perspectives on recent progress in BIOPHYSICS

By A. G. Tweet

The Symposium on Biophysics reported in these pages was held in conjunction with the celebration on April 18, 1963, of the 25th anniversary of the New York State Section of the American Physical Society, which was organized on April 2, 1938, at a meeting held at Union College in Schenectady. A. G. Tweet, the author of the present report, is a solid-state physicist who has been associated with General Electric since 1953.

"A BIOPHYSICIST is a physiologist who knows how to fix an amplifier." Thus spake Walter A. Rosenblith of MIT's Research Laboratory for Electronics during his discussion of signal processing in biological systems at the Symposium on Biophysics of the New York State Section of the American Physical Society. This symposium, held in the General Electric Research Laboratory auditorium at The Knolls, Schenectady, N. Y., April 19 and 20, was the eighth in the series of semiannual meetings of the Section devoted to special topics in physics.* It was held in conjunction with the 25th anniversary celebration of the founding of the Section at Union College.

The purpose of the symposium was avowedly tutorial. Hence the invited speakers had to be both fully qualified to assess the significance of recent experimental and theoretical results in a field somewhat removed from the purview of the typical member of the audience and able to keep the audience in a lively state throughout a program filled with unfamiliar terms, new concepts, and unsolved problems. All comments by those in attendance attest to the uniformly superb level of the presentations by the symposium panelists, who gave so freely of their time and erudition to make the program a success. The New York State Section is deeply grateful to them all.

* See: George W. Hazzard, High-School Physics Teachers and the Local Sections of Physics Societies, *Physics Today*, March 1963, p. 56.

The program was divided into two main parts, of which the first dealt with physical structures essential to life processes, proceeding down in scale of size from the entire free-living cell to the cellular fine structure, and then to nucleic acid and protein molecules.

M. D. Rosenberg (Rockefeller Institute) began the Friday morning session with a survey of the enormous variety of sizes and shapes of cells, emphasizing the relation among structures, function, and chemicophysical environment. By culturing individual cells from kidney tissues, for example, in an environment where they are able to maintain themselves as free-living organisms, it is possible to show the effect of change in acidity of the medium on the shape of the cell. There is as yet no understanding of these environmental influences on cell shape. Dr. Rosenberg next described the motion of cells. He presented striking time-lapse motion pictures (70× normal speed) made by his colleague, Paul Weiss of the Rockefeller Institute, which showed the streaming of chloroplasts in plant palisade cells, mitochondrial movement, cellular nuclear rotation, and a remarkable set of pictures of pulsating salmon eggs. Nothing is known about the forces giving rise to these motions, and Dr. Rosenberg pointed out the need for study of current conjectures, such as de Jong's suggestion that chemical potential gradients in coacervate-rich and coacervate-poor regions of the cell are responsible.

The next speaker, J. David Robertson (McLean Hospital, Belmont, Mass.), discussed the membranous fine structure of cells. An electron microscopist, Dr. Robertson began by describing in detail the techniques of preparation of biological materials for electron micrography. This is a very nettlesome point, since there is an understandable tendency on the part of the uninitiated to believe everything they see in an electron micrograph of a histological section until told how the specimen was fixed, stained, and sectioned, and thereafter to believe nothing. The speaker's clear presentation, however, was very helpful in providing perspective and in distinguishing between what is likely to be real and what is artifact in this highly technical subject.

Dr. Robertson showed, among other things (the projectionist confided to the reviewer that this speaker established a new course record for rate of slide presentation at our laboratory), pictures of the formation of mitochondria, the energy-converting bodies in the cell, with detail suggesting the mechanism of invagination of the inner membranes. He also presented some fascinating new research findings on nerve synapses which suggest the existence of a hexagonal net of point contacts between the nerve endings. The question of how ion flow takes place across these synaptic discs from one neuron to the next is basic to an understanding of biological information processing on the molecular level.

The next two speakers, Bruno H. Zimm (University of California, La Jolla) and J. L. Oncley (University of Michigan), carried the discussion directly to the molecular level, with papers on nucleic acids and proteins, respectively.

Dr. Zimm gave a brief tour of the nucleic acids, pointing to the importance of hydrogen bonding in determining physical properties such as melting curves of DNA. He mentioned recent work at La Jolla on the dependence of the melting point on the guaninecytosine (GC) content of the DNA. Hydrogen bonding in GC base pairs is stronger than in adenine-thymine base pairs and hence the melting point goes up with GC content. By heating the DNA of a virus to a certain temperature, it is possible to denature particular characteristics of the virus without harming others. This behavior is presumably related to the fact that the more heat-sensitive characteristics are coded on a part of the DNA which has a lower GC content.

Dr. Oncley introduced the audience to the polypeptide chain and to its secondary and tertiary structures. He then discussed the significance of the advances in understanding of proteins being brought about by sequential analysis and x-ray structure analysis. Both of these are very active fields at present, Dr. Oncley himself being one of the important contributors to the former. The problem of the relation of protein shape in vivo to its shape when crystallized for x-ray study is frequently mentioned, and the audience drew some comfort from the speaker's mention of the fact that ribonuclease shows enzymatic action even when in the crystalline state.

The afternoon session was devoted to dynamics of living systems, starting with a presentation by D. E. Green (University of Wisconsin Enzyme Institute) on the energy-conversion mechanism of the cell. Dr. Green stressed the ubiquitousness of the mitochondrion, the structure which changes food into energy, and of its principal product, adenosine triphosphate (ATP). This molecule is used as the energy-rich fuel in all biological syntheses, and is crucial in membrane transport regulation and muscle action. The speaker described work which has led to the concept of the elementary particle, or EP (of which there is happily only one, so far, in biology!), where most of the ATP is made. The point here is that the EP is a structure necessary for efficient utilization of food, even as the chloroplast is a structure necessary for photosynthetic storage of light energy, and that the significance of these structures is very imperfectly understood at present.

M. B. Hoagland (Harvard Medical School) next discussed the genetic code and protein synthesis. The dogma that DNA makes RNA makes protein is by now as thoroughly ingrained in all readers of the *Scientific American* as is the doctrine of the triplet code. Professor Hoagland summarized these theories clearly and concisely, and then went on to discuss the role of the ribosomes, with particular emphasis on the regulatory mechanism of protein synthesis. Hoagland suggests that the reason s-RNA is so much larger ($20\times$) than the base triplet, which presumably carries a single codon, is to provide for regulation and specificity of control of protein production. This extra information may be necessary in order for the cell to decide *which* protein to make and at what rate.

The question of control raised by Hoagland hung heavily in the air during the next two papers, which wound up the Friday session. The first, by F. O. Schmitt (MIT), one of the outstanding pioneers of biophysical science, dealt with the "wet" aspects of the neural network. That is, the facts about the neuron system which Dr. Schmitt listed were arrived at through histological, biochemical, and electrical measurements on living nerve tissue, or tissue which had been damaged as little as possible. The results themselves, however, are immediately recognizable by the physicist as providing important clues to the system characteristics of the nerve networks. For instance, nerve cells, whose total number is essentially fixed at birth, are rich in ribosomes: they consume oxygen faster than any other cells in the body, and the cells resynthesize themselves at a rate corresponding to three times their own volume per day! Why all this constant activity? Dr. Schmitt believes there must be a code which is constantly renewing and adjusting itself. Adjustment, or control, of the code, often called biological feedback, together with readout of the code, is closely related to the learning process. For example, there is evidence that when a rat is taught a new skill in a maze, the base ratios in the RNA of its brain change. Considering that memory is *not* in the part of the brain where the information arrived, but is rather distributed over the cerebral cortex according to some plan at present unknown, an incredible number of elementary chemical reactions must go on in a learning brain. Clearly these must be rapid reactions and must, furthermore, involve large molecules to ensure specificity of reaction. With these facts in mind, the challenge of Dr. Schmitt's final question is enormous: How can specificity of structure be read out in a fast reaction?

Dr. Walter Rosenblith, who was quoted out of context at the beginning of this report, presented the other side of the coin on neural networks. His discussion focused on the system performance aspects of the neuron system. With the use of highly refined experimental techniques, including liberal use of computers for averaging and correlating nerve-stimulation data, Dr. Rosenblith has been studying the pattern of auditory responses of animals. He has found that reliable data can be obtained from unanesthetized animals at a signal-to-noise ratio considerably less than one, if enough responses are averaged, and provided the time base is properly fixed. Using these techniques, he has been able to map out the response characteristics of auditory reactions and to show that a great deal of signal processing goes on as the signal ascends the auditory channel. For example, the first reaction to a sharp click in the ear of a cat is at ~ 20 μsec, although the entire cat takes $\frac{1}{4}$ sec to respond to the click. A study of the cochlear structure reveals a complex array of delay times, frequency responses, and wave forms in the neural output vs signal input. These results form a useful set of constraints on any mathematical model of the auditory system performance. However, the real problem, as Professor Rosenblith puts it, is not to simulate any one pattern of response, but rather to provide an economical model for the enormous variety of responses the system is capable of exhibiting.

Weary but undaunted, the membership and symposium speakers repaired to the Guest House at The Knolls, where they were the guests of the General Electric Research Laboratory at a pre-banquet cocktail hour. The evening's program was particularly festive, the spirit of the 25th anniversary celebration continuing to make itself felt. The retiring chairman of the New York State Section, D. R. Morey of Eastman Kodak, received a commemorative gavel and a good bit of chaff from incoming chairman K. H. Moore of Rensselaer Polytechnic Institute. Dr. Morey was the instigator of the series of symposia on special subjects which has done so much to enliven recent meetings of the Section, and his tenure as chairman was filled with spirited discussion and activity.

In the spirit of the symposium subject, the evening speaker, John C. Lilly, director of the Communication Research Institute, spoke to an overflow crowd on his work with dolphins at Miami, Florida, and Charlotte Amalie, St. Thomas, V. I. As was the case during the daytime session, those members of the audience who could not be seated in the auditorium of the Research Laboratory were accommodated in a nearby conference room with a closed-circuit television link.

Dr. Lilly spoke with the aid of a motion picture of his dolphins and tape recordings of their speech, which consists of noises as complicated in speed and variety of sound as are those of birds. Dr. Lilly is a very enthusiastic and able speaker, and at least one junior member of the audience made pointed comparisons between dolphin research in the blue Caribbean and his father's solid-state research in New York State.

Following a series of brief papers describing biophysical work in the tri-city area, the Saturday morning session of the symposium began with a discussion of the excited states of molecules of biological importance by J. R. Platt (University of Chicago). Dr. Platt discussed the particle-in-a-box model of condensed conjugated ring systems, and pointed to the probable biological significance of the long-lived triplet states of molecules. He also suggested that the so-called n-π^* transitions, in which an electron in a nonbonding orbital is promoted to an excited state in the cloud of conjugated π electrons, should be of biological importance because the states are localized and should be thus able to confer specificity on reactions. He noted, however, that such transitions should give rise to very little optical absorption because of poor overlap of the n and π^* orbitals.

Professor Platt was followed by E. Pollard (Pennsylvania State University), whose words concerning structure evidently struck a responsive chord with much of the audience. Dr. Pollard's remarks implied that until structure is well mapped out, understanding in the sense of the physicist would not be attainable, and that physicists would

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Fig. 1.

probably be intimately involved in settling the structural questions in the biosciences. The speaker's pioneering work in the effects of radiation on biological material is well known to all and formed the backbone of his lecture.

For the final speaker in the symposium, we were fortunate to have H. K. Hartline (Rockefeller Institute), who presented his views on biological sensors, as exemplified by the visual process. In a masterly discussion which placed the results of electron microscopy, electrophysiology, psychophysics, and signal-processing systems mathematics in logical relation to each other, he explained the present state of our knowledge of the process of seeing. Dr. Hartline particularly emphasized the fact that the processing of the incoming visual signals begins right at the receptor, and that interconnections among the receptors and the neural network leading up the visual pathway to the brain permit a highly complex set of enhancements and inhibitions to occur. Such a state of affairs seems almost essential when one considers that there are over 10^8 receptors in the human eye: If it were otherwise, we would be all nerve tissue!

As a simple but extremely suggestive example of the role of interconnections in neural nets, Dr. Hartline showed data on the so-called Mach bands (the same Ernst Mach that we all know from

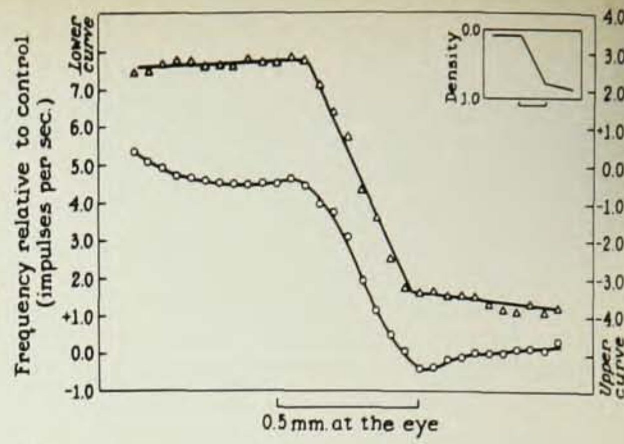

Fig. 2.

Mach's principle) as seen by the horseshoe crab, limulus. This crab has only $\backsim 10^3$ primary receptors in its eye, and it is relatively easy to study the output from a single isolated receptor or from the entire optic nerve. Fig. 1 is a photograph of a gray wedge. The light and dark bands seen at either side of the wedge are an optical illusion and are the Mach bands. In limulus, as in the human eye, the frequency of firing of an optical neuron is a measure of the intensity of light signal perceived (Fig. 2). If a single limulus receptor is isolated and scanned across the gray wedge, whose optical density as a function of position (prior to reproduction by half-tone processes), is given by the insert in Fig. 2, the rate of firing of the receptor cell, and hence is perception of light intensity, is a monotonic function of position (the triangular data points in Fig. 2), while if the entire eye is scanned, the average frequency of the pulses has two excursions from this value at the position of the Mach bands (the circular data points in Fig. 2). Hence, the "psychological" phenomenon of this "optical illusion" is really a property of an interconnected signal transmission system and not of the "mind" to which it is feeding data. Dr. Hartline's example beautifully epitomizes the problems, the challenges to interdisciplinary cooperation, and the great aesthetic satisfaction to be derived from studying biological systems, where we may be reasonably sure that answers to our questions can be achieved and where we can be equally sure that they will *not* be achieved without the best efforts of some of the best scientists.

In conclusion, the author of this summary would like to thank K. H. Moore and D. R. Morey for inviting him to organize this Symposium. He wishes also to thank W. W. Beeman of the University of Wisconsin and W. H. Johnson of RPI for valuable consultation concerning subject matter and speakers. H. M. Rozendaal was a valued consultant in all aspects of the planning.