

PHYSICS and BIOLOGY —Where Do They Meet?

Although biological phenomena must have physical origins, impedance matching between the two sciences turns out to be difficult. Unlike physics, biology is not a coherent field. Moreover physical concepts and the generalities of its mathematics often do not lead anywhere in life sciences. Social problems, too, impede the physicist who would turn biologist. But the problem exists: how to use physical instruments and methods to meet the challenges of medicine and biology. It behooves us to find a way.

by *Walter A. Rosenblith*

Few people would question the status of physics as a mature science. Physicists possess a highly developed and successful arsenal of techniques and instruments that serves them well in their quest for ever more encompassing conceptualizations. In contrast to physics and the physical sciences, the life sciences and medicine in particular have traditionally lacked precision in both measurement and concept. Until the Second World War the biological disciplines seemed condemned to a data-rich and theory-poor existence. The lack of deep insight was hardly compensated for by the philo-

sophical debates and doctrinaire battles fought under the banners of vitalism and reductionism.

The last two decades have witnessed an appreciable change. Students of living systems—ranging from macromolecules to man—eagerly embraced the armamentarium of the physical sciences. Those who had the least training in these sciences harbored great hopes that the systematic use of a precision instrument was going to yield substantive fringe benefits of a theoretical or at least conceptual nature. Such expectations proved more realistic with respect to molecular biology than in the area of brain function.

Clearly a deeper understanding of biological mechanisms cannot be gained without a greatly increased use of the tools of the physical sciences. However, new concepts are needed to deal with the “specificities” and “organized complexities” of multicomponent, multipurpose, multi-input, and multioutput systems that are both genetically determined and environmentally shaped. Concepts for living systems, which process, convert, and control mass, energy, and various forms of *information*, must obviously be compatible with the physical properties of the componentry. These physical properties represent as important a constraint for

On his way from Vienna to Cambridge the author has been exposed to problems in several disciplines: communication engineering, physics, psychoacoustics and neurophysiology. He has been at MIT (Department of Electrical Engineering and Center for Communication Sciences, Research Laboratory of Electronics) since 1951 and specializes now in the biophysics of certain aspects of brain function: neuroelectric activity, sensory communication, hearing. This article is based on an address Professor Rosenblith delivered recently before representatives of the Corporate Associates of the American Institute of Physics.



model making in this realm as the biological performance of the overall system does.

Finally, medicine does not prosper by conceptualization alone, and many a human life may be preserved with the help of chemicals or physical devices whose precise role in the functioning of the human body is not completely understood. In its quest for better health our society seems ready to engage massively its technological potential whether it be derived from defense, space, or even basic research. What seem to be lacking are social arrangements and trained personnel.

The biological physicists

In the history of physics there have been a number of outstanding men interested in biological problems. The names of Cavendish, Volta, Ohm, Helmholtz, Young, Maxwell, and Mach come to mind; indeed Schrödinger, before the days of quantum physics, wrote several papers on visual problems and returned to a biological theme late in his life. My first problem in biophysics led me back to the diaries of Faraday in which he described putting end-to-end some electric eels that Alexander von Humboldt had brought to him from the Amazon. This attempted high-voltage source could be considered a primitive model of a linear accelerator.

Let us assume that the biological phenomena we are able to understand best are those that have an accessible physical-chemical substrate. Then clearly any reasonable measurement, any reasonable investigation, of biological phenomena has to involve physics—that is, the concepts of physics, the techniques of physics, the instruments of physics. Thus workers in biology must not only have a mastery of physical instruments and techniques but also understand the extent to which the physical concepts on which these instruments and techniques are based apply to the biological problems they investigate. They may of course have to go beyond merely applying existing concepts and instead adapt them or even devise new ones that are testable by either the original or new physical methods.

There was a time when it was fashionable among young physicists, mathematicians, and engineers to be a bit over-optimistic about the effort it would take to “solve” the problems of living systems. Those who held these brave illusions quickly divided themselves into two categories: the quitters and those who stayed for dinner. Not all of the latter achieved Nobel prizes, but those who did so in the biophysical areas did not achieve them merely for superficial application of some

powerful technique or instrument they had brought along from their days as physical scientists. Those who shifted careers successfully were attracted by the challenge of complex living systems, a challenge that seemed to demand all their skills, all their logical capabilities, all their knowledge of physics together with an enormously important intuition about biological phenomena. To study systems so advanced, so well evolved that they excel in many ways, contemporary engineering systems added a special motivational spice.

When young physical scientists come to discuss their interest in switching their careers to a study of living systems, I am often led to pose the following question: “Are you mainly interested in living systems because you would like to aid man, because you would like to aid NASA, or because you would like to aid our understanding?” A colleague of mine added, “Don’t forget that people may want to get into this because it may be profit-making.” With regard to this fourth motivation, if it is one, I have little to recount.

Why study living systems?

The desire to help man is probably the strongest motivation of many of these young people who would like to advance human welfare. They have not come to this position because they share any guilt complex but because it seems to them a very normal human impulse. In many instances, however, they lack a clear picture of how, as physicists or electrical engineers, they might fit into the established institutions of human welfare.

Let me say, somewhat parenthetically, that if these institutions are going to make intelligent use of the talents of young physical scientists, they will have to change. To run a hospital today the way it was run when there was only a doctor and a nurse, with precious little to measure, is obviously impossible. Most good doctors and good hospital administrators realize this necessity for change. Health institutions are engaged in a process of differentiation that will result in a division of labor among a variety of experts. It is too early to foretell what the new hierarchical order will turn out to be and how responsibilities will in the future be allocated to physicians, physicists, computer engineers, social scientists, administrators, and so forth. But unless these experts can be attracted into medical institutions and offered a role in shaping their evolution, much of the good will and enthusiasm of young physicists will be wasted.

The symbol of the second motivation is NASA. It focuses around the man-machine systems of Mer-

CHARGED PARTICLES

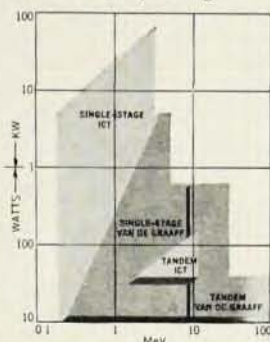


THE ICT CONCEPT:

new high-current machines
emerging from HVEC research

Development of higher energy Van de Graaff particle accelerators which retain high beam precision, stability, and homogeneity, remains a continuing contribution by HVEC to "energy-oriented" research.

To provide even greater freedom of experimentation, HVEC is also anticipating the need for the higher beam intensities required in power-oriented research projects. Invented by Dr. R. J. Van de Graaff, the new Insulating Core Transformer (ICT) accelerator now provides high beam currents with all the desirable beam char-



acteristics of Van de Graaff machines. As the graph shows, the high power levels available from the ICT accelerator now make possible a new realm of precision experimentation.

The Insulating Core Transformer

The ICT is essentially a three-phase power transformer with multiple secondaries, each of which is insulated from the other. Rectified current from the secondaries is series-connected to achieve total voltage. In the ICT, electrostatic and electromagnetic fields exist in the same space, as contrasted to the conditions in a conventional transformer. The result is a highly efficient dc power source capable of stable operation at elevated potentials and power levels.

A number of ICT accelerators and power generation systems are now available.

Single-Stage ICT Accelerators

Two types of single stage ICT accelerators have been developed for research use. The first incorporates an ICT power source coupled to the acceleration assembly through a coaxial cable.

	PROTON ENERGY (KeV)	CURRENT (MAX.) (Analyzed)	TANK HEIGHT Feet	HEIGHT Meters	TANK DIAMETER Feet	DIAMETER Meters
ICT 300	300	15 mA	4'4"	1.32	4	1.2
ICT 500	500	10 mA	5'3"	1.60	4	1.2

The second system utilizes a rigid transmission line to transmit electrical power to the accelerator terminal.

4 MeV ICT	ENERGY (MeV)	CURRENT	DIMENSIONS Length Feet	Length Meters
Positive Ions	1.5-4	3 mA	26'6"	8.08
Electron Conversion	1.5-3	10 mA	26'6"	8.08
3 MeV ICT Electrons	1.5-3	20 mA	29'	8.84

8 MeV ICT Tandem Accelerator

The 8 MeV ICT Tandem provides proton energies continuously variable from 3 to 8 MeV at a maximum guaranteed beam current of $2\mu\text{A}$. The ICT power source is capable of providing 12 mA at 4 mv which, in combination

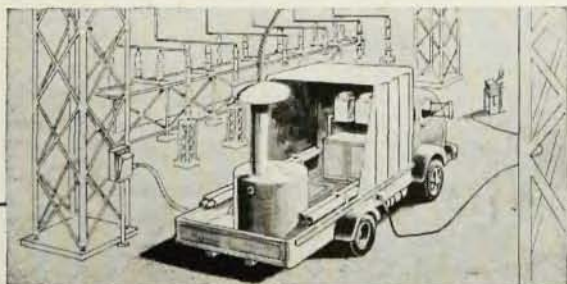
with newly developed components emerging from HVEC, will enable the accelerator to keep pace with future research requirements. The 8 MeV Tandem is convertible to single-stage ion or electron operation.

ICT Electron Processing Systems

Developed primarily as high-current sources of electrons for industrial processing applications, these systems allow extreme flexibility of operation. Two models are available: 300 kv at 30 mA maximum beam current and 500 kv at 20 mA maximum beam current.



Series 7 ICT Power Supplies



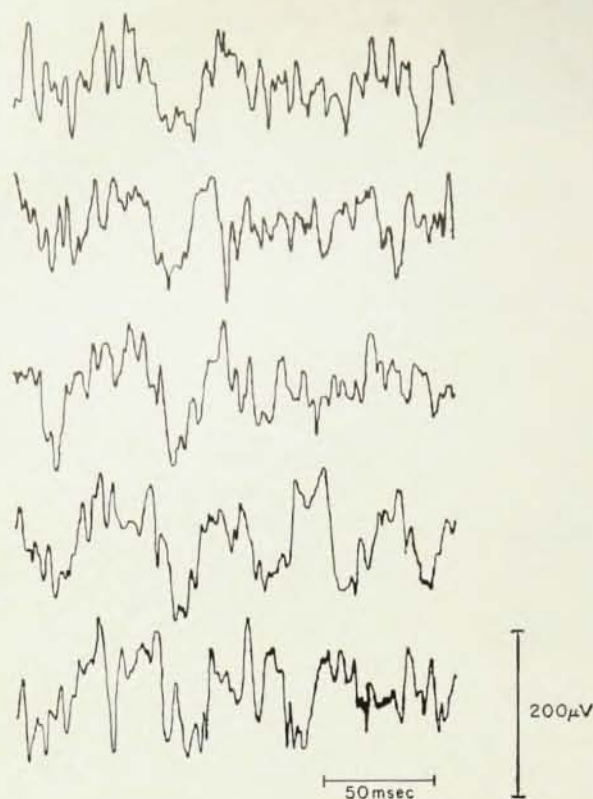
ICT equipment has crossed many barriers to dc operation at high particle energies and currents. There is no indication that a ceiling exists to further advances of similar importance.

Available with output ratings ranging from 240 kv at 80 mA to 600 kv at 20 mA, these highly stable power sources are suitable for use in high energy beam separator systems, r.f. transmission systems, plasma research and high voltage testing programs.

For detailed information, please write to Technical Sales, High Voltage Engineering Corporation, Burlington, Massachusetts.

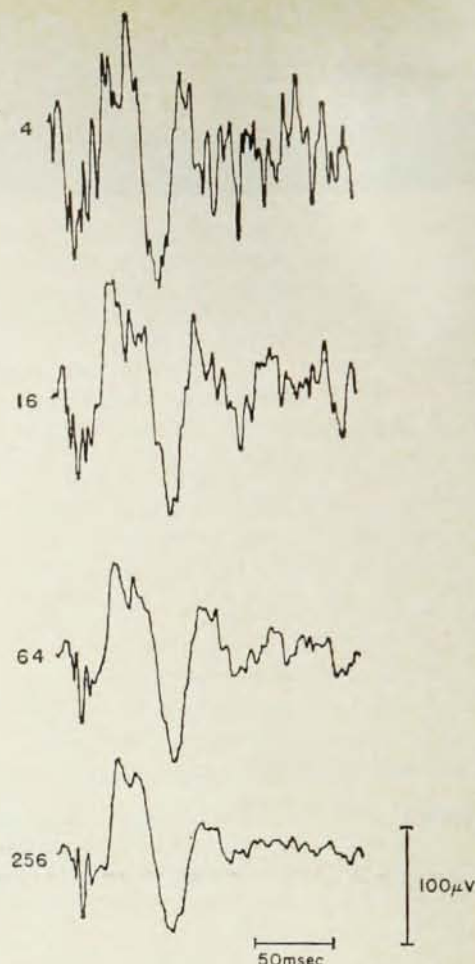


HIGH VOLTAGE ENGINEERING



PHYSICAL MEASUREMENTS FOR BIOLOGY. Five successive responses to audible clicks were recorded as electrical activity at the auditory cortex of an unanesthetized cat. Each trace (above) was started by a click of moderate intensity. Though not easily or clearly distinguishable, systematic deflections appear to be present in the five traces. The deflections seem especially pronounced 70 to 80 milliseconds after the beginning of each trace. (Both parts of Fig. 1 are from N. Y-S. Kiang.)

—FIG. 1a



COMPUTER ANALYSIS. The traces above depict computer averaging of, respectively, 4, 16, 64, and 256 responses evoked by clicks. The data used include the responses shown in Fig. 1a. Each average-response trace includes the responses used in plotting the preceding trace. This procedure shows how a patterned-response waveform can be extracted from a background activity of much higher voltage, provided that the various response deflections are time-locked to the delivery of the stimulus.

—FIG. 1b

cury, Gemini, and Apollo—our engineering cathedrals in space. Here two rather different aspects of biology are involved: that of exobiology and that of manned flight. In this field the aerospace industry has had to “buy in” on biology. This fact sometimes troubles thoughtful industrial managers because they are not quite sure what they are going to do with this life-science capability once a particular man-machine program has been phased out.

The third class of motivations is that of basic research. How can the particular skills and ways of looking at problems that young physicists acquire be brought to bear upon fundamental issues in the life sciences? Is there an ideal training and education for these young people that will permit them to contribute optimally? Let us postpone dealing with this point a bit because it

exemplifies a more general problem, that of how one educates for dynamically stable and productive combinations of the physical and biological sciences.

Quantification is hardly enough

Whatever their motivations the young physical scientists often feel that their major assets consist of a certain knowledge of mathematics, an ability to break a problem down into manageable parts, and, perhaps foremost, an ability to use quantitative methods for both description and prediction. There is a belief inculcated by Lord Kelvin when he said, “I often say that when you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it

MAGNION®

HARVEY-WELLS

STATE-OF-THE-ART IN

Laboratory Magnets for '66

A CAPSULE REVIEW OF THE LATEST IN LABORATORY ELECTROMAGNETS AND BEAM HANDLING SYSTEMS

IMPROVED MAGNETIC FIELD REGULATOR AND FIELD SWEEP CONTROLLER

THE LATEST IN PULSED NMR SPIN ECHO SPECTROMETERS . .

NEW 15" AND 22" POLE DIAMETER ELECTROMAGNETS AND 50 KW, HIGH REGULA- TION POWER SUPPLY

OUTSTANDING SPECIAL LABORATORY ELECTROMAGNETS

HIGH FIELD PRECISION SUPERCONDUCTING MAGNET SYSTEMS

ON-LINE COMPUTER CONTROL OF CHARGED- PARTICLE BEAM TRANSPORT SYSTEM

Magnion's model FFC-4 provides absolute field set accuracies of 5 parts in 10^5 , sweep linearities of 1 part in 10^4 , long-term stabilities of 1 part in 10^6 of the *operating field* or 5 milligauss, and an unmatched thermal stability of 5 parts in $10^7/^\circ\text{F}$ over the *entire field range*. The FFC-4's sweep range and rate are continuously adjustable and sweep modes include linear, repetitive triangular, and repetitive sawtooth sweeps. Field deviation output and control input jacks are provided. Optional FFC-4 accessories now available include: zero gauss field set and sweeps through zero gauss; ultra slow field sweeps; field modulation; and synchronizing circuitry for triggering external equipment at a preset field level.

Magnion's Model ELH-15 now produces a 100 watt pulsed signal with a wide selection of pulsed sequences and is intended to satisfy most experiments employing fluid samples. It can be easily converted to a 3000 watt, high-power, rapid recovery, solid-sample system and for operation at different frequencies. Signal processing accessories include box-car integrators and aperture scanners and a pulsed gradient accessory for diffusion measurements.

The model F-158, a fabricated 15" pole diameter electromagnet, provides a field uniformity of 1 part in 10^5 over a $1/2$ " diameter by $1/2$ " long working volume @ 27,000 gauss across a $1 3/4$ " gap with 6" diameter pole caps utilizing Magnion's μ -Shim* Inhomogeneity Compensator. The model F-228, a fabricated 22" pole diameter electromagnet, is capable of field strengths in excess of 30,000 gauss across a 2" air gap with high field uniformity. The Model HS-25200, a new 50 KW power supply, current regulated to 1 part in 10^5 , is designed for use with the F-228 and other large electromagnets.

*PAT. APPLIED FOR

Among our recently introduced special iron core electromagnets are an electromagnet for MHD research which provides fields of 20 kilogauss across a 4" gap, with pole pieces 6" wide and 36" long; 60° and 90° sector magnets for use in mass spectrometry; and a cast 15" pole diameter, "C" frame electromagnet providing maximum accessibility and high fields specially designed for nuclear polarization experiments. The latter magnet may be obtained with the field direction vertical or horizontal and provides field strengths in excess of 19 kilogauss across a 4" gap.



Niobium Zirconium Superconducting Solenoid with Niobium Tin Insert.

Commercial superconducting magnets wound with niobium-tin are now available and Magnion has achieved field strengths in excess of 80,000 gauss in a 2" inside diameter. Frequently, combination coils consisting of a niobium-tin coil inserted into a niobium zirconium coil have proven to appreciably reduce the cost of achieving very high field strengths. Considerable experience has also been acquired in the design and manufacture of "split" coils which permit radial access, coils compensated to provide high homogeneity, and systems with horizontal and vertical access to ambient temperature working volumes. New current controllers regulated to 1 part in 10^5 with a current range of 0 to 100 amperes for niobium-tin coils, and 0 to 30 amperes for niobium-zirconium coils are now available. Highly stable field sweep circuitry and automatic quench protection circuits are incorporated in these current controllers.

Magnion's beam transport system for Atomic Energy of Canada, Ltd. (Chalk River Laboratories) will deliver a beam of mass energy product 3 to 175, to 14 target locations. A modified FFC-4 field regulator serves as the heart of a programmable control system utilizing either on-line computer control or one-knob manual control of all switching and focusing elements on any beam run. Automatic degaussing to zero field is provided for the switching magnets having straight through beams. The system's high accuracy of field setability and repeatability (5 parts in 10^5) have generated widespread interest in its use as a versatile analyzing magnet control system for use with cyclotrons and other particle accelerators. New 2.25", 3" and 4" aperture quadrupoles featuring a high degree of coincidence between mechanical and magnetic axes have also been recently introduced.



Complete Low Power Spin Echo Spectrometer System with Model FFC-4 Field Regulator.



Model F-158 15" Pole Diameter Laboratory Electromagnet.

For further information on any of these products and capabilities, please write or call Magnion, Inc., 144 Middlesex Turnpike, Burlington, Mass. 01804.

MAGNION®

HARVEY-WELLS

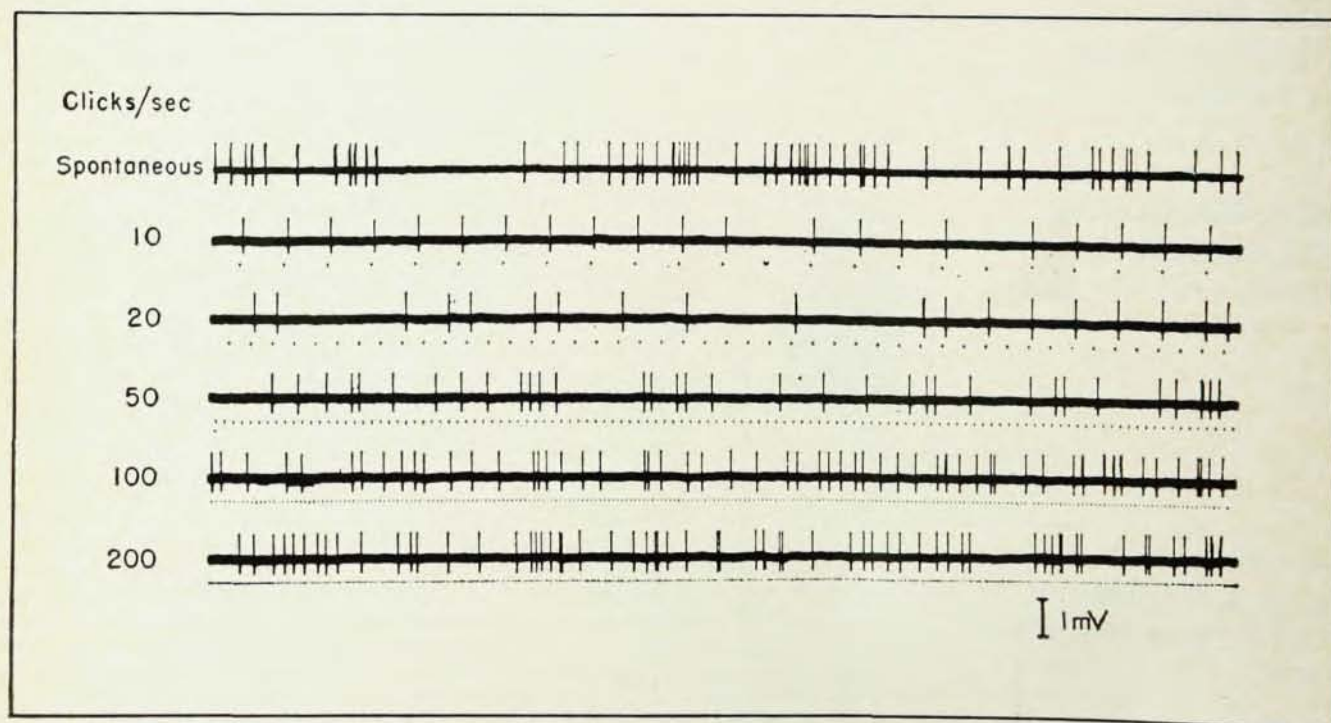
may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be." But is quantification really enough? One is tempted to quote Oppenheimer who in turn quotes Godel: "It is purely an historical accident that [mathematics] developed along quantitative lines."

Without philosophizing further about quantity versus quality or quantification for its own sake, let me illustrate my point by reference to a specific biological problem. Speech communication engineers have long been able to analyze speech or speech sounds with the aid of a well established measurement technology. Long in the past they knew that speech was a waveform with special properties. It remained intelligible in the presence of much interference: noise, narrow bandwidth, peak-clipping, and other hazards. Yet no matter how "precise" acoustic measurements were, they were not really satisfactory when the job was to predict whether a particular channel would provide satisfactory speech communication. These measurements were also not particularly useful in predicting the types of errors or confusions that might occur.

Without the insights of the linguist, the phonetician, the psychoacoustician, and the specialist in the physiology of speech production, the acoustical

measurements remained only precise. They were not closely enough related to the way in which people learn, produce, perceive, and confuse speech; they did not yield *by themselves* reasonable descriptions of the information-bearing features of speech; they were not predictive of how the intelligibility of a message is affected by the set of possible messages, by the "grammaticalness" of a sentence, etc. Today the various approaches to the study of language and speech communication show signs of having been at least exposed to each other. We are now able to ask such questions as the following: How do listeners decode an acoustic speech signal into a sequence of discrete linguistic symbols such as phonemes, and how do talkers encode a sequence of discrete linguistic symbols into a continuously changing speech signal? Does the intonation pattern of a sentence affect its processing by the listener? What characteristic features make for voice quality or identity? (It is known that we can get by with rather little precious bandwidth if all we are after is intelligibility and if we do not insist on recognizing whether we are talking to our mother or our brother.)

These and other unsolved problems still require careful physical measurements, but they are now made in the context of a model that aims at deal-



FELINE NERVE IMPULSES. This chart depicts nerve-pulse patterns in a neurone in the cochlear nucleus of a cat. The upper trace shows the spontaneous pattern of "spikes," or "all-or-none events," produced in the absence

of auditory stimulation. The lower traces are patterns recorded when audible clicks of moderate intensity were presented at rates ranging from 10 to 200 per second. (After G. L. Gerstein and N. Y-S. Kiang.)

—FIG. 2a

ing with the physical and biological (including psychological) events that occur as people speak and listen.

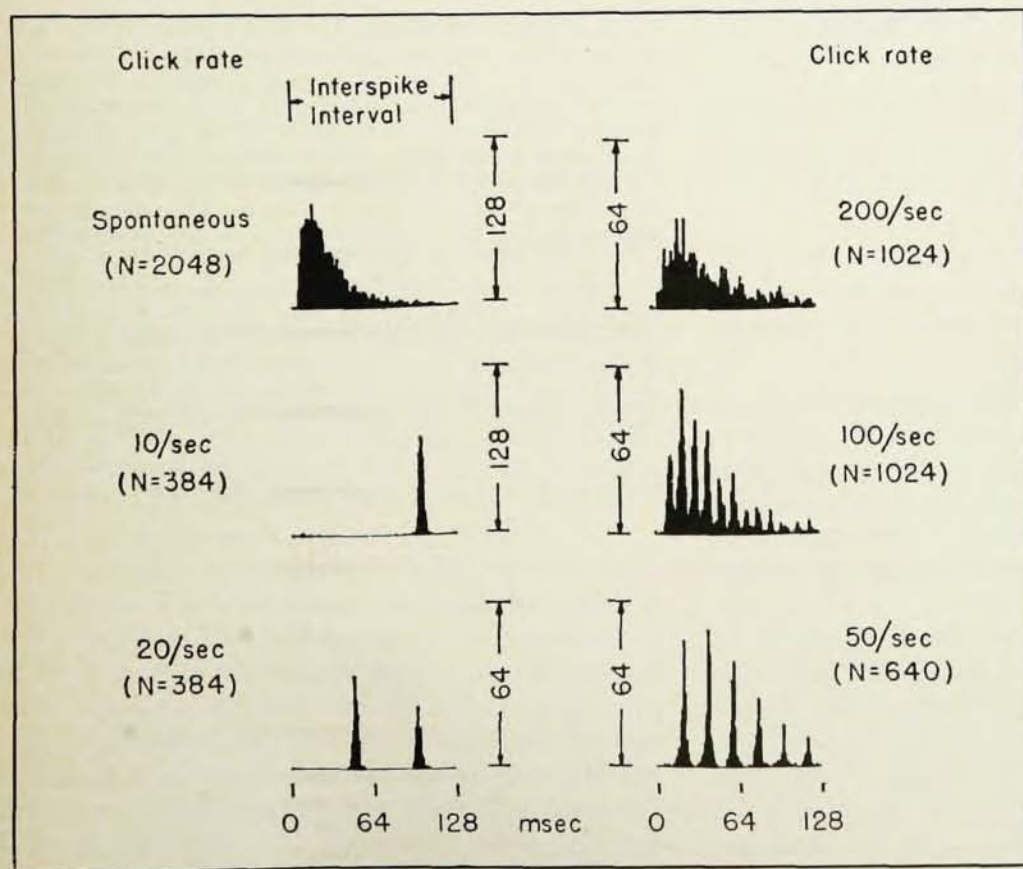
Properties of biological organization

When one talks about the degree to which present-day physical models apply to biological problems, one runs into the multiplicity of levels of biological organization. As we try to deal with the whole spectrum, from molecules to mind, we find that concepts that can be used meaningfully at several levels remain precious few. Energy, mass, and charge clearly have no obvious referents in the realm of human mental abilities. On the other hand these concepts are the very ones that have been so valuable in teaching us so much about the structure of biologically significant molecules.

However, when we talk about organized biological (that is, time-varying) materials, be they membranes or brains, our models of the structure of gases, liquids, and even solid-state materials must be greatly amended if the properties of highly specific living systems are to be described in a useful manner. Interactions between the elements that represent the biological componentry of a sensory or motor system raise issues of communication and control with which the physical sciences have not had to deal. Each level of biological

organization has developed its own phenomenology, and phenomenological descriptions of events have proliferated. Thus it has become extremely difficult to find quantities that can be measured in commensurable fashion at several levels, either simultaneously or at least in a related fashion. Membrane properties may serve as a useful example to illustrate our point. Membranes are physical or conceptual structures that constitute boundaries among certain systems. Across these interfaces are transferred physical quantities as such and also patterns of physical quantities that symbolically represent information. To measure the permeability of a cell membrane and to specify the largely symbolic traffic that flows across a man-computer interface is hardly a commensurable task. Each of these situations must ultimately be understood in terms of structures and events that have a physico-chemical substrate. But to expect that models can be formulated and made into a convertible conceptual currency capable of dealing with both of these extremes demands a degree of optimism that may be unusual even among young physicists.

Although conceptual models need to remain reasonably close to experimental verification or disproof, instruments or techniques can be used in the study of a great variety of biological problems as



HISTOGRAMS. The kind of information shown in Fig. 2a can be presented more effectively by the use of interval histograms. The histograms at left, corresponding to the sequences in Fig. 2a, were plotted from measurements of the intervals between the spikes of each sequence. (N is the number of spikes used in plotting each histogram.) Because of the number of spike events involved, such computations are done most conveniently with the aid of a computer. Interval histograms and other statistical displays readily lend themselves to mathematical model making. They also permit experimentation based on much more sharply formulated hypotheses than could be developed merely from information similar to that given in Fig. 2a. (After G. S. Gerstein and N. Y-S. Kiang.) —FIG. 2b

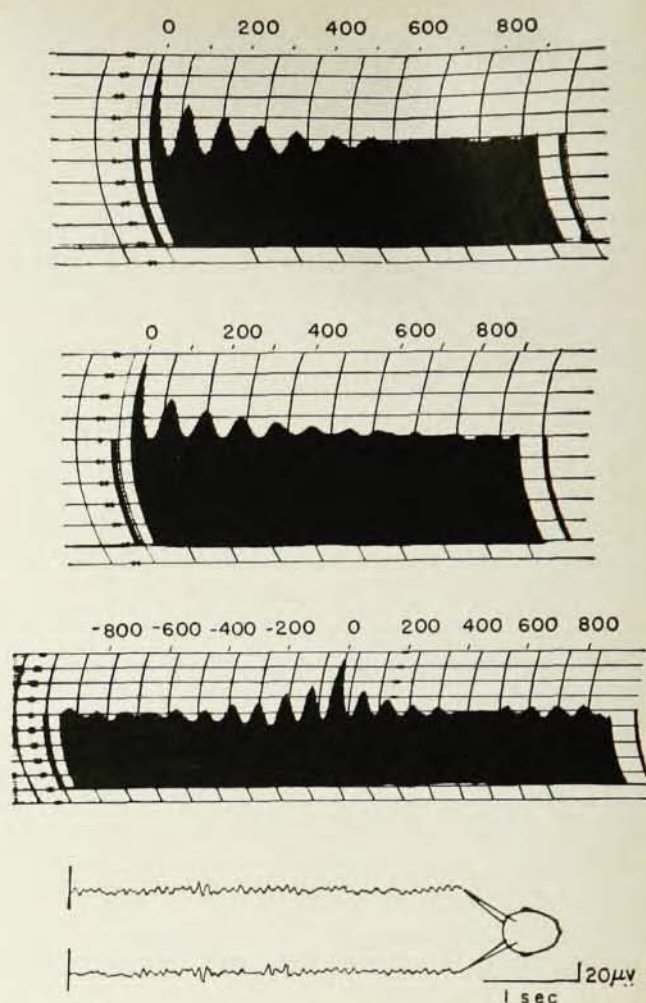
long as their use is guided by a fairly explicit model of the physical or symbolic operations of which the tool is capable. The technology that comes immediately to mind is that of electronic devices, among which computers deserve a place of their own. Electronic devices have made it possible to deal with a multitude of electric phenomena in biological structures involving quantities as small as microvolts and nanoseconds. Computer technology has not only enabled us to deal in symbolic form with a whole host of biological phenomena but it has also provided us with something akin to a prosthetic device for our logical capabilities. Thus we can process data "on line" (a fact that is of great importance in the analysis of the behavior of an organism whose "state" varies from instant to instant); we can write pattern-detecting programs; we can simulate the behavior of models that cannot be expressed in analytically manageable form. Contemporary biological research thus makes use not only of man's normal sensory, motor, and logical capabilities but enhances them by the tools that the species has developed in the course of cultural evolution. Without electron microscopes, micromanipulators, and computers, there would be little hope of inquiring successfully into the mechanisms of multi-component systems with many degrees of freedom.

Computers in life sciences

From among the many uses of computers in life sciences, I shall extract just three examples: one from the work of our group on the electrical activity of the brain and its neuronal componentry (Figs. 1, 2, 3), one from research in speech communication (Fig. 4), and a third from molecular biology.

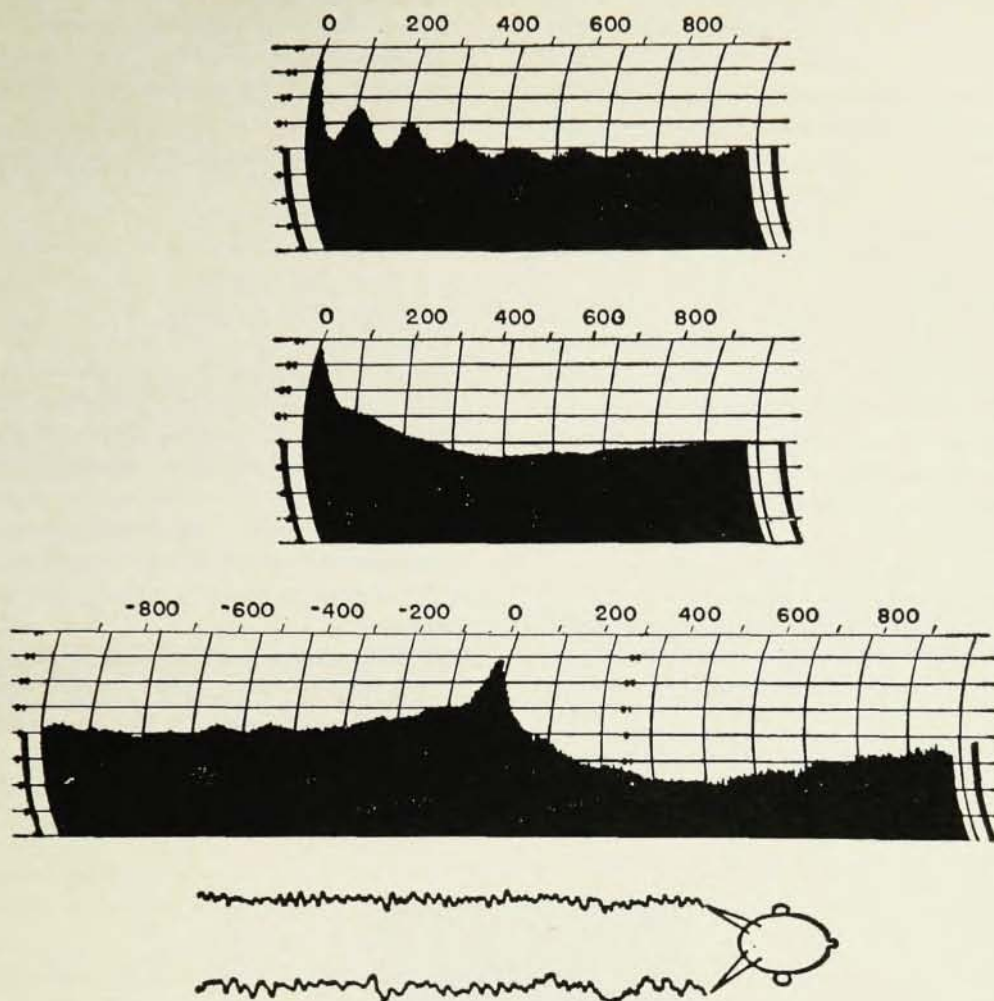
The physiological and acoustical events of speech production can be studied by modeling an appropriate mechanism. Once such a mechanism has been simulated or built, one can examine how it must be controlled if intelligible sequences of speech sounds are to be generated by the synthesizer. Synthesis of speech is achieved by specifying how certain parameters of the speech generating mechanism vary with time. These parameters control the behavior of the components of the model synthesizer.

In investigating procedures for the synthesis of certain speech sounds an experimenter may wish to modify the time function that specifies one or several control parameters. It then becomes imperative for him to be able to observe and assess the effects of such modifications on the synthesized speech. A facility that allows one to carry out



PHYSICS AND HEALTH. The correlograms above were computed from an electroencephalogram (EEG) of a normal human subject. At top is an autocorrelogram computed from the subject's EEG as recorded from above the left parietal-occipital area. Next below is an autocorrelogram computed from the EEG as recorded from the corresponding location on the right hemisphere of the subject's skull. In the third row is a cross-correlogram that gives further information on the relation between the electrical activity on the two sides: the fact that the highest value of the correlogram is at zero delay indicates that, on the average, the activity recorded at the two electrode locations was synchronous. The drawing at bottom illustrates a sample of raw data (ink traces) and shows the locations of the electrodes on the skull. The calibration marks below the drawing represent one second and 20 microvolts, respectively. Both parts of Fig. 3 are after Barlow, et al., in Rosenblith, W. A. (ed.), *Processing Neuroelectric Data*, MIT Press, Cambridge, Mass. (1959, 1962). —FIG. 3a

this type of experimentation has been set up by my colleague K. N. Stevens and his associates and is depicted in outline form in Fig. 4. Here the experimenter can (1) specify to the computer the desired behavior of the control parameters, (2) observe visually the control signal on a cathode-ray-tube display that is peripheral to the computer and (3) listen to speech that the computer-con-



EFFECT OF A TUMOR. These correlograms were computed from the EEG of a patient with a tumor in the right cerebral hemisphere. The upper correlogram represents activity in the left hemisphere, and the middle correlogram

activity in the right hemisphere. The asymmetrical cross-correlogram reflects the fact that the two hemispheres do not produce comparable rhythmic electrical activity. (Note dissimilarity of traces in drawing at bottom.) —FIG. 3b

trolled synthesizer generates. The experimenter reacts to what he hears and sees; he modifies instructions to the computer either through a typewriter or by drawing lines on the CRT with the aid of a *light pen*. The computer is programed to assemble a modified set of control parameters, to display them on the CRT and to direct the synthesizer to generate a revised utterance. The experimenter can iterate this exploratory procedure until he has obtained a satisfactory utterance. The latter can then be recorded on magnetic tape for use in a more formally designed experiment.

My colleague, Cyrus Levinthal (an ex-physicist who is now professor of biophysics in MIT's department of biology), has made use of computers in the arduous task of dealing with the structure of really large molecules. Let me quote a portion of a recent progress report by Professor Levinthal and his associates:

Many of the recent developments in molecular biology have depended on the understanding of the three-dimensional structure of large molecules. Such understanding is usually reflected in the ability to construct a three-dimensional model of the molecule under consideration. For really large molecules, however, such construction can be extremely difficult and time consuming and in addition it is virtually impossible to enumerate all of the many small interactions which contribute to the molecular stability. Thus, if a structure is known, physical models can be built, but the complexity of the process prevents one from using such models for examining a large number of different configurations.

During the last six months we have written a set of programs which allow us to construct, display and analyse macromolecules. . . . With the computer-controlled display and the real-time control of the projection of the molecule it is possible for the observer to obtain a true three-dimensional visualization of the molecule being studied. It is also possible

for him to interact with the program which generates the molecule by indicating the way in which particular parts of the structure are to be altered.

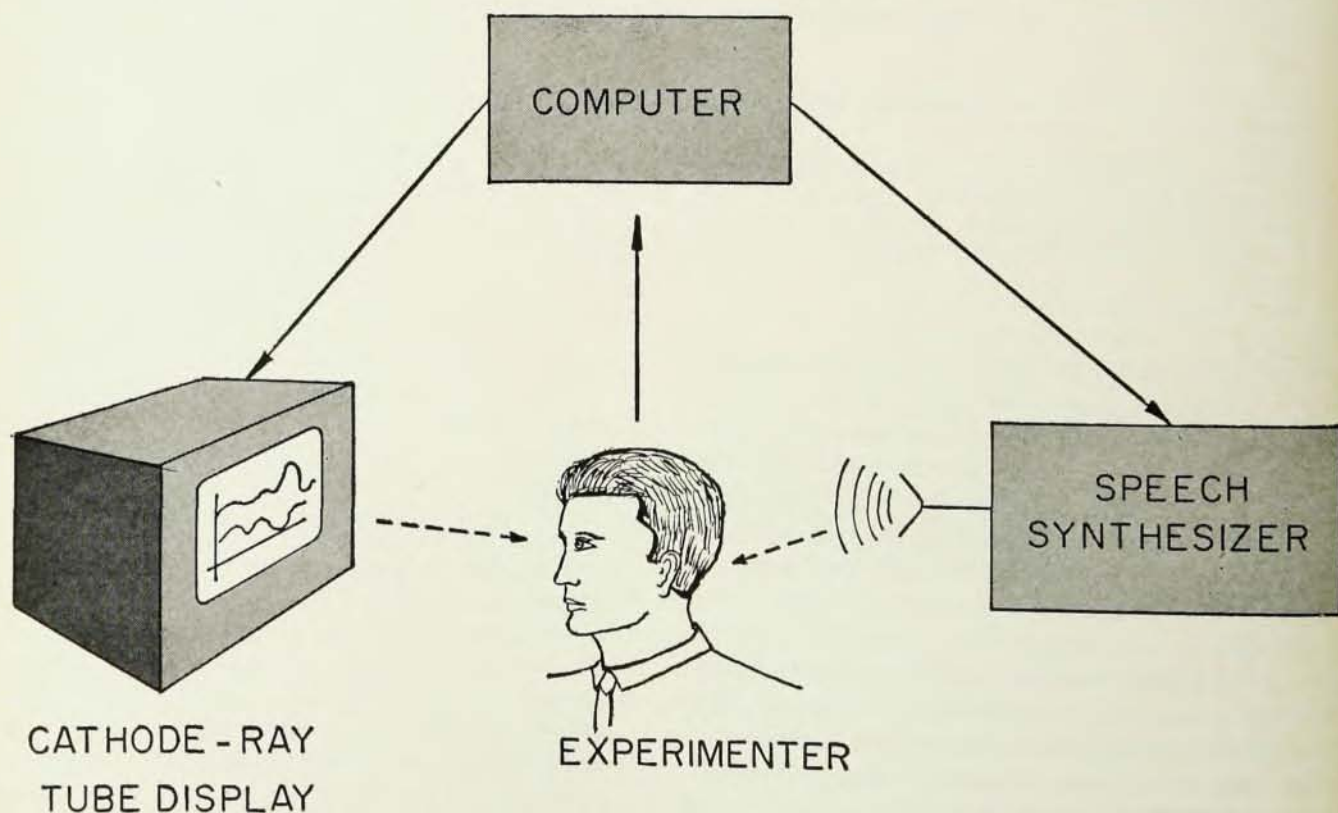
The first program written in this project calculated the coördinates of the atoms in a protein using as the input variables only those angles about which rotation is possible; all other rotation angles and chemical bond lengths were entered as rigid constraints in the program. The method of calculation involved treating each chemical bond along the linear peptide backbone as a translation and a rotation of a coördinate system attached to individual atoms. In this way the step from one backbone atom to the next involves a translation and a rotation matrix multiplication. The updating of the rotation matrix is determined either by the fixed rotation angles which are introduced as constraints in the program or as input data which the investigator adds to the program.

The basic data for these constraints on bond angles and lengths have been obtained over a number of years from the x-ray crystallographic studies of Pauling, Perutz, Kendrew and many others, and they are now very firmly based on experimental information.

Without dealing with the more technical details let me conclude by quoting a passage that conveys a feeling for the potential of this approach.

Since even a small protein molecule may contain 1500 atoms the total number of pairs to be tested is very large. In order to avoid the enumeration of all possible pairs, a set of programs has been written which divides space into cubes and then makes a list of all atoms in each cube. In this way it is possible to enumerate all pairs of neighboring atoms by searching through the cubes and listing those pairs in which one member is in a cube and a second member is in the same cube or one of the 26 surrounding ones. By using this list processing procedure it is also possible to define "holes" in a molecule by locating empty cubes surrounded by filled ones. In addition "insidedness" and "outsidedness" of the molecule can be determined by finding cubes which have filled neighbors on one side and empty neighbors on the other side. The knowledge of these aspects of the topology of a folded protein are necessary in order to evaluate the contributions resulting from the interaction of particular amino acid residues with the water which normally surrounds all protein molecules.

The foregoing examples illustrate several points: in the history of science decisive advances have often been made when it became possible to isolate modular elements ("atoms") of structure or of process. These modules made it possible to explore systematically consequences of either experimental



OBSERVING SYNTHESIZED SPEECH. To observe and assess the effects of control modifications on synthesized speech, an experimenter might use a facility like that sketched above. The experimenter could specify to a com-

puter the desired behavior of control parameters, he could observe the control signal on a cathode-ray tube, and he could listen to the speech sounds that the computer-controlled synthesizer generated.

—FIG. 4

or logical operations. Computer techniques whether used in the processing of data or in the filtering of possible models enable us to reduce in some sense the dimensionality of complicated systems. Attempts to characterize, design and inspect meaningful modular structures, operations or events at many levels of biological organization became thus possible.

Educational quandaries

It is now time to return to the problem of how one prepares oneself for work at this multifaceted, exciting, and unpredictable frontier between the physical and the biological sciences. Many diverse careers are possible, each constructed out of slightly different combinations of physical and biological or medical building blocks. Thus each career could require a different preparation, especially when we take account of how the life sciences shade over into the social sciences and into the art of medicine. Even in the academic sphere there is a certain lack of cohesion and communication among the various life sciences. This leads at times to a less-than-harmonious dialogue between the molecular and not-so-molecular tribes and even within these subgroupings. Prospective students may find this slightly cacophonous state of affairs a bit confusing.

Because we are in a period of rapid change in the physical sciences and engineering and since most of the problems that excite biologists today are likely to be either solved, shelved, or substantially reformulated twenty years from now, we must try to avoid training people who will become educationally obsolete in this fairly short time. This view forces us to consider the following requirements for young men and women who want to go into these areas: (1) an undergraduate education in the physical sciences and mathematics (including certain relevant engineering techniques) that is comparable in emphasis and quality to that given to students majoring in those fields, (2) early exposure to basic instruction in the life sciences, such as a course in molecular biology and another course dealing with complex living systems (whose understanding is likely to remain a challenge for some time to come), should provide both motivation and perspective, (3) concentration during graduate and postdoctoral study upon an area in the life sciences that has enough depth and breadth to remain an identifiable focus of lively research for an appreciable number of years.

What I am inveighing against is the illusion that one can design quasi-universal, viable, and neat educational packages by merely combining

two or three cut-rate curricula. Students who are interested in working in the life sciences from a physical viewpoint should not expect to find prefabricated programs of study that will lead them to clearly labeled "career slots" as painlessly and expeditiously as their fellow students who elect more monochromatic majors. Both students and academic institutions must be willing to experiment in these areas, and industry and government must be willing to support such educational experiments. Various government agencies have done so through important research and fellowship programs. However, neither industrial nor civil service positions nor even academic positions are always available for the young man or woman who cannot easily be "departmentally labeled." Elder scientific statesmen are often encouraged to roam into neighboring areas or even into philosophy, but our young postdoctorals in transition are sometimes forced to risk too much in terms of possible promotion or tenure if they have trouble passing through smooth departmental channels. Freedom to remain somewhat "uncommitted" during these productive years should pay off in terms of scientific results though admittedly it does not make for tidy organizational arrangements.

Needed: an incubator for a health industry

Given the amount of money we spend for health care—about 30 billions of dollars annually—and the increasing role that technology plays in this care, it is not very hard to prophesy that here is potentially a breeding ground for a great American industry. In contrast to the situation in the defense and space industries, however, relations between the "customer" and the industry remain largely unstructured. There exist no standard operating procedures for the development of health hardware (or for that matter software). The National Institutes of Health are being granted by Congress increasing funds to underwrite this type of development, but as yet they disburse much more for research than for development.

I do not mean to imply that there is too much support for basic research in the health sciences—far from it—but rather insufficient machinery to involve appropriate industries and applied research institutions in the development that must precede production and use.

Among the tasks that will have to be done before technologically up-to-date health systems can be engineered are the following:

1. An operations-analysis type of job needs to be done on health care—by teams consisting not only of health practitioners.

2. Most industries do not possess the biomedical competence required to qualify as prime contractors, and most health institutions are staffed by people whose education, training, and experience has left them barely acquainted with the resources of industry; hence some device must be found that will act as an effective impedance matcher between needs and capabilities.

3. The form that this impedance matcher should take is not entirely clear. We have little experience in this area and unusual risks are involved. (A vice-president of one of our biggest companies is reported to have said, "We cannot afford to have much newspaper publicity over the failure of one of our heart-lung machines. Imagine what this might do to our appliance sales." Industry is unwilling to face economic and prestige risks that are disproportionate to possible pay-offs.) Because of these risks it may be necessary to make a social innovation: American industry and the health professions might for instance form a special foundation with appropriate subsidiaries, or a public corporation could be formed to manage this job comparably to the way in which certain weapons or space systems are being managed.

4. Such a systems-managing organization, in which the public (that is, the many consumers) is represented, might assume responsibility for formulation of specifications, procurement of subsystems and components, appropriate market surveys, acceptance testing, the certification of new devices and systems, and undoubtedly also for a certain amount of advanced development.

5. Schools of management and engineering must prove responsive to the need for trained personnel in these areas.

The foregoing sketchy five points constitute no program of action; at best they point toward a necessary debate in which industry, government, the health professions, and medical and academic institutions must engage.

And in summary

What precedes is a potpourri of issues that rambles from the almost philosophical to the almost political. Talks to fairly heterogeneous audiences entail the danger that speakers will attempt to be more provocative than penetrating. The present overall topic tempts one to jump from point to point in the hyperspace in which the physical sciences and the life sciences meet and coexist.

Medawar recently distinguished four horizontal strata of biology (molecular biology, cellular biology, biology at the level of the whole organism, and biology concerned with populations or com-

munities of organisms), but one could without too much labor split some of these levels, especially if one were concerned with more applied aspects. However the four levels Medawar has chosen clearly emphasize the sizable gaps, the lack of overall cohesion, the absence of convertible models (mathematical or other) that beset contemporary biology. Nonetheless this state of affairs does not seem to interfere with vigorous, uneven growth; it seems even to have a particular attractiveness for people from the maturest of all sciences, physics. With the aid of instruments, techniques, and often inadequate concepts from the physical sciences, dramatic advances are being forced.

This progress carries along implications for the applicability of the new, more basic understanding of living structures. The technology of tomorrow promises to be physical technology *plus*—solid-state physics *and* molecular biology, computers *and* brains, pharmacological modifications of genetic constraints *and* defects, man *and* machines: these are some of the combinations of tomorrow. For society to reap the benefits of this mixed technology we must learn how to educate for it, how to provide the necessary social climate for it. We must encourage the emergence of institutions and values appropriate to this continuing technological revolution.

Research in communication sciences in the Research Laboratory of Electronics is supported by the Joint Services Electronics Program (Contract DA36-039-AMC-03200(E)), the National Science Foundation (Grant GP-2495), the National Institutes of Health (Grant MH-04737-05), and the National Aeronautics and Space Administration (Grant NsG-496).

References

1. G. L. Gerstein, N. Y-S. Kiang, An approach to the quantitative analysis of electrophysiological data from single neurons, *Biophysical J.* **1**, 15-28 (1960).
2. M. Halle, K. N. Stevens, Speech recognition: A model and a program for research, *IRE Trans. Inform. Theory*, **IT-8**, 155-159 (1962).
3. N. Y-S. Kiang, The use of computers in auditory neurophysiology, *Trans. Am. Acad. Ophthalmol. Otolaryngol.* **65**, 735-747 (1961).
4. D. Lerner (ed.), *Quantity and Quality*, The Free Press of Glencoe, New York (1961).
5. P. Medawar, A biological retrospect, *Advancement of Science* **22**, 357-362 (1965).
6. W. A. Rosenblith (ed.), *Processing Neuroelectric Data*, MIT Press, Cambridge, Mass. (1959, 1962).
7. E. Schrödinger, *What is Life?*, Cambridge Univ. Press (1944).
8. G. G. Simpson, Biology and the nature of science, *Science* **139**, 81-88 (1963).
9. G. Wolstenholme (ed.), *Man and His Future*, Little, Brown and Company, Boston (1963).