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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00002-25 OCB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Computer-aided Analysis of Electrocardiography

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.J. Bailey, M.D.	Medical Officer	OCB/DCRT
Others:	E.W. Pottala, Ph.D.	Electronic Engineer	DSB, DCRT
	R.W. Bowser, B.Sc.	Engineer	Creighton Univ
	D. MacAreavey, M.D.	Cardiologist	NHLB/CB
	R. Fletcher, M.D.	Chief, Cardiology	VA Med Ctr, Wash, DC
	J.P. Moak, M.D.	Director, EP Lab	Children's Natl Med Ctr

COOPERATING UNITS *(if any)*

Distriobuted Systems Branch, DCRT (E. Pottala); Cardiology Branch, NHLBI (D. MacAreavey); Creighton University Cardiac Center (R. Bowser); Electrophysiology Laboratory, Children's National Medical Center (J. Moak); Cardiology Department, Veteran's Affairs Medical Center, Washington, DC (R. Fletcher)

LAB/BRANCH Office of Computational Biosciences

SECTION

INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Md 20892-5650

TOTAL STAFF YEARS: 0.9	PROFESSIONAL: 0.8	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

These studies are directed toward evaluating the prognostic power of the electrocardiogram, when analyzed by advanced computer methodology, and the predictive accuracy of diagnostic criteria, when implemented in ECG computer programs. Appropriate use of digital signal processing in electrocardiography requires application of statistically-based techniques of information theory and mathematically-based engineering methods, as well as knowledge of its clinical relevance.

Additional studies are directed toward the analysis of heart rate, blood pressure and respiratory signals that affect syncopal patients during table-tilt testing, using autoregressive models and the corresponding power spectra. Syncope can be disabling for patients and, at times, life threatening. An understanding of the autonomic nervous system mechanisms responsible for syncope may indicate appropriate therapy.

These studies have been re-directed toward the analysis of ambulatory electrocardiography (AECGs). Despite extensive literature showing that information extracted by computer analysis of AECGs can be related to cardiac risk factors, there are no standard methods for the routine analysis of AECGs in this rapidly evolving field. The objective of this research is to carry forward previous work in biosignal analysis and to adapt methodologies, with the goal of implementing as much automation as possible to enable and expedite the interpretation of the huge streams of AECG data.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT0010-20 PSL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Mathematical and Computational Methods for Solving Nonlinear Equations

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.I. Shrager	Research Mathematician	DCRT/PSL
	G.H. Weiss, Ph.D.	Chief, PSL	DCRT/PSL
	P.J. Munson, Ph.D.	Section Chief	DCRT/LSB
Others:	M.S. Lewis, Ph.D.		NCRR/BEIP
	S-J. Kim, Ph.D.		NCI/DCBDC
	R. Berger, Ph.D.	Section Chief	NHLBI/LCB
	R. Hendler, Ph.D.	Section Chief	NHLBI/LCB
	R. Carson, Ph.D.	Research Mathematician	CC/NMD

COOPERATING UNITS (if any)

University of Milan, Italy (G.E. Rovati, Ph.D.); J. Nehru University, New Delhi, India (S. Bose, Ph.D.); Washington University School of Medicine, St. Louis (D.W. Myers, Ph.D., G.K. Ackers, Ph.D.); SmithKline Beecham Pharmaceuticals, King of Prussia, PA (M.L. Doyle, Ph.D.); University of California, San Diego (K.D. Vandegriff, Ph.D.); Tel-Aviv University, Israel (U. Shmueli, Ph.D., R. Schach, Ph.D., I. Goldberg, Ph.D.).

LAB/BRANCH: Physical Sciences Laboratory

SECTION:

INSTITUTE AND LOCATION: Division of Computer Research & Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project helps investigators cope with complex equations that model biological systems, and includes the following studies:

1) Ultracentrifuge (with M.S. Lewis, S-J. Kim): DNA-protein interactions are analyzed using pseudo-inverse matrices.

2) Hemoglobins (with K.D. Vandegriff, R.M. Winslow, V.W. MacDonald, M.L. Doyle): oxygenation and oxidation of hemoglobins are studied by spectrophotometry and singular value decomposition (SVD).

3) X-ray crystallography (with U. Shmueli, R. Schach, G.H. Weiss): methods were developed for rapid computation of the probability density function used in phase determination, and for improved estimation of background radiation in X-ray diffraction.

4) Imaging regional cerebral blood flow (with R.E. Carson): a method that does not require explicit (and invasive) measurement of arterial flow was programmed and tested.

5) Kinetics of Bacteriorhodopsin (with R.W. Hendler, S. Bose): several models of light-intensity dependence are being tested.

6) Kinetics of cytochrome aa3 (with R.W. Hendler, S. Bose): spectrophotometric studies involving SVD, pseudo-inverses, and other methods, are in progress.

7) Protein-ligand binding (with P.J. Munson, G.E. Rovati): a program for nonlinear least squares fitting of binding data is under development.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00014-27 PSL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Instrumental Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: G.H. Weiss, Ph.D. Chief, PSL DCRT, PSL

Others:

J.D. Bryngelson, Ph.D., S. Pajevic, Ph.D., R. Shrager, S. Sastry, Ph.D., Haim Taitelbaum, Ph.D. (DCRT/PSL); S. Bacharach, Ph.D., R. Carson, Ph.D. (CC/NM); J.A. Ferretti, Ph.D., Gruchus, Ph.D. (NHLBI/IR); M. Garner, Ph.D., R. Goans, Ph.D., A. Yergey, Ph.D. (NICHD/LTPB); B. Horowitz, M.D., J. van Meter, Ph.D. (NIA/LN); L. Yaroslavsky, Ph.D. (NCRR/BEIP)

COOPERATING UNITS (if any)

Frederick Cancer Research Facility (D. Covell, Ph.D.); Tel-Aviv University, Israel (U. Shmueli, Ph.D.)

LAB/BRANCH Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION Division of Computer Research and Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892

TOTAL MAN-YEARS: 2.50	PROFESSIONAL: 2.50	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has several components related to different biomedical instrumentation modalities. One type of study is to find optimal designs for measuring in vivo first-order rate constants by means of NMR magnetization transfer experiments. It is important to make these measurements as quickly as possible to minimize artefacts due to physiological changes that might occur during the course of the experiment. In the course of a project currently being completed, an easily-implemented optimal experiment was designed, using the assumption that the experimenter knows an a priori range for the rate constant, but also that the associated spin-lattice relaxation time (T_1) is known. This somewhat artificial assumption is dropped in the current approach to this problem.

A project related to many aspects of medical imaging has required the development of a simulation package to examine problems raised by positron-emission tomography (PET) and single-photon emission tomography (SPECT). For this purpose, a currently available program (SIMSET, developed at the University of Washington) has been modified to more accurately model the design of equipment in general hospital use. Several projects using this program will be undertaken in the coming year.

A monograph written by U. Shmueli and G.H. Weiss, "*An Introduction to Crystallographic Statistics,*" will be published by Oxford University Press in the forthcoming year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00017-22 PSL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Biophysical Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R.J. Nossal, Ph.D. Research Physicist DCRT, PSL

Others:

A. Gandjbakhche, Ph.D., A. Jin, Ph.D., G. H. Weiss, Ph.D. (DCRT, PSL); R. Bonner, Ph.D., J. Schmitt, Ph.D. (NCRR, BEIP); D. Sackett, Ph.D. (NIDDK, LBP); R. Dadmarz, Ph.D., D. J. Schwartzentruber, M.D. (NCI, Surg. Branch); A. C. Stevens, Ph.D., (NIAMS, LSB)

COOPERATING UNITS (if any)

National Institute of Standards and Technology (A.P. Andrews, Ph.D., S. Krueger, Ph.D.); Methodist Hospital, Houston (R. Agah, M.D.); University of Texas Medical Center (M. Motamedi, Ph.D.); Boston University (R. Bansil, Ph.D.); Universite de Paris (P. Cerasi, M.S.)

LAB/BRANCH Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION Division of Computer Research & Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892

TOTAL MAN-YEARS: 3.2	PROFESSIONAL: 3.0	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Quantitative physical and mathematical methods have been applied to several research problems in cell biophysics and tissue optics. In cell biophysics, recent emphasis has been on determining the mechanical and structural properties of large (mesoscopic) molecular structures. Particular attention is being given to the lattice rearrangements that occur when a network of clathrin triskelions initially located on a cell surface (a "coated pit") buds off to form a basket ("coated vesicle"). We developed a set of novel analytical and computational tools to relate the shape variations of triskelions to the underlying mechanical properties of the molecules. These methods are being used to obtain from electron micrographs quantitative information regarding the flexibility of the triskelion arms and the mechanical properties of the central hub where the arms are joined. The mesoscopic structure of macromolecular complexes are also being probed by diffraction measurements utilizing neutrons or light. During the past year, we continued our studies of agarose gels, which serve as models for various biopolymer matrices. Recent emphasis has been on understanding how solution properties affect network junctions, and how gel structure is changed by applied electric fields. Electric field effects are only weakly apparent on the length scales probed by neutrons, and to extend the range of observation, a collaborative study of small angle light scattering has been initiated with investigators at Boston University.

In our investigations of the theory and practice of tissue optics, we devised an optically-based noninvasive method to quantify thermal damage in tissue. That method was used to study thermal lesions induced in bovine myocardium in vitro. Algorithms, based on a photon random walk treatment of light diffusion, were developed to provide optical coefficients from the measured transmittances and reflectances. In collaboration with investigators from the National Cancer Institute, we are presently using similar methods to characterize the optical properties of human breast tissues. In a related project, we performed a theoretical analysis of resolution limits for time-resolved imaging of tumors in human breast. Photon migration theory was used to predict the spatial resolution of objects embedded at different depths within a finite slab, and dependencies on scattering cross section, sample thickness, and photon transmit time were determined.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00024-18 PSL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies in Applied Mathematics and Statistics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G.H. Weiss, Ph.D.	Chief, PSL	DCRT/PSL
	R. Goans, Ph.D., Ph.D., M.D.		NICHD/LTPB
	A. Szabo, Ph.D.		NIDDK/LCP
Others:	J. Bryngelson		DCRT/PSL

COOPERATING UNITS (if any)

Baylor College of Medicine, Houston (S.A. Abrams, M.D.); Karpov Institute of Physical Chemistry, Moscow (A.M. Berezhkovskii, Ph.D.); Bar-Ilan University, Israel (M. Gitterman, Ph.D., S. Havlin, Ph.D.); University of Barcelona, Spain (J. Masoliver); University of Illinois (P. Wolynes, Ph.D.)

LAB/BRANCH: Physical Sciences Laboratory

SECTION:

INSTITUTE AND LOCATION: Division of Computer Research & Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892

TOTAL MAN-YEARS:	1.50	PROFESSIONAL:	1.50	OTHER:	0

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [x] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A theory of the kinetics of the absorption of calcium into bone based on a previously published theory of chromatographic kinetics has been developed by G. Weiss and collaborators. The model has been tested on a number of different normal populations, yielding results to be expected from general physiological principles. The model has been applied to patients with dermatomyositis being treated with steroids, showing that the drug regimen impairs bone absorption to a considerable degree. Preliminary measurements have been made on different disease populations. These studies will be continued in the forthcoming year.

J. Bryngelson has developed a theoretical basis for protein folding, based on statistical properties of conformational energies. The theory has been used to improve the performance of currently used protein structure prediction programs. A continuation of this project relates to the effects of water exclusion in the initial collapse phase in protein folding. It has been shown that hydrogen bonds are increasingly effective in determining secondary structure, as the protein collapses.

A theory has been developed by G. Weiss to estimate the time for a gradient gel to separate peaks in electrophoresis, when diffusion effects are small but not negligible. This is combined with a concurrent measurement by M. Garner and A.Chrambach of boundary spreading as a function of the gel concentration.

Two monographs by G.Weiss have appeared this year, *Aspects and Applications of the Random Walk* (North-Holland, Amsterdam), and *Contemporary Problems in Statistical Physics* (Siam, Philadelphia).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00090-14-CBEL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Biomedical Image Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: B.L. Trus Chief, Image Proc Res Section CBEL, DCRT

Others:

M. Vivino, Comp Eng, CBEL, DCRT; M. Datiles, Chief, CCD, NEI; A. Mahurkar, Visiting Assoc, CCD, NEI ; L. Lopez, Visiting Assoc, CCD, NEI; W.Rasband, Comp.Analyst. NIMH/MHRIP; B. Magno, Visiting Assoc, CCD, NEI

COOPERATING UNITS (if any)

LAB/BRANCH Computational Bioscience and Engineering Laboratory

SECTION Image Processing Research Section

INSTITUTE AND LOCATION Division of Computer Research and Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892-5605

TOTAL MAN-YEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In this project, sophisticated image processing techniques are used to analyze biomedical images. The goal is to establish collaborations with biomedical experts who require new algorithms and possibly new hardware capability to solve difficult imaging problems. Typically, complex new mathematical algorithms as well as new combinations of existing algorithms are utilized. We attempt to integrate the best computer platform for each problem with the desired goal of the project, using such diverse computers as an Apple Macintosh, a DEC VAX or Alpha, a SUN workstation, or an Intel iPSC/860 supercomputer.

Two current projects include ophthalmic image analysis and general consulting to the NIH scientific community in biomedical image processing. In collaboration with the National Eye Institute, we continue the development of systems to quantitate lens opacities (cataracts) and to assist in diagnosis of ocular diseases. For cataract studies, it was possible to use the computer assisted instrumentation to observe the effects of anti-cataract drugs or for routine pathological grading. During the last year, we completed a system that analyses retro-illumination images. This device projects light onto the retina and then captures an image of the lens with reflected light. The technique of reflecting light off the retina does not always produce a perfect image, and sometimes leaves a distortion pattern in the image of the retina. While this distortion limits the device's effectiveness, it is the best system available to evaluate the anterior and posterior subcapsular cataracts. Before making quantitative morphological and densitometric measurements on these images, our software removes the distortion pattern.

An integral part of our image processing consulting is ongoing support for the NIH Image Program (by Wayne Rasband). Our support includes continuing development of new algorithms and four supporting documents, which are now distributed with the package. These documents are widely used and referenced both in the intramural program and by extramural biomedical scientists. These documents include a guide on how to modify source code, which is intended to help scientists develop new user applications or macros, a technical guide describing scientific application usage with the package, a list of frequently asked questions and answers, and finally support for a guide (by David Chow) concerning analysis of gels.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00092-13-CBEL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structural Biology: Image Processing of Electron Micrographs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: B.L. Trus — Chief, Image Proc Res Section — CBEL, DCRT

Others:

A.C. Steven, Chief, LSB, NIAMS; E. Kocsis, Visiting Sci., LSB, NIAMS; F. Booy, Visiting Sci., LSB, NIAMS; J. Conway, Visiting Sci., LSB, NIAMS; M.Misra, Visiting Sci., ,LSB, NIAMS; M. Cerritelli, Visiting Sci., LSB, NIAMS; J. Caston, Visiting Sci., LSB, NIAMS; J.T. Shiller, Ph.D., LCO, NCI; R. Roden, Ph.D., LCO, NCI

COOPERATING UNITS (if any)

University of Virginia, Charlottesville (J. Brown , Ph.D., W. Newcomb)
Purdue Univ., West Lafayette, Indiana (T.S.Baker, Ph.D.)
Upjohn, Kalamazoo, Michigan (F. Homa, Ph.D.)

LAB/BRANCH: Computational Bioscience and Engineering Laboratory

SECTION: Image Processing Research Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892-5605

TOTAL MAN-YEARS: 0.5	PROFESSIONAL: 0.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In this project, image processing techniques are used to analyze electron micrographs. To answer important questions in structural biology, it is necessary to obtain relatively high resolution 2- and 3-D structural information about biological macromolecules.

Biological specimens can be visualized in the electron microscope using a number of specimen preparation techniques. Cryo-electron microscopy, a relatively new technique, attempts to preserve "native" structure by surrounding the specimen with a layer of ice. Collaborative studies with LSB, NIAMS are currently under way on a number of projects, whereby electron micrograph images are computationally corrected, combined, averaged, reconstructed, or in some way computationally enhanced to improve the signal-to-noise ratio or to increase the interpretability of the structures being visualized. "Cryo" images are typically lower contrast and require greater computer processing than conventional electron microscopy to achieve satisfactory results.

Of particular interest to our research is the understanding of viral structures. At present we are continuing our efforts to investigate the structure of a large animal virus, human herpes simplex virus (type 1). We are completing the localization of the major capsid proteins and attempting to obtain higher resolution structures. Biological material for these herpesvirus reconstructions is provided through a collaboration with researches at the University of Virginia, Charlottesville, and from the Upjohn Co., Kalamazoo. The electron microscopy is performed in LSB, NIAMS. Interpretation of our 3-D reconstructions is performed jointly by all collaborators.

A number of other collaborative projects in structural biology are currently in progress. We are using 3-D reconstruction techniques to study the structure of icosahedral L-A virus (from yeast), papillomavirus, and polio virus. We have compared the structures of full (RNA containing) L-A virus with empty L-A virus. In a new study of papillomavirus (in collaboration with NIAMS and NCI), we have verified the known structure of bovine papillomavirus (bpv), and have recently obtained a 3D reconstruction of antibodies to the L1 protein of bpv. We hope to be able to localize the two major proteins of bpv, as well as to understand more of the function and activity of a number of papilloma antibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00138-11-CSL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biomedical Image Processing

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B.L. Trus	Chief, Image proc Res Section	CBEL, DCRT
Others:	M. Datiles, Chief, CCD, NEI	M. Vivino, Comp Eng, CBEL,DCRT	
		A. Mahurkar, Visit Assoc, CCD, NEI	
		B. Magno, Visiting Assoc, CCD, NEI	
		W. Rasband, Comp Analyst, NIMH/MHRIP	
		L. Lopez, Visting Assoc, CCD, NEI	

COOPERATING UNITS *(if any)*

LAB/BRANCH Computer Systems Laboratory

SECTION Laboratory and Clinical System Section

INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20892

TOTAL STAFF YEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The superposition and registration of differing tomographic views is a difficult problem for investigators attempting to correlate brain form (structure), derived from x-ray computed tomography (CT) images, with brain function (metabolism), revealed by nuclear medicine positron emission tomography (PET) images.

For this reason, an attempt is being made to develop techniques for the accurate correlation of CT structural data with PET metabolic information, in order to enhance our understanding of the processes underlying the generation of PET images.

Our approach has three stages: firstly, practical methods must be discovered for the accurate and reproducible placement of the head within a tomographic scanner's aperture; secondly, techniques for monitoring head position during the image acquisition process must be developed to correct for head movement before the image is generated; thirdly, simplified algorithms must be found for scaling and registering digitized images from different scanners on a digital display subsystem.

Precise orientation of the subject's skull within the scanner's aperture is monitored and recorded with a PC-based Polhemus position/orientation measurement subsystem, allowing simultaneous use of two independent sensors. The development of two inexpensive custom-molded oral appliances allows the Polhemus subsystem's sensor to be fixed to the subject's skull. A novel targeting algorithm was derived to provide to the system operator visual cues related to head position within a scanner's imaging volume. Two-sensor software was completed, and extensive evaluation has begun prior to its experimental use with test subjects.

An additional position/orientation measurement subsystem has been obtained and evaluated for linearity and for sensitivity to nearby metallic objects, a problem common to all electromagnetic-based tracking systems. This device's utilization of quasi-static fields was designed to increase its immunity to close proximity of certain types of metal. Although performance of this new position measurement system was good, it did not outperform the Polhemus system in the presence of PET scanners.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT
00199-05 DSB

PERIOD COVERED
October 1, 1993 to September 30, 1994

TITLE OF PROJECT
Image Management and Communications System (IMACS)

PRINCIPAL INVESTIGATOR

PI:	K.M. Kempner	Electronics Engineer	DSB, DCRT
OTHERS:	H.G. Ostrow	Electronics Engineer	NSB, DCRT
	R.L. Martino, Ph.D.	Electronics Engineer	CBEL, DCRT
	T.L. Lewis, M.D.	Medical Officer	DIR, CC
	J.F. Fessler	Engineering Technician	BEIP, NCR
	E.E. Tucker, M.D.	Medical Officer	CB, NHLBI
	P.G. Okunieff, M.D.	Medical Officer	ROB, NCI

COOPERATING UNITS *(IF ANY)*

LAB/BRANCH
Distributed Systems Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.80	0.80	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK

Medical images are an important component of the medical record generated during a patient's hospital stay or clinic visit. The NIH Clinical Center (CC), like most university and research hospitals, is attempting to solve the problem of consolidating medical images with the conventional alphanumeric medical record data in the Medical Information System (MIS) to more completely realize the goal of a comprehensive electronic medical record. DCRT, CC, and NCI are collaborating to develop a series of demonstration projects that explore image integration into the electronic medical record.

Chest X-rays are routinely obtained within the Diagnostic Radiology Department. In this application, we have been using a Vision Ten Rita! system, which contains a gray-scale sheet film digitizer, as an integral part of an image gateway. Communication of medical images between the Radiology Department's Film Library and remote sites is now possible. Future plans include the connection of two General Electric CT scanners into the Vision Ten image transmission and display environment.

In addition, we are planning a prototype high-speed image communication network based on Asynchronous Transfer Mode (ATM) Switch technology. The ATM Switch will allow 155 Mbit/sec multi-media communications between users. This prototype network would initially support high-performance radiation therapy planning, which is a collaborative effort between DCRT's Computational Bioscience and Engineering Laboratory (CBEL) and the NCI Radiation Oncology Branch (ROB). CBEL's Intel iPSC/860 Supercomputer will be utilized to apply the power of parallel computing methods to the computationally intensive calculations required for radiation therapy planning. A custom-designed Radiology Consultation WorkStation (RCWS) will be located in the NCI Radiation Oncology Branch (ROB), as well as in the same building as the CBEL Supercomputer.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00200-05 CBEL

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

High Performance Biomedical Computing

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: R. Martino, Chief — Computational Bioscience and Engr. Lab, DCRT

Others: C. Johnson, Com. Engr., DCRT; B. Trus, Research Chemist, CSL, DCRT; J. Pfeifer, Com. Engr., DCRT; T. Yap, Com. Engineer, DCRT; E. Suh, Com. Engr., DCRT; N. Weisenfeld, Com. Engineer, DCRT; C. Lanczycki, Com. Engr., DCRT

COOPERATING UNITS *(if any)*

DCRT/DSB; DCRT/MGSS; NIAMS/LSBR; NCI/DCT; CC/PET; NIMH/LPP; NIMH/CPB; NIA/LN; NCHGR; NIMH/CNB; NCI/LMB; University of Maryland; UCLA School of Medicine; Purdue University; George Mason University; Columbia University; NASA/GSFC; ARPA/CSTO; American Cyanamid Company; Intel Supercomputer Systems Division

LAB/BRANCH Computational Bioscience ad Engineering Laboratory

SECTION High Performance Computing Section

INSTITUTE AND LOCATION DCRT, NIH, 12A/2033, Bethesda, MD 20892

TOTAL STAFF YEARS: 6.0	PROFESSIONAL: 6.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goals of the high performance biomedical computing program are to identify and solve those computational problems in biomedicine that can benefit from high performance hardware, modern software engineering principles, and efficient algorithms. This effort includes providing high performance parallel computer systems for the NIH staff and developing parallel algorithms for biomedical applications.

Using high performance parallel computers, biomedical scientists can greatly reduce the time it takes to complete computationally intensive tasks and take new approaches in processing their data. This may allow the inclusion of more data in a calculation, the determination of a more accurate result, a reduction in the time needed to complete a long computation, or the implementation of a new algorithm or more realistic model. With proper computer network connections and interactive user interface, parallel computing is readily available to a biomedical researcher in the laboratory or clinic at the investigator's computer workstation.

In addressing these computational challenges, CBEL is developing algorithms for a number of biomedical applications that can benefit from computational speedup, including image processing of electron micrographs, radiation treatment planning, medical imaging, protein and nucleic acid sequence analysis, human genetic linkage analysis, protein folding prediction, nuclear magnetic resonance spectroscopy, x-ray crystallography, quantum chemical methods, and molecular dynamics simulations. The ultimate goal is to have high performance parallel computing facilitate the science that is done at NIH. While developing these computationally demanding applications, CBEL is investigating the following high performance computing issues: partitioning a problem into many parts that can be independently executed on different processors; designing algorithms so that delays of interprocessor communication can be kept to a small fraction of the computation time; designing the parts so that the computing load can be distributed evenly over the available processors or dynamically balanced; designing algorithms so that the number of processors is a parameter and the algorithms can be configured dynamically for the available machine; developing tools and environments for producing portable parallel programs and monitoring system performance; and proving that a parallel algorithm on a given machine meets its specifications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT 00226-04 LSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Statistical Methods for Molecular Biology, DNA and Protein Structure/Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: P.J. Munson, Ph.D. Section Chief ABS, LSB, DCRT

Others: None

COOPERATING UNITS (if any)

None

LAB/BRANCH Laboratory of Structural Biology

SECTION Analytical Biostatistics Section

INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been combined with Z01-CT00227-04 LSB.

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00227-04 LSB

PERIOD COVERED
October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Statistical and Computational Methods for Physiology, Pharmacology, Endocrinology & Mol. Biol.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	P.J. Munson, Ph.D.	Section Chief	ABS, LSB, DCRT
Others:	V. Di Francesco, Ph.D.	Visiting Fellow	ABS, LSB, DCRT
	J. Garnier, Ph.D.	Scholar -in-Residence	FIC, NIH
	G. Hutchinson, Ph.D.	Research Mathematician	ABS, LSB, DCRT
	R. Shrager, Ph.D.	Research Mathematician	PSL, DCRT
	A. Cushing	Computer Specialist	ABS, LSB, DCRT
	J. Barron, M.D.	Clinical Associate	DEB, NICHD
	C. Heinrichs	Visiting Fellow	DEB, NICHD
	G. Mastorakos, M.D.	Visiting Fellow	DEB, NICHD

COOPERATING UNITS (if any)
Hebrew University, Jerusalem, Israel (D. Lichtstein); University of Milan, Italy (E. Rovati); University of Campinas, Brazil (R. Porrelli).

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Analytical Biostatistics Section

INSTITUTE AND LOCATION: National Institutes of Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We are developing and evaluating statistical methods appropriate to prediction of protein structure from sequence. These methods include Fisher discriminant analysis, logistic discriminant analysis, artificial neural networks, density estimation techniques, cross-validation and bootstrap techniques, and computer graphical approaches. A new finding in this field is the apparent utility of homologous sequences in predicting the structure of an index sequence. An overall improvement of 4-5% is obtained using this approach, compared with others. We have sought to further increase the efficiency of these algorithms by optimizing the alignment of the homologous sequences, and by making use of ancillary information, such as the presence of gaps in the alignment.

In a study that attempts to refute the notion of saltatory or pulsatile growth in humans, an analysis of daily length measurements in humans was made . A new analysis method was proposed that is more efficient than previous approaches, yet is easily interpreted graphically and provides a precise definition of a saltatory growth process. Numerical simulations confirmed the performance characteristics of the method.

The statistical analysis of the relationships between placental corticotropin releasing hormone (CRH) and other hormones of the hypothalamic-pituitary-adrenal axis in third trimester pregnancy showed that, while adrenocorticotropin (ACTH) and cortisol are correlated over the 12 hour sampling period, CRH does not correlate significantly with ACTH or cortisol nor does it show circadian variation. Thus, there is no evidence of a regulatory role of glucocorticoids on placental CRH.

Statistical and mathematical modeling consultation and advice were given to several NIH investigators in areas of ligand binding and kinetic data analysis. Refinement to the computer programs LIGAND and ALLFIT were made, especially in the area of the user interface and graphics. Several hundred copies of these programs were distributed to users at NIH and elsewhere.

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00228-04 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Genobase - An Object oriented Genomic Database Accessible through the WWW/Mosaic

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R.C. Taylor Computer Specialist DCRT, DSB

Others:

COOPERATING UNITS (if any)

LAB/BRANCH Distributed Systems Branch

SECTION BioInformatics and Molecular Analysis Section

INSTITUTE AND LOCATION Division of Computer Research and Technology

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Work is ongoing to develop and provide an integrated framework for computational support of research in comparative DNA/protein sequence analysis and related areas across multiple genomes/species. The logic programming language PROLOG is used throughout this project, permitting data of disparate types to be combined rapidly and effectively, and permitting complex queries from the integrated data. Toolset development was performed in close collaboration with Drs. R. Overbeek and R. Hagstrom of Argonne National Laboratory.

Current work focuses on the addition of large volumes of data from multiple sources, resulting in a unique resource, combining data from a number of current sources such as GenBank, EMBL, Prosite, SwissProt and others including metabolic data from Dr. Overbeek's Russian collaborators. This will form an integrated database with DNA and protein sequence, motif, metabolic pathway and other data for multiple genomes. The work incorporates analysis of genomic organization and genetic regulation of metabolic pathways. This database and associated tools will permit answers to queries that are difficult or impossible to satisfy using the standard biological databases currently available.

This database is also the underlying data repository for a World-Wide Web (WWW) hypertext browser implemented by R. Taylor and A. Ginsburg, DCRT/BIMAS. It is expected that this WWW service will provide a unique resource to the biomedical research community over the Internet, employing simple and widely available end-user client tools, such as NCSA Mosaic for access. This will supplement present WWW servers at NCBI and at EMBL in Europe, providing unique services unavailable to date.

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00231-08 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Flow Cytometry Advanced Data Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	L. Barden	Electronics Engineer	DCRT, DSB
Others:	J. Powell	Electronics Engineer	DCRT, DSB
	S. Sharrow	Senior Investigator	NCI, DCBDC

COOPERATING UNITS (if any)

LAB/BRANCH: Distributed Systems Branch

SECTION: BioInformatics and Molecular Analysis Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The on-going seminar series "Topics in Analytical Cytology" hosted two sessions during the year under the auspices of the NIH Computer Training Program, with presentations by NIH, FDA and USUHS researchers in "Flow and Image Cytometry in B-cell Chronic Lymphocytic Leukemia," "Advanced Techniques in Quantitative Fluorescence Microscopy," "Studies of Drug and Carcinogen Efflux in Multi-drug Resistant Cells using Adherent Cell Laser Cytometry" and "In vivo Confocal Microscopy of the Human Eye".

The Cluster Analysis Program (CAP) has been ported from its originally designed VAX/VMS minicomputer and graphics terminal environment to a RISC OpenVMS Motif workstation platform, with some necessary changes to computational algorithms and data structures to take more complete advantage of the RISC architecture.

The Laboratory Analysis Package (LAP) was originally developed to run on SUN3 UNIX workstations as a general-purpose tool for both interactive and batch processing of laboratory data. LAP is currently implemented in C++ version 2.1. and has been ported to SUN4, VMS (VAX and Alpha), and Convex architectures. It is used extensively by two laboratories in NIDDK and numerous Flow Cytometry sites at NIH.

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00232-04 LSB

PERIOD COVERED
October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Molecular Dynamics Simulations of Biological Macromolecules

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.R. Brooks, Ph.D.	Research Chemist	MGS, LSB, DCRT
Others:	P.J. Steinbach, Ph.D.	Senior Staff Fellow	MGS, LSB, DCRT
	D. Chatfield. Ph.D.	NRC Research Associate	MGS, LSB, DCRT
	M. Hodoscek, Ph.D.	Visiting Fellow	MGS, LSB, DCRT
	D. Bhattcharyya. Ph.D.	Visiting Fellow	MGS, LSB, DCRT
	K. Eurenius, Ph.D.	NRC Postdoctoral Fellow	MGS, LSB, DCRT
	A. Szabo. Ph.D.	Chief	TBS, NIDDK
	S. Durrell, Ph.D.	IRTA Fellow	LMMB, NCI

COOPERATING UNITS (if any)
American Univ. (F.W. Carson); Howard Univ. (W.M. Southerland, J. Mack); FDA Center for Biol. Eval. and Research (R.M. Venable, R.W. Pastor); Walter Reed Army Inst. of Res. (Col. R. Reid); Inst. of Chem., Ljubljana, Slovenia (D. Janezic); Massey Univ., New Zealand (D. Parry); Purdue Univ., Lafayette, Indiana (C. Post); Univ. of Toronto, Canada (C. Lim)

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Molecular Graphics and Simulation

INSTITUTE AND LOCATION: National Institutes of Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	3.0	PROFESSIONAL:	3.0	OTHER:	0

CHECK APPROPRIATE BOX(ES)
- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Molecular Graphics and Simulation Section studies problems of biological significance using several theoretical techniques: molecular dynamics, molecular mechanics, modeling, *ab initio* analysis of small molecule structure, and molecular graphics. These techniques are applied to a wide variety of macromolecular systems.

Specific projects related to the study of AIDS proteins include: simulations of HIV-1 reverse transcriptase, analysis of inhibitor binding to the active site of HIV-1 protease, and investigation of the mechanism of action of HIV-1 protease.

Other research applied to molecules of biomedical interest uses molecular dynamics simulations to predict function or structures of peptides and proteins. Such projects include:
- Modeling intermediate filament (IF) proteins
- Identification of peptides that bind to human MHC DR1
- Modeling the V3 loop in HIV-1 correlating with syncytium formation
- Simulation of a large virus complex

Basic research is underway to provide a better understanding of macromolecular systems. The projects include studies of:
- Temperature effects on protein dynamics
- Effects of hydration on protein dynamics
- Protein anharmonicity and the role of dihedral transitions
- Molecular dynamics simulations on Staphylococcal nuclease: comparison with NMR data
- Harmonic analysis of large systems
- Modeling and simulation of lipid bilayers in crystal and gel phases
- Molecular dynamics simulation studies of DNA: the B-Z junction
- The mechanism of lysozyme elucidated by quantum mechanical/molecular mechanical (QM/MM) techniques
- The mechanism of ribonuclease A elucidated by QM/MM techniques

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00233-04 LSB

PERIOD COVERED
October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Development of Theoretical Methods for Studying Biological Macromolecules

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.R.Brooks, Ph.D.	Section Chief	MGS, LSB, DCRT
Others:	P.J. Steinbach, Ph.D.	Senior Staff Fellow	MGS, LSB, DCRT
	D.C. Chatfield, Ph.D.	NRC Postdoctoral Fellow	MGS, LSB, DCRT
	M. Hodoscek, Ph.D.	Visiting Fellow	MGS, LSB, DCRT
	S. Mathur, Ph.D.	Visiting Scientist	MGS, LSB, DCRT
	J. Zhou, Ph.D.	Guest Researcher	MGS, LSB, DCRT
	K. Eurenius, Ph.D.	NRC Postdoctoral Fellow	MGS, LSB, DCRT

COOPERATING UNITS (if any)
Howard University (W.M. Southerland); FDA Center for Biologics Evaluation and Research (R.M. Venable, R.W. Pastor); Courant Institute, New York University, New York (T. Schlick); Harvard University (Martin Karplus group); Carnegie Mellon Univ., Pittsburgh, PA (C.L. Brooks III).

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Molecular Graphics and Simulation

INSTITUTE AND LOCATION: National Institutes of Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	2.2	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

New theoretical techniques are often coupled with software and hardware development, such as the generation of new simulation techniques and the systematic testing and evaluation of methods. Specific projects include:

- Development of Langevin Piston methods for NPT simulation of periodic systems and for stochastic boundary molecular dynamics (MD) simulations
- Development of quantum mechanical potentials and appropriate algorithms for use in molecular dynamics simulations
- Determination of protein structure by NMR and molecular modelling
- Development of an optimized protocol for the preparation of low temperature states
- Development of flexible MD techniques that remove high-frequency degrees of freedom
- Development of the REPLICA/PATH method for determining reaction paths in complex systems using simulated annealing
- Free energy perturbation simulations in solution, examining the effect of restraints
- Conversion of physical models into three-dimensional coordinates for computer analysis and simulation
- Development of ray-traced molecular graphics software for HP workstations, high-resolution color printers and for movies using NTSC video equipment
- Adaptation of a Truncated Newton minimizer for CHARMM and biomolecular applications.

Parameter sets and models are generally available for most macromolecular systems, but there is considerable room for improvement, and alternate models that improve realism, or reduce computational costs, need to be examined. This effort involves the refinement of parameters and the exploration of alternate energetic models for molecules and environmental conditions. Ongoing projects include:

- Evaluation of parameter sets
- Approximation of long-range interactions in macromolecular simulation variants of the Ewald Sum method, using a particle mesh grid
- New methods for long-range truncation of the energy potential
- Evaluation and comparison of implicit and explicit water models for simulations examining the hydration of proteins
- Molecular dynamics simulation studies of DNA: analysis of the parameter sets using an infinite DNA helix

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00234-04 LSB

PERIOD COVERED
October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Development of Advanced Computer Hardware and Software

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.R. Brooks, Ph.D.	Research Chemist	MGS, LSB, DCRT
Others:	M. Hodoscek, Ph.D.	Visiting Fellow	MGS, LSB, DCRT
	S. Mathur, Ph.D.	Visiting Scientist	MGS, LSB, DCRT

COOPERATING UNITS (if any)

Harvard University, Cambridge, MA (M. Karplus), University of Maryland, College Park, MD (J. Saltz).

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Molecular Graphics and Simulation

INSTITUTE AND LOCATION: National Institutes of Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

With the advent of new computer technology amenable to large-scale scientific computing, software and hardware development efforts are essential for optimal use of these resources. The efforts include the developing of techniques to exploit parallel multi-machines, writing assembler code for commercial processors, and establishing a parallel workstation cluster for high-efficiency simulations at low cost.

Development of methods and software to make productive use of parallel MIMD machines for use in macromolecular simulations is under way. The initial global communication approach has been successful in providing an efficient full-feature version of CHARMM (Chemistry at HARvard Macromolecular Mechanics). This parallel version of CHARMM has been extended to run on almost any MIMD parallel computer platform: Intel iPSC/860, Intel delta, CM-5, IBM/SP1, Convex SP1, and on clusters of workstations. Our current development effort involves a scalable algorithm that promises to greatly reduce the communication cost for very large MPP machines or for large workstation clusters.

Current projects include:
- A scalable molecular dynamics algorithm for MPP machines and large workstation clusters.
- Development of parallel quantum mechanical/molecular mechanical (QM/MM) methods
- Development and efficient use of a high-speed workstation cluster of HP735s
- Development and support of CHARMM

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-CT00236-04 LSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Modeling the Mechanisms of Protein Folding

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R.J. Feldmann Computer Specialist LSB, DCRT

Others: None

COOPERATING UNITS (if any)

Towson State University, Dept. of Chemistry, Towson, MD (J. D. Rawn)

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Office of the Chief

INSTITUTE AND LOCATION: DCRT, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Computational folding of proteins moved in this year from an abstract geometry-free model developed during the previous year to a 3-dimensionally embedded constraint evaluation model. The geometry-free model was implemented as a series of topological connections between charged atoms representing the hydrophilic aspects of peptide biochemistry and another series of connections between groups of carbon atoms representing the hydrophobic aspects. The rule-based manipulation of topological connections is, computationally, relatively inexpensive.

In order to maintain a model that is physically reasonable, the sequential synthesis of the protein from N to C terminus is modeled. In ribosomal synthesis, it is only when the peptide emerges from the ribosomal that it begins to adopt a folded conformation. The linearly increasing peptide length keeps the DGEOM computation time to a minimum. We have found that the pattern of hydrophilic and hydrophobic constraints develops with the lengthening of the peptide in such a way that the peptide adopts conformations that are very close to the crystal or NMR structure observed after ribosomal emission. As the sequence for a helical portion of a peptide is emitted, it folds into a helix. As soon as the sequence for an antiparallel beta sheet is emitted, it too folds into the correct secondary structure. The most striking result from this year's simulations is the discovery that the strand-helix-strand peptide sequence forms a tertiary structure with the correct macroscopic handedness when it is emitted.

Ten classes of protein architecture are being studied in parallel, in an attempt to make the computational simulation of protein folding as general as possible. We have observed that, in all structural classes, the correct local secondary structure is formed, and often the correct macroscopic handedness is also formed. So far, the simulation program has not been able to reproduce the tightly packed atomic structure characteristic of crystal NMR structures. Rules and parameters are continually added and modified, in attempts to produce better packing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CT00239-03 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT

Real-Time Gamma Camera Image Correction

PRINCIPAL INVESTIGATOR

PI:	W.R. Gandler	Electronics Engineer	DSB, DCRT
OTHERS:	M.V. Green	Physicist	NMD, CC
	J.Seidel, Ph.D.	Visiting Fellow	NMD, CC
	K.M. Kempner	Electronics Engineer	DSB, DCRT

COOPERATING UNITS *(IF ANY)*

LAB/BRANCH

Distributed Systems Branch

SECTION

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	1.00	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

The Nuclear Medicine Department (NMD) of the Clinical Center has developed a small field-of-view (FOV) gamma camera which has great promise for practical, high-resolution imaging of small animals. The system is based on a single position-sensitive photomultiplier tube (PMT). Unfortunately, the position-sensitive PMT does not possess either a linear voltage analog of event position, or a uniform energy response across the tube face.

We have developed a Multibus II Image Correction System, comprising three coupled 386/486 processors, which allows first-order, geometric and energy corrections to be performed sequentially, in real-time on data from the small FOV gamma camera. The Image Correction System acts either as a stand-alone, two-processor data acquisition system for the small FOV gamma camera, or it is interposed between this camera and a commercial analog acquisition system, and used as a three-processor system, dynamically correcting the data transmitted to the Analog Acquisition System.

The three processors are dedicated to input (analog-to-digital conversion), computation (geometric, energy and motion correction), and output (digital-to-analog conversion or digital transmission), respectively. Software for system control, data acquisition, corrected and uncorrected image display, and data/image transmission has been developed. All geometric and energy correction software has been completed. It is possible to acquire up to ten simultaneous inputs via the high-speed analog-to-digital converter module.

Work is also beginning on the implementation of new algorithms for image acquisition in PET scanner mode that are suitable for use in imaging the human breast. This joint effort, involving DCRT, CC, NCI, and BEIP personnel, has the goal of early detection of breast cancer.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00241-03 LSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Direct Measurement of Forces Between Membranes or Macromolecules

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: V.A. Parsegian, Ph.D. Chief LSB, DCRT and OSD, NIDDK

Others: S. Leikin, Ph.D., R. Podgornik, Ph.D., N. Sidorova, Ph.D., H. Strey, Ph.D., C. Bonnet-Gonnet, Ph.D., DCRT/LSB; D.C. Rau, OD, NIDDK; K. Gawrisch, Ph.D., LMBB/NIAAA; N.L. Gershfeld, Ph.D., PB, NIAMS

COOPERATING UNITS (if any)

University of Minnesota (D.F. Evans); University of the Pacific (J.A. Cohen); Brock University, Canada (R.P. Rand); University of British Columbia, Canada (E.A. Evans); Scientific Center KFA, Germany (A.A. Kornyshev); Free University of Berlin, Germany (M.M. Kozlov).

LAB/BRANCH Laboratory of Structural Biology

SECTION Office of the Chief

INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 5.5	PROFESSIONAL: 5.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The theme of this work is to develop a useful, accurate science of the forces that organize biomolecules. To this end we have accelerated our efforts to measure forces between proteins, DNA double helices, and polysaccharides. We have also concluded a set of studies on the release of water upon DNA/protein and DNA/drug binding.

Force measurements between collagen triple helices have shown how decreasing temperature, lowering pH, or adding glycerol can remove the attractive forces that reconstitute collagen from solution. At least in this case, the independent action of these different changes in condition provides strong evidence against the popular assumption that "hydrophobic interactions" stabilize protein assembly.

This year, we published the first of our intended "toolbox" papers, which codify measured DNA-DNA forces in a form that can be used in computation and analysis of molecular assembly. These forces are themselves the center of our own investigation into the packing of DNA and its packaging into ordered assemblies, such as in viruses.

We have begun an extensive series of measurements on forces among stiff polysaccharides, the most neglected of all bio-materials. There is a strong technological as well as biological motivation for understanding these interactions.

This year has seen the first quantitative measurement of the amount of water released upon specific vs. non-specific binding of DNA to protein (lac repressor) or upon the binding of DNA to various drugs. There is an immediate energetic connection between these changes in molecular hydration and the powerful "hydration forces" measured between large molecules when they are brought into contact.

The growing catalog of information about these interactions continues to create a new logic of thinking about molecular recognition and folding.

U.S. GOVERNMENT PRINTING OFFICE: 1991 0-864-939

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CT00242-03 LSB

PERIOD COVERED
October 30, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Physics Ionic Channels and Other Proteins with Aqueous Cavities

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	V.A. Parsegian, Ph.D.	Chief	LSB, DCRT
Others:	S. Bezrukov, Ph.D.	Visiting Scientist	LBM, NIDDK
	I. Vodyanoy, Ph.D.	Guest Researcher	LBM. NIDDK and ONR
	R. Brutyan, Ph.D.	Guest Researcher	LBM, NIDDK
	D.C. Rau, Ph.D.	Guest Researcher	LBM. NIDDK
	J.J. Kasianowicz, Ph.D.	Guest Worker	LBM, NIDDK and NIST

COOPERATING UNITS (if any)
Johns Hopkins University, Baltimore, MD (A.J. Harris); Universidada Estadual Paulista, Sao Paolo, Brazil (M. Colombo, Ph.D); Hamel Institute, Philadelphia, PA (A. Feigin, Ph.D.).

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Office of the Chief

INSTITUTE AND LOCATION: DCRT, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 3.4	PROFESSIONAL: 3.4	OTHER: 0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Our studies have progressed by means of two strategies:

1) The structures of ionic channels can be interrogated by measuring their reaction to polymers of varied size
2) Sophisticated physical "noise" analysis allows one to follow the very rapid kinetics of ionic channels in several different processes, such as the passage of neutral polymers through the channels or the formation of channels by drugs added to one side of a membrane

Channels made from the peptide alamethicin have been observed while subjected to the osmotic action of differently sized neutral polymers. It is possible not only to see the degree of penetration of the polymers into the channel from their osmotic action but also to follow the kinetics of motion of small polymers through the ionic channel.

These channels are sensitive to the identity of the phospholipids in the bilayer into which they are incorporated; in particular, there is a strong correlation between the probability of high-conductance states and the tendency of the phospholipid to form non-lamellar structures.

The Hofmeister effect is shown to apply to transport properties of ionic channels. Chaotropic anions bind to roflamycoin channels for longer times, increase their conductance and induce cationic selectivity according to their position in Hofmeister series.

Studies of the one-sided action of the drug amphotericin B (with the drug added only from one side of the bilayer) were conduced on cholesterol- and ergosterol-containing bilayers. As administered, drugs act predominantly from one side; furthermore, the differential toxicity of drugs appears to depend on the different sterol content of the tissue and the infectious agent; thus, this would appear to be the appropriate protocol for determining toxicity. Differences of drug action were in accord with expected discrimination under administration.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CT 00243-03 LSB

PERIOD COVERED: October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Adaptive Computing and Biomedical Applications

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G. Hutchinson, Ph.D.	Research Mathematician	ABS, LSB, DCRT
Others:	G.S. Dunham	Computer System Analyst	ISB, DCRT
	G. Campbell, Ph.D.	Section Chief	BFSB, DIR, NINDS

COOPERATING UNITS (if any): None

LAB/BRANCH: Laboratory of Structural Biology

SECTION: Analytical Biostatistics Section

INSTITUTE AND LOCATION: DCRT, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A program in the Mathematica language was prepared for ALLFIT analysis making available a more generalized system of models. Due to problems with curve-fitting and retirement of the author of the program, this program was not made a production system.

A package of Mathematica functions for manipulation of polynomials with multiple variables was completed, and a talk was given on it at the Mathematica Developers Conference held in April 1994. A manuscript describing this package was submitted for publication in the Mathematica Journal.

Research in neural networks and preliminary investigations of the Boltzmann machine and the Gibbs sampler were discontinued due to the retirement of Dr. Hutchinson.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00246-03 CFB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Applied Object Technology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: K.E. Gorlen Chief, Distributed Systems Section CFB, DCRT

Others:

E.M. Persky, Computer Scientist, CFB, DCRT

COOPERATING UNITS (if any)

LAB/BRANCH: Computing Facilities Branch

SECTION: Distributed Systems Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892-5605

TOTAL MAN-YEARS: 0.1	PROFESSIONAL: 0.1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Distributed Systems Section (DSS) of the Computing Facilities Branch is pursuing a long-term investigation of scientific and administrative applications of object technology, such as object-oriented analysis, design, and programming, object-oriented user interfaces, object-oriented database management systems (OODBMS), and object-based distributed computing systems. This project is a continuation and extension of our previous work, begun as part of the Advanced Laboratory Workstation (ALW) Project, on object-oriented programming in C++, the OI user interface toolkit and builder, the ObjectStore OODBMS, and of our interest in emerging distributed system standards, such as the OSF Distributed Management Environment (DME) and the Object Management Group's (OMG) Object Management Architecture (OMA) and Common Object Request Broker Architecture (CORBA).

In FY94, we completed and deployed for beta test the first version of xemt, our first major C++ software application to use the OI user interface toolkit and builder. Xemt provides a graphical user interface to the Environment Maintenance Tool (EMT), which manages applications software for the Advanced Laboratory Workstation (ALW) system. This enables application maintainers and developers to more easily manage their own software collections, and to integrate them into the ALW environment. Unfortunately, upgrading to AFS 3.3 caused EMT to no longer work, so xemt cannot be used until the maintainers of EMT correct the incompatibility.

We have procured JAM, an object-oriented 4GL, and have begun using it to develop a business system to support ALW hardware and software maintenance.

We have also purchased several leading C++ class libraries to support C++ development as alternatives to the NIH Class Library, which we no longer have the resources to maintain.

Finally, we continued our membership in the Object Management Group (OMG), an industry organization dedicated to producing a framework and specifications for commercially available object-oriented environments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT000247-03 CFB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Distributed Computing Initiative

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: K.E. Gorlen Chief, Distributed Systems Section CFB, DCRT

Others:

R.B. Dew, Computer Engineer, CFB, DCRT
T. Ghebeles, Computer Engineer, CFB, DCRT
J.B. Kelley, Computer Engineer, CFB, DCRT,
J. Dickson, Supv. Computer Systems Programmer, CFB, DCRT

COOPERATING UNITS (if any)

LAB/BRANCH: Computing Facilities Branch

SECTION: Distributed Systems Section, High Performance Scientific Computing Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology, Bldg. 12A, Room 2007, Bethesda, MD 20892-5605

TOTAL MAN-YEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Computing Facilities Branch, the Communications Technology Section of the Personal Computing Branch, and the Scientific Computing Resource Center will collaborate on developing a successor to the Advanced Laboratory Workstation (ALW) system based on the Open Software Foundation's Distributed Computing Environment (DCE), and will also devise and carry out a plan for migrating the ALW system to its DCE successor. Migration to DCE is necessary because DCE, as an emerging de facto industry standard, will eventually supersede the AFS distributed file system upon which the current ALW system is based. Also, DCE will allow us to extend ALW distributed systems technology to the PC, Macintosh, and the Convex and IBM mainframes, thereby advancing DCRT's strategic plan to provide interoperability among these systems.

In FY94, we set up the hardware and software needed for a small DCE test cell, running DCE core services only (no distributed file system).

We played a prominent role in architectural management activities, contributing to the Architectural Management Staff (AMS) retreat, facilitated by the Gartner Group and the AMS NOS and E-mail subcommittees.

We successfully conducted a beta test of netatalk, a free software package developed at the University of Michigan, which enables Apple Macintosh computers to access AFS files. However, security and performance need to be improved before we release it for production use.

We have begun a partnership with UniPress Software, Inc., to add support for AFS to their LAN-Manager for UNIX (LMU) product. If successful, this will enable PCs running DOS and Windows to access AFS files. We have verified that LMU can already read and write AFS files, but that itdoes not perform authentication. We have developed an interface specification between the LMU server and an AFS authentication library, which we will implement.

We received two DCE-based software products: Encina, a distributed transaction monitoring system that can provide connectivity between DOS Windows and UNIX clients and DB2 running under MVS, and DAZEL, a distributed document delivery system. We have not had sufficient staff time to install Encina, which is an extremely complex system. We have installed DAZEL, but have not yet gotten it to work satisfactorily--it is still an immature, overpriced product.

We assisted the newly formed Customer Services Branch (CSB) this year in setting up UNIX servers for an electronic Help Desk support system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CT00250-02 DSB

PERIOD COVERED: October 1, 1993 to September 30, 1994

TITLE OF PROJECT: 3-D Flow Velocity Reconstruction from Color Doppler Ultrasound Images

PRINCIPAL INVESTIGATOR

PI:	D.R. Adam, Ph.D.	Visiting Scientist	DSB, DCRT
OTHERS:	K.M. Kempner	Electronics Engineer	DSB, DCRT
	M.A. Vivino	Electronics Engineer	DSB, DCRT
	E.E. Tucker, M.D.	Medical Officer	CB, NHLBI
	M.Jones, M.D.	Senior Investigator	SLAMS, NHLBI
	T.J. DeGraba, M.D.	Medical Officer	SB, NINDS

COOPERATING UNITS *(IF ANY)*

LAB/BRANCH: Distributed Systems Branch

SECTION:

INSTITUTE AND LOCATION: DCRT, NIH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.50	1.50	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK

Clinical color Doppler ultrasound technology is a popular, non-invasive, real-time, relatively inexpensive imaging modality, which currently allows the 2D visualization of blood flow within the heart and the vascular system. Doppler ultrasound flow velocity measurement is important for the determination of blood/oxygen supply to various organs, of arterial wall shear stress and blood-tissue gas exchange, as well as for the evaluation of myocardial and valvular function.

Initially, we have chosen to concentrate on the structure and flow in the carotid artery, due to the simplifications which this geometry allows. We have assembled instrumentation within a clinical echocardiography laboratory to acquire color Doppler ultrasound images along with time-encoded position/orientation data for the handheld transducer. A carotid artery/neck phantom was designed and fabricated to allow for calibration and testing of both the position/orientation measurement subsystem and the Doppler flow velocity measurement subsystem.

Flow velocity images have been transferred from the HP SONOS 1500 ultrasound system, as separate digital values of structure and flow velocity, onto the Macintosh Quadra 950 microcomputer, which is the heart of our image reconstruction system. All algorithms and procedures for correcting the flow velocity readings have been designed and outlined in detail, and all software has been described in flowcharts.

A patent application, covering the basic algorithm for correcting the color flow velocity measurements, is in process. This project is otherwise, currently inactive at the NIH; however, work in this area is continuing at the Technion in Israel, under the direction of the PI. It is hoped that our contribution may eventually find wide use in the non-invasive measurement of blood flow velocity, in research as well as in clinical practice.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00253-02 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Utilization of Specialized Hardware for DNA Sequence Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.I. Powell	Electronics Engineer	DCRT, DSB
Others:	M. Miller, Ph.D.	Research Chemist	NCI, LEC

COOPERATING UNITS (if any)

LAB/BRANCH: Distributed Systems Branch

SECTION: BioInformatics and Molecular Analysis Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
- ☐ (a1) Minors
- ☐ (a2) Interviews

☐ (b) Human tissues

☐ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

DCRT is making available an Applied Biosystems, Inc. Inherit (tm) system as a shared resource to the NIH intramural research community. This system employs a client/server architecture using an Apple Macintosh computer as the client platform. Scientists can purchase client software from ABI and access the Inherit (tm) system over the NIH network.

To speed results, Inherit (tm) makes use of highly specialized hardware. The Fast Data Finder (FDF) parallel processor can perform parallel pattern matching searches through large databases at a rate of over 15 million characters per second. This speed permits completion in hours of tasks that often require days using powerful UNIX (tm) workstations.

The system is best suited to: (1) assembly of medium to large sequences; (2) searching gene and protein databases for sequence homologies; and (3) rapid searches for genetic motifs such as regulatory elements. An integral pattern description language permits construction of very complex queries. DCRT has provided considerable feedback to ABI to improve the client user interface, and has explored the possibility of porting client software to additional platforms, such as UNIX (tm) workstations or the NIH CONVEX/SGI server.

This project highlights the potential of the NIH network to bring powerful and sophisticated resources through desktop computers to the scientist's benchtop.

Inherit is a trademark of Applied Biosystems, Inc.
UNIX is a trademark of X-Open.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CT00254-01 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Discovery of Novel Human Genes by Automated Sequencing of cDNA Libraries

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.I. Powell	Electronics Engineer	DCRT, DSB
Others:	L. Staudt, Ph.D.	Senior Investigator	NCI
	R.C. Taylor	Computer Specialist	DCRT, DSB

COOPERATING UNITS (if any)

LAB/BRANCH: Distributed Systems Branch

SECTION: BioInformatics and Molecular Analysis Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In an ongoing collaboration with Dr. L. Staudt, NCI, an attempt is being made to discover novel human lymphoid-specific genes by automated DNA sequencing of subtracted cDNA libraries. Software tools developed by DCRT are used to process and place the data into a SYBASE relational database system. These include tools for prescreening cDNA sequence against a local database, automated searching against the nonredundant databases on the NCBI network BLAST server, providing display of the results, and allowing user interaction to select information to be placed into the SYBASE database.

Work is under way to provide software to perform complex motif pattern matching analyses, such as searches for nuclear localization signals, on the cDNA sequences. This software, based on Genobase and its associated toolkit, will permit automated incorporation of results into the SYBASE database, with a graphical user interface for input and editing of search parameters.

To date, thousands of cDNA sequences have been analyzed, yielding homologies to a variety of proteins, including transcriptional regulators, signal transduction proteins and membrane receptors. Work is in progress to expand the scope of the database to include laboratory management information and data from other sources, such as northern blots.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00255-01 DSB

PERIOD COVERED

October 1, 1993 to September 30, 1994

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

A Critical Evaluation and Comparison of Computerized Sequence Analysis Programs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.I. Powell	Electronics Engineer	DCRT, DSB
Others:	M. Miller, Ph.D.	Research Chemist	NCI, LEC

COOPERATING UNITS (if any)

LAB/BRANCH: Distributed Systems Branch

SECTION: BioInformatics and Molecular Analysis Section

INSTITUTE AND LOCATION: Division of Computer Research and Technology

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

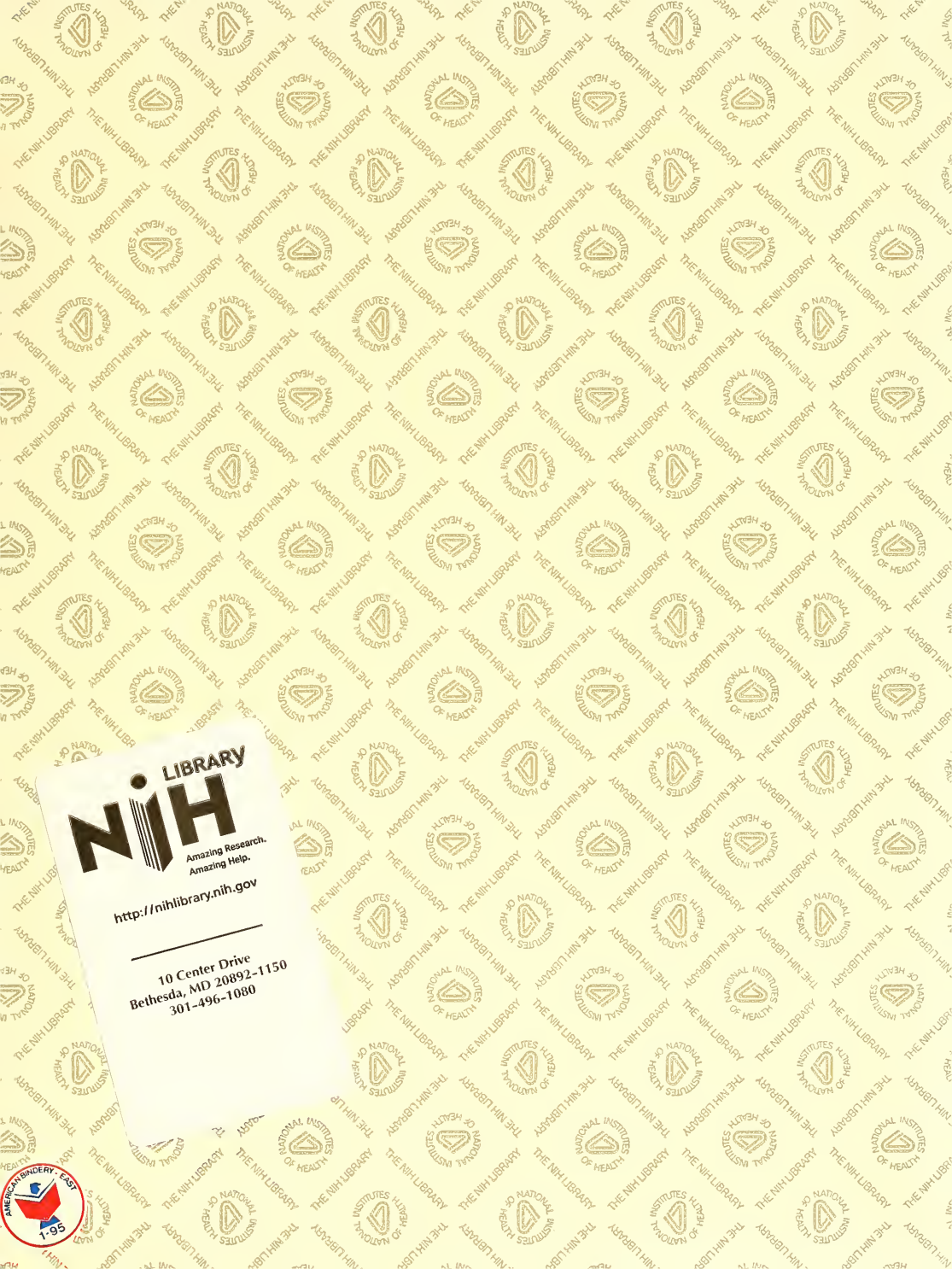
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In collaboration with Dr. M. Miller, NCI, a critical, quantitative analysis was done of several commercial sequence assembly and analysis packages. A fundamental problem in contemporary molecular biology is the determination and interpretation of DNA sequences. Due to limitations of current sequencing technology, sequence determination entails the piecing together of short, overlapping sequence fragments into a single, long contiguous sequence. A number of commercial computer programs have been marketed to automate this process. While reviews of individual packages have been published, this is the first known study that critically compares the accuracy of assembly by these programs.

Eleven programs were selected, primarily on the basis of their availability on the NIH campus. Sequence data is not random, but contains ordered repeated sequences. Likewise, errors in sequencing determinations are not randomly distributed. In order to provide a controlled and realistic dataset for measuring performance and accuracy, a known sequence, the rat multidrug resistance gene (RATMDRM, 5254 base pairs, accession number M62425) was split into 58 random overlapping fragments of 200 to 400 base pairs in length. These were then randomly seeded with 0 to 15% error based on the error distribution of the fragments originally used to determine the sequence. Errors were in the form of miscalled bases, deleted bases or added bases.

The programs tested fell into three general groups based on accuracy. In order to rule out conditions unique to the chosen test sequence, four other sequences of between 4500 and 4600 base pairs were used to repeat the tests. With one exception, the error rates were comparable to those encountered using RATMDRM. Additionally, some programs were tested with different permutations of RATMDRM to ascertain their capacity to properly assemble the sequence regardless of the order of input of the fragments. Ease of editing the assembled sequences was also compared. Results of this study were accepted for publication by the Journal of Biological Computation.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http://nihlibrary.nih.gov
10 Center Drive
Bethesda, MD 20892-1150
301-496-1080