Nervous System Research with Computers

Directly connected computer systems permit more complex research and conceptual analysis.

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Research on the nervous system has reached the state where answers to many of the important remaining questions will require extremely precise and complex experiments. For investigations of the relations between stimulus and response, the requirements are more precise and complex stimuli, the recording of many more simultaneous response events with greater detail and precision, and more sophisticated methods of data reduction to detect correlated responses among extremely noisy information. To achieve these objectives, the use of a properly designed information-processing system as an integral part of the experiments is required.

The California Institute of Technology instigated a comprehensive interdisciplinary program of research on the nervous system some 5 years ago. An important part of this effort has been the development, during the past 3 years, of a suitable data-processing and control system, directly connected to a group of experiments on sight sensory systems. The system is designed to perform the following basic functions: (i) control of stimulus-response experiments; (ii) collection of data and complete documentation of many channels of information; (iii) extraction of selected information; (iv) data display during the experiment for direct control of the experiment; and (v) complex conceptual analysis or modeling.

Coupled with the development of this system has been research on new methods of data reduction and analysis. Formal mathematics, as it exists today, evolved largely under the influence of the physical sciences, and efforts to apply it to nervous system research have so far produced very limited results. Only recently have new "non-numerical" concepts of information processing been developed which make it possible to deal with complicated living nervous systems. The modern digital computer is required for the simulation of the nervous system, and the use of such computers is an important part of the Caltech program.

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Description of the System

The general characteristics of this new information-processing system are illustrated in Fig. 1. The system includes four interconnected computers, a multiplicity of memory elements, multichannel remote stations, and a variety of devices for data display and control of stimuli used in the experiments.

The Biological Systems Laboratory, which is directly integrated with the central computing system, is so arranged that all of its experiments are connected to the biological control computer, which in turn directly communicates with the main system through the 7288 multiplexer (Fig. 1). The multiplexer has 48 main communication channels, each with a capacity of 375,000 6-bit characters per second, and a core memory which can momentarily store data until the data can be brought into the central system. The multiplexer is connected to and controlled by the IBM 7040 computer, which controls the flow of all information between the IBM 7094 system and the multiplexer.

The interplay between the IBM 7040 and the IBM 7094 is achieved by the four interconnections between the two computers (Fig. 1). The computers are interconnected through 25 million words of tape memory, 18.5 million words of disc memory, 64,000 words of core memory, and an instantaneous trap control. In a typical application, the IBM 7040 will set up the proper programs and data for each new problem in the disc memory, periodically interrupting the IBM 7094 to send it (via the core memory) an updated disc map and priority listing. As the IBM 7094 finishes each job it stores the output in the disc memory and interrupts the IBM 7040 with instructions for the removal of the output data.

A fourth computer (the Burroughs 220) performs certain peripheral processing operations that I illustrate in discussing the applications of the computer system to nervous system research. Details of the engineering and programming features of the system are given elsewhere (*2*).

Biological Systems Laboratory

The Biological Systems Laboratory was organized to integrate the disciplines of neurobiology and psychobiology with those of systems analysis and applied mathematics. Its present research is concentrated on visual systems, with experiments designed and conducted by interdisciplinary teams of workers. The main areas of research are (i) basic transducer properties of photoreceptors; (ii) the visual nervous systems of insects; (iii) pattern recognition in retinal visual systems; and (iv) human vision and eye movements.

With the exception of certain subsidiary biochemical and histological work, the experiments all involve light patterns as stimuli and various combinations of electrical response measurements by microelectrodes and gross electrodes implanted in the nervous system and optomotor responses, or (in studies of humans) conscious responses that can be described by the subject. The extent of the required interplay with the data-processing system varies with the stage of development of the experiment. The range includes qualitative explorations, experiments which merely require off-line data processing, experiments which can be controlled by the system on a pre-programmed basis, and experiments requiring stimuli that are complex functions of certain responses.

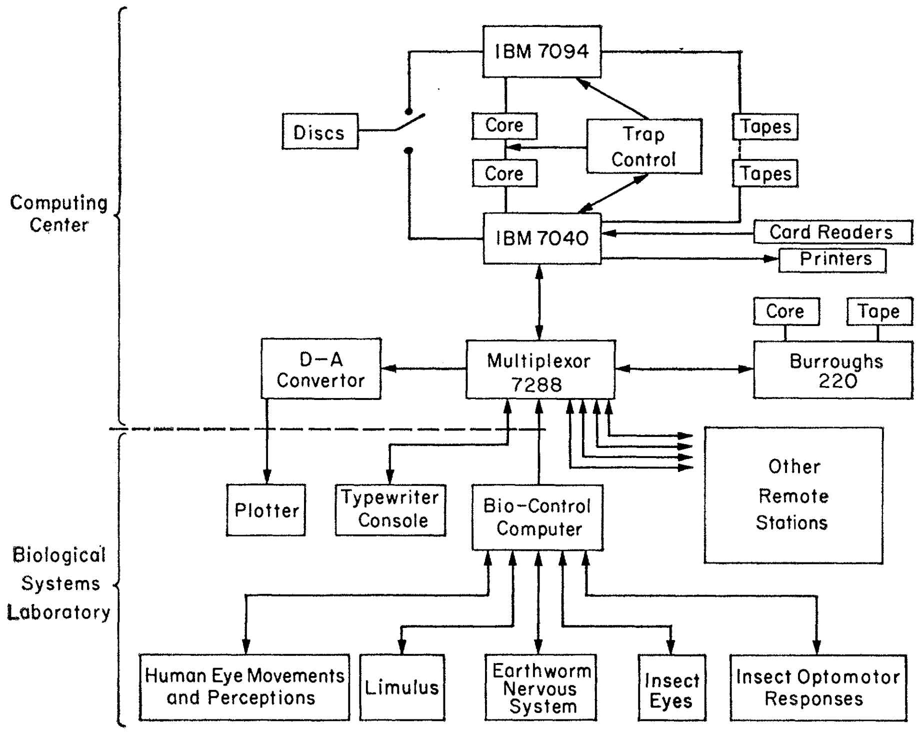


Fig. 1. Schematic diagram of the present computing system.

An important feature of the experimental system is that, however the system is used, data can be completely recorded and can, if desired, be exhaustively analyzed by the most complex data-processing techniques.

Basic Operational Modes

Several of the basic ways in which the data-processing system can be integrated into an experiment are illustrated by Figs. 2 and 3. Figure 2 illustrates the functions of the system for the initial collection of experimental data. Under the supervision of the "experiment control computer," data can be either recorded on parallel channels of analog tape or immediately digitized for storage on digital magnetic tape or in the disc memory. The element listed as the "experiment control computer" in Fig. 2 can abstract certain portions of experimental data in a variety of ways which minimize the amount of data that has to be sent to the central computer (*2*). A comprehensive program has been developed by which the system can process rapidly any of the initially digitized data and display it at any of the outputs. The various forms of available data output or display are shown in Fig. 3. Important elements of the system are the typewriter consoles. As shown in Fig. 3, these are used to control the collection of experimental data into the central computing system, the processing or analysis, and the form of output display, which may be the typewriter itself, a high-speed printer, graphical plotters, or a cathode-ray display tube.

Severe limitations have been imposed upon nervous system research by the immense complexity of its subject matter and the inherent noise of each experimental setup. The more complex the question asked by an experiment, the greater the precision and complexity required for both the stimulus and the response.

The true significance of an experiment cannot be assessed without knowledge of all components of the stimulus and the *correlated* portion of the response. There is ample evidence that in many previous investigations significant properties of what were assumed to be responses either were not actually correlated with the stimulus or resulted from an unknown and unintended property of the stimulus.

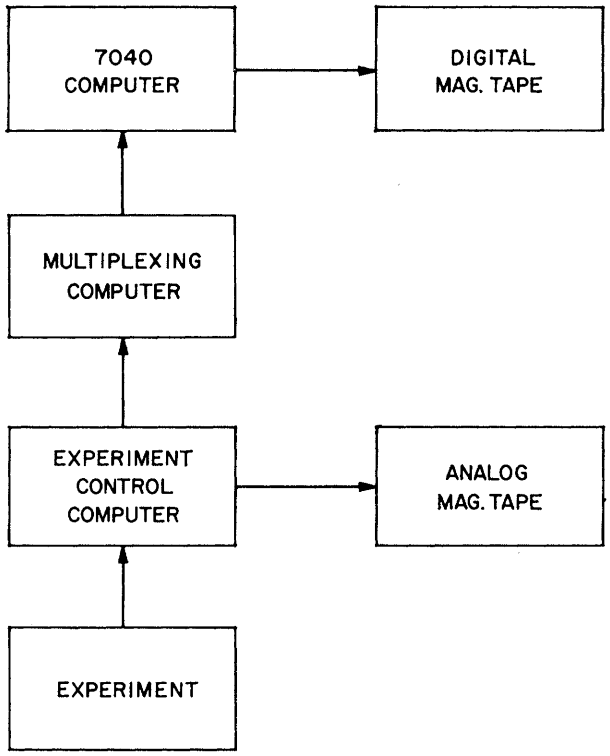
Insect Nervous System

An example of this basic problem and methods of computer processing that can be used to overcome it is presented by our work on the insect *Musca domestica* (*3*). This and several other insects are being used in an intensive study of correlations between stimulus and response, as outlined in Fig. 4. Responses to light stimuli are being studied in the retinular cells of the ommatidia of the faceted eye, in the first ganglion layer, in the ventral cord, and from optomotor responses as measured by head-turning and flight-turning torques.

The principal aim of this program is to determine the information-processing principles employed by the nervous system from input to optomotor responses. This is being done by a careful and precise correlation of each type of response both with the stimulus and with the other responses.

Previous experiments of this type have each been confined to a single type of response. For insects, response to light stimuli at the light receptor cells or at the ventral cord have been measured, or a single type of optomotor response has been studied. None of these previous investigations has determined the correlation between the stimulus and response with sufficient precision to give a very complete understanding of the transfer function. Nor have they determined what portion of the correlated response occurs at the successively higher stages of the nervous system; no precise correlations among the successive responses have been made. To make a sure correlation is the purpose of the study outlined in Fig. 4.

The use of the computer system for correlating stimuli and responses at one point in the nervous system can be illustrated by one of our investigations of the ways in which the insect detects motion and of the insect's visual acuity as determined from the responses to moving patterns whose intensity varies only in the direction of the motion. Uniform striped patterns or patterns with a single sinusoidal spatial distribution, moving at a constant velocity, have revealed important properties of the nervous systems. Such patterns have been used in a number of previous investigations (*4*), and some important misconceptions have resulted from the use of stimuli with unknown characteristics in addition to those intended. One of the principal reasons for these incorrect conclusions has been failure to appreciate the importance of possible low-magnitude components of the stimuli which may have a greater spatial wave-



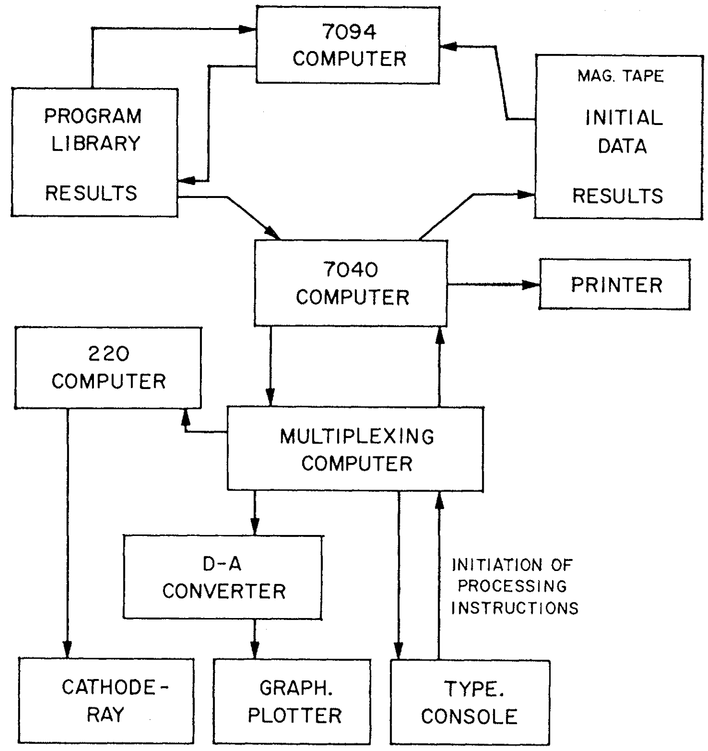


Fig. 2 (left). Sequence for initial collection of data. The experimental control computer correlates any number of channels of data on analog tape and digitizes and abstracts partial data for central processor. Fig. 3 (right). Steps in analysis and display of data.

length than that of the intended fundamental of the pattern.

These insects have faceted, or compound, eyes. The ommatidia are arranged behind individual lens systems, each system having its own axis of field orientation, as shown in Fig. 5, and a visual field of decreasing sensitivity about this axis. From Fig. 5, it can easily be seen (*3*) that a pattern which has only one wavelength and which moves at a constant velocity produces an intensity, I, of the form

$$I(\phi, t) = I\left[1 + m \sin \frac{2\pi}{\lambda} (\omega t + \phi)\right] \quad (1)$$

where λ is the wavelength of the pattern in radians, I is the mean light intensity of the pattern, m is its contrast ratio, and ω is the angular velocity of the pattern in radians per second. Preliminary estimates of the visual acuity of the photoreceptors can be obtained by assuming the field pattern to be Gaussian of the form

$$\exp - (4 \ln 2)(\phi^2 + \theta^2)/\alpha^2 \quad (2)$$

where ϕ and θ are the angular coordinates of Fig. 5 and α is the half-sensitivity angle of the receptor.

Equations 1 and 2 can be used to

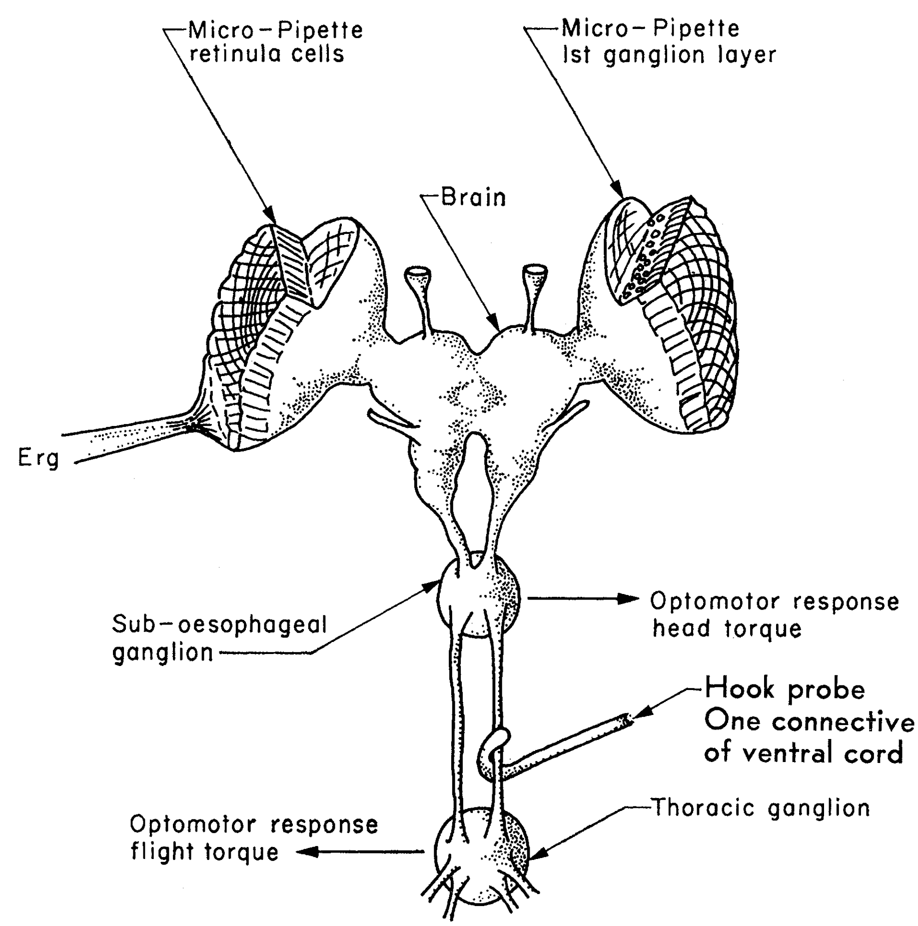


Fig. 4. Nervous system of *Musca domestica*, as studied with the aid of the computer system.

compute the total flux (*3*) in an ommatidium as a function of time [$F(t)$]. Thus:

$$F(t) = I\left(\frac{\pi\alpha^2}{4\ln 2}\right) \times$$
$$\left\{1 + \left[m \exp\frac{-\pi^2}{4\ln 2}\left(\frac{\alpha}{\lambda}\right)^2 \sin\frac{2\pi}{\lambda}\,\omega t\right]\right\} \quad (3)$$

This equation shows that the general sensitivity of a receptor should increase if its field width as defined by α is increased. However, it also has a term dependent on the spatial wavelength defined as the flux contrast function

$$m \exp\left[\frac{-\pi^2}{4\ln}\left(\frac{\alpha}{\lambda}\right)^2\right].$$

This defines its acuity and is plotted in Fig. 5 for several values of α.

The first significant property of this function to be noted is its rapid attenuation for pattern wavelengths below a critical value. Our investigations have established the field angle α for *Musca domestica* at about 3.5 degrees. From Fig. 5 it can be seen that such a photoreceptor should have equally high sensitivities for all wavelengths above about 15 degrees. However, its sensitivity to a 3-degree pattern is reduced by three orders of magnitude. Thus, in studies of the response to a 3-degree pattern, an equally strong reaction could be obtained from a 15-degree component of noise in the pattern even if it were only 0.1 percent as intense as the fundamental.

The angular separation between individual ommatidia must also be considered. This produces a stroboscopic effect (*3*) in the insect vision. The insect can evaluate the direction of motion correctly as long as the wavelength of the pattern is more than twice the distance between ommatidia. For wavelengths greater than, but less than twice, this distance, the insect interprets the motion as being in the reverse direction. Further polarity reversals occur at shorter wavelengths if the pattern is detectable.

Consider now some measurements of optomotor reaction made with various degrees of experimental precision. Figure 6 shows three reaction curves plotted as a function of the intended wavelength of the pattern. One curve represents the reaction to a perfect idealized pattern with only a fundamental spatial component, another the reactions as obtained with previously used patterns, and a third, reactions as recorded with precision patterns developed in our investigation (*2*). Spatial harmonic analyses for one of the previously used patterns and one of the precision patterns are given in Fig. 7, which shows that the previously used stimulus has subharmonics as high as 3 or 4 percent, while the precision pattern restricts them to about 0.1 percent.

The study in which the response curve with the noisy pattern (Fig. 6) was obtained did not determine either the noise content of the pattern or the true correlation between the response and the stimulus. Merely to repeat such an experiment with the precision pattern might produce the portion of the precision-pattern curve shown in Fig. 6, but it would also indicate reactions to patterns with very low wavelengths. It is only by correlating the response with the intended portion of the stimulus (its fundamental) that the indicated limit of de-

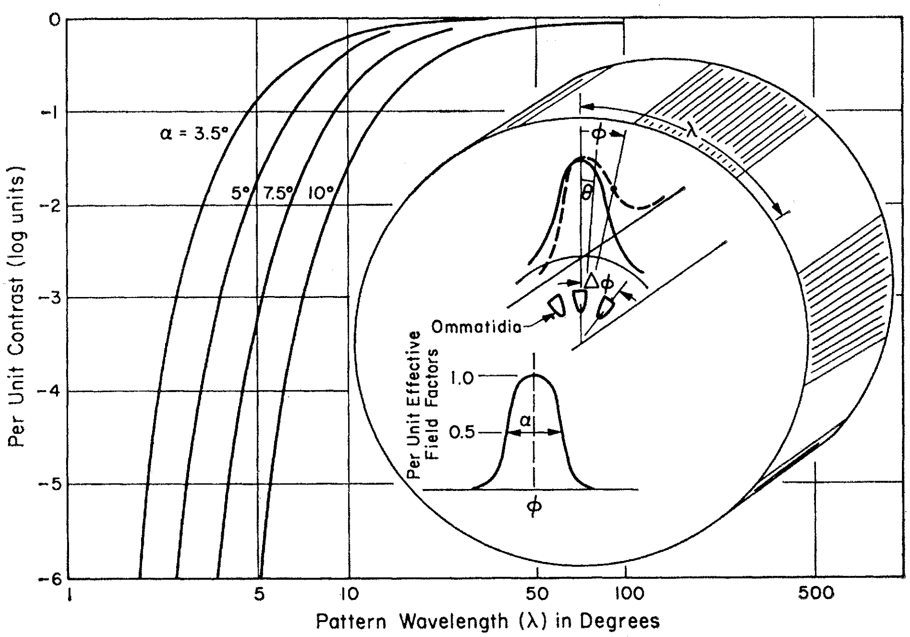


Fig. 5. Receptor light flux contrast functions from Eq. 2 and geometry of the insect ommatidia.

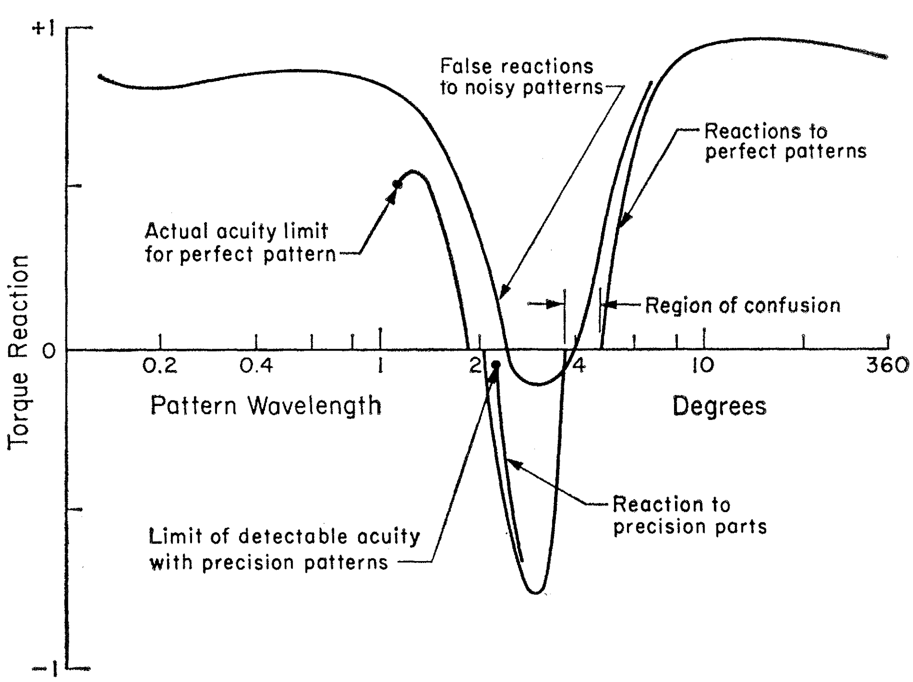


Fig. 6. Effects of stimulus inaccuracies and nervous system noise on studies of visual acuity of insects.

tectable acuity is actually established.

Such an investigation requires the continuous use of the data-processing system. Before each experiment the stimulus pattern is sampled by a photomultiplier probe, digitized, and analyzed by the computer. Each response also must be recorded precisely and then analyzed for correlation with the various components of the stimulus. Once such data-processing procedures have been established, it is possible to elicit more meaningful and detailed information about the nervous system of insects. For instance, precise response curves obtained (as in Fig. 8) for patterns with different wavelengths and as functions of the intensity of the pattern established the actual visual field of the photoreceptor. Further experiments have shown that the field angle α is a function of the state of light-adaptation of the eye, increasing about 40 percent when the eye is dark-adapted, the general sensitivity of the eye thus being raised at the expense of its acuity. This has been found to be produced by migration of a shielding pigment in cells surrounding the ommatidia.

Many other detailed properties of the insect visual system have been determined in this manner (*3*). It has been found, for example, that the optomotor responses resulting from the horizontal turning (yaw) of *Musca* during flight occur at light levels and contrasts so low as to reach the theoretical limit for the initial molecular interaction of photons with the visual pigment. It has been found that the process of detecting constant-velocity motion involves the interaction of only a few adjacent ommatidia, with the total response being given by a simple algebraic summation of these unit interactions which, however, ceases to be linear as the total reaction approaches an appreciable fraction of its maximum. By this summation procedure a very high signal-to-noise ratio for the overall system is obtained, whereas the signal-to-noise ratio obtained in experiments in which the retinular cells are studied by means of a microprobe is lower by three to six orders of magnitude.

Man-Computer Interactions

An inherent characteristic of present digital computers is their inability to process information until the required

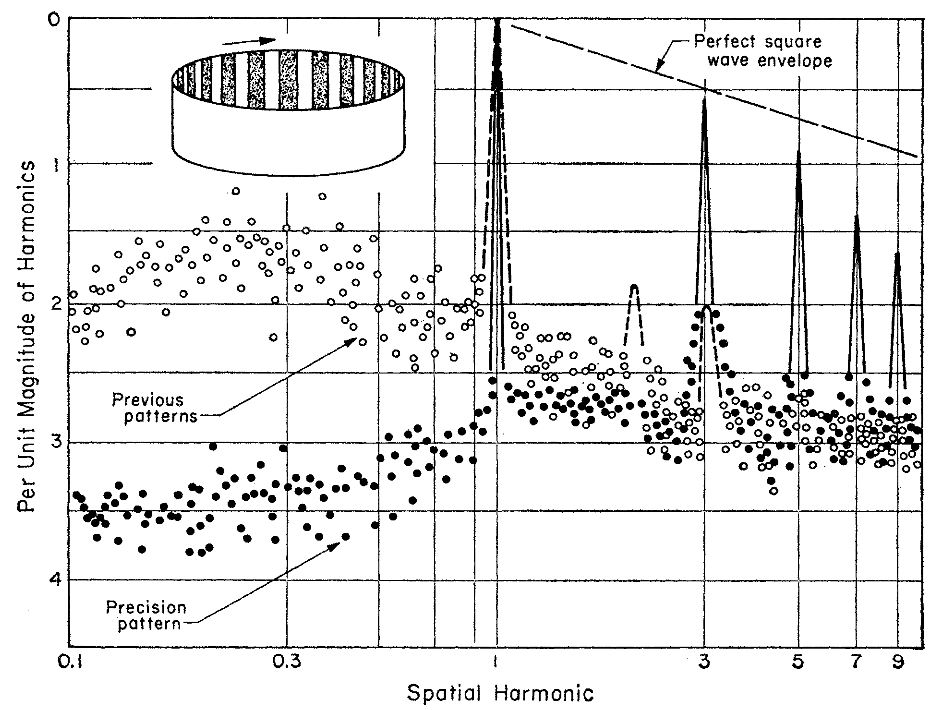


Fig. 7. Harmonic analysis of 3.6-degree striped patterns

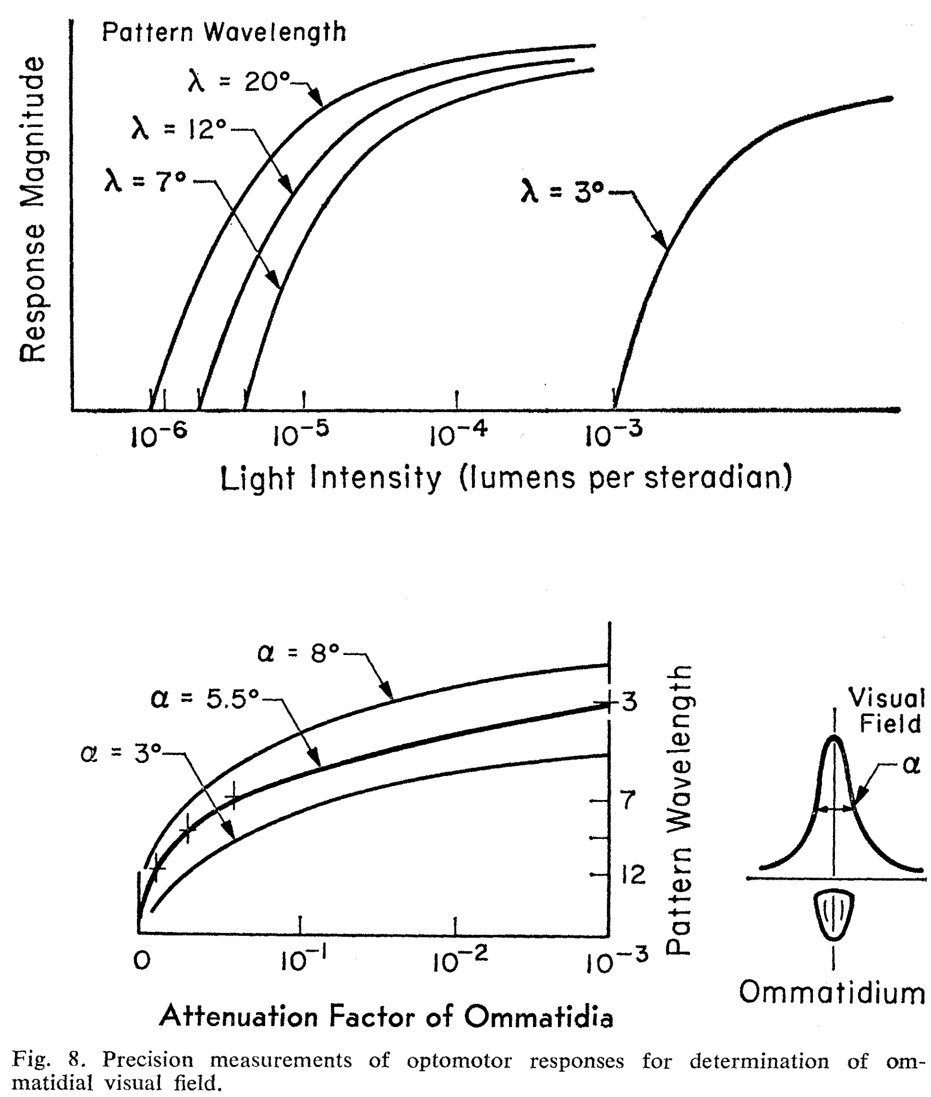


Fig. 8. Precision measurements of optomotor responses for determination of ommatidial visual field.

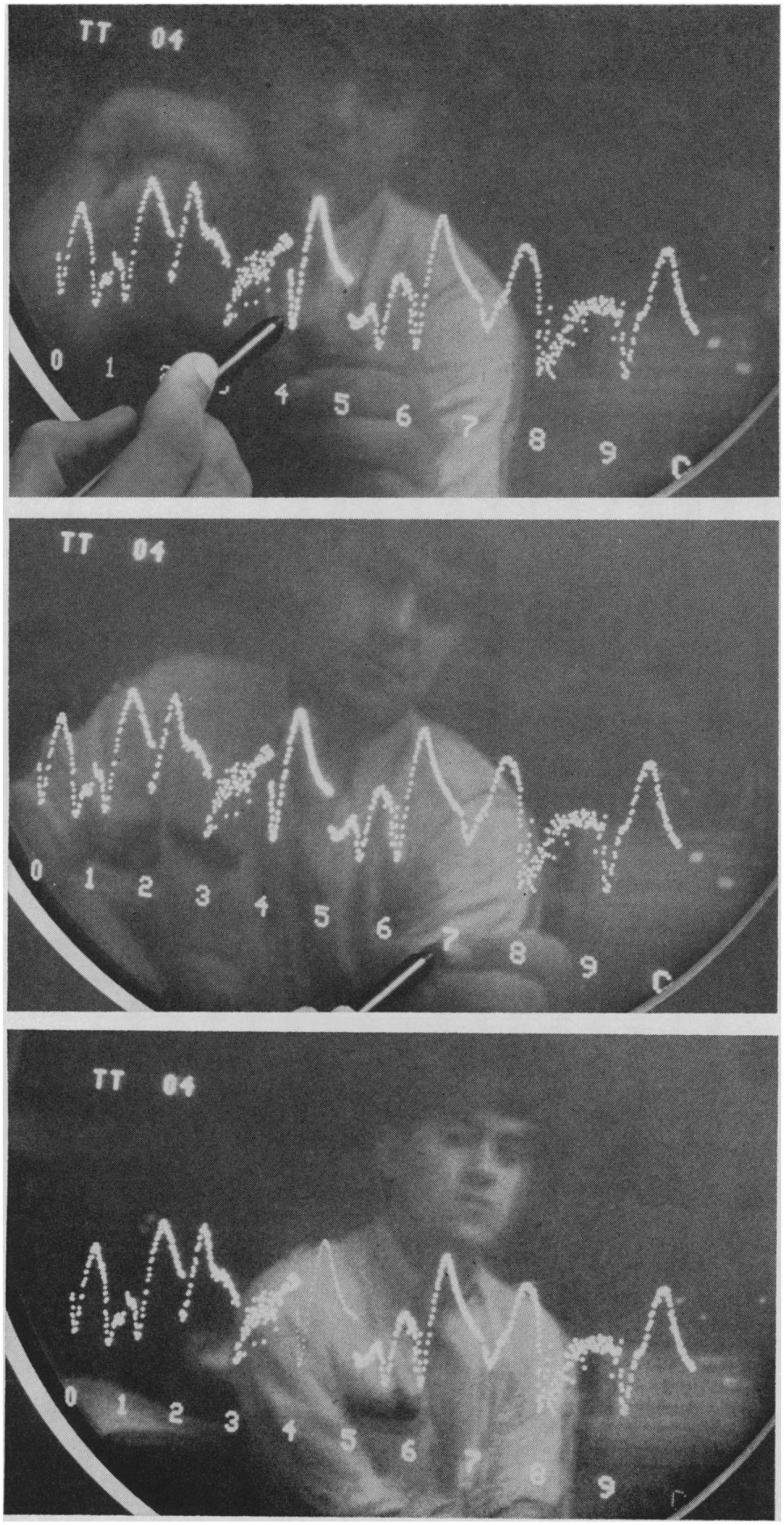


Fig. 9. Classification of multiple-spike record with digital cathode-ray oscilloscope and light pen. (Top) Selection of a spike; (middle) selection of class number; (bottom) dimming of spike verifies its classification by computer.

algorithms are precisely specified within the system as programs. In almost all experimental research there is a practical limit to the degree with which details of experiment control and analysis can be programmed. There are, however, many important cases in which much of the laborious data processing can be rapidly and efficiently performed by the computer if certain "heuristic" decisions are made by the human investigator and properly communicated to the machine. To make these decisions the computer and the human must also be able to communicate the proper information to each other.

Such a communication facility has been developed for the Caltech system. In this facility the Burroughs 220 computer, a typewriter control console, and a digital cathode ray display device are used, as shown in Fig. 9. Its application will be illustrated in connection with an important aspect of data analysis, the separation of different types of spikes in the response wave pattern.

Multiple Spike Separation

The ability to record the activity of more than one interneuron, as detected by an extracellular probe, or of more than one fiber in a bundle of axons, as detected by one hook electrode, and then to separate the data which come from the various sources, greatly enhances a probing experiment. The Bio-Control Computer (Fig. 1) digitizes the waveforms of the individual spikes of information from the nervous system and, via the Burroughs 220 computer, it presents the series of waveforms on the digital cathode-ray device (Fig. 3). It is now necessary to classify the individual spikes into separate categories. There have been cases where it has been possible to do this with a predetermined algorithm that can be used to correlate the waveforms with standardized waveforms or to compare similar properties of successive spikes. This is not, however, a generally practicable procedure. Having a human observer quickly scan either part or all of a record and classify a few or all of the spikes that do not have two or more superimposed waveforms greatly simplifies the classification problem.

This preliminary classification can be accomplished very rapidly by displaying groups of 10 or 20 spikes on the digital-display scope as shown in Fig. 9. If a quick visual observation of such successive portions of the record is adequate for classifying certain of the spikes into separate groups, the observer does so immediately with the light pen shown in Fig. 9. If he wishes comparison with a "template" wave shape, this can be done. If, after classifying a group, he wishes to redisplay all of a given class for reconsideration, this also can be done. The classification procedure adds a code number to the original digitized record; the central processing system can then use the record to process the separated data. It also provides a basis for training the computer to take over and classify a record after a preliminary period of classification by the human observer.

A computer, for example, can do a better job of identifying "smeared" records caused by closely spaced spikes than can a human being, if the computer is given the characteristics of all spikes that might be in the smeared record. Such a separation procedure has been used quite effectively in the studies of the insect ventral cord described in Fig. 4.

Conclusion

The experimental system described above has been in full-scale operation now for about one year. It has been possible in this short period only to begin the exploration of the potentialities of the system for aiding nervous system research. The most intensively developed programs have been those on the insect (*3*) and on human vision and eye movements (*5*). In both of these programs the facility has permitted new research techniques which have provided answers to important questions, answers which would have been unobtainable without such a data-processing and control system.

References and Notes

1. This multiplexer has magnetic-core memory to hold messages arriving from the many input channels long enough for the IBM 7040 computer to collect them.
2. G. D. McCann, K. J. Hebert, C. B. Ray, *Interstate Commerce Comm. Bull.* **3**, 71 (1964).
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News and Comment

The New Accelerator: Wide Open Race Under Way across the Nation To Provide Site for Vast Machine

The usually contentious Indiana General Assembly met last week in special session and quickly and unanimously voted to provide a $10-million lure for what the governor referred to as the "scientific prize of the century"—the $280-million, 200-bev accelerator for which the AEC is now seeking a site (*Science*, 19 March).

Meanwhile, at AEC headquarters in Germantown, Maryland, almost every mail during the past week or so brought detailed proposals propounding reasons why the "prize" should go to this or that region of the country. On Capitol Hill, Glenn T. Seaborg, chairman of the AEC, was closely questioned about the criteria that his agency would employ in selecting a site for the accelerator. And, this weekend, some 30 university presidents will meet at the National Academy of Sciences to complete arrangements for setting up a national corporation that will offer itself to the AEC as administrator of the accelerator. At the same time, an entirely separate committee appointed by the Academy was organizing itself to evaluate the site proposals after an initial screening by the AEC.

Quite clearly, never has a proposed scientific facility so stirred up the academic, scientific, and political worlds. And, in fact, the involvement and interest are of a magnitude which strongly suggests that regional interest, always there but often not very significant, is henceforth going to figure mightily in federal support of science. (Congressional hearings last week on the regional issue are discussed in another article in this section.)

As the costliest single scientific installation ever built, the $280-million accelerator—with operating costs estimated at about $50 million a year—could, of course, be expected to stir an unprecedented amount of agitation. But once the site decision, scheduled for the end of this year, is made, there will be some 40 or 50 also-rans who can be expected to sharpen and intensify their tactics when the next prize is announced.

The action of the Indiana General Assembly is a good example of the escalation of agitation. Last year, after the White House turned down plans to build a high-intensity 12-bev accelerator proposed by a combine of midwestern universities, Indiana engaged in a postmortem examination of the decision. One product of this was a memorandum that Governor Roger D. Branigin sent to the General Assembly at the beginning of this month, under the title, "Why Indiana Must Go All-Out in Its Bid for the U.S. Nuclear Research Center."

Referring to a report by Elvis J. Stahr, president of Indiana University, the memorandum states that the 12-bev accelerator "was abandoned because, among other things, the Midwest never quite united behind it. In the case of the current 200 bev machine, he [Stahr] said, the major midwestern universities have agreed to support whatever midwestern site appears to be most in the running after the initial screenings. 'It is also important,' [Stahr] said, 'that we agree to support whatever is finally adjudged to be the best site. If a 200 bev machine—and later a 1000 bev ma-