), total terminal connect time by project (Hours), and average file space in use by project (Pages, 1 page = 512 computer words). These data were accumulated for each project for the months between May 1981 and April 1982.

It should be noted that the Stanford projects have voluntarily shifted a substantial part of their development work to non-prime time hours which is not explicitly shown in these cumulative data. It should also be noted that a significant part of the DENDRAL, MYCIN, AGE, AI Handbook, and MOLGEN efforts, here charged to the Stanford aliquot, support development efforts dedicated to national community access to these systems. The actual demonstration and use of these programs by extramural users (e.g., the GENET community) is charged to the national community in the "AIM USERS" category, however.

Several of the projects admitted to the National AIM community use the Rutgers-AIM resource as their home base. We do not explicitly list these projects in this annual report covering the Stanford SUMEX-AIM resource. We do record information about the Rutgers resource itself, however, and note its separate resource status with the flag "[Rutgers-AIM]".

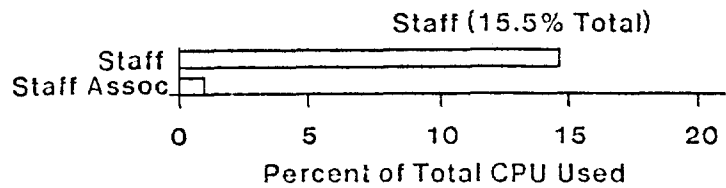
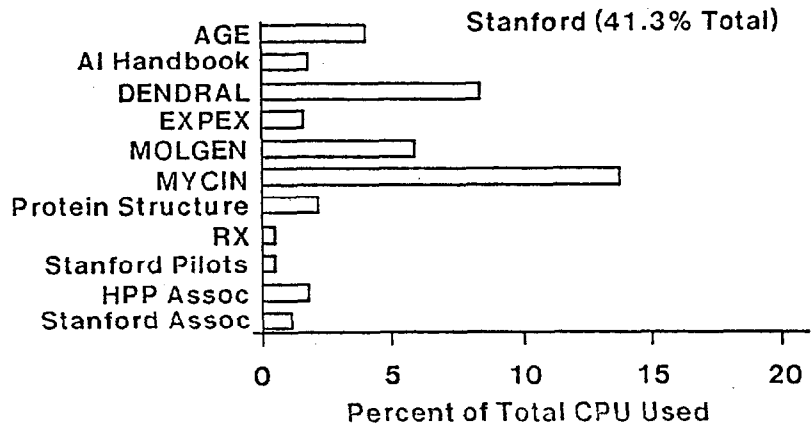
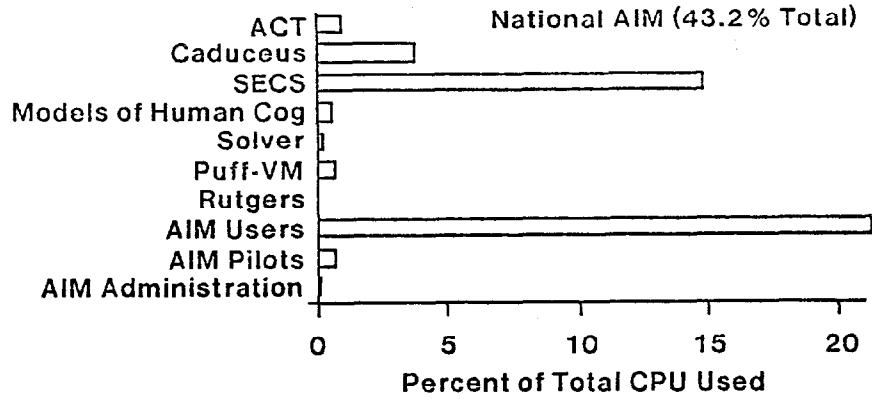


Figure 11. Cumulative CPU Usage Histogram by Project and Community

Resource Use by Individual Project - 5/81 through 4/82

<u>National AIM Community</u>	CPU (Hours)	Connect (Hours)	File Space (Pages)
1) ACT Project "Acquisition of Cognitive Procedures" John R. Anderson, Ph.D. Carnegie-Mellon Univ. NSF IST-80-15357 2/81-2/84 \$186,000	51.46	511.92	2702
2) CADUCEUS "Clinical Decision Systems Research Resource" Jack D. Myers, M.D. Harry E. Pople, Jr., Ph.D. University of Pittsburgh NIH RR-01101-05 7/81-6/82 \$202,632 NLM LM03710-02 7/81-6/82 \$126,746 NLM LM03589-02 Randolph A. Miller, M.D. 7/81-6/82 \$29,555 NLM New Invest LM 03889-01 Gordon E. Banks, M.D. 4/82-3/83 \$35,725	202.29	5471.02	8487
3) CLIPR Project "Hierarchical Models of Human Cognition" Walter Kintsch, Ph.D. Peter G. Polson, Ph.D. University of Colorado NIE-G-78-0172 9/80-8/81 \$46,537 NIMH MH-15872-14-16 7/81-6/82 \$37,370 ONR N00014-78-C-0433 Lyle E. Bourne, Jr., Ph.D. 7/81-6/82 \$78,125 IBM Michael E. Atwood, Ph.D. 1/82-12/82 \$104,000	31.51	725.42	1245

4)	PUFF-VM Project "Biomedical Knowledge Engineering in Clinical Medicine" John J. Osborn, M.D. Med. Research Inst., San Francisco Edward H. Shortliffe, M.D., Ph.D. Stanford University NIH GM-24669 9/78-8/81 \$164,000 (*) Johnson & Johnson 1 year \$50,000 (*)	34.95	1691.57	2751
5)	SECS Project "Simulation & Evaluation of Chemical Synthesis" W. Todd Wipke, Ph.D. U. California, Santa Cruz NIH RR-01059-03S1 7/80-12/81 \$36,949 NIEHS ES 02845-01 4/82-3/83 \$76,444 NIH GM 31173-01 6/82-5/83 \$221,381 (approval pending)	795.25	17123.86	13173
6)	SOLVER Project "Problem Solving Expertise" Paul E. Johnson, Ph.D. William B. Thompson, Ph.D. University of Minnesota NICHD T36-HD-17151 (1978-81) NICHD HD-01136 (1978-81) NSF/BNS-77-22075 (1979-82) NSF SE079-13036 (1981-82) NSF SES-8111295 (1981-83)	9.99	306.05	118
7)	*** [Rutgers-AIM] *** Rutgers Project "Computers in Biomedicine" Saul Amarel, D.Sc. Casimir Kulikowski, Ph.D. Rutgers U., New Brunswick NIH RR-00643 12/81-11/82 \$460,944	1.65	49.08	4358
8)	AIM Pilot Projects AI-COAG (Lindberg) DATA (Brooks) ----- AIM Pilot Totals	.56 36.25 ----- 36.81	55.75 283.01 ----- 338.76	86 1027 ----- 1113

9) AIM Administration	7.83	318.30	3871
10) AIM Users on Stanford Projects			
AGE	.09	.95	9
DENDRAL	105.51	896.34	1253
HPP	2.25	91.77	204
MOLGEN	983.58	8288.61	2012
MYCIN	11.37	428.06	300
AIM-Associates	25.20	732.48	2408
Guest (all projects)	14.50	140.06	380
	-----	-----	-----
AIM User Totals	1142.50	10578.27	6566
	-----	-----	-----
Community Totals	2314.24	37114.25	44384

<u>Stanford Community</u>	CPU (Hours)	Connect (Hours)	File Space (Pages)
1) AGE Project (Core) "Attempt to Generalize" Edward A. Feigenbaum, Ph.D. Dept. Computer Science ARPA MDA903-80-C-0107 (**) (partial support)	212.76	3135.87	3333
2) AI Handbook Project (Core) Edward A. Feigenbaum, Ph.D. Dept. Computer Science ARPA MDA903-80-C-0107 (**) (partial support)	96.25	4746.39	2972
3) DENDRAL Project "Resource Related Research: Computers in Chemistry" Carl Djerassi, Ph.D. Dennis H. Smith, Ph.D. Dept. Chemistry NIH RR-00612-13 5/82-4/83 \$170,710	448.49	8192.73	19913
4) EXPEX Project "Expert Explanation" Edward H. Shortliffe, M.D., Ph.D. Michael R. Genesereth, Ph.D. Depts. Medicine/ Computer Science ONR NR 049-479 1/81-12/83 \$456,622 NCHSR HS 04422 Randy L. Teach 3/81-8/82 \$19,950	84.27	2196.69	1680
5) MOLGEN Project "Computer Sci Application to Molecular Biology" Edward A. Feigenbaum, Ph.D. Bruce G. Buchanan, Ph.D. Laurence H. Kedes, M.D. Douglas L. Brutlag, Ph.D. Peter Friedland, Ph.D. Depts. Computer Science/ Medicine/Biochemistry NSF ECS-8016247 10/81-9/82 \$159,785 (*)	316.39	7417.28	8562

6)	MYCIN Projects	736.59	10591.49	15047
	"Knowledge Engineering for Med. Consultation"			
	Edward H. Shortliffe, M.D., Ph.D.			
	Bruce G. Buchanan, Ph.D.			
	Depts. Medicine/Computer Science			
	ONR/ARPA N00014-79-C-0302			
	3/79-3/82	\$396,325		
	NLM LM-03395 (ONCOCIN)			
	Edward A. Feigenbaum, Ph.D.			
	7/79-6/84	\$497,420		
	NLM LM-00048			
	7/79-6/84	\$196,425		
7)	PROTEIN Project	112.88	1665.96	3990
	"Heuristic Comp. Applied to Prot. Crystallog."			
	Edward A. Feigenbaum, Ph.D.			
	Dept. Computer Science			
	NSF MCS-81-17330			
	1/82-1/83	\$28,976		
8)	RX Project	26.09	1010.03	2299
	"Knowledge from Clinical Databases"			
	Robert L. Blum, M.D.			
	Gio C.M. Wiederhold, Ph.D.			
	Depts. Computer Science/ Electrical Engrg.			
	NLM New Invest LM-03370			
	7/79-6/82	\$90,000		
	NCHSR			
	4/79-3/81	\$35,000		
9)	Stanford Pilot Projects			
	ABARBANEL	2.21	56.78	236
	BRINKLEY	21.95	548.81	763
		-----	-----	-----
	Stanford Pilot Totals	24.16	605.59	999
10)	Stanford and HPP Assoc.	156.41	6802.63	10146
		-----	-----	-----
	Community Totals	2214.29	46364.66	68941

<u>SUMEX Staff</u>	CPU (Hours)	Connect (Hours)	File Space (Pages)
1) Staff	786.11	21146.04	12560
2) System Associates	47.52	1511.57	4123
3) Misc. Usage	.88	11.01	189
	-----	-----	-----
Community Totals	834.51	22668.62	16872

<u>System Operations</u>	CPU (Hours)	Connect (Hours)	File Space (Pages)
1) Operations	2525.35	101687.30	129753
	=====	=====	=====
Resource Totals	7888.39	207834.83	259950

(*) Award includes indirect costs.

(**) Supported by a larger ARPA contract MDA-903-80-C-0107 awarded to the Stanford Computer Science Department:

	Current Year (10/81-9/82)	Total Award (10/79-9/82)
Heuristic Programming Project	\$ 579,070	\$1,613,588
VLSI/CAD Network-based Graphics Development Resource	221,605	685,374
	-----	-----
Total award	\$ 800,675(*)	\$2,298,962(*)

4. Network Usage Statistics

The plots in Figure 12 and Figure 13 show the monthly network terminal connect time for TYMNET and ARPANET. This forms the major billing component for SUMEX-AIM TYMNET usage. The terminal connect time does not reflect the time spent in file transfers and mail forwarding.

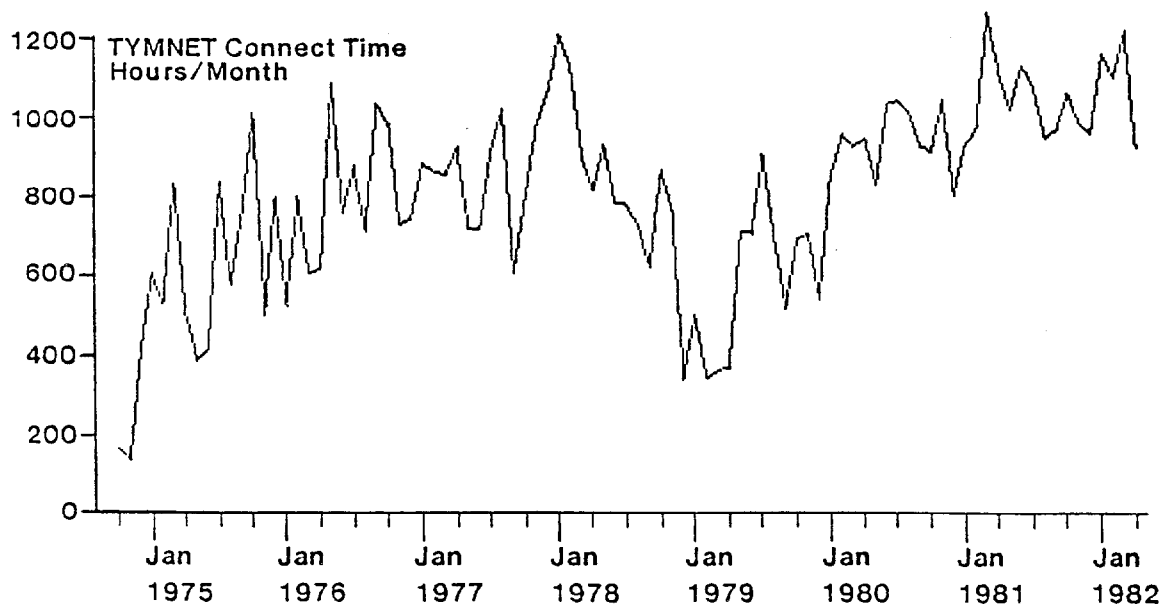


Figure 12. TYMNET Terminal Connect Time

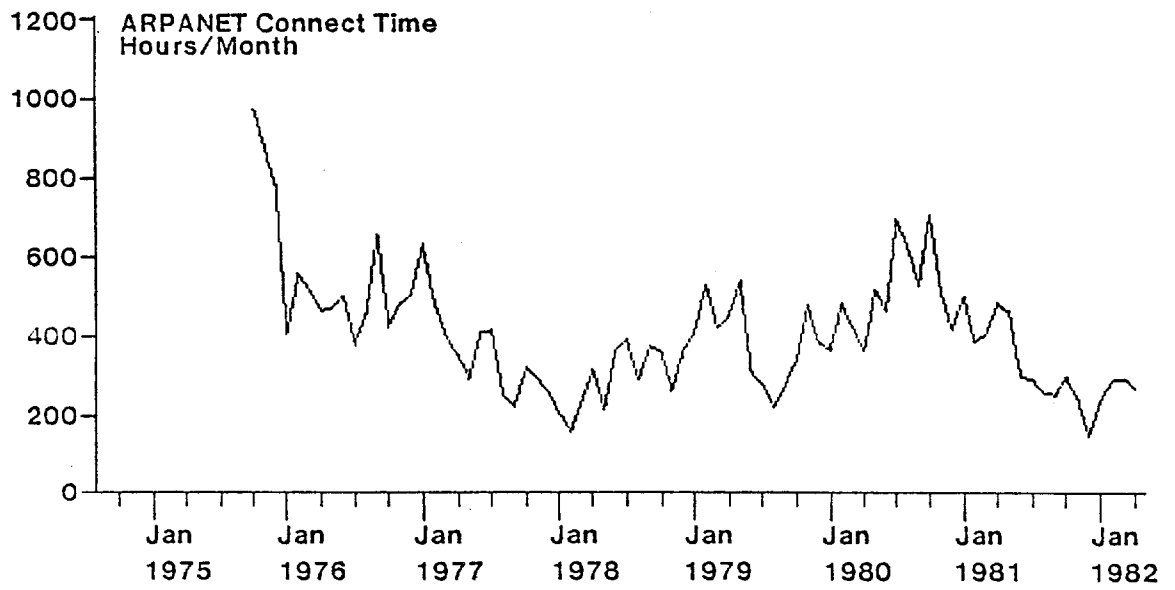


Figure 13. ARPANET Terminal Connect Time

5. System Reliability

System reliability has been very good on average with several periods of particular hardware or software problems. The table below shows monthly downtime for the past year. This includes scheduled maintenance periods, nominally 6 hours per week.

During July and August we experienced a number of serious failures in our Calcomp disk system, induced by poor maintenance practices and parts from Braegen Corporation. In September we switched the maintenance contract for the Calcomp equipment to TRW and have had excellent service and disk reliability since then.

	1981					1982						
	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR
Downtime (Hrs)	44	64	113	100	42	24	13	65	42	32	18	38

TABLE 1. System Downtime by Month

I.A.3.9 SUMEX Staff Publications

The following are publications for the SUMEX staff and include papers describing the SUMEX-AIM resource and on-going research as well as documentation of system and program developments. Many of the publications documenting SUMEX-AIM community research are from the individual collaborating projects and are detailed in their respective reports (see Section II on page 81). Publications for the AGE and AI Handbook core research projects are given there.

- [1] Carhart, R.E., Johnson, S.M., Smith, D.H., Buchanan, B.G., Dromey, R.G., and Lederberg, J., Networking and a Collaborative Research Community: A Case Study Using the DENDRAL Programs, ACS Symposium Series, Number 19, Computer Networking and Chemistry, Peter Lykos (Editor), 1975.
- [2] Levinthal, E.C., Carhart, R.E., Johnson, S.M., and Lederberg, J., When Computers Talk to Computers, Industrial Research, November 1975
- [3] Wilcox, C. R., MAINSAIL - A Machine-Independent Programming System, Proceedings of the DEC Users Society, Vol. 2, No. 4, Spring 1976.
- [4] Wilcox, Clark R., The MAINSAIL Project: Developing Tools for Software Portability, Proceedings, Computer Application in Medical Care, October, 1977, pp. 76-83.
- [5] Lederberg, J. L., Digital Communications and the Conduct of Science: The New Literacy, Proc. IEEE, Vol. 66, No. 11, Nov 1978.
- [6] Wilcox, C. R., Jirak, G. A., and Dageforde, M. L., MAINSAIL - Language Manual, Stanford University Computer Science Report STAN-CS-80-791 (1980).
- [7] Wilcox, C. R., Jirak, G. A., and Dageforde, M. L., MAINSAIL - Implementation Overview, Stanford University Computer Science Report STAN-CS-80-792 (1980).

Mr. Clark Wilcox also chaired the session on "Languages for Portability" at the DECUS DECsystem10 Spring '76 Symposium.

In addition, a substantial continuing effort has gone into developing, upgrading, and extending documentation about the SUMEX-AIM resource, the SUMEX-TENEX system, and the many subsystems available to users. These efforts include a number of major documents (such as SOS, PUB, TENEX-SAIL, and MAINSAIL manuals) as well as a much larger number of document upgrades, user information and introductory notes, an ARPANET Resource Handbook entry, and policy guidelines.

I.A.3.10 Future Plans

Our plans for the next grant year are based on the council-approved plans for our five-year renewal that began in August 1980. In addition to the specific plans for next grant year (discussed in some earlier sections too), we include a summary of the overall objectives for this five-year period to serve as a background. Near and long term objectives and plans for individual collaborating projects are discussed in Section II beginning on page 81.

Overall Goals

The goals of the SUMEX-AIM resource are long term in supporting basic research in artificial intelligence, applying these techniques to a broad range of biomedical problems, experimenting with communication technologies to promote scientific interchange, and developing better tools and facilities to carry on this research. Just as the tone of our renewal proposal derives from the continuing long-term research objectives of the SUMEX-AIM community, our approach derives from the methods and philosophy already established for the resource. We will continue to develop useful knowledge-based software tools for biomedical research based on innovative, yet accessible computing technologies.

For us it is important to make systems that work and are exportable. Hence, our approach is to integrate available state-of-the art hardware technology as a basis for the underlying software research and development necessary to support the AI work. SUMEX-AIM will retain its broad community orientation in choosing and implementing its resources. We will draw upon the expertise of on-going research efforts where possible and build on these where extensions or innovations are necessary. This orientation has proved to be an effective way to build the current facility and community.

We have built ties to a broad computer science community; have brought the results of their work to the AIM users; and have exported results of our own work. This broader community is particularly active in developing technological tools in the form of new machine architectures, language support, and interactive modalities.

Toward a More Distributed Resource

The initial model for SUMEX as a centralized resource was based on the high cost of powerful computing facilities and not being able to duplicate them readily. This role is evolving, though, with the introduction of more compact and inexpensive computing technology. Our future goals are guided by community needs for more computing capacity and improved tools to build more effective expert systems and to test operational versions of AI programs in real-world settings. In order to meet these needs, we must take advantage of a range of newly developing machine architectures and systems. As a result, SUMEX-AIM will become more

a distributed community resource with heterogeneous computing facilities tethered to each other through communications media. Many of these machines will be located physically near the projects or biomedical scientists using them.

We have actively supported proposals from the more mature AIM projects for additional computing facilities tailored to their particular needs and designed to free the main SUMEX resource for new, developing applications projects. To date, the Rutgers resource has acquired a DEC 2060 facility, part of which is allocated for AIM usage; the "Simulation of Cognitive Processes" project has acquired a VAX which supports their needs; and the CADUCEUS project has acquired a VAX to support experimental clinical testing of their program. Our future plans anticipate an even broader diversification of computing resources to meet the need of the AIM community.

The Continuing Role of SUMEX-Central

Even with more distributed computing resources, the central resource will continue to play an important role as a communication crossroads, as a research group devoted to integrating the new software and hardware technologies to meet the needs of medical AI applications, as a spawning ground for new application projects, and as a base for local AI projects. A key challenge will be to maintain the scientific community ties that grew naturally out of the previous colocation within a central facility.

Summary of Five-year Objectives

The long term objectives of the SUMEX-AIM resource nucleus during the follow-on five year period are summarized below. These are broken into three categories; resource operations, training and education, and core research.

Resource Operations

- 1) Maintain the vitality of the AIM community. We will continue to encourage and explore new applications of AI to biomedical research and improve mechanisms for inter- and intra-group collaborations and communications. While AI is our defining theme, we may entertain exceptional applications justified by some other unique feature of SUMEX-AIM essential for important biomedical research. To minimize administrative barriers to the community-oriented goals of SUMEX-AIM and to direct our resources toward purely scientific goals, we plan to retain the current user funding arrangements for projects working on SUMEX facilities. User projects will fund their own manpower and local needs; will actively contribute their special expertise to the SUMEX-AIM community; and will receive an allocation of computing resources under the control of the AIM management committees. There will be no "fee for service" charges for community members. We will also continue to exploit community expertise and sharing in software development; and to facilitate more effective information sharing among projects.
- 2) Provide effective computational support for AIM community goals. We will continue to expand support for artificial intelligence research and new applications work; to develop new computational tools to support more mature projects; and to facilitate testing and research dissemination of nearly operational programs. We will continue to operate and develop the existing central facility as the nucleus of the resource. We will acquire additional equipment to meet developing community needs for more capacity, larger program address spaces, and improved interactive facilities. New computing hardware technologies becoming available now and in the next few years will play a key role in these developments and we expect to take the lead in this community for adapting these new tools to biomedical AI needs.
- 3) Provide effective and geographically accessible communication facilities to the SUMEX-AIM community for effective remote collaborations, communications among distributed computing nodes, and experimental testing of AI programs. We will retain the current ARPANET and TYMNET connections for at least the near term and will actively explore other advantageous connections to new communications networks and to dedicated links.

Training and Education

- 1) Assist new and established projects in the effective use of the SUMEX-AIM resource. Collaborating projects continue to be responsible for the development and dissemination of their own AI programs but the resource staff will provide general support and will work to make resource goals and AI systems known and available to appropriate biomedical scientists. We will continue to exploit particular areas of expertise within the community for developing pilot efforts in new application areas.
- 2) Continue to allocate "collaborative linkage" funds to qualifying new and pilot projects to provide for communications and terminal support pending formal approval and funding of their projects. These funds are allocated in cooperation with the AIM Executive Committee reviews of prospective user projects.
- 3) Continue to support workshop activities including collaboration with the Rutgers Computers in Biomedicine resource on the AIM community workshop and with individual projects for more specialized workshops covering specific application areas or program dissemination.

Core Research

- 1) Continue to explore basic artificial intelligence research issues for knowledge acquisition, representation, and utilization; reasoning in the presence of uncertainty; strategy planning; and explanations of reasoning pathways with particular emphasis on biomedical applications. SUMEX core research funding is complementary to similar funding from other agencies and contributes to the long-standing interdisciplinary effort at Stanford in basic AI research and expert system design. We expect this work to provide the underpinnings for increasingly effective consultative programs in medicine and for more practical adaptations of this work within emerging microelectronic technologies.
- 2) Support community efforts to organize and generalize AI tools that have been developed in the context of individual application projects. This will include work to organize the present state-of-the-art in AI techniques through the AI Handbook effort and the development of practical software packages (e.g., AGE, EMYCIN, UNITS, and EXPERT) for the acquisition, representation, and utilization of knowledge in AI programs. The objective is to evolve a body of software tools that can be used to more easily build future knowledge-based systems and explore other biomedical AI applications.

Specific Plans for Year 10

Specific plans for the next grant year (10) are summarized in the paragraphs below. The directions and background for much of this work were given in earlier progress report sections and are not repeated in detail here.

Hardware Acquisition Plans

Our rationale for future hardware acquisitions is based on a balanced development of the SUMEX-AIM resource along the lines approved by council. As discussed in our progress report and supported by collaborating project reports, we have implemented an effective set of computing resources to support AI applications to biomedical research. Currently at the resource core are the dual KI-TENEX, 2020, shared VAX/UNIX, and Dolphin InterLisp systems, augmented by portions of the Rutgers and Stanford SCORE 2060 machines and the dedicated Caduceus VAX system at the University of Pittsburgh. These have provided an excellent set of tools for SUMEX-AIM development.

As the size of our community and the complexity of knowledge-based programs have increased, several issues have become crucial for the continued development and practical dissemination of AI programs. These have been thoroughly documented in our renewal proposal and previous reports and include the need for more computing capacity, the need for larger user virtual address spaces, and practical facilities to test and disseminate AI systems in the general biomedical community.

No single solution to these requirements for future development is available. We proposed and got peer approval to investigate a variety of machine architectures and approaches over the next grant period including new shared centralized systems, distributed single-user workstations, and improved communications tools to integrate these systems together effectively. Our approach is to integrate a heterogeneous set of network-connected hardware tools, some of which will be distributed through the user community. We will emphasize the development of system and application level software tools to allow effective use of these resources and continue to provide community leadership to encourage scientific communications.

Specific Hardware Plans for Year 10 -- Our equipment plan for year 10 is based on the council-approved grant award and previous experience gained with alternative systems.

Central Resource Upgrade: Having purchased the 5 InterLisp Dolphins last year, we are scheduled to upgrade the central resource this year. In our renewal application, this upgrade was tentatively planned to be a VAX system. However, based on our work during year 09 with using the shared VAX/UNIX system for AI Lisp development (see page 14), we feel the acquisition of additional VAX resources is not the most advantageous for the SUMEX-AIM community.

At the same time, the cost effectiveness of PDP-20 systems has been reemphasized. In addition to their demonstrated high performance and extensive software facilities, there is a growing suite of software that takes advantage of the recently available user version of extended addressing (including Lisp implementations). Thus, with the increasing isolation and expense of our local efforts to continue to develop and maintain the KI-10 system and the long-standing pressing need for more computing capacity in the SUMEX-AIM community, we are planning to upgrade the existing KI-10 system to a large DEC 2060 system. We will submit a plan for approval by the AIM Executive Committee, NIH, and council late this summer.

File Server Development: We began acquisition of initial components of a file server toward the end of year 09, including a VAX 11/750 processor and a starting configuration of non-DEC disks and tapes (see page 16). During year 10 we plan to add additional high capacity disk drives to this central server, accessible over the Ethernet, to help minimize the need for redundant large file systems on individual workstations and host machines.

Other Equipment: As part of the continued operation of the SUMEX-AIM resource, we also plan to buy additional required communications, Ethernet, terminal, interface, and test equipment to support community needs.

Continued Operation of Existing Hardware

The current SUMEX-AIM facilities represent a large existing investment. As indicated above, we plan to upgrade the KI-TENEX system to a 2060 TOPS-20 machine. We do not propose any substantial changes to the other hardware systems (2020, shared VAX, and Dolphins) and we expect them to continue to provide effective community support and serve as a communication nucleus for more distributed resources. The current file shortage will be remedied by access to the community file server, sharable and accessible via the Ethernet.

Communication Networks

Networks have been centrally important to the research goals of SUMEX-AIM and will become more so in the context of increasingly distributed computing. Communication will be crucial to maintain community scientific contacts, to facilitate shared system and software maintenance based on regional expertise, to allow necessary information flow and access at all levels, and to meet the technical requirements of shared equipment.

Long-Distance Connections -- We have had reasonable success at meeting the geographical needs of the community during the early phases of SUMEX-AIM through our ARPANET and TYMNET connections. These have allowed users from many locations within the United States and abroad to gain terminal access to the AIM resources and through ARPANET links to

communicate much more voluminous file information. Since many of our users do not have ARPANET access privileges for technical or administrative reasons, a key problem impeding remote use has been the limited communications facilities (speed, file transfer, and terminal handling) offered currently by commercial networks. Commercial improvements are slow in coming but may be expected to solve the file transfer problem in the next few years. A number of vendors (AT&T, IBM, Xerox, etc.) have yet to announce commercially available facilities but TELENET is actively working in this direction. We plan to continue experimenting with improved facilities as offered by commercial or government sources in the next grant term. We have budgeted for continued TYMNET service and an additional amount annually for experimental network connections.

High-speed interactive terminal support will continue to be a problem since one cannot expect to serve 1200-9600 baud terminals effectively over shared long-distance trunk lines with gross capacities of only 9600-19200 baud. We feel this is a problem that is best solved by distributed machines able to effectively support terminal interactions locally and coupled to other AIM machines and facilities through network or telephonic links. As new machine resources are introduced into the community, we will allocate budgeted funds with Executive Committee advice to assure effective communication links.

Local Intermachine Connections -- A key feature of our plans for future computing facilities is the support of a heterogeneous processing environment that takes advantage of newly available technology and shared equipment resources. The "glue" that links these systems together is a high speed local network. We have chosen Ethernet and the Xerox PUP [9, 12] protocols for these interconnections. This choice was based on the early availability of that technology and the economics of using already developed TENEX and other server software. We expect the Ethernet system to continue to meet our technical needs for the coming grant term and we plan to continue to use it. We are working closely with other groups here at Stanford and elsewhere to share hardware interface and software designs wherever possible.

Our goals are to continue development of the SUMEX-AIM network system including completion of the TIP server, development of a shared printer server for various existing serial printers, implementation of the necessary interface for the new 2060, improvement of the file service facilities between hosts and workstations, and beginning development of an Ethernet TYMNET gateway.

Resource Software

We will continue to maintain the existing system, language, and utility support software on our systems at the most current release levels, including up-to-date documentation. We will also be extending the facilities available to users where appropriate, drawing upon other community developments where possible. We rely heavily on the needs of the user community to direct system software development efforts.

Our plans for upgrading the SUMEX-AIM KI-TENEX system will entail substantial effort to assure smooth user transition to the new system. We will also have to reorient users as different versions of common utility programs run on the TOPS-20 system than under TENEX. Our goals will be to continue to derive as much software as possible from the TOPS-20, UNIX, and workstation user communities but we expect to have to do considerable work to adapt them to our biomedical AI needs.

Within the AIM community we expect to serve as a center for software sharing between various distributed computing nodes. This will include contributing locally developed programs, distributing those derived from elsewhere in the community, maintaining up-to-date information on subsystems available, and assisting in software maintenance.

Community Management

We plan to retain the current management structure that has worked so well, including the newly created GENET Executive Committee which oversees applications in molecular biology (see page 73). We will continue to work closely with the management committees to recruit the additional high quality projects which can be accommodated and to evolve resource allocation policies which appropriately reflect assigned priorities and project needs. We expect the Executive and Advisory Committees to play an increasingly important role in advising on priorities for facility evolution and on-going community development planning in addition to their recruitment efforts. The composition of the Executive committee will grow as needed to assure representation of major user groups and medical and computer science applications areas. The Advisory Group membership rotates regularly and spans both medical and computer science research expertise. We expect to maintain this policy.

We will continue to make information available about the various projects both inside and outside of the community and thereby promote the kinds of exchanges exemplified earlier and made possible by network facilities.

The AIM workshops under the Rutgers resource have served a valuable function in bringing community members and prospective users together. We will continue to support this effort. This summer the AIM workshop will be held at the University of Pittsburgh in conjunction with the American Association of Artificial Intelligence conference. We will continue to assist community participation and provide a computing base for workshop demonstrations and communications. We will also assist individual projects in organizing more specialized workshops as we have done for the DENDRAL and AGE projects.

We plan to continue indefinitely our present policy of non-monetary allocation control. We recognize, of course, that this accentuates our responsibility for the careful selection of projects with high scientific and community merit.

Training and Education Plans

We have an on-going commitment, within the constraints of our staff size, to provide effective user assistance, to maintain high quality documentation of the evolving software support on the SUMEX-AIM system, and to provide software help facilities such as the HELP and Bulletin Board systems. These latter aids are an effective way to assist resource users in staying informed about system and community developments and solving access problems. We plan to take an active role in encouraging the development and dissemination of community knowledge resources such as the AI Handbook, up-to-date bibliographic sources, and developing knowledge bases. Since much of our community is geographically remote from our machine, these on-line aids are indispensable for self help. We will continue to provide on-line personal assistance to users within the capacity of available staff through the SNDMSG and LINK facilities.

We budget funds to continue the "collaborative linkage" support initiated during the first term of the SUMEX-AIM grant. These funds are allocated under Executive Committee authorization for terminal and communications support to help get new users and pilot projects started.

Core Research Plans

SUMEX core research includes both basic AI research and development of community tools useful for building expert systems. Expert systems are symbolic problem solving programs capable of expert-level performance, in which domain-specific knowledge is represented and used in an understandable line of reasoning. The programs can be used as problem solving assistants or tutors, but also serve as excellent vehicles for research on representation and control of diverse forms of knowledge. MYCIN is one of the best examples.

Because the main issues of building expert systems are coincident with general issues in AI, we appreciate the difficulty of proposing to "solve" basic problems. However, we do propose to build working programs that demonstrate the feasibility of our ideas within well defined limits. By investigating the nature of expert reasoning within computer programs, the process is "demystified". Ultimately, the construction of such programs becomes itself a well-understood technical craft.

The foundation of all of our core research work is expert knowledge: its acquisition from practitioners, its accommodation into the existing knowledge bases, its explanation, and its use to solve problems. Continued work on these topics provides new techniques and mechanisms for the design and construction of knowledge-based programs; experience gained from the actual construction of these systems then feeds back both (a) evaluative information on the ideas' utility and (b) reports of quite specific problems and the ways in which they have been overcome, which may suggest some more general method to be tried in other programs.

One of our long-range goals is to isolate AI techniques that are general, to determine the conditions for their use and to build up a knowledge base about AI techniques themselves. SUMEX resources are coordinated for this purpose with the multidisciplinary efforts of the Stanford Heuristic Programming Project (HPP). Under support from ARPA, NIH/NLM, ONR, NSF, and private funding, the HPP conducts research on five key scientific problem areas, as well as a host of subsidiary issues [1]:

- 1) Knowledge Representation - How shall the knowledge necessary for expert-level performance be represented for computer use? How can one achieve flexibility in adding and changing knowledge in the continuous development of a knowledge base? Are there uniform representations for the diverse kinds of specialized knowledge needed in all domains?
- 2) Knowledge Utilization - What designs are available for the inference procedure to be used by an expert system? How can the control structure be simple enough to be understandable and yet sophisticated enough for high performance? How can strategy knowledge be used effectively?
- 3) Knowledge Acquisition - How can the model of expertise in a field of work be systematically acquired for computer use? If it is true that the power of an expert system is primarily a function of the quality and completeness of the knowledge base, then this is the critical "bottleneck" problem of expert systems research.
- 4) Explanation - How can the knowledge base and the line of reasoning used in solving a particular problem be explained to users? What constitutes an acceptable explanation for each class of users?
- 5) Tool Construction - What kinds of software packages can be constructed that will facilitate the implementation of expert systems, not only by the research community but also by various user communities?

Artificial Intelligence is largely an empirical science. We explore questions such as these by designing and building programs that incorporate plausible answers. Then we try to determine the strengths and weaknesses of the answers by experimenting with perturbations of the systems and extrapolations of them into new problem areas. The test of success in this endeavor is whether the next generation of system builders finds the questions relevant and the answers applicable to reduce the effort of building complex reasoning programs.

I.B Highlights

I.B.1 DENDRAL - Computers in Chemistry

The DENDRAL project at Stanford University is one of the founding projects in the SUMEX-AIM community. The roots of its pioneering research can be traced even farther back to the mid-1960's and the interdisciplinary collaboration of principal investigators Profs. Joshua Lederberg (Genetics), Edward Feigenbaum (Computer Science), and Carl Djerassi (Chemistry). DENDRAL is a resource-related research project concerned with symbolic computational techniques to assist with determining topological and stereochemical aspects of organic molecular structures based on information obtained from physical and chemical methods. The project has also worked energetically to disseminate these techniques to a wide community of biochemists.

DENDRAL has gained fame as one of the "classical" research efforts in artificial intelligence and it is worth highlighting its seminal contributions to computer science, chemistry, and the SUMEX-AIM community. DENDRAL was among the very earliest AI projects to point out the now well-established tenet that "knowledge is power". Its effectiveness as a consultant in structural chemistry problems does not derive from a powerful, universal, problem-solving engine. Rather it comes from the large amount of domain specific knowledge it has about the manipulation of molecular structure graphs, mass spectrometry, NMR spectrometry, and other areas of biochemical expertise. Most current AI projects now focus heavily on the issues DENDRAL raised about knowledge acquisition, representation, and utilization. The paradigm of knowledge-based expert systems promoted by DENDRAL research has received wide recognition in the AI literature.

From the viewpoint of the SUMEX-AIM and biochemistry communities, DENDRAL has been a path-finding project as well. It has traversed the full cycle of development from concept to "breadboard" to prototype to operational program, all the while pursuing innovative research on new application areas. The staff of the project has been dedicated to making the DENDRAL programs useful not only in their own laboratory but also to a broader community of biochemists. The significant impact of these programs on the biochemical community can be measured by the large number of productive collaborations that have developed between the DENDRAL staff and other research groups and the more than 20 sites running DENDRAL software.

DENDRAL has worked closely with the SUMEX staff in devising new and effective means for disseminating complex software systems through the various phases of project development. A wide range of approaches has been explored including network access to programs on SUMEX; graduate courses and hands-on workshops at Stanford; reprogramming parts of the system for export to other machine environments and network-accessible systems; and creation of an industrial affiliates group and licensing the programs through Stanford for commercial development, marketing, and maintenance. Similar approaches are now being used effectively by other projects in the community.

I.B.2 CADUCEUS - Diagnostic Assistance in Internal Medicine

For the past 10 years, Dr. Jack Myers has been collaborating with computer scientist Prof. Harry Pople at the University of Pittsburgh on the development of a computer program to assist with complex diagnoses in the broad field of internal medicine. Major achievements of this research using SUMEX-AIM have been the development and experimentation with an early diagnostic program called INTERNIST-I, the on-going design and implementation of an improved program called CADUCEUS, and the development of an extensive medical knowledge base covering many aspects of internal medicine.

INTERNIST-I has been used to analyze many hundreds of difficult diagnostic problems. In most cases, the program has performed at the level of a skilled internist and is one of the most spectacular examples of artificial intelligence applications in biomedicine. It is capable of handling multiple diagnoses of related or independent diseases in a given patient and has been exercised on complex cases published in medical journals (particularly Case Records of the Massachusetts General Hospital, in the New England Journal of Medicine), CPC's, and unusual problems of patients in the University of Pittsburgh Medical Center. Its failures have highlighted areas needing continued research and improvement leading to the refinements in the CADUCEUS program.

The medical knowledge base has continued to grow both in the incorporation of new diseases and the modification of diseases already profiled so as to include recent advances in medical knowledge. The knowledge base now includes 536 individual disease profiles, 3,679 manifestations of disease, and about 1,500 "links" or interrelationships among diseases as well as a myriad of miscellaneous pieces of information which are essential for the correct operation of the system. Twenty-two new diseases have been profiled during the past year and the pediatrics and neurology portions of the knowledge base have continued to grow as well. Approximately 200 additional diseases remain to be programmed and renewed effort in this direction is now being mounted.

Future development plans include continued refinement and testing of the extensive medical knowledge base; completing implementation of the improved program, CADUCEUS; initial clinical testing of CADUCEUS within the University of Pittsburgh and at other university health centers; and adaptation of the program and knowledge base for medical education.

I.B.3 GENET - Computing for Molecular Biology

Since early 1980, the MOLGEN project investigators at Stanford have made a new set of computing tools available to a national community of molecular biologists through a guest facility called GENET on the SUMEX-AIM resource. This experimental sub-community was started by Drs. Kedes, Brutlag, and Friedland in order to broaden MOLGEN's base of scientist collaborators at institutions other than Stanford and to explore the use of a SUMEX-like resource to disseminate sophisticated software tools to a generally computer-naive community. The enthusiastic response to our very limited announcement of this facility has continued to grow so that we have been obliged to place severe restrictions on the scope of services provided.

Since late 1980, we have limited the number of simultaneous GENET users to 2 and have established only a common shared directory among all the users with a very limited file space allocation. Even with such a relatively inhospitable working environment, in 1980-81 the GENET community consumed CPU resources at roughly half the rate of the largest AI research project on SUMEX. This year GENET used almost 50% more resources than the largest AI project! Currently GENET comprises several hundred users from over 60 research institutions.

We have offered three main programs to assist molecular genetics users: SEQ, a DNA-RNA sequence analysis program; MAP, a program that assists in the construction of restriction maps from restriction enzyme digest data; and MAPPER (written and maintained by William Pearson from Johns Hopkins University), a simplified version of the MOLGEN MAP program that is somewhat more efficient than the MOLGEN version. Some of the other more sophisticated programs being developed by MOLGEN research efforts have not been offered because they are not ready for novice users. In addition, the GENET users have had access to the SUMEX-AIM programs for electronic messaging, text editing, file searching, etc.

We have succeeded in the goals set out for GENET to the point that the response has been frankly overwhelming. The SUMEX resource is unable to provide the operational support needed for GENET computing without seriously diminishing the system capacity needed for other AI research. Efforts to expand our own capacity to provide for both communities have not been successful. Over the past year, however, commercial alternatives to the SUMEX GENET service have come into existence. We are therefore in the process of restructuring the GENET activity on SUMEX to reemphasize the computer science research aspect of these applications in molecular biology. A separate GENET Executive Committee has been established to help administer this part of the resource. Strictly production use of the current GENET programs on SUMEX will be discontinued shortly and such users will be assisted in finding alternatives.

I.B.4 Handbook of Artificial Intelligence

The AI Handbook is a compendium of knowledge about the field of Artificial Intelligence. It has been edited by Avron Barr, Paul Cohen, and Edward Feigenbaum at Stanford University, with textual contributions from students and investigators at several other research institutions across the nation. The scope of the work is broad: Hundreds of articles cover most of the important ideas, techniques, and systems developed during 26 years of research in AI. Each short article is a description written for non-AI specialists and students of AI. Additional articles serve as overviews which discuss the various approaches within a subfield, the issues, and the problems.

There is no comparable resource for AI researchers and other scientists and technologists who need access to descriptions of AI techniques and concepts. The research literature in AI is not very accessible. And the elementary textbooks are not nearly broad enough in scope to be useful to a scientist working primarily in another discipline who wants to do something requiring knowledge of AI. Furthermore, we feel that some of the Overview articles are the best critical discussions of activity in the field available anywhere.

The major work of this project is now finished. The Handbook material was completed in April 1982, and has been published in three volumes -- over 1500 pages. Both the first and second volumes of the Handbook have been selected by the Library of Science Book Club as main selections. The chapters also are appearing as Stanford Computer Science Department Technical Reports available through the National Technical Information Service. Work continues on developing a convenient mechanism for on-line access to the Handbook material. When that software is completed, the Handbook text will be available for browsing by the SUMEX-AIM community.

The AI Handbook Project was undertaken as a core activity by SUMEX in the spirit of community building that is the fundamental concern of the resource. We feel that the organization and propagation of this kind of information to the AIM community, as well as to other fields where AI is being applied, is a valuable service that we are uniquely qualified to support. The Handbook articles are a good example of community collaboration using the SUMEX-AIM communication facilities to prepare, review, and disseminate this reference work on AI techniques. All of our authors and reviewers have had access to these files via the network facilities and use the document-editing and formatting programs available at SUMEX. This relatively small investment of resources has resulted in what we feel is a seminal publication in the field of AI -- of particular value to researchers, like those in the AIM community, who want quick access to AI ideas and techniques for application in other areas.

The three volume Handbook was published by Wm. Kaufmann, Inc., Los Altos, California. Volume I appeared in May 1981, and Volumes II and III appeared in June 1982.

I.B.5 Professional Workstations - A First Step

One of the most exciting prospects of the coming decade in computing is the development of professional workstations. These may have a profound impact on biomedicine by serving as the vehicle for the practical export of expert artificial intelligence systems into the hands of the physician, chemist, biologist, engineer, or other users. The essential concept of these machines is simple -- a large-address-space, high-performance, microcoded processor tuned to the Lisp programming language; a high-speed, high-resolution graphics display station for convenient human interactions; a local disk; a local area network interface; and well-human-engineered software all compactly packaged and priced for the professional office environment. These systems differ from the popularly available microprocessor systems in terms of their specialization and performance to support large-address Lisp programs that form the core of AI research and in their use of large-format, bit-mapped graphics displays.

Several research Lisp machines have become available during this past year. SUMEX has acquired and integrated 5 Xerox Dolphin InterLisp workstations into the computing environment at Stanford so research projects could begin work on the important software issues facing us in order to exploit personal computing environments for AI systems. Much systems work on Ethernet services has been done to make the Dolphins work smoothly and effectively in our existing facility. This has been shared widely with other research groups outside of Stanford in order to broaden and assist the growing user community. Research has also begun on moving the ONCOCIN, MOLGEN, AGE, and GUIDON systems to run on the Dolphins with promising early results. Shortly, one of the SUMEX Dolphins will be installed at Rutgers to enable researchers there to begin exploring its potential for biomedical AI systems.

Still newer research Lisp machines that extend current capabilities in performance, Lisp dialects and software systems supported, and cost-effectiveness will become available in the next years. By the mid-1980's, we expect a much broader availability of such systems for use by biomedical professionals in general.

I.C Administrative Changes

There have been no significant administrative changes in the SUMEX-AIM resource this past year.

I.D Resource Management and Allocation

The mission of SUMEX-AIM, locally and nationally, entails both the recruitment of appropriate research projects interested in medical AI applications and the catalysis of interactions among these groups and the broader medical community. User projects are separately funded and autonomous in their management. They are selected for access to SUMEX on the basis of their computer and biomedical scientific merits as well as their commitment to the community goals of SUMEX. Currently active projects span a broad range of application areas such as clinical diagnostic consultation, molecular biochemistry, molecular genetics, belief systems modeling, mental function modeling, and instrument data interpretation (descriptions of the individual collaborative projects are in Section II beginning on page 81).

I.D.1 Management Committees

Since the SUMEX-AIM project is a multilateral undertaking by its very nature, we have created several management committees to assist in administering the various portions of the SUMEX resource. As defined in the SUMEX-AIM management plan adopted at the time the initial resource grant was awarded, the available facility capacity is allocated 40% to Stanford Medical School projects, 40% to national projects, and 20% to common system development and related functions. Within the Stanford aliquot, Prof. Feigenbaum and BRP have established an advisory committee to assist in selecting and allocating resources among projects appropriate to the SUMEX mission. The current membership of this committee is listed in Appendix D.

For the national community, two committees serve complementary functions. An Executive Committee oversees the operations of the resource as related to national users and makes the final decisions on authorizing admission for new projects and revalidating continued access for existing projects. It also establishes policies for resource allocation and approves plans for resource development and augmentation within the national portion of SUMEX (e.g., hardware upgrades, significant new development projects, etc.). The Executive Committee oversees the planning and implementation of the AIM Workshop series currently implemented under Prof. S. Amarel of Rutgers University and assures coordination with other AIM activities as well. The committee will play a key role in assessing the possible need for additional future AIM community computing resources and in deciding the optimal placement and management of such facilities. The current membership of the Executive committee is listed in Appendix D.

Reporting to the Executive Committee, an Advisory Group represents the interests of medical and computer science research relevant to AIM goals. The Advisory Group serves several functions in advising the Executive Committee; 1) recruiting appropriate medical/computer science projects, 2) reviewing and recommending priorities for allocation of

resource capacity to specific projects based on scientific quality and medical relevance, and 3) recommending policies and development goals for the resource. The current Advisory Group membership is given in Appendix D.

This past spring, the AIM Executive Committee authorized the establishment of a GENET Executive Committee to oversee the management of the now significant portion of the national portion of SUMEX allocated to molecular biology. The committee was established by NIH/BRP for this purpose and to advise BRP more generally in the management and long term planning of molecular biology support. The membership of the GENET Executive Committee is given in Appendix D. Its first task is to redirect the GENET resources from production use of the DNA sequence mapping programs that have grown so popular toward new computer science research for molecular biology is now underway.

These committees have actively functioned in support of the resource. Except for the meetings held during the AIM workshops, the committees have "met" by messages, net-mail, and telephone conference owing to the size of the groups and to save the time and expense of personal travel to meet face to face. The telephone meetings, in conjunction with terminal access to related text materials, have served quite well in accomplishing the agenda business and facilitate greatly the arrangement of meetings. Other solicitations of advice requiring review of sizable written proposals are done by mail.

We will continue to work with the management committees to recruit the additional high quality projects which can be accommodated and to evolve resource allocation policies which appropriately reflect assigned priorities and project needs. We will continue to make information available about the various projects both inside and outside of the community and thereby promote the kinds of exchanges exemplified earlier and made possible by network facilities.

I.D.2 New Project Recruiting

The SUMEX-AIM resource has been announced through a variety of media as well as by correspondence, contacts of NIH-BRP with a variety of prospective grantees who use computers, and contacts by our own staff and committee members. The number of formal projects that have been admitted to SUMEX has more than trebled since the start of the project to a current total of 7 national AIM projects and 8 Stanford projects. Others are working tentatively as pilot projects or are under review.

We have prepared a variety of materials for the new user ranging from general information such as is contained in a SUMEX-AIM overview brochure to more detailed information and guidelines for determining whether a user project is appropriate for the SUMEX-AIM resource. A questionnaire is available to assist users seriously considering applying for access to

SUMEX-AIM. Pilot project categories have been established both within the Stanford and national aliquots of the facility capacity to assist and encourage new projects in formulating possible AIM proposals and pending their application for funding support. Pilot projects are approved for access for limited periods of time after preliminary review by the Stanford or AIM Advisory Group as appropriate to the origin of the project. More recently we have established a category of "associates" representing both US and international groups working on their own machines on problems relevant to the SUMEX-AIM community and seeking more direct communication with SUMEX-AIM investigators. Associate community members are approved by the AIM Executive Community.

These contacts have sometimes done much more than provide support for already formulated programs. For example, Prof. Feigenbaum's group at Stanford previously initiated a major collaborative effort with Dr. Osborn's group at the Institutes of Medical Sciences in San Francisco. This project in "Pulmonary Function Monitoring and Ventilator Management - PUFF/VM" (see page 194) originated as a pilot request to use MLAB in a small way for modeling. Subsequently the AI potentialities of this domain were recognized by Feigenbaum, Nii, and Osborn and a joint proposal was submitted to and funded by NIH. Similarly, Prof. Feigenbaum and Ms. Nii have worked directly with Profs. Kintsch and Polson at the University of Colorado, introducing them to the newly developed AGE package for use in formulating their program on modeling aspects of human cognition.

A list of the fully authorized projects currently comprising the SUMEX-AIM community can be found with brief abstracts in Appendix C on page 277. More detailed descriptions of collaborative project activities can be found in Section II.

As an additional aid to new projects or collaborators with existing projects, we provide a limited amount of funds for use to support terminals and communications needs of users without access to such equipment. We are currently providing support for 6 terminals and 4 modems for users as well as a leased line between Stanford and the University of California at Santa Cruz for the Chemical Synthesis project.

I.D.3 Stanford Community Building

The Stanford community has undertaken several internal efforts to encourage interactions and sharing between the projects centered here. Professor Feigenbaum organized a project with the goal of assembling a handbook of AI concepts, techniques, and current state-of-the-art. This project has had enthusiastic support from the students and recently completed publication of volumes II and III of the 3 volume handbook set (see page 92 for more details).

Weekly informal lunch meetings (SIGLUNCH) are also held between community members to discuss general AI topics, concerns and progress of

individual projects, or system problems as appropriate. In addition, presentations from a substantial number of outside speakers are invited.

I.D.4 Existing Project Reviews

We have conducted a continuing careful review of on-going SUMEX-AIM projects to maintain a high scientific quality and relevance to our medical AI goals and to maximize the resources available for newly developing applications projects. At meetings of the AIM Advisory Group and Executive Committee this past year, all the national AIM projects were reviewed. These groups recommended continued access for most formal projects on the system. However, they recommended that the GENET effort be guided toward developing new computer science applications in molecular biology rather than continuing production use of the current DNA sequence analysis programs.

I.D.5 Resource Allocation Policies

As the SUMEX facility has become increasingly loaded, a number of diverse and conflicting demands have arisen which require controlled allocation of critical facility resources (file space and central processor time). Our policy for file space management starts with an allocation of file storage, defined for each authorized project in conjunction with the management committees. This allocation is divided among project members in any way desired by the individual principal investigators. System enforcement of project allocations is carried out each week. As the weekly file dump is done, if the aggregate space in use by a project is over its allocation, files are archived from user directories over allocation until the project is within its limits.

We have also implemented effective system scheduling controls to attempt to maintain the 40:40:20 balance in terms of CPU utilization and to avoid system and user inefficiencies during overload conditions. The initial complement of user projects justifying the SUMEX resource was centered to a large extent at Stanford. Since then, a substantial relative growth in the number of national projects was realized and in practice the 40:40 split between Stanford and non-Stanford projects is fairly well realized (see Figure 8 on page 37 and the tables of recent project usage on page 40).

Our job scheduling controls bias the allocation of CPU time based on percent time consumed relative to the time allocated with the 40:40:20 community split. The controls are "soft" however in that they do not waste computer cycles if users below their allocated percentages are not on the system to consume the cycles. In early years, the operating disparity in CPU use reflected a substantial difference in demand between the Stanford

community and the developing national projects, rather than inequity of access. For example, the Stanford utilization is spread over a large part of the 24-hour cycle, while national-AIM users tended to be more sensitive to local prime-time constraints. (The 3-hour time zone phase shift across the continent is of substantial help in load balancing.) During peak times under the overload control system reported previously, the Stanford community experienced mutual contentions and delays while the AIM group has relatively open access to the system.

This disparity in usage has disappeared in recent years though with the growth of the national user community and we enabled overload controls for the national community as well. For the present, we propose to continue our policy of "soft" allocation enforcement for the fair split of resource capacity.

Our system also categorizes users in terms of access privileges. These comprise fully authorized users, pilot projects, associates, guests, and network visitors in descending order of system capabilities. We want to encourage bona fide medical and health research people to experiment with the various programs available with a minimum of red tape while not allowing unauthenticated users to bypass the advisory group screening procedures by coming on as guests. So far we have had relatively little abuse compared to what other network sites have experienced, perhaps on account of the personal attention that senior staff gives to the logon records, and to other security measures. However, the experience of most other computer managers behooves us to be cautious about being as wide open as might be preferred for informal service to pilot efforts and demonstrations. We will continue developing this mechanism in conjunction with management committee policy decisions.

We have also encouraged mature projects to apply for their own machine resources in order to preserve the SUMEX-AIM resource for research and development efforts and to support projects unable to justify their own machines. The Rutgers resource has their own machine, part of which is allocated for AIM use, and the CADUCEUS project has installed a VAX machine to support their planned development and program testing work. Also Profs. Lesgold and Greeno's "Simulation of Cognitive Processes" project has moved to their own local VAX.

I.E Dissemination Efforts

Throughout its existence, SUMEX-AIM has devoted substantial efforts toward disseminating information about its activities as a resource and about the work of individual collaborative projects. We continue to make many presentations at professional meetings, to provide services to demonstrate developed AI programs for interested groups and individuals, to welcome visitors, and to work in organizing workshops within the SUMEX-AIM community to introduce our work to collaborating professional communities. We have also spent substantial efforts in the past working with the Research Resources Information Center to produce the "Seeds of Artificial Intelligence" monograph and other publications and press articles to address a broader community of technical and lay people.

Of special note, in addition to these general dissemination activities, is the development of the GENET molecular biology community:

GENET Background

The MOLGEN project at Stanford (see page 128) has focused on applications of artificial intelligence and symbolic computation to the field of molecular biology. The research began in 1975 and is currently working under a three year grant renewal. In early 1980 it was realized that some of the systems developed by MOLGEN were of direct utility to many scientists in the domain. Accordingly, with the cooperation of the SUMEX-AIM staff and close coordination with the AIM Executive Committee, it was decided in February 1980 to provide a carefully limited guest service for the community use of such systems.

There were two major reasons for the establishment of this guest service, which took the form of the GENET account on SUMEX. The first was to broaden MOLGEN's base of scientist collaborators, to find molecular biologists at institutions other than Stanford who could contribute actively to our knowledge-based approach to problem solving. The second was to introduce a generally computer-naive community to the benefits of resource sharing provided by a system like SUMEX, with the hope of serving as a model for the dissemination of other AI software and possibly for an eventual resource for molecular biology.

We believe that we have succeeded in these two goals. Many of our GENET guests have become active collaborators in core MOLGEN research. These collaborators include Professor Allan Maxam at Harvard Medical School, Dr. Walter Goad at Los Alamos, Dr. Richard Roberts at Cold Spring Harbor, Dr. William Pearson at Johns Hopkins, Drs. Walter Bodmer, Julia Bodmer, and Robert Kamen at the Imperial Cancer Research Fund, Dr. Andrew Taylor at University of Oregon, and Dr. Dan Davison of SUNY-Stonybrook. We are also pleased by the numerous comments SUMEX has received from GENET users praising the user-sensitive nature of the resource, especially in comparison to typical university computer centers.

GENET has been important both for MOLGEN and for the national community of molecular biology. It has ensured a steady flow of ideas for

the artificial intelligence research that is core to both the MOLGEN grant and the SUMEX-AIM mission. It has also provided a useful service to an international community that has not been readily available elsewhere.

GENET Community Management

Our decision to support the GENET guest experiment and our approach to doing so within the SUMEX-AIM resource has been reviewed and approved both by the AIM Executive Committee and by the Initial Review Group/National Advisory Research Resources Council in the course of the peer review of our latest SUMEX renewal application. We have tried to manage the GENET guest experiment in such a way that we maintain the "friendly" interface of the SUMEX-AIM resource for molecular biologists unfamiliar with computers while taking appropriate steps so that GENET usage does not detract from on-going AI research and so that we assure prudent administration SUMEX as an NIH-BRP resource. The key elements in our management approach include:

- 1) Controlled announcement of the GENET opportunity -- Beginning in February 1980, the availability of GENET services was announced, primarily by talks at professional conferences with accompanying program demonstrations. We decided against publishing "blanket" announcements in professional journals in order to maintain a very high standard of collaborator interest and scientific expertise within the limited group we could serve with available SUMEX resources.
- 2) Close coordination with the AIM Executive Committee -- We kept the AIM Executive Committee apprised of plans for the GENET experiment and of progress and growth of the community. At the August 1980 AIM Workshop meeting of the Executive Committee, Professor L. Kedes of the MOLGEN project made a presentation on the status of GENET. The Executive Committee approved continuation of the GENET service but because of the significant growth in the number of GENET users and their consumption of CPU resources, a limit of two simultaneous GENET jobs was placed on the community. The Executive Committee also approved the concept of a proposed Molecular Biology Computing Resource related to but separate from the existing SUMEX resource.
- 3) Careful control of GENET usage -- We have closely monitored the very rapid growth in GENET usage of SUMEX (see data below). With Executive Committee advice and in cooperation with the MOLGEN project personnel managing the GENET community, we have instituted several successively stringent controls on GENET users:
 - a) All GENET users run out of the same directory so scheduler control limits are enforced to hold GENET usage as a whole down relative to that of AI research projects during heavy loads.
 - b) The GENET directory has been intentionally limited in disk space allocation so that large numbers of files cannot be retained.

- c) Starting in October 1980, a limit of two simultaneous logged-in GENET jobs was placed on the community.
 - d) Starting in December 1980, a policy statement was issued restricting GENET use to academic collaborators. MOLGEN project management informed industrial collaborators that they could no longer use the GENET facility and actively monitored adherence to this policy. Previously, valuable feedback had been obtained from a small group of industrial collaborators for MOLGEN AI program development. However, with the rapid growth of the highly competitive molecular genetics industry, there was no way we could adequately control industrial users consistent with SUMEX's status as a federally funded national resource. Thus, we decided to exclude them. In April 1981, we instituted a GENET user password checking system to further control community access, particularly in regard to industrial users.
- 4) Limited commitment of SUMEX staff resources -- The day to day management of the GENET community has been the responsibility of MOLGEN project personnel. SUMEX personnel have only contributed to developing system facilities to help manage GENET (guest and GENET password capabilities), assisted with technical communications problems, and advised in establishing GENET management policies consistent with AIM Executive Committee and SUMEX Principal Investigator resource policies. The total commitment of staff time has been on the order of 1-2 man-months.
 - 5) Creation of the GENET Executive Committee -- With all of the previous limitations on the GENET community, its usage continued to grow to the point of dominating AI research use on the national side. Since previous efforts to establish a separate national resource for molecular biology were not funded and alternative services have started becoming available commercially, the AIM Executive Committee authorized establishing a GENET Executive Committee to manage the use of the GENET aliquot of SUMEX and to advise NIH/BRP more broadly on developing support for research in molecular biology. This committee has met and is now formulating a plan to remove the production use of SUMEX by GENET and to reallocate these resources to new computer science developments for the molecular biology community.

Scope of the GENET User Community

The GENET community consists of approximately 200-300 users from 63 research institutions. Of these users, approximately 35 are consistently active users. That is, they log in, run programs, and interact with the MOLGEN members on an almost daily basis. Many of these users have made valuable contributions to our work. About 100 others are frequent, but not regular users. They log in only when they have a major analysis task to perform, which seems to be on the order of once a month.

The remaining users rarely use the system. They have logged in a few times, but for one reason or another they never become regular users of the system. Quite often this is because a lab group will settle on having one or two graduate students or post-doctoral associates become the "computer experts" of the group, and as a result, the computer use by the other people in the lab drops to an almost non-existent level. Unfortunately, an equally prevalent reason for users to stop using the GENET account is a lack of resource time. Probably the major complaint that we get from GENET users is concerning the lack of compute time and availability of the system. One account just is not enough for that many people to share, especially when it is restricted to 2 jobs at one time. We constantly remind the GENET users to use their resources wisely. We encourage them to use the BATCH system to run job in the wee hours of the morning, and we remind them to be prepared to do their work quickly when they log in to the system, but their efforts do not seem to help the problem very much.

Most GENET users use only a small set of programs. These consists of text editors, which are used to set up the data files that for the MOLGEN analysis programs; XSEARCH, which GENET users use to effectively search through our database for sequences that can assist them in their research; and the electronic mail facilities. Very few of our GENET users actually feel comfortable using programs other than the ones that we maintain, not because the other programs would not be useful, but instead because the users do not have the computer time to experiment with what is available.

There are three note-worthy programs that we provide for GENET users that are used extensively. SEQ, a DNA-RNA sequence analysis program, is the most widely used. MAP, a program that assists in the construction of restriction maps from restriction enzyme digest data, is also used a great deal. Finally, a new program, MAPPER (written and maintained by William Pearson from Johns Hopkins University), is a simplified version of the MOLGEN MAP program that is somewhat more efficient than the MOLGEN version.

The MOLGEN UE program and special molecular genetics knowledge bases are not available to the general GENET user at this time for two reasons. First of all, the UE program is quite costly to use (in terms of computer cycles), and secondly, we feel that the knowledge base is not quite ready for the computer novice to learn and use without a significant amount of initial assistance. A few GENET users (mostly Stanford associates) that have had a significant interest in the knowledge base have become EXO-MOLGEN users and are developing knowledge bases on their own which we hope will eventually be added to the ones that MOLGEN is developing and maintaining.

GENET Usage Statistics

Following are plots of the monthly GENET CPU usage, connect time, and file usage data. The consumption of CPU time has continued to grow despite our rather stringent controls as seen in Figure 14. In fact, the cumulative GENET usage this past year is approximately 50% higher than the largest AI research project consumer as seen in Figure 11.

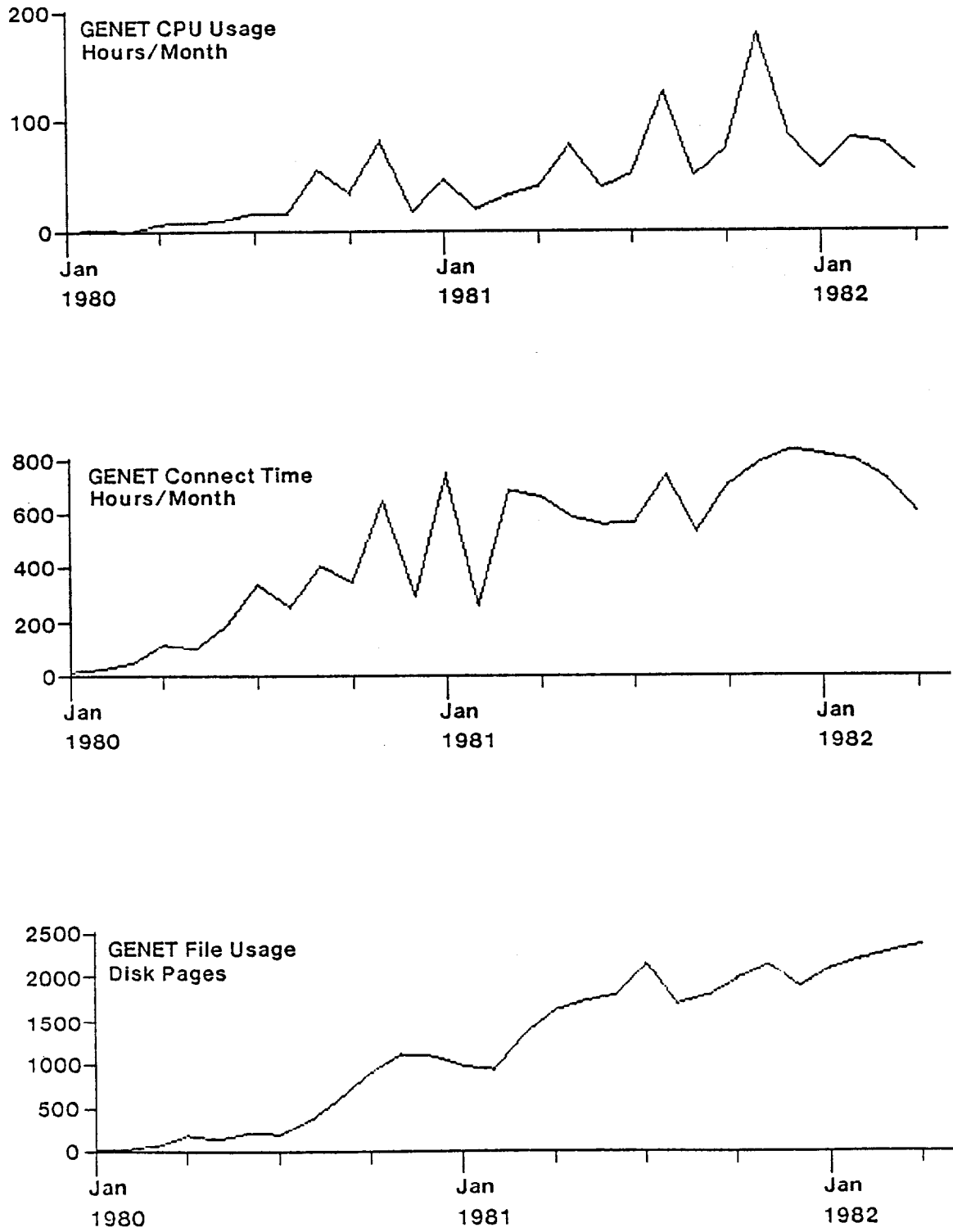


Figure 14. Monthly Resource Usage by GENET Community

I.F Comments on the Biotechnology Resources ProgramResource Organization

We continue to believe that the Biotechnology Resources Program is one of the most effective vehicles for developing and disseminating technological tools for biomedical research. The goals and methods of the program are well-designed to encourage building of the necessary multi-disciplinary groups and merging appropriate technological and medical disciplines. In our experience with the SUMEX-AIM resource, several elements of this approach seem to emerge as key to the development and management of an effective resource:

- 1) Effective Management Framework - there needs to be an explicit agreement between the BRP and the resource principal investigator that sets out a clear mandate for the resource and its allocation, provides worthwhile incentives for the host institution and investigator to invest the necessary substantial professional career time to develop and manage the resource, and ensures equitable distribution of resource services to its target community.
- 2) Close Working Relationship with NIH - a resource is a major and often long-term investment of money and human energy. A close and mutually supportive working relationship between resource management, its advisory committees, and the NIH administration is essential to assure healthy development of the resource and its relationship to its user community. We at SUMEX-AIM have benefited immensely from such a relationship with Dr. William R. Baker, Jr. in the evolution of the SUMEX-AIM community.
- 3) Freedom to Explore Resource Potential - a resource, by its nature, operates at the "cutting edge" in developing its characteristic technology and learning how to effectively disseminate it to the biomedical community at large. BRP should not impose artificial constraints on the resource for commercializing its efforts (fees for service) or developing its potential (funding duration limits or annual budget ceilings). Such artificial policy impositions can serve to undermine the very goals central to BRP's reason for existence. Satisfactory policies in this regard have been worked out recently and should be retained.

Electronic Communications

SUMEX-AIM has pioneered in developing more effective methods for facilitating scientific communication. Whereas face to face contacts continue to play a key role, in the longer term we feel that computer-based communications will become increasingly important to NIH and the biomedical community. We would like to see BRP take a more active role in promoting these tools within NIH and its grantee community. A concrete step would be to become a sponsoring agency for the ARPANET which remains the most effective means for a very broad spectrum of services to promote good

communications. This could serve as a base for interconnecting sponsored machines and offering a broader range of services and promoting broader collaboration among the biomedical community at large.

II Description of Scientific Subprojects

II.A Scientific Subprojects

The following subsections report on the AIM community of projects and "pilot" efforts including local and national users of the SUMEX-AIM facility at Stanford. Those using the Rutgers-AIM facility are annotated with "[Rutgers-AIM]". In addition to these detailed progress reports, we have included briefer summary abstracts of the fully authorized projects in Appendix C on page 277.

The collaborative project reports and comments are the result of a solicitation for contributions sent to each of the project Principal Investigators requesting the following information:

I. SUMMARY OF RESEARCH PROGRAM

- A. Project rationale
- B. Medical relevance and collaboration
- C. Highlights of research progress
 - Accomplishments this past year
 - Research in progress
- D. List of relevant publications
- E. Funding support (see details below)

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

- A. Medical collaborations and program dissemination via SUMEX
- B. Sharing and interactions with other SUMEX-AIM projects
 - (via computing facilities, workshops, personal contacts, etc.)
- C. Critique of resource management
 - (community facilitation, computer services, communications services, capacity, etc.)

III. RESEARCH PLANS (8/80-7/86)

- A. Project goals and plans
 - Near-term
 - Long-range
- B. Justification and requirements for continued SUMEX use
- C. Needs and plans for other computing resources beyond SUMEX-AIM
- D. Recommendations for future community and resource development

We believe that the reports of the individual projects speak for themselves as rationales for participation; in any case the reports are recorded as submitted and are the responsibility of the indicated project leaders.

II.A.1 Stanford Projects

The following group of projects is formally approved for access to the Stanford aliquot of the SUMEX-AIM resource. Their access is based on review by the Stanford Advisory Group and approval by Professor Feigenbaum as Principal Investigator.

II.A.1.1 AGE - Attempt to Generalize

AGE - Attempt to Generalize

H. Penny Nii and Edward A. Feigenbaum
Computer Science Department
Stanford University

ABSTRACT: Isolate inference, control, and representation techniques from previous knowledge-based programs; reprogram them for domain independence; write an interface that will help a user understand what the package offers and how to use the modules; and make the package available to other members of the AIM community and labs doing knowledge-based programs development, and the general scientific community.

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The general goal of the AGE project is to demystify and make explicit the art of knowledge engineering. It is an attempt to formulate the knowledge that knowledge engineers use in constructing knowledge-based programs and put it at the disposal of others in the form of a software laboratory.

The design and implementation of the AGE program is based primarily on the experience gained in building knowledge-based programs at the Stanford Heuristic Programming Project in the last decade. The programs that have been, or are being, built are: DENDRAL, meta-DENDRAL, MYCIN, HASP, AM, MOLGEN, CRYALIS [Feigenbaum 1977, 1980], and SACON [Bennett 1978]. Initially, the AGE program will embody artificial intelligence methods and techniques used in these programs. However, the long-range aspiration is to integrate those developed at other AI laboratories. The final product is to be a collection of building-block programs combined with an "intelligent front-end" that will assist the user in constructing knowledge-based programs. It is hoped that AGE will speed up the process of building knowledge-based programs and facilitate the dissemination of AI techniques by: (1) packaging common AI software tools so that they need not be reprogrammed for every problem; and (2) helping people who are not knowledge engineering specialists write knowledge-based programs.

B. Medical Relevance and Collaboration

AGE is relevant to the SUMEX-AIM Community in two ways: as a vehicle for disseminating cumulated knowledge about the methodologies of knowledge engineering and as a tool for reducing the amount of time needed to develop knowledge-based programs.

(1). Dissemination of Knowledge: The primary strategy for conducting AI research at the Stanford Heuristic Programming Project is to build

complex programs to solve carefully chosen problems and to allow the problems to condition the choice of scientific paths to be explored. The historical context in which this methodology arose and summaries of the programs that have been built over the last decade at HPP are discussed in [Feigenbaum 1977, 1980]. While the programs serve as case studies in building a field of "knowledge engineering," they also contribute to a cumulation of theory in representation and control paradigms and of methods in the construction of knowledge-based programs.

The cumulation and concomitant dissemination of theory occur through scientific papers. Over the past decade we have also cumulated and disseminated methodological knowledge. In Computer Science, one effective method of disseminating knowledge is in the form of software packages. Statistical packages, though not related to AI, are one such example of software packages containing cumulated knowledge. AGE is an attempt to make yesterday's "experimental technique" into tomorrow's "tool" in the field of knowledge engineering.

(2). Speeding up the Process of Building Knowledge-based Programs: Many of the programs built at HPP are intelligent agents to assist human problem solving in tasks of significance to medicine and biology (see separate sections for discussions of work and relevance). Without exception the programs were handcrafted. This process often takes many years, both for the AI scientists and for the experts in the field of collaboration.

AGE will reduce this time by providing a set of preprogrammed inference mechanisms and representational forms that can be used for a variety of tasks. Close collaboration is still necessary to provide the knowledge base, but the system design and programming time of the AI scientists can be significantly reduced. Since knowledge engineering is an empirical science, in which many programming experiments are conducted before programs suitable for a task are produced, reducing the programming and experimenting time would significantly reduce the time required to build knowledge-based programs.

C. Highlights of Research Summary

The plans made in 1976 for the AGE project included the construction of two systems. The development of the first of these systems, AGE-1, was officially concluded on October 31, 1981. The system, together with documentation, is now available for use.

Much of the year was spent in activities related to releasing AGE-1. The most time-consuming activity was finishing the documentation. Most of the knowledge specification editors and debugging facilities were rewritten to improve the user interface. In addition, several new features were added in the area of data input protocols and focussing mechanisms.

The current user interface is directed at teletype-like terminals; that is, terminals where information is presented linearly in a single window. For a complex system that has many inter-related components that

need to be specified and manipulated (such as AGE-1), this mode of interaction makes the system appear more complex than it is. We rewrote most of the user interface to alleviate many of the problem encountered by users in the past, but there are many problems that cannot be solved without moving to another medium of communication. With this motivation, we began our experiment in using multiple windows on the bit-map display of the Dolphin. The version of AGE-1 on the Dolphin is called AGE-1.5 -- the only difference from AGE-1 is the user interface protocols. (It should be noted that moving AGE, which was optimized for a time-sharing system, to a personal computer took several weeks.)

Our plans to begin the design of AGE-2 was postponed until 1982 (see Future Research section).

D. Publications

Nii, H. Penny and Aiello, Nelleke, "AGE: a knowledge-based program for building knowledge-based programs," Proc. of IJCAI-6, pp. 645-655, vol. 2, 1979.

Nii, H. Penny, "An Introduction to Knowledge Engineering, Blackboard Model, and AGE," HPP Working Paper, HPP-80-29.

Aiello, N. and Nii, H.P., "The Joy of AGE-ing: A User's Guide to AGE-1," October 31, 1981.

Aiello, N., Bock, C., Nii, H.P., White, W., "AGE Reference Manual," October 31, 1981.

AGE Example Series 1: "BOWL: A Beginner's Program."

AGE Example Series 2: "AGEPUFF: A Simple Event-Driven Program."

II. INTERACTION WITH THE SUMEX-AIM RESOURCES

AGE Availability

Currently AGE-1 is available on the PDP-10 at the SUMEX-AIM Computing Facility and on the PDP-20/60 at the SCORE Facility of the Computer Science Department. A tape of the compiled system that will run with Tenex or Tops-20 operating systems is available for a taping fee. The current implementation is described briefly in a later section.

Summary Description of AGE-1

Currently Implemented Tools: AGE-1 provides the user with a set of preprogrammed modules called "components". Using different combinations of these program modules, the user can build a variety of programs that display different problem-solving behavior. AGE-1 also provides a user interface modules can help the user in constructing and specifying the details of the components. A component is a collection of functions and

variables that support conceptual entities in program form. For example, production rule, as a component, consists of: (1) a rule interpreter that support the syntactic and semantic description of production-rule representation as defined in AGE, and (2) various strategies for rule selection and execution.

The components in AGE-1 have been carefully selected and modularly programmed to be useable in combinations. For those users not familiar enough to experiment with combining the components, AGE-1 provides the user two predefined configuration of components -- each configuration is called a "framework". One framework, called the Blackboard framework, is for building programs that are based on the Blackboard model [Lesser 77]. Blackboard model uses the concepts of a globally accessible data structure called a "blackboard", and independent sources of knowledge which cooperate to form hypotheses. The Blackboard model has been modified to allow flexibility in representation, selection, and utilization of knowledge. The other framework, called the Backchain framework, is for building programs that use backward-chained production rules as its primary mechanism of generating inferences.

The Front-End: To support the user in the selection, specification, and use of the components, AGE-1 is organized around four major subsystems that interact in various ways. Surrounding it is a system executive that allows the user access to these subsystems, as well as other user facilities, through menu selection. Figure 1. shows the general interrelationship among these subsystems.

The Design subsystems helps to familiarize the user with AGE-1 and to guide the user in the construction of his programs through the use of predefined frameworks. The second subsystem is a collection of interface modules that help the user specify the various components of the framework. The other subsystems are designed for testing and refining the user program. Each of the subsystem is described in more detail below:

DESIGN: The function of the DESIGN subsystem is to guide the user in the design and construction of his program through the use of predefined configuration of components, or framework. Each framework is defined in DESIGN-SCHEMA, a data structure in the form of AND/OR tree, that, on one hand, represents all the possible configuration of components within the framework; and, on the other hand, represents the decisions the user must make in order to design the details of the user program. Using this schema, the DESIGN subsystem guides the user from one design decision point to another. At each decision point, the user has access to the "help" file and also to advice regarding design decisions at that point. An appropriate ACQUISITION module can be invoked from the DESIGN subsystem so that general design and implementation specifications can be accomplished simultaneously.

ACQUISITION: For each component that the user must specify, there is a corresponding specification editor module that queries the user for task-specific information. The calling sequence of the acquisition module is guided by DESIGN-SCHEMA when the user is using the DESIGN subsystem. They can also be accessed directly from the system executive or Interlisp.

INTERPRETER: This subsystem contains several modules that help the user run and debug his program. The Check module checks for the completeness and correctness of the specification for an entire framework. For any error found, the system can call an appropriate editor to fix the error. The Interpreter executes the user program. The Trace and Break modules are run-time debugging aids. The Editor, Check, Trace, Break, and the Explanation (described below) modules are designed to complement each other, and to help the user observe the workings of his program and to make corrections as necessary.

EXPLANATION: AGE-1 has enough information to replay its execution steps, and it has reasonable justifications for the actions taken within the various frameworks. AGE-1 provides a trace-back explanation facility whereby questions related to the execution history can be answered by the system interactively. However, AGE is totally ignorant of the user's task domain and has no means of conducting a dialogue about the specifics of the domain. A detailed history of the execution steps is available to the user to build his own domain specific explanation, if necessary.

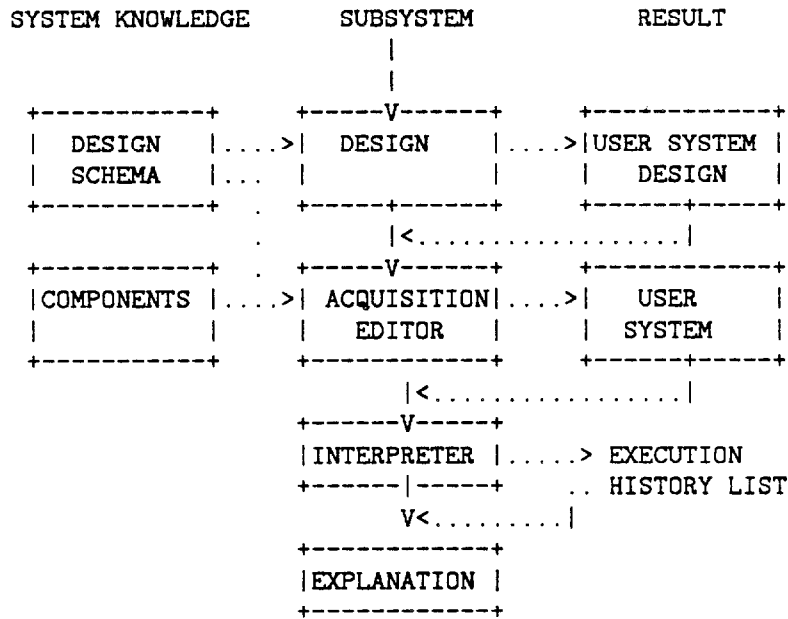


Figure 1. AGE System Organization
 (... = data flow; --- = control flow)

III. RESEARCH PLAN

The primary objective of the AGE Project was, and continues to be, to see if a software laboratory could be built to speed up the process of building Expert Systems. This task was subdivided into two major subtasks:

--tool building: to isolate inference, control, and representation techniques used in other Expert Systems and reprogram them for domain independence; and

--user interface: to build an intelligent front-end to guide the user in the use of the tools.

The strategy for the tool-building task was to take paradigms with a history of successful applications, decompose them into more or less independent parts, and reprogram them. The first paradigm to be thus decomposed and reimplemented was the Blackboard model as used in HASP and CRYSLIS. Currently, AGE-1 contains components for building programs that use a rule-based blackboard model, backward-chained rules, Units, and any combination of the three. In each decomposed components we tried to extend and/or generalize; for example, in AGE-1, the user can define separate methods to deal with uncertainty for different kinds of knowledge.

The task of intelligent front-end for AGE was further broken down into two stages based on different types of users:

--Stage 1 Task: Build a system usable by an AI scientist or knowledge engineer who knows Lisp and the production rule representation of knowledge; who is familiar with methods of building knowledge-based systems; and who wants to use AGE to avoid coding basic system components and to try different problem-solving techniques with minimum recoding.

--Stage 2 Task: Build a system for a person who has a good working knowledge of AI, but who is not familiar with building Expert Systems and needs guidance on what techniques to use.

AGE-1 is a Stage 1 system. AGE-2 is to be a system directed at novice knowledge engineers. Determining the shape of AGE-2 and implementing it involves a variety of research tasks described below.

FUTURE WORK

There are many difficulties encountered by the users of AGE-1. Ninety per cent of the difficulties can be attributed to complexity of the system. It contains many design options, the consequences of which the average user does not understand, nor needs to understand for many of the applications. (It should be noted that most people interested in systems like AGE at this point in time are novice knowledge engineers.) This difficulty is compounded by the need to specify and view many interrelated parts of the user program in a linear presentation.

Solving the first problem involves research in the design aspects of Expert Systems. Although AGE-1 can be used to design many different kinds of Expert Systems, the current Design module is minimal. It is minimal in two aspects: (1) it only keeps track of parts that need to be specified and what has been specified, with some suggestion on what part to work on next; and (2) it only knows about the design of programs based on blackboard

model and that of backward chained rules. This Design module needs to be replaced by one that can help the user match his problem characteristics with appropriate combination of AGE component codes and concepts. This leads to a difficult task of doing knowledge engineering on knowledge engineers. To do this, the current components will have to be re-represented in a uniform manner, and rules written to match aspects of user problem with AGE facilities. The immediate bottleneck is in representing parts of AGE which involve the description of interrelated processes.

The more immediately doable task is to replace the linear aspect of program specification (including knowledge acquisition) by using the graphic facilities available on the Dolphins. Before any changes can be made to AGE-1, it must be brought up on a Dolphin and various system maintenance facilities implemented. This is currently being done. The system on Dolphin with the AGE-1 internals and a multi-dimensional user interface will be called AGE-1.5.

AGE-1.5

In the current AGE System, as in most other expert system building tools, knowledge is acquired from the user serially. The user is asked questions and types in the answers. In general the user works on one part of his system at a time, and must exit the current editor or acquisition module to examine or look at another part of his system.

The questions in AGE are friendly and mostly self-explanatory, requiring minimum intervention or aid from the knowledge engineer. However the serial nature of the questions does cause a bottleneck. For experienced users the questions and prompts frequently become annoying and seem to get in the way of productive work. This is true in spite of the fact that the experienced user sees an abbreviated version of explanations, comments, questions, and prompts.

To ease this problem and speed up the knowledge acquisition process, our plan is to add graphic capabilities to AGE. Using Interlisp-D on a Dolphin, we will implement menu selection, windows and screen editors, and possibly, graphic display of blackboard contents. For information which can best be acquired using serial questions, menu selection will allow the user to select the proper answer with the touch of a button. (This is much faster than typing in enough of the correct response to ambiguate it from other possible answers.) We intend to display windows showing some of each component of the user's system. Again, by a touch of a (mouse) button, the user will be able to scroll a particular window to look at specific information, if it is not already visible. These windows will also be available to trace the execution of the user's program, with the relevant, changing information in each component visible in the window at any particular time. Finally, a screen editor will be implemented to allow the user to edit information in a window or move information between windows.

The window package in AGE will be designed to allow for experimentation with the sizes and locations of various windows. Tests will be conducted to compare AGE-1 and the graphic AGE-1.5 to show that the

graphics capabilities significantly improve the knowledge acquisition process. By improve we mean both to shorten the duration of the acquisition process and to improve its palatability. Similar experiments will be used to determine the most efficient layout of the windows in the graphic AGE system.

AGE-2

AGE-2 will try to address the second of the research tasks described above.

Although the current Design subsystem provides specification functions that allow the user to interactively specify the knowledge of the domain and the control structure, it does not (aside from simple advise) provide the user any help in the actual design process. For example, AGE should be able to provide some aids to the user on what kinds of inference mechanisms and representations are appropriate for his application problem. We have stated this problem in our previous reports without any promising ideas on how we might attack this problem. With the variety of feedbacks we received from our experimental users, we now understand a few of the problems the inexperienced users are faced with. With these in mind, we have begun, and will continue, to explore ways in which we can redesign and add facilities that will help users who are not familiar with knowledge engineering techniques and methodologies.

One of the major obstacles in the way of AGE-2 development is the way in which AGE-1 is implemented. Although the syntax of AGE-1 is clearly defined (see the Reference Manual), the semantics are not well-defined. They are defined in ad hoc fashion in the Editor, the Interpreter, and the Check modules. In order for AGE-2 to be able to conduct a dialogue about itself with the user, its semantics, as well as its syntax, must be uniformly represented. Since very little research results are available in the area of representing the semantics of systems (one exception is in the automatic programming research), we need to experiment with a variety of approaches. We have already begun to look into some alternative representations. In changing the representation of the AGE system, no new components will be added, and minimum amount of changes will be made to the definition of the existing components.

Concurrent with re-representing the AGE system, we will identify a dozen or so framework, in addition of the existing two, that have simpler constructs and are easier for the novice users to understand. The simplicity will be achieved by providing less options for the user -- options which, because of their nature, are confusing to new users. Limiting the degrees of freedom for the user has the side benefit of allowing AGE to provide more specific description and aids. For example, in a very constrained framework we can provide a library of "standard" predicates for the users, which can have associated with them English translations; with such texts available the rules and the back-trace explanation can be printed in English-like form. Once the user is comfortable with the more simple frameworks, he can add complexity simply by replacing the predefined options selected for the frameworks.

AGE-2 design will not begin until AGE-1.5 is further along and until we have more data points on how AGE-1 and AGE-1.5 are used.

Computing Resources and Management

We believe the computing and communication resources provide by the SUMEX Facility is one of the best in the country. The management is responsive to the needs of the research community and provides superb services. However, the system is getting to a point where no serious research and development is possible, because of the lack of computing cycles due to overcrowding. It is a compliment to the facility that there are so many users. On the other hand, our productivity has gone down in recent months, because of the heavy load on the system. It would appear that the situation will not improve on its own, since many of the projects that were small a few years ago are maturing into larger, more complex systems. Which is the way it should be. The environment in which the work is done also needs to grow. In short, without augmentation to the current computing power and storage space (which had never been generous), our ability to make research progress at SUMEX will be drastically curtailed.

II.A.1.2 AI Handbook Project

Handbook of Artificial Intelligence

E.A. Feigenbaum, A. Barr, and P. Cohen
Stanford Computer Science Department

I. SUMMARY OF RESEARCH PROGRAM

A. Technical Goals

The AI Handbook is a compendium of knowledge about the field of Artificial Intelligence. It has been edited by Avron Barr, Paul Cohen, and Edward Feigenbaum, with textual contributions from students and investigators at several research facilities across the nation. The scope of the work is broad: Hundreds of articles cover most of the important ideas, techniques, and systems developed during 26 years of research in AI. Each short article is a description written for non-AI specialists and students of AI. Additional articles serve as Overviews, which discuss the various approaches within a subfield, the issues, and the problems.

There is no comparable resource for AI researchers and other scientists and technologists who need access to descriptions of AI techniques and concepts. The research literature in AI is not very accessible. And the elementary textbooks are not nearly broad enough in scope to be useful to a scientist working primarily in another discipline who wants to do something requiring knowledge of AI. Furthermore, we feel that some of the Overview articles are the best critical discussions of activity in the field available anywhere.

To indicate the scope of the Handbook, we have included an outline of the articles as an appendix to this report (see page 269).

B. Medical Relevance and Collaboration

The AI Handbook Project was undertaken as a core activity by SUMEX in the spirit of community building that is the fundamental concern of the facility. We feel that the organization and propagation of this kind of information to the AIM community, as well as to other fields where AI is being applied, is a valuable service that we are uniquely qualified to support.

C. Progress Summary

The major work of this project is now finished. The Handbook material was completed in April, 1982, and has been published in three volumes--over 1500 pages. The chapters also are appearing as Stanford Computer Science Department Technical Reports available through the National Technical Information Service. Work continues on developing a convenient mechanism for on-line access to the Handbook material. When

that access software is completed, the Handbook text will be available for browsing by the SUMEX community.

Both the first and second volumes of the Handbook have been selected by the Library of Science Book Club as main selections.

D. List of Relevant Publications

"The Handbook of Artificial Intelligence, Volume I," Avron Barr and Edward A. Feigenbaum, Eds., William Kaufmann, Inc., Los Altos, California, May 1981.

"The Handbook of Artificial Intelligence, Volume II," Avron Barr and Edward A. Feigenbaum, Eds., William Kaufmann, Inc., Los Altos, California, June 1982.

"The Handbook of Artificial Intelligence, Volume III," Paul Cohen and Edward A. Feigenbaum, Eds., William Kaufmann, Inc., Los Altos, California, June 1982.

Many of the chapters of Volumes I and II of the AI Handbook have already appeared in preliminary form as Stanford Computer Science Technical Reports, authored by the respective chapter-editors. References follow. Chapters from Volume III will appear as Technical Reports in the summer and fall of 1982.

HPP-79-12 (STAN-CS-79-726)
Ann Gardner. Search.

HPP-79-17 (STAN-CS-79-749)
William Clancey, James Bennett, and Paul Cohen.
Applications-oriented AI Research: Education.

HPP-79-21 (STAN-CS-79-754)
Anne Gardner, James Davidson, and Terry Winograd.
Natural Language Understanding.

HPP-79-22 (STAN-CS-79-756)
James S. Bennett, Bruce G. Buchanan, and Paul R. Cohen.
Applications-oriented AI Research: Science and Mathematics.

HPP-79-23 (STAN-CS-79-757)
Victor Ciesielski, James S. Bennett, and Paul R. Cohen.
Applications-oriented AI Research: Medicine.

HPP-79-24 (STAN-CS-79-758)
Robert Elschlager and Jorge Phillips. Automatic Programming.

HPP-80-3 (STAN-CS-80-793)
Avron Barr and James Davidson. Representation of Knowledge.

E. Funding Support Status

The Handbook Project is partially supported under the Heuristic Programming Project contract with the Advanced Research Projects Agency of the DOD, contract number MDA903-80-C-0107, E. A. Feigenbaum, Principal Investigator and under the core research activities of the SUMEX-AIM resource.

II. INTERACTIONS WITH SUMEX-AIM RESOURCE

A. Collaborations and Medical Use of Programs via SUMEX

We have had a modest level of collaboration with a group of students and staff at the Rutgers resource, as well as occasional collaboration with individuals at other ARPA net sites.

B. Sharing and Interactions with Other SUMEX-AIM Projects

As described above, we have had moderate levels of interaction with other members of the SUMEX-AIM community, in the form of writing and reviewing Handbook material. During the development of this material, arrangements were made for sharing the emerging text. The published material will also be made available to the community as an on-line resource.

C. Critique of Resource Management

Our requests of the SUMEX management and systems staff, requests for additional file space, directories, systems support, or program changes, have been answered promptly, courteously and competently, on every occasion.

III. RESEARCH PLANS (8/80 - 7/83)

A. Long Range Project Goals

During 1982, all material will be published. The on-line access program will continue under development.

B. Justifications and Requirements for Continued SUMEX Use

The AI Handbook Project is a good example of community collaboration using the SUMEX-AIM communication facilities to prepare, review, and disseminate this reference work on AI techniques. The Handbook articles currently exist as computer files at the SUMEX facility. All of our authors and reviewers have had access to these files via the network facilities and have used the document-editing and formatting programs available at SUMEX. This relatively small investment of resources has resulted in what we feel is a seminal publication in the field of AI, of particular value to researchers who want quick access to AI ideas and techniques for application in other areas.

C. Needs and Plans for Other Computational Resources

We use document preparation programs at SUMEX and the Computer Science Department's SCORE machine. We have used and will continue to use a Computer Science Department phototypesetting machine, the Alphatype, to produce the final copy of the AI Handbook. The phototypesetting software called TEX, developed at Stanford, is the vehicle for this production.

The on-line access program will be written as a SUMEX systems resource.

D. Recommendations for Future Community and Resource Development

None.

II.A.1.3 DENDRAL ProjectThe DENDRAL Project
Resource-Related Research: Computers in ChemistryProf. Carl Djerassi
Department of Chemistry
Stanford UniversityI. SUMMARY OF RESEARCH PROGRAM

The DENDRAL Project is a resource-related research project. The resource to which it is related is SUMEX-AIM, which provides DENDRAL its sole computational resource for program development and dissemination to the biomedical community.

A. Project Rationale

The DENDRAL project is concerned with the application of state-of-the-art computational techniques to several aspects of structural chemistry. The overall goals of our research are to develop and apply computational techniques to the procedures of structural analysis of known and unknown organic compounds based on structural information obtained from physical and chemical methods and to place these techniques in the hands of a wide community of collaborators to help them solve questions of structure of important biomolecules. These techniques are embodied in interactive computer programs which place structural analysis under the complete control of the scientist working on his or her own structural problem. Thus, we stress the word assisted when we characterize our research effort as computer-assisted structure elucidation or analysis.

Our principal objective is to extend our existing techniques for computer assistance in the representation and manipulation of chemical structures along two complementary, interdigitated lines. We are developing a comprehensive, interactive system to assist scientists in all phases of structural analysis (SASES, or Semi-Automated Structure Elucidation System) from data interpretation through structure generation to data prediction. This system will act as a computer-based laboratory in which complex structural questions can be posed and answered quickly, thereby conserving time and sample. In a complementary effort we are extending our techniques from the current emphasis on topological, or constitutional, representations of structure to detailed treatment of conformational and configurational stereochemical aspects of structure.

By meeting our objectives we will fill in the "missing link" in computer assistance in structural analysis. Our capabilities for structural analysis based on the three-dimensional nature of molecules is an absolute necessity for relating structural characteristics of molecules to their observed biological, chemical or spectroscopic behavior. These

capabilities will represent a quantum leap beyond our current techniques and open new vistas in applications of our programs, both of which will attract new applications among a broad community of structural chemists and biochemists who will have access to our techniques. This access depends entirely on our access to and the continued availability of SUMEX-AIM. These issues are discussed in detail in the subsequent section, Interactions with the SUMEX-AIM Resource.

The primary rationale for our research effort is that structure determination of unknown structures and the relationship of known structures to observed spectroscopic or biological activity are complex and time-consuming tasks. We know from past experience that computer programs can complement the biochemist's knowledge and reasoning power, thereby acting as valuable assistants in solving important biomedical problems. By meeting our objectives we feel strongly that our programs will become essential tools in the repertoire of techniques available to the structural biochemist.

We are currently beginning the third year of our three year grant. This period represents a transition in the sense that we have pushed our research efforts in techniques for spectral interpretation, structure generation (e.g., CONGEN) and spectral prediction to their limits within the confines of topological representations of molecular structure. At this time, these techniques are perceived to be of significant utility in the scientific community as evidenced by our workshops, the demand for the exportable version of CONGEN and the number of persons requesting collaborative or guest access to our programs at Stanford (see Interactions with the SUMEX-AIM Resource). These existing techniques will, for some years to come, remain as important first steps in solving structural problems. However, in order to anticipate the future needs of the community for programs which are more generally applicable to biological structure problems and more easily accessible we must address squarely the limitations inherent in existing approaches and search for ways to solve them. Our major objectives are based on the following rationale.

None of our techniques (or the techniques of any other investigators) for computer-assisted structure elucidation of unknown molecular structures make full use of stereochemical information. As existing programs were being developed this limitation was less important. The first step in many structure determinations is to establish the constitution of the structure, or the topological structure, and that is what CONGEN, for example, was designed to accomplish. However, most spectroscopic behavior and certainly most biological activities of molecules are due to their three-dimensional nature. For example, some programs for prediction of the number of resonances observed in ¹³CMR spectra use the topological symmetry group of a molecule for prediction. However, in reality it is the symmetry group of the stereoisomer that must be used. This group reflects the usually lower symmetry of molecules possessing chiral centers and which generally exist in fewer than the total possible number of conformations. This will increase the number of carbon resonances observed over that predicted by the topological symmetry group alone. More generally, few of the techniques in the area of computer-assisted structure elucidation can be used in

accurate prediction of structure/property relationships, whether the properties be spectral resonances or biological activities.

A structure is not, in fact, considered to be established until its configuration, at least, has been determined. Its conformational behavior may then be important to determine its spectroscopic or biological behavior. For these reasons we are emphasizing in our current grant period development of stereochemical extensions to CONGEN, our newly-developed structure generator, GENOA (see References 17, 18), and related programs such as the C-13 Nuclear Magnetic Resonance (NMR) programs (see References 15, 16, 19-23), including machine representations and manipulations of configuration (see References 1, 10) and conformation (see Reference 19, 24, 26) and constrained generators for both aspects of stereochemistry (see References 6, 9, 11, 12).

None of the existing techniques for computer-assisted structure elucidation of unknown molecules, excepting very recent developments in our own laboratory, are capable of structure generation based on inferred partial structures which may overlap to any extent. Such a capability is a critical element in a computer-based system, such as we propose, for automated inference of substructures and subsequent structure generation based on what is frequently highly redundant structural information including many overlapping part structures. Important elements of our research are concerned with further developments of such a capability for structure generation (the GENOA program, (see Reference 17)).

Given the above tools for structure representation and generation, we can consider new interpretive and predictive techniques for relating spectroscopic data (or other properties) to molecular structure (see References 2, 3, 7, 8, 14, 15, 16, 19-23). The capability for representation of stereochemistry is required for any comprehensive treatment of: 1) interpretation of spectroscopic data (see References 15, 16, 19-23); 2) prediction of spectroscopic data (see References 15, 16, 19-23); 3) induction of rules relating known molecular structures to observed chemical or biological properties (see Reference 19, 24, 26). These elements, taken together, will yield a general system for computer-aided structural analysis (the SASES system) with potential for applications far beyond the specific task of structure elucidation.

Parallel to our program development we have embarked on a concerted effort to extend to the scientific community access to our programs, and critical parts of our research effort are devoted to methods for promoting this resource sharing. Our rationale for this effort is that the techniques must be readily accessible in order to be used, and that development of useful programs can only be accomplished by an extended period of testing and refinement based on results obtained in analysis of a variety of structural problems, analyzed by those scientists actively involved in solutions to those problems. Our efforts in this area are summarized in Section II.A, Scientific Collaboration and Program Dissemination).

B. Medical Relevance and Collaboration

The medical relevance of our research lies in the direct relationship between molecular structure and biological activity. The sciences of chemistry and biochemistry rest on a firm foundation of the past history of well-characterized chemical structures. Indeed, structure elucidation of unknown compounds and the detailed investigation of stereochemical configurations and conformations of known compounds are absolutely essential steps in understanding the physiological role played by structures of demonstrated biological activity. Our research is focussed on providing computational assistance in several areas of structural chemistry and biochemistry, with primary attention directed to those aspects of the problem which are most difficult to solve by strictly manual methods. These aspects include exhaustive and irredundant generation of constitutional isomers, and configurational and conformational stereoisomers under chemical, biological and spectroscopic constraints with a guarantee that no plausible stereoisomer has been overlooked.

Although our programs can be applied to a variety of structural problems, in fact most applications by our group and by our collaborators are in the area of natural products, antibiotics, pheromones and other biomolecules which play important biochemical roles. In discussions of collaborative investigations involved with actual applications of our programs we have always stressed the importance of strong links between the structures under investigation and the importance of such structures to health-related research. This emphasis can be seen by examination of the affiliations of current DENDRAL-related investigators and the brief description of current collaborative efforts in Interactions with the SUMEX-AIM Resource.

C. Highlights of Research Progress

In this section we discuss briefly some major highlights of the past year and research currently in progress.

1. Past Year

1.1 Programs for Interpretation and Prediction of Spectral Data.
We are actively pursuing several novel approaches to the automated interpretation of spectral data, concentrating on carbon-13 magnetic resonance (CMR), proton magnetic resonance (PMR) and mass spectral (MS) data. These approaches utilize large data bases of correlations between substructural features of a molecule and spectral signatures of such features. Our approaches are unique in that: 1) we can incorporate stereochemical features of substructures into the data bases; and 2) we can use the same data bases for both interpretation and prediction of data.

For either interpretation or prediction of magnetic resonance data, stereochemical substructure descriptors are absolutely essential. Resonance positions are a strong function of the local environment of a resonating atom, including position in space relative to other neighboring atoms. Descriptors which include the three dimensional relationships among

atoms in a substructure are required in order to obtain meaningful correlations. We now have programs for the interpretation (see References 15,19,21,23), prediction (see references 15,19-21), and assignment (see Reference 22) of carbon-13 nuclear magnetic resonance spectra which make use of an expanded carbon-13 NMR data base. We have completed preliminary work on a program for prediction of proton NMR spectra. All these programs use a structure and substructure representation which incorporates configurational stereochemistry (see reference 16) and make use of data bases.

Such data bases can be used to interpret spectral data to obtain substructures to be used in CONGEN and GENOA, the structure generating programs (see References 15, 17). Continued automation of this aspect of structure elucidation will significantly ease the burden on the structural biochemist because the computer-based files are much more comprehensive and easier to use than correlation tables or diffuse literature sources. The same data bases can be used to predict spectral signatures in the context of a set of complete molecular structures. Comparison of predicted and observed spectra allows a rank-ordering of candidates and will be very useful in directing the attention of the investigator to the most plausible alternatives (see References 7, 8, 15, 20).

1.2 Improvement in the GENOA program for structure generation with overlapping atoms. A significant improvement has been made to experimental versions of GENOA which remove the requirement that a fixed molecular formula be used. This allows a researcher to investigate problems in which this information is unknown. Instead of a fixed composition, a range of compositions is allowed. This program, named RANGEN, will be useful for less specified problems and in particular to the problem of designing molecules (see section 2.1 below).

1.3 Extension of treatment of stereochemistry to include conformations. A computer program has been designed and written which provides a unique (canonical) designation for a conformation of a chemical structure or substructure based on earlier theoretical work (see Reference 24). This program takes as input a structure with 3-dimensional coordinates or cruder conformation designations and gives as output a structure or substructure with a unique conformation designation. Each rotatable bond can have discrete designations which represent a range of torsional angle positions of arbitrary fineness. This program represents a significant step in filling the final "missing link" in our structure representation.

1.4 Molecular Modelling and Graphics. In the past year we have purchased a Megatek Whizzard 7210 vector refresh graphics system and software necessary to interface with our programs and the SUMEX computer system. We have written a program called BUILD3D (see reference 25) which takes as input an augmented (with configurational stereochemistry) connection table representation of a chemical structure and gives as output three-dimensional coordinates. These are converted to a picture on the screen of the Megatek. This picture can be rotated, translated, etc. on the terminal locally with no need of the host computer therefore not adding

to the load on SUMEX. In addition the Megatek is interfaced directly to the SUMEX 2020 rather than the more heavily loaded dual PDP-10 system. This graphics/software package, while not a major research result in itself, represents a significant improvement in the ease of use of our programs.

2. Research in Progress

The following are some highlights of research in progress. The common theme of these studies is representation of stereochemistry and use of stereochemical information in answering questions concerning the nature of known or unknown molecular structures.

2.1 Structure Design. We have frequently pointed out that while our computer programs (CONGEN, GENOA, etc.) are designed to be used for chemical structure elucidation, much of the software and code could find use in the problem of structure design. In a crude sense the problems differ only in that the design problem will generally require more than one molecular formula to start with and is expected to have more than a single structure as an "answer" or result. We have resolved the first difference with the RANGEN program which permits a range of molecular formulas (section 1.2 above). We are continuing work on the latter problem of dealing with the imposition of constraints efficiently (particularly geometric constraints) and the unmanageably large number of structures which usually result in problems of this kind. As has been our practice in the past, we are progressing with this program development while working on a real problem of biomedical significance, in this case the design of GABA (gamma-amino butyric acid) analogues. We hope to both contribute to software development and augment the list of GABA analogues by this effort.

2.2 Representation and manipulation of conformational stereochemistry. Intense efforts will continue to augment our programs to include conformational information in the structure representation. Our new programs for specification of conformational structures or substructures (section 1.3 above) will be further developed and integrated into our existing computer programs. Our efforts to generate conformations with constraints will also continue. Amongst the various alternative approaches we have chosen to proceed on this difficult problem by using the method of distance geometry. This appears to be a computationally tractable approach which can ensure an exhaustive and irredundant generation, the same standards achieved in our earlier structure generation programs (CONGEN, GENOA, STEREO). Such a computer program for conformation generation would find use both in structure elucidation and structure design.

2.3 Three-dimensional common substructures. The field of structure/activity relationships assumes that if each member of a collection of compounds exhibits a defined sort of activity (biological, spectroscopic, chemical...), there must be some common feature (substructure). The process of examining a collection of structures manually for common features is possible (particularly with sophisticated graphics terminals) but inefficient and inexact. We believe a better

approach is a computer search of the three-dimensional structures. Even this problem (an algorithm for an exhaustive search) is difficult since the problem involved is known to belong to a class of problems for which exhaustive, efficient solutions are extremely unlikely. We have implemented a preliminary method for doing this search using the methods of distance geometry (see Reference 26) and this work will continue.

D. List of Recent Publications

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- (2) C. Djerassi, D.H. Smith, and T.H. Varkony, "A Novel Role of Computers in the Natural Products Field," Naturwiss., 66, 9 (1979).
- (3) N.A.B. Gray, D.H. Smith, T.H. Varkony, R.E. Carhart and B.G. Buchanan, "Use of a Computer to Identify Unknown Compounds. The Automation of Scientific Inference," Chapter 7 in "Biomedical Applications of Mass Spectrometry, First Supplementary Volume," G.R. Waller and O.C. Dermer, Eds., John Wiley and Sons, Inc., New York, 1980, p. 125.
- (4) T.C. Rindfleisch, D.H. Smith, W.J. Yeager, M.W. Achenbach, and A. Wegmann, "Mass Spectrometer Data Acquisition and Processing Systems," in Chapter 3 of "Biomedical Applications of Mass Spectrometry, First Supplementary Volume," G.R. Waller and O.C. Dermer, Eds., John Wiley and Sons, Inc., New York, 1980, p. 55.
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- (6) J.G. Nourse and D.H. Smith, "Nonnumerical Mathematical Methods in the Problem of Stereoisomer Generation," Match, (No. 6), 259 (1979).
- (7) N.A.B. Gray, R.E. Carhart, A. Lavanchy, D.H. Smith, T. Varkony, B.G. Buchanan, W.C. White, and L. Creary, "Computerized Mass Spectrum Prediction and Ranking," Anal. Chem., 52 1095 (1980).
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- (9) J.G. Nourse, D.H. Smith, and C. Djerassi, "Computer-Assisted Elucidation of Molecular Structure with Stereochemistry," J. Am. Chem. Soc., 102, 6289 (1980).
- (10) J.G. Nourse, "Applications of Artificial Intelligence for Chemical Inference. 28. The Configuration Symmetry Group and Its Application to Stereoisomer Generation, Specification, and Enumeration," J. Amer. Chem. Soc., 101, 1210, (1979).

- (11) J.G. Nourse, "Application of the Permutation Group to Stereoisomer Generation for Computer Assisted Structure Elucidation.", in "The Permutation Group in Physics and Chemistry", Lecture Notes in Chemistry, Vol. 12, Springer-Verlag, New York, (1979), p. 19.
- (12) J.G. Nourse, "Applications of the Permutation Group in Dynamic Stereochemistry" in "The Permutation Group in Physics and Chemistry", Lecture Notes in Chemistry, Vol. 12, Springer-Verlag, New York, (1979), p. 28.
- (13) J.G. Nourse, "Selfinverse and Nonselfinverse Degenerate Isomerizations," J. Am. Chem. Soc., 102, 4883 (1980).
- (14) N.A.B. Gray, A. Buchs, D.H. Smith, and C. Djerassi, "Computer-Assisted Structural Interpretation of Mass Spectral Data," Helv. Chim. Acta., 64, 458, (1981).
- (15) N.A.B. Gray, C.W. Crandell, J.G. Nourse, D.H. Smith, and C. Djerassi, "Computer-Assisted Interpretation of C-13 Spectral Data," J. Org. Chem., 46 703 (1981).
- (16) N.A.B. Gray, J.G. Nourse, C.W. Crandell, D.H. Smith, and C. Djerassi, "Stereochemical Substructure Codes for C-13 Spectral Analysis," Org. Magn. Res., 15, 375 (1981).
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E. Funding Support

Title:

RESOURCE RELATED RESEARCH: COMPUTERS IN CHEMISTRY (grant)

Principal Investigator:Carl Djerassi, Professor of Chemistry, Department of
Chemistry, Stanford UniversityDennis H. Smith (Associate Investigator), Senior Research
Associate, Department of Chemistry, Stanford UniversityFunding Agency:Biotechnology Resources Program, Division of Research Resources,
National Institutes of HealthGrant Identification Number:

RR-00612-13

Total Award and Period:

Total - 5/1/80 - 4/30/83 ----- \$641,419

Current Award and Period:

Current - 5/1/82 - 4/30/83 ----- \$170,710

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

In the coming period of our research, our computational approaches to structural biochemistry will become much more general and we plan wide dissemination of the programs resulting from our work. These more general approaches to aids for the structural biochemist will yield computer programs with much wider applicability than, for example, the existing CONGEN, GENOA, STEREO and STRCHK programs. We expect that this will create a significant increase in requests for access to our programs, placing heavy emphasis on our relationship with SUMEX to provide this access (see Justification and Requirements for Continued SUMEX Use for additional details).

For these reasons, in our current grant period the SUMEX-AIM resource is identified as the resource to which our research is related. The SUMEX-AIM resource has provided the computational basis for our past program developments and for initial exposure of the scientific community to these programs. The resource is, however, funded completely separately from our own research; we are only one of a nationwide community of users of the SUMEX-AIM facility. Our relationship to SUMEX is one which goes far beyond mere consumption of cycles on the SUMEX machine. It has been the goal of the SUMEX project to provide a computational resource for research in symbolic computational procedures applied to health-related problems. As such research matures, it produces results, among which are computer programs, of potential utility to a broad community of scientists. A second goal of SUMEX has been to promote dissemination of useful results to that community, in part by providing network access to programs running on the SUMEX-AIM facility during their development phases. SUMEX does not, however, have the capacity to support extensive operational use of such programs. It was expected from the beginning that user projects would develop alternative computing resources as operational demands for their programs grew. Such a state has been reached for the CONGEN, GENOA, STEREO and STRCHK programs and future developments in the DENDRAL Project to yield more generally useful programs will simply magnify the problem.

We will, therefore, under our relationship with SUMEX-AIM, participate as before in the SUMEX-AIM community in sharing methods and results with other groups during development of new programs.

A. Scientific Collaboration and Program Dissemination

Scientific Collaborations:

The following is a brief description of collaborative efforts that have been taking place or will soon commence in the use of DENDRAL programs for various aspects of structural analysis.

1) Dr. Raymond Carhart, Lederle Laboratories.

Dr. Carhart (a former member of our group) is engaged in research concerned with computer applications to structure/activity relationships. Program development is done jointly between Lederle and Stanford with free exchange of software. Lederle applications are carried out on their own computer facility.

2) Dr. Janet Finer-Moore, University of Georgia.

Dr. Finer-Moore is engaged in structure analysis of alkaloids in Dr. Peletier's group at Georgia. This research makes extensive use of ^{13}C NMR. Our collaboration involves the development and application of our ^{13}C interpretive and predictive programs in structure elucidation of new compounds based on an extensive set of ^{13}C data available on closely related compounds. Access is via network to our programs at Stanford. We have just published a manuscript as a result of this collaboration. (See Reference 21) (Dr. Finer-Moore has recently moved to the University of California, San Francisco.)

3) Dr. Fred McLafferty, Cornell University.

Dr. McLafferty's research is involved with instrumental and analytical aspects of mass spectrometry. We are working with him on the development and application of an interface between his STIRS system and CONGEN/GENOA for structure determination based on mass spectral data. Part of this collaboration is development of IBM versions of some of our programs. Access is in part to Stanford, shifting primarily to Cornell as development proceeds.

4) Dr. David Cowburn, The Rockefeller University.

Dr. Cowburn's research is in the area of conformational analysis, primarily of peptides. We are working with him on the development and application of our programs for generation of molecular conformations. Dr. Cowburn's works with large ring peptides which represent a significant challenge for a conformation generator. His participation will help assure an eventual program of practical use rather than just theoretical interest. Collaboration will be via network access to our programs at Stanford.

5) Dr. D.C. Rohrer, Medical Foundation of Buffalo.
Research Laboratories, Buffalo, New York.

We have initiated a collaboration with Dr. Rohrer on the problem of finding the common 3-dimensional substructural features of a set of chemical structures. The use of such a program would be to postulate substructural features which are responsible for similar biological or spectral properties. The initial approach is similar to that used successfully to find the greatest common subgraph of a set of constitutional structures. Collaboration will be via network access to Stanford.

- 6) Dr. Peter Regan - Shell Biosciences Laboratory,
Sittingbourne, England.

Dr. Regan has made extensive use of our programs, especially the 13C nmr programs. He has given presentations on the use of CONGEN and has applied the program to the structure determination of a new acidic amino acid, 2,4-methanoglutamic acid, and other compounds from plant seeds. This work was done in collaboration with Prof. Jon Clardy at Cornell.

- 7) Dr. Margaret Wise - Smith Kline and French Laboratories.

We are collaborating with Dr. Wise on the development of programs for design of new structures. In particular, we are interested in designing GABA (gamma-amino butyric acid) analogues while developing our programs for this purpose (structure design).

- 8) Dr. Douglas Dorman - Eli Lilly.

Dr. Dorman has been one of our best users. He has given several presentations on the use of CONGEN and other programs. He has used the program as an aid in solving a number of structures including some beta-lactam antibiotic derivatives. He was a trial user of the 13C nmr programs given both his extensive knowledge of nmr and use of our programs. His evaluations of these programs has proven invaluable in their improvement and continued development.

- 9) Dr. J.N. Shoolery, Varian Associates, Palo Alto.

We are collaborating with Dr. Shoolery and others at Varian to obtain high quality C-13 spectra of several marine sterols available only in very small quantities. This is being done as part of our ongoing project to develop programs which are capable of spectral interpretation and prediction. The Varian people access our programs directly or via network.

Program Dissemination:

We have provided access to our programs to a community of collaborators via 1) distribution of the CONGEN program to other laboratories, and 2) guest or individual accounts on the SUMEX computer facility here at Stanford. These methods to promote the dissemination and use of our programs are elaborated below, followed by a brief description of some of our collaborations.

a) Program Export

The past two years we have distributed CONGEN to a number of laboratories owning computers on which the exportable version can now execute. These currently include DEC PDP-10 and -20 systems operating under the TENEX, TOPS-10 and TOPS-20 operating systems, and more recently, the beginnings of a version for IBM systems. The following persons are currently running CONGEN on their own laboratory computers:

- Dr. Larry Anderson - University of Utah
(work described in section on collaborations)
- Dr. Hartmut Braun - Organische-Chemisches Institut der
Universität Zurich, Switzerland
A former member of Prof. Wipke's group at UC Santa Cruz.
He has only recently installed the program at ETH, Zurich.
- Dr. Raymond Carhart - Lederle Laboratories
(work described in section on collaborations)
- Dr. Peter Regan - Shell Biosciences Laboratory, England
Dr. Carrington has used the program both as a guest user
and recently in export. He has given presentations on
the use of CONGEN and has applied the program to the
structure determination of a new acidic amino acid,
2,4-methanoglutamic acid, and other compounds from plant
seeds. This work was done in collaboration with
Prof. Jon Clardy at Cornell who is also a guest user.
- Dr. Robert Carter - University of Lund, Sweden
Dr. Carter obtained a version of the program for use of
several groups at Universities in Sweden.
- Dr. Daniel Chodosh - Smith, Kline & French Laboratories
He has installed CONGEN and written an extensive users'
manual for the use of SKF chemists.
- Dr. Henry Dayringer - Monsanto Agricultural Products Co.
He and Dr. Schwenzer (now at Gulf) were responsible
for obtaining and installing CONGEN. Primary use is
as an aid to structure elucidation of photoproducts and
metabolites of agricultural chemicals.
- Dr. Douglas Dorman - Lilly Research Labs
Dr. Dorman has been one of our best users. He attended our
1978 workshop and has given several presentations on the
use of CONGEN. He has used the program as an aid in
solving a number of structures including some beta-lactam
antibiotic derivatives.
- Dr. John Trent - Amoco Standard Oil (Indiana)
- Dr. Martin Huber - Ciba-Geigy, Switzerland
Dr. Huber is a former member of Prof. Wipke's group at
UC Santa Cruz. He has recently received the program and
is currently working to interest his coworkers at Ciba
in computer assisted structure elucidation.
- Dr. Carroll Johnson - Oak Ridge National Laboratory
Dr. Johnson is a long time colleague who spent a year
at Stanford in 1976. He is involved with the analytical
group at Oak Ridge and is using the program as an

analytical aid and as a model for programs he is developing.

- Dr. G. Jones - ICI Pharmaceuticals, England
He has installed CONGEN and is currently evaluating its utility for use by analytical chemists at ICI.
- Dr. Fred W. McLafferty - Cornell University
(work summarized under collaborations)
- Dr. Peter W. Milne - CSIRO Division of Computing Research,
Australia
He contacted us through his association with the Heuristic Programming Project at Stanford. He has acted as the Australian contact for distribution of CONGEN in that country.
- Dr. James Morrison - Latrobe University, Australia
(see Milne, above)
- Dr. David Pensak - E.I. duPont de Nemours and Company
(see EXODENDRAL account DUPONT, and workshop)
- Dr. Joseph SanFilippo - Rutgers University
Dr. SanFillippo is using CONGEN in conjunction with his work on superoxide chemistry and in the evaluation of mass spectral data for environmental samples.
- Dr. William Sieber - Sandoz, Ltd., Switzerland
He has installed CONGEN for use by structural chemists at Sandoz. Currently they are evaluating its utility.
- Dr. M.D. Sutherland - University of Queensland, Australia
(see Milne, above)
- Dr. R.O. Watts - Australian National University
(see Milne, above)

b) EXODENDRAL Account

We reserve a special account on SUMEX for persons interested in access to our programs. Initially, this account was used for anyone desiring access, independent of expected level of use or eventual interest. As the SUMEX system became more heavily loaded a mechanism for guest access was provided and at that point we began to differentiate our users by level of interest. For those desiring merely to try programs we provide guest access (see page 111). If there is interest in continuing collaboration, EXODENDRAL status is given, which provides access to more system facilities and good file management capabilities. The persons who have been active under EXODENDRAL status this year are the following (with the account name followed by the contact person and association):

<AMOCO>

Dr. John Trent - Standard Oil (Indiana)
Amoco Research Center

A workshop participant with several colleagues. They are using our programs in their analytical division.

<BRAEKMAN>

Dr. Jean-Claude Braekman - Universite Libre de Bruxelles,
Belgium

He is a former post doctoral fellow in our group, and accesses CONGEN from Belgium for natural products structure elucidation.

<BRAUN>

Dr. Hartmut Braun - Organische-Chemisches Institut der
Universitat Zurich, Switzerland

(see section on export)

<CARRINGTON>

Dr. Peter Regan - Shell Biosciences Laboratory, England

(see section on export)

<COWBURN>

Dr. David Cowburn - The Rockefeller University

(see section on collaborations)

<DORMAN>

Dr. Douglas Dorman - Lilly Research Laboratories

(see section on export)

<DREIDING>

Dr. Andre Dreiding - Organische-Chemisches Institut der
Universitat Zurich, Switzerland

He has used CONGEN and STEREO extensively in structural studies. He has also worked closely with Braun (see section on export under Braun).

<DUPONT>

Dr. Earl Abrahamson - E.I. duPont de Nemours and Company

Dr. Abrahamson and 4 colleagues attended our 1980 workshop. They are attempting to integrate our program into their overall computer software system which includes a wide variety of programs for applications to chemical problems.

<FINER-MOORE>

Dr. Janet Finer-Moore - University of Georgia

(see section on collaborations)

<GASH>

Dr. Kenneth Gash - California State College at Dominguez Hills

<HELLER>

Dr. Steven Heller - Environmental Protection Agency
We are continuing our work with the NIH/EPA Chemical Information System, through Heller, to attempt to find mechanisms for making CONGEN accessible through that system.

<HUBER>

Dr. Martin Huber - Ciba-Geigy, Switzerland
(see section on export)

<MILNE>

Dr. Peter W. Milne - CSIRO Division of Computing Research,
Australia
(see section on export)

<MONSANTO>

Dr. Henry Dayringer - Monsanto Company
(see section on export)

<MWOOD>

Dr. Mark Wood - Rutgers University

<RCARHART>

Dr. Raymond Carhart - Lederle Laboratories
(see section on collaborations)

<ROHRER>

Dr. Douglas C. Rohrer - Medical Foundation of Buffalo
(see section on collaborations)

<ROUSSEL>

Dr. Jean Mathieu - Roussel UCLAF
(see section on guest access under Delaroff)

<SIEBER>

Dr. William Sieber - Sandoz Ltd., Switzerland
(see section on export)

<SMITHKLINE>

Dr. Margaret Wise - Smith Kline and French Laboratories
(see section on collaborations)

<VARIAN>

Dr. James Shoolery - Varian Associates
(see section on collaborations)

c) GUEST Access

We have provided GUEST access to our programs for those persons desiring occasional access to study a structural problem and for those who

wish a "hands-on" introduction to the programs. Persons who have received information about this method of access and have actually logged in during the past year:

Dr. Robert Adamski - Alcon Labs

Dr. A. Bothner-by - Carnegie Mellon University

Dr. Bothner-by has requested access to aid others in the Chemistry Department with structure elucidation work.

Dr. Reimar Bruening - Institut fur Pharmazeutische

Arzneimittellehre der Universitat, West Germany

Dr. Bruening has used the program to aid in his solution of the structure of the alkaloid Cassine. He was a participant in our 1978 workshop and has maintained interest since then. He has given at least one presentation in Germany on our programs.

Dr. William Brugger - International Flavors and Fragrances

Dr. Brugger is interested in eventually obtaining CONGEN for use at IFF in natural products structure elucidation.

Dr. Robert Carter - University of Lund, Sweden

(see section on export)

Dr. Francois Choplin - Institut Le Bel, France

Dr. Jon Clardy - Cornell University

He has used CONGEN on occasion to determine the potential structural variety for an unknown prior to obtaining the X-ray crystal structure.

Dr. Mike Crocco - American Hoechst Corp.

Dr. Dan Dolata - University of California at Santa Cruz

He is one of our contacts with Prof. Wipke's group at UC Santa Cruz.

Dr. Bruno Frei - Laboratorium f. Organische Chemie, Switzerland

Dr. John Gordon - Kent State University

Dr. Gordon has been using CONGEN while working at Chemical Abstracts in Columbus, Ohio. He has been using CONGEN to investigate general issues of structure representation.

Dr. Richard Hogue - University of California at Santa Cruz

He is another contact with Prof. Wipke's group.

Dr. Suba Neir - Washington University, St. Louis

Dr. Neir used the program to aid in determination of the structure of a mutagen.

Dr. A. Neszmelyi - Central Research Institute for Chemistry of
the Hungarian Academy of Sciences

Ms. Connie Oshirio - Lawrence Berkeley Labs

Dr. Philip Pfeffer - USDA (Philadelphia)

Dr. Ned Phillips - University of Florida

Dr. J.D. Roberts - California Institute of Technology

Dr. Francis Schmitz - University of Oklahoma

Dr. Michael Zippel - Institut fur Biochemie Zentrale
Arbeitsgruppe Spectroskopie, Germany
Dr. Zippel used CONGEN to investigate the possible
connection with their spectral search system.

d) Industrial Affiliates Program

The high level of interest shown by industrial research laboratories in our programs has always presented us with delicate questions about access to SUMEX-AIM. In the past we have granted access for trials of our programs under the conditions that access is necessarily limited and that the recording mechanisms of our programs be used to ensure that all such trial use be in the public domain. As of April, 1980, we began solicitation of interested industrial organizations to participate in a DENDRAL Project Industrial Affiliates Program. As of May 1, 1982, we have seven members. We intend to use this program as a means by which we can offer collaborations with our on-going research to industrial organizations separate from SUMEX-AIM. Although EXODENDRAL accounts to such organizations are used to facilitate communication and sharing of new programs and concepts of interest with the community as a whole, all significant and certainly all proprietary use of our programs will be carried out on their own computational facilities.

e) Program License

During the past year we have completed a license agreement with Molecular Design, Ltd. of Hayward, California for exclusive rights to DENDRAL Project programs. We see this mechanism as serving the function of technology transfer in a very realistic way. We do not, as a research project, have the charter or the resources to do what is essentially final engineering of a program and integration of the program into an existing, larger system. Such "value added" effort is crucial to broad acceptance of a computer-based method. In addition, Molecular Design will take on the burden of maintenance, documentation and training, freeing our personnel to pursue our research objectives and to bring experimental programs to the level of performance where they, too, can be disseminated by licenses.

B. Interactions with Other SUMEX-AIM Projects

We routinely collaborate with other projects on SUMEX most closely related to our own research. In particular, these collaborations have taken place with the CRYNALIS project, MOLGEN, SECS and have begun with Dr. Carroll Johnson at Oak Ridge.

CRYNALIS is concerned with new approaches to the interpretation of X-ray crystallographic data. X-ray crystallography is another approach to molecular structure elucidation. One of our long-term interests is exploring ways in which CONGEN or GENOA generated structures might be used to guide the search of electron density maps. We are also communicating with Prof. Jon Clardy at Cornell on this problem. It is hoped that having narrowed down the structural possibilities for an unknown using physical and chemical data, the few remaining candidates can be used to guide interpretation of such maps.

Most of the structural problems investigated by MOLGEN involve much larger molecules than the size normally investigated in DENDRAL research. Thus, structural representations involving higher levels of abstraction are of utility in MOLGEN, making our structure manipulation tasks quite different. However, many of the ways in which MOLGEN manipulates its structural representations drew on past experience in DENDRAL in developing algorithms to perform these manipulations.

We collaborate frequently with the SECS project in a number of ways. Although our research efforts are in one sense directed toward opposite ends of work on chemical structures, SECS being devoted to synthesis, DENDRAL being devoted to analysis, the underlying problems of structural manipulation share many common aspects. We have exchanged software where possible, particularly in the area of chemical structure display. We have held several discussions in joint group meetings and at several symposia including the AIM Workshops on common problems, including substructure searching, canonical representations and representation and manipulation of stereochemistry. Persons visiting one laboratory often take the opportunity to visit the other. For example, recent visitors to both laboratories have included Prof. Andre Dreiding, Zurich, Dr. Martin Huber, Basel, and Prof. Robert Carter, Lund.

Dr. Carroll Johnson has collaborated on the CRYNALIS project in the past. More recently he has taken an interest in the use of knowledge-based programs for certain problems in spectral data interpretation. For this reason he is exploring the AGE and EMYCIN systems as frameworks for his program structure, and is involved in discussions with DENDRAL to see where common areas of data interpretation can be identified so that he can draw on our experience and programs. This effort is just beginning at this time; we plan to meet early in May at Stanford to continue discussions.

C. Critique of Resource Management

The SUMEX-AIM environment, including hardware, system software and staff, has proven absolutely ideal for the development and dissemination of

DENDRAL programs. The virtual memory operating system has greatly facilitated development of large programs. The emphasis on time-sharing and interactive programs has been essential to us in our development of interactive programs. Our experience with other computer facilities has only emphasized the importance of the SUMEX environment for real-world applications of our programs. To run CONGEN, for example, in a batch computing environment would make no sense whatever because the program (and our other, related programs) is successful in large part because an investigator can closely monitor and control the program as it works toward solution. We have no complaints whatsoever about the computing environment.

We do have, however, significant problems with SUMEX-AIM capacity, both in available computer cycles and on-line file storage. In a sense DENDRAL suffers from its success. The rapid progress made during the last grant period and now continuing into the next period has led to development of many new programs as adjuncts to CONGEN and GENOA and at the same time has inspired many persons in the scientific community to request some form of access to our programs. The net result is that it is often very difficult to carry on at the same time development and collaborations involving applications of our programs to structural problems due to high load average on the system.

The current overcrowding we see on SUMEX creates two major problems for us in the conduct of our research. First, it diminishes productivity as many people compete for the resource; the "time-sharing syndrome" leads to idle, wasted time at the terminal waiting for trivial computations to be completed. Second, the slow response time of the system is an aggravation to an outside investigator who is anxiously trying to solve a structural problem. At some point even the most interested persons will give up, log off the computer and resort to manual methods where possible.

We have taken many steps within our project to try to work around heavy use periods on SUMEX. Our group works a staggered schedule, both in terms of the actual hours worked each day and in terms of what days each week are worked. This results in some problems in intra-group communication, but fortunately the message and other communication systems of SUMEX help alleviate that situation. We try to run all demonstrations on the DEC-2020 to help ease the burden on the dual KI-10 system. We encourage our collaborators to avoid prime-time use of the system when possible. We have used our new Megatek Graphics terminal exclusively on the 2020. This terminal makes modest demand on the host computer and it was decided to use it only on the somewhat less used 2020 rather than the dual-KI system

For these reasons, we strongly support the planned augmentation of the SUMEX-AIM hardware. Any part of our computations which can be shifted to another machine will not only facilitate export of our software but will ease the load on the DEC-10s and make it easier to continue our research. Both will serve to make SUMEX more responsive and our productivity higher.

III. RESEARCH PLANS

A. Project Goals and Plans

Current research efforts were described in highlight form in the first section, Summary of Research Program. In this section we discuss in outline form the major goals of our current grant period (5/1/80 - 4/30/83), with an indication of the progress made to date.

Our goals include the following:

1) Develop SASES (Semi-Automated Structure Elucidation System) as a general system for computer aided structural analysis, utilizing stereochemical structural representations as the fundamental structural description. SASES will represent a computer-based "laboratory" for detailed exploration of structural questions on the computer. It will have as key components the following:

A) Capabilities for interpretation of spectral data which, together with inferences from chemical or other data, would be used for determination of (possibly overlapping) substructures. We have made considerable progress in the areas of mass spectrometry (see References 3, 14) and C-13 NMR spectroscopy (see References 15, 18);

B) The GENOA (structure Generation with Overlapping Atoms) program which will have the capability of exhaustive generation of (topological and stereochemical) structural candidates and include as an essential component the existing CONGEN program. We have developed Version I of GENOA for use by our collaborators (see Reference 17);

C) Capabilities for prediction of spectral (and biological) properties to rank-order candidates on the basis of agreement between predicted and observed properties. Again, we have made considerable progress in mass (see References 3, 7, 8) and C-13 NMR (see References 15, 16, 18) spectroscopy;

2) Develop automated approaches to both interpretation and prediction of spectroscopic data, including but not limited to the following spectroscopic techniques:

A) carbon-13 magnetic resonance (¹³CMR) (see References 15, 16, 18);

B) proton magnetic resonance (¹HMR);

C) mass spectrometry (MS) (see References 3, 7, 8);

The interpretive procedures will yield substructural information, including stereochemical features, which can be used to construct structural candidates using GENOA. We have illustrated this method in

recent publications (see References 14, 18, 21). The predictive procedures will be designed to provide approximate but rapid predictions of expected spectroscopic behavior of large numbers of structural candidates, including various conformers of particular structures. Such procedures can be used to rank-order candidates and/or conformers. The predictive procedures will also be designed to provide more detailed predictions of structure/property relationships for known or candidate structures in specific biological applications. These procedures have been illustrated in recent publications (see References 3, 7, 8, 15, 18, 20).

3) Develop a constrained generator of stereoisomers, (see Reference 9) including:

A) design and implement a complete and irredundant generator of possible conformations for a given known, or a candidate for an unknown, structure;

B) provide constraints for the conformation generator so that proposed structures for a known or unknown compound possess only those features allowed by: i) intrinsic structural features such as ring closure and dynamics of the chemical structure; and ii) data sensitive to molecular conformations (e.g., MCD, NMR);

C) integrate the stereochemical developments with the GENOA program as a final, comprehensive solution to the structure generation problem and allow for interface of the program with other methods dependent on atomic coordinates.

4) Promote applications of these new techniques to structural problems of a community of collaborators, including improved methods for structure elucidation and potential new biomedical applications, through resource sharing involving the following methods of access to our facilities and personnel;

A) nationwide computer network access, via the SUMEX-AIM computer resource;

B) exportable versions of programs to specific sites;

C) workshops at Stanford to provide collaborators with access to existing and new developments in computer-assisted structure elucidation in an environment where complex questions of utility and application can be answered directly by our own scientific staff;

D) interface to a commercially available graphics terminal for structural input and output, at as low a cost as possible, so that chemists can draw or visualize structures more simply and intuitively than with our current, teletype-oriented interfaces.

B. Justification and Requirements for Continued SUMEX Use

In previous sections we discussed the relationship between the DENDRAL Project and SUMEX-AIM, methods for using SUMEX-AIM for dissemination of our programs to a broad community of structural chemists and biochemists and a critique of resource management. In this section we wish to emphasize certain factors which were not discussed earlier and to show how our future directions and interests are closely related to the proposed continuation and augmentation of the SUMEX-AIM resource.

As resource-related research, DENDRAL is intimately tied to the SUMEX resource. Our involvement with SUMEX goes far beyond simple use of the facility. We use SUMEX as the focal point for a number of collaborative efforts, for export of our software and for the communication facilities essential to maintaining close contact with remote research groups working with us. SUMEX provides computational facilities for our workshops, where we bring outside investigators to Stanford to use new programs applied to real structural problems. We have already discussed in our critique the difficulties we have, in view of heavy SUMEX load, of maintaining both our research effort and the resource-sharing aspects of our project. To help ease these burdens we are making extensive use of the SUMEX 2020 system via one direct line and via the ETHERNET link from SUMEX to the 2020. Much of our work in graphics software, for example, is carried out on the 2020.

C. Needs and Plans for Other Computing Resources

For several years now we have directed some attention toward alternative computing resources which could be used to support all "production" use of our programs, i.e., all applications designed to use the programs to solve real problems. Although this would have the severe disadvantage of separating our research effort from many of the applications, it has been our hope that emerging technology in networking would enable us to keep in reasonably close contact with another resource. Two resources have emerged as candidates for systems where our programs can be accessed and used in problem-solving. Unfortunately, neither has so far proven feasible for several reasons (mentioned below). At this time we cannot determine if the problems will be resolved. Until such time, we will remain completely dependent on SUMEX for all our computational needs.

One alternative resource is the NIH/EPA Chemical Information System. For more than three years we have been working with them to obtain sufficient contract money to provide a version of CONGEN integrated into that system. The concept and the funds were approved but a contract has never been issued due to administrative problems at the EPA. Although there have been some developments recently, we still have no firm idea on when such a contract will be issued. If this effort is successful, then we can encourage persons who desire access to our programs to consider using the NIH/EPA system.

A second alternative is the National Resource for Computation in Chemistry (NRCC). This Resource has recently had its funding terminated.

We are now pursuing an alternative discussed previously, that of arranging license agreements with private industry for dissemination of our software. This will likely be the focus of our future efforts to disseminate programs to those researchers who merely wish to use them rather than work together with us in collaborative arrangements to develop more powerful programs.

D. Recommendations for Future Resource and Community Development

We have discussed previously our recommendation for the hardware augmentation, particularly with regards to purchase of small machines to facilitate future export. We also have increasing need for more file storage on-line. This is a result of building large data bases as part of our research in spectral interpretation. For the time being we are working with experimental programs and small data bases. As time progresses, however, these data bases will grow rapidly as our group and a number of our collaborators add additional structures and associated spectral data.

Another capability which is of increasing importance to our own work is access to low-cost graphics systems. Our programs will develop increasing dependence on graphics for visualization of three-dimensional molecular structures. Scientists desiring access to our programs will need a graphics terminal for optimum use of our systems. Currently available vector displays are simply too expensive for the average investigator. The emerging technology of low-cost raster display systems offers a more promising possibility. However, no currently available machine has the required capabilities for under \$10,000, and this is an area where machines like the Alto hold more promise. SUMEX could perhaps initiate an effort to obtain a system which has the hardware necessary for frame-based display. Such a system allows rotation of three-dimensional objects in a way which permits visualization of the actual shape of the object.

II.A.1.4 EXPEX Project

EXPEX - Expert Explanation Project

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I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

EXPEX is not a single project but a combination of efforts that are directed at the development of powerful representational schemes to facilitate knowledge acquisition and explanation. The work includes not only the study of fundamental representational formalisms but also the encoding of various types of knowledge, such as causal information and user models.

We believe that the productivity of basic computer science research tends to be heightened by experiments that deal with significant real world problem domains. Challenges drawn from chemistry, medicine, and molecular biology have introduced additional complexity to expert systems work at Stanford, but have simultaneously forced system developers to respond to pragmatic constraints and user demands that have had a significant impact on the basic AI techniques selected or developed. Thus, we believe that creative investigation into symbolic reasoning techniques is facilitated by working in real world settings where the application forces us to avoid oversimplification. Much of our research effort therefore deals with medical domains (viz., endocrinology and renal pathophysiology) and is being undertaken on SUMEX. Those aspects of the research that deal with nonmedical topics are using other computing resources at Stanford. Our report here will only describe EXPEX, the research on expert medical explanation.

B. Medical Relevance and Collaboration

Our interest in explanation derives from the insights we gained in developing explanatory capabilities for the MYCIN system. In the case of MYCIN and its descendents, we have been able to generate intelligible explanations by taking advantage of its rule-based representation scheme. Rules can be translated into English for display to a user, and their interactions can also be explicitly demonstrated. By adding mechanisms for understanding questions expressed in simple English, we were able to create an interactive system that allowed physicians to convince themselves that they agreed with the basis for the program's recommendations. The

limitations of the explanations generated in this way have become increasingly obvious, however, and have led to improved characterization of the kinds of explanation capabilities that must be developed if clinical consultation systems are to be accepted by physicians.

With this motivation in mind, we are involved in a series of research projects that address medical knowledge representation and explanation. The researchers involved meet regularly to guarantee that each benefits from the insights and progress of the others. We have been fortunate to enlist the collaboration of two additional medical faculty members, Dr. Larry Crapo (endocrinologist), who is helping us build an endocrinology knowledge base, and Dr. Roy Maffly (nephrologist), who is assisting in the development and evaluation of the renal failure work. In the area of endocrinology, the pathophysiology of calcium disorders is the focussed area we are studying because the relationships are well-understood and there are some challenging problems of feedback homeostasis that will need to be represented. The individual projects include the following:

- (1) Mr. Greg Cooper's NESTOR program is building on the knowledge base developed for INTERNIST/CADUCEUS and adding causal and temporal relationships. The program is designed to critique a physician's hypothesis regarding the explanation for a set of patient manifestations from the field of hypercalcemia.
- (2) Mr. John Kunz is representing the knowledge of renal pathophysiology, including the quantitative relationships that characterize relationships, to develop a consultation and analysis system that melds mathematics and AI techniques.
- (3) Mr. Randy Teach is completing a large formal study of the ways in which clinical experts (internists and endocrinologists) explain their findings and recommendations to other physicians. We hope that the results of his analyses will help define the most important characteristics of the explanation components for future medical expert systems.
- (4) Dr. Glenn Rennels is working with GUIDON project members on a collaborative effort to implement an explanation capability for the NEOMYCIN program. Because NEOMYCIN's control structure depends on explicit tasking and strategic information, the explanations offered by NEOMYCIN will be very different from those provided by MYCIN's goal-oriented mechanism for rule invocation. Because GUIDON/NEOMYCIN are described in detail in the section of this report dealing with the MYCIN projects, we will not describe this work further in this section.

C. Highlights of Research Progress

THE NESTOR SYSTEM

We have developed a preliminary version of a system that allows a user to input patient data plus an hypothesis, and then have the system critique that hypothesis in light of the data. The system, an evolving thesis project that is largely the work of Mr. Greg Cooper, is called NESTOR and it currently relies completely on information in the INTERNIST-I (CADUCEUS-I) knowledge base.

The more long term goal is to deepen the knowledge in the area of diseases that cause hypercalcemia. For these diseases causal knowledge will be added. A language will be developed to allow the user to state complex time relationships in his description of the patient. NESTOR will be able to accept causal and time statements in hypotheses and reason with them so as to return a hopefully lucid explanation of what it thinks about the user's current hypothesis.

The motivation behind all this research is the deeply held belief that physicians want active control of the diagnostic process and that they also want and need a system that explains, in a user-tailored way, its evaluation of the physician's hypothesis. There may be times when the user wants to give complete control to NESTOR and just be in a mode of answering questions, but we feel that this should be an option and not a requirement. It is observations such as these that have also accounted for the hypothesis assessment work underway in the ONCOCIN research described in the section of this report dealing with the MYCIN projects.

INTEGRATING MATHEMATICAL MODELS WITH AI METHODS

This research project, largely the work of Mr. John Kunz, integrates AI and simple mathematics to analyze a physiological model. In a selected medical domain, we are building a computer program based on these techniques. It analyzes physiological behavior, diagnoses abnormality, and explains the rationale for its analyses. The program fits data to the model, identifies whether the data are abnormal, and identifies the possible causes and effects of any abnormalities. The physiological model is based on knowledge about anatomy, the behavior of the physiological system, and the mechanism of action of the system. The program analyzes many of the problems discussed in Valtin's text Renal Function.

The specific aims of this project are to:

- (1) Develop a vocabulary for a physiological model. The vocabulary should represent the "basic physiology" of a biological system. This vocabulary should be adequate to express the concepts included in an introductory professional-level physiology text.
- (2) Develop a reasoning system which can solve problems expressed in the vocabulary.

- (3) Demonstrate the basic necessity, appropriateness and limitations of the vocabulary and reasoning procedure. This demonstration must be conducted within some limited problem domain.

In this project, mathematics is used in an AI system to compute quantitative values based on available data. Concurrently, AI enhances the simple mathematical models. AI is used to represent diverse knowledge about the problem, to match a solution technique with problems needing solution, and to interpret results. Results may be quantitative and qualitative. Results are explained in terms of their contribution to diagnostic and therapeutic decisions.

This research project was developed within the domain of renal physiology. The project develops a vocabulary for describing a physiological model. In addition to anatomy (structure), this vocabulary describes processes, substances, parameters and mechanisms of action. In general, values of parameters can be measured. Parameters may be related qualitatively or quantitatively. "Mechanism of action" characterizes behavior in terms of laws of physics, specifically including the conservation of mass and Ohm's law. Relations with an associated mechanism of action are characterized as causal. Lacking the mechanism of action, a relation is characterized as behavioral. The mechanism of action provides a very strong focus of attention for the problem solving process. Problems are analyzed in terms of conservation of mass and a search for factors which enable operation of Ohm's law. In addition, the mechanism of action helps to focus the process of acquiring new knowledge about a problem. The behavior, structure and mechanisms of the problem domain are organized as a physiological model.

Using these techniques, the system poses and answers questions such as the following:

"Is the patient oliguric; define oliguria; what are its causes, consequences and manifestations; what measurements can be made to confirm the diagnosis?"

According to our collaborating nephrologist, Dr. Roy Maffly,

"Appropriate management of patients with excesses or deficiencies of water and the major cations, sodium and potassium, requires an understanding of the basic physiology of these substances in the body. With such an understanding, therapy ordinarily becomes straightforward and logic replaces guesswork." [Maffly, R. Scientific American, 1981].

Early AI diagnosis systems all lack significant knowledge of physiology. The goal of this project is to test the hypothesis that it is possible to develop a computer-based system which uses physiology and an associated "understanding" of that physiology. The system should suggest causes, consequences, and actions which affect physiologically abnormal situations, within a limited medical domain.

PSYCHOLOGICAL STUDIES OF EXPLANATION

This project is aimed at elucidating the nature of expert explanations as they naturally occur in clinical medicine. As we described in last year's annual report, there is remarkably little formal information available regarding the characteristics of high quality explanations among physicians. Thus we decided that it would be valuable to study the way in which experts actually communicate with one another in hopes that these observations will help us arrive at formal design criteria for acceptable expert systems with explanation capabilities.

Mr. Teach brought to bear his background in educational psychology and experimental design to undertake a formal study of this kind. Three general internists and three endocrinologists participated as subjects. With the assistance of Drs. Crapo (endocrinology) and Shortliffe (general medicine), a set of 12 patient management problems was designed. The six subjects were administered the problems in a role-playing "thinking aloud" setting, each case being introduced by a letter from a presumed referring physician. The subjects obtained the history, physical examination, and laboratory information needed to reach a diagnosis and formulate a plan, and they were then asked to dictate a consultation letter back to the referring physician. The referral letters and assignment of cases were carefully controlled to permit optimal control of the variables that might influence the nature and quality of the explanations in the consultation reports. The subjects were not aware that it was the letters themselves (rather than their problem solving behavior) which was a particular area of interest to us. Thus their consultation reports, and the explanations they contain, have provided a basis for the evaluation of the explanations offered by an expert consultant to a physician requesting advice.

The data collection portion of this study is now complete, and the formal statistical analysis of the data is now well underway. A formal dissertation document will be available within the next several months, and several shorter reports on various aspects of the study are expected over the next year.

D. Publications Since January 1981

Wallis, J.W. and Shortliffe, E.H. Explanatory power for expert systems: studies in the representation of causal relationships for medical consultations. Submitted for publication, December 1981.

E. Funding Support

Grant Title: "The Development of Representation Methods to Facilitate Knowledge Acquisition and Exposition in Expert Systems"
Principal Investigator: Edward H. Shortliffe
Agency: Office of Naval Research
ID Number: NR 049-479
Term: January 1981 to December 1983
Total award: \$456,622

Grant Title: "Explanatory Patterns in Clinical Medicine"
 Principal Investigators: Randy L. Teach and Edward H. Shortliffe
 Agency: National Center for Health Services Research
 ID Number: 1 R03 HS 04422
 Term: March 1, 1981 through April 30, 1982 (extended through August 30,
 1982)
 Total award: \$19,950.00

II. INTERACTION WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

None of these new programs is yet ready for dissemination, although we hope to have prototypes of both NESTOR and the acute renal failure system within the next several months. Our past experience has shown that SUMEX provides a superb vehicle for demonstrating systems, even at a distance.

B. Sharing and Interaction with Other SUMEX-AIM Projects

Although our EXPEX work is young, we are already benefitting from interactions with other researchers who use the SUMEX-AIM resource. The NESTOR work, for example, has depended on access to the INTERNIST-1 knowledge base and on frequent exchange of messages with the researchers at the University of Pittsburgh. Similarly, our collaboration with the GUIDON research team for the implementation of an explanation capability would not have been possible without the facilitated communication and shared file access available via SUMEX.

C. Critique of Resource Management

Although we have not yet placed significant demands on SUMEX management, our previous experience working with Tom Rindfleisch and his staff would suggest that this new project will receive the same kind of laudatory service for which SUMEX has become known.

III. RESEARCH PLANS

A. Project Goals and Plans

THE NESTOR SYSTEM

In the coming year we plan to complete a more sophisticated version of NESTOR. The program will continue to be a decision support tool for diagnosis, but it will be capable of handling much more complicated cases. We envision four major enhancements to the current prototype:

- (1) To add a more formal probabilistic model than is used in the INTERNIST system which has greatly influenced our work. This will allow assumptions made by NESTOR to be explicit.
- (2) To represent temporal knowledge explicitly and to use it in reasoning.
- (3) To represent and use causal information to express the pathophysiology of diseases.
- (4) To incorporate abstract diseases into the representation (e.g., it will be possible to include CANCER as a component of a user's hypothesis if this seems more appropriate at the time than specifying BRONCHOGENIC-CARCINOMA or MYELOMA or RENAL-CELL-CARCINOMA).

We have already developed several techniques for utilizing time and causality in determining the probability of a disease. We have also developed search techniques that allow NESTOR to explore efficiently a very large search space in order to find the most probable (multiple disease) hypothesis. This technique is general and can be applied to many nonmedical problems where the goal is to find the most probable hypothesis among many possibilities.

INTEGRATING MATHEMATICAL MODELS WITH AI METHODS

The work to date has concentrated on analyzing physiological function using knowledge of anatomy, physiology and causality. During the coming months, the causal analysis will be generalized. The issue is how to make valid qualitative conclusions based upon the quantitative relations of a physiological model. Rules will be developed and tested for inferring qualitative relations such as the following:

- inferring the direction of change in a dependent parameter following change in an independent parameter;
- inferring whether qualitatively significant change in a dependent parameter may occur as a consequence of a qualitatively significant change in an independent parameter; and
- inferring that a dependent parameter has a qualitatively significant value.

Questions of the following type will build on the other structures, incorporating the kinds of mathematical descriptions of human physiology necessary to predict the effects of quantitative deviations from normal:

"What is the effect of infusing hyperosmotic saline? How much should be used to return plasma volume to normal? How fast will normalization occur?"

PSYCHOLOGICAL STUDIES OF EXPLANATION

Within the next several months, Mr. Teach will have completed all data analysis for his research and will have completed most of his dissertation writing. Thereafter we will work on analyzing the results in light of our interest in the design of explanation capabilities for medical expert systems. We expect to have several papers based on this work completed or in preparation by this time next year.

EXPLANATIONS FOR A RULE-BASED EXPERT SYSTEM

As described in the GUIDON report elsewhere in this document, Dr. Rennels and others from the NEOMYCIN project will continue in their effort to implement a system to provide explanations for that program. This project will allow us to learn about optimal techniques for encoding and explaining the strategic tasking knowledge that is interfaced with that system's domain knowledge.

B. Requirements for Continued SUMEX Use

All the work we are doing is totally dependent on the SUMEX resource. As of yet, none of these young projects has been sufficiently mature to justify their transfer to one of the SUMEX personal workstations, so the KI-10's continue to be key elements in our research plan.

In addition, we have long appreciated the benefits of GUEST and network access to the programs we are developing. SUMEX greatly enhances our ability to obtain feedback from interested physicians and computer scientists around the country. As our programs mature in the months ahead, it will become increasingly important that we be able to make them available for demonstration and for access by distant collaborators via the SUMEX network.

C. Requirements for Additional Computing Resources

The mainframe machine should continue to provide a suitable environment for our work in the months ahead. We have no plans to transfer to other hardware soon. However, the response time on the main machine continues to be a major problem, even though the SUMEX workstations have provided additional cycles to permit off-loading of some users from the PDP-10.

D. Recommendations for Future Community and Resource Development

We concur with the suggestion, expressed by some of the other project reports, that consideration should be given to an upgrade of SUMEX to a more modern central mainframe machine.

II.A.1.5 MOLGEN Project

MOLGEN - A Computer Science Application to Molecular Biology

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I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The MOLGEN project has focused on research into the applications of symbolic computation and inference to the field of molecular biology. This has taken the specific form of systems which provide assistance to the experimental scientist in various tasks, the most important of which have been the design of complex experiment plans and the analysis of nucleic acid sequences. We plan to expand and improve these systems and build new ones to meet the rapidly growing needs of the domain of recombinant DNA technology. We do this with the view of including the widest possible national user community through the facilities available on the SUMEX-AIM computer resource.

It is only within the last few years that the domain of molecular biology has needed automated methods for experimental assistance. The advent of rapid DNA cloning and sequencing methods has had an explosive effect on the amount of data that can be most readily represented and analyzed by computer. Moreover we have already reached a point where progress in the analysis of the information in DNA sequences is being limited by the combinatorics of the various types of analytical comparison methods available. The application of judicious rules for the detection of profitable directions of analysis and for pruning those which obviously lack merit will have an autocatalytic effect on this field in the immediate future.

The MOLGEN project has continuing computer science goals of exploring issues of knowledge representation, problem-solving, and planning within a real and complex domain. The project operates in a framework of collaboration between the Heuristic Programming Project (HPP) in the Computer Science Department and various domain experts in the departments of Biochemistry, Medicine, and Genetics. It draws from the experience of several other projects in the HPP which deal with applications of artificial intelligence to medicine, organic chemistry, and engineering.

We have begun a transition from being primarily a computer science research project to being an interdisciplinary project with a strong applications focus. The tools that we have already developed will be improved to the point where they make a significant contribution to both research and engineering in the domain of molecular biology.

B. Medical Relevance and Collaboration

The field of molecular biology is nearing the point where the results of current research will have immediate and important application to the pharmaceutical and chemical industries. Already, clinical testing has begun with synthetic interferon and human growth hormone produced by recombinant DNA technology. Governmental reports estimate that there are more than 200 new and established industrial firms already undertaking product development using these new genetic tools.

The programs being developed in the MOLGEN project have already proven useful and important to a considerable number of molecular biologists. Currently several dozen researchers in various laboratories at Stanford (Prof. Paul Berg's, Prof. Stanley Cohen's, Prof. Laurence Kedes', Prof. Douglas Brutlag's, Prof. Henry Kaplan's, and Prof. Douglas Wallace's) and over 400 others throughout the country are using MOLGEN programs over the SUMEX-AIM facility. We have exported some of our programs to users outside the range of our computer network (University of Geneva [Switzerland], Imperial Cancer Research Fund [England], and European Molecular Biology Institute [Heidelberg] are examples).

C. Highlights of Research Progress

Accomplishments:

The current year has seen intensive work on what might be termed a second-generation experiment design system. We have also begun to explore the capabilities of the SUMEX Dolphin computers for MOLGEN work. This section will summarize those projects as well as continuing work on other MOLGEN research.

1. Representation Research

The domain of molecular biology has proven a fruitful testbed in the development of a flexible software package, the Unit System, for symbolic representation of knowledge. The package is already in use by a variety of research projects both within the Heuristic Programming Project at Stanford and at other institutions. It provides for acquisition and storage of many different types of knowledge, ranging from simple declarative types like integers and strings to complex declarative types like nucleic acid restriction maps to procedural types like a rule language in a subset of English.

However, it has become clear that there are several bottlenecks in practical use of the Unit System on the main SUMEX computer system. First, there is the address space limitation. It is well known that Interlisp

programs on the DEC 10 and 20 series of computers have relatively little user memory available. Several of the MOLGEN knowledge bases have already exceeded that limitation. Second, it is clear that communication with the Unit System via 1200 baud display terminals does not allow the presentation of enough information at a fast enough speed. We are very optimistic that both of these problems will be solved by use of the Xerox Dolphin workstation computer. The Dolphin has a far larger address space than DEC 10 and 20 computers, as well as a large bit-map display with window and graphic capabilities.

Our initial experiments on the Dolphin have been encouraging. We were able to move the Unit System to the Dolphin with almost no difficulties. We have implemented a simple display interface that allows far more information to be directly accessible to the knowledge base builder. We are now in the state of allowing several MOLGEN biologists to begin using the Dolphins as practical knowledge entry tools.

2. Planning Research

The problem of designing laboratory experiments in molecular biology has been fundamental to MOLGEN research. Previous work consisted of two major subparts, each resulting in a doctoral thesis in computer science. The two systems, developed by Peter Friedland and Mark Stefik, produce reasonable experiment designs on test problems suggested by laboratory scientists.

The last year has seen the design and construction of a hybrid planning system combining the best of the previous two experiment planning systems. This work was done by Yumi Iwasaki, a master's candidate in computer science. The system, known as SPEX, uses Friedland's method of experiment design by the stepwise refinement of abstracted or "skeletal" plans, and Stefik's method for planning strategy control by "layers of planning spaces." It also keeps extensive records of all decisions made during the planning process; this will allow SPEX to be used as an experimental laboratory for work on explanation, verification, optimization, and debugging of plans.

In addition to the above general planning work, Rene' Bach has designed and implemented a small expert system for the problem of suggesting sequencing strategies for large nucleic acid molecules. The system, MAXIMIZE, was built entirely within the Unit System. It takes information about a given molecule (restriction map, already sequenced regions, etc.) along with information specific to the laboratory (how many bases may be comfortably sequenced by that lab, enzymes available, etc.) and provides an optimal or near-optimal strategy.

3. Knowledge Base Construction

Over seven man-years have now been spent in constructing knowledge bases for various fields of molecular biology. A new project was initiated this year with Professors Stanley Falkow and Esther Lederberg of the Stanford Medical Microbiology Department. Also, an entire series of

knowledge-base development projects has begun at the Imperial Cancer Research Fund in London, England, using the Unit System which was exported to a DEC 2060 at the ICRF.

The knowledge bases developed under the MOLGEN grant have begun to find their way into the daily laboratory practice of many of the scientists associated with the project. They have provided a mechanism for managing the explosive growth of data and strategies in many areas of molecular biology without the necessity of building special purpose systems for each area. Also, the expert scientists themselves have been able to design and build their own systems, avoiding the time and reliability problem of a knowledge base passing through the filter of a computer scientist intermediary. The knowledge bases have served as "intelligent encyclopedias," as simulation systems, and as training vehicles.

It should also be noted that the Unit System allows for the easy transfer of knowledge from one knowledge base to another, and indeed the various expert molecular biologists have freely shared information as they work on related knowledge bases.

4. Other Applications of Symbolic Computation to Molecular Biology

MOLGEN work in the previous year has concentrated on basic research, there now being adequate commercial avenues for applied development of symbolic computation tools for molecular biology. However, we have continued to support large-scale guest access to the SEQ program for nucleotide sequence analysis and the Los Alamos Nucleic Acid Sequence Library. The GENET guest community has continued to grow. Because of this growth, a committee, headed by Professor Allan Maxam of Harvard University, has been formed to set policy for future guest access via SUMEX or other possible nationally networked systems.

We believe that GENET has been a clear demonstration that SUMEX is a model for building national communities of research scientists. We hope that the GENET committee will find adequate mechanisms for supporting this community without detracting from the primary research goals of SUMEX-AIM.

Research in Progress:

The next year will be spent in testing the SPEX experiment design system in the domain of cloning experiments, continuing the testing of the Dolphins for knowledge acquisition, and starting to explore the areas of plan debugging and explanation. We are also beginning work on automatic acquisition of experiment design strategies and discovery of gene regulation signals in the nucleic acid sequence library.

1. Cloning Advisory System

The SPEX experiment design system is now operational. In parallel with its development, we have begun to construct a large knowledge base specific to tools and techniques used during cloning experiments. The basic strategy or skeletal plan of all cloning experiments is quite

straight-forward: First, isolate the piece of DNA you wish to clone, second, select a vector to carry the clone, third, insert the DNA into the vector, fourth, select a host for expression of the hybrid molecule, fifth, insert the hybrid into the host, and sixth, select for the protein or nucleic acid product that was the eventual goal of the cloning experiment. Following this skeletal plan, the cloning knowledge base will contain information on DNA isolation methods, cloning vectors, insertion methods, hosts, host insertion methods, and selection methods. Professor Stanley Falkow and several others are assisting us in the building of this expert knowledge base.

We expect the cloning knowledge base to be essentially complete by the end of this year. We will also have accumulated substantial experience with running SPEX on that knowledge base. Sometime during this year, we will release the cloning advisory system to several of our molecular biologist colleagues for further testing and improvement. We also hope to gain more information about experiment design heuristics in general, using SPEX as a laboratory for this testing. The issues to be studied include optimal methods for plan expansion: depth-first breadth-first, and heuristic are among the possibilities, and how abstract or detailed to make the skeletal plans which drive the experiment design system.

2. Research on Plan Debugging and Explanation

SPEX keeps complete records of all decisions made during the course of designing an experiment. These include strategic decisions as to which general planning heuristics to employ and which domain-specific skeletal plans to use, as well as tactical decisions made in the course of choosing specific operators to instantiate a plan step. In addition, SPEX keeps a dynamic model of the world state as assumed after the execution of each plan step.

We will now make use of this information to add plan explanation and debugging facilities to the SPEX system. Users of SPEX will be able to easily determine which strategies and rules led to each planning decision. A limited querying interface will be added, probably more graphical through the Dolphin facilities than natural language.

Plan debugging can take two general forms. First, the debugging of plans generated originally by SPEX. In that case the debugging process will consist of attempting to ascertain the point at which the plan failed by comparing the actual state of the experiment at various points with SPEX's model of the world at those points. Presumably this will lead to identifying the instantiation step which failed; if no step failed, then the skeletal plan which generated the experiment design must have been faulty. In the former case, an alternate instantiation will be suggested (and possibly the knowledge base updated to reflect the error). In the latter case, an alternate skeletal plan will be used and the faulty one will be corrected (initially manually, but we hope by some automated means in the future).

The second general form of plan debugging occurs when the plan was generated outside of SPEX. In this case a plan verification step must first take place to ensure that the original plan design and model correspond to the knowledge base. If errors are found, then alternatives will be suggested, if not then debugging will proceed as above.

3. Further Developments of the Unit System

Considerable effort will be spent in taking full advantage of the many capabilities for graphical interaction of the Dolphin. We expect improvements to be opportunistic as our molecular biologist collaborators begin to do their routine knowledge base development on the Dolphin.

4. Work in Plan and Model Discovery

Initial exploration has begun in two new projects in what might be termed automated knowledge acquisition. The first has to do with acquiring skeletal plans for the SPEX knowledge base. Currently skeletal plans are described directly by molecular biologists. We would like to explore means of automatically extracting these abstracted plans from successful experiment designs, either from the literature or in an interactive mode from scientists. One of the major questions to be resolved concerns determining how specific or abstract to make the skeletal plans; specificity leads to efficiency, abstractness leads to generality--a balance is needed.

The second project is in the automated discovery of rules for the regulation of genes from the data stored in the nucleotide sequence library. It is well known that close to 90% of all DNA in higher organisms does not code directly for proteins, but has to do with the regulation of those genes that do code for proteins. There is currently no widely believed mechanism which explains even an appreciable fraction of regulatory processes. The information used for gene regulation is stored somewhere within the nucleotide sequence itself. We have access to a large collection of such sequence data (over 600000 bases) and to the best currently available sequence analysis system (SEQ). We plan to add semantic pattern finding procedures to SEQ, probably through a Unit System interface, that will allow proposed theories to be tested on the data base.

D. Publications

Bach R., Friedland P., Brutlag D., Kedes L., MAXIMIZE, A DNA Sequencing Strategy Advisor, Nucleic Acids Research, Volume 10, Number 1, 295-304 (January 1982) Brutlag D., Clayton J., Friedland P., Kedes L., SEQ: a Nucleotide Sequence Analysis and Recombination System, Nucleic Acids Research, Volume 10, Number 1, 279-294 (January 1982)

Clayton J., Kedes L., GEL, a DNA Sequencing Project Management System, Nucleic Acids Research, Volume 10, Number 1, 305-321 (January 1982)

Feitelson J., Stefik M.J., A Case Study of the Reasoning in a Genetics Experiment, Heuristic Programming Project Report HPP-77-18 (Working Paper) (May 1977)

- Friedland P., Knowledge-Based Experiment Design in Molecular Genetics, Proceedings Sixth International Joint Conference on Artificial Intelligence, 285-287 (August 1979)
- Friedland P., Knowledge-Based Experiment Design in Molecular Genetics, Ph.D. Thesis, Stanford CS Report CS79-760 (December 1979)
- Friedland P., Kedes L., Brutlag D., MOLGEN--Applications of Symbolic Computation and Artificial Intelligence to Molecular Biology, Proceeding of the Battelle Conference on Genetic Engineering (April 1981)
- Friedland P., Acquisition of Procedural Knowledge from Domain Experts, Proceedings Seventh International Joint Conference on Artificial Intelligence, 856-861 (August 1981)
- Friedland P., Kedes L., Brutlag D., Iwasaki Y., Bach R., GENESIS, a Knowledge-Based Genetic Engineering Simulation System for Representation of Genetic Data and Experiment Planning, Nucleic Acids Research, Volume 10, Number 1, 323-340 (January 1982)
- Iwasaki Y., and Friedland P., SPEX: A Second-Generation Experiment Design System, to appear in Proceedings of the Second National Conference on Artificial Intelligence (August 1982).
- Martin N., Friedland P., King J., Stefik M.J., Knowledge Base Management for Experiment Planning in Molecular Genetics, Fifth International Joint Conference on Artificial Intelligence. 882-887 (August 1977)
- Stefik M., Friedland P., Machine Inference for Molecular Genetics: Methods and Applications, Proceedings of the National Computer Conference, (June 1978)
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E. Funding Support

The MOLGEN grant is titled: MOLGEN: A Computer Science Application to Molecular Biology. It is NSF Grant ECS-8016247. Current Principal Investigators are Edward A. Feigenbaum and Bruce G. Buchanan, Professors of

Computer Science, Laurence H. Kedes, Investigator, Howard Hughes Medical Institute and Associate Professor of Medicine, and Douglas L. Brutlag, Associate Professor of Biochemistry. MOLGEN is currently funded from 10/81 to 9/82 at \$159,785 including indirect costs as the second year of a three year renewal.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

SUMEX-AIM continues to provide the bulk of our computing resources. The facility has not only provided excellent support for our programming efforts but has served as a major communication link among members of the project. Systems available on SUMEX-AIM such as INTERLISP, TV-EDIT, and BULLETIN BOARD have made possible the project's programming, documentation and communication efforts. The interactive environment of the facility is especially important in this type of project development.

Unfortunately, the computing environment at SUMEX has suffered in the recent past from heavy demands on cycle time creating serious real-time delays for programmers and knowledge-base building especially. The Units Editor is especially sensitive because of its relatively large demands on cpu-resources. Accordingly, a significant fraction of the MOLGEN group activity has been transferred to the SCORE computer in the Department of Computer Science at Stanford. When SUMEX hardware is updated, we anticipate that its response time will improve and the MOLGEN computing will return full time to SUMEX. It is clear, however, that the MOLGEN project continues to thrive and prosper because of the computing environment only available at SUMEX: the interactive environment including instantaneous communications among collaborators who are physically distant (even on the Stanford campus), and especially the unique telecommunications facilities that have allowed the development of the GENET community with its access to MOLGEN applications tools are two clear examples.

We have taken advantage of the collective expertise on medically-oriented knowledge-based systems of the other SUMEX-AIM projects. In addition to especially close ties with other projects at Stanford, we have greatly benefitted by interaction with other projects at yearly meetings and through exchange of working papers and ideas over the system.

The ability for instant communication with a large number of experts in this field has been a determining factor in the success of the MOLGEN project. It has made possible the near instantaneous dissemination of MOLGEN systems to a host of experimental users in laboratories across the country. The wide-ranging input from these users has greatly improved the general utility of our project.

We find it very difficult to find fault with any aspect of the SUMEX resource management. It has made it easy for us to expand our user group, to give demonstrations (through the 20/20 adjunct system), and to disseminate software to non-SUMEX users overseas.

III. RESEARCH PLANS

A. Justification and Requirements for Continued SUMEX Use

The MOLGEN project depends heavily on the SUMEX facility. We have already developed several useful tools on the facility and are continuing research toward applying the methods of artificial intelligence to the field of molecular biology. The community of potential users is growing nearly exponentially as researchers from most of the bio-medical fields become interested in the technology of recombinant DNA. We believe the MOLGEN work is already important to this growing community and will continue to be important. The evidence for this is an already large list of pilot exo-MOLGEN users on SUMEX.

SUMEX is currently having difficulty meeting the research needs of the MOLGEN project adequately. We expect to need more file space as our knowledge bases grow; perhaps an additional 5000 disk blocks in the next few years for that work. Our real difficulties will come in the applications testing of MOLGEN tools. We support with great enthusiasm the acquisition of satellite computers for technology transfer and hope that the SUMEX staff continue to develop and support these systems. One of the oft-mentioned problems of artificial intelligence research is exactly the problem of taking prototypical systems and applying them to real problems. SUMEX gives the MOLGEN project a chance to conquer that problem and potentially supply scientific computing resources to a national audience of bio-medical research scientists.

II.A.1.6 MYCIN Projects Group

MYCIN Projects

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I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The MYCIN Projects are a set of related research programs, each devoted to the development of knowledge-based expert systems for application to medicine and the allied sciences. The name was derived from our first system, the MYCIN program. That research has now given way to three sub-projects (EMYCIN, GUIDON, and ONCOCIN), each of which is discussed in the sections that appear below. The key issue for all sub-projects has been to develop programs that can provide advice similar in quality to that given by human experts, and to develop systems that are easy to use and acceptable to physicians and medical students.

The success of the original MYCIN infectious disease consultation program has led us to try to generalize and expand the methods employed in that program to a number of ends:

- (1) to develop consultation systems for other domains (our generalized system-building tool is known as "Essential MYCIN", or EMYCIN, and has been applied in several new areas; ONCOCIN is our a more recent consultation system and was inspired by EMYCIN although it is an entirely new program);
- (2) to explore other uses of the MYCIN knowledge base (our tutoring system, GUIDON, uses the infectious disease knowledge in MYCIN to teach medical students about diagnosis and management of infections);
- (3) to continue to improve the interactive process, both for the developer of a knowledge-based system, and for the user of such a system (both EMYCIN and ONCOCIN have stressed simplified techniques for interacting with a knowledge base and entering data); and
- (4) to experiment with alternate techniques for knowledge representation, recognizing that the pure production rule method used in MYCIN was inadequate at times and frequently led to confusion regarding the separation of strategy or control processes from domain knowledge (ONCOCIN uses production rules as only one of several knowledge

representation techniques, and the work on GUIDON has led to a more robust revised version of MYCIN known as NEOMYCIN).

B. Medical Relevance and Collaboration

By utilizing our EMYCIN system to collaborate on building the PUFF program, we learned that it is possible in a short period of time to develop a clinically useful consultation system using the domain-independent parts of MYCIN. EMYCIN has since been applied in a number of additional medical domains. With each successive application we learn more about the representation of medical knowledge and the scope and limitations of the production rule formalism used in EMYCIN. For example, it has become clear that "shallow" rules relating signs and symptoms to diagnoses through a few intermediate concepts can be sufficient for high performance in medical diagnosis. On the other hand, such shallow rules are not always sufficient for teaching medical students because they lack the deeper causal links needed for justifying and remembering the more shallow associations (see GUIDON discussion below).

Although EMYCIN was not used to build our new ONCOCIN program, the lessons learned in building prior production rule systems have allowed us to create a large oncology protocol management system much more rapidly than was the case when we started to build MYCIN. We introduced ONCOCIN for use by Stanford oncologists in May 1981. This would not have been possible without the active collaboration of Stanford oncologists who helped with the construction of the knowledge base and also kept project computer scientists aware of the psychological and logistical issues related to the operation of a busy outpatient clinic.

In addition, there is a growing realization that medical knowledge, originally codified for the purpose of computer-based consultations, may be utilized in additional ways that are medically relevant. Using the knowledge to teach medical students is perhaps foremost among these, and GUIDON continues to focus on methods for augmenting clinical knowledge in order to facilitate its use in a tutorial setting. A particularly important aspect of this work is the insight that has been gained regarding the need to structure knowledge differently, and in more detail, when it is being used for different purposes (e.g., teaching as opposed to clinical decision making). This aspect of the GUIDON research has led to the development of a modified version of MYCIN, NEOMYCIN, which is an evolving computational model of medical diagnostic reasoning that we hope will enable us to better understand and teach diagnosis to students.

C. Highlights of Research Progress

1. Accomplishments This Past Year

EMYCIN

In the last year, work on EMYCIN was brought to a conclusion. The program was "frozen" and documentation completed. The program remains a

vehicle for computer science research, but there is no funding for continued development of the tool. Our work centered around the following activities:

- (1) One of the most significant experiments with the program is the development of ROGET, a knowledge acquisition program that aids a system builder with the definition and creation of a new knowledge base for an EMYCIN system. ROGET itself is written in EMYCIN. Design was completed in this year and programming started, as described in more detail below.
- (2) We continued to help users in the SUMEX community with new applications of EMYCIN and with questions about on-going applications. These are described below.
- (3) Buchanan and Shortliffe have begun writing up the results of many years' work on MYCIN and EMYCIN. Because we view AI as an experimental science, we believe there is much to be learned in a detailed analysis of the experiments performed with rule-based consultation systems by the MYCIN group. This work is also briefly described below.

ROGET: A KNOWLEDGE-BASED SYSTEM FOR THE DESIGN OF EXPERT SYSTEMS

ROGET is a program under construction which is designed to assist an expert with the initial formulation of an EMYCIN consultant. The ROGET system is intended (1) to help the expert properly delimit the scope and function of a consultant, (2) to identify the major types of inferences it will make and their requisite facts, and (3) to educate the expert about the use of the particular representation system being used to construct the consultant.

Current expert-system building tools provide little or no guidance to an expert during the initial formulation of a consultant system. A knowledge engineer provides the expert with advice about what tasks the consultant might have to perform and, more importantly, how to employ a particular representation system to achieve this performance. Previous work by Davis, Reboh, and van Melle have emphasized tools and techniques that are appropriate only considerably after the basic "inference structure" of the consultant has already been designed and placed on-line. These tools are meant to assist the refinement of a knowledge base and they make the implicit assumption that the expert is already fairly familiar with (i.e., has at least reading knowledge of) the representation system.

In contrast, the primary function of ROGET will be to guide and instruct the expert as he selects the relevant concepts and inferences required to solve a problem, indicate how they have been typically represented within a specific representational framework, and provide hands-on instruction regarding the tool's actual use. ROGET will provide an interactive environment in which the expert can construct a prototypical inference structure for a consultant and some of its "connective tissue". In this manner, the expert can become familiar enough with the

representation system to use the existing knowledge acquisition tools to further refine the knowledge base.

This research is predicated on the observation that several computer-based consultants, particularly of the diagnostic variety, employ similar types of inference, provide similar types of advice, and require similar types of data. Furthermore, the actual representation of the domain-specific counterparts of this knowledge within a particular representation system has also taken rather stereotypic forms. This research will attempt to capitalize on these "standard" forms by representing this type of knowledge and developing a system that will use it to guide the acquisition of new expertise in different domains.

Helping the expert identify an appropriate task for the consultation system is a major function of any knowledge engineer. ROGET will assist the expert with the proper scoping of the consultant by identifying the applicable inferences for this problem and by suggesting the most appropriate inferences for the current consultant to make. These suggestions can be made on the basis of information about the experts background, his experience with system construction, any constraints on his time and other resources, and, most importantly, a description of the "consultation setting", where and how the consultant will interact with prospective clients.

The education of the expert about the intricacies of a particular representation system is currently accomplished primarily through the use of examples taken from other expert systems constructed with this tool. ROGET will mimic this behavior as well. In addition to providing domain-specific examples of each of the inference, advice, and data types mentioned above, ROGET will also give examples of how the inference engine interprets example knowledge bases. Again, knowing about the consultation setting will help ROGET focus attention on specific portions of complete knowledge bases that demonstrate how certain types of knowledge are needed to make certain features of the inference engine run.

ROGET will be developed to assist an expert design an EMYCIN consultant. To represent the consultation setting a simple, script-like representation of the major events, people, and information flow for various consultation scenarios will be developed. In the case of diagnostic consultants this representation must be adequate to capture most "clinical settings" at some fairly high level of abstraction. The expert will then identify specific types of people, information, and events that are applicable to his domain and use this perspective to identify points in the information flow where a consultant would be most appropriate and effective.

This same script-like representation will also be used to capture the stereotypic inference steps that EMYCIN diagnostic consultants employ, to identify what types of data are expected at certain points in the consultation, and to understand how the advice the consultant gives will be used by the client. The current inference engine of EMYCIN will be modified to operate on the basis of this new representation of control knowledge, in

addition to the normal backward-chaining of rules. Furthermore, the explanation machinery will be updated to provide alternative explanations of the consultant's line of reasoning about a case based on this representation of control.

Representation of this scriptal knowledge, the hierarchies of inferences, data, and advice for each task, and the examples themselves will employ a simple UNITS-style representation system embedded within the current EMYCIN system. A trace of the design process for individual consultants will be kept and used as the basis for "developmental explanations" that could be used to indicate why the consultant is scoped to perform certain tasks to the exclusion of others and to identify parts of the knowledge base that are under-developed.

The initial ROGET system will be considered "done" when it can successfully scope and design the basic inference structures for the following EMYCIN consultants: MYCIN, GRAVIDA, PUFF, and SACON. At least one general consultant task must be represented; currently this task is diagnosis and simple therapy selection. Another potential task would be the design of objects or plans by configuring schematic designs (ROGET itself, R1, and Friedland's MOLGEN are examples of this type of "configuration" consultant).

In summary, then, this project seeks to make explicit some important aspects of knowledge-engineering expertise. It will identify a taxonomy of the kinds of expert systems in terms of common tasks and how their place in a larger information context effects their final design. This knowledge will be used to help scope the initial design of a consultant and to educate the expert about a representation system. It is concerned with identifying expertise required for initial expert system design and this, in turn, will require an analysis of the nature of expertise itself and the current limitations on its representation, especially within the EMYCIN system.

EMYCIN Applications

We spoke with many physicians around the country about potential applications of EMYCIN in their own work. We encouraged several to submit applications to SUMEX for pilot status. We collaborated with one physician at length on a prototype system named COAGS, described below.

COAGS

During January and February of 1982 James Bennett and Robert T. Wall, M.D., a hematologist at the Stanford Medical School, collaborated to construct a prototype hematology consultant using the EMYCIN system. The consultant, named COAGS, deals with patients about to undergo surgery when routine coagulation screening tests indicate a potential bleeding problem. The surgeon will typically refer the patient to a hematologist for a more complete set of tests to confirm the disorder and to receive a recommendation about any treatment that might allow the operation to proceed.

The consultant requests that various collections of tests be performed in an attempt to confirm that a problem does exist. Most of the coagulation tests are not particularly accurate and repetition of critical tests with appropriate controls is an essential part of hematologists' attempts at confirmation. The tests can be expensive to perform and the consultant has been constructed to minimize the cost of diagnosing the most specific bleeding disorder possible.

The EMYCIN system did not require any improvements or modifications to represent Dr. Wall's clinical expertise. The consultant was constructed in a two month time period on weekly meetings between expert and knowledge engineer. We believe that this represented approximately 6 person-days.

ANALYSIS OF EXPERIMENTS WITH MYCIN & EMYCIN

Artificial Intelligence, or AI, is largely an experimental science in that at least as much progress has been made by building and analyzing programs as by examining theoretical questions. MYCIN is one of several well-known programs that embody some intelligence and provide data on the extent to which intelligent behavior can be programmed. As with other AI programs, its development was slow and not always in the forward direction. But we feel we learned some lessons in the course of over eight years of work on MYCIN, and related programs. The purpose of this analysis, then, is to share the results of many experiments performed in that time, and to paint a coherent picture of the work.

The MYCIN project is one of the clearest representatives of the experimental side of AI. It was begun in the spring of 1972 with a set of discussions among medical school and computer science researchers interested in applying more intelligence to computer programs that interpret medical data. Shortliffe's PhD dissertation in 1974 discusses the problem context and the MYCIN program that implemented a solution.

In itself, the 1974 version of MYCIN represents an experiment. We were testing the hypothesis, tentatively advanced in the DENDRAL work, that a production rule formalism was sufficient for the high performance, flexibility, and understandability that we demanded in an expert system. The positive answer to this question is one of the best-known lessons in the history of AI.

In addition to, or rather because of, the original MYCIN program and the knowledge of blood infections and meningitis that was accumulated for that work, many derivative projects explored variations on the original design. In a book-length analysis currently underway, we are examining many of the experiments that evolved in the period from 1972 to 1980 based on the 1972-74 design effort. We have chosen those pieces of work which, at least in retrospect, can be seen as posing clear questions and producing clear results that were documented in the AI or medical literature, or occasionally in technical reports.

Some of those other projects are discussed in this annual report, for example GUIDON and NEOMYCIN. Others have come to a logical conclusion:

TEIRESIAS, VM, CENTAUR, and now EMYCIN. In those major pieces of work, and several others as well, the questions posed and the answers we derived from program construction and testing are important scientific results. Documenting these results will, we hope, benefit the entire AI community.

Because almost all of the computing work was done on the SUMEX-AIM computer resource at Stanford, we recognize that this set of experiments would not have been possible without funding from the Division of Research Resources of the National Institutes of Health.

GUIDON

The purpose of the GUIDON project is to develop a tutorial program that uses a knowledge-based system for teaching material. Research over the past five years has shown that a knowledge representation that is adequate for developing a consultation system with good performance may be inadequate for teaching. Our study of MYCIN's meningitis rule base (1979-1980) led us to develop a new representation in which kinds of knowledge important to teaching are represented separately and explicitly. Using this new system, which we call NEOMYCIN, we proceeded in 1981 to develop a student modelling program that will be used in a tutorial program for teaching diagnostic strategies to students.

CONTINUING DEVELOPMENT OF NEOMYCIN

NEOMYCIN is distinguished from other AI consultation programs by its uses of an explicit set of domain-independent meta-rules for controlling all reasoning. These rules constitute the diagnostic procedure that we want to teach to students: the stages of diagnosis, how to focus on new hypotheses, and how to evaluate hypotheses. It has been a major undertaking, separate from the problem of representing disease knowledge, to design and test this diagnostic procedure. For example, this year we extracted the forward-directed reasoning that had previously been embedded in NEOMYCIN's interpreter and represented this as a "task" with 4 meta-rules (one meta-rule each for: follow-up questions, antecedent rules, trigger (hypothesis-suggesting) rules, and forward application of rules that confirm hypotheses already under consideration). By the end of the year, attention turned to extending NEOMYCIN's disease knowledge to include more diseases that present similarly to, or are confused with, meningitis.

THE IMAGE STUDENT MODELLING PROGRAM

Teaching diagnosis involves recognizing the intent behind a student's behavior, so that missing knowledge can be distinguished from inappropriate strategies. The teacher interprets behavior, critiques it, and provides advice about other approaches. To do this successfully and efficiently in a complex domain, the teacher benefits from multiple, complementary modeling strategies. IMAGE is a student modelling program that uses NEOMYCIN's meta-rules and disease knowledge to understand student diagnostic plans by a dual search strategy. IMAGE first produces multiple predictions of student behavior by a model-driven simulation of NEOMYCIN. Focused, data-driven searches then explain incongruities. By supplementing

each other, these methods lead to an efficient and robust plan understander.

A model of student strategies in medical diagnosis must disambiguate the possible purposes and knowledge underlying the student's actions. The approaches followed by other plan recognizers and student modelers are not sufficient here because:

- (1) the complex domain makes thorough searches impractical, whether top-down or bottom-up;
- (2) we are not modeling only facts and rules used in isolation, but also the procedures for applying them;
- (3) every one of the student's actions must be monitored in case the teaching module decides to interrupt;
- (4) his behavior must be evaluated and not just explained; and
- (5) we might not have any explicit goal statements from the student, so we expect to rely only on his queries for problem data as evidence for his thinking.

The IMAGE program is now operational and will soon be tested in experiments with medical students.

SHORT-TERM PLANS FOR NEOMYCIN AND GUIDON

The next stages in the development of the GUIDON2 tutorial program (using IMAGE and NEOMYCIN) are:

- (1) additions to NEOMYCIN's disease knowledge so we can fairly evaluate the program's focussing strategies;
- (2) experimentation to determine the capabilities of IMAGE for explaining student (non-expert) behavior;
- (3) development of an explanation system for NEOMYCIN, to serve as a testbed for explanations to be generated by the tutorial program (including use of a student/user model and condensation methods for presenting explanations at the appropriate level of detail) (Drs. Clancey and Shortliffe, and their graduate students, are collaborating on this project);
- (4) design of various teaching scenarios for teaching NEOMYCIN's meta-rules, and representation of this teaching knowledge in a prototype version of GUIDON2.

ONCOCIN

The oncology chemotherapy consultation system, named ONCOCIN, has achieved many of its goals since work on the project began in July 1979. We are developing an interactive system to be used by oncology faculty and fellows in the Debbie Probst Oncology Day Care Center at Stanford University Medical Center.

The ONCOCIN research goals are directed both towards the basic science of artificial intelligence and towards the development of clinically useful oncology consultation tools.

We have undertaken AI research with the following aims:

- (1) to implement and evaluate recently developed techniques designed to make computer technology more natural and acceptable to physicians [formal studies are underway to assess the success of our prototype system in achieving these goals];
- (2) to extend the methods of rule-based consultation systems to interact with a large database of clinical information; and
- (3) to continue basic research into the following problem areas: mechanisms for handling time relationships, techniques for quantifying uncertainty and interfacing such measures with a production rule methodology, approaches to acquiring knowledge interactively from clinical experts, assessment of knowledge base completeness and consistency.

The clinic system itself is intended to have a number of performance capabilities when it is completed. We outline those goals here, citing those which have been completely or partially accomplished and indicating those that have yet to be achieved:

- (1) to assist with identification of current protocols that may apply to a given patient [not yet undertaken; will not be relevant until more protocols than lymphomas have been encoded]
- (2) to assist with determining a patient's eligibility for a given protocol [not yet undertaken because lymphoma patients have been fully screened before they come to chemotherapy clinic];
- (3) to provide detailed information on protocols in response to questions from clinic personnel [a query system is just now being started; it is being designed to assist both physicians and those building a protocol knowledge base];
- (4) to assist with chemotherapy dose selection and attenuation for a given patient [fully implemented and being evaluated for patients under treatment for lymphoma];

- (5) to provide reminders, at appropriate intervals, of follow-up tests and films required by the protocol in which a given patient is enrolled [fully implemented and being evaluated for patients under treatment for lymphoma];
- (6) to reason about managing current patients in light of stored data from previous visits of (a) the individual patients [partially achieved, but much work remains], or (b) the aggregate of all "similar" patients [not yet attempted].

In the early years of the project, we developed a prototype of the ONCOCIN consultation system, drawing from programs and capabilities developed for the EMYCIN system-building project. We also undertook a detailed analysis of the day-to-day activities of the Stanford Oncology Clinic in order to determine how to introduce ONCOCIN with minimal disruption of an operation which is already running smoothly. Subsequently we completed the development of a special interface program that responds to commands from a customized keypad. Software protocols were developed for achieving communication between the interface program and the reasoning program, and we coordinated the printing routines needed to produce hardcopy flowsheets, patient summaries, and encounter sheets. Finally, lines were installed in the Stanford Oncology Day Care Center, and, beginning in May 1981, eight fellows in oncology began using the system three mornings per week for management of their patients enrolled in lymphoma chemotherapy protocols.

The introduction of the system last year has largely determined the nature of our subsequent research effort. That experience has proved to be a constant source of new ideas and challenges for system improvement. Much of our work in the last year has been in response to the lessons learned by observing the strengths and weaknesses of the computing system now that it is in routine use by physicians. Formal evaluation studies have continued in parallel with the ongoing development effort, and the data collection for them is within three months of completion; we expect to begin data analysis before the end of June.

IMPLEMENTATION OF ONCOCIN IN THE STANFORD ONCOLOGY CLINIC

ONCOCIN was introduced smoothly into the Oncology Clinic in May and June of 1981. Each oncology fellow was given approximately 45 minutes of training in the system's organization and in use of the terminal interface. They found it to be extremely easy to learn, and additional help was seldom needed after the training session. During the first several months our data manager was routinely present in the clinic to assist with questions, but it became clear that this was not necessary and since January of this year we have simply asked the physicians to call our project office if a problem arises.

Our Clinical Specialist Dr. Carlson, himself a fellow in oncology, has regularly reported to us the informal reactions of the physicians to the system. We will soon have formal data regarding their attitudes (see Study 1 below), but the informal feedback and suggestions were important

because they led to the design and implementation of several additional features that have required a good deal of programmer time during the past year. For example, the communications between the Reasoner and Interviewer were streamlined for efficiency, and major changes were made to a special category of data entries known as "special questions". These frequently annoyed the physicians because they tended to interrupt the smooth flow of the dialogue with the machine. The revised version of the interface inserts these questions more benignly into the flowsheet data form.

Two major problems were identified that relate to knowledge representation in ONCOCIN and control of the reasoning process. One of these is the inability of the program to manage complex inferences that are dependent upon analyzing a patient's response to therapy over all previous visits to the clinic. This kind of analysis is typically ignored in the formal protocols but is routinely used by experienced oncologists and is, of course, a desirable capability for a consultation program in this area. The development of techniques for managing temporal reasoning is a major interest of our group and is of particular importance in dealing with expert decision making in a domain such as cancer chemotherapy. Our oncology collaborators are finding this aspect of their knowledge particularly difficult to distill, and we expect that our attempts to develop computer-based approaches to the problem will provide particularly stimulating challenges in the months ahead.

The second problem was unanticipated until the system was implemented but is having a major impact on our future plans. ONCOCIN provides a therapy recommendation for the physician but allows those recommendations to be overridden if the physician prefers an alternate treatment. If the fellows change the therapy, they are asked to indicate the reason for preferring their therapy to what ONCOCIN suggested. When there is a major disagreement between the fellow and the computer, the physicians seldom object to indicating the reasons for the change, and their entries have been useful in further debugging the program's knowledge of lymphoma treatment. However, the changes they make are frequently minor ones that are more stylistic than substantive (e.g., some physicians prefer always to give prednisone in multiples of 20 mgs when they are dealing with large doses; others prefer to be more precise in their dosing and will ask patients to take combinations of 5 and 20 mg tablets). In these cases, the physicians tend to be annoyed by requests for reasons that they have disagreed with ONCOCIN; they do not see the slight adjustments as being real disagreements. We have attempted to respond to this problem by developing criteria for determining when a physician's preferred treatment is a clinically significant difference from what ONCOCIN has recommended. The knowledge for determining what changes are "important" is different from the kind of knowledge in the protocols themselves. It is more "judgmental" and imprecise, but seems to be an important addition to the program's knowledge base. Furthermore, this issue, and the observation that the physicians frequently believe they know what to do and would rather not be bothered by the program's suggestions, has led us to propose a modified version of ONCOCIN that will verify the physician's plan rather than offer a therapy recommendation for every case. We have referred to this new work as "hypothesis assessment" (see below).

EVALUATIONS OF THE ONCOCIN SYSTEM

All three ONCOCIN evaluations are approaching completion, and we expect to have data analyzed and formal reports written by this time next year.

Study I is an evaluation of the program's impact on the attitude of the oncology fellows towards computers in general and ONCOCIN in particular. All physicians were administered questionnaires and structured interviews in the Spring of 1981 before ONCOCIN was introduced. The same questionnaires have recently been distributed to them once again, and follow-up interviews are just now underway. Pre- and post-ONCOCIN results will be analyzed as described in last year's annual report.

Study II is an evaluation of the program's impact on the completeness and accuracy of flowsheet data recorded with and without ONCOCIN. Research programmers have written routines to formally analyze on-line flowsheets for completeness and accuracy. Pre-ONCOCIN flowsheets have been entered into the system exactly as they were originally recorded by the physician. The same analytic routines will analyze these pre-ONCOCIN flowsheets and we will compare the pre- and post-ONCOCIN results. We expect to begin analysis of the post-ONCOCIN data within the next two months when a sufficient number of patient visits have been recorded to permit a statistically significant comparison.

Finally, Study III is examining the comparison between ONCOCIN's therapeutic advice and the treatment decisions made by oncology fellows in the same setting. As described in last year's report, expert evaluators are rating treatment plans without knowing whether the recommendation is that of ONCOCIN or one of the clinic physicians. Over 200 flowsheets are currently being evaluated by Stanford lymphoma experts, and we expect to have their ratings returned for analysis by the end of May.

THE INTERVIEWER/REASONER MODEL

We have continued to refine ONCOCIN's communication system for permitting the physician to interact with a rapid interface program while a slower reasoning program considers treatment options in a second process. After the system was implemented, several unexpected problems resulting from the use of asynchronous processes were discovered and required resolution. For example, the reasoning program has no straightforward way of knowing whether a piece of information that it needs has been skipped on the flowsheet by the physician or whether the doctor has simply not reached that part of the flowsheet yet. Similarly, the Reasoner needs techniques for dealing with changes to flowsheet entries that are made after the initial entry has been transmitted by the Interviewer and has been used by the Reasoner in its decision making process.

HYPOTHESIS ASSESSMENT

As mentioned above, we have decided to consider modifications to ONCOCIN that would permit it to function as an "observer" of the physician's own decisions rather than as a primary source of advice. By permitting the physician to enter his or her own therapy plan on the flowsheet, we can acknowledge the oncologist's ability to reach appropriate therapeutic decisions for most patients. ONCOCIN will simply compare the physician's plan with what it believes is the proper therapy. If the system agrees with the physician, or determines that small differences are clinically insignificant, no advice from the computer will be necessary. If significant disagreements occur, on the other hand, ONCOCIN will need to respond with warnings and explanations for why it feels that an alternate therapy plan may be preferable. Our early experience with ONCOCIN since its clinic implementation suggests that this mode of interaction may be preferred by the clinic physicians. It will require minimal changes to ONCOCIN's decision making approach, but the determination of what differences are clinically significant, and the optimal method for explaining their importance to the physician, will be exciting challenges and important theoretical problems. This work is just getting underway and will receive much attention during the coming year.

QUERY SYSTEM

We have also recently started work on the development of a query system that will permit easy access to the large ONCOCIN knowledge base. Now that we have encoded several hundred rules, it is becoming unwieldy for system builders to work from large hard-copy listings of the knowledge base, and physicians will also require direct access to the program's knowledge. The query system is being designed to permit this kind of access. Rather than dealing with natural language understanding by computer, we are designing ways that menu selection and the high-speed interface can be used to permit access to the information that is needed by a physician or system builder.

VERIFYING THE COMPLETENESS AND CONSISTENCY OF THE KNOWLEDGE BASE

An important question for AI researchers involved with the development of expert systems is how to ascertain that a knowledge base for a consultation program is complete and consistent. Dr. Motoi Suwa, a visitor to Stanford from Japan two years ago, became fascinated with this question and collaborated with us on a formal analysis of the developing ONCOCIN knowledge base. However, the programs that he wrote were never formally linked to our system for writing rules and modifying other parts of the knowledge base. As a result, we have recently spent time modifying his code so that it will operate as an integral part of ONCOCIN. The development of an improved interface to permit this program to be used by our expert collaborators is also planned for the coming year.

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19. Shortliffe, E.H. The Computer and Medical Decision Making: Good Advice is not Enough. Guest Editorial to appear in IEEE Engineering in Medicine and Biology Magazine, June 1982.
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21. Clancey, W.J. Methodology for Building an Intelligent Tutoring System. To appear in Problems of Methods and Tactics in Cognitive Science. Kintsch, Polson, and Miller, Eds., 1982.
22. London, B. & Clancey W. J. Plan Recognition Strategies in Student Modeling: Prediction and Description. Submitted to AAAI-82.

E. Funding Support

Contract Title: "Exploration of Tutoring and Problem-Solving Strategies"

Principal Investigator: Bruce G. Buchanan

Agency: Office of Naval Research and

Advanced Research Projects Agency (joint)

ID number: N00014-79-C-0302

Term: March 1979 to March 1982

Total award: \$396,325

[This project has recently been renewed for another three years. It will be jointly funded by the ONR and the ARI (Army Research Institute). The contract number has not yet been assigned, and the precise budget is still undergoing revision.]

Grant Title: "Research Program: Biomedical Knowledge Representation"

Principal Investigator: Edward A. Feigenbaum

Co-Principal Investigator (ONCOCIN Project): Edward H. Shortliffe

Agency: National Library of Medicine

ID Number: LM-03395

Term: July 1979 to June 1984

Total award: \$497,420

Grant Title: "Symbolic Computation Methods For Clinical Reasoning"

Principal Investigator: Edward H. Shortliffe

Agency: National Library of Medicine

ID Number: LM-00048

Term: July 1979 to June 1984

Total award: \$196,425

II. INTERACTION WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

A great deal of interest in MYCIN, GUIDON, ONCOCIN, and EMYCIN has been shown by the medical and computer science communities. We are frequently asked to demonstrate these programs to Stanford visitors or at meetings in this country or abroad. For example, in March 1982 Dr. Clancey demonstrated MYCIN in Helsinki, Finland for physicians at the University of Helsinki. Physicians have generally been enthusiastic about these programs' potential and what they reveal about current approaches to computer-based medical decision making. In all cases, the demonstrations have been performed on-line using network access to the SUMEX computer. The TYPER program, originally developed for the 1980 AIM Workshop by SUMEX staff in collaboration with Dr. Larry Fagan, has continued to be used to good effect for system demonstrations. As recently as May 1982 it was used when a group of physicians from the first meeting of the American Medical Informatics Association (held in San Francisco) visited Stanford to learn about SUMEX and our AIM research.

EMYCIN has generated considerable interest in the academic and business communities. We receive frequent requests for copies of the system and have been distributing it on a non-exclusive basis to anyone who wishes a copy.

NEOMYCIN was presented by Dr. Clancey at a Cognitive Science methodology conference sponsored by the Sloan Foundation in Boulder, Colorado in August 1981. Presentations of this kind carry SUMEX-AIM results out to cognitive psychologists from around the country. Dr. Clancey also presented GUIDON research to a seminar in the Stanford School of Education. Following directly from these contacts, Dr. Derek Sleeman, a computer scientist from Leeds, England with experience in computer-based education, will be arriving later in 1982 to coordinate collaboration between Education and Computer Science researchers at Stanford. We expect that several professors in Education, in particular Dr. Decker Walker, will become involved in our experiments with medical students and begin to participate in our study of medical education.

Several medical school and computer science teachers have also asked to use MYCIN in their computer science or medical computing courses, and we continue to make the programs available frequently to researchers around the world who access SUMEX using the GUEST account.

B. Sharing and Interaction with Other SUMEX-AIM Projects

We have continued collaboration with the PUFF and VM projects. Our development of a domain-independent system (EMYCIN) is facilitated by having a number of very different working systems on which to test our additions and modifications to the program. All the projects have provided us with useful comments and suggestions. Similarly, several researchers around the country, such as Professor Szolovits and students at MIT, have studied MYCIN in detail by running the system on SUMEX and interrupting to analyze the code and reasoning at key steps in a consultation. Thus MYCIN continues to be a vehicle for community building and a stimulus to the application of newer AI techniques that have been used to reimplement portions of MYCIN for experimental purposes.

The community created on the SUMEX resource has other benefits that go beyond actual shared computing. Because we are able to experiment with other developing systems, such as INTERNIST, and because we frequently interact with other workers (at the AIM Workshop or at other meetings around the country), many of us have found the scientific exchange and stimulation to be heightened. Several of us have visited workers at other sites, sometimes for extended periods, in order to pursue further issues which have arisen through SUMEX- or Workshop-based interactions. In this regard, the ability to exchange messages with other workers, both on SUMEX and at other sites, has been crucial to rapid and efficient exchange of ideas. Certainly it is unusual for a small community of researchers with similar scholarly interests to have at their disposal such powerful and efficient communication mechanisms, even among those on opposite coasts of the country.

C. Critique of Resource Management

The SUMEX facility has maintained the high standards that we have praised in the past. The staff members are always helpful and friendly, and work as hard to please the SUMEX community as to please themselves. As a result, the computer is as accessible and easy to use as they can make it. More importantly, it is a reliable and convenient research tool. We extend special thanks to Tom Rindfleisch for maintaining high professional standards for all aspects of the facility.

Finally, we continue to feel the need for more computing power. Much of our research and development continues to take place in the hours from 7 p.m. to 10 a.m., but it is unreasonable to expect all our programming staff to adjust their own schedules around a computer. The existence of the 2020 has been helpful in permitting demonstrations with good response time, and it has allowed us to introduce ONCOCIN in a real clinical environment, but ongoing R&D on the main machine remains difficult much of the time. Even the evening hours are now seeing higher load averages than was once the case. The addition of personal workstations is helping somewhat, but a great deal of research continues to require access to the central SUMEX machine. In this regard, we must note that the KI-10 hardware is becoming increasingly outmoded and is much less capable of managing the load placed upon it than would be the case with some of the newer large machines (e.g. a DEC 2060). Response time aside, we have shifted our development of GUIDON to the Xerox Dolphin in order to take advantage of the larger address space. This has also freed up disk space so that we can comfortably develop NEOMYCIN on SUMEX.

III. RESEARCH PLANS

A. Project Goals and Plans

EMYCIN

As we have noted, EMYCIN is now completed and we do not contemplate further work on the program. The research elements have largely shifted to the NEOMYCIN program under development by Dr. Clancey and colleagues as part of the GUIDON effort. During the coming year, therefore, we expect no direct work on EMYCIN but will be continuing two of the associated projects described in the progress report above:

- (1) development of ROGET will continue and is likely to be complete by the end of 1982;
- (2) the retrospective analysis of MYCIN/EMYCIN will be written by Buchanan and Shortliffe; the book should be largely complete and a publisher identified by this time next year.

GUIDON

Some of the long-range (2-3 years) goals of NEOMYCIN/GUIDON research are summarized below:

- (1) to extend NEOMYCIN's model of diagnostic strategy to include common, non-expert approaches. Besides improving the program's ability to model the student, this enumeration of the space of strategies will allow us to follow a plan of research similar to Brown's and Burton's, but in the domain of diagnostic strategy as opposed to subtraction procedures. Eventually, we want to develop a principled psychological model that will relate strategies to knowledge and processing abilities.
- (2) further studies of expert reasoning in domains that require "forming a picture" of a malfunctioning process. Experience with NEOMYCIN showed that expert diagnosticians attempt to order the data they collect causally, on a time line. Interpretation of observations can be partially understood as an attempt to match this description of onset, course, severity (intensity, frequency), and causal relations of findings onto known malfunctions that are recalled (indexed) by these process variables. This work will build upon recent advances in understanding causality (e.g., deKleer and Brown).
- (3) exploitation of new technology for experimentation with teaching methods. How can we take advantage of the Dolphin's graphic capabilities in a GUIDON tutorial? Besides graphically presenting rule relationships, we might show the student the same kind of diagrams that we use when describing our knowledge bases to our AI colleagues (hierarchies, diagrams relating compiled associations to underlying causal chains). Other than presentation strategies, we would like to experiment with different interfaces, perhaps to break away from a continuous dialogue to use the screen more as a work space for annotating and examining the knowledge base, and organizing data and hypotheses in a diagnostic problem.
- (4) incorporate GUIDON as an integral part of the curriculum in in medical diagnosis at Stanford. We propose to make GUIDON available at the Fleischmann Learning Center at Stanford Medical School, just as the traditional programs built at Massachusetts General and Ohio State were made available. In addition, we will work with one or more teaching fellows at the medical school to include GUIDON as part of the "physical diagnosis" course which is taught regularly at Stanford. This will continue our commitment to empirical research to develop our model of diagnosis and the teaching procedures.

ONCOCIN

There are five areas in which we expect to expend our efforts on the ONCOCIN System during the next few years:

- (1) We will complete the three ONCOCIN evaluations described earlier.
- (2) We will spend time improving the system's documentation and will prepare formal technical reports as well as clinical reports on the results of the evaluation studies.
- (3) We will continue to develop the hypothesis assessment approach to consultation that was briefly described above.
- (4) We will continue development of the query system and integration of the rule analysis system to aid in knowledge base development.
- (5) We will begin encoding additional protocols if time permits.

We shall continue to relate the requirements of the system we are developing to the underlying artificial intelligence methodologies. We are convinced that the basic science frontiers of AI are best explored in the context of systems for real world use; thus ONCOCIN serves as a vehicle for developing an improved understanding of the issues that underlie all forms of knowledge engineering.

B. Requirements for Continued SUMEX Use

All the work we are doing (EMYCIN, GUIDON, ONCOCIN, plus continued use of the original MYCIN program) is totally dependent on continued use of the SUMEX resource. Although some of the GUIDON and ONCOCIN work is shifting to Xerox Dolphins, the SUMEX KI-10's and the 2020 continue to be key elements in our research plan. The programs all make assumptions regarding the computing environment in which they operate, and the ONCOCIN design in particular depends upon proximity to the DEC 2020 which enables us to use a 9600 baud interface.

In addition, we have long appreciated the benefits of GUEST and network access to the programs we are developing. SUMEX greatly enhances our ability to obtain feedback from interested physicians and computer scientists around the country. Network access has also permitted high quality formal demonstrations of our work both from around the United States and from sites abroad (e.g., Finland, Japan, Sweden, Switzerland).

We plan to continue development of NEOMYCIN and GUIDON on a SUMEX Dolphin that will be dedicated to this purpose. However, the project now includes 3 graduate students (one of whom is working jointly with Dr. Shortliffe on explanation research), a full-time programmer, and Dr. Clancey, so it will be necessary to continue use of the SUMEX DEC system for some of our programming (the development of NEOMYCIN's explanation system). Keeping our programs compatible with either system offers the advantage that they can be accessed over the network by remote users.

However, GUIDON2 will eventually be too large for the DEC system address space, so compatibility in the long run is only possible for NEOMYCIN.

C. Requirements for Additional Computing Resources

The acquisition of the DEC 2020 by SUMEX has been crucial to the growth of our research work, both to insure high quality demonstrations and to enable us to develop a system such as ONCOCIN for real-world use in a clinical setting. As we continue to develop systems that are potentially useful as stand-alone packages (e.g., an exportable EMYCIN), the addition of personal workstations has provided particularly valuable new resources. It is not yet clear which machines are optimal for the LISP-based applications we are developing, and an opportunity to test our systems on several small-to-medium machines will be invaluable and in keeping with our desire to move some of the AIM products into a community of service users.

As we have mentioned, the response time on the main machine continues to be a major problem, both during the daytime hours and frequently in the evenings as well. The SUMEX workstations have provided additional cycles to permit off-loading of some users from the PDP-10, and this has significantly benefited the SUMEX research community. In addition, we believe that our GUIDON and ONCOCIN experiences using the Dolphin personal computer are a significant part of our research. First, the Dolphin's large address space is permitting development of the large knowledge bases that these systems require. Second, the Dolphin's graphics will enable us to develop new methods for presenting material to naive users. Third, the Dolphin will provide a reliable, constant "load-average" machine, for running experiments with physicians and students. Finally, the development of ONCOCIN and GUIDON on the Dolphin will demonstrate the feasibility of running intelligent consultation or tutoring systems on small, affordable machines in physicians' offices, schools and other remote sites.

D. Recommendations for Future Community and Resource Development

Because the AI community has largely transitioned to DEC 20 systems running TOPS-20, it is becoming increasingly difficult to share software among sites. Even here at Stanford, there is considerable overhead in providing duplicate versions of our systems so that development work can be shared between SUMEX and the SCORE 2060. Utility software developed elsewhere also cannot be easily transferred to SUMEX for our use. In light of the age of the main SUMEX hardware and the divergence of our resource from related resources available elsewhere in the AIM and general AI communities, we would like to suggest consideration of an upgrade of SUMEX to a more modern central mainframe machine.

II.A.1.7 Protein Structure Project

Protein Structure Modeling Project

Prof. E. Feigenbaum and Mr. Allan J. Terry
Department of Computer Science
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Technical Goals

The goals of the protein structure modeling project are to 1) identify critical tasks in protein structure elucidation which may benefit by the application of AI problem-solving techniques, and 2) design and implement programs to perform those tasks. We have identified two principal areas which are of practical and theoretical interest to both protein crystallographers and computer scientists working in AI. The first is the problem of interpreting a three-dimensional electron density map. The second is the problem of determining a plausible structure in the absence of phase information normally inferred from experimental isomorphous replacement data. Current emphasis is on the implementation of a program for interpreting electron density maps (EDM's).

B. Medical Relevance and Collaboration

The biomedical relevance of protein crystallography has been well stated in an excellent textbook on the subject (Blundell & Johnson, Protein Crystallography, Academic Press, 1976):

"Protein Crystallography is the application of the techniques of X-ray diffraction ... to crystals of one of the most important classes of biological molecules, the proteins. ... It is known that the diverse biological functions of these complex molecules are determined by and are dependent upon their three-dimensional structure and upon the ability of these structures to respond to other molecules by changes in shape. At the present time X-ray analysis of protein crystals forms the only method by which detailed structural information (in terms of the spatial coordinates of the atoms) may be obtained. The results of these analyses have provided firm structural evidence which, together with biochemical and chemical studies, immediately suggests proposals concerning the molecular basis of biological activity."

The project involves a collaboration between computer scientists at Stanford University and crystallographers at Oak Ridge National

Laboratories (Dr. Carroll Johnson), the University of California at San Francisco (Dr. Robert Langridge), and the University of California at San Diego (under the direction of Prof. Joseph Kraut). We also collaborate with Dr. Eric Grosse at Bell Laboratories, whose field is numerical analysis.

C. Progress Summary

We have spent most of the last year adding to the knowledge base. As a result of this work, CRYNALIS can now be considered a successful demonstration system. While the program is not mature enough to warrant its release to the general crystallographic community, it can solve some non-trivial proteins at a expert level of performance. Details can be found in publication nine.

CRYNALIS now consists of eight tasks. In the last year we have added two tasks for locating new islands of certainty in the hypothesis when the initial set has been used up. We have also implemented a task for computing a complete set of atomic coordinates from the set of superatoms found by CRYNALIS. In conjunction with this last task, we are developing FORTRAN algorithms for matching peptide and sidechain templates against the data to further refine the atomic locations.

Finally, we are compiling documentation on the system and the knowledge it embodies. These documents should be sufficiently complete so that we, or other groups, will have little difficulty picking up where we leave off. We also feel that explicit documentation of our model-building heuristics will be useful to the crystallographic community as it provides a new viewpoint, complementary to traditional crystallographic methods.

D. List of Publications

- (1) Carroll Johnson and Eric Grosse, "Interpolation Polynomials, Minimal Spanning Trees, and Ridge-Line Analysis in Density Map Interpretation", American Crystallographic Association Program and Abstracts, 4:2, Evanston, Ill. Aug. 1976
- (2) Robert S. Engelmores and H. Penny Nii, "A Knowledge-Based System for the Interpretation of Protein X-Ray Crystallographic Data," Heuristic Programming Project Memo HPP-77-2, January, 1977. (Alternate identification: STAN-CS-77-589)
- (3) E.A. Feigenbaum, R.S. Engelmores, C.K. Johnson, "A Correlation Between Crystallographic Computing and Artificial Intelligence," in Acta Crystallographica, A33:13, (1977). (Alternate identification: HPP-77-15)
- (4) Robert Engelmores and Allan Terry, "Structure and Function of the CRYNALIS System", Proc. 6IJCAI, 1979. pp250-256 (Alternative identification: HPP-79-16)

- (5) R.S. Engelman, A. Terry, S.T. Freer, and C.K. Johnson, "A Knowledge-Based System for Interpreting Protein Electron Density Maps", Abstracts of Amer. Crystallographic Ass. 7,1 (1979) p38
- (6) E.H. Grosse, "Approximation and Optimization of Electron Density Maps", Stanford University Ph.D. Thesis, Dec. 1980 (Alternative identification: STAN-CS-80-835)
- (7) R. Engelman and A. Terry, Article VII.C3 (Crysalis) in Barr, A., and Feigenbaum, E. A. (eds.), The Handbook of Artificial Intelligence, Vol. II, Stanford Ca., HeurisTech Press, Los Altos, Ca.: Kaufman, 1982
- (8) A. Terry and R. Engelman, "A Knowledge-Based Approach to the Interpretation of Protein Electron Density Maps", in Machine Intelligence, Infotech State of the Art Report, Series 9, Number 3, Pergamon Infotech Ltd. Maidenhead, England, 1981
- (9) A. Terry, "Hierarchical Control of Production Systems", Ph.D. Thesis, Dept. of Information and Computer Science, Univ. of Calif., Irvine, (forthcoming)

E. Funding status

Grant title: The Automation of Scientific Inference: Heuristic Computing Applied to Protein Crystallography

Principal Investigator: Prof. Edward A. Feigenbaum

Funding Agency: National Science Foundation

Grant identification number: MCS 81-17330

Term of award: January 15, 1982 through January 14, 1983

Amount of award: \$28,976 (direct costs only)

II. INTERACTION WITH THE SUMEX-AIM RESOURCE

A. Collaborations

The protein structure modeling project has been a collaborative effort since its inception, involving co-workers at Stanford and UCSD (and, more recently, at Oak Ridge, UCSF, and Bell Laboratories). The SUMEX facility has provided a focus for the communication of knowledge, programs and data. Without the special facilities provided by SUMEX the research would be seriously impeded. Computer networking has been especially effective in facilitating the transfer of information. For example, the more traditional computational analyses of the UCSD crystallographic data are made at the CDC 7600 facility at Berkeley. As the processed data, specifically the EDM's and their Fourier transforms, become available, they are transferred to SUMEX via the FTP facility of the ARPA net, with a

minimum of fuss. (Unfortunately, other methods of data transfer are often necessary as well -- see below.) Programs developed at SUMEX, or transferred to SUMEX from other laboratories, are shared directly among the collaborators. Indeed, with some of the programs which have originated at UCSD and elsewhere, our off-campus collaborators frequently find it easier to use the SUMEX versions because of the interactive computing environment and ease of access. Advice, progress reports, new ideas, general information, etc. are communicated via the message and/or bulletin board facilities.

B. Interaction with Other SUMEX-AIM Projects

Our interactions with other SUMEX-AIM projects have been mostly in the form of personal contacts. We have strong ties to the MYCIN, AGE and MOLGEN projects and keep abreast of research in those areas on a regular basis through informal discussions. The SUMEX-AIM workshops provide an excellent opportunity to survey all the projects in the community. Common research themes, e.g. knowledge-based systems, as well as alternate problem-solving methodologies were particularly valuable to share.

C. Critique of Resource Services

The SUMEX facility provides a wide spectrum of computing services which are genuinely useful to our project -- message handling, file management, Interlisp, Fortran and text editors come immediately to mind. Moreover, the staff, particularly the operators, are to be commended for their willingness to help solve special problems (e.g., reading tapes) or providing extra service (e.g. immediate retrieval of an archived file). Such cooperative behavior is rare in computer centers.

There are several facilities we wish to single out as particularly useful in furthering our research goals. Since the members of the project are physically distant, the MSG program is very useful. Similarly, the file system, the ARCHIVE facility, and the general ease of getting backup files from the operator greatly aid our efforts at coordinating the efforts of collaborators using many large data sets and programs. The crystallographers in the project find SUMEX to be a friendly environment which allows them to do their work with a minimum of dealing with operating system details.

It has become increasingly evident, however, that as CRYVALIS expands, the facility cannot provide enough machine cycles during prime time to support the implementation and debugging of new features. For example, our segment-labeling preprocessor requires about an hour of machine time per 100 residues of protein (this is typically five to eight hours of terminal time during working hours) even when the LISP code is compiled.

III. USE OF SUMEX DURING THE REMAINING GRANT PERIOD (8/79 - 7/81)

A. Long-Range Goals

We have decided to end the project sometime in the fall. We have developed the system to where it demonstrates the basic soundness of our ideas. Unfortunately, development of the system into a generally-useful product would require the full-time assistance of an expert crystallographer. This person would need to restructure the knowledge base, pull the numerous FORTRAN data-reduction programs into a unified package, and extend the crystallographic knowledge contained in the system. We have not found a crystallographer willing to take over these responsibilities, so our goal is to thoroughly document the system and leave the code in a stable, runnable condition.

B. Justification for Continued Use of SUMEX

We feel that SUMEX is the ideal vehicle for further research on CRYNALIS. While some of our work is numerical in nature and uses such facilities as FORTRAN, our main interest is in artificial intelligence. Besides being an expert system of use to the crystallographic community, CRYNALIS is an exploration of the general signal processing problem. We are vitally concerned with issues such as proper architecture for using a wide variety of heuristics effectively and hypothesis formation when both data and model are poor. The utility of our work to the AI community is partially demonstrated by the development of the AGE project, an extension of Ms. Nii's early work on CRYNALIS.

This project progresses by the collaboration of several physically-separated groups. SUMEX provides a unique resource, an electronic community of researchers in our field, through the many systems such as net mail, country-wide access, and community workshops. We feel that CRYNALIS would not be possible outside of such a community.

While we plan to terminate active development work on CRYNALIS in the fall, we request continued use of SUMEX until the end of our grant. This period would be used for dissemination of results. We request use of SUMEX so that we can distribute programs to the crystallographic community and so that we can run demonstrations of our programs.

C. Needs and Plans for Other Computing Resources

We will make minor use of the Stanford Computer Science Department's SCORE machine, mostly for sending files to the Dover printer until such a facility is available on SUMEX.

D. Recommendations for Future Community and Resource Development

There are two recommendations we wish to make, the first and most important is to expand the computing power available to SUMEX users. CRYNALIS is an inherently-large problem. Proteins contain hundreds, to thousands of atoms which means large hypothesis structures, large

quantities of data, and a compute-bound inference program. As the system grows to maturity, we expect increasingly serious problems with address space limitations and with machine cycle availability.

The second recommendation is that SUMEX develop some relatively inexpensive file transfer facility for machines not on the ARPAnet. Software for this already exists in the form of the TTYFTP program (or possible future programs like it, but in a more portable language), the development needed is in hardware and in the TENEX operating system so that transfer rates greater than 1200 baud can be achieved. We are motivated to recommend this not only by our own need for such a facility, but also by the belief that it would aid other collaborations involving SUMEX and outside computers (the SECS project for example), and aid in the dissemination of useful programs from the research setting of SUMEX to user laboratories.

II.A.1.8 RX ProjectThe RX Project: Deriving Medical Knowledge from
Time-Oriented Clinical Databases

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Stanford University

Gio C. M. Wiederhold, Ph.D.
Departments of Computer Science and Electrical Engineering
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Technical Goals

Introduction:

Medical and Computer Science Goals

The long range objectives of our project, called RX, are 1) to increase the validity of medical knowledge derived from large time-oriented databases containing routine, non-randomized clinical data, 2) to provide knowledgeable assistance to a research investigator in studying medical hypotheses on large databases, 3) to fully automate the process of hypothesis generation and exploratory confirmation. For system development we have used a subset of the ARAMIS database.

Computerized clinical databases and automated medical records systems have been under development throughout the world for at least a decade. Among the earliest of these endeavors was the ARAMIS Project, (American Rheumatism Association Medical Information System) under development since 1969 in the Stanford Department of Medicine. ARAMIS contains records of over 17,000 patients with a variety of rheumatologic diagnoses. Over 62,000 patient visits have been recorded, accounting for 50,000 patient-years of observation. The ARAMIS Project has now been generalized to include databases for many chronic diseases other than arthritis.

The fundamental objective of the ARAMIS Project as well as of all other clinical database researchers is to use the data that have been gathered by clinical observation in order to study the evolution and medical management of chronic diseases. Unfortunately, the process of reliably deriving knowledge has proven to be exceedingly difficult. Numerous problems arise stemming from the complexity of disease, therapy, and outcome definitions, from the complexity of causal relationships, from errors introduced by bias, and from frequently missing and outlying data. A major objective of the RX Project is to explore the utility of symbolic computational methods and knowledge-based techniques at solving some of these problems.

The RX computer program is designed to examine a time-oriented clinical database such as ARAMIS and to produce a set of (possibly) causal relationships. The algorithm exploits three properties of causal relationships: time precedence, correlation, and nonspuriousness. First, a Discovery Module uses lagged, nonparametric correlations to generate an ordered list of tentative relationships. Second, a Study Module uses a knowledge base (KB) of medicine and statistics to try to establish nonspuriousness by controlling for known confounders.

The principal innovations of RX are the Study Module and the KB. The Study Module takes a causal hypothesis obtained from the Discovery Module and produces a comprehensive study design, using knowledge from the KB. The study design is then executed by an on-line statistical package, and the results are automatically incorporated into the KB. Each new causal relationship is incorporated as a machine-readable record specifying its intensity, distribution across patients, functional form, clinical setting, validity, and evidence. In determining the confounders of a new hypothesis the Study Module uses previously "learned" causal relationships.

In creating a study design the Study Module follows accepted principles of epidemiological research. It determines study feasibility and study design: cross-sectional versus longitudinal. It uses the KB to determine the confounders of a given hypothesis, and it selects methods for controlling their influence: elimination of patient records, elimination of confounding time intervals, or statistical control. The Study Module then determines an appropriate statistical method, using knowledge stored as production rules. Most studies have used a longitudinal design involving a multiple regression model applied to individual patient records. Results across patients are combined using weights based on the precision of the estimated regression coefficient for each patient.

B. Medical Relevance and Collaboration

As a test bed for system development our focus of attention has been on the records of patients with systemic lupus erythematosus (SLE) contained in the Stanford portion of the ARAMIS Data Bank. SLE is a chronic rheumatologic disease with a broad spectrum of manifestations. Occasionally the disease can cause profound renal failure and lead to an early death. With many perplexing diagnostic and therapeutic dilemmas, it is a disease of considerable medical interest.

In the future we anticipate possible collaborations with other project users of the TOD System such as the National Stroke Data Bank, the Northern California Oncology Group, and the Stanford Divisions of Oncology and of Radiation Therapy.

We believe that this research project is broadly applicable to the entire gamut of chronic diseases that constitute the bulk of morbidity and mortality in the United States. Consider five major diagnostic categories responsible for approximately two thirds of the two million deaths per year in the United States: myocardial infarction, stroke, cancer, hypertension, and diabetes. Therapy for each of these diagnoses is fraught with controversy concerning the balance of benefits versus costs.

- 1) Myocardial Infarction: Indications for and efficacy of coronary artery bypass graft vs. medical management alone. Indications for long-term antiarrhythmics ... long-term anticoagulants. Benefits of cholesterol-lowering diets, exercise, etc.
- 2) Stroke: Efficacy of long-term anti-platelet agents, long-term anticoagulation. Indications for revascularization.
- 3) Cancer: Relative efficacy of radiation therapy, chemotherapy, surgical excision - singly or in combination. Optimal frequency of screening procedures. Prophylactic therapy.
- 4) Hypertension: Indications for therapy. Efficacy versus adverse effects of chronic antihypertensive drugs. Role of various diagnostic tests such as renal arteriography in work-up.
- 5) Diabetes: Influence of insulin administration on microvascular complications. Role of oral hypoglycemics.

Despite the expenditure of billions of dollars over recent years for randomized controlled trials (RCT's) designed to answer these and other questions, answers have been slow in coming. RCT's are expensive of funds and personnel. The therapeutic questions in clinical medicine are too numerous for each to be addressed by its own series of RCT's.

On the other hand, the data regularly gathered in patient records in the course of the normal performance of health care delivery are a rich and largely underutilized resource. The ease of accessibility and manipulation of these data afforded by computerized clinical databases holds out the possibility of a major new resource for acquiring knowledge on the evolution and therapy of chronic diseases.

The goal of the research that we are pursuing on SUMEX is to increase the reliability of knowledge derived from clinical data banks with the hope of providing a new tool for augmenting knowledge of diseases and therapies as a supplement to knowledge derived from formal prospective clinical trials. Furthermore, the incorporation of knowledge from both clinical data banks and other sources into a uniform knowledge base should increase the ease of access by individual clinicians to this knowledge and thereby facilitate both the practice of medicine as well as the investigation of human disease processes.

C. Highlights of Research Progress

1. 1 July 1981 to 1 May 1982

Our predominant objective was to detail the overall conceptual framework for the knowledge base and to develop the extensive computational machinery necessary for creating an adequate statistical study design, executing that study design on an on-line statistical package, and interpreting and incorporating the medical results.

The RX Knowledge Base (KB) :

The central component of RX is a knowledge base of medicine and statistics, organized as a frame-based, taxonomic tree consisting of frames with attached data and procedures. Frames representing diseases and therapies contain procedures that use a variety of time-dependent predicates to label the patient records, facilitating the retrieval of time-intervals of interest in the records. Other frames representing statistical techniques are used to map hypotheses onto study designs and event definitions. Implementing the algorithms and data structures of this KB was one of the major tasks of the current year.

At the current time the RX KB contains about 250 frames of which 150 contain definitions and other relevant information pertaining to disease courses, effects of drugs, lab values, etc. This information comprises a small subset of medical knowledge dealing with some of the signs and symptoms of systemic lupus erythematosus (SLE) as well as the effects and indications of some drugs used for this disease. Other frames contain machine-readable knowledge of statistical techniques needed for testing entered hypotheses. There are approximately 40 time-dependent functions used to map from the database values onto defined frames.

The entire RX system currently contains approximately 400 INTERLISP functions accounting for 200 disk pages of code. The KB is about 60 disk pages. One disk page = 512 words * 36 bits per word. Also one disk page = approx. 1.5 typed pages on 8.5 by 11.5 inch paper.

Statistical Interfaces:

Once the relevant data have been abstracted from patient records they must be analyzed statistically. To do this we have recently adopted the IDL or Interactive Data-Analysis Language package developed at the Xerox Palo Alto Research Corp. IDL is a matrix manipulation language similar to APL and is built upon INTERLISP as is RX itself. The use of IDL for statistical analysis confers a tremendous advantage in that analyses are now highly interactive. IDL has completely supplanted our previous use of SPSS.

Time-Oriented Graphics Package:

This package enables data on an individual patient to be graphed over time, either linearly by visit or by calendar time with a "telescoping" capability. The program overlays graphs of both point data and data represented as episodes.

Clinical Study: The Effect of Prednisone on Cholesterol

As a testbed for the prototype system we have been investigating the hypothesis that the steroid, prednisone, produces a significant elevation of plasma cholesterol. To test this hypothesis, the records of 50 patients with systemic lupus erythematosus (SLE) were transferred from the ARAMIS Database to SUMEX. Of these patients, 18 were found to have five or more

cholesterol determinations and to have had sufficient variance in their prednisone regimens to be testable. The KB is used to elaborate a complex causal model for the prednisone/cholesterol hypothesis that is tested using a hierarchical multiple regression method with time-lagged values. The KB is used to determine sources of possible bias and to control for those variables in the regression or to eliminate corresponding time-intervals from records. An empirical Bayes method is used to average the estimated effects in patients with varying amounts of data.

The result, a highly statistically significant elevation of cholesterol by prednisone, will be submitted for publication during the coming year.

2. Research In Progress

Much work remains to be done in expanding the system software and in expanding the knowledge base. Current work is addressed to increasing the flexibility of the time-segmentation functions and enriching the data structures that encode relationships between objects.

We are trying to make increasingly general the class of medical hypotheses that the system can analyze automatically. This requires incorporating knowledge of additional statistical methods into the KB. We are also attempting to generalize our algorithms for selecting the set of variables that may potentially confound a given hypothesis. As a means for testing and expanding the system's capabilities we intend to perform several specific studies of importance in the management of the rheumatic diseases. Our study of the effect of prednisone on cholesterol was mentioned above. Other studies now being planned include the effect of chronic aspirin ingestion on liver function in rheumatoid arthritis, the specific incidence of infectious complications of steroids as a function of dose and duration, and the utility of various autoantibodies in the prediction of flares of SLE as compared to the utility of other indicators.

Finally, we are continuing to develop the Discovery Module in an attempt to make fuller use of the knowledge base to constrain the search space of hypotheses. This work is being pursued as doctoral dissertation research by Mark Erlbaum, a member of our group.

D. Publications

Blum, Robert L., Automated Induction of Causal Relationships from a Time-Oriented Clinical Database: The RX Project, Proceedings of the AMIA Congress, American Medical Informatics Association, San Francisco, 1982.

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E. Funding Support Status

- 1) Integrating Medical Knowledge and Clinical Data Banks
Robert L. Blum, M.D.: Principal Investigator
National Library of Medicine, New Investigator Award
LM-03370
Total award: \$90,000 (direct)
Term: July 1, 1979 through June 30, 1982
- 2) Deriving Knowledge from Clinical Databases
Gio C. M. Wiederhold, Ph.D.: Principal Investigator
National Center for Health Services Research
HS-4389
Total award: \$127,000 (direct)
Term: September 30, 1981 through September 29, 1983

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Collaborations

Since our project is relatively new, we do not yet have public versions of the programs. There is, however, a large sphere of collaboration that we expect in the future. Once the RX program is developed, we would anticipate collaboration with some of the ARAMIS project sites in the further development of a knowledge base pertaining to the chronic arthritides. The ARAMIS Project at the Stanford Center for Information Technology is used by a number of institutions around the country via commercial leased lines to store and process their data. These institutions include the University of California School of Medicine, San Francisco and Los Angeles; The Phoenix Arthritis Center, Phoenix; The University of Cincinnati School of Medicine; The University of Pittsburgh School of Medicine; Kansas University; and The University of Saskatchewan. All of the rheumatologists at these sites have closely collaborated with the development of ARAMIS, and their interest in and use of the RX project is anticipated. We hasten to mention that we do not expect SUMEX to support the active use of RX as an on-going service to this extensive network of arthritis centers, but we would like to be able to allow the national centers to participate in the development of the arthritis knowledge base and to test that knowledge base on their own clinical data banks.

B. Interactions with Other SUMEX-AIM Projects

Several of the concepts incorporated into the design of the RX Project have been inspired by other SUMEX-AIM Projects. The RX knowledge base is similar to the Units Package of the MOLGEN PROJECT. The production rule inference mechanism used by us is similar to that in the MYCIN Project.

Several programs developed by the MYCIN group are regularly used by RX. These include disk hash file facilities, text editing facilities, and miscellaneous LISP functions. Regular communication on programming details is facilitated by the on-line mail system.

C. Critique of Resource Management

The SUMEX KI-10 has been severely overloaded for at least a year. Working in LISP is impossible during the day and is even difficult at times which were formerly low utilization times. This has forced us to rely increasingly on other local computation facilities.

The SUMEX resource management, per se, has always been accessible and cooperative in trying to provide our project with adequate resources subject to prevailing constraints.

III. RESEARCH PLANS

A. Project Goals and Plans

The overall goal of the RX Project is to develop a computerized medical information system capable of accurately extracting medical knowledge pertaining to the therapy and evolution of chronic diseases from a database consisting of a collection of stored patient records.

1. Short-Term Goals

Goals for the year August, 1982 through July, 1983 have been detailed in section IC. above on research in progress. To summarize that section, our main short-term goal is to generalize and refine our methods for representing causal relationships and for extracting those relationships from empirical data. We are further interested in refining our methods for constraining the hypothesis search space explored by our Discovery Module by more fully utilizing information from the knowledge base.

2. Long-Range Goals: August, 1982 through July, 1986

There are two inter-related long-range goals of the RX Project: 1) automatic discovery of knowledge in a large time-oriented database and 2) provision of assistance to a clinician who is interested in testing a specific hypothesis. These tasks overlap to the extent that some of the algorithms used for discovery are also used in the process of testing an hypothesis.

We hope to make these algorithms sufficiently robust that they will work over a broad range of hypotheses and over a broad spectrum of data distributions in the patient records.

B. Justification for Continued Use of SUMEX

Computerized clinical data banks possess great potential as tools for assessing the efficacy of new diagnostic and therapeutic modalities, for monitoring the quality of health care delivery, and for support of basic medical research. Because of this potential, many clinical data banks have recently been developed throughout the United States. However, once the initial problems of data acquisition, storage, and retrieval have been dealt with, there remains a set of complex problems inherent in the task of accurately inferring medical knowledge from a collection of observations in patient records. These problems concern the complexity of disease and outcome definitions, the complexity of time relationships, potential biases in compared subsets, and missing and outlying data. The major problem of medical data banking is in the reliable inference of medical knowledge from primary observational data.

We see in the RX Project a method of solution to this problem through the utilization of knowledge engineering techniques from artificial intelligence. The RX Project, in providing this solution, will provide an important conceptual and technologic link to a large community of medical

research groups involved in the treatment and study of the chronic arthritides throughout the United States and Canada, who are presently using the ARAMIS Data Bank through the CIT facility via TELENET.

Beyond the arthritis centers which we have mentioned in this report, the TOD (Time-Oriented Data Base) User Group involves a broad range of university and community medical institutions involved in the treatment of cancer, stroke, cardiovascular disease, nephrologic disease, and others. Through the RX Project, the opportunity will be provided to foster national collaborations with these research groups and to provide a major arena in which to demonstrate the utility of artificial intelligence to clinical medicine.

SUMEX as a Resource:

To discuss SUMEX as a resource for program development, one need only compare it to the environment provided by our other resource, the IBM 370/3081 installation at SCIP - the major computing resource at Stanford. Of the programs which we use daily on SUMEX - INTERLISP, MSG, TVEDIT, BBD, LINK - there is nothing even approaching equivalence on the 370, despite its huge user community. These programs greatly facilitate communication with other researchers in the SUMEX community, documentation of our programs, and the rapid interactive development of the programs themselves. The development of a program involving extensive symbolic processing and as large and complex as RX at the CIT facility, would require a staff many times as large as ours. The SUMEX environment greatly increases the productive potential of a research group such as ours to the point where a large project like RX becomes feasible.

Computation Resources Required by RX:

Disk Allocation:

RX requires the use of two large data files that need to be kept on-line: the patient database (DB) and the knowledge base (KB). In the course of testing a hypothesis several other files are used: inverted files, source files for statistical processing, LISP SYSOUT files, etc. Our current total disk allocation of 1500 pages for all RX group members has been just adequate. In the future, with anticipated expansions in numbers of patients and size of the KB, we intend to request an increase of our total allocation to 2000 pages.

C. Other Computational Resources

It is clear that the scope of potential application of the RX Project is large. Within the term of the SUMEX-AIM grant projected through July, 1986, we anticipate the involvement of several of the national ARAMIS collaborating institutions in developing and testing arthritis knowledge bases that reflect their own patient populations and therapeutic biases. The current SUMEX machine configuration will not be able to support this national interaction because the central processors of the KI-10 are already taxed to the limit. Ours is among the SUMEX groups that would

greatly benefit by the addition of one or more PDP-10 compatible machines, that could provide support to our anticipated national user community. Another resource that would be highly desirable is a faster and more reliable means for transferring data interactively between SUMEX and the CIT IBM 370. Our current method utilizes a 2400 baud line with transmission from CIT to SUMEX only, and is fraught with a high error rate. The addition of a reliable local network facility would greatly facilitate our ability to transfer patient files from CIT to SUMEX.

D. Recommendations for Resource Development

SUMEX is heavily loaded everyday and almost every evening. Program research is next to impossible during those periods. Program development would be greatly facilitated by the addition of any resources that lessened this loading: upgrading the current machine to a KL or 20/60 or adding core to decrease page swapping.

II.A.2 National AIM Projects

The following group of projects is formally approved for access to the AIM aliquot of the SUMEX-AIM resource or the Rutgers-AIM resource. Their access is based on review by the AIM Advisory Group and approval by the AIM Executive Committee.

II.A.2.1 Acquisition of Cognitive Procedures (ACT)

Acquisition of Cognitive Procedures (ACT)

Dr. John Anderson
Carnegie-Mellon University

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

To develop a production system that will serve as an interpreter of the active portion of an associative network. To model a range of cognitive tasks including memory tasks, inferential reasoning, language processing, and problem solving. To develop an induction system capable of acquiring cognitive procedures with a special emphasis on language acquisition and problem-solving skills.

B. Medical Relevance and Collaboration

1. The ACT model is a general model of cognition. It provides a useful model of the development of and performance of the sorts of decision making that occur in medicine.
2. The ACT model also represents basic work in AI. It is in part an attempt to develop a self-organizing intelligent system. As such it is relevant to the goal of development of intelligent artificial aids in medicine.

We have been evolving a collaborative relationship with James Greeno and Allan Lesgold at the University of Pittsburgh. They are applying ACT to modeling the acquisition of reading and problem solving skills. We have made ACT a guest system within SUMEX. ACT is currently at the state where it can be shipped to other INTERLISP facilities. We have received a number of inquiries about the ACT system. ACT is a system in a continual state of development but we periodically freeze versions of ACT which we maintain and make available to the national AI community.

C. Highlights of Research Progress

Our ACTF system is a production system that operates in a semantic network data base. Our learning work has been focused on ways of increasing the power of production systems for performing various tasks. One class of learning mechanisms concern what we call knowledge compilation. This involves automatic mechanisms for creating productions that directly perform behavior that formerly required interpretative processing of knowledge in the semantic network. These compilation mechanisms also model the process by which human experts develop special purpose procedures to deal with the different types of problems that occur in their domain of expertise.

Another class of learning mechanisms are concerned with tuning existing procedures so that they apply more appropriately. There are various mechanisms concerned with extending or generalizing the range of application of a procedure. In the past year we have been working at reducing these different generalization processes to a common partial matching process. In addition to generalization, tuning occurs in the ACTF system by means of discrimination and composition. Discrimination is a process for restricting the range of applicability of a production. Composition attempts to build macro-operators out of a series of productions.

The third direction of our learning work has been concerned with developing a flexible strength-based set of conflict resolution rules. Here we are concerned with modelling the gradual improvement seen in human cognitive skills and also providing the system with the resilience so that it can recover from noise and changes in environmental contingencies.

We have been applying this theory in detail to a simulation of how students acquire proof skills in geometry. We have a more or less thorough analysis of how students learn new postulates of geometry; we initially use these postulates in an interpretative fashion, integrating them with prior knowledge; how they compile special purpose procedures that directly apply this knowledge to proof generation; and how these procedures become tuned with practice. This application has provided strong evidence for most of the learning developments in the ACT system. It has also forced us to develop formalisms for how planning and problem-solving should be structured within a production-system framework.

D. List of Project Publications

- [1] Anderson, J.R. Language, Memory, and Thought. Hillsdale, N.J.: L. Erlbaum, Assoc., 1976.
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- [11] Neves, D.M. & Anderson, J.R. Knowledge compilation: Mechanisms for the automatization of cognitive skills. In J.R. Anderson (Ed.), Cognitive Skills and their Acquisition. Hillsdale, N.J.: Lawrence Erlbaum Associates, 1981.
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- [15] Anderson, J.R. A general learning theory and its application to the acquisition of proof skills in geometry. In R. Michalski, J. Carbonell, and T. Mitchell (Eds) Machine Learning, forthcoming.
- [16] Anderson, J.R. A.C.T. Cambridge, MA: Harvard University press, 1983.
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E. Funding Support

An information-processing analysis of learning in geometry
 John R. Anderson, Principal Investigator
 National Science Foundation (IST-80-15357)
 \$186,000 Feb 15, 1981 - Feb 15, 1984

II. INTERACTION WITH THE SUMEX-AIM RESOURCE

A. Collaborations, Interactions, and Sharing of Programs via SUMEX.

We have received and answered many inquiries about the ACT system over the ARPANET. This involves sending documentations, papers, and copies

of programs. The most extensive collaboration has been with Greeno and Lesgold who were also on SUMEX.

We find the SUMEX-AIM workshops ideal vehicles for updating ourselves on the field and for getting to talk to colleagues about aspects of their work of importance to us.

Due to memory space problems encountered by ACT we expect that soon we will need to make use of the smaller version of INTERLISP developed at SUMEX for use in the CONGEN program.

B. Critique of Resource Management

The SUMEX-AIM resource has been well suited for the needs of our project. We have made the most extensive use of the INTERLISP facilities and the facilities for communication on the ARPANET. We have found the SUMEX personnel extremely helpful both in terms of responding to our immediate emergencies and in providing advice helpful to the long-range progress of the project. Despite the fact that we are not located at Stanford, we have not encountered any serious difficulties in using the SUMEX system; in fact, there are real advantages in being in the Eastern time zone where we can take advantage of the low load on the system during the morning hours. We have been able to get a great deal of work done during these hours and try to save our computer-intensive work for this time.

Two location changes by the ACT project (from Michigan to Yale in the summer of 1976 and from Yale to Carnegie-Mellon in the summer of 1978) have demonstrated another advantage of working on SUMEX: In both cases we were back to work on SUMEX the day after our arrival.

III. RESEARCH PLANS (8/80-7/86)

A. Project Goals and Plans

Our long-range goals are: (1) Continued development of the ACT system; (2) Application of the system to modeling of various cognitive processes; (3) Dissemination of the ACT system to the national AI community.

This is a period of major evolution for the ACT theory. We have been developing three special versions of the ACTF learning that allow us to more efficiently simulate learning in three domains: proving theorems in geometry, speaking a new language, and writing programs in LISP. We are also performing special purpose simulations of the processes of spreading activation in memory retrieval and of pattern-matching processes in reading. We will be assimilating our experiences with these special purpose simulations in putting forth a major revision of the ACT theory. A research monograph is being written setting forth this theory and is scheduled for publication in Spring, 1983. Subsequent to the writing of this monograph we intend to implement the ACT* successor to ACTF that will embody the new conceptions.

B. Justification for Continued Use of SUMEX:

Our goal for the ACT system is that it should serve as a ready-made "programming language" available to members of the cognitive science community for assembling psychologically-accurate simulations of a wide range of cognitive processes. Our intention and ability to provide such a resource justifies our use of the SUMEX facility. This facility is designed expressly for the purpose of developing and supporting such national AI resources and is, in this regard, clearly superior to the facilities we have available locally from the Carnegie-Mellon computer science department. Among the most important SUMEX advantages are the availability of INTERLISP on a machine accessible by either the ARPANET or TYMNET and the existence of a GUEST login. It appears that, at least for the time being, ACT has no hope of being a national resource unless it resides at SUMEX.

C. Needs and Plans for Other Computational Resources

Carnegie-Mellon's is upgrading its PDP-10 hardware to emerging state-of-the-art machines (PERQ, VAX, LISP machines, etc.) promises to provide an excellent resource, and we hope to have access to that resource as it develops. A major decision that needs to be made in the next 6 months is whether to implement the ACT* system locally or on SUMEX.

D. Comments and Suggestions for Future Resource Goals

We are beginning to feel squeezed by various limitations of the SUMEX facility. The problem of peak load is quite serious. We have also been struggling with the address limitations of the current INTERLISP which is made more grievous by the amount of space INTERLISP requires. The computation time and address space limitations have meant that we have not been able to pursue certain projects that we would have otherwise. We applaud any efforts to increase computational power, to increase the address space of INTERLISP (e.g. VAXes), or to create significantly more space efficient versions of INTERLISP.

It seems clear that the eventual trend will be to do more and more computation locally on the ever more powerful and cheaper machines. SUMEX could help us in the choices we are facing in terms of local computation. If we could have experimental access to the new machines like Dolphins, related software, and software advice, it would be easier to make decisions about new resources. It would also be very helpful to develop programs on the SUMEX machines which could eventually be transferred to local machines when acquired. Finally, and perhaps most important, it seems important to make an effort to promote communication among local machines to maintain the community that has been built up through SUMEX.

II.A.2.2 CADUCEUS Project (INTERNIST)

CADUCEUS Project

J. D. Myers, M.D. and H. Pople, Ph.D.
University of Pittsburgh
Pittsburgh, Pennsylvania

I. SUMMARY OF RESEARCH PROGRAM

A. Medical Rationale

The principal objective of this project is the development of a high-level computer diagnostic program in the broad field of internal medicine as an aid in the solution of complex and complicated diagnostic problems. To be effective, the program must be capable of multiple diagnoses (related or independent) in a given patient.

A major achievement of this research undertaking has been the design of a program called INTERNIST-I, along with an extensive medical knowledge base. This program has been used over the past 10 years to analyze many hundreds of difficult diagnostic problems in the field of internal medicine. These problem cases have included cases published in medical journals (particularly Case Records of the Massachusetts General Hospital, in the New England Journal of Medicine), CPCs, and unusual problems of patients in our Medical Center. In most instances, but by no means all, INTERNIST-I has performed at the level of the skilled internist, but the experience has high-lighted several areas for improvement.

The INTERNIST-I system, in complex cases with multiple diagnoses, operates in a sequential manner. The leading diagnostic hypothesis, i.e. the one with the most supportive clinical evidence both positive and negative, is worked on initially until confirmed or downgraded and replaced by a second hypothesis which is now the stronger. When the first diagnosis is confirmed, the system awards credit to all other diseases which are related ("linked") to the confirmed diagnosis so as to favor, as is logical, a set of related diagnoses rather than independent ones. This sequential analysis can be time consuming and at times involves "false starts." The skilled clinician, instead of focusing on disease A, confirming it, and then moving on to related disease B, etc., will consider from the onset of hypothesis of disease A plus disease B, in other words a diagnostic complex. We believe that our second generation system, CADUCEUS, can be built to accomplish this same form of logical analysis. To do so requires refinement of the computer diagnostic algorithms as well as some reorganization of the medical knowledge base.

The concept of "facets" of diseases has been introduced. Facets are selected pathophysiologic processes or concepts which apply to a broad range of individual diseases. They include such items as cholestasis, coagulopathy of liver disease, acute hemorrhage, and respiratory acidosis.

Facets are comprised of individual clinical manifestations of disease, and the number of the latter in a facet varies from a few to as many as fifteen. A more general or higher level facet may include a number of more specific or limited facets in its structure. Drs. Myers and Miller have reorganized the 57 individual hepatobiliary diseases profiled in the medical knowledge base into facets. Some manifestations of disease are specific predisposing factors and others are specific findings, e.g. bacterial cultures, but the vast majority of manifestations are subsumed into facets. It is reassuring that, taking facets, predisposing factors and specific findings together, all significant manifestations of each of the 57 hepatobiliary diseases are included in the reorganization. The number of facets per disease varies from a half-dozen to more than a dozen.

The use of facets provides certain advantages. The diagnostic analysis starts from broader concepts and more basic pathophysiological and patho-biochemical ones. The use of facets should overcome a present disadvantage of INTERNIST-I, namely that the first diagnosis with which a clinical finding is compatible explains that finding even though some other disease present in the patient is a better and more potent explanation. In the new system, individual manifestations are often assigned to multiple facets and thus may be utilized more prudently in the diagnostic analysis.

Manifestations, as well as facets, are being modified so as to portray important anatomical information, a point often underplayed in INTERNIST-I.

It is planned that CADUCEUS will as well include a better time axis in regard to the development of a disease process or the sequence of diseases.

B. Medical Relevance and Collaboration

The program inherently has direct and substantial medical relevance.

The institution of collaborative studies with other institutions has been deferred pending completion of the programs and knowledge base enhancements required for CADUCEUS. The installation of our own, dedicated VAX computer will be expected to aid considerably any future collaboration.

C. Highlights of Research Progress

Accomplishments This Past Year:

During the past year, there has been continued expansion of the CADUCEUS knowledge base within the context of the original INTERNIST-I system, which is operational at SUMEX-AIM. In addition, there has been a concerted effort to develop an in-house capability to enable programs originally written in INTERLISP to be run in our new local VAX/FANZLISP environment. To this end, we have developed a set of macro capabilities that handle the major dissimilarities of these two LISP host processors. In particular, we now have within FRANZLISP reasonably complete CLISP and RECORD package facilities.

Our objective has been to make operational in the local setting the new CADUCEUS diagnostic programs and knowledge base editors, which had been developed at SUMEX. At this writing, this conversion process is virtually complete. Because of extensive machine dependencies in the original INTERNIST-I code, and because of known deficiencies in the logic and structure of that program there are no current plans to convert INTERNIST-I to run in the VAX/FRANZLISP environment.

The modified manifestations and the newly devised facets are in process of entry into our new VAX computer, and extensive testing of the reorganized medical knowledge base and the computer operating program (in FRANZLISP) is planned for the next year.

The medical knowledge base has continued to grow both in the incorporation of new diseases and the modification of diseases already profiled so as to include recent advances in medical knowledge. The knowledge base now includes 536 individual disease profiles, 3,679 manifestations of disease, and about 1,500 "links" or interrelationships among diseases as well as a myriad of miscellaneous pieces of information which are essential for the correct operation of the system. Twenty-two new diseases have been profiled during the past year and the pediatrics knowledge base has continued to grow as well. In addition, neurologists Gordon Banks and Bruce Weimer, who have recently become associated with the project, have begun developing CADUCEUS knowledge structures for selected problem areas in neurology.

Research in Progress:

There are five major components to the continuation of this research project:

- 1) The completion, continued updating, refinement and testing of the extensive medical knowledge base required for the operation of INTERNIST-I.
- 2) The completion and implementation of the improved diagnostic consulting program, CADUCEUS, which has been designed to overcome certain performance problems identified during the past five years' experience with the original INTERNIST-I program.
- 3) Institution of field trials of CADUCEUS on the clinical services in internal medicine at the Health Center of the University of Pittsburgh.
- 4) Expansion of the clinical field trials to other university health centers which have expressed interest in working with the system.
- 5) Adaptation of the diagnostic program and data base of CADUCEUS to subserve educational purposes and the evaluation of clinical performance and competence.

Current activity is devoted mainly to the first two of these, namely, the continued development of the medical knowledge base, and the implementation of the improved diagnostic consulting program.

D. List of Relevant Publications

1. Pople, H.E. "The Formation of Composite Hypotheses in Diagnostic Problem Solving: An Exercise in Synthetic Reasoning", Proceedings of the Fifth International Joint Conference on Artificial Intelligence, Boston, August 1977.
2. Pople, H.E. "On the Knowledge Acquisition Process in Applied A.I. Systems", Report of Panel on Applications of A.I., Proceedings of Fifth International Joint Conference on Artificial Intelligence, 1977.
3. Pople, H.E., Myers, J. D. & Miller, R.A. "The DIALOG Model of Diagnostic Logic and its Use in Internal Medicine, Proceedings of the Fourth International Joint Conference on Artificial Intelligence, Tbilisi, USSR, September 1975.
4. Pople, H.E. "Artificial Intelligence Approaches to Computer-based Medical Consultation, Proceedings IEEE Intercon, New York, 1975.
5. Myers, J. D. "The Process of Clinical Diagnosis and Its Adaptation to the Computer," in The Logic of Discovery and Diagnosis in Medicine, University of Pittsburgh Series in the Philosophy and History of Science, University of California Press (in press).
6. Myers, J. D., Pople, H. E. & Miller, R. A. "INTERNIST: Can Artificial Intelligence Help?" in Clinical Decision and Laboratory Use, University of Minnesota Press (in press).
7. Pople, H. E. "Coming to Grips with the Multiple Diagnosis Problem," in Computer-Assisted Decision Making Using Clinical and Paraclinical (Laboratory) Data. B. Statland & S. Bauer (eds.) Mediad Inc., Tarrytown, N. Y., 1980, pp. 81-88. Reprinted in The Logic of Discovery and Diagnosis in Medicine, University of Pittsburgh Series in the Philosophy and History of Science, University of California Press (in press).
8. Pople, H. E. "Heuristic Methods for Imposing Structure on Ill-structured Problems: The Structuring of Medical Diagnostics," in Artificial Intelligence in Medicine, AAAS Symposium Series, Westview Press (forthcoming 1982).

E. Funding Support

1. Clinical Decision Systems Research Resource

Harry E. Pople, Jr., Ph.D.
Associate Professor Business

Jack D. Myers, M.D.
University Professor (Medicine)
University of Pittsburgh

Division of Research Resources
National Institutes of Health

5 R24 RR01101-05

07/01/80 - 06/30/85
\$1,607,717

07/01/81 - 06/30/82
\$202,632

2. INTERNIST: A Computer-Based Diagnostic Consultant

Harry E. Pople, Jr., Ph.D.
Associate Professor of Business

Jack D. Myers, M.D.
University Professor (Medicine)
University of Pittsburgh

National Library of Medicine
National Institutes of Health

5 R01 LM03710-02

07/01/80 - 06/30/85
\$817,884

07/01/81 - 06/30/82
\$126,746

3. New Computer-Based Patient Case Simulator

Randolph A. Miller, M.D.
 Assistant Professor of Medicine
 University of Pittsburgh

National Library of Medicine - New Investigator
 National Institutes of Health

5 R23 LM03589-02

07/01/80 - 06/30/83
 \$87,005

07/01/81 - 06/30/82
 \$29,555

4. Neurologic Consultation Computer Program

Gordon E. Banks, M.D.
 Assistant Professor of Medicine
 University of Pittsburgh
 National Library of Medicine - New Investigator
 National Institutes of Health

5 R23 LM03889-01

04/01/82 - 03/31/85
 \$107,675

04/01/82 - 03/31/83
 \$35,725

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A, B. Collaborations and Medical Use of Program Via SUMEX

CADUCEUS remains in a stage of research and development. As noted above, we are continuing to develop better computer programs to operate the diagnostic system, and the knowledge base cannot be used very effectively for collaborative purposes until it has reached a critical stage of completion. These factors have stifled collaboration via SUMEX up to this point and will continue to do so for the next year or two. In the meanwhile, through the SUMEX community there continues to be an exchange of information and states of progress. Such interactions particularly take place at the annual AIM Workshop.

C. Critique of Resource Management

SUMEX has been an excellent resource for the development of CADUCEUS. Our large program is handled efficiently, effectively and accurately. The staff at SUMEX have been uniformly supportive, cooperative, and innovative in connection with our project's needs.

III. RESEARCH PLANS (7/81-6/86)

A. Project Goals and Plans

The prototype CADUCEUS programs and the trial reorganization of the liver and biliary tract diseases will be tested in the VAX/FranzLisp environment over the summer and fall of this year. As rapidly as possible and pending further refinement and reorganization from experience with the new system, the remainder of the medical knowledge base will be entered. Local and later collaborative field trials must necessarily be postponed until this development has been accomplished.

At least 200 important medical diseases remain to be programmed. Renewed effort in this direction is now being expanded now that other tasks have been surmounted. Expanded efforts in the fields of neurology and pediatrics are included as described above.

B. Justification and Requirements for Continued SUMEX Use

Our use of SUMEX will obviously decline with the installation of our VAX. Nevertheless, the excellent facilities of SUMEX are expected to be used for certain developmental work. It is intended, further, to keep INTERNIST-I at SUMEX for comparative use as CADUCEUS is developed here. Our team hopes to remain as a component of the SUMEX community and to share experiences and developments.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM

Our predictable needs in this area will be met by the dedicated VAX computer recently installed.

D. Recommendations for Future Community and Resource Development

Whether a program like CADUCEUS, when mature, will be better operated from centralized, larger computers or from the developing self-contained personal computers is difficult to predict. For the foreseeable future it would seem that centralized, advanced facilities like SUMEX will be important in further program development and refinement.

II.A.2.3 Hierarchical Models of Human Cognition

Hierarchical Models of Human Cognition (CLIPR Project)

Walter Kintsch and Peter G. Polson
University of Colorado
Boulder, Colorado

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The two CLIPR projects have made progress in their research in this past year. This progress is almost completely due to our access to the SUMEX facility. The prose comprehension group has completed one major project, and is currently interacting with other SUMEX projects with the goal of building a prose comprehension model that reflects state-of-the-art knowledge from psychology and artificial intelligence.

The main activity of the planning group during the last year has been completion of the analysis of thinking-out-loud protocols collected from both expert and novice software designers. SUMEX facilities have been used to store, edit, and reformat the raw protocols to facilitate later analysis. Results of successive analyses are then input to SUMEX, and SUMEX facilities are used to collate the various results. In addition, we have just started a new project studying the psychological factors underlying device complexity and the difficulties that nontechnically trained individuals have in learning to use devices like work processors.

Technical Goals:

The CLIPR project consists of two subprojects. The first, the text comprehension project, is headed by Walter Kintsch and is a continuation of work on understanding of connected discourse that has been underway in Kintsch's laboratory for over eight years. The second, the planning project, is headed by Peter Polson of the University of Colorado and Michael Atwood of Bell Telephone Laboratories, Denver, formerly of Science Applications Incorporated, Denver, and is studying the processes of planning using software design tasks. In addition, Polson in collaboration with David Kieras of the University of Arizona, Tucson, is studying the learning and problem solving processes involved in the utilization of devices like word processors.

The goal of the prose comprehension project is to develop a computer system capable of the meaningful processing of prose. This work has been generally guided by the prose comprehension model discussed by Kintsch and van Dijk (1978), although our programming efforts have identified necessary clarifications and modifications in that model (Miller & Kintsch, 1980, 1981; Kintsch & Miller, 1981; Miller, 1982). In general, this research has emphasized the importance of knowledge and knowledge-based processes in

comprehension, and we are accordingly working with the AGE and UNITS groups at SUMEX toward the development of a knowledge-based, blackboard model of prose comprehension. We hope to be able to merge the substantial artificial intelligence research on these systems with psychological interpretations of prose comprehension, resulting in a computational model that is also psychologically respectable.

The primary goal of the planning project is the development of a model of human performance on software design tasks. We have concentrated on developing a deeper understanding of our protocol data, to increase our knowledge of the details of the planning processes and the knowledge structures that experts use in the process of planning. We have developed a method of protocol analysis that essentially involves the transforming of the protocol into a low level theoretical description of the processes used to solve the design problem. We have assumed a very simplified version of a blackboard model that is described in Jeffries, Turner, Polson, and Atwood (1981). We currently carry out our analysis by hand, developing a form of this low level model for each protocol.

The goal of the device complexity project is to develop explicit models of the user-device interaction. Our current plan is to model the device as a nested automata and the user as a production system. The purpose of developing such models would be to make explicit kinds of knowledge that are required to operate different kinds of devices and to specify the processing loads imposed by different implementations of a device. We feel that this offer are tools that are being developed at SUMEX--in particular AGE and the UNIT package--will dramatically facilitate our abilities to generate such models of the user-device interface.

B. Medical Relevance and Collaboration

The text comprehension project impacts indirectly on medicine, as the medical profession is no stranger to the problems of the information glut. By adding to the research on how computer systems might understand and summarize texts, and determining ways by which the readability of texts can be improved, medicine can only be helped by research on how people understand prose. Development of a more thorough understanding of the various processes responsible for different types of learning problems in children and the corresponding development of a successful remediation strategy would also be facilitated by an explicit theory of the normal comprehension process.

Note that our goal of a blackboard model is particularly relevant to the understanding of learning difficulties. One important aspect of a blackboard model is the separation of cognitive processes into a set of interacting subprocesses. Once such subprocesses have been identified and constructed, it would be instructive to observe the model's performance when certain of these processes are facilitated or inhibited. Many researchers have shown that there are a variety of cognitive deficits (insufficient short-term memory capacity, poor long-term memory retrieval, and such) that can lead to reading problems. Having a blackboard model in which the power of individual components could be manipulated would be a significant step in determining the nature of such reading problems.

The planning project is attempting to gain understanding of the cognitive mechanisms involved in design and planning tasks. The knowledge gained in such research should be directly relevant to a better understanding of the processes involved in medical policy making and in the design of complex experiments. We are currently using the task of software design to describe the processes underlying more general planning mechanisms that are also used in a large number of task oriented environments like policy making.

Both the text comprehension project and the planning project involve the development of explicit models of complex cognitive processes; cognitive modelling is a stated goal of both SUMEX and research supported by NIMH.

The on-going development of the prose comprehension model would not be possible without our collaboration with the AGE and UNITS research groups. We look forward to a continued collaboration, with, we hope, mutually beneficial results. Several other psychologists have either used or shown an interest in using an early version of the prose comprehension model, including Alan Lesgold of SUMEX's SCP project, who is exporting the system to the LRDC vax. We have also worked with James Greeno -- another member of the SCP project -- on a project that will integrate this model with models of problem solving developed by Greeno and others at the University of Pittsburgh. Needless to say, all of this interaction has been greatly facilitated by the local and network-wide communication systems supported by SUMEX. There has been considerable communication between members of the prose comprehension and AGE/UNITS groups as program bugs have been discovered and corrected; the presence of a mail system has made this process infinitely easier than if telephone or surface mail messages were required. The mail system, of course, has also enabled us to maintain professional contacts established at conferences and other meetings, and to share and discuss ideas with these contacts.

C. Progress Summary

The prose comprehension project has completed an initial version of a model of prose comprehension (Miller & Kintsch, 1980). This model has been applied to a large number of texts, and has yielded quite reasonable predictions of recall and readability. Psychologists from other universities have used this system to derive reading time and recall predictions for their own experimental materials. We are currently using the AGE and UNITS packages to extend this model toward one that can make use of world knowledge in its analyses; this model is discussed in Miller and Kintsch (1981) and Miller (1982).

The planning group has completed the detailed analysis of several long thinking-out-loud protocols collected from both expert and novice software designers. These analyses involved the development of a lower level model for each of the protocols. See Atwood and Jeffries (1980) for details and examples.

The device complexity project is just getting underway. One of our primary objectives for this year is to develop an explicit model for the knowledge structures involved in the user-device interaction and we will then consider designs for possible simulation programs.

D. List of Relevant Publications

- Atwood, M. E., & Jeffries, R. Studies in plan construction I: Analysis of an extended protocol. Technical Report SAI-80-028-DEN, Science Applications, Incorporated, Denver, Co. March, 1980.
- Atwood, M. E., & Jeffries, R. Studies in plan construction II: Novice design behavior. Technical Report SAI-80-154-DEN, Science Applications, Incorporated, Denver, Colorado, December, 1980.
- Atwood, M. E., Polson, P. G., Jeffries, R., and Ramsey, H. R. Planning as a process of synthesis. Technical Report SAI-78-144-DEN, Science Applications, Incorporated, Denver, Co. December, 1978.
- Jeffries, R., Turner, A., , Polson, P. G., & Atwood, M. E. The process of designing software. J. R. Anderson (Ed.), Cognitive skills and their acquisition. Hillsdale, N.J.: Erlbaum, 1981, 254-285.
- Kieras, D. E. and Polson, P. G. An outline of a theory of the user complexity of devices and systems. Working Paper No. 1, Device Complexity Project, Universities of Arizona and Colorado, May 1982.
- Kintsch, W. On modelling comprehension. Invited address at the American Educational Research Association convention. San Francisco, April 10, 1979.
- Kintsch, W. and van Dijk, T. A. Toward a model of text comprehension and production. Psychological Review, 1978, 85, 363-394.
- Miller, J. R., & Kintsch, W. Readability and recall of short prose passages: A theoretical analysis. Journal of Experimental Psychology: Human Learning and Memory, 1980, 6, 335-354.
- Miller, J. R., & Kintsch, W. Readability and recall of short prose passages. Text, 1981, 1, 215-232.
- Miller, J. R. A knowledge-based mode of prose comprehension: Applications to expository text. Paper presented at the American Educational Research Association meeting, April, 1981.
- Kintsch, W., & Miller, J. R. Knowledge-based processes in prose comprehension. Paper presented at the 21st annual meeting of the Psychonomics Society, St. Louis, November, 1980.
- Miller, J. R. A knowledge-based model of prose comprehension: Applications to expository text. In B. K. Britton and J. B. Black (Eds.), Understanding expository text. Hillsdale, N. J.: Erlbaum, 1982.

E. Funding Support Status

1. Readability and Comprehension.
Walter Kintsch, Professor, University of Colorado
National Institute of Education
NIE-G-78-0172
9/1/78 - 8/31/81: \$96,627
9/1/80 - 8/31/81: \$46,537
2. Text Comprehension and Memory
Walter Kintsch, Professor, University of Colorado
National Institute of Mental Health
5 R01 MH15872-14-16
7/1/81 - 6/30/84: \$148,693
7/1/81 - 6/30/82: \$37,370
3. Comprehension and Analysis of Information in Text
Walter Kintsch, Professor, University of Colorado, and
Lyle E. Bourne, Jr., Professor, University of Colorado
Office of Naval Research, Personnel and Training Programs
ONR N00014-78-C-0433
6/1/78 - 6/30/82: \$225,265
7/18/81 - 6/30/82: \$78,125
4. Procedural Net Theories of Human Planning and Problem Solving
Michael Atwood, Research Psychologist, Science Applications,
Incorporated, Denver, Colorado
Office of Naval Research, Personnel and Training Programs
ONR N0014-78-C-0165
1/25/78 - 12/31/80: \$230,000
1/1/80 - 6/30/81: \$85,000
5. User Complexity of Devices and Systems
David Kieras, Associate Professor, University of Arizona
Peter G. Polson, Professor, University of Colorado
International Business Machines Corporation
1/1/82-12/31/82: \$104,000

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Sharing and Interactions with Other SUMEX-AIM Projects

Our primary interaction with the SUMEX community has been the work of the prose comprehension group with the AGE and UNITS projects at SUMEX. Feigenbaum and Nii have visited Colorado, and one of us (Miller) recently attended the AGE workshop at SUMEX. Both of these meetings have been very valuable in increasing our understanding of how our problems might best be solved by the various systems available at SUMEX. We also hope that our experiments with the AGE and UNITS packages have been helpful to the development of those projects.

We should also mention theoretical and experimental insights that we have received from Alan Lesgold and other members of the SUMEX SCP project. The initial comprehension model (Miller & Kintsch, 1980) has been used by Dr. Lesgold and other researchers at the University of Pittsburgh, as well as researchers at Carnegie-Mellon University, the University of Manitoba, Rockefeller University, and the University of Victoria.

B. Critique of Resource Management

The SUMEX-AIM resource is clearly suitable for the current and future needs of our project. We have found the staff of SUMEX to be cooperative and effective in dealing with special requirements and in responding to our questions. The facilities for communication on the ARPANET have also facilitated collaborative work with investigators throughout the country.

III. RESEARCH PLANS

A. Long Range Projects Goals and Plans

The primary long-term goal of the prose comprehension group is the development of a blackboard-based model of prose comprehension. Correspondingly, we anticipate continued use of the AGE and UNITS packages. These packages allow us to model the knowledge structures possessed by people and the inferential processes that operate upon those structures, and are essential to our work.

The primary goal of the device complexity project is the development of a theory of the processes and knowledge structures that are involved in the performance of routine cognitive skills making use of devices like word processors. We plan to model the user-device interaction by representing the users processes and knowledge as a production system and the device as a nested automata. We are also studying the role of mental models in learning how to use them.

B. Justification and Requirements for Continued SUMEX Use

The research of the prose comprehension project is clearly tied to continued access to the AGE and UNITS packages, which are simply not available elsewhere. We hope that our continued use of these systems will be offset by the input we have been and will continue to provide to those projects: our relationship has been symbiotic, and we look forward to its continuation.

C. Needs and Plans for Other Computational Resources

We currently use two other computing systems located at the University of Colorado. One is the Department of Psychology's VAX 11/780, which is used primarily to run real-time experiments to be modeled on SUMEX. The second is the University of Colorado's CDC 6400, which is used for various types of statistical analysis.

When the ARPA-sponsored Vax/Interlisp project is completed, we would be most interested in experimenting with becoming a remote AGE/UNITS site. It would seem that this sort of development is the ultimate goal of the package projects, and this type of interaction, once it becomes feasible, would be a logical extension of our association with the SUMEX facility.

D. Recommendations for Future Community and Resource Development

Our primary recommendation for future development within SUMEX involves (a) the continued support of INTERLISP, which is needed for AGE and for other work we have underway on SUMEX and (b) the continued development of the AGE and UNITS projects. In particular, we would like to see an extension of AGE to include a wider variety of control structures so that our psychological models would not be confined to one particular view of knowledge-based processing. The limited physical capacity of SUMEX, both in terms of address space and overloading, is, as before, a major problem. The prose comprehension group can no longer use the publicly released AGE/UNITS system due to its severely limited address space, and has had to build a personal AGE system from a stripped-down version of Interlisp and a selected subset of AGE and UNITS. We heartily endorse the plans underway to obtain more computing capacity for the SUMEX project.

Given our acquisition of a VAX, we particularly support the ongoing and continued development of INTERLISP for the VAX, so that local use of AGE and UNITS would be possible. Since we, as well as other psychologists, need the real-time capability of VAX/VMS to run on-line experiments, we hope that the INTERLISP system to be developed will be compatible with VMS. Note that this need for real-time work coincides with real-world applications of SUMEX programs, in which a VAX might be devoted to both real-time patient monitoring and diagnostic systems such as PUFF or MYCIN.

II.A.2.4 PUFF-VM Project

PUFF-VM: Biomedical Knowledge Engineering in Clinical Medicine

John J. Osborn, M.D.
The Medical Research Institute of San Francisco
Pacific Medical Center

and

Edward H. Shortliffe, M.D., Ph.D.
Department of General Internal Medicine
Stanford University Medical Center
Stanford University

The immediate goal of this project is to develop knowledge-based programs to interpret physiological measurements made in clinical medicine. The interpretations are intended to be used to aid in diagnostic decision making and in therapeutic actions. The programs will operate within medical domains which have well developed measurement technologies and reasonably well understood procedures for interpretation of measured results. The programs are:

- (1) PUFF: the interpretation of standard pulmonary function laboratory data which include measured flows, lung volumes, pulmonary diffusion capacity and pulmonary mechanics, and
- (2) VM: management of respiratory insufficiency in the intensive care unit.

The second, but equally important, goal of this project is the dissemination of Artificial Intelligence techniques and methodologies to medical communities that are involved in computer aided medical diagnosis and interpretation of patient data.

I. SUMMARY OF RESEARCH PROGRAM

PUFF:

A. Project Rationale

The task of PUFF program is to interpret standard measures of pulmonary function. It is intended that PUFF produce a report for the patient record, explaining the clinical significance of measured test results. PUFF also must provide a diagnosis of the presence and severity of pulmonary disease in terms of measured data, referral diagnosis, and patient characteristics.

B. Medical Relevance and Collaboration

Interpretation of standard pulmonary function tests involves attempting to identify the presence of obstructive airways disease (OAD: indicated by reduced flow rates during forced exhalation), restrictive lung disease (RLD: indicated by reduced lung volumes), and alveolar-capillary diffusion defect (DD: indicated by reduced diffusivity of inhaled CO into the blood). Obstruction and restriction may exist concurrently, and the presence of one mediates the severity of the other. Obstruction of several types can exist. In the laboratory at the Pacific Medical Center (PMC), about 50 parameters are calculated from measurement of lung volumes, flow rates, and diffusion capacity. In addition to these measurements, the physician may also consider patient history and referral diagnosis in interpreting the test results and diagnosing the presence and severity of pulmonary disease.

Currently PUFF contains a set of about 400 physiologically based interpretation "rules". Each rule is of the form "IF <condition> THEN <conclusion>". Each rule relates physiological measurements or states to a conclusion about the physiological significance of the measurement or state.

C. Progress Summary

The results of the PUFF system are reviewed in more detail in the 1978 SUMEX annual report and [3]. A version of the PUFF system is now in routine daily use at Pacific Medical Center. Reports are reviewed by a physician pulmonary physiologist. Over 85 % of the reports are accepted by the physician without change; they are signed and entered into the patient record. Most of the remaining reports are edited on-line to modify a small point in the test interpretation.

The PUFF system was developed on SUMEX in INTERLISP. It was converted to BASIC to run on a PDP11. It has interpreted the data of about 4000 patient cases since it became clinically operational late in 1978. The hospital has paid the Medical Research Institute for each clinical test interpreted by the system since it became fully operational. The program has been extended and maintained by research personnel during this period. PMC is now contracting to have PUFF converted to run on its own stand-alone micro computer (in BASIC). At that time, PUFF will have been fully moved from the research environment to the full responsibility of the end user.

D. Relevant Publications

- [1] "A Physiological Rule-Based System for Interpreting Pulmonary Function Test Results", J.C. Kunz, R.J. Fallat, D.H. McClung, B.A. Votteri, J.S. Aikins, H.P. Nii, L.M. Fagan, E.A. Feigenbaum, HPP 78-154, Stanford Heuristic Programming Project, 1978.
- [2] "Prototypes: An Approach to Knowledge Representation for Hypothesis Formation", Aikins, J.S., HPP-79-10 (working paper), 1979. Also Int. Joint Conf. on Artif. Intell., Tokyo, Japan, August, 1979.

- [3] "A Physiological Rule-Based System for Interpreting Pulmonary Function Test Results", J.C. Kunz, R.J. Fallat, D.H. McClung, B.A. Votteri, J.S. Aikins, H.P. Nii, L.M. Fagan, E.A. Feigenbaum, Proceedings of Computers in Critical Care and Pulmonary Medicine, IEEE Press, 1979.
- [4] "The Art of Artificial Intelligence: Themes and Case Studies of Knowledge Engineering", E.A. Feigenbaum, Proceedings of the IJCAI, (1977). (Also Stanford Computer Science Department Memo STAN-CS-77-612).

VM:

A. Project Rationale

The Ventilator Manager program (VM) interprets the clinical significance of time varying quantitative physiological data from patients in the ICU. This data is used to manage patients receiving ventilatory assistance. An extension of a physiological monitoring system, VM (1) provides a summary of the patient's physiological status appropriate for the clinician; (2) recognizes untoward events in the patient/machine system and provides suggestions for corrective action; (3) suggests adjustments to ventilatory therapy based on a long-term assessment of the patient status and therapeutic goals; (4) detects possible measurement errors; and, (5) maintains a set of patient-specific expectations and goals for future evaluation. The program produces interpretations of the physiological measurements over time, using a model of the therapeutic procedures in the ICU and clinical knowledge about the diagnostic implications of the data. These therapeutic guidelines are represented by a knowledge base of rules created by clinicians with extensive ICU experience.

B. Medical Relevance and Collaboration

To assist in the interpretation process, VM must be able to recognize unusual or unexpected clinical events (including machine malfunction) in a manner specifically tailored to the patient in question. The interpretation task is viewed as an ongoing process in the ICU, so that the physiological measurements must be continually reevaluated producing a current clinical picture.

This picture can then be compared with previous summary of patient status to recognize changes in patient condition upon which therapy selection and modifications can be made. The program must also determine when the measurements are most likely to be sensitive to error or when external measurements would be of diagnostic significance.

VM offers a new approach toward more accurate recognition of alarm conditions by utilizing the history and situation of the patient in the analysis. This is in contrast to the use of static limits applied to measurements generated to fit the "typical patient" under normal

conditions. Our program uses a model of interpretation process, including the types and levels of conclusions drawn manually from the measurements to provide a summary of patient condition and trends. The program generated conclusions are stated at levels more abstract than the raw data; for example, the presence of hemodynamic stability/instability rather than in terms of heart rate and mean arterial pressure. When the data is not reliable enough to make these conclusions, additional tests may be suggested. The recognition of important conclusion for which external verification is sought, will also elicit the suggestion for confirming tests from the program.

C. Progress Summary

VM is provided with the values of 30 physiological measurements on a 2- or 10-minute bases by an automatic monitoring system. The output is in the form of suggestions to clinicians and periodic summaries. During the past year, the VM system was run extensively to validate the contents of its knowledge base. The knowledge representation and system output are discussed more extensively in the 1981 SUMEX report and in (Fagan 80).

During the past year, VM was tested on several dozen patients. Rule modifications were made to improve system accuracy. Limits of expected values were refined, and rules relating ventilatory management to hemodynamic function were extended.

During the past year, basic research was started on knowledge representation for a physiological model. This research project integrates Artificial Intelligence (AI) and simple mathematics to analyze a physiological model. In the domain of renal physiology, a computer program is being implemented based on these techniques. It analyzes physiological behavior, diagnoses abnormality, and explains the rationale for its analyses. The program fits data to the model, identifies whether the data are abnormal, and identifies the possible causes and effects of any abnormalities. The physiological model is based on knowledge about anatomy, the behavior of the physiological system, and the mechanism of action of the system.

In this project, mathematics is used in an AI system to compute quantitative values based on available data. Concurrently, AI enhances the simple mathematical models. AI is used to represent diverse knowledge about the problem, to match a solution technique with problems needing solution, and to interpret results. Results may be quantitative and qualitative. Results are explained in terms of their contribution to diagnostic and therapeutic decisions.

During this year, work was also initiated to convert alarm rules from VM into computer programs which routinely analyze patient monitoring data. VM rules have been elaborated and recoded to detect instrument error in respiratory and hemodynamic monitoring data. Additional VM rules have been recoded to detect simple physiological abnormalities. One of the original VM goals was to provide prompt feedback to clinicians about the presence of error conditions. Alarm checking rules have been incorporated into the

operating data interpretation programs. Integrating these rules with the production monitoring system software allows this feedback to be prompt and associated naturally with the other monitoring system output.

D. Relevant Publications

Fagan, L.M., Kunz, J.C., Feigenbaum, E.A. and Osborn, J.J.: A symbolic processing approach to measurement interpretation in the intensive care unit. Proc. Third Annual Symposium Computer Applications in Medical Care, Silver Spring, Maryland, October, 1979, pp. 30-33.

Fagan, L.M., Shortliffe, E.H. and Buchanan, B.G.: Computer-based medical decision making: From MYCIN to VM. *Automedica* 3(2), 1980.

Fagan, L.M.: VM: Representing Time-Dependent Relations in a Medical Setting, Ph.D. dissertation, Stanford University, 1980.

Osborn, J.J., Fagan, L.M., Fallat, R.J., et al: Managing the data from respiratory measurements. *Med. Instrumentation*, November-December, 1979. (Winner of the 'Best Article of the Year' Award for AAMI - 1979.)

Sierra, D.: Development of a smart respiratory alarm system using artificial intelligence (abstract), presented at AAMI meeting, May 1982.

Mitchell, R.R.: The Need for closed loop therapy. Accepted for publication, *Critical Care Medicine*, 1982.

Mitchell, R.R., Wilson, R.M., Holzapfel, L., Benis, A.M., et al: The Oxygen washing method for monitoring Functional Residual Capacity. Accepted for publication, *Critical Care Medicine*, 1982.

E. Funding Support

PUFF-VM was supported by NIH grant GM24669 from 1978 - 1981. A renewal application was approved and not funded.

Research is now supported by a \$50,000 grant from the Johnson and Johnson foundation, John J. Osborn, PI. This grant includes some indirect costs. The grant is for one year.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Collaborations and Medical Use of Programs via SUMEX

The PUFF-VM project requires very close collaboration between investigators at two institutions separated by fifty miles. This kind of collaboration, in which program development and testing proceeds concurrently on the same application system, requires a computer network facility for sharing of code, data and ideas. SUMEX has been used at PMC for running programs developed concurrently by Stanford and PMC staff, and

data has been taken from the PMC computer system and transferred to SUMEX on magnetic tape for program development and testing. The SUMEX staff has developed a cooperating set of computer programs to allow the PMC computer and the SUMEX/2020 systems to actively exchange files and program data and output.

We also use the SUMEX system for purposes other than program development. Joint PMC-Stanford reports on PUFF and VM are being prepared entirely through the the communications and word processing capabilities of SUMEX. Investigators from the two institutions have collaborated in writing reports together; the separate contributions are prepared on SUMEX, edited and merged with an exchange of messages but without ever requiring actual meetings. We have also used the system for trading bibliographic information with other AIM users. We have also experimentally run the Internist program using SUMEX.

B. Sharing and Interactions with Other SUMEX-AIM Projects

We have participated in the AIM workshop and had very fruitful interaction with a number of other SUMEX users, directly influencing our perception of important problems and potentially appropriate solutions. Personal contacts at other conferences, at Stanford AI weekly meetings, and at PMC with visiting members of the AIM community, have also been very helpful in keeping abreast of the current thinking of other members of the AI community and with members of the medical community interested in computer based physiological analysis and diagnosis. We believe that the use of a common machine and the existence of the AIM conference encourages increased recognition and better communication with other AIM workers. Within AIM we most closely collaborate with the MYCIN, MOLGEN and DENDRAL projects, who share common space, common techniques, and common attitudes.

C. Critique of Resource Management

The SUMEX community continues to be an extremely supportive environment in which to do research on uses of artificial intelligence in clinical medicine. The community has two equally vital resources -- the people with knowledge and interest in AI and the facility on which AI system development can proceed. They are equally excellent as resources, helping hands when faced with problems, and friendly support for continued productive research. The availability of INTERLISP; of a facility on which routine data processing functions (eg. manipulating magnetic tapes and making long listings) can take place; and of message-sending among remote users are all vital functions for our project. SUMEX provides them in an environment which is friendly and reliable. Management of the SUMEX facility is consistent and excellent.

III. RESEARCH PLANS

A. Long Range Goals and Plans

The main emphasis of this project changed in 1979 from the development of the PUFF system to the development, extension and evaluation of the VM system. That change was consistent with the transition of PUFF from a research project to an operating program in a clinical setting. In addition, we want to pursue some promising research opportunities in the richer VM setting. Some long term interests, such as consensus building between experts, may be examined using both application areas.

The long range clinical research goal of the VM project is to develop and evaluate an interpretation system that will improve patient care in the ICU. The basic research goal continues to be to develop new Artificial Intelligence techniques which contribute to progress toward that clinical research goal. Within our relatively limited current funding opportunities, we plan to continue research toward these goals. We plan to exploit the knowledge in the VM rules in the current generation of monitoring system software and to develop improved AI techniques for doing diagnosis using models of physiology.

The VM alarm detection rules will be refined and incorporated into the operating monitoring system analysis programs. Some of these rules could not be fully exploited with VM itself because, running at SUMEX, VM typically received data only every 10 minutes. Incorporated into the analysis routines, the alarm detection rules can immediately obtain additional confirming data as necessary. This proximity to the data will allow both improved rules and more effective clinical use of the available rules.

Extending VM rules into the operating data analysis programs is an activity which follows in the tradition of PUFF. The original problem was analyzed and formalized in the computationally rich SUMEX environment. Once the knowledge of the problem is relatively well understood then it can be represented in the comparatively restrictive environments of BASIC on a PDP11 (in the case of PUFF), or the C language on a microcomputer (in the case of the VM alarm rules). This mode of transfer of knowledge seems to be one important way for knowledge developed in AI systems to be brought into wide use.

The near-term goals for the physiological modeling activity are to continue to develop a theory of physiological modeling within an AI system and to continue development of a computer program which demonstrates the power of that theory. The computer program is designed to demonstrate the following processing capabilities: identify the causes and effects of abnormal values of routine physiological measurements; define an abnormality (e.g. oliguria) identifying its possible causes, effects, and associated therapeutic goals; identify the normal physiological consequences of routine physiological behavior, such as drinking a fluid; identify the physiological consequences of abnormal physiological or anatomical situations.

B. Justification and requirement for continued SUMEX use

The research extending VM depends critically upon continued SUMEX support. This support is of two kinds: computer resources and community interaction. Exploiting the VM knowledge requires use of the SUMEX computer resource for several purposes. First, there is the need to continue run the VM program itself to test new rules, to identify the interaction of old and new rules, and to validate new kinds of rules. VM was built to run on SUMEX in INTERLISP, and its use depends upon use of SUMEX. In addition, the knowledge refinement process requires occasional use of SUMEX facilities such as MLAB, to test new mathematical models, and SPSS to analyze the results of studies. Finally, the SUMEX text processing support is tremendously useful.

Continuing as a part of the SUMEX community is particularly important intellectually. The general theme of AI -- representation and manipulation of knowledge -- lies at the heart of the research we conduct on interpretation of medical data. The exploitation of that knowledge involves both basic research into the nature of that knowledge and more applied research to refine and exploit it. It is extremely important that we continue to participate in the research of the AI community in representation and manipulation of knowledge.

D. Recommendations for Future Community and Resource Development

We perceive the evolution of our AI capability as moving from a highly speculative development state, for which the interactive development capabilities of SUMEX are vital, to a more stable but still changing validation-and-evaluation state. Ultimately we foresee rather stable specification of a program for routine clinical use. Thus, we see the need to transfer our AI techniques from the SUMEX PDP-10 to a local host. For this transfer, a principal long-range need is for software systems that will allow us to run AI systems on a mini-computer after they have been developed on the more powerful SUMEX facility. If the validation of PUFF-VM in the PMC clinical setting shows the programs to be effective in health care, then we hope and expect to be able to provide the capability on a routine basis.

We would also like to encourage SUMEX's role as a facilitator of information transfer between AIM users. This can happen by scheduling on-line demonstrations that any other user can "connect to," or by providing a common depository for AI and medicine information. This might take the form of on-line bibliographies, collecting common user packages, or connecting common research interests together. This communication service would complement the technical service facilities currently provided by the SUMEX staff.

II.A.2.5 Rutgers Computers in Biomedicine Project [Rutgers-AIM]

Rutgers Computers in Biomedicine

Rutgers Research Resource--Computers in Biomedicine

Principal Investigators: Saul Amarel and C. A. Kulikowski
Rutgers University
New Brunswick, New Jersey

I. SUMMARY OF RESEARCH PROGRAM

A. Goals and Approach

The fundamental objective of the Rutgers Resource is to develop a computer based framework for significant research in the biomedical sciences and for the application of research results to the solution of important problems in health care. The focal concept is to introduce advanced methods of computer science - particularly in artificial intelligence into specific areas of biomedical inquiry. The computer is used as an integral part of the inquiry process, both for the development and organization of knowledge in a domain and for its utilization in problem solving and in processes of experimentation and theory formation.

At present, the total number of investigators who participate in scientific activities of the Resource is 97, of these, 24 have Rutgers appointments, 25 are outside investigators who participate in collaborative research projects that are mainly located at Rutgers, and 48 are investigators from collaborative national AIM projects that are located in different parts of the country. In addition, the Resource has 11 other members in Administrative, Computer Systems/Operations and general programming and secretarial functions. Thus, the Rutgers Resource community numbers at present a total of 108 participants.

Resource activities include research projects (collaborative research and core research) training/dissemination projects, and computing services in support of user projects.

B. Medical Relevance and Collaborations

In 1981-82 we continued the development of several versatile systems for building and testing consultation models in biomedicine. The EXPERT system has had many of its capabilities enhanced in the course of collaborative research in the areas of rheumatology, ophthalmology, and clinical pathology.

In rheumatology, our collaboration with Drs. Donald Lindberg and Gordon Sharp at the University of Missouri-Columbia has continued at a very active level. The model for rheumatological diseases was expanded to include detailed diagnostic criteria for 26 major diseases, and management

advice/treatment planning was begun for several of them. Dr. Sharp's group continues to develop the knowledge base in this area, with formalization of the knowledge carried out in conjunction with Dr. Lindberg's group and the Medical Expert Systems Group at Rutgers. The Resource researchers have developed new representational elements for EXPERT in response to the needs of the rheumatology research, and Politakis has developed a coordinated system called SEEK (System for Empirical Experimentation with Expert Knowledge) which provides interactive assistance to the human expert in testing, refining and updating a knowledge base against a data base of trial cases.

In treatment planning, the system for treatment selection and planning developed by Kastner has been used in ophthalmology (infectious eye diseases), where Dr. Chandler Dawson of the Proctor Foundation, University of California at San Francisco has developed an expert reasoning model.

In clinical pathology our main collaboration has been with Dr. Robert Galen (Overlook Hospital and Columbia University), where we continued development of the serum protein electrophoresis model so that it was usable clinically and incorporated into an instrument - the scanning densitometer manufactured by Helena Laboratories. The new instrument with interpretive reporting capabilities is now on the market, and represents the first known spin-off of AI expert systems research in the field of laboratory instrumentation.

In biomedical modeling applications we continued to experiment with prototype models in conjunction with Dr. David Garfinkel (enzyme kinetics) and Dr. William Yamamoto (respiration models).

C. Highlights of Research Progress

1. Expert Medical Systems (C. Kulikowski, S. Weiss)

Research has continued on problems of representation, inference and control in expert systems. More emphasis has been placed this year on problems of knowledge base acquisition, empirical testing and refinement of reasoning (the SEEK system), and treatment planning strategies over time. From a technological point of view the market availability of the interpretive reporting version of a scanning densitometer represents an important achievement for AIM research in showing a practical impact in medicine.

1.1 SEEK: A System for Empirical Experimentation with Expert Knowledge

SEEK is a system which has been developed to give interactive advice about rule refinement during the design of an expert system. The advice takes the form of suggestions for possible experiments in generalizing and specializing rules in an expert model that has been specified based on reasoning rules cited by a human expert. Case experience, in the form of stored cases with known conclusions, is used to interactively guide the

expert in refining the rules of a model. The design framework of SEEK consists of a tabular model for expressing expert-modeled rules and a general consultation system for applying a model to specific cases. This approach has proven particularly valuable in assisting the expert in domains where the logic for discriminating two diagnoses is difficult to specify; and we have benefitted primarily from experience in building the consultation system in rheumatology.

1.2 Treatment Planning

The ranking and selection strategies developed as a stand-alone system last year have been incorporated into the EXPERT framework. New capabilities for expressing reasoning over time have been added, so stored chart reviews can be carried out automatically, summarizing various patterns of findings over time, and abstracting the major features of interest for prognostic advice or treatment recommendations. Applications have been in infectious eye disease modeling, rheumatology treatment, and sequential advice in interpretation and sequencing of cardiac enzyme tests (e.g. CPK/LDH isoenzymes).

1.3 Technology Transfer

The automated translation of an EXPERT model with some representational constraints into an algorithmic model which is then also translatable automatically into a microprocessor assembly language has been demonstrated by producing the serum protein electrophoresis model for interpretation.

1.4 Representational Extensions to EXPERT

We have created a number of special front-end and reporting facilities to make it easier to enter data, and to flexibly format advice at the output.

We have developed an entirely new representation for expressing time dependencies of actions that are first recommended and then monitored for matching over time.

We have developed a new representation for creating a special class of instantiations in the conclusions of EXPERT without sacrificing the efficiency of model precompilation.

1.5 Learning with Prior Structural Knowledge

We have developed a multiple knowledge source/blackboard model for learning with prior knowledge, and applied it in the area of glaucoma and thyroid modeling.

2. Models of Planning and Commonsense Reasoning (C. Schmidt, N.S. Sridharan)

2.1 Plan Generation

In the last year, we have incorporated several features into the plan generation process that enables it to deal with incomplete knowledge of situations. Our planning programs include explicit annotations of decisions taken and assumptions made. These annotations, coupled with a structured representation of the planning process, provide a basis for plan revision when new information becomes available. Our plan generator has now the capacity to construct and manipulate descriptions of objects required in the plan even though knowledge of the situation may not include explicit information about the existence of these objects.

2.2 Reasoning with Commonsense Concepts

In this work we assume that (i) concepts are structured hierarchically and (ii) associated with a concept are intentional descriptions which define either necessary or typical aspects of individuals that are members of the concept set. Proceeding within the framework of default reasoning developed by Reiter, we have defined and implemented a system which uses the concept hierarchy and associated intentional descriptions to systematically generate default theories from which default inferences about an individual may be drawn.

3. Artificial Intelligence: Representations, Reasoning, System Development

3.1 Representations and Inference in AIMDS (N.S. Sridharan)

The two main applications of AIMDS continue to be Psychological models for Commonsense Reasoning and Cognitive models of Legal Argumentation. In addition to work in these application areas, we introduced recently new features to the system, and we made progress in performance enhancements and in improved interfaces to the user. The new features include refinements of the formalism of Descriptions, mechanisms for representing and using structured definitions, and the introduction of a limited facility for arithmetic functions. We devoted considerable effort to the development of short-term and long-term solutions to questions of improved system performance. AIMDS was adapted to run with Elisp, to give us more address space. Improvements in user interface included a facility for loading a knowledge base in pieces from a collection of external files, and an interactive facility for composition of Descriptions.

3.2 Expertise Acquisition (S. Amarel, T. Mitchell)

There are two main research activities in this area. One is focusing on the task of learning problem solving heuristics by experimentation, and the other is concerned with improvements in problem solving expertise via shifts in problem representation, i.e., via reformulation.

We have now completed the initial design, implementation, and partial testing of a heuristic search program, called LEX, that learns heuristics to guide its search in a particular task area: solving symbolic integration problems. More recently, we completed a prototype 'Problem Generator' module, which will allow LEX to generate its own practice problems. We view the current system as a laboratory in which we can now conduct experiments and study specific issues related to machine learning of expertise.

In recent work on changes in Expert Behavior via problem reformulations we developed a conceptual framework for handling problem formulations in which the grammatical specification of solutions for a problem class plays a key role. Within this framework, we conducted theoretical studies of representational shifts in specific classes of problems of reasoning about actions. Relationships between characteristics of 'intelligent expert' systems and developmental processes of problem reformulation were explored; and specific conclusions were obtained regarding the types of knowledge and the nature of mechanisms needed for an expert system to improve its performance with experience.

3.3 Programming Environment for AI Research (C. Hedrick)

During the last year we have been concentrating on two issues: (i) solving the address space problem with the PDP-10 architecture; and (ii) exploratory work with personal computers and networking. We have now completed versions of Rutgers/UCI LISP, PASCAL and SETL that use the full 23-bit address space available on the DEC-2060 processor; and we are currently working on a large-address space implementation of Common LISP for DEC-20. We expect to install in the summer of '82 two Dolphin personal computers, and we developed much of the Ethernet software that we will use to connect the Dolphins with each other and with the DEC-20. SUMEX staff has been providing help in planning for the Dolphins and for the local network.

D. Up-to-Date List of Publications

The following is an update of publications in the Rutgers Resource for the period 1981 and 1982 (only publications not listed in previous SUMEX annual reports are presented here).

Amarel, S. "Problems of Representation in Heuristic Problem Solving; Related Issues in the Development of Expert Systems." Feb. 1981. CBM-TR-118, also to appear in "Methods of Heuristics", Groner, Groner and Bishof (eds), Laurence Erlbaum.*

Amarel, S. "Expert Behavior and Problem Representations." Feb. 1982. CBM-TR-126; also to appear in "Artificial and Human Intelligence," Elithorn and Banerji (eds), 1982.

Bresina, J. "An Interactive Planner that Creates a Structured, Annotated Trace of its Operation." Sept. 1981. CBM-TR-123.

Drastal, G. and Kulikowski, C. "Knowledge Based Acquisition of Rules for Medical Diagnosis", Department of Computer Science Technical Report No. CBM-TM-92, Rutgers University, March 1981.*

Keller, R.M. and Nagel, D.J. (1981), "Some Experiments in Abstraction of Relational Characteristics", Department of Computer Science Technical Report No. DCS-TM-15. Rutgers University, March 1981.*

Kulikowski, C.A. "Computers and Logic: Expert Systems for Thyroid Function Testing", Diagnostic Medicine, 99-102, July 1981.* Kulikowski, C.A., Weiss, S., Galen, R.S. (1981). "Computerized Diagnosis in the Lab", Medical Laboratory Observer: 41-57, July 1981.*

Mitchell, T.M. (1981). "Generalization as Search", Artificial Intelligence, to appear 1981.*

Mitchell, T.M. (1981). "Combining Empirical and Analytical Methods for Inferring Heuristics", Proceedings at the NATO Symposium on Artificial and Human Intelligence, Lyon, France, October 1981, Department of Computer Science Technical Report No. LCSR-TR-21.*

Mitchell, T.M., Utgoff, P.E., Nudel, B. and Banerji, R. (1981). "Learning Problem-Solving Heuristics through Practice", Department of Computer Science Technical Report No. LCSR-TR-15, Rutgers University, July 1981; also in Proceedings at IJCAI 7, Vancouver, BC, August 1981.*

Nudel, B. and Utgoff, P. "A Bibliography on Machine Learning." April 1981. CBM-TR-120.

Schwanke, R. "Common Virtual Arrays in PDP-11 Fortran: An Exercise in Software Engineering." Nov. 1981. CBM-TR-124.

Smith, D. (1981). "A Strategic Interaction Paradigm for Language Acquisition", forthcoming Ph.D. dissertation, Department of Computer Science, Rutgers University, expected December, 1981.*

Sridharan, N.S. "Representing Knowledge in Introduction Using TAXMAN Examples." Nov. 1981. CBM-TR-125/LRP-TR-12.

Sridharan, N.S., Goodson, J.L. and Schmidt, C.F. "A Research Strategy for Computational Studies of Event and Action Perception." July 1981. CBM-TR-122.

Weiss, S., Kern, K., Kulikowski, C. and Ushchold, M. "A Guide to the Use of the EXPERT Consultation System." May 1981. CBM-TR-94.

Weiss, S., Kulikowski, C. Expert Consultation Systems: The EXPERT and CASNET Projects, Machine Intelligence, Pergamon INFOTECH, Series 9, Number 3, pp. 339-352 (1981).*

Weiss, S., Kulikowski, C.A. and Galen, R. "Developing Microprocessor Based Expert Models for Instrument Interpretation." June 1981, CBM-TR-121, also in Proceedings IJCAI 7, Vancouver, BC, August 1981.*

*Indicates that the resource was given credit.

E. Funding Support

The Rutgers Resource is funded through an NIH grant entitled "Rutgers Research Resource on Computers in Biomedicine" -- grant number P41RR643. The Co-Principal Investigators are Dr. Saul Amarel, Professor, Chairman Department of Computer Science, and Director of the Laboratory for Computer Science Research, and Dr. Casimir Kulikowski, Professor of Computer Science, Rutgers, the State University of New Jersey.

This grant is in the second year of its fourth 3-year renewal extending from December 1, 1980 through November 30, 1983. The total direct cost awarded for the 3-year period is \$1,404,075 with second year funding of \$460,944 in direct costs from December 1, 1981 through November 30, 1982.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Dissemination

The SUMEX-AIM facility provides a backup node where some of our medical collaborators can access programs developed at Rutgers. The bulk of the medical collaborative work outlined in I.B. above is centered at the Rutgers facility (the Rutgers-AIM node).

Dissemination activities continue to be an important responsibility of the Rutgers Resource within the AIM community. The following activities took place in the last year:

1) Seventh AIM Workshop (1981):

Organized by C. Kulikowski at the Rutgers Research Resource, it was held at the University of British Columbia in conjunction with IJCAI. It consisted of a very successful one-day of summary presentations by members of the AIM community about work in progress, and an evening dinner meeting at which Dr. Allen Newell presented the keynote address.

2) IJCAI-81:

Presentations were made by several Resource investigators, including Drs. Kulikowski, Weiss, and graduate students on the medical projects (SPE densitometer interpretation, treatment planning); and also by Dr. Sridharan and Dr. Mitchell.

3) Society for Computer Medicine Meeting:

Dr. Kulikowski presented work on expert systems in a panel session at the Washington, DC conference of the Society for Computer Medicine.

4) Hawaii International Conference On Systems Sciences:

Dr. Weiss and George Drastal presented papers on the SEEK system, and the a-priori learning model at the medical sessions of this conference.

5) American Association of Clinical Pathologists:

Dr. Kulikowski presented the work on expert systems, and their application in clinical pathology at this meeting, while Drs. Lindberg and Galen also participated and touched on these topics in tutorials and papers.

6) American Rheumatology Association:

Dr. Sharp and his group presented the rheumatology knowledge base and consultation program at this meeting in a poster session.

7) New York Academy of Medicine:

Dr. Kulikowski presented a paper on the expert systems in medicine at the March '82 meeting of the Academy.

8) Conference of Computers in Health Care, 1981:

The Rutgers Resource was a co-sponsor.

9) NATO Symposium on Human and Artificial Intelligence:

Dr. Amarel and Dr. Mitchell presented papers on Expertise acquisition at this Symposium, which was held in Lyon, France in October 1981.

10) Lectures at Jilin University, China:

Dr. Amarel and Dr. Kulikowski were invited to Jilin University for a series of lectures. Work on medical expert systems and AI was presented in these lectures.

B. National AIM Projects at Rutgers

The national AIM projects, approved by the AIM Executive Committee, that are associated with the Rutgers-AIM node are the following:

1) BRIGHT project, under the direction of Dr. W. Gordon Walker of Johns Hopkins University, mostly for research in clinical medicine.

2) CONGEN project on Computers in Chemistry, under Dr. Djerassi and Dr. D. Smith from Stanford University, are predominantly at SUMEX; they are using the Rutgers facility as a backup for demonstrations.

3) INTERNIST/CADUCEUS project, headed by Dr. Myers and Dr. Pople from the University of Pittsburgh, has been using the Rutgers Resource as a backup system for development and experimentation.

4) Medical Knowledge Representation project, headed by Dr. Chandrasekaran from Ohio State University, is doing most of its research on the Rutgers system.

5) PURSUIT project, directed by Dr. Greenes from Harvard University, is doing most of its research on a Goal-Directed Model of Clinical Decision-Making at Rutgers.

6) Biomedical Modeling, by Dr. Garfinkel from the University of Pennsylvania.

7) MEDSIM project: This is a pilot project designed to provide resource-sharing and community building facilities for about 25 researchers in biomathematical modeling and simulation.

C. Critique of SUMEX-AIM Resource Management

Rutgers is currently using the SUMEX facility primarily for communication with other researchers in the AIM community and with SUMEX staff, and also for backup computing in demonstrations, conferences and site visits. Our usage is currently running at less than 50 connect hours per year at SUMEX, with an overall connect/CPU ratio of about 30.

In addition to the computer usage, we have benefitted extensively from SUMEX staff expertise in the area of local networking and personal computers. The AIM Executive Committee has allocated to the Rutgers-AIM node one of the Xerox Dolphins acquired by SUMEX, so that - together with a second Dolphin provided by DARPA to Rutgers - we can develop experience with the new personal machine environment for research in AI systems. We expect the Dolphins to be installed at Rutgers in summer '82. The SUMEX staff has provided the software that we will be using to implement Ethernet service for the personal computers, as well as advice on the logistics of installing them. As in the past, the quality of support and cooperation given by SUMEX staff has been very high.

III. RESEARCH PLANS

A. Project Goals and Plans

We are planning to continue along the main lines of research that we have established in the Resource to date. Our medical collaborations will continue with emphasis on development of expert consultation systems in rheumatology, ophthalmology and clinical pathology. The basic AI issues of plan recognition/generation and default reasoning will continue to receive attention. Our core work will continue with emphasis on further development of the EXPERT framework and also on AI studies in representations and problems of knowledge and expertise acquisition. We

also plan to continue our participation in AIM dissemination and training activities as well as our contribution -- via the RUGERS/LCSR computer -- to the shared computing facilities of the national AIM network.

B. Justification and Requirements for Continued SUMEX Use

Continued access to SUMEX is needed for:

- 1) Backup for demos, etc.
- 2) Programs developed to serve the National AIM Community should be runnable on both facilities.
- 3) There should be joint development activities between the staffs at Rutgers and SUMEX in order to ensure portability, share the load, and provide a wider variety of inputs for developments.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM

Beyond the current SUMEX-AIM facility there is need for access to a more 'personal' type of computing facilities (e.g., Dolphins).

D. Recommendations for Future Community and Resource Development

We strongly support the efforts of SUMEX staff to develop personal computing resources. Our own local planning efforts have been helped considerably by the assistance of SUMEX. As physical facilities are spread out in more and more places, we believe that centers such as SUMEX can play a growing role in keeping track of technology, planning, and technical support of users. It may also prove convenient for SUMEX to serve as a center for mail and other communications activities carried out by personal computers at remote sites.

Our experience during the last year confirms our opinion that an increasingly important role of the SUMEX staff will be to function as a central consulting and software development organization. They are currently performing this role in regard to personal computers and networking, as well as more traditional roles such as INTERLISP support.

II.A.2.6 SECS - Simulation and Evaluation of Chemical Synthesis

SECS - Simulation and Evaluation of Chemical Synthesis

Principal Investigator: W. Todd Wipke
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Coworkers:

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J. Chou	(Postdoctoral)
P. Condran	(Postdoctoral)
T. Moock	(Postdoctoral)
A. Cabral	(Postdoctoral)

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The long range goal of this project is to develop the logical principles of molecular construction and to use these in developing practical computer programs to assist investigators in designing stereospecific syntheses of complex bio-organic molecules. Our specific goals this past year included conversion of SECS to machine independent code, continued exploration of strategies based on starting materials, developing a reasoning program, and expansion of the ALCHEM language for handling precursor evaluation.

The objectives for the XENO project were to establish extensive collaborations with metabolism experimentalists to test XENO predictions and to begin development on methods for assessing the potential biological activity of each metabolite.

B. Medical Relevance and Collaboration

The development of new drugs and the study of how drug structure is related to biological activity depends upon the chemist's ability to synthesize new molecules as well as his ability to modify existing structures, e.g., incorporating isotopic labels or other substituents into biomolecular substrates. The Simulation and Evaluation of Chemical Synthesis (SECS) project aims at assisting the synthetic chemist in designing stereospecific syntheses of biologically important molecules. The advantages of this computer approach over normal manual approaches are many: 1) greater speed in designing a synthesis; 2) freedom from bias of

past experience and past solutions; 3) thorough consideration of all possible syntheses using a more extensive library of chemical reactions than any individual person can remember; 4) greater capability of the computer to deal with the many structures which result; and 5) capability of computer to see molecules in a graph theoretical sense, free from the bias of 2-D projection.

The objective of using XENO (a spinoff of SECS) in metabolism studies is to predict the plausible metabolites of a given xenobiotic in order that they may be analyzed for possible carcinogenicity. Metabolism research may also find this useful in the identification of metabolites in that it suggests what to look for. Finally, one may envision applications of this technology in problem domains where one wishes to alter molecules in order to inhibit certain types of metabolism.

C. Highlights of Research Progress

1. SECS Program Developments

The Simulation and Evaluation of Chemical Synthesis (SECS) program has undergone many additions to improve its capabilities and usefulness to synthetic chemists. We have added a capacity for user-defined transforms, SECS library augmentation, and for multiple step strategies. In addition we have augmented SECS with the SST and QED programs, the former for selection of starting materials for a synthetic target, and the latter for interpreting and maintaining a rule database of chemical synthetic strategies.

a. Perception and Evaluation of Synthetic Precursors: Extensions to the ALCHEM Language

The ALCHEM language has been extended to handle transforms with two sections, one for the reactants and one for the products. This required complete logic revamping so that the precursors can be perceived and evaluated in the same manner as the original target. Symmetry and steric constraints are now expressible with respect to the precursors. Additionally, the ALCHEM compiler has been given semantic checking capabilities for greater error detection.

b. User Defined Transform / Library Augmentation Module

As part of a concerted effort to improve and maintain the SECS library database, we have implemented the capability for acquisition of chemical knowledge at execution time. This capability complements the existing offline acquisition capability involving translation of detailed transforms written in the chemistry-specific language ALCHEM.

The User Defined Transform module is accessible through both graphical and textual interfaces with the user. The module is designed to accept all information necessary to stereospecifically convert the target molecule to the desired precursor. The reaction specifications may, at the users option, be recorded so that they may be generalized, stored, and

later applied to structurally similar molecules in the current (as well as in future) analysis. Currently the Library Augmentation Module possesses the capability to acquire scope, limitations, and reference information, as well as perform consistency checking to minimize the possibilities for including erroneous information in the database.

It should be noted that the above capability to accept expert knowledge from the chemist at runtime is unique among automated synthesis design programs. Further additions to allow the input of more defined scope and limitations data (i.e. functional group sensitivities and effects of substrate structure on yields, etc.) and separation from the synthesis design program would allow development of a query-driven automatic transform writer. The existence of such a program would do much toward improving the quality and size of the program's database by facilitating and structuring the input of reaction data.

c. Multistep Strategy Implementation in SECS

Currently under development is a SECS facility for allowing the chemist to construct and implement multistep synthetic plans for the target molecule and allow these plans to guide subsequent application of chemical transforms. The plans are updated for each precursor produced in accordance with those long-term goals which have been satisfied by its creation. The planning list structure has been designed such that it is self-modifying, e.g. strategic goals may be activated or removed from the list as called for by other goals in the list, and multiple plans may be implemented simultaneously. The capability for temporally ordering goals is also included so that the chemist may specify the order in which bonds of the target structure are to be disconnected. Design of the module is such that strategic guidance is implemented in the form of both planning goals and strategic constraints. In addition to enabling the use of strategic disconnective and reconnective goals for specifying a general retrosynthetic strategy, the use of constraint information holds promise for shaping synthetic analysis around potential starting materials.

This planning module currently runs in a simulated environment; our plans are to interface it to the synthesis program in the very near future.

d. QED, an Inference Engine for Strategic Chemical Planning

The QED program was developed to provide an experimental workbench for exploring the use of inference and logic in planning chemical synthesis.

QED performs inferences based upon a database consisting of synthetic axioms expressed in the first order Predicate Calculus. The database is first written in mathematical english, and a stand-alone program translates these rules into an associative form useful to QED, as well as allowing for creating new predicates, performing semantic checking, and incremental updating of existing rulebases.

In addition to the separate data base, QED's control structure is based on an agenda list which is created as the rules are examined. Items have priorities assigned when they are created, and QED examines them in the order of their priority. By changing the prioritizing routine, the user can explore the efficiency of various heuristics to guide the search. In this manner we are exploring several approaches, including depth first, best first, and one based on cost-effective examination, where nodes which would not greatly increase the knowledge of the world-picture may be neglected as being too costly to examine.

Currently we are improving QED's database creation routine so that it can examine the rules for improper recursion, and the entire data base for improper recursion, inconsistency and completeness. This will be especially important as more chemists attempt to add rules to the QED data base. We are also allowing QED to create new objects and create a hierarchical inheritance network for these new objects. In this fashion QED could efficiently reason about entities at a higher level with a richer vocabulary, thus extending the power of the inferences.

Finally, we are exploring the axiomatization of the principles of organic synthesis. QED provides a tool for the rapid exploration of various axiomatic schemas with various control structures, thus providing an exciting opportunity to attempt to provide some sort of formal statement of principles governing the design of organic syntheses.

e. Starting Material Strategies - SST

The importance of selecting good starting materials for a synthesis has been known for a long time, but only recently has work started on applying computer techniques to the selection process. We have developed a set of rules useful for the initial selection of potential starting materials (SM's) from an on-line library, and written a program named SST to implement these rules.

The program works in two stages, applying the following rules sequentially:

- 1) Select from the library file the set of molecules whose basic framework is sufficiently close to the target.
- 2) Take the molecules selected and see if their functionality is appropriate for the desired target.

Since questions of functionalization are dealt with at a later point in our algorithm, we did not need all of the fine detail of the molecules in the library. In fact, the high level of detail can hinder a search, obscuring potentially important relationships. We decided to limit the similarity search to carbon graphs, which eliminates the functionality and reduces the size of the search tremendously.

Once the library file and the target molecule have been thus abstracted, we need to apply an algorithm to them to determine which are 'sufficiently close'. We saw four general categories to describe common relationships between target and starting molecules.

- | | |
|-------------------|----------------------|
| I) Target = SM | Identical match |
| II) Target > SM | Superstructure match |
| III) Target < SM | Substructure match |
| IV) None of these | Similarity match |

For a search over our abstracted file, the identical match means that the target and starting materials are identical except for functionalization. The superstructure match is the case where we must make carbon-carbon bonds during a synthesis. The substructure match is the case where the starting material is larger than the target, so carbon-carbon bonds have to be degraded. Finally, the similarity match is where carbon-carbon bonds have to be both made and broken during the synthesis.

The methods for dealing with supergraph and subgraph searching are close but not identical. In particular, for the subgraph search over the abstracted library (Target < SM), the user get the opportunity to further reduce the carbon graph of the target molecule before searching. This might be useful if there are carbon atoms on the target graph which are labile and easily constructed at the end of a synthesis.

Once we have a set of starting material candidates, we then evaluate the functionality to see if it is appropriate.

We have seen good results with this two step algorithm; currently, we are working on extending the first part of it to allow for common subgraph searching over the entire file. In this manner starting materials which need both synthesis and degradation to make the target can be discovered.

2. XENO Program Developments

a. Species Information Implementation

One of the most important biological or hereditary factors affecting the metabolism of a xenobiotic is the metabolic variability between species. Species variations may appear as (1) qualitative differences in the actual pathways of metabolism, and/or (2) quantitative differences in the pathways of metabolism which are common to several species.

In order to represent the quantitative and qualitative species variations in a transform, two types of ALCHEM statements have been developed: One is the qualitative character statement which specifies the species requirement for a transform. This is done in the header of the transform. This character statement, SPECIES <species name(s)>, means the transform is applicable to <SPECIES name(s)> only, not to the other species. The other one is a query statement which reflects the

quantitative variation by adjusting the priority or doing something else for the specified species as shown below:

```
IF SPECIES IS RAT THEN ADD 10
or
IF SPECIES IS MOUSE THEN
  BEGIN
  .
  .
  .
  DONE
ELSE
```

The species protocol for the analysis is established by the user.

b. Biological Activity Evaluation

Many rational methods in structure-activity relations(SAR) studies have been developed. However, these methods have been applied to the SAR of the biological activity and parent compounds rather than metabolites. Frequently, the observed biological activity is not due directly to the xenobiotic compound, instead due to one or more of its metabolites.

We are exploring a unique approach to the problem of evaluating the potential biological activity for metabolites. We have developed a rule-based method for representing the expert knowledge of structure-activity relations. First, we extract the structure requirement (pharmacophore) for the specific biological activity from examples. Then, rules affecting the activity derived from these examples are encoded in the ALCHEM language.

Development of series of rules for each class of compounds to relate structure to biological activity is underway. Current work includes studies on diazo compounds, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines, and alkylating agents.

c. Collaborative Efforts:

We have been collaborating with metabolism pharmacologists in order to test XENO's prediction for compounds actively being studied in the laboratories. Initial feedback from Mead Johnson on a particular drug indicates that major metabolites were correctly predicted and that some XENO proposed metabolites lead them to further investigation. However, three compounds generated by XENO were not detected in their studies. Other collaborations with investigators at ICI of UK, NIH and the National Australian University are in progress.

D. List of Current Project Publications

- P. Gund, E.J.J. Grabowski, D.R. Hoff, G.H. Smith, J.D. Andose, J.B. Rhodes, and W.T. Wipke, "Computer-Assisted Synthetic Analysis at Merck," J. Chem. Info. and Comput. Sci., 20, 288 (1980).
- S.A. Godleski, P.v.R. Schleyer, E. Osawa, and W. T. Wipke, "The Systematic Prediction of the Most Stable Neutral Hydrocarbon Isomer," Progress in Physical Organic Chemistry, Vol. 13, 1981, pp. 63-118.
- R.E. Carter and W.T. Wipke, "SECS--EH Hjalpmedel Vid Organisk Syntesplanering," Kemisk Tidskrift, No. 7, June 20-25(1981)
- W.T. Wipke and M. Huber, "Symmetry and Organic Synthetic Design", Tetrahedron, submitted.
- W.T. Wipke, G.I. Ouchi, and J.T. Chou, "Computer-Assisted Prediction of Metabolism", in Structure-Activity Correlations as a Predictive Tool in Toxicology, edited by Leon Goldberg, New York: Hemisphere Publishing Corp., 1982 (in press).

E. Funding Status

1. Computer-Assisted Prediction of Xenobiotic Metabolism
Principal Investigator: W. Todd Wipke, Professor, UCSC
Agency: NIH, Environmental Health Sciences
No: ES02845-01
4/1/82-3/31/83 \$ 76,444 TDC
2. Forward Synthesis and Reaction Analysis
Principal Investigator: W. Todd Wipke, Professor, UCSC
Agency: NIH
No: GM 31173-01
6/1/82-5/31/83 \$ 221,381 TDC (Pending approval)

F. Research Environment

At the University of California, Santa Cruz, we have a GT40 and a GT46 graphics terminal connected to the SUMEX-AIM resource by 1200 and 2400 baud leased lines (one leased line supported by SUMEX). We also have a TI745, Heath Data Terminal, CDI-1030, DIABLO 1620, and an ADM-3A terminal used over 300 baud leased lines to SUMEX. UCSC has only a small IBM 370/145, a PDP-11/45, 11/70 and a VAX 11/780, (the 11's are restricted to running small jobs for student time-sharing) all of which are unsuitable for this research. The SECS laboratory is located in a newly renovated room with raised floor in 125 Thimann Laboratories, adjacent to the synthetic organic laboratories at Santa Cruz so the research environment is excellent.

II. INTERACTIONS WITH SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

SECS is available in the GUEST area of SUMEX for casual users, and in the SECS DEMO area for serious collaborators who plan to use a significant amount of time and need to save the synthesis tree generated. Much of the access by others has been through the terminal equipment at Santa Cruz because graphic terminals make it so much more convenient for structure input and output. Demonstrations and sample synthetic analyses were generated for Drs. Terry Brunck and Steve Roman of Shell Development, John Harper of Amoco Chemicals, Prof. Fujiwara, University of Tsukuba, Japan, Dr. Peder Berntsson, Hassle, Sweden. Other visitors included Dr. M. Onozuka, A. Tomonaga and H. Itoh, Kureha Chemical Co., Tokyo, Japan. Demonstrations of SECS in Sweden were performed by Dr. R. E. Carter, University of Lund, Sweden, at many universities and companies. A synthesis of vellerolactone, a substance found to be toxic and teratogenic was generated for Professor Carter. Dr. S. Imahori of Mitsubishi Chemical visited our laboratories for 3 months. Carroll Johnson of Oak Ridge is experimenting with the use of XENO for predicting decomposition pathways in toxic waste materials.

Professor Wipke has also used several SUMEX programs such as CONGEN in his course on Computers and Information Processing in Chemistry. Communication between SECS collaborators is facilitated by using SUMEX message drops, especially when time differences between the U.S. and Europe and Australia makes normal telephone communication difficult. Testing and collaboration on the XENO project with researchers at the NCI depend on having access through SUMEX and TYMNET.

B. Examples of Cross-fertilization with other SUMEX-AIM Projects

This year the SECS and XENO project have made use of the teletype plot program which Ray Carhart of the CONGEN project wrote at Stanford. We modified the program to fit the needs of our projects. This was facilitated by being able to transfer the programs within areas on the same computer system at SUMEX. We continue to have intellectual interactions with the DENDRAL and MOLGEN project in areas where we have common interests and have had people from those projects speak at our group seminars. SUMEX also is used for discussions with others in the area of artificial intelligence on the ARPANET.

C. Critique of Resource Services

We find the SUMEX-AIM network very well human engineered and the staff very friendly and helpful. The SECS project is probably one of the few on the AIM network which must depend exclusively on remote computers, and we have been able to work rather effectively via SUMEX. Basically we have found that SUMEX-AIM provides a productive and scientifically stimulating environment and we are thankful that we are able to access the resource and participate in its activities.

SUMEX-AIM gives us at UCSC, a small university, the advantages of a larger group of colleagues, and interaction with people all over the country. We especially thank SUMEX for support of the leased line for our GT40, and for helping develop our remote print capability.

The only notable area in which the SUMEX facility has fallen short of our needs lies in the occasional periods of persistently high system loading on the KI-10's. In order to obviate this difficulty somewhat, we are currently installing SECS on the 2020 so that we may make use of that system's additional computing capabilities.

D. Collaborations and Medical Use of Programs via Computers other than SUMEX

SECS 2.9 now resides on the CompuServe computer networks so anyone can access it without having to convert code for their machine. This has proved very useful as a method of getting people to experiment with this new technology. Dr. George Purvis of Battelle is accessing SECS via CompuServe, as are Gene Dougherty of Rohm and Haas and many others. SECS also resides on the Medicindat machine at the University of Gothenborg, Sweden, and is available all over that country by phone. Similarly in Australia, SECS resides at the University of Western Australia and is available throughout the country over CSIRONET. Plans for implementing a similar facility in Japan are currently being examined.

III. RESEARCH PLANS (6/82-6/83)

A. Long Range Project Goals and Plans

The SECS project now consists of two major efforts, computer synthesis and metabolism, the latter being a very young project. Our plans for SECS for the next year include completing the high level reasoning module for proposing strategies and goals, and providing control which continues over several steps. This reasoning module also will be able to trace the derivation of goals and thus explain some of its reasoning. We also plan to focus on bringing the transform library up in sophistication to improve the performance and capabilities of SECS. In particular we plan to allow a transform to have access to the precursors generated as well as the product, this will allow much greater control and more natural transform writing, but it requires extensive changes in the SECS control structure to permit this.

We will continue to explore starting material oriented strategies based on the Aldrich Chemical file we now have implemented. We especially are interested in chirality based strategies which we feel are very strong.

We plan to explore running SECS on a virtual memory 32-bit computer like a VAX-11/780 or a PRIME since many chemistry departments now have these machines available and thus could run SECS.

The XENO metabolism project will be expanding the data base to cover more metabolic transforms, including species differences, sequences of transforms, and stereochemical specificities of enzymatic systems. Development of the second phase which assesses the biological activity of the metabolites will continue as will efforts to simulate excretion and incorporation, the endpoints of metabolism. Finally, application of the

current program to the molecules actively being investigated by metabolism researchers will occur concurrently to test and verify the work done to date on XENO and provide examples for publication.

In the next five years we foresee the SECS and XENO projects reaching a stage of maturity where they will find much application in other research groups. Our research will continue in these areas, but turn to some new programs that approach the problems from different viewpoints and allow us an opportunity to begin fresh taking advantage of what we have learned from the building of SECS and XENO.

B. Justification and Requirements for Continued Use of SUMEX

The SECS and XENO projects require a large interactive time-sharing capability with high level languages and support programs. As a member of the campus computing advisory committee and the UC systemwide computing advisory committee, Professor Wipke has ascertained that the UCSC campus is not likely in the future to be able to provide this kind of resource. Further there does not appear to be in the offing anywhere in the UC system a computer which would be able to offer the capabilities we need. Thus from a practical standpoint, the SECS and XENO projects still need access to SUMEX for survival.

Scientifically, interaction with the SUMEX community is still extremely important to our research and will continue to be so because of the direction and orientation of our projects. Collaborations on the metabolism project and the synthesis project need the networking capability of SUMEX-AIM, for we are and will continue to be interacting with synthetic chemists at distant sites and metabolism experts at the National Cancer Institute. Our requirements are for good support of FORTRAN.

C. Needs Beyond SUMEX-AIM

We do plan to acquire a virtual memory minicomputer like a VAX or PRIME in the future to offload some of our processing from SUMEX. Such a machine would enable us to do some production and development work locally and would explore the feasibility of those types of machines as hosts for SECS and XENO. Acquisition of a local machine would lead to decreased loading on SUMEX, although we anticipate a continued need for SUMEX access since (1) we plan to continue to develop and maintain the PDP-10 version of SECS and (2) we require the networking capabilities of SUMEX for purposes of collaboration and testing. In the event that no local facilities are forthcoming, we foresee our SUMEX load contribution increasing as our group grows and as we start new projects and maintain existing large programs.

D. Recommendations for Community and Resource Development

The AIM Workshops have been excellent in the past and should be continued. In view of current congestion of the SUMEX resource, we feel the community would benefit if large remote users such as ourselves had a virtual minicomputer in order to distribute the computing load more effectively. This would free SUMEX, with its networking facilities, to

allow netwide testing/utilization of SECS and XENO by members of the community and by groups working in collaboration with our own.

II.A.2.7 SOLVER Project

SOLVER: Problem Solving Expertise

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I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

This project focuses upon the development of strategies for discovering and documenting the knowledge and skill of expert problem solvers. In the last fifteen years, great progress has been made in synthesizing the expertise required for solving extremely complex problems. Computer programs exist with competency comparable to human experts in diverse areas ranging from the analysis of mass spectrograms and nuclear magnetic resonance [DENDRAL] to the diagnosis of certain infectious diseases [MYCIN].

Design of an expert system for a particular task domain usually involves the interaction of two distinct groups of individuals, "knowledge engineers," who are primarily concerned with the specification and implementation of formal problem solving techniques, and "experts" (in the relevant problem area) who provide factual and heuristic information of use for the problem solving task under consideration. Typically, the knowledge engineer, after consulting with one or more experts, decides on a particular knowledge representational structure and inference strategy. Next, "units" of factual information are specified. That is, properties of the problem domain are decomposed into a set of manageable elements suitable for processing by the inference operations. Once this organization has been established, major efforts are required to refine representations and acquire factual knowledge organized in an appropriate form. Major research problems exist in developing more effective representations, improving the inference process, and in finding better means of acquiring information from either experts or the problem area itself.

Programs currently exist for empirical investigation of some of these questions for a particular problem domain [AGE, UNITS, RLL]. These tools allow the investigation of alternate organizations, inference strategies, and rules bases in an efficient manner. What is still lacking, however, is a theoretical framework capable of reducing dependence on the expert's intuition or on near exhaustive testing of possible organizations. Despite their successes, there seems to be a consensus that expert systems could be

better than they are. Most expert systems embody only the limited amount of expertise that individuals are able to report in a particular, constrained language (e.g. production rules). If current systems are approximately as good as human experts, given that they represent only a portion of what individual human experts know, then improvement in the "knowledge capturing" process should lead to systems with considerably better performance.

B. Medical Relevance and Collaboration

Collaboration with Dr. James Moller in the Department of Pediatrics, Dr. Donald Connelly in the Department of Laboratory Medicine, and students and staff in the University of Minnesota Medical School.

C. Highlights of Research Progress

Accomplishments of this past year. Prior research at Minnesota on expertise in diagnosis of congenital heart disease has resulted in a theory of diagnosis and an embodiment of that theory in the form of a computer simulation model which diagnoses cases of congenital heart disease. This past year the work has been extended to a system called Galen.

Galen is a computer program that simulates the diagnostic process in pediatric cardiology. It is descended from two earlier programs written here at Minnesota: Diagnoser and Deducer [Swanson, 1977]. Deducer is a program that builds hemodynamic models of the circulatory system that describe specific diseases. The models are built by using knowledge about how idealized parts of the circulatory system are causally related. Diagnoser is a recognition-driven program that performs diagnoses by successively hypothesizing one or more of these models, matching them against patient data. The models that match the best are used as the final diagnosis. A series of experiments carried out at Minnesota have shown that Diagnoser/Deducer performs as well (and sometimes better) than expert human cardiologists [Johnson et al., 1981].

Despite the success of Diagnoser and Deducer, the programs have become increasingly difficult to use as a research tool in recent years. They lack a clean, comprehensible structure that is necessary for the kind of experiments we wish to perform. To remedy this problem, a new version, called Galen, is nearing completion here. Galen is intended as a version of Diagnoser/Deducer that is easy to use and modify.

Like its predecessors, Galen is strongly recognition-driven. The program consists of three knowledge sources, referred to as the guesser, the reviewer, and the modeler. The guesser is a set of production rules that propose initial hypotheses on the basis of patient data: a "first guess" about what is wrong with the patient. A hypothesis can be regarded as a set of models (or other hypotheses) and a set of rules that choose the most appropriate members of the set for further consideration. The reviewer uses these hypothesis-specific rules to refine each hypothesis to the most specific form that still satisfactorily accounts for the data. The modeler is a group of production rules that builds new models and

attaches them to existing (precompiled) hypotheses. It runs in isolation from the other two knowledge sources, and is used to initialize the system.

In a typical diagnostic session, Galen is given abstracted data one piece at a time from the patient's chart. Each new piece of data examined by the guesser. Next, each hypothesis that is currently in contention is examined by the reviewer. When this is complete, a new piece of data is requested and the process repeats until all data has been examined. Once this occurs, the models that remain in contention are scored according to how well they explain the data. The two or three top scoring models are then used as a final diagnosis.

We are investigating several research questions within the architecture of the Galen system. First, we are experimenting with ways of qualitatively scoring cardiovascular models, to replace the somewhat ad-hoc numeric scoring method now in use. Second, we are investigating ways in which Galen can be made to ask for additional information about the patient at the appropriate time. Third, we are studying ways in which the modeler (our causal reasoning component) can be integrated with the guesser and the reviewer (our prototypic reasoning components). In particular, we are interested in exploring ways in which causal reasoning can replace (or aid) prototypic reasoning when it proves inadequate to reach a diagnosis.

Research in progress. The methodology of our research derives from the discipline of cognitive science, and from our study of expert problem solvers in a number of fields. This methodology consists of: (1) extensive use of verbal thinking aloud protocols as well as other experimental data as a source of information from which to make inferences about underlying cognitive structures and processes; (2) development of computer models as a means of testing the adequacy of inferences derived from the protocol studies; (3) testing and refinement of the cognitive models based upon the study of human and model performance in experimental settings.

We are constructing recognition based computer models of diagnosis in several fields (medicine, law, science) with expertise comparable to highly expert practitioners. Since humans are notoriously poor at describing their own perceptual knowledge, the first phase of this work requires creating a series of tasks through which experts can reveal their criteria for initiating hypotheses and the associated expectations required for acceptance or rejection. The first type of task requires experts to solve real and simulated problems. Based on studies of performance in these tasks, a model is created to explain the ways in which recognition prototypes are selected for further evaluation. A catalog of these prototypes are produced. Expert performance cannot, however, be realized until these prototypes are associated with highly accurate recognition templates to be matched against input data. While our experts are not particularly adept at generating these templates, we have discovered they can frequently describe causal models of the underlying process. We therefore attack the problem of generating templates by first constructing a causal model of relevant parts of the underlying process. The model is intended as a tool to "capture" knowledge useful for a non-causal reasoning system. In a sense, we use a causal model to "compile" a recognition model

of expertise. The output of the model is then compared with the performance of experts on a third task in which they judge the appropriateness of specific template features. Discrepancies are reduced by a "tuning process" until the match cannot be further improved.

The techniques employed in designing templates for diagnosis results in a representation of expertise at a fairly global level of knowledge and skill; they do not provide detailed information regarding the control processes through which experts are able to guide the course of diagnostic reasoning. These control processes incorporate highly refined heuristics about which the experts are almost wholly unaware. To discover the needed control knowledge we ask experts to complete tasks in which we have systematically perturbed aspects of the problem data. The data in these tasks are chosen so that members of an overlapping set of hypotheses will be elicited during the course of a problem solving episode. Eventual success depends on ability to overcome an initially plausible candidate in favor of a later, more correct alternative.

Results of the investigations to date reveal that problem solvers, even at the expert level, make frequent reasoning errors. Such errors are overcome either by the use of highly developed specific problem solving heuristics or by shifting to more detailed levels of reasoning. When our models are run on these same tasks, they initially make errors like the more expert subjects who are not able to shift levels in reasoning or otherwise recover from their initial (incorrect) hypothesis. By careful study of the behavior of experts who are able to solve such problems, a set of problem solving heuristics are identified. When these heuristics are incorporated into the model, it performs like the successful experts.

D. List of Relevant Publications

- Connelly, D., & Johnson, P.E., Medical problem solving. Human Pathology, 1980, 11, (5), 412-419.
- Elstein, A., Gorry, A., Johnson, P., & Kassirer, J. Proposed research efforts. In Clinical Decision Making and Laboratory Use. D. C. Connelly, E. Benson, & D. Burke (Eds.), University of Minnesota Press (in press).
- Feltovich, P. J., Knowledge based components of expertise in medical diagnosis. Unpublished doctoral dissertation, University of Minnesota, 1981.
- Feltovich, P. J., Johnson, P. E., Moller, J. H., & Swanson, D. B., The role and development of medical knowledge in diagnostic expertise. In W. Clancey & E. H. Shortliffe (Eds.), Readings in Medical AI, (in press)
- Johnson, P. E. Cognitive models of medical problem solvers. In D. C. Connelly, E. Benson, & D. Burke (Eds.) Clinical Decision Making and Laboratory Use. University of Minnesota Press (in press).
- Johnson, P. E., What kind of expert should a system be. The Journal of Medicine and Philosophy, (in press).

- Johnson, P. E., Severance, D. G., & Feltovich, P. J. Design of decision support systems in medicine: Rationale and principles from the analysis of physician expertise. Proceedings of the Twelfth Hawaii International Conference on System Sciences, Western Periodicals Co., 1979, 3, 105-118.
- Johnson, P. E., Duran, A., Hassebrock, F., Moller, J., Prietula, M., Feltovich, P., & Swanson, D. Expertise and error in diagnostic reasoning. Cognitive Science, 1981, 5, 235-283.
- Johnson, P. E., Hassebrock, F., Validating computer simulation models of expert reasoning. In Proceedings of the Sixth European Meeting on Cybernetics and Systems Research, Vienna, Austria, April 1982, (in press).
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- Moller, J. H., Bass, G. M., Jr., & Johnson, P. E. New techniques in the construction of patient management problems. Medical Education, 1981, 15, 150-153.
- Swanson, D. B., Computer simulation of expert problem solving in medical diagnosis. Unpublished doctoral dissertation, University of Minnesota, 1978.
- Swanson, D.B., Feltovich, P. J., & Johnson, P. E., Psychological analysis of physician expertise: Implications for the design of decision support systems. In D. B. Shires & H. Wold (Eds.), Medinfo77. Amsterdam: North-Holland Publishing Co., 1977, pp. 161-164.

E. Funding and Support

Work being done in scientific reasoning this past year has been sponsored under a current NSF (SE079-13036; 1981-82) grant to Paul Johnson. The work in Law is being supported by a grant from the NSF Law and Social Science Program (NSF SES-8111295; 1981-83). The work in medicine has been sponsored by the University of Minnesota Medical School and by NICHD (T36-HD-17151 and HD-01136; 1978-81) and NSF (NSF/BNS-77-22075; 1979-82) grants to the Minnesota Center for Research in Human Learning of which Paul Johnson is principal investigator.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

We have made use of the SUMEX system to consult with Dr. Benjamin Kuipers of Tufts University and Richard Keller of Rutgers University on issues relevant to the design of the Galen system. We have similarly

consulted with Dr. N. S. Sridharan and Dr. L. Thorne McCarty of Rutgers University about our work in lawyer reasoning.

B. Sharing and Interactions with Other SUMEX-AIM Projects

Our work is complementary to many of the current projects supported on SUMEX-AIM. We will be investigating certain aspects of expert problem solving in order to develop better organizational and knowledge acquisition strategies. Such work requires that we be able to build upon the extensive experience in knowledge engineering within the SUMEX-AIM communities. Specifically, we first need to investigate the number of existing programs in order to determine the degree to which they satisfy the design goals which we will be establishing. We then hope to use the program construction tools that are available in order to build prototype systems to illustrate our ideas.

C. Critique of Resource Management

(None)

III. RESEARCH PLANS

A. Project Goals and Plans

Near term. Our research with the SUMEX-AIM resource has two components. First, we are involved in selective reimplementations of the diagnosis program, as described above. Second, we are making extensions to the original work of knowledge capturing, also described above. In the coming year, we plan to use the architecture of the Galen program to direct further studies of expertise in medical diagnosis, law and science. These studies are aimed at understanding the problem solving knowledge of individuals at three levels of expertise: novice, apprentice, and expert. This work should be of use in the development of CAI systems by providing hypotheses about the student model, as well as in the design of interfaces between expert systems and non-expert users.

In a related effort, we are studying the way in which experts determine the appropriate level of abstraction at which to analyze a particular problem. An important aspect of this process is to discover how the expert can recover from an initial incorrect choice of levels. We hope to determine the extent to which the difference between causal and prototypic modes of reasoning can be modeled as a difference in level of abstraction. If we are successful in this effort, we will be able to produce a common model for the two types of reasoning under study.

Long range. We propose to investigate the "knowledge capturing" process that occurs in the early stages of the development of expert systems when problem decomposition and solution strategies are being specified. Several related questions are being addressed: what are the performance consequences of different organization approaches, how can these consequences be evaluated, and what tools can assist in making the

best choice? How can organizations be determined which not only perform well, but are structured so as to facilitate knowledge acquisition from human experts?

B. Justification and Requirements for Continued SUMEX Use

Our current model development is taking advantage of the sophisticated LISP programming environment on SUMEX. We have also benefited greatly from the interaction with other researchers facilitated by the SUMEX system. We expect to use SUMEX to allow other groups access to the Galen program. We hope in the future to make greater use of some of the knowledge engineering tools available on SUMEX.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM.

Once the Galen program has been fully implemented and tested, it will be ported to our VAX-11/780. The software is structured to allow simultaneous maintenance of both Interlisp and Franz Lisp versions. Computationally intense validation runs will be done on our VAX. SUMEX will continue to be used for collaborative activities and for program development requiring tools not available on the VAX.

D. Recommendations for Future Community and Resource Development

(None)

II.A.3 Pilot Stanford Projects

The following are descriptions of the informal pilot projects currently using the Stanford portion of the SUMEX-AIM resource pending funding, and full review and authorization.

II.A.3.1 Protein Secondary Structure Project

Protein Secondary Structure Project

Robert M. Abarbanel, M.D.
University of California Medical Center
University of California at San Francisco

I. SUMMARY OF RESEARCH

A. Project Rationale

Development of a protein structure knowledge base and tools for manipulation of that knowledge to aid in the investigation of new structures. System to include cooperating knowledge sources that work under the guidance of other system drivers to find solutions to protein secondary structure problems. Evaluations of structure predictions using known proteins and other user feedbacks available to aid user in developing new methods of prediction.

B. Medical Relevance and Collaboration

Many important proteins have been sequenced but have not, as yet, had their secondary or tertiary structures revealed. The systems developed here would aid medical scientists in the search for particular configurations, for example, around the active sites in enzymes. Predictions of secondary structure will aid in the determination of the full "natural" configuration of important biological materials. Development of systems such as these will contribute to our knowledge of medical scientific data representation and retrieval.

C. Highlights of Research Progress

The prediction of beta-alpha protein structures is nearly complete. A system has been developed on a VAX 11/750 at the University of California, San Francisco, to allow researchers to describe patterns of amino acid residues that will be sought in the sequences under study. The presence or absence of these "primary" patterns are then combined with other measures of structure, like hydrophobicity, to suggest possible alpha helix or beta sheet or turn configurations.

The segments of a sequence between turns are then analyzed to determine the allowable extent of the possible secondary structure assignments. Any segments remaining are then used to generate all possible complete structures. Only two beta strands with the character of sheet edges are allowed in any prediction. This heirarchical generation and pruning results in nearly 95% turn prediction accuracy, and excellent delimiting of helices and sheets. In some cases, one and only one secondary structure are predicted.

Research in Progress -- Funding of this research has been difficult during the year. An all volunteer effort to date has produced some very impressive results. Should some funding be acquired soon, work on other classes of proteins will continue. The original system written in the C language, will be constructed with a good scientist-user interface using facilities at SUMEX-AIM. The scheme of building structures by refinement of regions and higher level views of larger and larger sub-structures, will be expanded with a knowledge-engineered blackboard model. Preliminary design of these tools is under way.

D. List of Relevant Publications

The first paper on beta-alpha-beta protein structures is in preparation.

E. Funding Support

New Investigator Award approved but not funded by the National Library of Medicine, N.I.H.

II. INTERACTIONS WITH SUMEX-AIM RESOURCE

A. Medical Collaborations

None.

B. Sharing and Interactions with SUMEX Projects

This project is closely allied with the MOLGEN group, both in computer and scientific interests. Some pattern matching methodology created for the protein data base has been adopted and used in the various DNA knowledge bases. The principal persons in the MOLGEN group have contributed to this project's use and understanding of knowledge base software and resources.

C. Critique of Resource Management

The system load at SUMEX-AIM was so overwhelming so as to discourage the use of the DEC-10 system for development of tools. All programming and structure investigation has been done on the UNIX (TM) system at the University of California, San Francisco.

Resource management remains excellent. The staff are friendly and responsive. They cannot, however, despite large personal efforts, make up for the sorry lack of computing power that has plagued this project. It is hoped that improvements in load or hardware will allow continued development of the SUMEX-AIM software during 1982-83.

III. RESEARCH PLANS

A. Project Goals and Plans

Design of rules modules in UNITS editor that will allow an inexperienced user to express algorithms for structure prediction in near-natural language. These prediction schemata will then be translated into appropriate combinations of invocations of knowledge sources, editors, and feedback tools to aid the user in further refinement of his algorithms.

Systems to be developed for the discovery of rules and/or algorithms that can transform a protein sequence into a secondary structure, possibly with implications about tertiary structure. This will involve an effort along the lines of the meta-DENDRAL project.

Expansion of techniques used for beta-alpha prediction to other classes of proteins. Improvement of user interfaces to allow use of this sequence analysis system for problems of homology and energetics.

B. Need for Resources

1. SUMEX Resources

The availability of UNIX (TM) under SUMEX-AIM control will greatly aid in the transferability of existing algorithms. The environment of knowledge base tools and people is the primary motive for doing this work using SUMEX. Access to both established and developing systems aids this project in setting down standards of excellence, forward thinking about computing tools and methodologies, and active exchange of techniques and ideas. The close collaboration with the MOLGEN researchers is particularly useful in this regard.

2. Other Computing Resources

A soon to be established network connection with the Computer Graphics Laboratory at UCSF will provide access to 1) the latest in protein structural information, and 2) color line drawing graphics facilities for evaluation and display of this projects product. A real time display using color graphics will become a possibility.

Recommendations -- First and most important -- EXPAND the computing power available to SUMEX users. Facilitate networking with other computing environments like the Computer Graphics Laboratory at UCSF so that protein structural information may be exchanged and their hardware for 3d structure display may be utilized as a part of a complete biological structures analysis system.

II.A.3.2 Ultrasonic Imaging Project

ULTRASONIC IMAGING PROJECT

James F. Brinkley, M.D.

W.D. McCallum, M.D.

Depts. Computer Science, Obstetrics and Gynecology
Stanford UniversityI. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The long range goal of this project is the development of an ultrasonic imaging and display system for three-dimensional modelling of body organs. The models will be used for non-invasive study of anatomic structure and shape as well as for calculation of accurate organ volumes for use in clinical diagnosis. Initially, the system has been used to determine fetal volume as an indicator of fetal weight; later it will be adapted to measure left ventricular volume, or liver and kidney volume.

The general method we are using is the reconstruction of an organ from a series of ultrasonic cross-sections taken in an arbitrary fashion. A real-time ultrasonic scanner is coupled to a three-dimensional acoustic position locating system so that the three-dimensional orientation of the scan plane is known at all times. During the patient exam a dedicated microcomputer based data acquisition system is used to record a series of scans over the organ being modelled. The scans are recorded on a video tape recorder before being transferred to a video disk. 3D position information is stored on a floppy disk file. In the proposed system the microprocessor will then be connected to SUMEX where it will become a slave to an AI program running on SUMEX. The SUMEX program will use a model appropriate for the organ which will form the basis of an initial hypothesis about the shape of the organ. This hypothesis will be refined at first by asking the user relevant clinical questions such as (for the fetus) the gestational age, the lie of the fetus in the abdomen and complicating medical factors. This kind of information is the same as that used by the clinician before he even places the scan head on the patient. The model will then be used to request those scans from the video disk which have the best chance of giving useful information. Heuristics based on the protocols used by clinicians during an exam will be incorporated since clinicians tend to collect scans in a manner which gives the most information about the organ. For each requested scan a prototype outline derived from the model will be sent to the microcomputer. The requested scan will be retrieved from the video disk, digitized into a frame buffer, and the prototype used to direct a border recognition process that will determine the organ outline on the scan. The resulting outline will be sent to SUMEX where it will be used to update the model. The scan requesting process will be continued until it is judged that enough information has been collected. The final model will then be used to determine volume and other quantitative parameters, and will be displayed in three dimensions.

We believe that this hypothesize verify method is similar to that used by clinicians when they perform an ultrasound exam. An initial model, based on clinical evidence and past experience, is present in the clinician's mind even before he begins the exam. During the exam this model is updated by collecting scans in a very specific manner which is known to provide the maximum amount of information. By building an ultrasound imaging system which closely resembles the way a physician thinks we hope to not only provide a useful diagnostic tool but also to explore very fundamental questions about the way people see.

We are developing this system in phases, starting with an earlier version developed at the University of Washington. During the first phase the previous system has been adapted and extended to run in the SUMEX environment. Clinical studies have been initiated to determine its effectiveness in predicting fetal weight and left ventricular volume. At the same time computer vision techniques are being studied in order to develop the system further in the direction of increased applicability and ease of use. We thus hope to develop a limited system in order to demonstrate the feasibility of the technique, and then to gradually extend it with more complex computer processing techniques, to the point where it becomes a useful clinical tool.

B. Medical Relevance

This project is being developed in collaboration with the Ultrasound Division of the Department of Obstetrics at Stanford, of which W.D. McCallum is the head.

Fetal weight is known to be a strong indicator of fetal well-being: small babies generally do more poorly than larger ones. In addition, the rate of growth is an important indicator: fetuses which are "small-for-dates" tend to have higher morbidity and mortality. It is thought that these small-for-dates fetuses may be suffering from placental insufficiency, so that if the diagnosis could be made soon enough early delivery might prevent some of the complications. In addition such growth curves would aid in understanding the normal physiology of the fetus. Several attempts have been made to use ultrasound for predicting fetal weight since ultrasound is painless, noninvasive, and apparently risk-free. These techniques generally use one or two measurements such as abdominal circumference or biparietal diameter in a multiple regression against weight. We recently studied several of these methods [McCallum 79] and concluded that the most accurate were about +/-200 gms/kg, which is not accurate enough for adequate growth curves (the fetus grows about 200 gms/week). The method we have developed is based on the assumption (which we have shown to be correct this past year [Brinkley 82d]) that fetal weight is directly related to volume since the density of fetal tissue is nearly constant. We have shown this year [Brinkley 82e] that by utilizing three dimensional information more accurate volumes and hence weights can be obtained.

In addition to fetal weight, the current implementation of this system has been evaluated for its ability to determine other organ volumes

in vitro. In collaboration with Dr. Richard Popp of the Stanford Division of Cardiology we have evaluated the system on in vitro kidneys and latex molds of the human left ventricle [Brinkley 82b]. Left ventricular volumes are routinely obtained by means of cardiac catheterization in order to help characterize left ventricular function. Attempts to determine ventricular volume using one or two dimensional information from ultrasound has not demonstrated the accuracy of angiography. Therefore, three-dimensional information should provide a more accurate means of non-invasively assessing the state of the left ventricle.

C. Highlights of Research Progress

During the past year we have completed most of the evaluation of the first phase of our implementation and have analyzed and submitted the results for publication. The results have also been presented at three separate conferences. As mentioned in previous reports the first phase involves the manual outlining of scans with a light pen and the interpolation of an ad hoc model to the data. The system as it stands now is entirely data driven and hence has no notion of what kind of organ it is looking at. However, our results suggest that the data driven approach will still give more accurate volumes than any now obtainable, and thus will provide the medical impetus for continued research into knowledge driven approaches. The following evaluations have been completed:

1. Engineering evaluations: [Brinkley 82a], [Brinkley 82b] describe the implementation of the first phase of the system as well as the engineering evaluations. The evaluations included the reproducibility of three dimensional point determination and the accuracy of volumes computed on progressively more irregular objects. The reproducibility of 3D point determination was found to be about 6 mm. The various sources of this error were analyzed and found to come mostly from the ultrasound resolution of about 3 mm, and the position locator resolution of about 3 mm.

Thirty volume trials on 10 water filled balloons gave 27 out of 30 calculations within 1.8 percent of true volume. Eighteen trials on 6 kidneys gave 17 out of 18 calculations within 5.1 percent of true volume. Fifteen trials on 5 human left ventricular molds gave 13 out of 15 calculations within -5.9 percent of true volume.

2. Fetal weight estimation in vitro: [Brinkley 82c], [Brinkley 82d] describe an evaluation of the ability of ultrasonic three-dimensional head and trunk reconstructions to estimate fetal weight on 25 dead neonates imaged in a water bath. The correlation between head plus trunk volume and measured weight was $r=.985$ with a standard error of 190 grams, over a weight range of 364 to 3650 grams. In this study we also established the empirical relationship between weight and volume: the correlation was $r=.999$, with a standard error of 37 grams.

3. Fetal weight estimation in utero: [Brinkley 82e] is in the final draft stages. It describes the results from our clinical study to determine the ability of volumes found by three dimensional ultrasonic head and trunk reconstructions to estimate in utero fetal weight. 41 live term fetuses were imaged within 48 hours prior to delivery. Head and trunk volumes calculated by the reconstruction technique were compared with measured birthweight in multiple linear regressions. In addition to the reconstruction volumes the three dimensional coordinates of various landmarks on the fetus were obtained with the system. The 3D distances between these landmarks were used to create additional predictor variables such as lengths, diameters, circumferences and simple volumes. The correlation between head and trunk volumes by reconstruction and the natural log of birthweight was $r=.892$, $SE=91$ g/kg. The best set of predictor variables was found by stepwise regression to be a head volume model as the product of three distances in the head, a trunk volume model as the product of three distances in the trunk, and the trunk volume by reconstruction. The correlation between these 3 predictors and the natural log of birthweight was $r=.941$, $SE=69$ g/kg. For comparison the accuracy reported by most methods in the literature have been about 100 g/kg. We have thus improved the clinical prediction of fetal weight by about 30 percent over current methods.

4. Conclusions from the evaluations of the data driven system: The in vitro results have shown that, in spite of a fairly poor 3D point reproducibility of 6 mm, we were able to obtain quite accurate volumes on balloons, kidneys and left ventricular molds. We feel that this accuracy was obtainable because the volumes were done on objects with fairly continuous surfaces, so the ability to exactly pinpoint the location of a point on that surface was not so critical. We also showed that, as expected, accuracy degrades as the irregularity of the objects increases. Nevertheless, all in vitro volumes were very accurate when compared with current clinical methods. We would therefore expect the data driven system to provide useful clinical estimates of organ volume, for example, left ventricular volume.

The evaluations of the system's ability to predict fetal weight have demonstrated that, as expected, accuracy degrades when going from the in vitro to the in utero situation. Nevertheless, we have shown that the addition of 3D information improves the clinical estimation of fetal weight by about 30 percent. We would expect that this accuracy could improve even more as more appropriate volume models are developed which include the limbs.

As mentioned previously the volume models developed in the current system are interpolated to whatever 3D surface data is

available. They are therefore subject to noise and missing data. In addition, the system is extremely cumbersome to use because of the manual outlining of scans and the interactive nature of the volume process. The successful evaluations of the first phase of our implementation provide encouragement and medical justification for continued development of a knowledge driven system.

The research that is currently underway includes the following:

1. Completion of the survey of knowledge driven systems which could be useful for knowledge driven organ modelling.

2. Refinement of the second implementation phase: a knowledge driven modelling system which uses 3D surface points obtained with the data acquisition system developed in the first phase. This 2nd implementation phase will be designed for non-structured models and will be initially evaluated on balloons.

D. Recent Publications

[Brinkley 82a] Brinkley, J.F., McCallum, W.D., Popp, R.L. Ultrasonic three-dimensional imaging and volume: an in vitro evaluation. The American Journal of Cardiology 49:897, 1982. Abstract presented at the 31st Annual Scientific Session, American College of Cardiology, Atlanta, Georgia, April 25-29, 1982.

[Brinkley 82b] Brinkley, J.F., Muramatsu, S.K., McCallum, W.D., and Popp, R.L. In vitro evaluation of an ultrasonic three-dimensional imaging and volume system. 1982. to be published in Ultrasonic Imaging.

[Brinkley 82c] Brinkley, J.F., McCallum, W.D., Muramatsu, S.K., and Liu, D.K. The Use of Ultrasonic Three-Dimensional Volume Measurements in the Estimation of Fetal Weight. In Proceedings of the 29th Annual Meeting, pages 6. Society for Gynecologic Investigation, Dallas, Texas, March, 1982.

[Brinkley 82d] Brinkley, J.F., McCallum, W.D., Muramatsu, S.K., and Liu, D.Y. Fetal weight estimation from ultrasonic three-dimensional head and trunk reconstructions: evaluation in vitro. 1982. submitted to Amer. J. Obstetrics Gynecology.

[Brinkley 82e] Brinkley, J.F., McCallum, W.D., Muramatsu, S.K., and Liu, D.Y. Fetal weight estimation from ultrasonic three-dimensional head and trunk reconstructions: evaluation in vivo. 1982. in preparation.

[Brinkley 82f] Brinkley, J.F. and McCallum, W.D. Organ volume determination by ultrasonic three-dimensional reconstruction. In Proceedings of the First AMIA Congress on Medical Informatics, pages 178-182. American Medical Informatics Association, San Francisco, May, 1982.

[McCallum 79] McCallum, W.D. and Brinkley, J.F. Estimation of fetal weight from ultrasonic measurements. Amer. J. Obstet. Gynecol. 133(2):195-200, 1979.

E. Funding Status

"Ultrasonic Three-dimensional Organ Modelling", individual postdoctoral fellowship.

Fellow: James F. Brinkley

Sponsor: W.D. McCallum

Funding Agency: National Institute of General Medical Sciences

Number: 1 F32 GM08092

Total term and direct cost: 7/1/81-6/30/84 (3 years) \$55,452 (stipend)

Current funding from this fellowship: 7/1/81-6/30/82 (1 year) \$17,892

II. INTERACTIONS WITH SUMEX-AIM RESOURCE

A. Collaborations

We are collaborating more with medical people than anyone else. The project is located in the Obstetrics Department at Stanford where W.D. McCallum manages the ultrasound patients. We have also been collaborating with Dr. Richard Popp in the Division of Cardiology at Stanford.

B. Sharing and Interactions with SUMEX Projects

Mostly personal contacts with the Heuristic Programming Project and MYCIN project at Stanford. The message facilities of SUMEX have been especially useful for maintaining these contacts. Since the first phase of the project is now essentially complete we have been interacting more with other SUMEX projects in order to develop the AI ideas.

C. Resource Management

In general SUMEX has been a very usable system, and the staff has been very helpful. The only complaint is that it is impossible to get anything done in the afternoons since we always get bumped.

III. RESEARCH PLANS

A. Project Goals and Plans

As mentioned in Part I we are implementing this system in phases, each phase requiring use of more sophisticated artificial intelligence techniques. The major phases are as follows (in chronological order):

1. Set up prototype system. Perform engineering tests and clinical evaluations of the ability of the system to predict fetal weight, heart and kidney volume.

As mentioned under Highlights of Research Progress, this first implementation phase is complete, as are the initial engineering and clinical evaluations. The evaluations have shown that the data driven system can provide more accurate volumes and weights than are currently clinically available. However, our patient studies have demonstrated the basic limitations of the system, which are inadequate models and difficulty of use. From a medical point of view the next phases will be attempts to remove these limitations.

2. Explore other methods for geometric modelling, AI techniques of goal directed problem solving.

In order to develop adequate models and control strategy it will be necessary to examine other AI methods of generating models and using them to guide problem solving programs. This phase of the research is now nearing completion. For this aspect of our research the SUMEX-AIM community has been especially useful.

3. Develop program, as outlined in the introduction, with several limitations--

- only a simple organ will be modelled at first, ie not the entire fetus including limbs

- the computer will still request certain scans to be retrieved from the video disk but the operator will outline them with the light pen. Since ultrasound image quality is improving so rapidly it makes sense to wait as long as possible before attempting automated border recognition. The models and control strategies developed during this phase should be useful when actual border recognition is attempted however. This version of the system should have application in left ventricular volume calculations.

4. Extend the technique to more irregular objects structured models will be developed so that the fetal limbs can be included.
5. Add image processing hardware, develop automated border recognition software.

The models developed in the last two phases will be used to guide the border recognition process. As these phases are implemented they will continue to be tested against the clinical data acquired and stored on floppy disk by the data acquisition system. In this way we can develop new ideas while continually upgrading the clinical utility of the system.

B. Justification and Requirements for Continued SUMEX Use

The goals of this project seem to be compatible with the general goals of SUMEX, i.e., to develop the uses of artificial intelligence in medicine. The problem of three-dimensional modelling is a very general one

which is probably at the very heart of our ability to see. By developing a medical imaging system that models the way clinicians approach a patient we should not only develop a useful clinical tool but also explore some very fundamental problems in AI.

The availability of a large well supported facility like SUMEX has been and will continue to be very valuable as we develop and test further implementations of the system. Our current share of the SUMEX resources is adequate.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM

Judging from our present experience it appears that SUMEX could not handle the amount of data required for image processing on digitized ultrasound scans. This is one of the main reasons we are proposing a distributed system in which SUMEX only directs a smaller machine to do the actual number crunching. It is also one of the reasons we are postponing direct digitization until later. As microprocessors become more powerful they will be capable of acting as slaves to an intelligent SUMEX program. The AI program will direct the image processing functions of the micro so that the data is processed in an intelligent way, but SUMEX will only see the results of that processing, not the actual data. We will thus need to keep track of developments in microcomputers so that we can develop this kind of distributed system.

D. Recommendations

Since we are planning to develop a distributed system we would hope to see these kind of systems being developed by the SUMEX resource. Projects that would be of direct interest are networks (such as ETHERNET), personal computer stations, graphics displays, etc.

II.A.4 Pilot AIM Projects

The following are descriptions of the informal pilot projects currently using the AIM portion of the SUMEX-AIM resource or the Rutgers-AIM resource pending funding, and full review and authorization.

II.A.4.1 AI-COAG: Coagulation Expert Project

AI-COAG: Coagulation Expert Project

Donald A. B. Lindberg, M.D.
School of Medicine
University of Missouri-Columbia

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

Experiment to form a clinical consultant program based on a formal representation of the medical knowledge of the expert in human hemostasis.

B. Medical Relevance and Collaboration

Experts in hemostasis are few and are poorly distributed, often found only at University teaching hospitals and large tertiary care centers. It would be helpful to other physicians if the specialty knowledge of these experts were accessible through a computer-based consultant system.

Such a system would have medical relevance in diagnosis, management, and continuing medical education.

The team at the University of Missouri-Columbia consists of the following individuals:

Lamont W. Gaston, M.D.
Lawrence C. Kingsland III, Ph.D.
Donald A. B. Lindberg, M.D.
Anthony D. Vanker, Ph.D.
Johannes Yesus, M.D.

Dr. Gaston is a consulting hematologist and Director of the University of Missouri Health Sciences Center Coagulation Laboratory. Dr. Kingsland is a Post-doctoral Fellow whose Ph.D. is in Electrical Engineering with a concentration in Bioengineering. Dr. Lindberg is Director of the Information Science Group and Principal Investigator. Dr. Vanker is a Post-doctoral Fellow whose Ph.D. is in Physiology. Dr. Yesus is Director of the University of Missouri Health Sciences Center Blood Bank.

Subject matter expertise and the facilities of a coagulation laboratory and patient records are being provided by the University of Missouri-Columbia to build and test the consultant system. Additional testing and consultation has been obtained from Heinz Joist, M.D., Director of the Coagulation Laboratory at the St. Louis University Hospitals.

A formal research proposal was submitted to NIH on October 27, 1980. The proposal was based on initial studies performed on the SUMEX-AIM facility and at the University of Missouri-Columbia. This proposal was approved and funded for the five-year period from July, 1981 through June, 1986.

C. Highlights of Research Progress

Accomplishments:

An initial model of the coagulation consultant was created using the AGE/UNITS package on the SUMEX-AIM facility.

A feasibility test with an early textbook-level consultant model was created using EMYCIN on the SUMEX-AIM facility.

The knowledge base of these initial models was expanded and built into a new system on local Digital Equipment Corporation LSI-11 microcomputers. A laboratory interpretation system and a hemostasis history evaluation system are operational.

The laboratory interpretation system provides a differential interpretation of the results of a six-test coagulation screening battery. It has been tested on 315 cases from the files of the University of Missouri-Columbia and the St. Louis University Coagulation Laboratories. Forty-one patterns of results of the six screening tests were encountered.

The current system contains in its knowledge base interpretations for 54 combinations of the six coagulation screening tests. TMM (Tell Me More) and TMR (Tell Me Reference) knowledge sources contain additional supporting information for the user who wishes more detail.

A hemostasis history acquisition system has been added to the consultant program. Multi-level branching logic allows a totally negative history interaction in only 10-12 CRT frames, yet the system can request, tabulate and score responses to more than 200 elements of the hemostasis history.

Research in progress:

Current research is focused on the linkage of the laboratory interpretation and the hemostasis history sub-systems, with the final result the suggestion of additional coagulation laboratory tests leading to a diagnosis.

D. List of Relevant Publications

Gaston, LW; Lindberg, DAB; Vanker, AD; Kingsland, LC III: AI/COAG, a knowledge based surrogate for the human hemostasis expert. Missouri Medicine 79:6, June 1982 (in press).

Kingsland, LC III; Gaston, LW; Vanker, AD; Lindberg, DAB: A knowledge-based consultant system for problems in human hemostasis. Proceedings of the American Medical Informatics Association Congress 82 (San Francisco, May 1982). New York: Masson Publishing Co., pp. 325-9.

Lindberg, DAB; Gaston, LW; Kingsland, LC III; Vanker, AD: AI/COAG: A knowledge-based system for consultation about human hemostasis disorders; progress report. Proceedings of the Fifth Annual Symposium on Computer Applications in Medical Care (Washington DC, November 1981). New York: IEEE, pp. 253-7.

Gaston, LW; Lindberg, DAB; Kingsland, LC III; Vanker, AD: AI/COAG: A knowledge-based system for consultation about human hemostasis disorders; progress report. Proceedings of the 1981 Fall Meeting of the American Society of Clinical Pathologists and the College of American Pathologists (Las Vegas, October 1981).

Vanker, AD; Gaston, LW; Kingsland, LC III; Lindberg, DAB: Coagulation consultation system II: AI/COAG, a progress report. Presented at the Spring 1981 Meeting, National Library of Medicine Training Programs in Health Sciences and Computer Technology (Bethesda, May 1981).

Lindberg, DAB; Gaston, LW; Kingsland, LC III; Vanker, AD; Ueno, H.: A knowledge-based system for consultation about blood coagulation studies. Proceedings of the 10th Annual Conference of the Society for Computer Medicine (San Diego, September 1980).

Vanker, AD; Gaston, LW; Lindberg, DAB; Kingsland, LC III; Ueno, H.: Coagulation consultant system: interpretation of laboratory test data. Presented at the Spring 1980 Meeting, National Library of Medicine Training Programs in Health Sciences and Computer Technology (Ohio State University, May 1980).

E. Funding support

Title of Grant:
Knowledge-Based Hemostasis/Transfusion Consultant System

Principle Investigator:
Donald A. B. Lindberg, M.D.

Funding Agency:
Department of Health and Human Services,
National Heart Lung and Blood Institute.

Grant Identification Number:
DHHS 1 RO1 HL 27857-01

Total Award (dates and amounts, direct costs):
July 1, 1981 to June 30, 1986 -- \$433,886

Current Period (date and amount, direct costs):
July 1, 1981 to June 30, 1982 -- \$85,604

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

We have had both personal and network contacts with members of the SUMEX community during the development of the coagulation consultant system. Personal contacts at professional meetings (Society for Computer Medicine, Symposium on Computer Applications in Medical Care, International Joint Conference on Artificial Intelligence, American Medical Informatics Association, American Society of Clinical Pathologists) have been both interesting and rewarding. Network contacts allow dissemination of ideas and feedback on new work.

B. Sharing and Interactions with Other SUMEX-AIM Projects (via computing facilities, workshops, personal contacts, etc.)

In February of 1980, David Goldman, a medical student at University of Missouri-Columbia and former pre-doctoral fellow in the Information Science Group, spent a week at Stanford University. Mr. Goldman became acquainted with several of the artificial intelligence systems under development at SUMEX, and with the help of members of the SUMEX-AIM community was able to implement a simple coagulation model in EMYCIN.

In March of 1980, Dr. Haruki Ueno attended a workshop on AGE at Stanford. Dr. Ueno learned through this workshop considerable information of direct benefit to our work. He was able to return to Columbia and implement using AGE and UNITS a more extensive coagulation consultant model.

In August of 1980, Dr. Lindberg, Dr. Gaston and Dr. Vanker attended the AIM tutorial at Stanford.

Many of the AI systems of interest to us are running on the SUMEX-AIM resource. Documentation available on-line, and personal contacts facilitated by the electronic-mail capabilities at SUMEX, have been invaluable in the development of our consultant system.

The existence of the SUMEX-AIM system and the facilities it provides for the development of knowledge-based computer consultant systems, made it possible for us to achieve early in our study the degree of competence required to build our own system. SUMEX is well set up for this type of ice-breaking assistance: the AI programs are in place and running; users can study the operational systems, work with the representation structures such as those of EMYCIN and AGE, and build the understanding of their chosen research problems which enables them to strike out on their own. Feedback is always available through the electronic-message facilities. and questions or pleas for help receive prompt response.

C. Critique of Resource Management

(community facilitation, computer services, communications services, capacity, etc.)

The SUMEX-AIM professional and technical staff have been uniformly helpful and extremely competent. Busy people have given freely both of their time and their ideas. The spirit of community fostered by the SUMEX resource and its messaging facilities is extraordinary for a group of such wide geographic distribution.

The SUMEX-AIM system is well run, but sometimes shows the signs of its success in symptoms of overloading: disk space is tight, response time slows down, and files may take several minutes to open or copy. Barring occasional problems with noisy telephone lines which are not the province of the SUMEX staff, we have had few other troubles with the system.

It has been our experience that some of the SUMEX-AIM systems are sufficiently complex (and in such a state of flux and continuing development) that the designation of a particular Stanford computer scientist as a collaborator would be extremely desirable. Typically, this would involve a graduate student working on a problem suitable for dissertation research. This points up the fact that the personal component of a collaboration loses none of its importance in remote interactions: that the training, education and dissemination aspects of SUMEX should be considered as important as merely providing computational resources.

III. RESEARCH PLANS

A. Project Goals and Plans

Near-term:

We are working to link the reasoning and the results of the laboratory test interpretation subsystem with those of the hemostasis history evaluation subsystem. The outcome will be the suggestion of specific next tests to perform, leading toward diagnosis of a particular coagulation defect.

Long-range:

Additional modules will be added to the consultant system for the diagnosis of Hemophilia A and B and von Willebrand's disease, for the management of oral anticoagulant therapy, for the diagnosis of disseminated intravascular coagulation, the diagnosis of circulating anticoagulants, and the diagnosis of platelet disorders.

B. Justification and Requirements For Continued SUMEX Use

The current resources allocated to this SUMEX-AIM pilot project are sufficient for the development and dissemination of our ideas and concepts as the knowledge-based coagulation consultant model progresses. We find

membership in the SUMEX community a valuable intellectual resource from which we continue to derive major benefits.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM

We will continue to develop on local microcomputer and minicomputer systems such portions of the coagulation consultant model as are appropriate to the smaller systems. It is both useful and important to us to know that should we need the special resources of the SUMEX-AIM facility for larger or more complex problems, they would be available to us.

D. Recommendations for Future Community and Resource Development

The concept of individual Work Stations is important for future SUMEX-AIM developments. Since we also collaborate with Rutgers using the EXPERT system, it would make more sense from our point of view if the ultimate Work Station were to be a small VAX, perhaps the VAX-11/730. This would permit support of both Lisp and Fortran systems, in contrast to the Dolphin which seems limited to Lisp.

II.B Books, Papers, and Abstracts

The publications for the various collaborative projects are summarized in their respective progress reports. Tables of these publications have been submitted separately to the Biotechnology Program Office in the special format requested. These are not reproduced here to avoid redundancy.

II.C Resource Summary Table

Detailed resource usage information is summarized starting on page 40. Tabulations of this information have been submitted separately to the Biotechnology Program Office in the special format requested. These are not reproduced here to avoid redundancy.

Appendix AInterlisp-VAX Study Report

Addendum to
Interlisp-VAX: A Report

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(HPP-81-14)

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January 20, 1982

Since Larry Masinter's "Interlisp-VAX: A Report" is being circulated widely, it is important that it be as accurate as possible. This note represents the viewpoint of the implementors of Interlisp-VAX, as of January, 1982.

The review of the project and the discussions with other LISP implementors that provided the basis for the Report took place in June, 1981.

We believed at the time, and still believe now, that the Masinter Report is largely a fair and accurate presentation of Interlisp-VAX, and of the long-term efforts necessary to support it. We now have the advantage of an additional 6 month's development effort. There are some areas where progress and performance have been better than anticipated in the Report, and we would like to report on our current status.

AVAILABILITY AND FUNCTIONALITY

Interlisp-VAX has been in use for testing purposes both here at ISI and at several sites around the ARPANET, since November, 1981.

We are planning the first general release for February, 1982--ahead of the schedule that was in effect in June, 1981.

The current implementation includes all of the features of Interlisp-10 with very few exceptions. There is no noticeable gap in functionality among Interlisp-10, Interlisp-D and Interlisp-VAX, except for features that are inherently peculiar to some implementations (e.g., windows on the Dolphin, JSYS and TENEX on the PDP-10).

Among the Interlisp systems we are running here are KLONG, AP3, HEARSAY, and AFFIRM.

PERFORMANCE

Masinter's analysis of the problems of maximizing performance was excellent, both for Interlisp generally and for the VAX particularly. It is now reasonable to quantify the performance based on experience with real systems. The analysis of the performance of Lisp programs is quite complex, and single numbers are often more misleading than representative. It is hard to give a complete analysis, so we will only give general performance numbers.

CPU speed (on a single-user VAX/780) is, for many of the programs we have measured, currently in the range of 1/4 the speed of Interlisp-10 (on a single-user DEC 2060). We believe that a factor of two overall performance improvement is achievable.

Currently, it seems reasonable to allow 1 MByte real memory per active user.

Interlisp-VAX: A Report

Larry Masinter
Xerox Palo Alto Research Center
Palo Alto, California

August 1, 1981

Contents:

- I. Introduction
- II. Interlisp-VAX: Overview and Status
- III. What will Interlisp-VAX be like?
- IV. Conclusions

The views expressed in this report are those of the author; they do not necessarily reflect those of the Xerox Corporation, Stanford University, or the University of Southern California.

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I. INTRODUCTION

Since November 1979, a group at the Information Science Institute of the University of Southern California has been working on an implementation of Interlisp for the DEC VAX-series(1) computers. This report is a description of the current status, future prospects, and estimated character of that Interlisp-VAX implementation. It is the result of several days of discussion with those at ISI involved with the implementation (Dave Dyer, Hans Koomen, Ray Bates, Dan Lynch); with John L. White of MIT, who is working on an implementation of another Lisp for the VAX (NIL); with the implementors of Interlisp-Jericho at BBN (Alice Hartley, Norton Greenfield, Martin Yonke, John Vittal, Frank Zdybel, Jeff Gibbons, Daryle Lewis); with the implementors of Franz Lisp and Berkeley Unix(2) at U.C. Berkeley (Richard Fateman, Bill Joy, Keith Sklower, John Foderaro); and with my colleagues at Xerox PARC.

An earlier draft of this report was circulated to the parties involved in the Interlisp-VAX discussions. This document has been revised as a result of comments received.

Why Interlisp-VAX? In early April, 1981, a meeting was held at SRI of ARPA-sponsored or related Lisp users, to discuss the status and future of Lisp. Those of the community who were current Interlisp users felt strongly that: (1) there was a need for Interlisp to continue to be a viable programming environment in the 1980's, strongly standardized among all implementations; and (2) the most important new implementation of

Interlisp would be for the VAX. There were several reasons for the choice of both the VAX and Interlisp.

Why VAX? The primary reason is that many sites already have VAXes, where they are and will continue to be used not only for Lisp and AI research, but also for use as general purpose, time-shared computing resources, for running FORTRAN, business computing, etc. The VAX is considered to be the most important "technology transfer" vehicle for Interlisp AI programs in the early through mid '80s: it is already spread widely throughout industry and industrial laboratories; and it is very widespread among ARPA's military clientele. It is unlikely that researchers who develop application-oriented AI systems in Interlisp will want to re-implement them in some other language, and it is unlikely that these institutions (private and military) will buy machines specifically for AI programs if those programs constitute only an occasional part of their computing needs. The VAX is believed to be the most likely vehicle for transferring applications to those institutions.

In addition, VAX (for better or for worse) appears to be the machine that many computer science departments around the country have chosen for their "next generation" machine. Insofar as there is a need to spread the concepts and software technologies developed in Interlisp to these departments, it is believed that there is a need to have Interlisp running on the VAX.

Why Interlisp? The Interlisp programming environment has been in wide use in the Artificial Intelligence community for a number of years. It is a powerful, integrated environment, having evolved over the years into a stable system. The availability of multiple, compatible implementations on a number of machines means that researchers can easily transport their programs from any implementation to another.

Why this report? Because of the perceived importance of Interlisp-VAX to the community, and because of my experience with Interlisp and its implementations, I was asked by Stanford and ISI to evaluate the status of the on-going project at ISI, and to estimate the magnitude of the tasks remaining, expected performance and character of the resulting product. Many ongoing research institutions are making plans for their future computational requirements, and many of the decisions about choice of programming language and hardware hinge on the prospects for Interlisp-VAX. In light of the large amount of confusion in the community about the future availability of Interlisp on a VAX, it was thought important to have an outside assessment of the future of the project.

II. INTERLISP-VAX: OVERVIEW AND STATUS

A. Project definition and history

While the Interlisp-VAX project started in November 1979, most of the first year was taken up with project startup and training of personnel (none of the project members were originally familiar with the C programming language, UNIX, or Interlisp, either as a programming

environment or its overall implementation). Thus, most of the work on the implementation to date has been accomplished since November 1980.

The goal of the project has been to produce a version of Interlisp which runs on a VAX, which:

Is as compatible with Interlisp-10 as practical.

While it is difficult to give a metric for compatibility, the goal of the project is that most Interlisp programs in the community will run in Interlisp-VAX merely by recompiling them. At a bare minimum, the Interlisp-VAX code must run the standard Interlisp packages such as the Interlisp Editor, Masterscope, Break Package, Record Package, DWIM, CLisp, and so forth.

Uses the extended virtual address space of the VAX.

One of the primary motivations for investing in the VAX is that the VAX potentially has a large (at least 2**30 bit) address space. Many Interlisp-10 users long ago have run out of address space, and spend much of their time trying to squeeze programs into available address space.

Has adequate performance.

The Lisp produced is expected to make reasonable use of the hardware. It is difficult to give a single number which describes the performance of a system (because some things will run faster and some slower), but the average performance of Interlisp-VAX must be within a factor of 2 of other Lisps which run on the VAX (e.g., Franz and NIL). In addition, Interlisp-VAX must be competitive in price/performance to a DEC-20 for the size of programs which it is now able to run, and also be able to handle larger programs.

B. Summary of the Interlisp-VAX architecture

Interlisp-VAX is a non-microcoded implementation more similar in architecture to Interlisp-10 than Interlisp-D or Interlisp-Jericho. This is appropriate for the VAX, which has a powerful "native" instruction set and is time-shared between a number of users, not all of whom would be running Interlisp. Interlisp-VAX is intended to run on top of the Berkeley Unix operating system. Unlike Interlisp-10, in which the kernel is written in assembly language, the kernel of Interlisp-VAX is written in the high-level systems implementation language C. This might well simplify the transportation of Interlisp-VAX to another machine which had a C compiler and similar characteristics (byte addressable memory, UNIX, 32-bit registers).

Without going into great detail, the important aspects of the Interlisp-VAX architecture are as follows: deep binding; full implementation of "spaghetti stacks"; compilation to VAX native code (with no "block compiler"); memory allocation in 64 KByte "sectors" with sector-table giving type per sector; no CDR-coding (CONS cells take 64 bits); a "stop and copy" garbage collector; 31-bit immediate integers (with plans, but no implementation, of "bignums"). These design choices seem reasonable for the VAX, with exceptions noted below in the section on performance.

Interlisp-VAX has the following component pieces:

1. Machine-independent "higher-level" Interlisp code. This includes, for example, the Interlisp editor, file package, the Masterscope program analyzer. This code is shared, intact, with Interlisp-10, Interlisp-D and Interlisp-Jericho.
2. Interlisp-D code. This is Lisp code which, although shared with Interlisp-D (and Interlisp-Jericho), is not used in Interlisp-10. For example, the implementation of Terminal Tables and Read Tables may be shared with the other Interlisp implementations.
3. VAX-specific Lisp code. This code is necessary to interface to the C kernel and perform other VAX-specific operations. For example, the implementation of the DATATYPE package, while in Lisp, must satisfy constraints placed by the Interlisp-VAX garbage collector, and thus has some essential differences from the version of the DATATYPE package for other Interlisp implementations.
4. C kernel. The C kernel handles memory management, garbage collection, the interpreter, "Spaghetti stack" support (including FUNARGs, RESUME for processes/coroutine support), bootstrapping and interface to the operating system.
5. Lisp/C interface. A small amount of VAX machine code is necessary for the interface between Lisp and code generated by the C compiler. Primarily of interest here is the code which is part of function call and return.
6. VAX code-generator. The VAX native-code generator takes the output of the Interlisp-D Byte-Compiler and generates VAX native code. The Byte-Compiler [Masinter & Deutsch 1980] is a machine independent optimizing compiler which produces intermediate "linearized lisp" code for an abstract stack machine.

C. Current implementation status of Interlisp-VAX: what's been done?

Many of the major design decisions for Interlisp-VAX have been made, including layout of memory, important code sequences (e.g., function call and return for all of the various cases), representations of pointers and system data types, and many parts of the interface to the operating system. In addition, the following tasks have been accomplished:

1. Higher level Interlisp software. The "shared" Interlisp software has been examined, and a few problems identified and fixed; the rest will run in Interlisp-VAX with little change.
2. Interlisp-D code. An initial pass over the Interlisp-D code identifying which portions can be shared has been made.

3. VAX-specific Lisp code. The major pieces which have been written are a version of the DATATYPE package, an array package, and the compiled code loader and parser.
4. C kernel. Most of the C kernel has been completed, in the sense that the code is there and has passed preliminary tests.
5. Lisp/C interface. This has been completed.
6. VAX code-generator. A first version of the VAX code generator has been produced and, to a great extent, debugged. The important design decisions about function call sequences, as well as some of the important open-coding sequences (e.g., CAR and CDR), have been made.

D. Tasks remaining in existing code

1. Higher level Interlisp software. Problems may arise in implementing Interlisp's notions of files, versions, and dates under UNIX; if so, it may be necessary to fix those portions of the Interlisp higher-level software to be more implementation independent.
2. Interlisp-D code. Unfortunately, Interlisp-D is a "moving target" and it is difficult to rely on the sources staying compatible. Insofar as code is shared between Interlisp-D and Interlisp-Jericho, the same code will most likely run under Interlisp-VAX. Problems may arise insofar as the lower levels of Interlisp-VAX differ.
3. Vax-specific Lisp code. The DATATYPE implementation requires some work. The array package seems to be relatively complete, although the program has not been extensively tested. The compiled code loader/parser has been completed and tested in "cross-compilation" mode, while running in Interlisp-10.

The VAX/UNIX I/O package still requires much work. The interface between Interlisp and UNIX is to be accomplished via (1) the Interlisp-D FILEIO package, which gives an interface to buffered, random access files from higher level Interlisp software, (2) some VAX-specific Lisp code, which then interfaces to (3) some pieces of the C kernel. The interfaces between many of these pieces are being designed, but some of the pieces have not been written.

There is a body of the Interlisp environment which, although nominally not part of the "core" of Interlisp, forms a useful part of most of its implementations. For example, the DIRECTORY package and GETFILEINFO are Interlisp-10 facilities which, while not part of the Moore VM document, can be implemented in Interlisp-VAX, are part of Interlisp-10, Interlisp-D and Interlisp-Jericho, and are used by Interlisp application programs.

Interface with UNIX's notion of terminals and interrupts has been considered, but the final details have not been worked out. Initial versions of Interlisp-VAX will have a very simple notion of interrupts.

4. C kernel. Future changes will likely be required depending on the needs of the Lisp-level I/O package, interrupts, and a new version of UNIX which will allow Interlisp to use the high end of memory. The C kernel contains some especially "tricky" areas: interpreter, stack management and garbage collection. These were not completed as of June 1981. Experience with other Lisp/Interlisp implementations has been that debugging and complete testing are difficult. Bugs often are found in the handling of obscure and rare cases, as the code interacts with many other parts of the system. I expect Interlisp-VAX to have its share of problems in these areas.
5. Lisp/C interface. Changing the Lisp/C interface will only be necessary in response to fixing some of the expected "performance bugs" of Interlisp-VAX, e.g., free-variable-pointer-caching (discussed below) may require changes in the function-call sequences.
6. VAX code-generator. My examination of the Vax code generator uncovered a few minor problems due to a misunderstanding of conventions required by the ByteCompiler, and undoubtedly a few more will surface.

More importantly, the current code generator for VAX native code will (as planned) require much work to bring it to the point where it generates production-quality code. In particular:

- a. A register-allocating version of the code generator (in some ways a complete rewrite) would significantly improve performance on the VAX.
- b. A "peephole optimizer" for VAX instructions would enable Interlisp-VAX to take advantage of the VAX's complex instruction repertoire.
- c. More "open" compilation of frequently used routines will be necessary in many circumstances. Although many open-coding sequences have been incorporated, adding more will of course require additional time and effort.
- d. Modification of the ByteCompiler to suppress boxing of intermediate results would have payoff in speed for integer calculations and space for floating arithmetic.

E. Other areas requiring work

In addition to the areas outlined above, a number of other areas need attention:

1. Free variable pointer caching. There is a very serious performance problem in Interlisp-VAX, the correction of which will require major changes to the Interlisp-VAX system. Interlisp-VAX uses deep binding. While deep binding is a reasonable choice for Interlisp-D (because of microcoded free variable lookup) it may be a source of a large performance penalty in Interlisp-VAX, especially in interpreted code. In any case, there is currently no mechanism for "caching" free variable pointers, and so free variables are "looked up" at every reference, even within an inner loop. This is clearly unacceptable. A design needs to be worked out and integrated into the compiler and stack access mechanism. No one scheme is clearly optimal. It is clear that whatever scheme is chosen will require changes to the compiler, interpreter, garbage collector and stack manipulation routines.
2. Bootstrapping. Bootstrapping is as complicated in Interlisp-VAX as it is in other Interlisp implementations for a variety of reasons. For example, debugging "low level" pieces of the system is made more difficult because bootstrap-load order requirements are difficult to detect without running the (time consuming) bootstrap process. This traditionally is merely a source of frustration rather than an insurmountable barrier.
3. Documentation. Documentation of Interlisp-VAX discussing its differences from other Interlisps and areas such as interface to UNIX is needed. In addition, there is some intention to participate in the upcoming major revision of the Interlisp Reference Manual.
4. Access to UNIX facilities. Interface from Lisp to UNIX facilities such as pipes, processes, Shell programs will greatly increase the utility of Interlisp-VAX. These facilities are not necessary for running current Interlisp-10 programs except insofar as they replace Interlisp-10 facilities (e.g., SUBSYS).
5. SYSOUT. The current Interlisp-VAX SYSOUT facility dumps the entire allocated virtual memory of the Lisp system (currently, without any of the "shared" Interlisp code over 1 MByte.) At some future date, Berkeley UNIX will provide a mechanism which will allow writing out individual pages and a page map, making SYSOUT files more manageable.
6. Porting to other VAX operating systems. Many sites do not run the Berkeley UNIX operating system, instead choosing VMS (the DEC-supplied operating system for the VAX), or EUNICE (a UNIX compatibility package developed at SRI.) These are candidates for

"other implementations" of Interlisp-VAX. Because of Interlisp's heavy use of the operating system's memory management facilities, porting Interlisp-VAX to these other operating systems will likely prove quite difficult.

III. WHAT WILL INTERLISP-VAX BE LIKE?

Assuming the above tasks are completed, the question remains: what will it be like? There are two issues: in what way will Interlisp-VAX differ from other Lisp implementations, and what performance can be expected?

A. Comparison of Interlisp-VAX to other systems

Full Interlisp-VAX is intended to be highly compatible with Interlisp-10, to the point where many complex programs would move gracefully between it and other Interlisp implementations; the only areas of incompatibility are those which are necessarily not shared between any implementations: access to machine code within Lisp routines, etc. In addition, there are currently no plans for "linked" function calls in Interlisp-VAX, nor for a "block" compiler. These are minor difficulties.

Interlisp-VAX will be able to access some of the facilities of the UNIX environment to good effect, e.g., one might imagine using it as an interactive "shell" programming language.

Interlisp-VAX will not have any particular CAPABILITIES for bit-mapped graphics.

Interlisp-VAX will have a larger "small" arithmetic range.

B. Performance

There are two major factors in the performance of Interlisp on the VAX: the first is in the actual CPU time to complete various operations, and the second is in the amount of time spent paging.

1. CPU performance

The performance profile of a Lisp system is complex, and there are many areas where Interlisp-VAX's relative performance to other Interlisp implementations will vary over a wide range. There seem to be a few areas of critical performance to any program: function call, variable reference, data structure access, arithmetic, and garbage collection. An appropriate weighted average of performance in those areas is a good overall measure of total system performance.

One important way of estimating performance of Interlisp-VAX is to use the code in other Lisp implementations for the same task as a comparison, taking into account the differences in the various code sequences. Comparisons are made between Interlisp-VAX and Franz, NIL, and Interlisp-10.

a. Function call and return

A function call for Interlisp-VAX will be at least twice as slow as a similar function call in Franz Lisp, partly because of language requirements (Franz does not check that the number of arguments passed matches the number of arguments expected) and partly because of the design of the Interlisp-VAX stack format (variable names are pushed as well as the values.)

In Franz Lisp, a minimal call/return takes 17 microseconds (VAX 11/780). Call/return in Interlisp-VAX may be as high as 100 microseconds, although the average will most likely be nearer to 40 microseconds.

In Interlisp-10 on a DEC 2060, a block-internal call takes on the order of a microsecond (PUSHJ, POPJ), the minimal (non-block) call/return takes 57 instructions (roughly 25 microseconds) while some functions, because of the Interlisp Swapper, may take more than 200 instructions for call/return (100 microseconds). The variation in function call time will apparently be high for Interlisp-VAX and Interlisp-10; for some functions, Interlisp-VAX function call will be slightly faster; for calls which in Interlisp-10 would be block internal, an Interlisp-VAX call might be 50 times slower. Note that benchmarks which purport to make comparisons with Interlisp-10 should explicitly control for the possibly enormous variation in Interlisp-10 function call time.

b. Variable reference

Performance ON LOCAL variable reference in Franz and Interlisp-VAX will be similar if Interlisp-VAX delivers its optimizing, register allocation code generator. Currently, variable reference will often be slightly slower. More importantly, free variable access will be very significantly slower in Interlisp-VAX, even after a variable caching scheme is implemented, because of the cost of variable lookup when using deep binding.

c. Garbage collection

The "stop and copy" variety of garbage collection, while compacting the address space and thus reducing the working set of subsequent computations, is more expensive in CPU time and memory usage than the "mark and sweep" variety, by a nominal factor of two. Garbage collections, even using mark and sweep, for large address space systems can be expensive. A full VAXSYMA garbage collection is reported to take on the order of 3 seconds cpu time. A garbage collection of a 2 MByte address space in Rutgers Lisp [Hedrick] on a 2060 with extended virtual addressing reportedly took 20 seconds cpu time. These figures are not particularly

consistent. It seems likely that (1) garbage collection is swap limited, and (2) the respective operating systems used to gather those times do not do a particularly good job of filtering out swap overhead from cpu time. It is not unreasonable to expect, however, that a Interlisp-VAX garbage collection will take twice as long as a Franz Lisp collection, because of the intrinsic overhead of "stop and copy" over "mark and sweep".

An alternative computation can be made as follows: Assuming an Interlisp-VAX system to use 4 MBytes of memory, then with a compacting garbage collection but no other memory localization algorithms, I believe that most user programs would "dirty" at least 1/4 of all system pages (i.e., 1 MByte) within a relatively small amount of time. Let us suppose a garbage collection occurs after a user has allocated the equivalent 40K CONS cells, or .32 MB of storage. This would involve referencing 1.6 MB of memory. This would mean that a garbage collection would take, at a minimum, between 2 and 20 seconds of CPU time on a VAX 11/780.

2. Paging Performance and Real Memory Requirements

I spent a considerable amount of time trying to estimate the number of users or sizes of Lisp systems that some typical VAX configurations might support. I believe that this is one of the most important factors in Interlisp-VAX performance, because of the predicted large virtual address spaces of Interlisp-VAX programs (one of the main reasons for going to Interlisp-VAX in the first place.)

a. Operating system considerations

Interlisp-VAX will be implemented on top of the Berkeley UNIX operating system. Another possible candidate for a host operating system is a UNIX compatibility package by the name of EUNICE, written at SRI, which runs under DEC-supplied operating system VMS. There is some controversy over the relative performance and functionality of VMS vs. UNIX. A fairly comprehensive set of benchmarks [Kashtan] showed that VMS out-performed UNIX in a variety of paging configurations. It is claimed by the Berkeley UNIX implementors that (a) many of the benchmarks were atypical of real computations, and (b) tests were run on an early version of Berkeley UNIX, and performance has improved considerably since then. I believe that the choice of operating system can be made on grounds other than predicted performance for running Interlisp: reliability, maintenance, cost, etc. and further, that converting Interlisp-VAX to run under EUNICE rather than Berkeley UNIX will be a relatively minor job compared to the magnitude of the Interlisp-VAX implementation itself. It seems that the difference between operating systems makes for only a relatively small factor in the overall performance, if the real memory available is too small to hold the "working set" of the programs attempting to run at any one time.

b. Real memory requirements of Interlisp-VAX

There are a variety of ways of estimating memory needs. The best estimates seem to come from: (1) comparison with MACSYMA in Franz Lisp (VAXSYMA), (2) comparison with Interlisp-10 and Interlisp-D.

1) Virtual Address space (minimum). Many current Interlisp-10 programs run with a virtual address space of 2 MByte (2 full "forks"). A similar system, in Interlisp-VAX, will probably require 4 MByte of address space because: (1) there is expansion for 32 rather than 18 bit addresses (no CDR coding); (2) the copying garbage collector will require, when it runs, twice the allocated space; and (3) Interlisp-VAX allocates storage in quanta of 64 KByte sectors rather than a 2 KByte "page" as in Interlisp-10, giving more "breakage" per datatype. This figure is consistent with numbers extrapolated from Interlisp-D.

2) Working set. In current Interlisp-10, the "working set" of many programs is .5 MByte or more (that is, the amount of real memory outside of the "system" necessary to keep the program from spending more than half of its time paging). Extrapolating using the same figures as above, the working set of a "typical" Interlisp-VAX application will be over 1 MByte. This figure is consistent with memory requirements extrapolated from Interlisp-D.

3) Calculation of real memory requirements. If there are i users, j of whom are active, they will need $i*31$ KBytes of page table (31 KByte = 4 MByte/128), plus $.75*j$ MByte bytes for their working set. For example, 5 users, 2 of whom are actively running at any one time, would require less than 2 MByte of real memory (outside of i/o buffers, etc.).

However, if systems increase in allocated space (independent of the working set) because more programming or data is contained in their virtual address space, one might imagine a situation where the virtual address spaces were in the 20-30 MByte range. (Many users do not believe that a 2^{24} byte virtual address space, 16 MByte, is big enough for applications they plan in the near future.) In such a situation, each such Interlisp process would require as much as .2 MByte of real memory for its page table, independent of its activity. This might severely limit the number of users who could be active on the system at any one time.

c. Problem areas

There are some problem areas, both with UNIX and with VMS, which will have to be resolved:

1) Sharing. VMS currently has more flexibility in allowing sharing of space among users in a piecemeal fashion. In the current Interlisp-VAX design, only .1 MBytes of the address space are "pure" in the sense that Berkeley UNIX would allow it to be shared among multiple users. Insofar as multiple users have the same large virtual address space (e.g., they are running the same program with a large, fairly static "knowledge base"), sharing is important to improving the number of users allowable at any one time.

2) Problems with large virtual address space. VMS requires disk/swap space to be pre-allocated, at system generation time, for the maximum allowable in the system. With multiple users with large address space programs, this adds considerably to the amount of disk space required on

the system (even if most of those users are inactive.) In addition, VMS requires an additional swap file to be pre-allocated, which contains J*W pages, where J is the maximum number of processes with independent address spaces (100 would not be an unreasonable figure for a machine used by many users for editing, background processing, etc.) while W is the maximum "working set" of a single process (which, for large address space processes should be at least 2 MByte.)

On the other hand, Berkeley UNIX currently requires the page tables of all processes to be "locked down", which may be a significant drain for very large address space programs where the data in the address space is in fact infrequently referenced.

IV. CONCLUSIONS: WHITHER INTERLISP VAX

A. There aren't any good alternatives

Given the requirements of TECHNOLOGY transfer to universities, industrial and military sites, there are few other options: even though Interlisp-VAX will probably not be cost effective for intensive Lisp users, it may be for those whose requirements are for casual and occasional use of Interlisp or tools developed in it. There are a few alternatives which could benefit from further exploration:

Interlisp-370

There is a version of Interlisp for IBM/370 machines, originally developed at Uppsala University and modified at the Weizmann Institute [Raim]. Interlisp-370 might be a possibility for some sites, although reports from several sources are that the Interlisp-370 is incomplete, and not particularly compatible with other Interlisps, and has serious performance and reliability problems. However, I believe that this alternative should be more seriously explored.

Implementing Interlisp on top of NIL or Franz

This might have been a reasonable way to approach the initial Interlisp-VAX implementation, but it does not seem cost effective at this point.

Emulating Interlisp-D on a VAX

An alternative, not presently explored in any detail, would be to write an Interpreter for Interlisp-D byte codes and run Interlisp-D on a VAX (cf. [Rowan]). Performance would be poor (perhaps a factor of 4-5 slower than currently projected), but code would be more easily transportable.

Automatic conversion of Interlisp programs to other VAX Lisps

This is an approach which has rarely succeeded. Programs which convert between language dialects are heuristic at best, and require considerable hand-holding; for any particular program, converting to another language might be cost effective, but on the whole, it is not.

B. Performance: mixed results

Performance in the Lisp community is often measured in DEC KA-10 or KL-10 equivalents, e.g., "1/4 of the speed as on a KL-10." One would like to be able to draw the inference that, if a KL-10 adequately supports 40 users with 8 actively computing (the rest editing, reading mail, etc.), 1/4 of that would amount to 10 users with 2 actively computing. Unfortunately, these performance figures can be misleading, first because of the wide variation in Interlisp-10 speeds on the same problem, and second because timings on small benchmarks do not give an accurate picture of the number of active users who can be supported in a working environment.

More reasonable estimations of performance can be drawn from experience with VAXes running Franz Lisp or VAXSYMA; while no exact figures are available, experience has been that a VAX 11/780 with 4 MByte real memory can support 30 users, of whom 3 are actively using VAXSYMA. Interlisp working-set and virtual address space requirements will exceed those of VAXSYMA.

Although the VAX is purported to be quite cost effective for FORTRAN, the instruction set is not PARTICULARLY effective for Lisp, and even less so for Interlisp; the "CALLS" instruction, which is intended to be used for function calls in high level languages, assumes a model of the stack which does not match Interlisp's. While the Interlisp-VAX design takes advantage of "CALLS" in a clever way, function call is still relatively more expensive than it is on microcoded machines which can have an Interlisp-specific function call instruction.

Virtual address space and real memory

Although the VAX is a large virtual address space machine, the address space may not be particularly usable on configurations typical in many installations. For example, the following configurations were proposed as "typical" VAX installations:

VAX-11/750 with 2 MByte real memory (maximum for 750)

VAX 11/780 with 4 MByte real memory

VAX 11/780 with 8 MByte real memory (requires additional memory controller)

Also proposed are configurations not currently available: "single-user" VAX machines with memory in the 1-2 MByte range, or 750's and 780's with more memory (requiring 64K RAM chips.)

Because of Interlisp-VAX's large virtual address space and working set, a machine with only 2 MByte of real memory might be able to support at most one or two large address space active users at a time. Generous amounts of disk, swapping space, and real memory will be required -- more so than in Interlisp-10 to support the same users, and much more so than in Interlisp-D or Interlisp-Jericho. Very few time-sharing systems have adequately dealt with giant address spaces for multiple users. The success

of very large-address-space Interlisp-VAX will depend on the cooperation and support of the Berkeley UNIX implementors.

C. There is much left to do

There is an unfortunate tendency to underestimate the magnitude of the task of transporting a system the size and complexity of Interlisp. Interlisp is not merely an interpreter and a few utility routines, but a rich and complex programming environment, with facilities which were heavily influenced by Tenex, its original host operating system. Porting it to another machine and continuing to upgrade it is a major undertaking. I cannot stress this enough.

The publication of the Interlisp Virtual Machine specification [Moore], was an important step forward in the creation of transportable Interlisp, in that it identified a major portion of what the "higher-level" Interlisp support software required in order to run. Unhappily, as complete and well written as that document was, it is not an accurate guide for the construction of a useful Interlisp implementation, in that many areas are designated as being left to the implementor while many Interlisp applications require exact compatibility with Interlisp-10. The VM is also not a good measure of the magnitude of implementing Interlisp. For example, the VM mentions the compiler only in passing; however, providing a reasonable Interlisp compiler is a major portion of the task of transporting Interlisp to a new (non-microcoded) machine.

Transporting Interlisp is harder than merely implementing "some" Lisp dialect. It is much more difficult to be strictly compatible while using the underlying power of the machine to the fullest. Compatibility makes the implementation harder because there is an existing standard against which the implementation can be judged. For a "new" Lisp, it is always possible to declare oneself "done" at almost any point. The necessity of emulating exactly the behavior of another system is what makes the task more difficult.

How much is left to do?

It is difficult to give a "man-month" figure for Interlisp-VAX for several reasons. First, of course, the notion of "man-month" independent of implementor is a well-known paradox: start-up time and personnel training, can delay a project for many months (as in the early months of the Interlisp-VAX project).

Second, there are several tasks ahead which will undoubtedly encounter unforeseen problems. "System shakedown" is a catch-all phrase which can cover many months of discovering problems or previously undetected system requirements. Software completion is not measured well by proportion of lines-of-code written.

Finally, there is a wide range of variation of what is meant by "Interlisp-VAX." On the one hand, an initial version may be available relatively soon. This version will likely have serious performance problems (mainly because of free variable reference and non-tuned code generation),

and will likely be not fully functional or compatible with Interlisp-10. The task of bringing Interlisp-VAX to the level of functionality, performance and reliability of Interlisp-10 and Interlisp-D remains awesome.

Unfortunately, there is not a good perception in the Interlisp user community of the amount of work between the first release and a system which will be acceptable to current Interlisp users; for this reason, the recent "pre-announcement" message [Dyer] was at best misleading for those trying to make plans based on Interlisp-VAX availability. While this initial version might in fact be a reasonable alternative to, say, converting a large Interlisp program to Franz Lisp, (because the conversion cost would be higher than the performance difference would warrant), it will not be comparable with most other Interlisp implementations (-10, -D, -Jericho).

The Interlisp-VAX project is and has been from the beginning drastically undermanned. The initial proposal for implementation of Interlisp-VAX in one year with no existing personnel was at best wishful thinking. Hans Koomen will be leaving within the near future. This is a serious, although possibly not fatal, blow to the continuation of the project, even with the addition of additional staff members (Ray Bates and Don Voreck).

The project needs a team of implementors who are committed to its goals, are qualified to carry it out, and will stick with the project once the initial release has been made: if Interlisp-VAX is to be viable, there needs to be a long-term (3-4 year) commitment to its maintenance and support by a team of qualified personnel. This level of support or greater has been required by every other serious implementation of Lisp that I know of, including Interlisp-10, Interlisp-D, Interlisp-Jericho, and Lisp Machine Lisp. There is no reason why anyone should imagine that Interlisp-VAX would be different.

NOTES

- (1)VAX is a trademark of Digital Equipment Corporation.
- (2)Unix is a trademark of Bell Laboratories.

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Appendix BAI Handbook Outline

Volumes I and II by Avron Barr and Edward A. Feigenbaum
Volume III by Paul R. Cohen and Edward A. Feigenbaum
Computer Science Department
Stanford University

This is a list of the Chapters in the Handbook. A list of all of the articles in each Chapter follows.

VOLUME I:

- I. Introduction
- II. Search
- III. Knowledge Representation
- IV. Understanding Natural Language
- V. Understanding Spoken Language

VOLUME II:

- VI. Programming Languages for AI Research
- VII. Applications-oriented AI Research: Science
- VIII. Applications-oriented AI Research: Medicine
- IX. Applications-oriented AI Research: Education
- X. Automatic Programming

VOLUME III:

- XI. Models of Cognition
- XII. Automatic Deduction
- XIII. Vision
- XIV. Learning and Inductive Inference
- XV. Planning and Problem Solving

VOLUME I

I. INTRODUCTION

- A. Artificial Intelligence
- B. The AI Handbook
- C. The AI literature

II. SEARCH

- A. Overview
- B. Problem representation
 - 1. State-space representation
 - 2. Problem-reduction representation
 - 3. Game trees
- C. Search methods
 - 1. Blind state-space search
 - 2. Blind AND/OR graph search
 - 3. Heuristic state-space search
 - a. Basic concepts in heuristic search
 - b. A*--Optimal search for an optimal solution
 - c. Relaxing the optimality requirement
 - d. Bidirectional search
 - 4. Heuristic search of an AND/OR graph
 - 5. Game tree search
 - a. Minimax procedure
 - b. Alpha-beta pruning
 - c. Heuristics in game tree search
- D. Sample search programs
 - 1. Logic Theorist
 - 2. General Problem Solver
 - 3. Gelernter's geometry theorem-proving machine
 - 4. Symbolic integration programs
 - 5. STRIPS
 - 6. ABSTRIPS

III. KNOWLEDGE REPRESENTATION

- A. Overview
- B. Survey of representation techniques
- C. Representation schemes
 - 1. Logic
 - 2. Procedural representations
 - 3. Semantic networks
 - 4. Production systems
 - 5. Direct (analogical) representations
 - 6. Semantic primitives
 - 7. Frames and scripts

IV. UNDERSTANDING NATURAL LANGUAGE

- A. Overview
- B. Machine translation
- C. Grammars
 - 1. Formal grammars
 - 2. Transformational grammars
 - 3. Systemic grammar
 - 4. Case grammars
- D. Parsing
 - 1. Overview of parsing techniques
 - 2. Augmented transition networks
 - 3. The General Syntactic Processor
- E. Text generation
- F. Natural language processing systems
 - 1. Early natural language systems
 - 2. Wilks's machine translation system
 - 3. LUNAR
 - 4. SHRDLU
 - 5. MARGIE
 - 6. SAM and PAM
 - 7. LIFER

V. UNDERSTANDING SPOKEN LANGUAGE

- A. Overview
- B. Systems architecture
- C. The ARPA SUR projects
 - 1. HEARSAY
 - 2. HARPY
 - 3. HWIM
 - 4. The SRI/SDC speech systems

VOLUME II

VI. PROGRAMMING LANGUAGES FOR AI RESEARCH

- A. Overview
- B. LISP
- C. AI programming-language features
 - 1. Overview
 - 2. Data structures
 - 3. Control structures
 - 4. Pattern matching
 - 5. Programming environment
- D. Dependencies and assumptions

VII. APPLICATIONS-ORIENTED AI RESEARCH: SCIENCE

- A. Overview
- B. TEIRESIAS
- C. Applications in chemistry
 - 1. Chemical analysis
 - 2. The DENDRAL programs
 - a. Heuristic DENDRAL
 - b. CONGEN and its extensions
 - c. Meta-DENDRAL
 - 3. CRYNALIS
 - 4. Applications in organic synthesis
- D. Other scientific applications
 - 1. MACSYMA
 - 2. The SRI Computer-based consultant
 - 3. PROSPECTOR
 - 4. Artificial Intelligence in database management

VIII. APPLICATIONS-ORIENTED AI RESEARCH: MEDICINE

- A. Overview
- B. Medical systems
 - 1. MYCIN
 - 2. CASNET
 - 3. INTERNIST
 - 4. Present Illness Program
 - 5. Digitalis Therapy Advisor
 - 6. IRIS
 - 7. EXPERT

IX. APPLICATIONS-ORIENTED AI RESEARCH: EDUCATION

- A. Overview
- B. ICAI systems design
- C. Intelligent CAI systems
 - 1. SCHOLAR
 - 2. WHY
 - 3. SOPHIE
 - 4. WEST
 - 5. WUMPUS
 - 6. GUIDON
 - 7. BUGGY
 - 8. EXCHECK
- D. Other applications of AI to education

X. AUTOMATIC PROGRAMMING

- A. Overview
- B. Methods of program specification
- C. Basic approaches

- D. Automatic programming systems
 - 1. PSI and CHI
 - 2. SAFE
 - 3. The Programmer's Apprentice
 - 4. PECOS
 - 5. DEDALUS
 - 6. Protosystem-1
 - 7. NLPQ
 - 8. LIBRA

VOLUME III

XI. MODELS OF COGNITION

- A. Overview
- B. General Problem Solver
- C. Opportunistic problem solving
- D. EPAM
- E. Semantic network models of memory
 - 1. Quillian's semantic memory system
 - 2. HAM
 - 3. ACT
 - 4. MEMOD
- F. Belief systems

XII. AUTOMATIC DEDUCTION

- A. Overview
- B. The resolution rule of inference
- C. Nonresolution theorem proving
- D. The Boyer-Moore theorem prover
- E. Nonmonotonic logic
- F. Logic programming

XIII. VISION

- A. Overview
- B. Blocks-world understanding
 - 1. Roberts
 - 2. Guzman
 - 3. Falk
 - 4. Huffman-Clowes
 - 5. Waltz
 - 6. Shirai
 - 7. Mackworth
 - 8. Kanade
- C. Early processing of visual data
 - 1. Visual input
 - 2. Color

- 3. Preprocessing
- 4. Edge detection and line finding
- 5. Region analysis
- 6. Texture
- D. Representation of scene characteristics
 - 1. Intrinsic images
 - 2. Motion
 - 3. Stereo vision
 - 4. Range finders
 - 5. Shape-from methods
 - 6. Three-dimensional shape description and recognition
- E. Algorithms for vision
 - 1. Pyramids and quad trees
 - 2. Template matching
 - 3. Linguistic methods for computer vision
 - 4. Relaxation algorithms
- F. Vision systems
 - 1. Robotic vision
 - 2. Organization and control of vision systems
 - 3. ACRONYM

XIV. LEARNING AND INDUCTIVE INFERENCE

- A. Overview
- B. Rote learning
 - 1. Issues
 - 2. Rote learning in Samuel's Checkers Player
- C. Learning by taking advice
 - 1. Issues
 - 2. Mostow's operationalizer
- D. Learning from examples
 - 1. Issues
 - 2. Learning in control and pattern-recognition systems
 - 3. Learning single concepts
 - a. Version space
 - b. Data-driven rule-space operators
 - c. Concept learning by generating and testing plausible hypotheses
 - d. Schema instantiation
 - 4. Learning multiple concepts
 - a. AQ11
 - b. Meta-DENDRAL
 - c. AM
 - 5. Learning to perform multiple-step tasks
 - a. Samuel's Checkers Player
 - b. Waterman's Poker Player
 - c. HACKER
 - d. LEX
 - e. Grammatical inference

XV. PLANNING AND PROBLEM SOLVING

- A. Overview
- B. STRIPS and ABSTRIPS
- C. Nonhierarchical planning
- D. Hierarchical planners
 - 1. NOAH
 - 2. MOLGEN
- E. Refinement of skeletal plans

Appendix C

Community Growth and Project Synopses

This appendix contains a graphical display of the development of the SUMEX-AIM community over the years and brief synopses of currently active projects. Figure 15 below illustrates the substantial growth in the cumulative number of projects in the Stanford, national SUMEX, and Rutgers-AIM communities since the resource began operation in 1974.

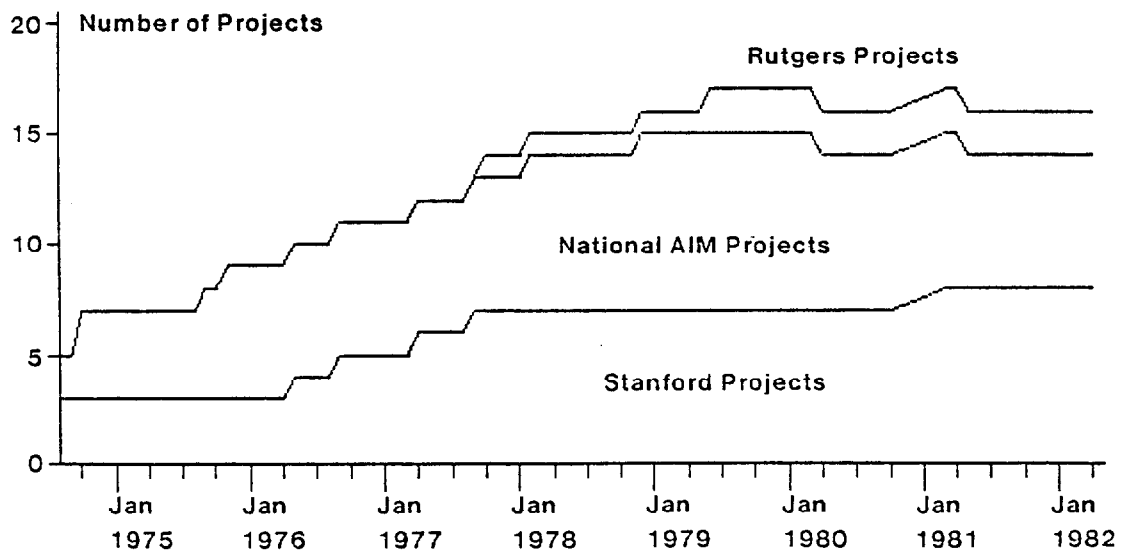


Figure 15. SUMEX-AIM Growth by Community

National AIM Project: ACQUISITION OF COGNITIVE PROCEDURES (ACT)

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The ACT Project combines a semantic network data-base with a production system to simulate human cognition. Prominent among the reasons for using a production system architecture as a framework for developing such a program is the possibility of modeling learning as the acquisition of new productions. ACT possesses a number of learning mechanisms which have been used to model the learning of procedural skills such as language comprehension and geometry theorem proving. Some of these mechanisms have the effect of either extending or restricting the set of circumstances in which a particular behavior is performed so as to produce better performance. Others have the effect of speeding up cognitive operations by compressing the effects of a series of production applications into the application of a single production. Out of this set of productions ACT applies those that usually result in desirable outcomes. In this way it is able to model the human ability to learn even when given unreliable feedback. Another feature of ACT that reflects its psychological orientation is its willingness to model human limitations. Here the hope is that by being faithful to the human mind even in its failings, it eventually may be possible to emulate its successes.

SOFTWARE AVAILABLE ON SUMEX

The ACT production system is available to GUEST users of SUMEX.

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National AIM Project: CADUCEUS (formerly INTERNIST)

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The major goal of the CADUCEUS Project is to produce a reliable and adequately complete diagnostic consultative program in the field of internal medicine. Although this program is intended primarily to aid skilled internists in complicated medical problems, the program may have spin-off as a diagnostic and triage aid to physicians' assistants, rural health clinics, military medicine and space travel. In the design of CADUCEUS and its predecessor INTERNIST I, we have attempted to model the creative, problem-formulation aspect of the clinical reasoning process. The program employs a novel heuristic procedure that composes differential diagnoses, dynamically, on the basis of clinical evidence. During the course of a CADUCEUS or INTERNIST I consultation, it is not uncommon for a number of such conjectured problem foci to be proposed and investigated, with occasional major shifts taking place in the program's conceptualization of the task at hand.

SOFTWARE AVAILABLE ON SUMEX

Versions of INTERNIST are available for experimental use, but the project continues to be oriented primarily towards research and development; hence, a stable production version of the system is not yet available for general use.

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National AIM Project: HIERARCHICAL MODELS OF HUMAN COGNITION

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The CLIPR Project is concerned with the modeling of complex psychological processes. It is comprised of two research groups. The prose comprehension group has completed a project that carries out the microstructure text analysis described by Miller and Kintsch (1980), yielding predictions of the recall and readability of that text by human subjects. More recently, this group has been interacting with the Heuristic Programming Project at Stanford, using the AGE and UNITS packages to build a more complex model of the knowledge-based processes characteristic of prose comprehension. The planning group is working toward a model of the planning processes used by expert computer software designers. The initial development of this model requires the detailed analysis of expert software design protocols for subsequent simulation.

SOFTWARE AVAILABLE ON SUMEX

A set of programs has been developed to perform the microstructure text analysis described in Kintsch and van Dijk (Psychological Review, 1978) and Miller and Kintsch (1980). The program accepts a propositionalized text as input, and produces indices that can be used to estimate the text's recall and readability. A more complex model based in AGE and UNITS, which emphasizes the knowledge-based aspects of comprehension, is currently under development.

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National AIM Project: BIOMEDICAL KNOWLEDGE ENGINEERING
IN CLINICAL MEDICINE (PUFF-VM)

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The PUFF-VM Project has produced two knowledge-based programs for the interpretation of physiologic measurements made in clinical medicine. The interpretations are intended to aid in diagnostic decision-making and in selecting therapeutic actions. The programs are: PUFF--the evaluation of pulmonary function laboratory data, and VM--the evaluation and management of respiratory status for patients in the intensive care unit.

The task of the PUFF PROGRAM is to interpret standard measures of pulmonary function. In the laboratory at the Pacific Medical Center (PMC), about 50 parameters are calculated from measurement of lung volumes, flow rates, and diffusion capacity. In addition to these measurements, patient history and referral diagnosis also are used to interpret the test results. PUFF produces a report for the patient record, explaining the clinical significance of measured test results. It also provides a diagnosis of the presence and severity of pulmonary disease. The interpretation process is accomplished by examination of expert knowledge represented by a set of production rules. Each rule relates physiologic measurements or states to a conclusion about the physiologic significance of the measurement or state. A version of the PUFF program is used daily at the PMC.

The VENTILATOR MANAGER (VM) PROGRAM is designed to interpret on-line physiologic data in the intensive care unit (ICU). These data are used to manage post-surgical patients receiving mechanical assistance in breathing. VM is an extension of a physiologic monitoring system, and is designed to perform 5 specialized tasks in the ICU: 1) to detect possible measurement errors; 2) to recognize untoward events in the patient/machine system and suggest corrective action; 3) to summarize the patient's physiologic status; 4) to suggest adjustments to therapy based on the patient's status over time, and long-term therapeutic goals; and 5) to maintain a set of patient-specific expectations and goals for future evaluation by the program. The program produces interpretations of the physiologic measurements over time, using a model of the therapeutic procedures in the ICU and clinical knowledge about the diagnostic implications of the data.

SOFTWARE AVAILABLE ON SUMEX

The PUFF and VM programs will be available to GUEST users for use on pre-existing (non-identifiable) cases. No packages currently exist for program development.

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Rutgers AIM Project: RUTGERS RESEARCH RESOURCE -
COMPUTERS IN BIOMEDICINE

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The broad objective of the Resource is to apply advanced methods in computer science, particularly in artificial intelligence (AI), to biomedical problems. The Resource has three major areas of study: 1) Medical Modeling and Decision Making in several medical domains with emphasis on collaborative development of consultation systems in rheumatology and ophthalmology; 2) Modeling of Belief Systems and Commonsense Reasoning with emphasis on the psychology of plan recognition and handling of stereotypes; and 3) Artificial Intelligence studies with emphasis on Representations, Interpretation processes, and problems of knowledge and expertise acquisition. The studies in Medical Modeling and Decision Making are performed jointly by computer and medical scientists at Rutgers and elsewhere in the Country and abroad.

The Resource also sponsors national Artificial Intelligence in Medicine (AIM) Workshops for the AIM community.

SOFTWARE AVAILABLE ON SUMEX

CASNET--System for consultation in the diagnosis and treatment of glaucoma.

Documentation available:

"A Model-Based Method for Computer-Aided Medical Decision Making" Weiss, S., Kulikowski, C., Amarel, S., Safir, A., (1978) pp. 145-172, AI Journal, North Holland Press, 1978.

EXPERT--System for designing and applying consultation models using a relatively simple language to describe the models. It has been used in a variety of medical and non-medical applications (mainly rheumatology, ophthalmology and endocrinology).

Documentation available:

"A Guide to the Use of the EXPERT Consultation System" Weiss, S., Kern, K., and Kulikowski, C., CBM-TR-94, 11/78.

"EXPERT: A System for Developing Consultation Models," Proceedings IJCAI, Tokyo, August 1979, pp. 942-947, (also Rutgers Computer Science Report CBM-TR-97).

Anyone interested in using CASNET or EXPERT may contact either Kulikowski@Rutgers or Weiss@Rutgers.

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National AIM Project: SIMULATION AND EVALUATION
OF CHEMICAL SYNTHESIS (SECS)

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The SECS Project aims at developing practical computer programs to assist investigators in designing syntheses of complex organic molecules of biological interest. Key features of this research include the use of computer graphics to allow chemist and computer to work efficiently as a team, the development of knowledge bases of chemical reactions, and the formation of plans to reduce the search for solutions. SECS is being used by the pharmaceutical industry for designing syntheses of drugs.

A spin-off project, XENO, is aimed at predicting the plausible metabolites of foreign compounds for carcinogenicity studies. First, the metabolism is simulated; then the metabolites are evaluated for possible carcinogenicity.

SOFTWARE AVAILABLE ON SUMEX

SECS-- An organic synthesis design program available with a reaction library of over 500 reactions. The program is accessible to users via a teletype or DEC GT40 type graphics terminal.

XENO-- A program for prediction of metabolites of xenobiotic compounds. Although the project is still in the early development stages, this program is available for preliminary exploration and testing.

PRXBLD--A facility for building approximate 3-dimensional molecular models from their 2-dimensional representations. The program employs an energy minimization approach and is available both stand-alone and as part of SECS.

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National AIM Project: PROBLEM SOLVING EXPERTISE

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The Minnesota SOLVER project focuses upon the development of strategies for discovering and representing the knowledge and skill of expert problem solvers. Although in the last 15 years great progress has been made in synthesizing the expertise required for solving complex problems, most expert systems embody only the limited amount of expertise that individuals are able to report in a particular constrained language (e.g. production rules). What is still lacking is a theoretical framework capable of reducing dependence upon the expert's intuition or on the near exhaustive testing of possible organizations. Our methodology consists of: (1) extensive use of verbal thinking aloud protocols as a source of information from which to make verbal inferences about underlying cognitive structure and process; (2) development of computer models as a means of testing the adequacy of inferences derived from protocol studies; (3) testing and refinement of the cognitive models based upon the study of human and model performance in experimental settings. Currently, we are investigating problem-solving expertise in domains of medicine, science, and law.

SOFTWARE AVAILABLE ON SUMEX

A version of the DIAGNOSER simulation model is being implemented on SUMEX. It should be available this summer.

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Stanford Project: GENERALIZATION OF AI TOOLS (AGE)

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The long-range objective of AGE, a SUMEX CORE RESEARCH Project, is to build a software laboratory for building knowledge-based, application programs. It is an attempt to define and accumulate knowledge-engineering tools, with rules to guide in the use of these tools. The design and implementation of the AGE program will be based primarily on the experiences gained in building knowledge-based programs by the Stanford Heuristic Programming Project in the last decade (The programs that have been or are being built are: DENDRAL, META-DENDRAL, MYCIN, HASP, AM, MOLGEN, GUIDON, CRYALIS, PUFF, VM and SACON.). The initial AGE program contains a collection of tools suitable for constructing user programs based on the Blackboard paradigm (used in HASP and CRYALIS) and Backward-chained production rules (used in MYCIN). In addition, AGE has facilities to aid the user in the construction, debugging, and running of his program.

SOFTWARE AVAILABLE ON SUMEX

AGE-1 is available on an experimental basis to a limited number of users. A public version of the programs, together with reference manuals and user guides, is planned for July, 1980.

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Stanford Project: HANDBOOK OF ARTIFICIAL INTELLIGENCE

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The AI Handbook Project is a part of SUMEX CORE RESEARCH aimed at making the important results of AI research accessible to the large, multi-disciplinary community of scientists who want to build AI systems in their own problem areas. Students and researchers at Stanford and other AI laboratories have prepared over 300 short articles describing the fundamental ideas, useful techniques, and exemplary programs developed in the field over the last 20 years. These articles have been written for computer-literate scientists and engineers in other fields who are unfamiliar with AI research and jargon. The Handbook will provide a scientist who, for instance, might want to know what a "heuristic" is or how to build a "natural language" front end, with information about all of the relevant AI techniques and existing systems, as well as abundant pointers into the field's literature.

The Handbook is being published in report and book form. It also will be made available to the SUMEX community via an on-line information retrieval system. Following is a TOPIC OUTLINE for Volumes I and II:
HANDBOOK OF ARTIFICIAL INTELLIGENCE

INTRODUCTION: The Handbook of Artificial Intelligence; Overview of AI Research; History of AI; An Introduction to the AI Literature

SEARCH: Overview; Problem Representation; Search Methods for State Spaces, AND/OR Graphs, and Game Trees; Six Important Search Programs

REPRESENTATION OF KNOWLEDGE: Issues and Problems in Representation Theory; Survey of Representation Techniques; Seven Important Representation Schemes;

AI PROGRAMMING LANGUAGES: Historical Overview of AI Programming Languages; Comparison of Data Structures and Control Mechanisms in AI Languages; LISP

NATURAL LANGUAGE UNDERSTANDING: Overview - History and Issues; Grammars; Parsing Techniques; Text Generation Systems; Machine Translation; The Early NL Systems; Six Important Natural Language Processing Systems

SPEECH UNDERSTANDING SYSTEMS: Overview - History and Design Issues; Seven Major Speech Understanding Projects

APPLICATIONS-ORIENTED AI RESEARCH--SCIENCE AND MATHEMATICS: Overview;
TEIRESIAS - Issues in Expert Systems Design; Research on AI
Applications in Mathematics (MACSYMA and AM); Research on AI
Applications in Chemistry (DENDRAL, CRYNALIS, etc.); Other
Scientific Applications Research

APPLICATIONS-ORIENTED AI RESEARCH--MEDICINE: Overview of Medical
Applications Research; Six Important Medical Systems

APPLICATIONS-ORIENTED AI RESEARCH--EDUCATION: Historical Overview of
AI Research in Educational Applications; Issues and Components of
Intelligent CAI Systems; Seven Important ICAI Systems

AUTOMATIC PROGRAMMING: Overview; Techniques for Program Specification;
Approaches to AP; Eight Important AP Systems

The following sections of the Handbook are still in preparation and
will appear in Volume III: Theorem Proving; Vision; Robotics; Information
Processing Psychology; Learning and Inductive Inference; Planning and
Related Problem-solving Techniques.

Stanford Project: DENDRAL--RESOURCE RELATED RESEARCH -
COMPUTERS IN CHEMISTRY

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The DENDRAL Project involves research in computer-assisted structure elucidation of unknown organic compounds of biological importance. This research has three major components: 1) program development; 2) biochemical applications; and 3) resource-sharing.

Recent program developments have been directed toward building more powerful interactive programs to assist chemists in the three major areas of structure elucidation: analysis of data to yield substructural information about an unknown ("planning"), advanced methods for assembly of substructures into complete structures ("structure generation"), and the prediction of data for structural candidates to rank-order the candidates by comparison of predicted and observed data ("testing"). Important problems of structure representation have been solved which have enabled dealing with stereochemical (three-dimensional) aspects of structure throughout the procedures.

Major areas of application of the programs in the research of this group and other collaborative projects include: a) marine natural products, particularly marine steroids and halogenated compounds which display biological activity; b) antibiotics and other derivatives of known or potential drugs; c) terpene alkaloids; d) photoproducts related to vitamin A; and e) conformational studies of narcotic analogs and polypeptides.

These programs are shared among a community of collaborators and guest users at SUMEX, with communication via computer network from a variety of sites in the U.S., Europe and Australia. Exportable versions of some programs are maintained. These versions have been installed successfully in more than 15 research laboratories throughout the world.

SOFTWARE AVAILABLE ON SUMEX

CONGEN--An interactive program for structure generation to yield candidate structures for an unknown based on inferred substructural components (exportable).

GENOA--An advanced structure generator capable of handling overlapping substructural information; uses CONGEN as a core component (exportable).

Meta-DENDRAL--An INTSUM, RULEGEN and RULEMOD sequence for automatic rule

formation to relate observed data to substructures in mass spectrometry and carbon magnetic resonance spectroscopy.

REACT--A program for carrying out a complex sequence of chemical reactions and exploration of the consequences of those reactions.

NMR--For substructural inference and spectrum prediction in carbon magnetic resonance spectroscopy (will be exportable).

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Stanford Project: EXPEX -- THE EXPERT EXPLANATION PROJECT

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EXPEX is a recent Stanford research project that is involved with the development of new representation schemes to facilitate knowledge acquisition and explanation. This includes not only the study of fundamental representational formalisms but also the encoding of various types of knowledge, such as causal information and user models. The explanation portion of the research effort is dealing with a medical domain (endocrinology) and is being undertaken on SUMEX, whereas the knowledge acquisition portion deals with nonmedical topics and uses other computing resources at Stanford.

Our interest in explanation derives from the insights we gained in developing explanatory capabilities for the MYCIN system. In that system and its descendants, we were able to generate intelligible explanations by taking advantage of a rule-based representation scheme. The limitations of the justifications generated using MYCIN's explanation capabilities have become increasingly obvious, however, and have led to improved characterization of the kinds of explanation capabilities that must be developed if clinical consultation systems are to be accepted by physicians. EXPEX is devoted to the development of new theoretical insights into this problem.

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MYCIN Projects (continued)

SOFTWARE AVAILABLE ON SUMEX

MYCIN-- A consultation system designed to assist physicians with the selection of antimicrobial therapy for severe infections. It has achieved expert level performance in formal evaluations of its ability to select therapy for bacteremia and meningitis. Although MYCIN is no longer the subject of an active research program, the system continues to be available on SUMEX for demonstration purposes and as a testing environment for other research projects.

EMYCIN-- The "essential MYCIN" system is a generalization of the MYCIN knowledge representation and control structure. It is designed to facilitate the development of new expert consultation systems for both clinical and non-medical domains.

GUIDON-- A system developed for intelligent computer-aided instruction. Although it is being developed in the context of MYCIN's infectious disease knowledge base, the techniques are generalizable to any EMYCIN domain. The current research emphasis has been on an improved understanding of how the expert thinks so as to optimize the learning experience for the student.

ONCOCIN--This system is designed to provide oncologists with consultations regarding the management of patients receiving chemotherapy for cancer. Much of the knowledge in this domain is already well-specified in protocol documents, but expert judgments also need to be understood and modeled. Other research topics include human engineering and the development of capabilities to help achieve clinical acceptance of the program.

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Stanford Project: PROTEIN STRUCTURE MODELING (CRYBALIS)

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The CRYBALIS system is an application of artificial intelligence methodology to the task domain of protein crystallography. The focus is the structure determination problem: the derivation of an atomic model of the protein from an indistinct image of the electron density. The crystallographer interprets these data in light of the known chemical composition of the protein, general principles of protein chemistry, and his own experience. The goal of the CRYBALIS Project is to integrate these diverse sources of knowledge and data into a program that matches the crystallographer's level of performance in electron density map interpretation. A successful solution to this problem must deal with issues such as representation and management of a large knowledge base, opportunistic reasoning, and appropriate description of the emerging hypothesis, while keeping human engineering considerations in sight. Automation of this task would shorten the time for protein determination by several weeks to several months and would fill a major gap in the construction of a fully-automated system for protein crystallography.

SOFTWARE AVAILABLE ON SUMEX

CRYBALIS DATA REDUCTION PROGRAMS (in FORTRAN):

A density map skeletonizer (SKEL37) based on an improved version of Greer's algorithm.

A package for locating the critical points in a map.

A general map-manipulation utility (INSPCT) that can find peaks, display regions, and compute various statistics.

TWO LISP SYSTEMS (with the caveat that both are under active development):

A system (SEGLABELING) which heuristically parses the segmented map into labels similar to those a crystallographer would use.

The inference system (CRYBALIS).

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