

ANNUAL REPORT FOR 1967 ON

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Center for Theoretical Biology

Faculty of Health Sciences

State University of New York at Buffalo

4248 Ridge Lea Road

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I. INTRODUCTION.

This grant has again been used principally as seed money to promote the activities of a number of working parties. In this connection, we have supported some secretaries and other support staff, paid graduate student stipends, brought in outside consultants and paid part salary for some faculty members. The number of faculty members concerned has increased during the year from 30 to 33. We have had four visiting professors, nine post-doctoral associates, and nine graduate students. Sixteen departments now participate in the work of the Center.

The most noteworthy event of the year not included in the bulk of this report, has been our move to 4248 Ridge Lea Road, a building designed for our purposes. We have thus been able to bring together all our working parties and expect valuable interaction between members of the working parties to develop. The Office of Planning and Development of the University has done an excellent job in providing for our needs.

We benefitted substantially by a visit from our Advisory Committee, a copy of whose report immediately follows this introduction.

Dr. J. F. Danielli

Dear Dr. Danielli,

At our visit to the Center for Theoretical Biology on February 2, 1967 we were impressed by the stature and approach of your interdisciplinary program. It is, without serious doubt, destined to become influential in leading the study of living things out of the semi-empirical stage and into one in which the theoretical development of principles will guide instruction and research and lead to discovery. The financial support on which you have built this very promising program needs a widerbase. It is our suggestion that the time has come for a grant in the nature of those awarded for "centers of excellence" to be secured. Your program is ideal for it and, with care, it should succeed. Your contribution to the teaching of biology, both undergraduate and graduate, should be encouraged and it would be hoped that the University could find additional support for this endeavor.

Otto W. Schmitt

Otto Schmitt

Mones Berman

Mones Berman

Howard W. Emmons

Howard Emmons

Ernest Pollard

Ernest Pollard

Terrell L. Hill

Terrell L. Hill

II. ORGANIZATION OF THE CENTER FOR THEORETICAL BIOLOGY

Director, J. F. Danielli

Assistant Director, K. N. Leibovic

The business of the Center for Theoretical Biology is carried on through the work of a number of committees with academic and administrative responsibilities.

The names of these committees, their terms of reference and their membership are given below:

The Executive Committee is concerned with the general nature of the program of the Center, with the maintenance of relationships with Departments, and with general budgetary policy. The Committee consists of:

J. F. Danielli - Chairman

A. I. McMullen

I. H. Shames

F. M. Snell

D. Tamari

D. A. Yphantis

The Academic Advisory Committee is concerned with the academic policy of the Center, academic research programs, teaching activities and post-doctoral training. The Committee consists of:

J. F. Danielli - Chairman

K. N. Leibovic - Co-chairman

D. J. Cadenhead

J. Hamann

K. Jeon

H. Landahl

A. I. McMullen

R. Rein

R. Rosen

D. J. Triggle

V. S. Vaidhyanathan

The Seminar, Library and Publications Committee is responsible for scheduling seminars, special lecture series and symposia, administering the library, including the purchase of books and periodicals and edit Center for Theoretical Biology publications, such as the Center for Theoretical Biology Quarterly Bulletin, which is to appear shortly. The Committee consists of:

K. N. Leibovic - Chairman

P. B. Bright

N. Findler

R. J. Good

J. Hoffman

A. Isihara

R. A. Jensen

D. A. MacGillivray

A. I. McMullen

C. Saltarelli

D. J. Triggle

The Budget Committee meets quarterly to discuss appropriations and expenditures of funds provided for the Center. The Committee consists of:

J. F. Danielli - Chairman

H. Collins

P. Ford

K. N. Leibovic

D. J. Triggle

R. J. Wagner

The General Purposes Committee meets once each month and is responsible for all services and supplies. The Committee consists of:

H. Collins - Chairman

P. Ford

K. Maher

R. J. Wagner

The External Advisory Committee is a group of distinguished outside consultants who meet once a year at the Center for Theoretical Biology to evaluate the progress of the Center and advise on future plans. The Committee Members are:

M. Berman

H. W. Emmons

T. L. Hill

E. C. Pollard

O. Schmitt

III. FACULTY AND FIELDS OF INTEREST

Professors:

Eric A. Barnard	Active centers of enzymes, properties of enzymes in cells
James F. Danielli	Membrane phenomena, cell theory, cytoplasmic inheritance, relational biology
Robert J. Good	Surface chemistry and physics
Joseph G. Hoffman	Quantitative measurement of heat released by mammalian tissue cells
Akira Isihara	Statistical mechanics
Arnold I. McMullen	Theoretical aspects of the physics of intra- and intermolecular interactions
David Pressman	Biochemistry and immunology
Irving H. Shames	Continuum mechanics
Fred M. Snell	Transport and membrane phenomena, nonequilibrium thermodynamics, theoretical biology
Dov Tamari	Algebra; furthering mathematical thought in biology
Sol W. Weller	Heterogeneous and homogeneous catalysis; chemical reaction kinetics
David A. Yphantis	Biology

Associate Professors:

Robert Abbott	Surface physics; physisorption and chemisorption of molecules and macromolecules on solid surfaces
G. R. Blakely	Population studies

David A. Cadenhead	Surface chemistry-monolayer studies and molecules of biological interest
Mac S. Hammond	Linguistics and poetics
K. Nicholas Leibovic	Processes of communication and control in biological systems, especially the central nervous system
A. D. MacGillivray	Perturbation theory, including its application to macromolecular systems
Donald C. Mikulecky	Membrane phenomena; nonequilibrium thermo-dynamics transport across biological membranes
Charles Paganelli	Transport across biological membrane
Robert Rein	Quantum chemistry of organic and biomolecules
Robert Rosen	Biological systems analysis
David J. Triggle	Theories and mechanisms of drug-receptor interactions, receptor isolation
V. S. Vaidhyanathan	Statistical mechanics, membrane transport interfacial physics, mathematical biophysical chemistry

Assistant Professors:

Moises Derechin	Protein structure. Relation between configuration and activity
Kwang W. Jeon	Cytology and cell physiology
John F. Moran	Mechanisms of Drug Action, Deuterium isotope; effects in biological systems; receptor isolation
Dorita A. Norton	X-ray studies in sterols

Shinpei Ohki	The structure and the permeability of membranes
Armin H. Ramel	Biochemical Pharmacology
Cora G. Saltarelli	Physiology and genetics of pathogenic yeasts; bioengineering
Robert A. Spangler	Irreversible thermodynamics, biological transport processes
Darold C. Wobschall	Electrical properties of membranes and organic semiconductors

Research Associates:

John D. Abernethy	Central nervous system and sensory communication
Luigi M. Bianchi	Central nervous system and sensory communication
Peter B. Bright	Theoretical foundations of transport phenomena for the study of neuronal membranes
Shym S. Chatterjee	Medicinal organic chemistry
Mary Danielli	Anthropological studies bearing on man's control of environment and of his reaction to it.
Jon R. Hamann	Structure of Science, Pharmacology, Quantum Theory
Marian May	Estrogen receptor isolation and identification
Fred Ridley	Medicinal organic chemistry; heterocyclic synthesis; drug-receptor interactions
Joan Lorch Staple	Nucleo-cytoplasmic relationships in protozoa and other cells.

Graduate Assistants:

Howard Allen

John Bircher

John Borst

Michael Davids

Richard Demchak

Joseph Goren

Joel Pursner

Lyn Spees

Miki Wadati

Visiting Professors:

Alan Goldup

Lipid bilayers

Herbert Landahl

Mathematical biology

Hugo Martinez

Central nervous system models

Paul Weiss

Developmental biology, specifically
neurogenesis

Consultants:

Narendra Goel

Statistical mechanics

Sasa Svetina

Intermolecular forces, cell-cell
interaction, quantum and statisti-
cal mechanical study of DNA

Martynas Ycas

Molecular biology and cell physi-
ology

SUPPORT STAFF

Harry Collins

Paulette Davis

Dennis DeGweck

Priscilla Ford

Thomas Maddocks

Kathleen Maher

LaVerne O'Neil

Noreen Ritchie

Margaret I. Smith

Le-I Su

Robert Wagner

Evelyn M. Wood

Charles J. Volk

Laboratory Manager

Key Punch Operator

Computer Programmer

Administrative Assistant

Instrument Maker

Supervising Secretary

Secretary to Director

Literature Searcher

Secretary to Assistant Director

Computer Programmer

Accountant

Artist

Photographer and Model Builder

Technicians:

Mary O'Hagen

Ruth Morgan

Lorraine Powers

Eleanor Sattler

Secretaries:

Betty Barry

Ursel Busch

Lee Gordon

Ruth Harvey

Enez King

Ruth Kuhfahl

Doris Mertens

Alice Richards

IV. RESEARCH REPORTS

ANNUAL REPORT FROM WORKING PARTY ON QUANTUM BIOCHEMISTRY

1. DEFINITION OF FIELD OF INTEREST:

This research program is mostly, but not exclusively, concerned with electronic and quantum mechanical aspects of biological systems on the molecular and macromolecular level. The quantum mechanical studies are performed primarily to obtain the ground state and its properties for different biological molecules. These are used to evaluate interactions between various such molecules. From here biological inferences, in some cases enhanced by the use of statistical mechanical methods, can be made.

2. FINANCIAL SUPPORT:

The group activities were financed in large measure through the National Aeronautics and Space Administration (Grant NGR 33-015-016), the National Institutes of Health (Grant GM 11603), another grant for computations from the National Institutes of Health FR-00126, and a grant from the United Health Foundation of Western New York (G-GG-UB-12). In addition, support of certain group activities were added through an Intramural Grant of the University of California at Riverside.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

Robert Rein

Working Party Chairman
Principal Cancer Research Scientist
Dept. Exp. Path., Roswell Park
Memorial Institute and Dept. of
Biophysics, School of Pharmacy

Frank E. Harris	Associate Professor of Chemistry Stanford University, California visiting C.T.B. (1 month)
Michael Pollak	Associate Professor of Physics University of California, Riverside visiting C.T.B. (2 months)
George A. Clarke	Assistant Professor of Chemistry Dept. of Chemistry
Jon Hamann	Assistant Research Professor
Sasa Svetina	Cancer Research Scientist Dept. Experimental Pathology Roswell Park Memorial Institute Permanent affiliation: Institute Joseph Stephan, Ljubljana, Yugoslavia
Nobuo Fukuda	Research Associate, School of Pharmacy Permanent affiliation: National Institute of Radiological Sciences, Japan (7-1-65 -- 7-1-67)
Narendra Goel	Assistant Professor of Physics University of Rochester Consultant
Mitja Rosina	University of Ljubljana, Yugoslavia visiting C.T.B. (1 month)
Harry King	Associate Professor of Chemistry Dept. of Chemistry (summers '66 and '67)
Keith M. Wellman	Assistant Professor of Chemistry Dept. of Chemistry
Philip Cota	Research Assistant Dept. of Biophysics

Dennis DeGweck

Computer Programmer

Michael Davids

Research Assistant
Dept. of Mathematics

David L. Harris

Research Assistant
Dept. of Chemistry

Collaborators from Other Institutions:

Pierre Claverie

Laboratoire Chimie Quantique
Institut Biologie Physico-Chimique
Paris, France

Jost Manassen

Department of Polymers
Weizmann Institute of Science
Rehovoth, Israel

M. May

Department of Chemistry
New York University, New York

Distinguished Visiting Professors: Professor Per Olov

"Lowdin, from the University of Uppsala, Sweden and University of Florida, Gainesville, Florida was the guest of the Quantum Group for a few days in February '67. Professor Lowdin addressed a joint seminar of the Center and the Departments of Chemistry, Biology and Biophysics; and spoke about his recent work in the field of Quantum Biology. The scientific program included also a colloquium on the research program of the group, followed by extensive discussions with Professor Lowdin.

Professor Robert G. Parr from John Hopkins University during his visiting Professorship in Theoretical Chemistry in Buffalo, spent generously from his time with members of the group for discussions concerned with current research programs.

Professor Joshua Jortner from the University of Tel-Aviv, Israel, and University of Chicago visited at the Center in October and presented a seminar on his recent work on charge transfer complexes.

4. RESEARCH PROGRAM:

A considerable effort has been directed toward the semi-empirical approaches of molecular orbital theory. Especially emphasized were the development and evaluation of molecular orbital methods for the treatment of the complete electronic structure of substituted purine and pyrimidine bases. Various ground state properties of chemical and physical interest were obtained and correlated with experimental data. This work has now been extended to amino acids, where one of the aims is to study quantitatively the relationship between electronic and structural factors and acidity (p K).

Another major area of our interest is the theory of intermolecular interactions. These interactions, including hydrogen bonding and stacking, play a significant role in the stabilization of ordered macromolecular configurations. Thus the calculation of these forces often represent a first step toward a quantitative theory of macromolecular stability.

The physical nature of these forces are not simple in the sense that the electron systems of the interacting molecules are not exactly separable. In addition, the dipole approximation of the conventional London technique also fails here. We were thus concerned with the development of more appropriate computational methods for the treatment of interactions in the weakly overlapping range. These methods have been applied to the study of various interactions in DNA. For example, the stacking interactions between the bases for all possible configurations have been calculated. Other interesting applications of the technique involve the study of the energetics of the Crick Wobble hypothesis and the energetics of various hydrogen bonding schemes. Further aspects of hydrogen bonding were also under investigation and included an analysis of the proton vibrational states in the hydrogen bonds connecting the DNA bases. As a first step in the investigation of water structure and solvation effects, a study of hydrogen bonding between water molecules was begun.

Another area of our research interest is in the development of theories which connect the microscopic interaction energies with macroscopic observations. To this end we used an extension of the Ising model to analyze experimental melting curves on synthetic DNA-like polymers. The stacking energies obtained from this analysis are in good agreement with the values calculated by quantum mechanical methods.

A. Iterative Extended Hückel Theory (IEHT) (G. Clarke, F. E. Harris, R. Rein)

An iterative extended Hückel theory approach, based in part on an earlier procedure, has been applied to the study of a wide range of diatomic and polyatomic molecules in order to investigate and characterize the properties of the iterative method, and hopefully, obtain some insight into the general aspects of molecular electronic structures. A reliable semi-empirical method - one which incorporates at least all of the valence electrons in a reasonably self-consistent fashion - would undoubtedly be of the greatest utility for the wide range of problems in chemistry and biology presently beyond the reach of good ab initio calculations.

The procedure is basically one which allows each of the atom orbitals in the molecule to be represented by one or two Slater-type basis functions with pre-set effective nuclear charges and linear coefficients. All overlap integrals and dipole integrals are calculated exactly and the Hamiltonian matrix is initially determined with "optimized" coulomb parameters and resonance integrals estimated in the Cusachs approximation. Atom charges, based on single center contributions and two center contributions determined from projections of overlap charge centroids on to a line joining the centers, are determined and serve the iterative procedure by allowing the coulomb parameters, (and therefore the resonance parameters) to be modified by the output

charges of a previous calculation. The coulomb parameter for each orbital is assumed to be a linear function of the net atom charge, i.e. $\alpha_{ii} = \alpha_{ii}^0 + q_i \Delta \alpha_{ii}^0$ with $\Delta \alpha_{ii}^0$ an empirically adjusted orbital parameter. Calculations are repeated with adjusted parameter sets until the atom charges of two successive calculations agree to within a preset value (0.01e).

Extensive calculations with various C, N, H, and O containing compounds indicate that Slater rule orbital exponents ($Z_{\text{Hyd}} = 1.2$) with adjusted Clementi - Cusachs and Reynolds valence state orbital energies (and $\alpha_{\text{Hyd}} = -11.6$) are adequate to satisfactorily reproduce most molecular ionization potentials and dipole moments with single orbital basis sets. Calculations were carried out on the following types of polyatomic molecules: alkanes, alkenes, alkynes, amines, cyanides, nitrogen and oxygen heterocycles, alcohols, acids and ketones. In general we find rather good agreement between the experimental and calculated dipole moments and ionization potentials with the characteristic trends adhered to; also reasonable (order of magnitude) barriers and good correlations between calculated and experimental substituent effect (charges, etc.) can be obtained.

Applications of the method to specific problems of physical and chemical interest follow. Further work is in preparation for publication.

References: Robert Rein, Nubuo Fukuda, Htain Win, George A. Clarke and Frank E. Harris, J. Chem. Phys., 45, 4743 (1966).

B. Modified CNDO2 Method (J. Hamann, D. DeGweck, R. Rein)

A previously developed semiempirical SCF-LCAO-MO model, namely the CNDO/2 method of Pople and Segal, in both a closed shell Restricted Hartree-Fock formulation and an open shell Unrestricted Hartree-Fock formulation, is being extended and adapted for the SUNYAB IBM 7044 computer. The program has been linked to the IEHT program. Hence the CNDO/2 calculation begins with a set of starting coefficients obtained from the Hückel calculation and continues until self-consistency has been achieved. The principle merit of the CNDO/2 method relative to the extended Hückel approach is that there is included an explicit, albeit approximate, consideration of electron interaction.

C. Electronic Structure of Nucleotide Bases (R. Rein, N. Fukuda, G. A. Clarke, J. Hamann, and F. E. Harris)

Iterative Extended Hückel and Complete Neglect of Differential Overlap calculations are made for adenine, cytosine, guanine, thymine, and uracil. An extensive comparative analysis of these total valence electron models, relative to the π -electron methods conjoined to a simple σ -electron model, have been performed. The results are qualitatively similar throughout. There are quantitative differences, however, including, for example, the predicted order of the ionization potentials.

D. Studies of the Electronic Structure of Amino Acids and Peptides by Means of the Iterative Extended Hückel Theory (R. Rein and P. Cota)

Earlier MO Studies of peptides have considered only the pi-electronic structure (Evans, M. G., and Gergely, J. (1949); Biochimica et Biophysica Acta 8, 188-197; Yomosa, S. (1964): Biopolymers Symposia 1, 1-33). This approach, although useful in investigating such problems as energy banding, is not appropriate for studying properties which depend on complete electronic structure. Recently, MO methods which include sigma as well as pi-electrons have been developed which lead to more satisfactory calculations of these properties. One such method, the Iterative Extended Hückel Theory (Rein, R., et al (1966): Journal of Chemical Physics, 45, 4743-4744), is used to study the electronic structure of a representative group of amino acids and peptides. Specifically, 1) the predictive value of the theory is evaluated by studying the correlation between theoretically calculated and experimentally determined values of dipole moment and ionization potential, and 2) theoretical studies of the effect of substituent groups on acidity and correlations between indices of calculated electronic structure and measured pK values are presented and discussed.

E. Water and Its Dimers in the Iterative Extended Hückel Theory Approximation (G. A. Clarke, F. E. Harris and R. Rein)

The IEHT method described previously, with some further modifications including the handling of overlap charges, and allow-

ing for an expanded orbital basis set, has been used to study the electronic structure of a water molecule and some water dimers. We find the method gives an adequate description of the equilibrium properties of the water molecule excepting the energy variations with respect to bond distance. The calculated equilibrium angle, dipole moment and ionization potential are 100° , 2.23 debyes and 10.63 ev., respectively, compared with the experimental values of 104.46° , 1.85 debyes and 12.85 ev.

For the planar dimers, at fixed oxygen-oxygen distances, a single energy minimum is found for the proton potential function. However, the physical implications of this finding is uncertain. Another interesting feature of the dimer calculations is the observation of charge transfer through the hydrogen bond.

F. Electronic Structure and Conformational Isomerism of Polyenes: Applications to Carotenoids and Visual Pigments (R. Rein and J. Manassen)

The Chemistry of Polyenes is of considerable interest in view of the role which compounds such as carotenoids vitamin A, rhodopsin and related molecules play in living processes. The problem of conformational isomerism of these compounds is of particular interest. An insight into the structural factors influencing the relative stability of the various isomers, as well the quantitative features of the isomerisation process, may be of substantial value for understanding the nature of biochemical processes in which these molecules play a role. Earlier investigations of the electronic structure of this class of compounds

were mostly restricted to π electron methods. This restriction limited the consideration of the conformational problem to a qualitative level.

As a first step in this on this project we are now calculating the electronic structure and rotational potential functions for a few simpler model compounds. In this connection we are making use of both semi-empirical and more sophisticated Gaussian ab-initio methods.

G. Study of Amidines and Related Compounds (D. L. Harris and K. M. Wellman)

We are in the early stages of a research project designed to apply extended molecular orbital theory to determine the kinetic and thermodynamic properties of amidines, guanidines and biguanidines and their conjugate acids. The early goal of the M. O. calculations is the correlation of the electron densities with the experimentally determined protonation sites and rotational barrier about certain C-N partial double bonds. The position of mono- and di-protonation of amidines, guanidines biguanidines have been experimentally determined in our laboratories. In addition we have determined the energy barriers to rotation about the C-N partial double bonds in amidines(I) and amidinium ions(II) as a function of the phenyl substituent, X. Since the rotational barriers have been shown to give excellent Hammett plots, the M.O. calculations will provide a rare theoretical probe into the basis of linear free energy relationships. Finally, the trans-cis

equilibrium, IIA $\rightleftharpoons$ IIB, represents an unusual experimental study of competing steric and electronic interactions which should be amenable to the sophisticated calculations used in this work. The calculations will be done using the most up to date IEHT and Pople's CNDO2 program.

H. Methods for Calculation of Intermolecular Interaction Energies (R. Rein, M. Pollak and P. Claverie)

A method for the calculation of interaction energies between molecules has been developed. Particular emphasis was given to computational applicability, and most specifically to large molecules for which wave functions are known in the Pariser-Pople-Parr approximation. The important constituents of biopolymers are in this category. The method is an application and extension of methods previously developed by Coulson's and Hirschfelder's groups. The electrostatic, polarization, and dispersion energies are calculated for the π electron and the σ electron systems, the exchange energy is also calculated, but for the π electron system only. The knowledge of the perturbation of the electronic systems by an electric field is needed for the calculations of the polarization and dispersion energies. Where possible (π electrons), this is obtained theoretically; elsewhere (σ electrons) from experiments on polarizability of bonds. Work done in collaboration with the University of Uppsala, University of California at Riverside, and University of Paris.

References: R. Rein and M. Pollak, J. Chem. Phys. 47, 2039 (1967);

M. Pollak and R. Rein, J. Chem. Phys. 47, 2045 (1967);

R. Rein, P. Claverie and M. Pollak, Intern. J. Quant. Chem., in press.

I. Interactions Between Bases of Nucleic Acids
(M. Pollak, R. Rein and P. Claverie)

The above methods have been applied to study various interactions between the bases. The interactions of stacking between bases in the usual DNA configuration were computed for all possible configurations. They include all the possible single stranded and double stranded dimers and trimers which can occur in DNA. The horizontal interaction energy of bases was evaluated both for Watson-Crick and for Hoogsteen configurations. The results are consistent with observations. Other possibilities of horizontal interaction, such as the interactions in Löwdin's replication plane, have also been investigated. Work done in collaboration with University of California at Riverside.

Reference: M. Pollak and R. Rein, J. Theor. Biology 11, 490 (1966);

M. Pollak and R. Rein, Abstracts, II Internat. Biophys. Congress (1966); R. Rein, A. I. McMullen, and M. Pollak, Ibid.

J. Comparison with Experiments - Denaturation of DNA
(N. Goel, N. Fukuda and R. Rein)

Since the well known phenomenon of DNA denaturation depends exactly on those interaction energies which we calculated by quantum mechanical methods, the melting experiments were used to provide a test for the calculations. For that purpose a theory

was developed which connects the macroscopic observations with the microscopic interaction energies. The theory is an extension of the Ising model. The correspondence between the values thus obtained from melting data and those obtained from quantum mechanical calculations is good. In collaboration with University of Rochester.

References: N. Goel, N. Fukuda, and R. Rein, in press J. of Theor. Biology; R. Rein, N. S. Goel, N. Fukuda, M. Pollak and P. Claverie, in press, Annales N. Y. Academy of Sciences.

K. Minimum Energy Configurations (M. Pollak and R. Rein)

Our most refined theory for the interaction energies was programmed in such a way that configurations could be automatically varied in a predetermined way, the interaction energies computed for each configuration, and the configuration with the least energy automatically selected. In this way it is not only possible to determine the interaction energies of known configurations, but also to find unknown stable configurations. The technique was applied to determine whether the Wobble configurations, which were proposed by Crick to account for the degeneracy of the biological code, are feasible from energy considerations. The results justify Crick's proposal. In collaboration with the University of California at Riverside.

References: M. Pollak and R. Rein, J. Theor. Biology, in press.

L. Electrically Induced Denaturation of Biopolymers
(M. Pollak and R. Rein)

Collaboration was initiated on a project which is under way at the University of California at Riverside. The project further explores the predicted possibility that electric fields may cause partial denaturation in biopolymers. In DNA this partial denaturation should closely resemble the process of biological replication, as it is believed to occur. The phenomenon of electrical denaturation is of interest both on account of its resemblance to the process of biological replication of DNA, and because it is likely to be of great use in the study of physical properties of biopolymers.

References: M. Pollak and R. Rein, J. Theor. Biology, in press.

M. Study of the Hydrogen Bonding in DNA
(S. Svetina and R. Rein)

The existing data (Rein-Harris) on the potential surface for the two protons in hydrogen bonds of the guanine-cytosine and adenine-thymine base pairs of DNA have been used to study the proton vibrational problem. The numerically given potential surfaces were fitted with a polynomial up to the sixth order in the coordinates of both protons. The approximate solution of the Schrodinger equation for the system was obtained using a linear combination of the products of the infinite square well potential wave functions of the two protons. The results have been compared with the existing infrared data, as well as used to determine different configurations of hydrogen bonded base

pairs. The results of this work have been presented in "Slater Symposium" in Sanibel Island, January 1967, and in R. Rein and S. Svetina, in press, International J. of Quantum Chemistry.

N. Study of Polyelectrolyte Solutions (S. Svetina and R. Rein)

In order to understand better and consequently improve different existing models of polyelectrolytes, a theoretical physico-chemical study of multiply ionized ions in electrolyte solution, as are for instance bolaform ions, is in progress. The numerical method is being developed to determine the average electric potential due to known fixed charges embedded in electrolyte solution with the use of Poisson-Boltzman equation approximation, with the aim to use these data for the determination of activity coefficients.

O. Calculation of Molecular Properties by Direct Variation of the Reduced Two-Particle Density Matrix (M. Rosina, S. Svetina, H. King, M. Pollak and R. Rein)

The quantum mechanical calculation of ground state and some excited state properties of molecular systems would be revolutionized if a practical solution of the N-representability problem were discovered.

A project is underway which aims to promote the search for an exact solution to the N-representability problem, but with the more immediate purpose of exploring expedient, less rigorous solutions based on necessary but insufficient conditions on the 2-matrix. Following earlier suggestions by Bopp, Coleman, Garrod,

Percus and others, computations are being carried out to study the effect of various constraints on the 2-matrix.

The first alternative being explored for the lithium hydride molecule is to restrict the 2-matrix to obey the usual symmetry and normalization conditions as well as constraints on the eigenvalues. Further studies are to include conditions on Garrod's G matrix.

P. Calculation of Molecular Properties by Hartree-Rock Theory Using Gaussian Basis Functions (H. King and C. D. Ritchie)

A computer program has been written to calculate accurate LCAO-MO-SCF wave functions for small molecules. The basis functions are Gaussian s- and p-type functions or fixed linear combinations of these. Calculations have been carried out for a number of small molecules to determine optimum choices for parameters. Special features of the computer program make it especially efficient for the computation of potential energy surfaces.

The program has been used to compute accurate surfaces for proton transfer in simple systems such as hydrogen molecule hydroxide ion, and methane-hydride ion, also for the ionic interaction of lithium ion-hydroxide ion.

V. PUBLICATIONS, PAPERS AND SEMINARS.

R. Rein

1. "Molecular Orbital Studies of Intermolecular Interaction Energies." Part I. On the Role of π Electrons in Intermolecular Interactions with Some Application to DNA. Rein, R., and Pollak, M., J. Chem. Phys., 47, 2039 (1967)
2. "Molecular Orbital Studies of Intermolecular Interaction Energies." Part II. Approximations Concerned with Coulomb Interaction and Comparison of the Two London Schemes. Pollak, M. and Rein, R.
3. "On the Calculation of Van der Waals-London Interactions in a Monopole-bond Polarizability Approximation with Application to Interaction between Purine and Pyrimidine Bases Rein, R., Claverie, P., Pollak, M., In press, International J. of Quantum Chemistry
4. "Theory of Intermolecular Interactions: The Long Range Terms in Dipole-dipole, Monopole-dipole and Monopoles-Bond Polarizabilities Approximations.", Claverie, P. and Rein, R. To be submitted International Jour. Quantum Chemistry
5. "On the Calculation of Stacking Energies in DNA.", Rein, R., Goel, N. S., Fukuda, N., Pollak, M., and Claverie, P., In press, Anales N. Y. Academy of Sciences
6. "A Semi-empirical Analysis of Stacking and Bond Energies in DNA." Goel, N., Rein, R., and Fukuda, N., Abstracts 154 A.C.S. meeting, Abstract V121.

7. "A Semi-Empirical Analysis of the Melting Curves of Synthetic DNA Molecules and the Calculation of the Stacking and Pairing Energies and Entropies in DNA."
Goel, N., Fukuda, N. and Rein, R., In press. J. of Theor. Biology
8. "An Examination of the Energetics of Crick's Wobble Hypothesis.", Pollak, M. and Rein, R., In press. J. of Theor. Biology
9. "An Electrical Mechanism for Strand Separation in DNA."
Pollak, M. and Rein, R., In press. J. of Theor. Biology
10. "The Two Proton Vibrational States in Nucleic Acid Hydrogen Bonds.", Rein, R. and Svetina, S., In press, International J. of Quantum Chemistry

VI*. Meetings:

Dr. Rein presented papers at the following meetings:

1. International Symposium on the Quantum Theory of Atoms Molecules and Solids, Sanibel Island
2. New York Academy of Sciences on π -electron Interactions, New York City
3. Eurochem Conference on Hydrogen - Bonding, Elmau, Germany
4. American Chemical Society 154 meeting, Chicago, Illinois

Dr. Clarke presented papers:

1. American Chemical Society 154 meeting, Chicago, Illinois.

Dr. Sasa Svetina attended:

1. Winter Institute in Quantum Chemistry at the University of

Florida, Gainesville and Sanibel Island, Florida.

2. Symposium on Density Matrixes, University of Queens,
Kingston, Ontario, Canada.

VII. Contribution to University Teaching:

Direction of graduate students by R. Rein

VIII. Miscellaneous Activities;

Dr. Rein Visited the Weizmann Institute of Science,
Rehovoth, Israel during the spring semester and presented
a graduate course (40 hours) on selected Topics in Quantum
Chemistry.

Dr. Rein presented invited lectures in a number of other
laboratories including:

1. Institute Joseph Stephan, Ljubljana, Yugoslavia
2. University of California, Berkeley, California

Further laboratories visited by Dr. Rein were:

1. University of California, Riverside, California
2. Laboratoire Chimique Quantique, Institute de Biologie
Physico-Chimique, Paris
3. Max Planck Institute fur Physik und Astrophysik, Gruppe
Quantenchemie München, Germany
4. Institute Boris Kidric, Bergrad, Yugoslavia

ANNUAL REPORT FROM WORKING PARTY ON
THE STUDY OF MACROMOLECULES

1. DEFINITION OF FIELD OF INTEREST:

A theoretical study of the role of electrostatic free energy on macromolecule interactions in biological systems, especially the 'DNA helix-coil transition'.

2. FINANCIAL SUPPORT:

N.A.S.A. Grant No. NGR 33-015-016

N.I.H. Grant No. GM 11603

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

A. I. McMullen, Working Party Chairman
Professor, Biophysics, Department,
School of Pharmacy

A. D. MacGillivray, Mathematics Department

4. RESEARCH PROGRAM:

Work continued on developing the theory for calculations of electrostatic free energy of the 'helix' and 'coil' format of DNA-type polyelectrolytes. A 'banded' model with an axial periodicity of charge has been used in obtaining results for the melting of 'poly AT' and is presently being supplanted by a more sophisticated model with helical axial periodicity. This gives a more complex problem involving the solution of three differential equations instead of two and consequently the trial-and-error determinations of the constants of integration are very time-consuming. The problem is only partly solved as yet.

Preliminary 'in vacuo' calculations have been made on the transfer-messenger RNA geometry, according to the hypothetical model of Fuller and Hodgson (1) in order to 'correct' the codon-anticodon binding energies calculated by Nash and Bradley (2) on an erroneous geometry. This work is in the preliminary stages. A CRE (Cambridge Repetition Engineers) model of the PHE-TYR messenger-transfer interaction complex has been built and is being employed for the calculations in question.

CRE models of lysozymes and myoglobin have also been built from co-ordinate data supplied by Prof. Phillips (Oxford) and Dr. Kendrew (Cambridge) and preliminary work is proceeding on the building of a 'working' model of haemoglobin. This will comprise 2 pairs of α - and β -subunits containing only the charged atoms and will be rotatable around the four axes according to the data of Perutz (3). A program is being constructed to calculate (in vacuo) the electrostatic energy during these rotations, from the structure with oxygen liganded, to the structure without oxygen. [References (1): Nature (1967) 215, 817. (2): Biopolymers (1965) 3, 261. (3): J. Mol. Biol. (1967) 28, 117.]

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Theory of helix-coil transitions based on the non-linear Poisson-Boltzman equation", A. D. MacGillivray and A. I. McMullen. In press J. Theoret. Biol.

2. "The electrostatic free energy of macromolecular systems",
A. I. McMullen, N. Y. Acad. of Sciences Conf. in Electronic
Aspects of Biochemistry, 1967, New York.
3. "The role of dimension on the behavior of solutions of the
Poisson-Boltzman Equation", A. D. MacGillivray, submitted
to J. Theoret. Biol.

6. MEETINGS:

A. I. McMullen visited Dr. Phillips laboratory at Oxford, Dr. Perutz's laboratory at Cambridge, and obtained the most recent, unpublished x-ray crystallographic data on lysozyme and myoglobin for use as described above. He arranged for Mrs. Browne, of Dr. Phillips laboratory, to visit Buffalo for three weeks during August to organize a "Summer School for Molecular Model Building" in co-operation with the Institute for Crystallography, RPMI. A separate report on this successful course is available. Dr. North from the Oxford laboratory also visited to consult and deliver a seminar on lysozyme structure and activity. Professor A. E. Alexander from the Chem. Dept., University of Sydney, Australia, also visited on a consultancy basis for three weeks during June, to discuss problems in surface and colloid chemistry with various groups within the University and the Center for Theoretical Biology. From this visit emerged the engagement by the Center for Theoretical Biology of one of his post-doctorates who joins the group in September 1968.

8. MISCELLANEOUS ACTIVITIES:

1. Center for Theoretical Biology Executive Committee
2. Center for Theoretical Biology Academic Committee
3. Center for Theoretical Biology Sub-Committee on Education
4. Center for Theoretical Biology Seminar, Library and Publications Committee.
5. Macromolecule Study Group

ANNUAL REPORT FROM WORKING PARTY ON
STATISTICAL MECHANICS IN BIOPHYSICAL SYSTEMS

1. DEFINITION OF FIELD OF INTEREST:

The working party has been concerned with the theory of transport as applied to biophysical systems and various transport processes taking place across membranes.

Various systems of equilibrium properties are also being investigated.

2. FINANCIAL SUPPORT:

Funds for the financial support for this work have come from numerous departmental and university sources, in addition to the following grants.

GU-1864

N.A.S.A. - NgR-33-015-016

N.I.H. - GM 11603

PHS 5-K3-GM-10,333-02

PHS - 5T01-00718-08

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

The faculty of this working party consisted of the following members who have participated in the regular study group meetings:

V. S. Vaidhyanathan, Working Party Chairman, Associate
Professor, Biophysics Department,
School of Pharmacy

Peter Bright, Biophysics Department, Research Associate

Jon Hamann, Assistant Research Professor

Daphne Hare, Biophysics Department

Shinpei Ohki, Assistant Professor, Biophysics Department,
School of Pharmacy

Fred M. Snell, Professor, Biophysics Department, School
of Medicine

Robert Spangler, Assistant Professor, Biophysics Department,
School of Medicine

Kuan Wu, Biophysics Department

4. RESEARCH PROGRAMS:

One of the objectives of this working party has been to hold informal discussions on various aspects of statistical mechanics and its application to problems of biophysical interest. Individual research projects undertaken, completed and contemplated were presented by the various members of the group in meetings regularly held on each Thursday morning.

A. Stability and Electrostatic Mobility-(V. S. Vaidhyanathan)

a. The electrostatic interactions of charged species in aqueous electrolyte media acting across a lipid phase are investigated. The nonvanishing part of this electrostatic energy is calculated on the basis of which it is concluded that one may reasonably suspect the existence of a minimum in electrostatic free energy and the existence of long range attractive force. It is demonstrated that the thickness corresponding to the minimum is of comparable magnitude with experimentally observed thicknesses of such films. Close analogy between our calculations and charge fluctuation interactions of polyampholytes at isoelectric point is suspected.

b. On the basis of some general considerations, it is shown

that the conclusions regarding the existence or nonexistence of a minimum in the electrostatic free energy of interactions of charged species of double layers acting across a hydrocarbon medium arrived at by the author are reasonable. Efforts made in connection with countering any objection that one may entertain regarding our analysis of double layer interactions are included.

B. Mechanical Reactions, Mean Return Processes and Long Range Forces in Lipid Films - (Peter B. Bright)

This year's progress has taken the form of three manuscripts in various stages of completion.

a. "The Nature and (In) Significance of "Anisotropic" Contributions of Chemical Reactions to the Flow Equations"

A continuing discussion in the literature concerns how chemical reactions, represented by scalar sources or sinks, relate to vector flows and are involved in active transport. With the appeal to Currie's principle which denies coupling between scalars and vectors in an "isotropic" medium, considerable confusion arises concerning the meaning of isotropy. Previous papers (Bright, 1967, Bull. Math. Biophysics, 29, 95, 123) showed the nature and significance of the locally isotropic contribution to the global integrated form for the flow equations. A statistical mechanical development identifying the flux density J with momentum density shows that local coupling may exist when the kinetics of the chemical reactions form a vectorial momentum source or sink. From this the

scalar mass source p or sink q (or turnover rate p/c) may be factored out leaving a coefficient which is the average molecular velocity of the particles when they first or last appear. The local form of the equation is given by

$$\bar{v}_i = \sum_j R_{ij}^* J_j + v_i^p (p_i/c_i) - v_i^q (q_i/c_i) - (1/c_i) (d c_i v_i / dt)$$

The global of integral form is given by

$$\Delta \bar{u}_i = \sum_j R_{ij} F_j + \sum_j \int_a^b A R_{ij}(r) (p_j - q_j - \partial c_j / \partial t) dr - \int_a^b (1/c_i) \left(v_i^p p_i - v_i^q q_i - \frac{\partial c_i v_i}{\partial t} \right) dr$$

Several cases are examined which suggest that the "anisotropic" contribution is probably negligible for biologically plausible situations while the "isotropic" contribution to the global form is very significant. This will be shortly submitted to the Biophysical Journal for Publication and will be presented to the Biophysical Meeting in February. Work on this manuscript was held up for a while because of basic conceptual inconsistencies concerning the introduction of irreversibility to the frictional coefficients. These difficulties are discussed in the second manuscript.

b. "Mean Return Processes in Statistical Mechanics"

This manuscript incorporates this years' advances in an on-going project concerning the conceptual foundations of Statistical Mechanics.

Various stochastic models have been used in physics to describe how "irreversible" frictional effects act to make a perturbed

system return to a mean or equilibrium configuration. In most of these, the sample or path functions are in some way non-differentiable and are viewed as "approximations" to the "exact" differentiable models. It is curious, however, that in some ways the "approximations" match up with experiment more easily than the "exact" models. It is interesting that the various assumptions as to the regularity properties of the sample functions give qualitatively different results which should give a basis for experimentally distinguishing between them.

The progress this year has involved the weakening of the condition of a particle's velocity to the mean of an exponential return to simplify a process in the velocity which initially returns to the mean (not necessarily exponentially.) Even with the weakened condition, one can show that the passage of current through a metal or solution could not increase the temperature (variance of the velocity distribution) if the velocity is assumed to be differentiable. It is also shown that Statistical mechanical understructure of irreversible Thermodynamics as presented by DeGroot and Mazur is a generalization to N dimensions of the Brownian motion process which implies non-differentiable path functions or degeneracy to no fluctuations.

c. A third project involving the "Nature and Detectability of Long Range Forces in Lipid Films" has been initiated. Here it is shown that long range intersurface forces can exist in non-

symmetrical situations e.g., when an electrical voltage is applied across the lipid film. Although the electrostatic contribution in the symmetrical situation is zero, there may be other possible sources (dispersion) forces. It is pointed out that their presence should be detected and how they might be used to evaluate the significance and role of the long range forces.

C. Time Dependent Processes -(Jon Hamann)

On the basis of the method of optimal-entropy-inference conjoined to a Markovian model of the real, a formulation of the statistical mechanics of time-dependent phenomena has been presented. It was shown that the path probability method of Kikuchi as it is employed is equivalent to the optimal-entropy formulation. In view of this relationship, the demonstration of the consistency of the path probability method with certain fundamental principles of irreversible thermodynamics applies also to the optimal-entropy-method. Although our results are valid only for systems which can be imaged by Markov structures defined by classical probabilities, the generalization of the method to more complex stochastic systems is conceptually straightforward.

D. Lipid Films - (S. Ohki)

In order to elucidate the structure of the monolayers, the expanded phase of monolayers has been considered as a two-dimensional lattice gas, using an analogy between the nature of the lattice gas and the Ising model of ferro-magnetism. The relation-

ship between the surface pressure (π) and the available area per molecule (A), and also the phase transition in the expanded phase have been analyzed.

Water permeability of a lipid bilayer model has been discussed on the basis of the irreversible thermodynamics. Permeability coefficients of water both in an osmotic measurement have been calculated in terms of the frictional coefficients of membrane-water and water-water, or the effect size of a hole in the membrane and the number density of the holes in the membrane. Interpretation for experimental data has been made.

One of the main purposes of the non-equilibrium statistical mechanics is to classify the foundation of the equation of hydrodynamics-continuity equation, equation of motion and equation of energy transport. The attempt to clarify the foundation of the equation of flow-system including chemical reactions has been done. Statistical mechanical investigation is being made.

E. Transport Coefficients - (Fred M. Snell)

During the past year considerable progress has been made in providing a clearer molecular picture of diffusion and flow in multicomponent systems. Commencing with the general equations of molecular dynamics as used by Bearman and Kirkwood, the hydrodynamic equations of motion are derived for each component in an isothermal multicomponent system consisting of sensibly spherical nonreacting molecules. It was the primary purpose of the investigation, of

which this is a report, to attempt to obtain a microscopic statistical basis for the macroscopic phenomenologic development of Snell and Spangler (J. of Phys. Chem., 71:2503 (1967), especially in regard to their new formulation for the partial molecular stress tensors. An expansion of the number densities in pair space of perturbed nonequilibrium states alternate to that used by Bearman and Kirkwood was employed. Our expansion explicitly recognize the position vector arguments of both the number densities in singlet space and the local mean velocities of the individual components, as well as for the equilibrium pair correlation function. The quantities were then expanded about the central position vector in Taylor's series. The results are corroborative of the previous phenomenologic development when the flows of the individual components are solenoidal and attention is confined to systems in which the kinetic contribution to the stress tensor is negligible in comparison to the contribution arising from intermolecular interaction. A report of this development has been accepted for publication in the Journal of Chemical Physics and is to appear shortly.

In addition further developments are now complete which bear upon the molecular dynamics of energy transport. In this development we have employed techniques similar to those used considering mass transport and in particular have utilized the new expansion of the pair correlation function mentioned above. The resultant equations assumed a clarity and simplicity not present in the

~~development of others.~~ Further work, however, is necessary to translate energy transport into entropy transport which will provide a molecular basis for the dissipation function for non-equilibrium transport processes in multi transport systems.

In both of the above developments it has emerged that there still remains an inherent weakness in the expansion of the pair correlation function about the equilibrium state as linear functions of the perturbing forces. This weakness is identified as a residual non spherically symmetric (anisotropic) pair correlation function in the quasi or pseudo equilibrium state achieved by the imposition of auxiliary external forces. Although arguments may be advanced that this residual anisotropy contributes negligibility when the function is integrated over space and is odd in the intermolecular vector $\vec{r}$, the actual error involved is difficult to access at best and uncertain at worst.

Recently a new pair correlation function has been studied which now leaves the equilibrium pair correlation function truly isotropic and permits therefore, a consideration of systems of more general interest with certain rather sharp inhomogeneities. Furthermore, the resultant integral equations may be interrupted phenomenologically. The material is currently being prepared for publication for it appears to possess some distinct advantages of the development of Van Leeuwen, Groeneveld and DeBoer (Physica, 25, 792, 1959), Lebowitz and Percus (J. of Math. Phys. 4, 116, 1961)

and Stillinger and Buff (J. Chem. Phys., 37, 1 (1962), which incorporate Mayer's cluster expansion.

F. Multicomponent Fluids - (Robert A. Spangler)

My major activities in statistical mechanics over the past year have been in collaboration with Dr. Fred M. Snell in an approach directed toward establishing the relationship between the macroscopic phenomenologic properties of a multicomponent fluid, viscosity for example, and the parameters of intermolecular interaction as derived by Bearman and Kirkwood upon the basis of the pair correlation function. In order to eliminate certain inconsistencies arising in the original Bearman-Kirkwood treatment, a new formulation of the statistical development, again starting from the pair correlation, has been derived which, in addition, extends the generality of the treatment. Two publications have resulted from this work.^{1,2}

Certain problems arising from this work remain to be investigated more fully. On the one hand, the treatment should be extended to non-spherically symmetric particles, thus involving the orientation of the molecule as an additional degree of freedom. On the other hand, the mathematical nature of the pair correlation function itself remains to be clarified. For example, a relationship between the deviation of the correlation function from spherical symmetry (relative to its second argument) and gradients of the function in its first argument must certainly exist. The

significance of this dependence, however, and the limitations it may impose upon a self-consistent formulation have not been fully elucidated. We anticipate pursuing these directions of investigation.

Aspects of an investigation of the non-equilibrium properties of mechano-chemical systems (carried out at the Polymer Department, Weizmann Institute of Science, Israel) have been cast in statistical mechanical terms. This work has been largely exploratory, however, has not been published, and remains to be fully developed.

5. PUBLICATIONS, PAPERS AND SEMINARS:

V. S. Vaidhyanathan

1. "Electrical Conductance of Semipermeable Membranes"
Biophysical Journal, 7, 974 (1967)
2. "Electrostatic Energy Across Lipid Films", to be published.
3. "Further Comments on Electrostatic Free Energy Across Lipid Films", to be published.
4. "Electrical Conductance of Lipid Films", to be published.
5. "Some Theoretical Aspects of Biological Transport"
In Symposia of International Society for Cell Biology,
Acad. Press, New York (1967) (edited by K. B. Warren)

P. B. Bright

1. "The Basic Flow Equations of Electro-physiology in the Presence of Chemical Reactions; Part I. Development of Equations", Bright, P. B., Bull. Math. Biophys. (March, 1967) 29 (1967).

2. "The Basic Flow Equations of Electro-physiology in the Presence of Chemical Reactions; Part II. A Practical Application Concerning the Voltage and pH Effects Accompanying the Diffusion of O₂ Through Hemoglobin Solution." Bright, P. B., Bull Math. Biophys. (March, 1967), 29, 123 (1967).
3. Seminar given to Biophysics Journal Club "Incompatibility of Linear Regression Laws and Fluctuation Theory". October 13.
4. First Seminar given to Department of Statistics "Mean Return Processes in Statistical Mechanics". October 30.
5. Second Seminar given to Department of Statistics "Mean Return Processes in Statistical Mechanics". November 7.

J. R. Hamann

1. "A Note on Optimal-Entropy-Inference In the Statistical Mechanics of Time-Dependent Phenomena", Hamann, J. R., submitted to Nuovo Cimento.
2. "On the Logical Foundations of Semiempiricism", Hamann, J. R., accepted for publication in Scientia.

S. Ohki

1. "Application of the Lattice Gas Theory to Lipid Monolayers" Ohki, S.
2. "Influence of pH, Sodium and Calcium Ions on the D. C. Resistance of Black Egg Lecithin - Cholesterol Films", Ohki, S. and Goldup, A., to be published in Nature.

F. M. Snell and R. A. Spangler

1. J. Phys. Chem. 71, 2503, Snell, F. M. and Spangler, R. A.
2. J. Chem. Phys. in press, Snell, F. M., Aranow, R., and Spangler, R. A.

6. MEETINGS:

V. S. Vaidhyanathan

1. February 22 - 24, Biophysical Society Meeting, Boston.
2. June 19 - 23, 41st National Colloid Symposium
3. August, Gordon Research Conference on Ion Exchange
4. September 1 - 5, American Chemistry Society Meeting, Chicago
5. October 3 - 5, Symposium on Lipid Bilayers

Peter B. Bright

1. February 22 - 24, Biophysical Society Annual Meeting, Houston, Texas.
2. June 19, 41st National Colloid Symposium, American Chemical Society, State University of New York at Buffalo.
3. October 3 - 5, Symposium on Lipid Bilayers, Center for Theoretical Biology, State University of New York at Buffalo.

S. Ohki

1. Bilayer Symposium (The American Oil Chemist's Society), New Orleans, May 8 - 10, 1967.
2. 41st National Colloid Symposium, Buffalo, New York, June 19 - 23, 1967.

3. Symposium of Lipid Bilayers, Buffalo, New York, October
3 - 5, 1967
4. Biological Interfaces (New York Heart Association), New
York, December 8 - 9, 1967.

Robert A. Spangler

1. Second International Biophysics Congress, Vienna, Sept.
1966.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

V. S. Vaidhyanathan - Biophysics 522 participant

8. MISCELLANEOUS ACTIVITIES:

V. S. Vaidhyanathan - Member of the Academic Committee

Referee for Journal of Theoretical Biology

Biophysical Journal

Journal of Physical Chemistry

Journal of Chemical Physics

Fred Snell - Dean of Graduate School

Jon Hamann - Member of the Academic Committee

ANNUAL REPORT FROM WORKING PARTY ON

MONOMOLECULAR FILM STUDY

1. DEFINITION OF FIELD OF INTEREST:

Monomolecular film studies of various amphipathic molecules of biological interest including fatty acids, glycerides, phospholipids, sterols and sterol-like structures.

2. FINANCIAL SUPPORT:

Financial support during 1967 came from NASA Grant No. NGR-33-015-016 and NIH Grant No. P01 GM 11603-05.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

D. A. Cadenhead	Working Party Chairman, Associate Professor, Chemistry Department
M. C. Phillips	Post-Doctoral Research Fellow
R. J. Demchak	Graduate Student-full time
L. Czonka	Undergraduate-part time
J. Czonka	Technician-full time

4. RESEARCH PROGRAM:

Monolayer characterization of various amphipathic molecules of biological interest. Studies have been carried out on the following:

1. A wide range of glycerides, mono- di- and triglycerides of varying chain length and location.
2. Two synthetic phospholipids 1, 2 dimyristoyl-3-lecithin and 1, 2 decanoyl-3-lecithin over a wide temperature range.

3. A variety of substituted estradiols.

Condensing Effects of Cholesterol in Mixed Monomolecular Films

An extensive study has been made of the condensing effects of cholesterol on the expanded isotherms of a variety of components including fatty acids and esters, glycerides and synthetic phospholipids. The results indicate an alternative phase-change explanation for Dervichian's "molecular complexes" and that molecular interactions between the cholesterol and the expanded component are the primary cause of the observed condensation effects.

Expanding Effects of Glycerol

A study of the effects of adding varying amounts of glycerol to a monomolecular film substrate was undertaken in view of the use of this material as a low temperature cell preservative. Significant interaction between the hydrophobic chains of the amphipathic molecules and the glycerol enriched substrate was found to lead to film expansion. Work was carried out over the temperature range -10°C to 40°C .

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Monolayer Characteristics of 1,2-Dimyristin, 1,2 Dimyristoyl-3-Cephalin and 1,2-Dimyristoyl-3-Lecithin at the Air-Water Interface", D. A. Cadenhead, R. J. Demchak and M. C. Phillips, *Colloid-Z. u. Z. Polymere*, 220, 59 (1967).
2. "Monolayers of Some Naturally Occurring Polycyclic Molecules", D. A. Cadenhead and M. C. Phillips, *J. Coll. and Interface Sci.*, August Issue (1967).

3. "Elaidic Acid Monolayers on Aqueous-Glycerol Substrates", D. A. Cadenhead and R. J. Demchak, J. Coll. and Interface Sci., August Issue (1967).
4. "Molecular Interactions of Mixed Monolayers", D. A. Cadenhead and M. C. Phillips, Advances in Chemistry Series: "Molecular Interactions in Biological and Related Systems", in press.
5. "Monomolecular Films: Films of Phospholipids and Films on Aqueous Glycerol Substrates", R. J. Demchak, Ph.D. Thesis, State University of New York at Buffalo, Buffalo, New York, 1967.
6. MEETINGS:
 1. American Chemical Society Spring Meeting Miami, April, 1967. Presented paper "Molecular Interactions in Mixed Monomolecular Films", as part of symposium "Molecular Interactions in Biological and Related Systems".
 2. Gordon Research Conference on Interfaces, July, 1967. Presented short talk "Condensation Effects in Monomolecular Films".
 3. Symposium on Lipid Bilayers, Theoretical Biology Center, Buffalo, October, 1967. Presented paper, "Monolayer Characteristics of Some Possible Bilayer Components".

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

Courses taught through the Chemistry Department:

1. Undergraduate Physical Chemistry (An undergraduate course with laboratory slanted for biochemical interest) Chemistry 319-320 and 319-320L.
2. Surface Chemistry, Chemistry 534. A graduate course open to all graduate students. Part of this course was used to discuss monolayers of molecules of biological significance.

ANNUAL REPORT FROM THE WORKING PARTY ON MEMBRANES

1. DEFINITION OF FIELD OF WORK

Theoretical and experimental studies on Lipid Bilayers

2. FINANCIAL SUPPORT

a. NASA Grants

NGR 33-015-016

NsG 501

b. NIH Grant

GM 11603

c. Department of Biophysics and School of Pharmacy, State University of New York at Buffalo

3. FACULTY & PARTICIPATING RELATIONSHIP

Dr. J. F. Danielli (Professor of Theoretical Biology, Biophysics
Department, School of Pharmacy, and Department of Biology)

Dr. S. Ohki (Assistant Professor, Biophysics Department, School
of Pharmacy)

Dr. A. Goldup (Visiting Professor)

Mr. J. Borst (Graduate Student)

Mrs. R. Morgan (Research Assistant)

Mr. J. Pursner (Graduate Assistant)

Miss L. Frei (Technician)

4. RESEARCH PROGRAM:

In the previous year, Danielli published a basic theory of
thin lipid membranes, in which it was shown that the free energy

for a bilayer is less than that for a membrane of any other thickness. Consequently, the lipid bilayer is a basic unit of structure in the same sense that the protein α -helix and the DNA double helix are basic units of structure.

A large amount of work in 1967 was spent on developing this theory and its consequences. Danielli has shown that there are probably at least three and possibly four different possible bilayer structures, and has worked out the condition for spontaneous bilayer formation from bulk lipid.

Ohki has studied interlayer interaction of a lipid bilayer model. According to second-order perturbation theory, a general expression for interlayer interaction energies is obtained for induced dipole-induced-dipole, dipole-induced dipole and dipole-dipole interactions for the bilayer system. It is concluded that the interaction energy between two oriented hydrocarbon monolayers is lower than that between an oriented layer and random hydrocarbon phases, by about 10 ergs/cm^2 .

He also studied the interaction energy between water and a hydrocarbon phase. He deduced that the energy between water and a hydrocarbon phase in which hydrocarbon chains are oriented perpendicular to the interface is energetically more favored than that of water and a hydrocarbon phase in which hydrocarbon chains are oriented parallel to the interface.

Ohki has calculated the dielectric constant and the refrac-

tive index of a bilayer as a function of the interchain distance of a hydrocarbon chain and the thickness of the bilayer. By using two different experimental data (capacitance and optical measurements) for a lipid bilayer, he deduced the thickness and the interchain distance of the lecithin bilayer.

J. Borst worked on the theory of surface free energy, particularly on the role of the London dispersion forces. He obtained a method for evaluating the interaction energy term, involving summation over a finite number of points and integration over the remaining points. He is studying statistical methods for the characterization of the proper model to give meaningful results. He has also calculated the entropy curves for myelin and monolayers from the experimental data.

Recently J. Borst has studied trans-bilayer interactions between macromolecules.

A. Goldup has examined alcohol transport through bilayer membranes experimentally. As a result, he obtained no specific permeability for alcohol transport through bilayer membranes, and he concluded that the predominant factor of alcohol transport could be due to the stagnant water layer of the bilayer.

Ohki and Goldup have studied the effect of pH, Na^+ and Ca^{2+} on the D.C. resistance of black lecithin-cholesterol films. Changes in pH can alter the resistance of lecithin-cholesterol membranes. The changes however depend upon whether Na^+ or Ca^{2+} is present in

the aqueous phase. In the presence of 0.1 M Na Cl the resistance-pH curve passes through a maximum whereas in 0.1 N Ca Cl₂ a continuous increase of resistance with increases in pH is observed.

5. PUBLICATIONS, PAPERS AND SEMINARS:

J. F. Danielli

1. The Problem of Receptors in Relation to Regulation of the "Milieu Interieur" in "Les Concepts de Claude Bernard sur le Milieu Interieur"; Masson & Cie, Editeurs - Paris, 1967, p. 63-73 (Danielli).
2. Formation, Physical Stability and Physiological Control of Pauci-molecular Membranes. (Danielli) Symp. Int. Soc. Cell Biol. (Academic Press 1967).
3. Danielli, J. F., Goldup, A. and Ohki, S. "Review of Lipid Bilayers" to be published in "Progress in Surface Science" S. Ohki
 1. Ohki, S. "Application of the Lattice Gas Theory to Lipid Monolayers", J. Theoret. Biol. 15, 346 (1967).
 2. Ohki, S. and Fukuda, N. "Interlayer-interaction for a Lipid Bilayer Model" J. Theoret. Biol. 15, 362, (1967).
 3. Ohki, S. and Fukuda, N. "Interaction Energy Between Water and Hydrocarbon Phases", Journal of Theoretical Biology.
 4. Ohki, S. "Dielectric Constant and Refractive Index of a Lipid Bilayer", Journal of Theoretical Biology.

5. Ohki, S. and Goldup, A. "Influence of pH, Sodium and Calcium Ions on the D. C. Resistance of Black Egg Lecithin-cholesterol Films" to be published in Nature.
6. Ohki, S. "Thickness of Lipid Bilayers", Journal of Theor. Biol.

6. MEETINGS ATTENDED:

1. Jan. 13, 1967, Canada Packers, Ltd., Toronto, Canada
2. Jan. 22-25, 1967, Seminar to Dept. of Pharmacology & Therapeutics, Univ. of Manitoba, Winnipeg, Canada.
3. Feb. 11-18, 1967, Council - ICRO and Journal for Theoret. Biology, Paris, France and London, England
4. Feb. 26 - Mar. 3, 1967, Conference: Membrane Structure & Functions, Alpine Inn, St. Marquerite, Quebec.
5. May 3-14, 1967, Symposium: Molecular Assn. in Biology, England & Paris.
6. June 6-July 12, 1967, Int'l. Conference on Biological Membranes, Rome, Italy, London, England
7. July 16-24, 1967, Artificial Synthesis of a Cell Conference, Ft. Collins, Colo.
8. Sept. 10-15, 1967, Symposium on Cytolysis by Detergent & Other Agents, Chicago, Illinois.
9. Oct. 16-17, 1967, Seminar: Ion Transport & Electrophysiology of Nerve & Muscle, Charlottesville, Virginia.
10. Nov. 7-8, 1967, Conference: Blood Research Institute, Boston, Mass.

11. A. Goldup and S. Ohki

Title: Bilayer Symposium (The American Oil Chemist's
Society)

Place: New Orleans, La.

Date: May 8-10, 1967

12. A. Goldup and S. Ohki

Title: Symposium on Lipid Bilayers

Place: Center for Theoretical Biology, State University
of New York at Buffalo

Date: October 2-4, 1967

13. S. Ohki

Title: Biological Interfaces (New York Heart Association)

Place: New York

Date: December 8-9, 1967

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

J. F. Danielli taught a graduate course on General Theory of the Cell, and also part of a graduate course "Introduction to Biology for Non-biologists."

ANNUAL REPORT FROM WORKING PARTY ON RECEPTORS

1. DEFINITION OF FIELD OF INTEREST:

1. Structure and Function of Pharmacological Receptors.
2. Kinetic Isotope Effects in Biological Systems.
3. Agents that Affect DNA, RNA Systems.
4. Enzyme Inhibitors (folate reductase enzymes).

2. FINANCIAL SUPPORT:

The work has been supported by the following Grants:

CA-06645, GM-11603, HE-09336 and GM-14084 from the National Institute of Health and NSG 501 from N.A.S.A.

3. FACULTY AND PARTICIPATING RELATIONSHIPS

D. J. Triggle	Working Party Chairman, Associate Professor, Departments of Biochemical Pharmacology and Biophysics, School of Pharmacy
S. S. Chatterjee	Senior Research Associate
M. May	Senior Research Associate
F. H. Ridley	Senior Research Associate
J. F. Moran	Department of Biochemistry, School of Pharmacy
B. Avner	Graduate Student
R. Deth	Assistant
D. Garrison	Assistant
C. Liarakos	Assistant
De Maio	Assistant
V. Skowronski	Assistant
A. Wayne	Assistant

4. RESEARCH PROGRAM:

1. There are a large number of unsolved problems that relate to the structure and function of pharmacological receptors. We have been concerned with a number of these including the following:

- (A) Problems and techniques in the isolation of receptor material - with particular reference to the adrenergic α -receptor.
- (B) The analysis of mutual molecular complementarity between receptors and agonists or antagonist molecules with reference to adrenergic, cholinergic, analgetic and steroid receptors.
- (C) The relationship between stimulus and pharmacological response.

Under heading (A) work has continued on the application of single and double label techniques to the problem of specifically (or selectively) labelling the adrenergic α -receptor. A report of some of this work will be found in publications 1 and 2. Our principal approach to the problem of receptor isolation lies in the design of irreversibly acting norepinephrine analogs that will covalently bind to the receptor locus at which the agonist interacts. This approach is, however, deceptively simple to the extent that we find that the chemical and pharmacological specificities of such

compounds are quite different and that until (and unless) an absolutely specific alkylating agent is developed the single-label isolation technique cannot be successful.

Under heading (B) we have been concerned with the development of new adrenergic blocking agents and with a detailed analysis of the mode of binding of acetylcholine analogs at the cholinergic receptor. A report of some of the latter work appears as publication 3. Our approach in the latter problem is based on the premise that conformationally flexible molecules cannot give information relevant to the geometrical characteristics of the complementary receptor surface because one has no knowledge of the conformation of the receptor-bound drug molecules. Information concerning this latter point may, however, be available from a study of the activities of conformationally rigid acetylcholine analogs: because of the high cholinomimetic activity of cis - 2 - methyl - 4 - dimethylaminomethyl - 1, 3 - dioxolane methiodide we are studying rigid mono and bicyclic analogs of this compound.

Other related problems under investigation include the synthesis of new estradiol analogs and an analysis of the estradiol binding site.

Under (C) is included one of the most important problems in molecular pharmacology. It is particularly important that information should become available on, for example:

1. Whether maximum tissue response requires 100% occupation of the receptors.

2. What relationship exists between the number of receptors occupied and the pharmacological response.

In our previous work (see publication 2) on the adrenergic α -receptor of the rabbit aorta, we were able to demonstrate that 100% response occurs with 100% receptor occupation and that a direct proportionality exists between the response and the number of receptors occupied. Further work suggests, as anticipated, that this conclusion may be quite generally true for adrenergic α -receptors. We have been applying the same general approach to the cholinergic (muscarinic) receptor of the rat intestine: it is quite apparent that significant differences exist between the cholinergic and adrenergic receptors. Thus, maximum activation of the cholinergic system seems to require the occupation of as little as 5% of the receptors with acetylcholine or as much as 100% with $\text{BuN}^+\text{Me}_2\text{Et}$. This work, which is still in progress, offers great scope for a critical evaluation of the parameters underlying both the binding of drugs to receptors and the initiation of the biological response.

3. Agents that affect DNA, RNA systems.

In view of the known antitumor action of miracil D (a thioxanthene derivative) and its proposed mode of action via inhibition of RNA synthesis through intercalation between DNA base pairs, we have synthesized a number of potentially irreversibly acting analogs. In collaboration with Dr. Z. F. Chmielewicz (School of Pharmacy) it has been established that certain of these new compounds have very

high activity in decreasing the template activity of calf thymus DNA in an RNA polymerase system.

4. Enzyme Inhibitors.

Work has continued on our structure activity analysis of 5-arylazopyrimidines as inhibitors of folate reductases. By a systematic analysis of the various factors affecting binding of these molecules extremely potent inhibitors of dihydrofolate reductase have been found, some of which approach amethopterin in their potency.

5. PUBLICATIONS, PAPERS AND SEMINARS

1. "Studies on the Noradrenaline α -Receptor I", J. F. Moran, M. May, H. Kimelberg and D. J. Triggle, Mol. Pharmacol., 3, 15, (1967).
2. "Studies on the Noradrenaline α -Receptor, II", M. May, J. F. Moran, H. Kimelberg and D. J. Triggle, Mol. Pharmacol. 3, 28, (1967).
3. "Studies on the Cholinergic Receptor I", M. May, and D. J. Triggle, to be published in J. Pharm. Sci.
4. "5-Substituted Pyrimidines II", A. M. Triggle and D. J. Triggle, J. Med. Chem., 10, 285 (1967).
5. "The Analgesic, Hypothermic and Depressant Activities of N-Substituted, α -5, 9-dimethyl -6, 7-benzomorphans", M. May, L. Czoncha, D. R. Garrison and D. J. Triggle, J. Pharm. Sci.
6. "The Adrenergic Hormone", D. J. Triggle, Ed. A. Burger (3rd Edition), in Medicinal Chemistry

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

Biochemical Pharmacology 525 (Molecular Pharmacology)

Biochemical Pharmacology 405 (Pharmacology) - Participated
in this course.

ANNUAL REPORT FROM WORKING PARTY ON

CELL PHYSIOLOGY

1. DEFINITION OF FIELD OF INTEREST:

Genetic control of amoebae, with special reference to cytoplasmic inheritance.

2. FINANCIAL SUPPORT:

Supported by the U.S.P.H.S. Grant No. GM 11603 of N.I.H.

3. FACULTY AND PARTICIPATING RELATIONSHIPS

K. W. Jeon	Working Party Chairman, Research Associate
J. F. Danielli	Professor of Theoretical Biology Biophysics Department, School of Pharmacy, and Department of Biology
J. F. Moran	Asst. Professor of Biochemistry, School of Pharmacy
I. J. Lorch	Research Associate

All are participating in active research.

4. RESEARCH PROGRAM:

The main project of this laboratory's research has been to identify the physico-chemical entity of heredity determinants that are present in the amoeba cytoplasm. Studies employing the techniques of nuclear transplantation and cytoplasmic injection showed that certain cell characters of amoebae are under the partial control of cytoplasm. In order to elucidate the mechanisms of cytoplasmic inheritance, amoeba cytoplasm of one strain is homogenized, fractionated by centrifugation, and injected into single cells of another strain. Then the resulting changes in phenotypic characters of the host strains are studied, the characters currently studied

including responses to anti-amoebea sera and the rate of attachment of cells. Also further search for cytoplasmically determined cell characters is in progress.

In addition to the main project, physiological studies on amoebae have been carried out: these include responses of amoebae to various chemicals, intra-cellular bacterial infection, cell movement, and cell growth and division.

With a partial financial support from the Center, a pre-doctoral research fellow, H. Allen, has been studying the hexosamine metabolism in amoebae. The main objective of this work has been to elucidate the factors and mechanisms controlling cell surface turnover, and to recognize possible differences between various strains of amoebae. Some of the cytoplasmically controlled characters of amoebae appear to be related to the cell surface, and the findings of this work could be useful in the study of cytoplasmic inheritance.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. A Modified Oil Chamber for Micrurgy on Large Cells, K. W. Jeon, Exptl. Cell Res. 46, 609 (1967).
2. Cytoplasmic Inheritance in Amoebae, K. W. Jeon, I. J. Lorch, J. F. Moran, A. Muggleton and J. F. Danielli, Experimental Cell Res. 46, 615 (1967).
3. Unusual Intra-Cellular Bacterial Infection in Large, Free-Living Amoebae, K. W. Jeon and I. J. Lorch, Exptl. Cell Res. 48, 236 (1967).

4. Inheritance of the Life-Spanning Phenomenon in Amoeba proteus,
A. Muggleton and J. F. Danielli, Exptl. Cell Res., in press.
5. A New, Simple Method of Micrurgy on Living Cells, K. W. Jeon
and I. J. Lorch, submitted for publication in Nature.
6. Nuclear Control of Cell Movement in Amoebae: Nuclear Trans-
plantation Study, K. W. Jeon, submitted for publication in
Exptl. Cell Res.

6. MEETINGS

1. K. W. Jeon attended the 2nd International Conference on
Cell Synchrony held in April, 1967, at Oak Ridge, Tenn.,
and read a contributed paper entitled "Cell Synchrony in
Large, Free-Living Amoebae (Preliminary study)".
2. I. J. Lorch and K. W. Jeon attended the 20th Annual Meeting
of the Society of Protozoologists held in June, 1967, in
Toronto, Canada, and read a paper entitled "Intra-Cellular
Bacterial Infection in Large Free-Living Amoebae".

ANNUAL REPORT FROM WORKING PARTY ON
SYSTEM THEORY AND RELATIONAL BIOLOGY

1. DEFINITION OF FIELD OF INTEREST:

The working party on System Theory and Relational Biology is mainly concerned with problems relating to system-theoretic aspects of regulation and control in biological systems, and with the physical basis of regulatory mechanisms. The main emphasis has been on cellular control, but part of the thrust of our work has been to show that in a precise sense, the cellular control mechanisms are analogues of mechanisms occurring at higher levels of biological organization, from the physiological level through the ecological. The approach has been from the standpoint of relational biology; i.e. to characterize global functional aspects of regulatory mechanisms and study their abstract properties; i.e. independent of any particular physical realization, and then to pass to specific individual physical realizations using a principle of Optimal Design.

2. FINANCIAL SUPPORT:

At present the main financial support for this work is from NASA grant # NGR-33-015-016 (50-861A). An independent proposal for a research grant in this area is pending at NASA, and one has recently been submitted to NIH as well.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

The following individuals have carried out activities related to the research projects of the Working Party:

Robert Rosen	Associate Professor of Biophysics and Mathematics, Working Party Chairman
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John Myhill	Professor of Mathematics
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Hinrich Martens	Professor of Electrical Engineering
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In addition, Professor K. N. Leibovic and Professor N. Findler have been consulted from time to time concerning activities of the Working Party, as has Professor M. Ycas, Department of Microbiology, Upstate Medical Center, Syracuse, N. Y.

In addition to the above, Mr. Lynn Spees, graduate student in the Department of Mathematics, has been supported on a fellowship from Center funds, and is embarked on a program of study and research related to the activities of the Working Party.

4. RESEARCH PROGRAM:

Robert Rosen

A. Dr. Rosen has been mainly concerned during the past year with formulating in precise terms the relationships which exist between independent digital and continuous descriptions of metabolic activity. This is important because each of these descriptions possesses certain conceptual advantages in special areas, but neither by itself is completely satisfactory as an overall theoretical basis for an understanding of regulatory mechanisms in biological systems. The work has proceeded on two

levels: (a) an elucidation of the formal homologies which exist between the continuous and discrete descriptions, and (b) a search for a kind of "correspondence principle" which would enable us to directly relate these independent descriptions of the same system within a unified framework.

Another aspect of this work has been concerned with the formal aspects of passing between levels of organization of a particular system. This is attacked by assuming a particular system to be given (i.e. a set of state variables and a set of equations of motion governing their kinetics), and then choosing an arbitrary set of observables of this system to define the new state variables of a "subsystem" of the original system. These new state variables inherit equations of motion from the old system. Question: when can we find a set of observables which will inherit a prescribed set of equations of motion from the original set which defined the given system? Question: when can the study of the inherited set of equations of motion give information regarding the original set? These and related questions have important methodological implications for biology (and for other sciences as well), and bear directly on current "reductionist" ideas concerning the relation of global biological activities to molecular terms.

R. Rosen, H. Martens, M. Ycas

B. As a concrete illustration of some of the above ideas in a real biological problem of independent interest, these individuals have been engaged in an analysis of the problem of cell sorting in populations of disaggregated embryonic cells. The point of departure for this work is the experiments of Malcolm Steinberg, who showed that unique cellular morphologies arise from widely different experimental starting points. Steinberg also proposed an interesting formal model which gives a sufficient condition for this phenomenon. We have been interested in exploring this system further, to derive necessary and sufficient conditions for this uniqueness (which would imply that information gained from cell sorting experiments would bear directly on real morphogenetic questions in the intact embryo) and also to construct the classes of algorithms necessary to specify the formation of particular histological structures (e.g. tubules). Some preliminary discussions with Prof. Martens concerning computer simulation of these systems have been undertaken, and Prof. Ycas has participated in some of these discussions.

John Myhill

C. Prof. Myhill was supported during the summer by CTB funds, and devoted himself to further work relating to the digital description of biological systems. Some years ago R. Rosen raised the question as to whether Turing computability raises a real limitation to the properties of biological and physical systems;

i.e. whether computability enters into physics and biology in the same way as e.g. the Second Law of thermodynamics in precluding the existence of particular kinds of physical systems. Prof. Myhill has investigated this question further, and suggested a variety of physical conditions which, if realized, would enable a physical device to compute a non-recursive function. This work suggests that the relationship between simple concepts of digital description and the physical world is a good bit deeper than previously imagined, and bears again directly on the work described above, on finding ways of supplementing digital descriptions for purposes of general biological analysis.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. Optimality Principles in Biology, Butterworth's & Co., Ltd. February 1967.
2. "Two-Factor Models, Neural Nets and Biochemical Automata", Journal of Theoretical Biology (1967) 15, 282-297.
3. "Recent Developments in the Theory of Control and Regulation of Cellular Processes", International Reviews of Cytology, to appear.
4. "Some Comments on the Physico-Chemical Description of Biological Activity", Journal of Theoretical Biology, to appear.

6. MEETINGS:

1. Biophysical Society, Feb. 22-24, 1967, Houston, Texas.
2. Federation Meetings, April 17-21, 1967, Chicago, Illinois.
3. American Mathematical Society Summer Meetings, August 28-31, 1967, Toronto, Canada.
4. American Society for Cell Biology, Oct. 13-15, 1967, Denver, Colorado. Contributed paper, "Some Theoretical Aspects of Pattern Formation in Mixed Cell Populations, and its Role in Morphogenesis".
5. McGill University, Dept. of Bioengineering. "Optimal Design in Theoretical Biology", Feb. 15, 1967.
6. Univ. of Chicago, Committee on Mathematical Biology. "Alternate Realizations of Two-Factor Elements", Feb. 20, 1967.
7. Symposium on Differentiation (organized by M. Ycas, sponsored by NASA). Boston, Mass. March 11-12, 1967.
8. "Microsymposium on Differentiation" (M. Steinberg, organizer) Woods Hole, Mass. June 24, 1967. "Pattern Generation in Model Mixed Cell Populations".
9. Karl-Marx University, Leipzig, Symposium on Biocybernetics, Sept. 19, 1967. "Biocybernetics and Relational Biology".
10. Third Helgoland Symposium on Quantitative Biology of Metabolism. Sept. 26, 1967. "Discrete and Continuous Representations of Metabolic Events".

11. Invited Remarks at Opening Session of Symposium on Regulatory Mechanisms in Biology with Special Reference to Biological Time Constants (sponsored jointly by Argonne National Laboratories and Association of Midwestern Universities), Oct. 23, 1967.
 12. American Statistical Association Annual Meetings (invited talk at Session on Biomathematics, A. F. Bartholomay, organizer), Washington, D. C., Dec. 28, 1967.
7. CONTRIBUTIONS TO UNIVERSITY TEACHING:
- Biophysics 511-512 (Techniques in Biophysical Research). Responsible for orientation of graduate students in theoretical biophysics. (Fall 1966, Spring 1967 semesters).
- Biophysics 510 (Mathematical Modeling in Biophysics - Relational Biology. Course jointly listed as Mathematics 523). (Spring 1967).
8. MISCELLANEOUS ACTIVITIES.
1. Refereeing of manuscripts for Journal of Theoretical Biology, Bulletin of Mathematical Biophysics, Biophysical Journal, Reinhold, Benjamin.
 2. Compiling and Editing Multi-volume Text on Mathematical Biology for Academic Press.
 3. Reviewing of papers on Biomathematics and Mathematical Biology for Zentralblatt für Mathematik.

4. Member, Academic Committee of Center for Theoretical Biology, and Subcommittee on projected Center for Theoretical Biology course programs, with responsibility for undergraduate course projections.

ANNUAL REPORT FROM WORKING PARTY ON
MODELS OF THE CENTRAL NERVOUS SYSTEM AND SENSORY COMMUNICATION

1. DEFINITION OF FIELD OF INTEREST :

This working party has been concerned with the theory of information processing in the central nervous system and primarily with information transfer in the visual pathway.

2. FINANCIAL SUPPORT :

The financial support for this work has come largely from N.I.H. Grant No. RO1-NB-06682-01 to K.N. Leibovic and R.A. Spangler, a Buswell fellowship awarded through the School of Medicine to J.D. Abernethy and Center funds from N.A.S.A. Grant No. NGR-33-015-016 made available to K.N. Leibovic, J.D. Abernethy, L.M. Bianchi and P.B. Bright by Professor James F. Danielli.

3. FACULTY AND PARTICIPATING RELATIONSHIPS :

K.N. Leibovic	Working Party Chairman, Associated Professor, Department of Biophysics, School of Medicine.
J.D. Abernethy	Post-Doctoral Fellow, Department of Biophysics, School of Medicine.
L.M. Bianchi	Post-Doctoral Fellow, Department of Physics, Faculty of Science and Mathematics.
P.B. Bright	Post-Doctoral Fellow, Department of Biophysics, School of Medicine.
N. Findler	Professor, Department of Computer Sciences, Faculty of Engineering & Applied Sciences.

J.R. Hamann	Assistant Professor, Department of Physiology, School of Medicine.
H. D. Landahl	Visiting Professor, Mathematical Biology.
M. Licker	Assistant Professor, Department of Physiology, School of Medicine.
W.K.Noell	Professor, Department of Physiology, School of Medicine.
R. A. Spangler	Assistant Professor, Department of Biophysics, School of Medicine.

Graduate Students :

G. Allen	Department of Physiology.
D. Faber	Department of Physiology.
G. Lord	Department of Mathematics.
T. Mathieson	Department of Biophysics.
R. Rosser	Department of Electrical Engineering.

Undergraduate Students :

L. Opler	Harvard
E. Raiken	Physics

The core of this working party consists of K.N.Leibovic, Working Party Chairman, J.D.Abernethy and L.M.Bianchi whose primary interests are in the above named field, together with R.A.Spangler and P.B.Bright who, however, are also devoting a substantial portion of their time to other areas of research.

During the summer this faculty was joined by three graduate students: Tom Mathieson (Biophysics), Graham Lord (Mathematics), Bob Rosser (Electrical Engineering) and two undergraduates: Eliot Raiken, and Lewis Opler (Harvard). Thus a closely knit group was

formed with good interaction from different disciplines.

Tom Mathieson is continuing his work with this group.

In addition to the above, the following people have participated in our study group which has met at 10:00 a.m. on Fridays : Don Faber, Garry Allen, W.K.Noell (Physiology), N. Findler (Computer Sciences), H.D.Landahl (Mathematical Biology).

4. RESEARCH PROGRAM :

Starting out from the premise that an understanding of CNS operation presupposes a knowledge of the sensory information input, our research has been concerned with the analysis of information processing in the visual pathway since there are more experimental data on this than on any other sensory pathway. The following specific problems are or have been under investigation.

(a) Information Input (K.N.Leibovic): The nature of the information accepted by the visual system can be investigated by considering various relevant mechanisms in the eye. Thus, flicker fusion frequency gives a measure of the serial information capacity; involuntary eye movements and their statistical properties suggest that the visual world is sampled in a random or pseudo-random manner until a package of information is assembled for processing; a short term visual memory serves to back up the information package. Based on these observations a model of the information input has been suggested as described in the papers below. The implications of the model for the nature of visual sensation remain under investigation.

References:

K. N. Leibovic: "A Note on Visual Integrative Mechanisms",
Bull. Math. Biophy. Special Issue, 27, 205-310, 1965.

K. N. Leibovic: "The Quantization of Visual Information",
2nd International Biophysics Congress, Sept. 1966.

K. N. Leibovic: "Observations on Some Experiments on Visual
Masking", J. Gen. Psych. (To be published).

(b) Information Processing in the Retina (K. N. Leibovic,
R. A. Spangler, J. D. Abernethy, T. Mathieson, L. Opler, E. Raiken,
G. Lord, R. Rosser):

Receptive fields appear to be present on all sensory surfaces and this gives promise that any general concepts relating to retinal receptive fields, which are the most extensively investigated experimentally, will apply also to sensory communication theory in general. Our interest has centered on the organization of the retinal network.

The anatomical basis of the distribution of response strength observed in the receptive field when a spot stimulus is used has long been a mystery. In many cases the response as a function of position in the receptive field, can be approximated by a Gaussian distribution. We advanced the hypothesis that this distribution is based on the membrane area of the dendritic tree of the ganglion cell available for synaptic inputs over the receptive field. This has been checked with experimental data and good agreement has been

obtained.

The temporal features of cat ganglion cell responses have been analyzed and have led us to a model which postulates three response components. Computer simulation studies have given satisfactory agreement with experimental data. Some suggestions for the neural mechanisms responsible for the various response components are under investigation. In this connection further studies of transretinal potentials and mechanisms of adaptation are proceeding. Computer studies have so far been based on the digital computer, but the design of a special purpose analog computer has also been considered.

A comprehensive review of the literature on retinal receptive fields is being made. Concurrently with this we are proposing logic networks which simulate the response properties.

J. D. Abernethy is studying the possible role of the amacrine cells in surround inhibition. On the basis of existing data there is good reason to believe that there is a negative feedback loop at the amacrine level, i.e. bipolars $\rightarrow$ amacrines $\rightarrow$ bipolars and that this may be the basis for the observed, apparently nonlinear pre-synaptic inhibition.

A mathematical model consisting of two first order nonlinear differential equations has been set up. Preliminary mathematical analysis and computer simulation studies have given promising results with respect to data on flashing spot stimuli and the oscilla-

tory behaviour of retinal ganglion cells.

J. D. Abernethy has also been concerned with the "wiring diagram" of "Off center cells". It has been assumed that these cells are simply wired as mirror images of "on center cells" by the reversal of synaptic polarity at the level of the ganglion cell. But it seems more probable for a number of reasons that this "mirror imaging" is achieved within the network, possibly through the agency of horizontal cells. Further work on this problem is proceeding.

(c) Information Processing beyond the Retina (K. N. Leibovic, L. M. Bianchi):

Most available experimental information, both anatomical and physiological relates to the retina. Partly the relative lack of data beyond the retina is due to greater experimental difficulties, but partly it is also due to the problem of what one should look for. In this situation theoretical studies of possible mechanisms assume a special significance.

A fruitful approach is to ask which of the perceptual tasks we know to occur cannot take place at the retinal level on the basis of the known properties of retinal receptive fields. It turns out, for example, that estimates of length and size and even the simultaneous estimates of position and intensity of a spot of light cannot be made on the basis of the response of just one retinal receptive field. Thus, possible mechanisms of size estimation were considered earlier and a theory was developed based on geometric probability.

Similarly, a possible method for estimating position and intensity of a spot stimulus was developed.

The anatomy and physiology of the lateral geniculate nucleus and visual cortex remain under active study with a view to developing further the ideas outlined here.

(d) Physio-Psychological Studies (L. M. Bianchi, K. N. Leibovic):

Just as physiological phenomena have an anatomical basis, so the psychological and behavioral phenomena are rooted in physiological processes. Our efforts in this context are directed as follows:

To find possible analogies between mathematical and formal pattern recognition techniques and form perception in biological systems.

To search for correlates of form perception in the operations performed at various stages of the visual pathway.

To look for possible unifying criteria applicable to various forms of perception.

L. M. Bianchi has also established a good collaboration with Dr. R. M. Pritchard and his experimental group at McMaster University in Hamilton, Ontario, and is working on fragmentation phenomena in stabilized vision.

In addition, L. M. Bianchi is interested in the possible applications of statistical mechanics to biological systems, starting out from the work of E. Kerner on Volterra systems and Goodwin

on Biochemical Systems.

(e) Neurons and Nerve Nets (P. B. Bright):

A review was prepared for discussion with the working party entitled "Development of the Formal Study of the Physiological Basis of Information Processing". It contained an account of some of the earlier mathematical attempts to describe the relations between nerve excitation, information processing and the underlying physical and chemical mechanisms. The paper was useful in aiding the design of electrical analogue networks to simulate some visual phenomena.

A second paper "Proper Subtraction" was also presented to the working party. This is concerned with the development of mathematical techniques for dealing with thresholds.

5. PUBLICATIONS, PAPERS AND SEMINARS:

K. M. Leibovic

1. "Observations on Some Experiments on Visual Masking", J. Gen. Psych. (to be published).
2. "Some Aspects of Visual Information Input and Transmission" N. Y. Acad. of Science Conference on Rein Control, 13 - 14, April, 1967.
3. "Models of the Visual Pathway", Gordon Research Conference on Biomathematics, 10 - 14, July, 1967.
4. "Information Flow in the Visual Pathway", Seminar to Biomathematics Group, State University of North Carolina, Raleigh, N. C., 4 April, 1967.

5. "Communication between Cells" - Seminar at Center for Theoretical Biology given in the Seminar Series on Cell Systems Theory, April, 1967.
6. "Communication in Cell Systems" - Seminar at Center for Theoretical Biology given in the Seminar Series on Cell Systems Theory, April, 1967.
7. "Problems of Information Processing in the Visual Pathway", Center for Theoretical Biology Seminar, 19 October, 1967.

J. D. Abernethy

1. "The Effect of an Artificial Fog on Airways Resistance in Patients with Bronchitis", Thorax, (in press).
2. "Physiological Variations in the Urinary Nitrogen Gas Tension in the Human", J. Appl. Physiol. (in press).
3. "Countercurrent Multiplication of Inert Gases in the Fish Swimbladder", (to be submitted for publication).
4. "Countercurrent Multiplication of Inert Gases in the Kidney" (to be submitted for publication).

L. M. Bianchi

1. "Some Possible Models for Visual Information Processing", Center for Theoretical Biology Seminar, 12 October, 1967.

P. B. Bright

1. "Relations Between Components and Systems Behaviour", to be Published in "Cybernetic Problems in Bionics", Gordon & Breach.

6. MEETINGS:

K. N. Leibovic

1. Symposium on Systems Theory in Biology, Case Inst. of Tech., October, 1966.
2. Biophysical Society Annual Meeting, Houston, Texas, 22-24 February, 1967.
3. Conference on "Rein Control", N. Y. Acad. Sc., New York, 13-14 April, 1967.
4. Gordon Research Conference on Biomathematics, Proctor Academy, N. H., 10-14 July, 1967.

J. D. Abernethy

1. Symposium on Systems Theory in Biology, Case Inst. of Tech., October, 1966.
2. Biophysical Society Annual Meeting, Houston, Texas, February, 1967.
3. Federation Meetings, Chicago, 1967.
4. Conference on "Rein Control" in Biological Systems, New York, 1967.
5. Gordon Research Conference on Biomathematics, N. H. July, 1967.

L. M. Bianchi

1. Symposium on "Mathematical Systems Theory", Penn State Univ., 11-15 Sept., 1967.

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

K. N. Leibovic

In addition to the summer student program and the seminars mentioned above, the following course teaching was also done:

Participation in Biophysics 401: Introduction to Biophysics

Participation in Biophysics 404: Introduction to Biophysics

Participation in Biophysics 511-2: Techniques in Biophysical Research.

Biophysics 655-6: Research Course.

P. B. Bright

Participation in Biophysics 401: Introduction to Biophysics

8. MISCELLANEOUS ACTIVITIES:

K. N. Leibovic

1. Organization of Lecture Series on "Cell Systems Theory" under the auspices of the Center for Theoretical Biology, 10-18 April, 1967.
2. Chairman of Center for Theoretical Biology Seminar, Publications and Library Committee.
3. Co-chairman of Center for Theoretical Biology Academic Committee.
4. Refereeing for Journal of Theoretical Biology and Biophysical Journal.

J. D. Abernethy

1. Visits to Drs. W. Rall, J. E. Dowling, and P. Gouras, at the National Institutes of Health and John Hopkins Medical School, to discuss problems in relation to neural and retinal modeling.
2. Three courses in mathematics have been attended, one on Modern Algebra, one on Probability Theory and one on Relational Algebra in Biology.
3. Weekly discussion meetings on Sensory Communications have been held.

L. M. Bianchi

1. Refereeing for Biophysical Journal and Bulletin of Mathematical Biophysics. Supervision of Center for Theoretical Biology Library.

THE FOLLOWING REPORTS ARE OF WORK WHICH HAS BEEN DONE
OUTSIDE THE FRAMEWORK OF ANY ONE GROUP FORMALIZED AS A
CENTER FOR THEORETICAL BIOLOGY WORKING PARTY AT THE
PRESENT TIME

CANCER CHEMOTHERAPY COMMITTEE

MEMBERS:

Dr. A. Mittleman, General Clinical Research Center,
Roswell Park Memorial Institute

Dr. J. F. Danielli, Biophysics Department, School of
Pharmacy and Biology Department

Dr. J. Ambros, Department of Coagulation, Roswell
Park Memorial Institute

Dr. T. J. Bardos, Department of Medicinal Chemistry,
School of Pharmacy

Dr. P. Hebborn, Department of Biochemical Pharmacology,
School of Pharmacy

Dr. R. Jones, General Clinical Research Center, Roswell
Park Memorial Institute

Dr. W. Meeker, General Clinical Research Center, Roswell
Park Memorial Institute

Dr. H. Mihick, Department of Experimental Therapeutics,
Roswell Park Memorial Institute

Dr. U. Kim, Pathology, Roswell Park Memorial Institute

Dr. D. Triggle, Departments of Biochemical Pharmacology
and Biophysics, School of Pharmacy

This committee has studied the rate-limiting factors in the
development of new drugs for cancer chemotherapy. In the course
of this, plans have been developed for an in-house drug design and
evaluation program which should greatly accelerate the development

of new compounds. It is expected that these plans will become effective in 1968, and if our expectations are fulfilled, a detailed report will be prepared in that year.

1. DEFINITION OF FIELD OF INTEREST:

STRUCTURE OF SCIENCE .

2. FINANCIAL SUPPORT:

(a) N.A.S.A. Grant No. NGR 33-015-016 - Principal

Investigator: Professor J. F. Danielli.

(b) National Science Foundation Grant to the Linguistic
String Project, Institute for Computer Research in
the Humanities, New York University, New York, N.Y.

Project Director - Naomi Sager.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

State University of New York at Buffalo

Jon Ray Hamann	Assistant Research Professor Center for Theoretical Biology, Principal Investigator.
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Other Institutions:

Y. P. Carignan	Feltman Research Laboratories, Picatinny Arsenal, Dover, N. J.
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W. Giordano	Clinical Research Department, Sandoz Pharmaceuticals, Inc. Hanover, N. J.
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J. J. Kaufman	Research Institute for Advanced Studies (RIAS) 1350 South Rolling Road, Baltimore, Maryland
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4. RESEARCH PROGRAM:

A. Generalized Probability Theory.

The problem of providing an acceptable interpretation of the notion of probability persists and is characterized by the diversity of opinion concerning the degree to which probabilities are subjective, objective or purely formal. In that the concept of probability is fundamental to most theories of inductive inference, there is a corresponding confusion in this area of logic. Regardless of the particular viewpoint concerning interpretation it seems to be invariably held that the probabilities in question satisfy the axioms of the ordinary (classical) calculus of probabilities. That this is not universally true, however, is now rather generally accepted in the case of quantum theory and is gaining acceptance in optimal decision theory. A note offering certain comments on a possible resolution of this problem and outlining an approach to the axiomization of quantum probability theory has been presented.

B. Adaptive Systems Theory.

Within the framework of a generalized stochastic decision-theoretic interpretation of physical theories, an effort is underway to formulate the phenomenological laws of systems in terms of optimization principles for the system probability function (and its subsumed persistency function).

C. Stochastic Axiomization of Quantum Theory.

On the basis of the above formalization of quantum probability theory and within the framework of the adaptive systems structure, an approach to the presently nonexistent "natural" axiomization of quantum theory has been suggested.

D. Semiempiricism.

Implicit in the method of optimal-entropy-inference is the fact that the ordinary minimum-energy principle is a special case of the minimum free-energy principle which in turn can be shown to be equivalent to the maximum-entropy principle. If constraints are included in the minimum-energy method in a manner equivalent to their role in optimal-entropy-inference, then one has a logical foundation for semiempirical quantum theory in terms of the existent constrained-energy-minimization procedure.

E. Stochastic Theory of Cross Linking in Polymers.

In conjunction with the experimental study of Dr. Carignan on cross-linking in nitrocellulose work is being initiated to develop an adequate stochastic model of polymer cross-linking within the framework of the optimal-entropy formulation of irreversible statistical mechanics. Correlations of the theoretical calculations with network characteristics as determined by swelling and tensile strength measurements is anticipated.

F. Variational Principles in Quantum Chemistry.

A formal investigation of the relation between the Minimum Energy Principle and the Maximum Overlap Principle as well as a numerical study of the range of validity of the latter is underway in collaboration with Dr. Kaufman and Dr. Giordano.

G. Linguistics.

As a consultant (in Chemical Physics) to the National Science Foundation supported Linguistic String Project, Institute for Computer Research in the Humanities, New York University, New York, N. Y. directed by N. Sagar and growing out of the linguistic studies of Professor Z. S. Harris at the University of Pennsylvania, an effort is underway to apply the methods of formal linguistic analysis in the development of automated information retrieval techniques for scientific discourse.

H. Project in Science Education.

Work is continuing on a project directed to the development of texts, particularly at the elementary school level, for the teaching of the conceptual structure of science (including Mathematics, Physical Science and Language), on the basis of a single inferential structure.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "A Note on the Foundations of Generalized Probability Theory", J. R. Hamann, submitted to SYNTHESE.
2. "On the Logical Foundations of Semiempiricism", J. R. Hamann, accepted for publication in SCIENTIA.
3. "On the Constrained-Variation Method and the Inferential Structure of Semiempirical Quantum Theory", J. R. Hamann and W. Giordano, submitted to THEORETICAL CHEM. ACTA.

1. DEFINITION OF FIELD OF INTEREST:

THEORETICAL PHARMACOLOGY

2. FINANCIAL SUPPORT:

N.A.S.A. Grant NGR 33-015-016, Principal Investigator:

Professor J. F. Danielli.

3. FACULTY AND PARTICIPATING RELATIONSHIPS:

State University of New York at Buffalo

Jon Ray Hamann	Assistant Research Professor Principal Investigator.
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R. Rein	Associate Research Professor, Biophysics Department, School of Pharmacy
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D. J. Triggle	Departments of Biochemical Pharma- cology and Biophysics, School of Pharmacy
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Other Institutions:

B. Calesnick	Hahnemann Medical College, Philadelphia, Pa.
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Sister Christopher	Chemistry Department Fordham University, New York, N.Y.
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R. D. Cloney	Chemistry Department Fordham University, New York, N.Y.
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S. Gabay	Biochemistry Department V. A. Hospital, Brockton, Mass.
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W. Giordano	Clinical Research Department Sandoz Pharmaceuticals, Inc. Hanover, N. J.
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J. P. Green	Dept. of Pharmacology, Cornell University Medical College, New York, N. Y.
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J. J. Harkins	Research Institute for Advanced Studies, Baltimore, Maryland.
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J. J. Kaufman

Research Institute for Advanced
Studies, Baltimore, Maryland.

J. Olsen

Chemistry Department, New York
University, New York, N. Y.

4. RESEARCH PROGRAM:

An intensive program previously undertaken to extend pharmacological structure-activity studies so as to include the electronic structure of drugs as determined quantum mechanically and to employ these data in statistical mechanical models has been continued during this period. Specific aspects of this program include the following:

A. Antidotes to Organophosphorous Poisons.

The quantum mechanical studies of the oxime reactivators of organophosphorous blocked cholinesterases were continued via extension of the calculations to the other methyl pyridinium oxime isomers as well as the pyridine oximes. Initial attempts to correlate the calculated electronic distributions with pharmacological activity were undertaken. This effort has involved the collaboration of Dr. W. Giordano, Mr. J. Olsen, Dr. B. Calesnick, Dr. J. J. Kaufman and Mr. J. J. Harkins and is being extended with the collaboration of Dr. D. J. Triggle and Dr. R. Rein.

B. Cholinomimetics.

In conjunction with Drs. Triggle and Giordano the above work is being extended to the muscarinic systems and related compounds in an effort to uncover the nature of the stereo and optical specificity of these systems.

C. Indoles.

In conjunction with an experimental program of Dr. J. P. Green, calculations on an extensive series of indoles have been initiated, the objectives of this work include the elucidation of the mechanism of their hallucinogenic action.

D. Enzymatic Hydroxylation.

Also in collaboration with Dr. Green, a theoretical study of the mechanism of enzymatic hydroxylation is underway. This work is intended in part, to supplement the experimental studies on the role of enzymatic hydroxylation in the biochemistry of the amines.

E. Tranquilization.

In conjunction with an experimental study of Dr. S. Gabay on the relation of the tranquilizing action of the phenothiazines to their ability to inhibit, via competition with FAD, a highly purified D-amino acid oxidase apoenzyme preparation, we are beginning a series of calculations on the phenothiazines in order to elucidate the mechanism of binding.

F. Insectides.

In collaboration with R. D. Cloney and Sister Christopher a quantum mechanical study of the mechanism of the synergistic and antagonistic action (suggested by the studies of Dr. D. J. Hennessy) of the methylenedioxybenzene-type compounds is now being initiated.

5. PUBLICATIONS, PAPERS AND SEMINARS:

1. "Quantum Mechanical Calculation of Stability in 2-Formyl N-Methyl Pyridinium (Cation) Oxime (2-PAM) Conformers", W. Giordano, J. R. Hamann, J. J. Harkins and J. J. Kaufman, Mol. Pharmacol. 3, 307, (1967).
2. "Quantum Mechanically Derived Electron Distributions in the Conformers of 2-PAM", W. Giordano, J. R. Hamann, J.J. Harkins and J. J. Kaufman, in Physical-chemical Aspects of Drug Action, ed., E. J. Ariens, in press.
3. "Comparative Evaluation of Pi-Electron and Total Valence Electron Models", J. R. Hamann, W. Giordano and J. Olsen, submitted to Tetrahedron Letters.
4. "Quantum Mechanical Calculations on the Pyridine Aldoximes: The CNDO/2 Model", J. R. Hamann, W. Giordano and J. Olsen, submitted to J. Medicinal Chem.
5. "Quantum Mechanical Calculations on the Pyridine Aldoximes: Comparative Evaluation of the HMO, PPP, and XHMO Models", J. Olsen, J. R. Hamann and W. Giordano, submitted to Mol. Pharmacol.
6. "Comparison of the Quantum Mechanically Determined Electronic Structure of the Three Pyridinium Oxime Isomers (2-PAM, 3-PAM, and 4-PAM)", J. R. Hamann, W. Giordano, B. Calesnick, J. J. Kaufman and J. J. Harkins, to be submitted.

7. "Formal Semiempirical Quantum Theoretical Models in the Study of Carcinogenesis", J. R. Hamann, lecture presented in the Department of Environmental Medicine, New York University Medical School, New York, N. Y.
 8. "Intramolecular Electronic Structure in the Study of Drug Action", J. R. Hamann, lecture presented in the Department of Pharmacology, Cornell University Medical College, New York, N. Y.
6. MEETINGS:
1. Sanibel Symposium on Quantum Chemistry, Solid State Physics and Quantum Biology, Sanibel Island, Florida, January 1967. Symposium was in honor of Professor J. C. Slater.
 2. "Quantum Mechanical Calculations on the Pyridine Aldoximes: The CNDO/2 Model", presented before the American Society of Pharmacology and Experimental Therapeutics, Washington, D. C., August, 1967.
 3. "Quantum Mechanical Calculations on the Pyridine Aldoximes: Comparative Evaluation of the HMO, PPP, and XHMO Models", presented before the Division of Medicinal Chemistry, American Chemical Society, Chicago, Ill., September, 1967.

The following two staff members have also been supported by the Center for Theoretical Biology:

1. Dr. Enn Elbing, working with Professor R. J. Good, in the Chemical Engineering Dept.
2. Mr. B. Englander with D. A. Whaley in the Department of Biophysics.

Their work is described below:

1. Dr. Elbing's work has had two parts:

Construction and use of high pressure interfacial tension system. This has proceeded at a satisfactory rate. The cell has been fabricated and the system has been assembled. De-bugging of the apparatus is in progress. Preliminary runs indicate that the design is clumsy (in that the weight of the cell is excessive) but the system is quite workable.

Primary standard for liquid-liquid interfacial tension. It had been found, in the course of earlier work in this Laboratory, that there exists no absolute standard for liquid-liquid interfacial tension comparable to water, the "standard" for liquid-vapor interfacial tension. There is as much as 3% discrepancy among methods ordinarily considered reliable -- methods which agree perfectly in the measurement of the surface tension of water.

Work is in progress to establish a "standard value" for the benzene-water interface. This calls for use of at least two independent methods, if it is to be convincing

Work is now in progress on the Wilhelmy plate method; and agreement within better than 1% with the drop weight method has been achieved.

2. Mr. Englander's work has consisted of the following:

He helped build a combination thermoelectric and ice cooling device for use during fine dissection of nerve bundles under a dissecting microscope.

He built most of the power supply and control circuit for a separate thermoelectric cooler used in the final experimental setup to control the temperature of fluid inflow to the observation chamber.

He has worked extensively in the design and construction of a somewhat elaborate marine aquarium for the housing of experimental animals.

He has become a specialist in the drawing, filling and testing of our glass capillary micropipette electrodes.

Finally, he has shared many hours of experiment time with David Whaley frequently lending a very helpful second pair of hands.

V. REPORT FROM CENTER COMMITTEES

ACADEMIC COMMITTEE

The Academic Committee was formed concurrently with the move of the Center for Theoretical Biology to its new building on the interim campus, and has met at two week intervals since the beginning of September.

The primary responsibility of this committee is to coordinate the academic work of the Center for Theoretical Biology by extending and strengthening our research programs and promoting their symbiotic relationships by attending to our interactions with postdoctoral fellows and students through research and teaching, and by formulating and staffing new teaching programs.

Each member of the Academic Committee represents a working party or major research project in the Center, and at each meeting one member of the Committee presents his/or his group research program which is then discussed round the table. In addition to acquainting each other more closely with our work it has stimulated new ideas and suggestions for solutions to existing problems. The academic programs are described more fully in the section "Research Reports".

The committee has considered the teaching of theoretical biology, through existing courses and the implementation of new courses. For this purpose an education subcommittee has been formed to consider the problems at the undergraduate, graduate and postdoctoral levels. While the possibilities in undergraduate

teaching are under active consideration, several graduate courses are already in existence and postdoctoral training is approached in a flexible manner through existing courses and through the program handled by the Seminar Committee.

Next semester, a new graduate course in Theoretical Biology will be given, cosponsored by the Center for Theoretical Biology, the Biophysics and Biology Departments, and it will treat the following topics: (i) Spontaneous Assembly of Macromolecules, (ii) The Mechanism of Receptor Action, (iii) Models of Central Nervous System.

Among other courses cosponsored by the Center for Theoretical Biology and various University Departments next semester are:

Communication and Control in Biological Systems
(Biophysics 540)

Regulation in Biological Systems
(Biophysics 524)

GRADUATE STUDENT LUNCHEON COMMITTEE

The Graduate Student Luncheon Group continued throughout the year to meet on an informal level. No definite funds were available but we were able to meet for discussion, sometimes with a speaker. Invited speakers covered a wide range of interest in both the Arts and Sciences with topics varying from the Albright-Knox art exhibitions to drugs and drug addiction.

In spite of the informality it was felt that the meetings were a great success, with an average attendance of fifteen people each week. Following the move to our new quarters on the Interim Campus, we are planning to convert this into a weekly Center luncheon for all Center personnel, their wives and husbands. Ideas are being requested from members of the Center for speakers, topics, etc.

SEMINAR, PUBLICATIONS AND LIBRARY COMMITTEE

This has been a very active year for the committee.

There has been a full program of seminars, which has included outside and S.U.N.Y.A.B. speakers and has attracted support and attention from a wide academic circle.

A number of special lecture series and symposia were organized, which included distinguished visiting speakers.

The library has been reorganized and expanded, and last, but by no means least, careful consideration has been given to the publication of a C.T.B. Quarterly Bulletin, which will serve as a medium of communication with the rest of the University and other research groups and academic communities beyond our own borders. Publication of this Bulletin will start this year. The first issue and every future end of year issue will be the C.T.B. annual report, while the other quarterly issues will have a less formal style and may contain lengthier expositions of specific research topics and reports on Center activities.

Following are:

Program and brief synopses of the special lecture series and symposia sponsored by the C.T.B., which were:

(a) A series of lectures and discussions on Cell Systems

Theory was held from 10 - 18 April, 1967.

- (b) A lecture and seminar series by Dr. Paul Weiss, Professor Emeritus at Rockefeller University, from 1-15 May, 1967 was cosponsored with the Biology Department.
- (c) A lecture series by Dr. Mitja Rosina on Density Matrix Formalism to the Ground state of Molecules, was held from 18 - 27 September, 1967.
- (d) A symposium on Lipid Bilayers was held from 2 - 5 October, 1967.

(a)

CELL SYSTEMS THEORY

TO BE HELD BETWEEN APRIL 10th - 18th, 1967 AT

210 Winspear Avenue

Lectures will be from 9:00 A.M. - 10:30 A.M.

Discussion Groups from 2:00 P.M. - 3:30 P.M.

on Mondays, Wednesdays and Fridays

The following lecture schedule has been arranged.

- 9:00 A.M. 10th April, 1967: Introduction and Survey
Lecturer : J. F. Danielli, Director, C.T.B.
- 9:00 A.M. 12th April, 1967: Physical Principles for the Aggregation of Cells
Lecturer : N. Goel, Rochester University
- 9:00 A.M. 14th April, 1967: Cell Growth as a Stochastic Process
Lecturer : J. Hoffman, CTB and Dept. of Physics
- 9:00 A.M. 17th April, 1967: The Tertiary Structure of Proteins and the implications for Molecular Interactions in an Ensemble.
Lecturer : D. Shear, C.T.B. and Dept. of Biophysics
- 9:00 A.M. 19th April, 1967
21st April, 1967: Communication Between Cells and Cell Systems
Lecturer : K. N. Leibovic, C.T.B. & Dept. of Biophysics
- 9:00 A.M. 24th April, 1967
26th April, 1967: Metabolic Control Theory in Relation to Epigenetic and Genetic Models, Biochemical Automata and Selfreproduction.
Lecturer : R. Rosen, C.T.B. and Depts. of Biophysics & Math.
- 9:00 A.M. 28th April, 1967: Concepts of Molecular Mechanisms of Metabolic Control
Lecturer : H. L. Segal, Chairman, Dept. of Biology

LECTURE ABSTRACTS

April 10, 1967

J. F. Danielli

The general framework and content necessary for a generalized cell theory was set out, and a variety of approaches defined such as the use of the theory of molecular interactions, information theory, and communication and control theory. It was emphasized that in many areas of cell biology no theory exists, and that in particular the theory of the behavior of the cell as a unit remains to be developed.

April 12, 1967

Narendra S. Goel

Rochester University

AGGREGATION OF CELLS

The development of a multicellular organism includes the multiplication of the cells, followed by their differentiation and aggregation to form different organs. The nature of the processes by which tissue is generated, the various forms of the structure generated and the principles necessary for the particular form of this structure will be discussed. It will be emphasized that the minimum surface free energy requirement of thermodynamics dictates, to a large extent, the form of the structure. Various experiments done in the past for and against this hypothesis will be described and critically evaluated. To test the hypothesis, various calculations involving the hypothesis on the model cells which have been done and should be done will be described, together with the various

experiments which should be done to test the results of these calculations.

April 14, 1967

J. Hoffman

CELL GROWTH AS A STOCHASTIC PROCESS

Monte Carlo calculations of cell volume distribution using the digital computer are discussed. A random generation time, whose probability density distribution is based on data, is used to study the general equation for the growth of cell volume, V , with cell age t :

$$dV/dt = C_1 V^n + C_2 V^m$$

where C_1 , C_2 , n , and m are characteristic parameters. Adjustment of the latter can lead to the major known volume growth functions: (a) The Exponential (mass law), (b) linear with age, (c) growth rate dependence on surface area, and (d) self-limiting growth (a modified exponential). By adjustment of parameters the volume distribution are compared with observed data.

Basic factors causing a spread in cell volumes are illustrated in the case wherein cell volume growth rate is proportional to the cell volume. This is the mass law: $V = V_0 e^{\alpha t}$. A clone grown from a single cell shows groups of cells whose volumes differ by a factor of 2, regardless of the distribution of generation times. This kind of volume distribution is not observed. The conclusion to be drawn is that the constant α is in reality a variable. While

this is an extreme case of volume growth it shows that cell populations are probably heterogeneous in respect to volume growth rates. Factors contributing to this heterogeneity are: non-uniformity of available metabolites, temperature variation throughout the cell mass, cell interactions, phenotypic variations, and possibly mutations.

Another source of randomness in growth is discernible in the known phases of the cell cycle, namely, g_1 , S, g_2 , and m, where g_1 is the phase of protein synthesis and characteristic chemical differentiation, S is the DNA synthesis phase, g_2 the post synthesis period immediately preceding the mitotic phase, m. The concatenation of 4 time phases, each of which is subject to at least minor variations in length, will give rise to a random variation in their sum, a common observation in operations analysis. Hence, even though the volume growth parameters of a cell are constant, the generation times may be randomly variable.

A survey of the spread of generation times, of cell volumes, and the loss of synchrony in synchronized populations shows that the variation of generation time is the dominant factor. The volume growth rate parameters are of secondary importance. The data are reviewed on such organisms as bacteria, protozoans, and mammalian tissue cells, and are found to support the idea that the variations in length of the cell cycle phases is the primary cause of random growth.

April 17, 1967

D. Shear

THE TERTIARY STRUCTURE OF PROTEINS AND THE IMPLICATIONS
FOR MOLECULAR INTERACTIONS IN AN ENSEMBLE

It is possible that the tertiary structure, or conformation of proteins, is not completely determined by the sequence of amino acids in the polypeptide. In fact, it is clear that the state of proteins depends upon the environmental parameters, such as temperature, pH, etc. In addition, the fact that various enzymes undergo spontaneous denaturation may indicate that the native state of these proteins is a metastable state, and depends upon the history of the enzyme; that is upon the environment at the time of formation. It is suggested that the mechanical or dynamic properties of proteins in solution, and the existence of nonlinear oscillations of the molecule might serve (1) as a stability criterion for metastable states, and (2) as a means of interaction of individual molecules in an ensemble. Possible implications for isoenzymes, the immune response, autocatalytic kinetics of denaturation and renaturation, and extra-genetic adaption will be discussed.

April 19 - 21, 1967

K. N. Leibovic

COMMUNICATION BETWEEN CELLS AND CELL SYSTEMS

- (a) A review of neuron properties and some models of neurons in relation to signal transmission.
- (b) The activity of assemblies of neurons, examples of their organization and the significance in terms of information.

April 24 - 26, 1967

R. Rosen

METABOLIC CONTROL THEORY IN RELATION TO EPIGENETIC AND GENETIC
MODELS, BIOCHEMICAL AUTOMATA AND SELF-REPRODUCTION

- (a) General theoretical framework for control theories;
discrete and continuous input and state spaces.
- (b) Feedbacks and Stability
- (c) Epigenetic control models
- (d) Genetic control models and their analysis
- (e) Discrete control models; biochemical automata, self-reproduction, etc.

April 28, 1967

H. L. Segal

CONCEPTS OF MOLECULAR MECHANISMS OF METABOLIC CONTROL

The molecular mechanisms underlying the response of metabolic pathways in higher organisms to alterations in the environment, such as changes in hormone or nutrient level to drugs, to changes in physical parameters, etc., remains elusive. In approaching this problem the distinction between the basis of the selection pressure on unicellular and multicellular organisms should be considered. The obvious experiments into the question of how hormones control the flux through metabolic pathways have not revealed the underlying mechanisms. This failure suggests that there are some basic concepts lacking required for the design of meaningful experiments.



(b) Lecture Series



Dr. Paul

Weiss

• PROFESSOR EMERITUS
ROCKEFELLER UNIVERSITY

SPONSORED BY THE STATE UNIVERSITY OF NEW YORK AT BUFFALO
DEPARTMENT OF BIOLOGY AND THE CENTER FOR THEORETICAL BIOLOGY

DR. PAUL WEISS

"The hazards of a stress-free life" which Dr. Weiss describes in one of his lectures may be something he has never experienced. It would seem so, when one considers that since his birth in Austria in 1898 he has accomplished the following tasks. After three years as an officer in World War I he received his doctorate from the University of Vienna in 1922. Other academic degrees include a Ph.D., M.D. (hon.), Sc.D. (hon.), Dr. med. et Chir. (hon.). In Europe he worked in a number of laboratories as a traveling fellow of the Rockefeller Foundation before coming to the U.S. in 1930, where he has served in varying capacities in 24 universities. His scientific work is published in three books and 290 articles and he has served on editorial boards of 17 scientific journals. (He is a member of the National Academy of Science and also President of the International Society for Cell Biology.) His fields are developmental, cellular, neural and theoretical biology. During World War II he was Principal Investigator in charge of government research on nerve repair. He has received national and international recognition of his work, including citations from Germany, France, England and the United States. He speaks and writes three languages, is married and lives in New York City.

Seminar Schedule

MONDAY, MAY 1 - Cell Contact Specificity and Contact Inhibition
THURSDAY, MAY 18 - The Problem of Specificity in the Nervous System
(Health Sciences Building, Room 101 - 3:30 p.m. - 5:00 p.m.)

Lecture Schedule

TUESDAY, MAY 2 - Biological Concepts, Problems and Principles
THURSDAY, MAY 4 - The Living Cell and its Dynamics
TUESDAY, MAY 9 - The Cell Community
THURSDAY, MAY 11 - Technology of Pattern Formation
TUESDAY, MAY 16 - Differentiation and Morphogenesis
THURSDAY, MAY 18 - Growth and Growth Control
TUESDAY, MAY 23 - Neuronal Growth and Axonal Flow
THURSDAY, MAY 25 - Perspectives of Brain Function
(Health Sciences Building, Room 237 - 10:00 a.m. - 11:30 a.m.)

(c) ATTEMPTS TO APPLY THE DENSITY MATRIX FORMALISM
TO THE GROUND STATE OF MOLECULES

by

Mitja Rosina
Department, of Physics, University of Ljubljana
and
Nuclear Institute "J. Stefan"
Ljubljana, Yugoslavia

These lectures will take place at 210 Winspear Avenue from
9:00 A.M. to 9:50 A.M.

Monday, September 18 :

The concept of reduced density matrices.

Why use density matrices? Some advantages and disadvantages
of describing a many-particle system by its two-particle density
matrix instead of by its wave function.

Wednesday, September 20 :

Formal properties of reduced density matrices.

Some conditions on the one-particle and two-particle density
matrix in order that they represent a system of fermions.

Friday, September 22 :

Variational determination of the two-particle density matrix.

The difficulties of the variational calculation will be pointed
out. Some convenient approximate methods will be described. The
type and size of problems which are manageable will be discussed.

Monday, September 25 :

The connection between the density matrix and transition amplitudes.

The two-particle density matrix of the ground state contains some information about transition probabilities from the ground state to one-particle excited states (e.g. by light absorption).

Wednesday, September 27 :

The application of the density matrix approach to some molecular problems.

Discussion.

(d) SYMPOSIUM ON LIPID BILAYERS AT THE CENTER FOR THEORETICAL
BIOLOGY, S.U.N.Y.A.B. 3rd - 5th October, 1967

One of the most exciting developments of recent years has been the preparation of black lipid films of bimolecular structure. These resemble closely the Danielli-Davson model of the plasma membrane and their study could well throw considerable light on the structure and behaviour of natural membranes. During the last three years the Center has been actively interested in these structures and a symposium on Lipid Bilayers was held at the new Interim Campus on October 3 - 5th, 1967.

The first two days were allocated to recent experimental and theoretical findings on the formation, structure and properties of black lipid films. Papers were presented covering a range of topics including thermodynamics of bilayer formation, bilayer bubbles, and the mechanism of thinning. A paper on monolayer characteristics of bilayer amphiphiles was presented by Dr. D. A. Cadenhead of the Center and included an outline of some recent findings on the intriguing lecithin-cholesterol condensation in mixed monolayers. Two further papers presented by members of the Center dealt with dielectric constant and refractive index of lipid bilayers (Dr. S. Ohki) and the nature of the underlying forces responsible for their stability and thickness (Dr. V. S. Vaidhyanathan). Papers were also read on the effect of the double layer capacitance on the overall capacitance of lipid films and on the nature of the predominant

intermolecular forces controlling the lamellar thickness and inter-lamellar distance in bimolecular leaflet-water liquid crystalline phases. One session was devoted to the permeability properties of lipid bilayers and the transport of water, various organic solutes and ions, including ion selectivity induced by valinomycin, were discussed.

On the final day attention was turned towards the more biological aspects. In recent months it has been shown that action potential characteristics resembling closely those observed in nerve tissues may be induced into artificial bilayer membranes by the addition of certain proteinaceous materials. The meeting was fortunate in having Drs. Mueller and Rudin present (co-discoverers of black lipid films and induces excitation) to give detailed accounts of these findings and their views of the molecular mechanism responsible for those remarkable electrokinetic effects. A further paper stressed the importance of lipid composition on excitation phenomena. To conclude the meeting a free for all discussion was held on the relevance of artificial bilayer studies to natural membranes.

Wednesday, October 4th

COHERENT LIPID PHASES AND RELATED THEORIES

(Chairman - Dr. M. H. F. Wilkins)

- 9:15 A.M. Structure and Polymorphism in Lipid Water Systems - V. Luzzati
- 10:00 A.M. COFFEE
- 10:30 A.M. What are the Effects of r^{-6} Potential in a Lamella Lattice ? - V. A. Parsegian
- 11:15 A.M. The Electrostatic Free Energy of Interaction in Lipid Films - V. A. Vaidhyanathan
- 12:00 LUNCH

PERMEABILITY OF BILAYERS

(Chairman - Dr. A. Goldup)

- 2:00 P.M. The Effect of Cholesterol on the Water Permeability of Thin Lipid Membranes - A. Finkelstein and A. Cass
- 2:45 P.M. Permeation of Lipid Bilayer Membranes by Organic Molecules - R.C. Bean and W.C. Shepherd
- 3:30 P.M. TEA
- 4:00 P.M. Non-Electrolyte Permeability of the Lipid Bilayer - R. E. Wood
- 4:45 P.M. Ionic Permeability Properties of Thin Lipid Membranes - T. E. Andreoli
- - - - -
- 8:00 P.M. Dinner (Skylon, Niagara Falls)

SYMPOSIUM ON LIPID BILAYERS

LOCATION : Room 29, Center for Theoretical Biology
4248 Ridge Lea Road, Amherst, N. Y.

PROGRAM

Monday, October 2nd 8:00 P.M. Symposium Mixer
Maple Leaf Motor Lodge
1620 Niagara Falls Boulevard

Tuesday, October 3rd STRUCTURE AND PROPERTIES OF BILAYERS

(Chairman - Dr. F. M. Snell)

9:00 A.M. Introductory Remarks - Dr. J. F. Danielli

9:10 A.M. The Thermodynamic Properties of Bi-Molecular
(Black Lipid Membranes) - H. Ti Tien

10:00 A.M. COFFEE

10:30 A.M. Spherical Lipid Bilayer Membranes - R. Pagano
and T. E. Thompson

11:15 A.M. Monolayer Characteristics of Some Possible
Bilayer Components - D. A. Cadenhead

12:00 A.M. LUNCH

DIELECTRIC CONSTANT & CAPACITANCE OF LIPID BILAYERS

(Chairman - Dr. V. A. Parsegian)

2:00 P.M. Dielectric Constant and Refractive Index of
Lipid Bilayers - S. Ohki

2:45 P.M. The Electrical Capacitance of Lipid Bilayers
in Aqueous Solutions - C. T. Everitt and
D. A. Haydon

3:30 P.M. TEA

FILM PRESENTATION

4:00 P.M. Soap Films and Some Fundamentals of Thin
Liquid Films - K. J. Mysels

Thursday, October 5th

EXCITABILITY OF BILAYERS

(Chairman - Dr. T. E. Thompson)

9:15 A.M.	Action Potentials in Lipid Bilayer Membranes - D. O. Rudin
10:00 A.M.	COFFEE
10:30 A.M.	Molecular Mechanisms of Membrane Excitability- P. Mueller
11:15 A.M.	Compositional Factors in Excitability Characteristics of Lipid Bilayer Membranes - R. C. Bean, W. C. Shephard, H. Chan and J. T. Eichner
12:00	LUNCH

NATURAL MEMBRANES AND BILAYERS

2:00 P.M.	Natural Membranes and Bilayers - Discussion (Chairman - Dr. J. F. Danielli) Discussion starters: Dr. D. F. Parsons Dr. F. A. Vandenheuval
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Seminars held at the Center for Theoretical Biology and the
abstracts as they appeared on the notices:
January 5, 1967 Dr. Ruth Aranow, Research Institute Advanced
Studies, Baltimore, Maryland.

THERMODYNAMICS OF IRREVERSIBLE PROCESSES

IN INHOMOGENEOUS SYSTEMS

The equilibrium equations of Hart for inhomogeneous pure systems are generalized to include multicomponent systems in an external conservative force field. The rate of change of entropy is then calculated. The equations will be compared to equations of the homogeneous case and transport equations for isotropic inhomogeneous systems discussed using regular solution theory.

January 12, 1967 Dr. James F. Danielli, Director of Center for
Theoretical Biology

THE STABILITY OF LIPID MEMBRANES

The consequences will be explored of the orientation of the hydrocarbon chains on the properties of lipid bilayers.

January 26, 1967 Dr. Fred M. Snell, Professor of Biophysics

ON A STATISTICAL MECHANICAL DERIVATION OF THE HYDRODYNAMICAL EQUATIONS OF MOTION IN MULTICOMPONENT SYSTEMS

Employing an expansion of the perturbed nonequilibrium pair correlation functions which to an alternate to that used by Bearman and Kirkwood, the equations of motion may be derived in which the partial molecular stress tensor for each component acquire a new form. This new form under conditions of solenoidal flow of each

component is identical to that derived by Snell and Spangler from phenomenologic considerations and thus may be given macroscopic definition.

February 9, 1967

Dr. Lynn Sagan, Department of Biology,
Boston University

ON THE ORIGIN OF EUKARYOTIC CELLS

The eukaryotic (mitosing or higher) cell hypothetically arose as a result of symbioses between various prokaryotic cell lines. The origin of these prokaryotes, the evolution of mitosis in the resulting symbiont and the support of these ideas by evidence from biochemical cytology and the fossil record will be discussed.

February 16, 1967

Dr. Per-Olov Lowdin, Professor of Quantum Chemistry, University of Uppsala, Uppsala, Sweden, and Graduate Research Professor of Chemistry and Physics, University of Florida, Gainesville, Florida.

THE SIGNIFICANCE OF QUANTUM THEORY IN GENETICS

March 2, 1967

A. T. Steegman, Jr., Assistant Professor,
Anthropology Department

HUMAN RACE AS BIOLOGICAL ADAPTATION

A brief review of man's biological congruence to the "ecological rules" will be presented, followed by more detailed comments on the human head and face. Hypothetical models of facial form and its evolutionary biology will be stressed.

March 9, 1967

Chairman - Dr. K. N. Leibovic

Panelists - Drs. J. F. Danielli, D. Harker,
R. Rosen and F. M. Snell

PANEL DISCUSSION

Relationship between pure and applied research and the implications for useful and applied results of advances in basic knowledge.

March 16, 1967

Dr. David Harker, Director, Center for
Crystallographic Research, Roswell Park
Memorial Institute

STRUCTURE OF THE RIBONUCLEASE MOLECULE

Elucidation of the structure of the ribonuclease molecule by X-ray diffraction methods will be described, and the structure itself exhibited at a resolution of 2 Å

March 21, 1967

Dr. H. J. Bremerman, University of California
Berkeley, California

AN INFORMAL SEMINAR AND DISCUSSION MEETING

INFORMATION ESTIMATES IN BIOLOGY

March 23, 1967

Mr. V. V. Griffith, Goodyear Aerospace
Corporation, Akron, Ohio

A MODERN ALGEBRA APPROACH TO LEARNING THEORY

Recent advances in Algebraic System Theory and discrete optimal control appear applicable to behavior theory. It will be demonstrated for example that some very weak assumptions about goal directed behavior lead to existence of a valid drive reduction

hypothesis. One possible interpretation of the theoretical results is that there may be antidromic communication between neurons which would not be observed during conventional physiological experimentation.

March 30, 1967

Dr. V. S. Vaidhyanathan, Associate Professor,
Center for Theoretical Biology

SOME OLD BUT UNFAMILIAR RESULTS

Results of significance to the behavior of small ions near polymeric face with reference to activity coefficients, osmotic coefficients and thermodynamic potentials will be discussed. Some aspects of stability of lipid films will be presented.

April 6, 1967

Dr. Michael E. Fisher, Department of Chemistry
Cornell University, Ithaca, N. Y.

PHASE TRANSITIONS ON BIOPOLYMERS

The "melting" of a double stranded helical polymer (polynucleotide) is discussed theoretically. It is shown that in the limit of an infinitely long molecule a true phase transition can occur, the nature of which is determined by the effects of the excluded volume of the disassociated polymer loops.

April 13, 1967

Mrs. Mary Danielli, Research Associate,
Center for Theoretical Biology

A MNEMONIC MODEL FROM MADAGASCAR

Primitive conceptions of human environment are projected into a series of interlocking patterns, the whole forming a model at an early level, probably predating literacy, of man's environment relationships.

April 20, 1967

Dr. David A. Cadenhead, Associate Professor
of Chemistry, S.U.N.Y. at Buffalo

MONOMOLECULAR FILM CHARACTERISTICS OF SOME
PHOSPHOLIPIDS AND STEVOLS

Surface pressure and surface potential measurements have been carried out with chromatographically purified/synthetic materials, using a continuously recording, full automated Langmuir/Wilhelmy trough. Characteristics of single-component and mixed component films will be discussed with particular reference being made to cholesterol-phospholipid mixed films. Some biological implications will be pointed out.

April 27, 1967

Nicholas V. Findler, Professor of Mathematics
And Computer Research Scientist

AN APPROACH TO LEARNING, PATTERN RECOGNITION
AND SELF-ADAPTATION

Five different but interrelated computer models of learning are described and compared with human behavior.

May 4, 1967

A. I. McMullen, Professor, Theoretical Biology

THOUGHTFUL MACROMOLECULES

A theory of polynucleotide involvement in cognitive memory describes processes of storage, recall, Pavlovian conditioning and association in a reasonable manner, on the basis of induced "quantum micro-mutation".

May 11, 1967

Dr. Edmund M. Glaser, University of Maryland,

School of Medicine, Department of Physiology

NEURAL NETWORKS

Behavior of a large network of logical elements with neuronal properties is discussed. Particular attention is devoted to the ability of such networks to exhibit, under the proper circumstances, stable levels of spontaneous activity bearing some resemblance to that observed in physiological preparations. The approach is an analytical one employing no computer simulation.

May 25, 1967

Dr. Charles J. Mode, Associate Professor,

Mathematical Statistics, S.U.N.Y. at Buffalo

SOME REMARKS ON A STOCHASTIC CALCULUS WITH

APPLICATIONS IN EVOLUTIONARY GENETICS

A stochastic differential and integral calculus based on limits on quadratic mean and in probability will be discussed. Some simple stochastic differential equations describing the evolution of gene frequencies in populations will be derived.

June 8, 1967

Dr. Darold C. Wobschall, Biophysics Dept.
Roswell Park Memorial Institute

AN ELECTRET MODEL OF THE NERVE MEMBRANE

A theoretical model of the nerve membrane is considered in which individual layers of a bilayer are assumed to have the properties of an electret or ferro-electric. Computer calculations show the model displays the main features of nerve excitations; in particular, the initiation of the action potential by a reduction in the membrane voltage, the automatic return of the resting state, and accommodation.

June 15, 1967

Dr. Edmond Dewan, Data Sciences Laboratory
Air Force Cambridge Research Laboratory
(AFCRL) Bedford, Massachusetts

CYBERNETICS ENTRAINMENT AND BIOLOGICAL RHYTHMS

The speaker will discuss certain fundamental aspects of cybernetics and nonlinear oscillations and their relevance to mathematical models of such biological rhythms as EEG, circadian rhythms, fertility cycles, and REM cycles. In addition a theory for REM (or dreaming sleep) will be discussed. Time permitting, a short moving picture will be shown which demonstrates voluntary control of occipital alpha rhythms by alteration of eye position and lens accommodation.

June 23, 1967

Dr. A. E. Alexander, Professor of Physical
Chemistry, University of Sydney, Australia

INTERACTION OF PROTEINS WITH IONISED SUBSTANCES

Studies of model systems, using the techniques of insoluble monolayers and adsorbed films, will be presented. The changes in surface rheological properties are particularly striking and require theoretical interpretation.

June 27, 1967

Dr. S. Levine, Ph.D., D.Sc., Reader in Applied
Mathematics, Univ. of Manchester, England

NATURE OF THE APPROXIMATIONS IN CLASSICAL ELECTROLYTE

DOUBLE LAYER THEORY

Survey of developments during the past decade, relating to the validity of the Gouy-Chapman theory (based on the Poisson-Boltzmann equation) of the electric double layer. An appraisal of the limitations and potentialities of this theory.

June 29, 1967

Professor René Thom, Institute des Hautes
Études Scientifiques, Strasbourg, France

A DYNAMICAL THEORY FOR MORPHOGENESIS

Professor Thom is one of France's outstanding mathematicians, and has long been concerned with the determination of the global properties of manifolds and differential systems from local specifications. For some years, Professor Thom has been deeply interested in the relation between his mathematical work and the properties of

developmental systems in biology, as described, e.g. by Waddington.

His seminar will deal with the following points:

1. Structural Stability in Differential analysis and in biology.
2. A mathematical formulation of the notion of morphogenetic field.
3. Sketch of a global model for embryological development and metabolic regulation.

Professor Thom's seminar is sponsored jointly by the Department of Mathematics and the Center for Theoretical Biology.

July 6, 1967

Dr. Hugh Van Liew, Department of Physiology

COUPLING OF GAS DIFFUSION WITH CAPILLARY BLOOD FLOW:

EXPERIMENTS WITH SUBCUTANEOUS GAS POCKETS IN RATS

Equations (analogous to Warburg's classical equation for penetration of oxygen into a thick slice of tissue in a respirometer) have been developed for diffusion of gases across a gas-tissue interface in living animals when the tissue is perfused with capillary blood. Experimental data with several different gases are consistent with expectations based on the theory.

July 26, 1967

Dr. Anthony C. T. North, Laboratory of
Molecular Biophysics, Dept. of Zoology,
Oxford, England

THE STRUCTURE AND ACTIVITY OF LYSOZYME

X-ray crystallographic studies have revealed the conformation of the lysozyme molecule, and have been shown that inhibitor molecules bind in a surface cleft, thus allowing a tentative model of enzyme activity to be proposed.

July 27, 1967

Dr. Richard Bearman, Chemistry Department,
University of Kansas

THERMO-OSMOSIS OF GASES

Special seminar sponsored by the Center for Theoretical Biology and the Department of Biophysics.

August 3, 1967

Dr. Roberto Moreno-Diaz, Research Staff,
M.I.T. Instrumentation Laboratory, Cambridge,
Mass.

LOOPS IN NETS OF FORMAL NEURONS

Analysis of a net with loops. Stability and modes of oscillation. Criteria of stability. Synthesis of a net with loops. Maximum number of modes of oscillation. Realizability of a net capable of all modes of oscillation.

September 21, 1967

Dr. Joshua Jortner, Professor of Chemistry
University of Tel Aviv and University of
Chicago

THEORY OF EXCITON AND CHARGE TRANSFER STATES

September 28, 1967

Dr. Gilbert N. Ling, Director of Theoretical
Biology, Pennsylvania Hospital

MEMBRANE THEORY: ANOTHER VIEW -

A summary of recent theoretical and experimental work concerning the molecular mechanisms and their control in cell physiology with special emphasis on ion solution and water distribution and transport problems.

October 12, 1967

Dr. Luigi M. Bianchi, Postdoctoral Research
Fellow, Department of Physics and Center
for Theoretical Biology

SOME POSSIBLE MECHANISMS ON VISUAL INFORMATION PREPROCESSING

Partial review of problems in the visual pathway. Survey of some attempts to simulate the visual pathway. Attempts to describe the physiological and anatomical requirements for a meaningful simulation and modeling - PAPA-like system.

October 19, 1967

Dr. K. N. Leibovic, Department of Biophysics
and Center for Theoretical Biology

PROBLEMS OF INFORMATION PROCESSING IN THE VISUAL PATHWAY

Some problems of sensory communication will be discussed, which can be fruitfully studied theoretically and which shed light on the operation of the central nervous system.

October 26, 1967

Dr. Joseph G. Hoffman, Department of Physics,
and Center for Theoretical Biology

LUMINESCENCE IN METABOLIZING CELLS

Studies of luminescence in salting-out and in acid-base neutralizations will be described. The general question of radiationless transitions in cell metabolism provides a theoretical background for luminescence studies.

November 2, 1967

Dr. Roy M. Pritchard, Department of Psychology,
McMaster University, Hamilton, Ont.

CORTICAL CONDITIONS FOR FUSED BINOCULAR VISION

Single neuron discharge patterns in the cortex of cats under fused binocular stimulation.

November 9, 1967

Dr. Robert Featherstone, Chairman, Department
of Pharmacology, University of California

MOLECULAR STUDIES OF ANESTHESIA

The binding of xenon and cyclopropane to specific sites in myoglobin and hemoglobin, as studied by X-ray diffractions and other techniques, will be described. These associations, which involve binding energies of 10 Kcal/mole, will form the basis for a discussion of anesthesia mechanisms from the molecular end of biology, rather than from the usual correlation of physical properties with anesthetic potency.

November 16, 1967

Dr. Michael Scriven, Department of Philosophy,
University of California

PROBLEM OF METHODOLOGY IN BIOLOGY

November 30, 1967

Dr. Manfred E. Clynes, Chief Research
Scientist and Director, Biocybernetics
Laboratories, Rockland State Hospital,
Orangeburg, N. Y.

THE INNER PULSE SHAPES OF MUSIC AS A PSYCHO-PHYSIOLOGIC
MEASUREMENT RELATED TO THE PERSONALITY OF THE COMPOSER

A musical thought includes an inner musical pulse. It is found that there are characteristic pulse shapes for different composers, when the subjects are discerning musicians, such as Serkin and Casals. Shapes are measured by thinking musical pieces only (without actual sound). Shapes are seen to be consequences of "presence" program algorithms and appear to reveal aspects of both the inner emotional makeup of the composer and of the elements of emotional existence in man.

December 7, 1967

Dr. Robert Rein, Principal Cancer Research
Scientist, Department of Experimental Path-
ology, Roswell Park Memorial Institute and
Center for Theoretical Biology and Department
of Biophysics

QUANTUM ASPECTS OF DNA

A review of the current status of the Quantum Chemistry of DNA will be presented. The topics to be discussed will include:

- a) electronic structure and spectra of the nucleotide bases
- b) band structure in DNA
- c) calculation of intermolecular forces, i.e. stacking and hydrogen bonding energies.
- d) role of Quantum mechanical methods in testing biologically significant models.
- e) Quantum mechanical contribution to the theory of the helix coil transition

December 14, 1967

Dr. Herbert Jehle, Physics Department,
The George Washington University

SYMMETRY IN PHYSICS AND BIOLOGY :

BILATERAL SYMMETRY IN MORPHOGENESIS OF EMBRYOS

December 21, 1967

Dr. Donald F. Parsons, Biophysics Department,
Roswell Park Memorial Institute

NEW X-RAY DIFFRACTION DATA ON MYELIN MEMBRANE

AND A RECONSIDERATION OF ITS INTERPRETATION

A sensitive Koatky small angle x-ray camera has been used to obtain more precise data on myelin. It appears that the swelling experiments of Finean do not phase the data with certainty. We have made calculations that show several different models can be adjusted to fit the data. The merits of these different models will be discussed.