

The Jacques Loeb Memorial Lecture

The Jacques Loeb Memorial Lecture was established by Detlev Bronk in 1968 to commemorate the 50th Anniversary of *The Journal of General Physiology* of which Professor Loeb was the first Editor, and to recall Loeb's devotion to "investigation of life processes from a physico-chemical viewpoint." It was Dr. Bronk's desire that the Lecture be sponsored jointly by the Marine Biological Laboratory and the Woods Hole Oceanographic Institution in recognition of the close ties between the two organizations and their new cooperation in graduate education.

INTRODUCTORY REMARKS

Detlev W. Bronk

Jacques Loeb, the man, I never knew, but Jacques Loeb, the scientist and socially concerned humanist, I have known for many years. He had a profound influence upon my life.

One summer, while I was a graduate student of physics at Ann Arbor, I attended a course of lectures on Electrical Discharge Through Gases by Karl Compton. While searching for a suggested reference in that section of the University Library dealing with electricity, I saw, by sheer chance, a book entitled "Electro-biologie" by Bernstein. I knew so little of biology that I was surprised to see that there is a connection between electricity and life.

My curiosity was aroused. To learn more about what is now known as biophysics I was told to write to Simon Flexner, Director of The Rockefeller Institute for Medical Research, for advice. He replied that the one best able to advise me would have been his recently deceased colleague, Jacques Loeb. "But," said Flexner, "he left a classic book that you should read: 'The Mechanistic Conception of Life.'" I read it then and have reread it many times. I recall sentences such as these: "Heliotropic animals are therefore in reality photometric machines . . . We do not yet know whether or not Bunsen's law holds good for them. If it does, we shall have to substitute this law for what the metaphysician calls the will of these animals." And again: "Chemical substances in the chromosomes are responsible for the hereditary transmission of a quality." Concepts such as those led me across the ford between physics and biology.

Fifty years ago Loeb published the following announcement: "The physico-chemical methods of analyzing life phenomena have thus far made little inroad into the domain of zoology and botany. Under these circumstances, it has happened that what might be regarded as the most fundamental of all the biological sciences, namely general physiology, has not come to have a journal of its own. It is this condition which the establishment of *The Journal of General Physiology* is intended to correct."

This Lecture commemorates 50 years of that Journal and the new relations of the Marine Biological Laboratory to the Woods Hole Oceanographic Institution, the establishment of which was eagerly desired by Loeb and his associates Henry Bigelow, Frank Lillie, and W. J. V. Osterhout.

As we considered who could appropriately deliver the first lecture in memory of Loeb, our thoughts kept returning to Loeb's Preface to his "Physiology of the Brain." There he said: "I am convinced that for the establishment of the laws of life-phenomena there is need for the broad basis of a comparative physiology which includes all classes of the animal kingdom. My experience in the course on comparative physiology at Woods Hole indicates that this transition from the old physiology of vertebrates to the comparative physiology can be most readily accomplished through the physiology of the nervous system."

The more we recalled the ideals of Jacques Loeb, the surer we were that he would have been pleased to have Theodore Bullock chosen from among the moderns to speak on this occasion. Bullock, like Loeb, has ranged widely through comparative physiology to extend our knowledge of the nervous system.

The Reliability of Neurons*

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ABSTRACT The prevalent probabilistic view is virtually untestable; it remains a plausible belief. The cases usually cited can not be taken as evidence for it. Several grounds for this conclusion are developed. Three issues are distinguished in an attempt to clarify a murky debate: (a) the utility of probabilistic *methods* in data reduction, (b) the value of *models* that assume indeterminacy, and (c) the validity of the inference that the nervous system is largely indeterministic at the neuronal level. No exception is taken to the first two; the second is a private heuristic question. The third is the issue to which the assertion in the first two sentences is addressed. Of the two kinds of uncertainty, statistical mechanical (= practical unpredictability) as in a gas, and Heisenbergian indeterminacy, the first certainly exists, the second is moot at the neuronal level. It would contribute to discussion to recognize that neurons perform with a *degree* of reliability. Although unreliability is difficult to establish, to say nothing of measure, evidence that some neurons have a high degree of reliability, in both connections and activity is increasing greatly. An example is given from sternarchine electric fish.

I

How reliable are neurons? That is, how dependably do they do the same thing under the same conditions? In this meaning of reliability the question is relevant to or directly raised by much contemporary discussion of the principles of operation of the nervous system as an information machine. (Cragg and Temperley, 1954; Allanson, 1956; Scholl, 1956; Beurle, 1962; Arbib, 1964; Kogan, 1964; Ten Hoopen, 1966; Burns, 1968; Caianiello, 1968; Walter, 1968; Isaacs and Lamb, 1969; Segundo et al., 1969).

Early successes with stimulus-response curves of single sensory neurons were so gratifying in the precision of coding by nerve impulse frequency and the tightness of the scatter of points that emphasis was understandably placed on the unit as a discriminating and predictable performer.

The pendulum has now swung to the other extreme. The prevailing view, at least among writers and speakers at symposia, regards the brain as basically operating in a probabilistic manner with unreliable components. This view is

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partly attributable to the impression of the large number of neurons available, partly to appreciation of the inherent limitations of accuracy in a machine employing analogue steps, partly to the irregular, ongoing brain wave activity and to the variability of responses, both of units and of compound evoked potentials to repeated physically identical stimuli. The near fit of a Poisson distribution to certain examples of trains of events in units is another basis.

This view is reinforced by the development of concepts, growing out of information theory, computer theory, and systems theory as to how a reliable system could work with unreliable components (Von Neumann, 1956; Verbeek, 1961). It is further encouraged by the success of the widely used technique of averaging many successive responses to pull out feeble signals in the presence of fluctuating background activity of nervous tissue and to make responses consistent (as averaged evoked potentials and poststimulus time histograms).

Whatever the grounds, and remarkably enough most authors do not feel the need of making a case, the position is strongly stated. We may quote from a recent book that is representative of a prevalent opinion (Burns, 1968, pp. 18–19):

“A meaningful statement can only be made about the relation between stimulus and response in terms of the *probability* that the unit will respond

...

“This indeterminacy . . . is a concept of neural activity which is far more likely to be of use [than older concepts based on apparent predictability]. I am after all an unpredictable machine; if you call ‘Burns;’ there is a high probability that I shall turn my head . . . but . . . always less than unity . . .

“It is, then, the stochastic nature of the behaviour of central neurones which forms the main theme of this book . . . this new concept . . .”

Speaking of the work of FitzHugh (1957) and Kuffler, Fitzhugh, and Barlow (1957) on retinal ganglion cells, Burns says (pp. 27–28):

“Clearly . . . any statement attempting to relate an individual response to a particular single stimulus, would be senseless. The only meaningful statement that can be made about the relation between stimulus strength and response must be in terms of average behaviour.”

These views are far from exceptional today. They are highly plausible. Indeed let me emphasize here that I believe they are correct—for some parts of the nervous systems in some animals.

But, and this is one of the main points of this essay, the postulate that

neurons are basically so unreliable that only a probabilistic statement about their message content is meaningful, is inherently nearly impossible to establish and has probably not been established yet in any single case. Therefore the extrapolated conclusion that the nervous system operates on this principle generally or in the main or in its highest functions will be even harder to validate.

In contrast many cases of relatively high dependability are directly demonstrable. I *believe* there are some noisy nerve cells. I *know* there are some quite reliable nerve cells.

II

Let us examine some bases for these statements, beginning with those about the difficulties of validating a postulate of unreliability. I will mention four.

1. First, it must be recognized that variation in response to physically identical external stimuli may mean the *state of the system has changed* in a biologically significant way. Delisle Burns may be unpredictable to us but that does not mean he is unreliable, uncertain, or inconsistent with himself.

I can plot my speed on different trips, driving over the same 50 mile per hour zone and obtain a broad histogram, apparently only consistent on the average. "Obviously" either my sensory system reads "50" unreliably or my motor system executes the command erratically. Unfortunately for these "stochastic" inferences, I can obtain additional information for this system such as is not usually available for neurons. The lower speeds may correlate with trips to the dentist, to the tax office and similar destinations, or with glimpses in my rear view mirror of official looking cars; the higher speeds may correlate with trips following bad committee meetings, good experiments and late starts for a good dinner, or with an open road.

I can test my sensory and motor systems on a similar stimulus with a different context. The histogram of cash paid out for 50 cent hamburgers is exceedingly narrow!

The meaningful changes in state of the system that can affect the responses to the "same" stimulus are conceivably quite multifarious; general and specific, phasic and tonic, anticipatory and retrospective, intrinsically spontaneous and triggered by events external to the brain, which may be visceral or somatic. There are so many reasons to believe in such influences, so many direct demonstrations of their effectiveness that in general we should assume them until a showing is made otherwise.

This is particularly true of higher order brain cells. But even retinal ganglion cells and cochlear nerve fibers are subject to background influence that cannot be accepted as biologically meaningless noise, whether from intrinsic, lateral, or centrifugal sources. It might be said that this makes the problem almost hopeless; we cannot expect to eliminate all influences impinging on a

cell in the central nervous system except in special cases. Quite true and that is my point. Unreliability is hard to establish. It is certainly legitimate, if one wishes, to *assume* explicitly, for the sake of exploring models or to permit data reduction, that the cell is in a stationary state so that all variation is either stimulus caused or "noise." But the results cannot justify the conclusion that observed variation is in fact only noise.

2. The second class of possible reasons that observed variation need not mean unreliability is *measurement of an irrelevant output variable*.

In one demonstration of this point I showed a 1 per sec sweep on a cathode ray oscillograph, triggered by identical flashes of light and recording four clusters of blips, highly varying from sweep to sweep and consistent only on the average. This replicates the typical evidence cited in support of unreliable performance (Fig. 1). Then we revealed the "preparation," which was a

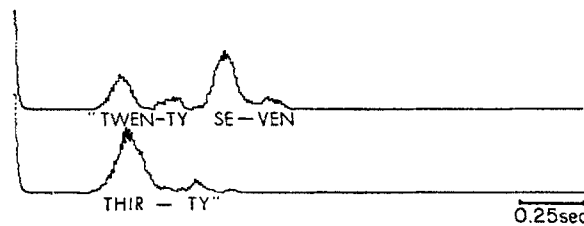


FIGURE 1. Averaged poststimulus time histogram of pulses triggered by clipped, amplitude-discriminated voice-derived voltage peaks. Stimulus was a brief flash illuminating a card bearing the symbols 27 or 30.

man sitting at a microphone and audibly reading "27" lettered on a card illuminated once a second. The stimuli were physically identical, the system of voice detection, amplification, filtering, clipping, peak discriminating, and standard pulse triggering was all of the best quality to present a high fidelity record. However, knowing something of the meaning of the stimulus to the subject, we now realized the response parameter measured, voice peaks, is irrelevant to the estimation of reliability of the 27-reading system. We were unknowingly studying the fluctuations due to intonation, inflection, head position, and volume. In fact, when the voice was made audible to all of us, it was clear to English-speaking listeners, that this system was completely reliable. It never responded to the stimulus by saying "28". But to appreciate the real reliability we had to know the relevant aspect of response and the code. A finding of variation even were it in a single unit of the laryngeal muscle, would not be evidence for stochastic or probabilistic performance.

Parenthetically, our black box-averaging system seems quite sensitive to small discriminanda and we therefore gain a false sense of the relevance of our measure. By merely rearranging the same light flux and dark shapes into a new stimulus "30" we changed the average response to two humps! This is

reminiscent of much of our current work with poststimulus time histograms of unit spikes and evoked potentials. It *does* show discrimination but it can give no evidence of unreliability even if carefully done and even though spike count is the best known code. In a recent catalogue Perkel and I (1968) made an incomplete list of more than 25 candidate codes at the single and few neuron levels; there are doubtless more when many neurons are involved.

Actually our unit sampling in the cortex is a little like recording the activity of the "e" lever of typewriter 147 in the stenographic pool at the Pentagon. Variable response need not mean indeterminate behavior. The probabilistic assumption is bound to lead to treatment that will smear details with determinate causes as well as smoothing true noise.

3. A third possible class of reasons is *assumption of the wrong input*. In experiments like those on retinal ganglion cells we naturally tend to assume that light intensity, other things being equal, is part of the relevant input and when we see variation of response that does not correlate with it, we are likely to brand it noise. But we now know of visual units that follow other parameters and do not vary with light intensity, or are influenced by it in subtle and complex ways.

It is quite possible that what has been taken for scatter, when plotting response against a stimulus believed to be appropriate, is really due to uncontrolled variation in an aspect of the total stimulus situation more interesting to the unit than the controlled parameter.

4. Closely related is the body of evidence that *apparent noise may have significant physiological value*. Apparently random activity is not necessarily noise or fully indeterminate and irregularity should not be called noise without a showing or argument that in the context of the function of the system it is irrelevant and undesirable. It may be a useful signal and deterministically following some condition, as in the *Limulus* eye (Ratliff, Hartline, and Lange, 1968) in which standard deviation of impulse intervals is an index of the stage of light adaptation. Or it may be useful in some other way as in the microsaccades that permit our vision, the flutter of the pupil diameter that aids in control of light flux into the eye (Stark, 1968), or the jitter of intervals that permits transmission of rhythmic signals without spurious patterns due to phase locking (Perkel et al., 1964; Schulman, 1969; Reid, 1969; Levy et al., 1969; Roberge, 1969).

This last refers to theoretical as well as experimental evidence that, as Stein (1970) puts it "noise permits the neuron to convey accurate information over a much larger range of frequencies than would otherwise be possible." This is because a regular carrier frequently receiving sinusoidal or periodic input generates recurring patterns that may extend over many cycles (Fig. 2).

Von Neumann (1956, p. 88) pointed out the utility of randomness in any multiplexed system with feedback like the nervous system; without it there is

more danger of spurious correlations and magnification of errors. For quantitating the effect of noise a particularly elegant preparation is that of the tonic stretch receptor of crayfish which has a single inhibitor axon that exerts a strong effect. You can drive the inhibitor at will, using different mean frequencies, with and without jitter. By setting the stretch, one can start from any desired level of firing of the receptor neuron which acts as a pacemaker. The beauty of this preparation is that the strong inhibition acts with virtually

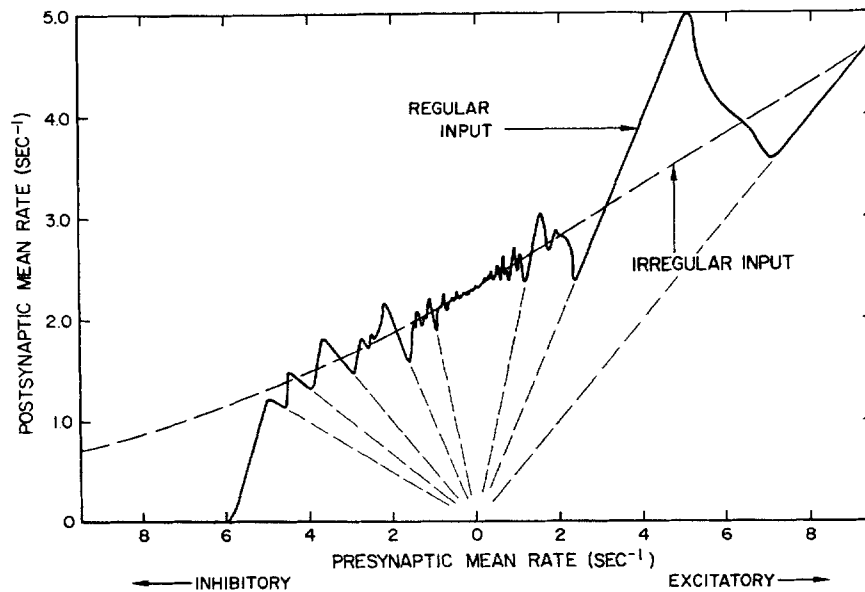


FIGURE 2. Mean firing frequency of a computer-simulated pacemaker neuron, subject to excitation and inhibition as a function of mean input frequency. If the input and output rhythms are regular, phase locking at integral ratios can give paradoxical reversals (the segments whose projections, shown in dashed lines would intersect zero input); if the input is irregular these effects are smoothed out and the range extended (Perkel et al., 1964). This illustrates one potential value of irregularity; if applicable it should not be called noise.

no delay or summation but depends on the time of arrival of the inhibitor spike relative to the receptor pacemaker cycle. Therefore one gets phase locking and with it paradoxical driving-bands of inhibitor frequency within which increasing input actually accelerates (Fig. 2). The critical points, steep slopes, and odd-ratio notches (e.g., 2:3) occur with regular inhibitory intervals and are smoothed out by injecting some jitter into this train.

If noise is taken to be fluctuation without relevant cause, the weight to be given to any argument depending on this class of observation is proportional to the evidence cited against relevant cause. One might say: assume no cause, find no cause.

The main point of the argument so far is that unreliability is intrinsically hard to prove. We need not abandon it; it can be preserved as a reasonable belief. I believe it is true—in some degree, and in some parts of the nervous system, both unknown. Von Neumann (1956, p. 87) clearly recognized what he called the duality of construction of nervous systems, the simultaneous existence of fixed patterns, in some respects, and of variations “which make one suspect a merely statistical design.”

What we do know is the fact of a large amount of reliability. Reliability surely comes in degrees and these vary from neuron to neuron quite widely and in a given neuron from time to time, according to its inputs and history, as Von Neumann already assumed in 1956 (p. 90).

III

Let us remind ourselves of the types of evidence of reliability in the nervous system.

1. *Histological Organization and Development of Connectivity* There is no need to review familiar evidence of the elegance with which embryonic cells take up positions, send out processes, and make connections so as to achieve for instance the characteristic structure of the cerebellar cortex, the connections of the eye muscle nuclei, the point-to-point projection of retina upon tectum and cerebral cortex, the 17 distinct cell types of the insect optic ganglia, each ending in characteristic layers of the neuropile. What may be helpful is to point out that we have no way of establishing a limit to this precision of connectivity. The challenge is very asymmetrical between finding evidence of precision and finding evidence of randomness; the former is constantly progressing, the latter almost inherently impossible. New work with light microscopic and electron microscopic and electrophysiological methods is steadily adding details of consistent specificity—of connections to different parts of the dendritic tree of cortical pyramids; of relations between several elements in complex synaptic glomeruli in the thalamus, cerebellum, olfactory bulb, and elsewhere (Szentagothai, 1970; Scheibel and Scheibel, 1970); of branching, stratification, and contacts in the optic neuropiles of flies (Trujillo-Cenoz, 1965; Braitenberg, 1967; Strausfeld and Blest, 1970); of transverse point-to-point projection between left and right optic tecta of amphibians (Gaze, see Jacobson, 1970).

The impression of randomness from looking at sections may be like the difficulty of seeing pattern in a snapshot of a crowded modern dance floor. The intricacy of axonal and dendritic ramifications and our chiefly static, two-dimensional methods could explain the difficulty. I am sure that with the third dimension added and a large speedup in sampling rate by the observer, recurring regularities of geometric relations at a much more complex

level than heretofore known are likely to become evident. For example, cine-projection of well-registered successive electron micrographs going through many examples of glomeruli, optic cartridges, or Purkinje cells would take advantage of the pattern-recognizing computer in our heads and increase the chance of noticing the same feature in different views.

Even given a clear demonstration of a random scatter of connections, the conclusion may not be permissible that this supports the hypothesis of unreliability. A beautiful case showing that apparently random scatter may have functional value is the phenomenon of receptive field disparity in units of simple type in the striate cortex of the cat. Bishop (1969, 1970) shows a gaussian scattergram of receptive field centers mapped via one eye when the field centers via the other eye have been brought to a common point, in a population of binocular cortical units all within a few degrees of the visual axis. This scatter of disparities may form the basis of binocular depth discrimination, for the fields will be exactly superimposed at different planes and Bishop finds marked facilitation when they are exactly superimposed, but mutual inhibition when there is even a slight departure from correspondence in stimuli on the two retinae. Thus the normal flicks and saccades will bring stimuli into and out of the precise position for strong signalling and could provide the basis for stereopsis. Bishop proposes "In embryological development there is presumably a limit to the precision with which the fibres from corresponding parts of the two retinae can come together on neurons in the striate cortex. It is possible that this initially random element in the fibre connections is subsequently developed into a 'known' pattern of receptive field disparities and used as a basis for binocular depth discriminations."

2. *Identifiable Neurons* Until a few years ago the only examples of neurons identifiable or constant among individuals of a species were Mauthner's neuron in many teleosts and aquatic amphibians, giant neurons in several invertebrate groups, eutelic nervous systems in a few lower invertebrate groups, like nematodes and some other exceptional special cases (Bullock and Horridge, 1965). This situation has changed radically with the convergence of methods so that today we regard as not exceptional the demonstration of several to many identifiable, consistent cells in gastropods, insects, and leeches, thus from three different phyla (Coggeshall, 1967; Cohen, 1970; Nicholls and Baylor, 1968; Stuart, 1969). In each case there is evidence, more or less detailed, that not only is the soma individually recognizable but also that its input and output connections are specified consistently including the relative effectiveness of each one.

This is a discovery and a trend in discoveries of the deepest significance. Already the number of such cells catalogued is far greater than it was when Horridge and I summarized the invertebrate literature. (How do you count them? Do you multiply by the number of species, however closely related; or

genera; or families? The more meaningful statement is the subjective opinion that such cells are probably commonplace in at least the three major groups named, in addition to the previous examples.)

As so often with revolutionary discoveries we are getting blasé about reports of new examples before the implications for our general theoretical framework ("paradigm" in Kuhn's, 1962 usage) have been absorbed (Bullock, 1970). In this case the implication is that by a greatly increased amount, we must push back the scope of any randomness in both connectivity and dynamic properties.

How far such individuality and specificity go is a highly subjective question of extrapolation. In my opinion we must reckon with the likelihood that they go a very substantial way and not only in invertebrates. To assume that the

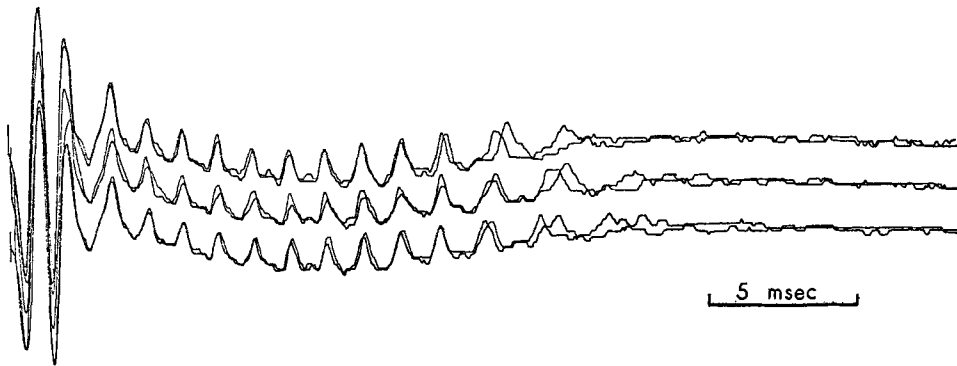


FIGURE 3. Burst of sensory impulses recorded in a bundle of a few afferent fibers of the lateral line nerve of *Hypopomus occidentalis* in response to a single brief (0.5 msec) electric pulse injected into the water near the fish. A few fibers fire only 2 or 3 times, one or a few fire extremely dependably 13 or 14 times. 6 independent samples each of 32 successive bursts, averaged by a digital computer.

look-alike cells in a populous higher center in the vertebrate brain are not individualized is almost like assuming that the people of Tokyo, based on fragmentary, two-dimensional views, are not individualized.

It may be the necessary, economical assumption until proved wrong—I do not disagree with that. My point is only that there is not appreciable force of evidence for randomness and the assumption is based on ignorance. Since we know of specifications extending down from the level of gross anatomy to Purkinje, granule and basket cell types, and glomerular makeup, the sophisticated approach will be to ask how much farther we can discern regularities. The frontier, as proposed in the preceding section, is moving and exciting.

3. Reliable Afferent Units Not all first-order sensory neurons respond as variably to repeated stimuli as the ones usually cited in support of stochastic interpretations. As an example of a relatively dependable type, Fig. 3 shows

the responses of electroreceptor units in electric fish to quasi-normal identical, 1 msec pulses of current in the water. Some units, not of interest here, fire only two or three times after each stimulus but others, probably only a single unit here, fire 14 or 15 spikes, fewer than this or more than this according to the intensity of the pulse. The point of this illustration is that there is a machine-like regularity of the long train of spikes; even averaging 32 successive responses there is only some uncertainty in the latency of occurrence of the last two spikes, all others are not even dispersed in latency enough to broaden the averaged spike.

4. *Recognition Units* Higher order units that respond to a limited class of stimulus configurations bespeak both a relative precision of anatomical connections and of dynamic properties of those connections (Bullock, 1961). Examples include the complex feature-extracting cells like those ending in the frog optic lobe, that respond to small, dark moving objects in a certain visual field, providing there is little or no motion in the surrounding field. These have been shown by the Grüssers (1969) and coworkers to be reliable enough to code contrast, size, and velocity. Evidence of such specific recognition units has increased explosively in recent years. In the visual system they are found at various levels in crustaceans (Waterman and Wiersma, 1963; Wiersma, 1967; Wiersma and Oberjat, 1968), insects (Vowles, 1966; Swihart, 1968; Bishop and Keehn, 1967; Bishop et al., 1968; McCann and Dill, 1969), fish (Sperry, 1963), frogs, lizards (Grüsser et al., 1963), birds (Maturana and Frenk, 1963), rabbits (Oyster, 1968; Barlow and Levick, 1969), squirrels (Michael, 1966), cats (Hubel and Wiesel, 1962; Marchiafava and Pepeu, 1966; Straschill and Hoffman, 1968; Bishop, 1969), monkeys (Hubel and Wiesel, 1968). Deserving of special mention is the crayfish visual motion unit of Wiersma and Yamaguchi (1966) that quantitatively integrates body position input so that its receptive field is shifted just enough to compensate for body tilt, therefore remaining fixed relative to the world. In the auditory system equivalent units occur up to and including cortical levels (Galambos et al., 1959; Suga, 1967, 1969; Grinnell, 1969).

Another class of positive evidence is exemplified by Mountcastle's (1967) demonstration of precise preservation in a certain class of neurons at the cortical level of the frequency and phase of low-frequency vibratory stimuli to the skin.

5. *Command Neurons* Recent years have also seen the discovery of an extensive class of units which trigger, upon stimulation, complex, specific behavioral acts. These are known chiefly in invertebrates (Wiersma, 1967; Wilson, 1970) but Mauthner's cells in fishes and aquatic amphibia are a simple example and the electromotor command cells in the medulla of electric fish suggest that Mauthner's are not the only cases among vertebrates.

6. *Regular Rhythms* In addition to the class of rather complex achievements there is the class of cases manifesting simply a high regularity of inter-impulse intervals in a train, under steady conditions. The argument goes like this. While neurons with large variation of intervals may or may not represent unreliability, depending on a showing of irrelevance of the variation, cases with small variation cannot support unreliability and are at least potentially, reliably signalling some steady state. Therefore it is interesting to look at the neurons with less variation. Classically regular neurons like the crayfish stretch receptor (Schulman, 1969), many primary vestibular afferents (Rupert et al., 1962), certain insect optic lobe interneurons (Kuiper and Leutscher-Hazelhoff, 1965) have standard deviations in the range of 2 or 3% of the mean interval, which is really very small. Such a train of impulses seems very rhythmic to our ears, eyes, and touch and such a variation in a measured behavior would be considered remarkably small—about like singing the right note within a quarter tone.

The most extreme cases of reliability appear to be in the pacemakers of the electric discharge of electric fish. Together with R. H. Hamstra, Jr., I have recently examined the structure of the train of discharges in *Sternarchus* and *Eigenmannia*, two of the South American gymnotids with constant electric organ firing, night and day, at about 800–1000 Hz and 300–500 Hz (25°C), respectively (Watanabe and Takeda, 1963; Larimer and McDonald, 1968; Howe, Erskine, and Granath, 1969; Bullock, 1969). These fish show a very small fluctuation of successive intervals (Fig. 4). An 850 Hz *Sternarchus* was found to have a standard deviation of 0.012%; this means 0.14 μ sec, measuring every interval by gating a 10 MHz clock. Temperature fluctuations limit the long-term estimation (minutes), but have been reduced below this level for at least a few minutes, by suspending a well-stirred experimental chamber in a large, closely regulated water bath. The fish discharge frequency has a Q_{10} , in this range of about 1.7, so that a variation of 0.012% could be caused by about 0.001°C. The measured short-term drift of temperature, due to cycling and other factors, is somewhat less than this over periods of many seconds.

There are several reasons why this high regularity is of interest. (a) It is the expression of a pacemaker in the medulla which is a true physiological unit. Szabo and Enger (1964) and Bennett et al. (1967) have found this pacemaker and shown that it comprises a group of neurons connected together by low resistance, electrotonic coupling, and therefore firing in enforced synchrony. Downstream stages in relaying this command to the electric organs are probably incapable of reducing the variation of intervals but may increase it.

(b) This regular train is an important piece of normal behavior as such; it is not equivalent to a train of muscle action potentials that is transduced into smoothed mechanical movement before contributing to behavior. Very brief changes in frequency are known to be significant social signals.

(c) The nearly constant frequency is not fixed but labile and under constant, tonic control. This is shown by the so-called "jamming avoidance response" (Bullock, 1969), first discovered by Watanabe and Takeda in 1963. To a highly restricted class of stimuli, namely alternating current or pulses at a frequency not identical to, or far from, but close to its own, the fish reacts by shifting its frequency away, as though to maintain privacy. Our quantitative

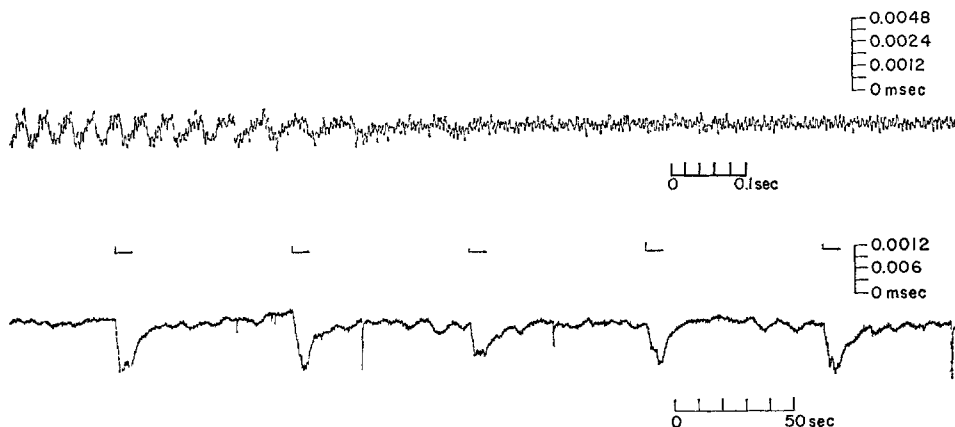


FIGURE 4. Upper, interval as a function of time in the discharge of the electric organ of an intact electric fish, *Sternarchus albifrons*. The mean discharge frequency is 850 Hz. Every discharge triggers a 10.935 MHz clock count, measuring the last interval to $\pm 9 \times 10^{-8}$ sec or better than 1 part in 10,000. This sample of spontaneous activity shows the end of a bout of wide, systematic fluctuation of interval and resumption of "resting," minimum fluctuation. Both are of unknown cause though believed to be in the pacemaker nucleus of the medulla. Lower, jamming avoidance responses to a succession of five stimuli. Mean resting frequency in this fish is 942 Hz. The discharge is averaged every 32 intervals (= about 30 msec). The stimulus was an AC voltage of $0.5 \mu\text{v}/\text{cm}$ across the fish (ca. 30 db above threshold), at a frequency of 8.0 Hz below the fish's, at the times indicated by the markers. The responses are shortening of intervals by about $0.1\% = 1.0 \mu\text{sec}$. The spikes of various sizes are a special form of "voluntary" social signal called chirps (Bullock, 1969).

study of this shows relatively reliable graded responses as small as 0.1% in frequency shift, or $1 \mu\text{sec}$ in *Sternarchus* at 1 kHz (Fig. 5). Reliable here means the response occurs on each trial, easily visible to our eye, above the background fluctuation. (It also means a feeble stimulus has been detected, e.g. one that is only 1.0 Hz different from the fish's at moderate voltage, or only $0.5 \mu\text{v}/\text{cm}$ across the fish at the optimum frequency difference of 3 Hz.)

(d) The jamming avoidance response invites attention in other connections that cannot be developed here. The driving unit is an example of a decision unit (Bullock, 1961, 1969), that receives complex, graded input with several parameters, evaluates according to preset weighting functions, sums separate

input parameters, triggers behavior according to its threshold at its own pace, mixing response with spontaneity. It is a unit with redundancy and independence of failure of individual cells. Besides knowing completely the output of a normal behavioral act, and using extracorporeal electrodes to do so, we are

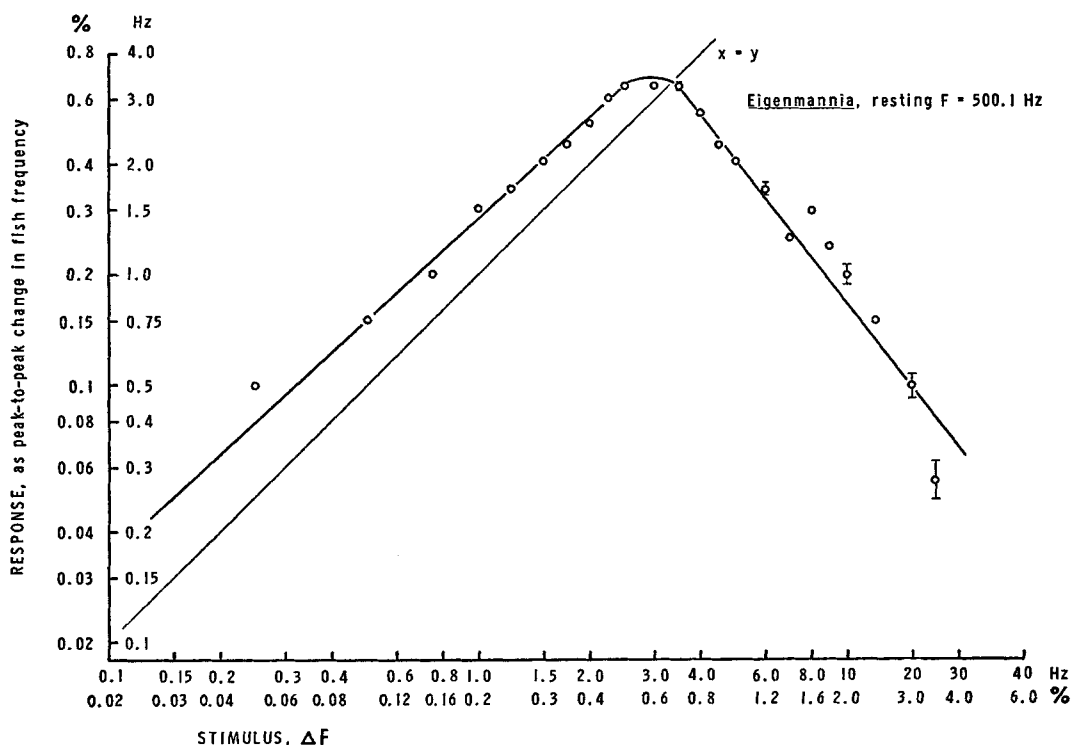


FIGURE 5. Jamming avoidance response of *Eigenmannia* sp. as a function of the stimulus expressed as ΔF , the difference between the applied stimulus and the fish's own discharge frequency. The stimulus is applied alternately above and below the fish's frequency. The ΔF is maintained by a "frequency clamp" circuit operating on the sum of four intervals. Response is measured as mean change in fish frequency from the peak of the avoidance shift for stimuli below his own, to the peak response for stimuli above his own frequency. Vertical bars are estimated confidence limits and are drawn too small by a factor of two. The slope of stimulus = response is given merely for convenience.

tantalizingly close to knowing the relevant input quantitatively. This is due to the extensive studies on the electroreceptor units in the lateral line nerve (Bullock et al., 1961; Bullock and Chichibu, 1965; Hagiwara et al., 1962, 1963, 1965). There are several types of afferent fibers, coding intensity of electric field in different ways, adding an interest for coding theory as well as decision theory, social signalling and, probably cerebellar function. This last is based on evidence that the cerebellum is involved, not in coordinating motor action, but, while the fish is virtually motionless, in continuously analyzing the

exteroceptive input about the position of the body relative to objects in space.

But the relevance to the reliability question is the main interest here. This case tells us that standard vertebrate neural units can exhibit exceedingly low noise of successive spike interval duration. This means that both rate of rise of pacemaker potential and threshold of firing are highly regular; small changes are meaningful. It is not to be assumed that observed and unaccountable variation in spike intervals is noise, even with a physically constant stimulus.

IV

How reliable is reliable? One difficulty with the debate has been an implicit assumption of either-or operation. But patently the probabilistic position can mean that neurons are relatively, or within limits, uncertain and the deterministic position always implies a limit at least on our demonstration of predictability. This limit can be given for each studied case, as a lower bound on reliability (as on p. 575). The situation is asymmetrical since it is more difficult to place a meaningful upper bound on uncertainty and this is almost never done.

The limits to reliability are widely different in different neurons. Quite possibly variation is sometimes averaged to salvage information. The evidence cited does not argue against probabilistic operation. But to say that beyond some limit indeterminacy prevails is not, without quantitative evaluation, to establish it as a prime principle of signalling.

Limits on uncertainty, beyond which variation is useful without averaging, are difficult to set. We know of some cases in which variation is not used, and is therefore noise, and others in which it is a good signal of another message, based on parallel processing of the same input for different uses. "He is 6 ft tall" (said in a high-pitched voice) and "He is 6 ft tall" (said in a low-pitched voice) show a conspicuous variation that is irrelevant to the message about height, but a true signal of something about the speaker.

What do authors actually mean when they speak of the probabilistic view of the nervous system being the only sensible approach? The answer is apparently quite different with different authors and is often not formulated but implied.

Lamb and Isaacs (1966) and Isaacs and Lamb (1969) argue that real Heisenberg indeterminacy extends in the biological cell up to include the molecular level and hence the operation of synapses. Eccles (1953) believed the same thing and speculated that volition rests on this uncertainty.

Wald (1965) on the other hand rejects Heisenberg uncertainty at the molecular level. He attributes free will to unpredictability from ignorance of the complex determinacy, emphasizing how small is the area of behavior in which free will or really unpredictable outcome can range.

Let us try to clarify a rather muddled area by isolating issues that are really

distinct. Walter (1968) usefully distinguishes three quite different questions. One is the *utility* of using probabilistic treatment as a data reduction tactic without presumption about reliability or what is noise. Of course, one can take no exception to this since it recognizes that it is not necessary to assume unpredictability in order to make use of stochastic analysis. This accounts for much of the literature and raises no fundamental problems but only tactical and strategic ones (Moore et al., 1966).

A second question is, in Walter's words, "whether the only route to deeper understanding of neural function is via a model" that assumes probabilistic or indeterministic operation. He states that his prejudice is "Yes" but that this is still very much open to argument. I will call this a private question of heuristic (unless it rears its head in relation to priorities in granting aid or assigning machine time)! It makes no assertion about the principles of operation of nerve cells in the brain.

The third question is whether the nervous system *is* indeterministic and this is the one I have been addressing, at the level of the neuronal unit.

Here we must distinguish two alternatives. One is the Heisenberg type of indeterminacy which means, according to Bohr, more than an unknowability of the state of each unit in practice, but a fundamental property. The other is the statistical mechanical type exemplified by a population of molecules, as in a gas. Most people probably have this in mind though I have mentioned several who assert the first and Walter (1968) believes "that the brain is essentially less determinate than the gas."

There can hardly be any argument if one has the gas model in mind. This model does not deny predictable, determinate behavior of neural units but only says that in practice we cannot know enough in the usual case to predict their behavior. It leads to the use of stochastic analysis as a matter of utility. If one asserts that the fundamental indeterminacy of Heisenberg operates at physiological levels in the nervous system, there can hardly be any debate since barring very special knowledge of the ultimate mechanism in each case, this is essentially a statement of belief.

At the level of the chief argument of this essay, it may contribute to clarification if we recognize, instead of sweeping generalizations about neuronal performance, that they appear to exhibit a *degree* of irrelevant variation or noise and a *degree* of reliable response or signal. This would advance us to the quantitative level of justifying the degree to be assigned each component, which seems to vary widely. This in turn would force us to justify the qualitative labels, "noise" and "signal," a most difficult challenge since it inherently depends on knowing the complete use the system makes of each channel.

Noise in the nervous system must in general be treated as a tentative hypothesis since apparent noise may have any of several uses (Part II, section 4, above).

So the pitfalls in the two attitudes are not symmetrical. The probabilist—and I don't mean the one who simply uses statistical methods or sets up models to test, but the one who proposes that the system really works that way or that the only route to understanding is the Heisenberg assumption—the probabilist runs the risk of taking an apparent unreliability or noise for real. And he may overlook solid cases of reliability. I don't know any "precisionists" or determinists, wet physiologists dealing with special biological cases, who extrapolate to the assumption of invariant noise-free operation, or to highly reliable operation of all neurons in a population, or who deny a probabilistic component, now larger, now smaller. The asymmetry with respect to the difficulty of showing reliability vs. showing unreliability does not argue against a largely probabilistic operation of the nervous system but it does warn that basically that case rests on plausibility.

In our present state of understanding the eclectic attitude seems most reasonable. Saying this is not being nondiscriminating. It means that taking all evidence into account suggests the conclusion that the nervous system operates with a full battery of principles: sometimes with population averaging, sometimes with single or a few equipotent units. The finding of variation should be an opening wedge to looking for its causes and its consequences.

The horizon is wide because it encompasses not only statistical models but also closer study of the amount, the kinds, the origins, and the meanings of fluctuations; of how signals are read, and of who takes averages to refunnel dispersed populations into reliable output. These questions are accessible, concrete, and realistic. My deliberate one-sidedness today will not be wasted if it serves to help steer us out of a circle and toward that horizon.

SUMMARY

A prevalent view regards "indeterminacy (as) a concept of neural activity which is far more likely to be of use" than concepts based on apparent predictability, and the probabilistic approach as the only sensible treatment. In an attempt to clarify a rather murky literature, three distinct issues can be isolated. One is the utility of probabilistic methods for data reduction, without presumption about underlying neuronal uncertainty. No questions are here raised on this issue. A second is the value of models that assume indeterminacy. This is a private question of heuristic and is not discussed. The third is whether the nervous system *is* largely indeterministic and this is the issue addressed here, at the neuronal level.

Of the two alternative types of uncertainty, there can hardly be any argument that the equivalent of statistical mechanical or practical unpredictability exists, as in a gas, because of the unknowability of all antecedents in practice. But the assertion of an additional contribution from Heisenbergian indeterminacy is essentially a statement of belief.

It may contribute further to clarification to recognize that neurons perform with a *degree* of irrelevant variation or noise and a *degree* of reliable response or signal. This advances the problem to the quantitative level of justifying the degrees to be assigned and the labels noise and signal.

The main argument is that the proposition that the nervous system operates mainly probabilistically with unreliable components is an unprovable article of belief, whereas relatively reliable connections and performance are demonstrable. I believe the probabilistic assumption to be correct, for some parts of the nervous system, in some degree, both unknown. Purported evidence of unreliability in neurons is subject to several limitations.

Evidence of reliability on the other hand is ever increasing, including unexpected anatomical and physiological developments.

One hitherto unappreciated measurement is given of a highly regular rhythm in electric fish (*Sternarchus*) electromotor command units. Normal intervals between discharges (in a typical case 1.2 msec), have a standard deviation of $0.012\% = 0.14 \mu\text{sec}$ and weak stimuli are relatively reliably signalled by interval changes of $0.1\% = 1 \mu\text{sec}$. This is a socially significant behavioral response determined by a physiologically unitary pacemaker sensitive to specific electroreceptor input. Neurons can be quite reliable.

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REFERENCES

- ALLANSON, J. T. 1956. The reliability of neurons. Proceedings of the 1st International Congress on Cybernetics. Namur Gauthier-Villars, Paris. 687.
- ARBIB, M. A. 1964. Brains, Machines and Mathematics. McGraw-Hill Book Co., New York.
- BARLOW, H. B., and W. R. LEVICK. 1969. Three factors limiting the reliable detection of light by retinal ganglion cells of the cat. *J. Physiol. (London)* **200**:1.
- BENNETT, M. V. L., G. D. PAPPAS, M. GIMINEZ, and Y. NAKAJIMA. 1967. Physiology and ultrastructure of electrotonic junctions. IV. Medullary electromotor nuclei in gymnotid fish. *J. Neurophysiol.* **30**:236.
- BEURLE, R. L. 1962. Storage and manipulation of information in random networks. *In Aspects of the Theory of Artificial Intelligence*. C. A. Muses, editor. Plenum Publishing Corp., New York. 19.
- BISHOP, L. G., and D. G. KEEHN. 1967. Neural correlates of the optomotor response in the fly. *Kybernetik.* **3**:288.
- BISHOP, L. G., D. G. KEEHN, and G. D. McCANN. 1968. Motion detection by interneurons of optic lobes and brain of the flies *Calliphora phaenicia* and *Musca domestica*. *J. Neurophysiol.* **31**:509.
- BISHOP, P. O. 1969. Neurophysiology of binocular single vision and stereopsis. *In Handbook of Sensory Physiology*. Springer-Verlag KG, Berlin. 7.
- BISHOP, P. O. 1970. Cortical beginning of visual form and depth discrimination. *In: The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- BRAITENBERG, V. 1967. Patterns of projection in the visual system of the fly. I. Retinal-lamina projections. *Exp. Brain Res.* **3**:271.
- BULLOCK, T. H. 1961. The problem of recognition in an analyzer made of neurons. *In Sensory Communication*. W. A. Rosenblith, editor. Technology Press, Cambridge., U.S.A. 717.

- BULLOCK, T. H. 1969. Species differences in effect of electroreceptor input on electric organ pacemakers and other aspects of behavior in electric fish. *Brain, Behavior and Evolution*. 2:85.
- BULLOCK, T. H. 1970. Operations analysis of nervous functions. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- BULLOCK, T. H., and S. CHICHIBU. 1965. Further analysis of sensory coding in electroreceptors of electric fish. *Proc. Nat. Acad. Sci. U.S.A.* 54:422.
- BULLOCK, T. H., S. HAGIWARA, K. KUSANO, and K. NEGISHI. 1961. Evidence for a category of electroreceptors in the lateral line of gymnotid fishes. *Science (Washington)*. 134:1426.
- BULLOCK, T. H., and G. A. HERRIDGE. 1965. Structure and Function in the Nervous Systems of Invertebrates. W. H. Freeman & Co., San Francisco, Calif. 1 and 2.
- BURNS, B. D. 1968. *The Uncertain Nervous System*. Edward Arnold (Publishers) Ltd., London.
- CAIANIELLO, E. R. 1968. *Neural Networks*. Springer Verlag, New York Inc.
- COGGESHALL, R. E. 1967. A light and electron microscope study of the abdominal ganglion of *Aplysia californica*. *J. Neurophysiol.* 30:1263.
- COHEN, M. J. 1970. Structural and functional correlates in the neurons of vertebrates and invertebrates. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- CRAGG, B. G., and H. N. V. TEMPERLEY, 1954. The organization of neurones: a cooperative analogy. *Electroencephalogr. Clin. Neurophysiol.* 6:85.
- ECCLES, J. C. 1953. *The Neurophysiological Basis of Mind*. Oxford University Press.
- FITZHUGH, R. 1957. The statistical detection of threshold signals in the retina. *J. Gen. Physiol.* 40:925.
- GALAMBOS, R., J. SCHWARTZKOPFF, and A. RUPERT. 1959. Microelectrode study of superior olivary nuclei. *Amer. J. Physiol.* 197:527.
- GRINNELL, A. D. 1969. Comparative study of hearing. *Annu. Rev. Physiol.* 31:545.
- GRÜSSER, O.-J., and U. GRÜSSER-CORNEHLS. 1969. Neurophysiologie des Bewegungsehens. *Ergeb. Physiol.* 61:178.
- GRÜSSER-CORNEHLS, U., O.-J. GRÜSSER, and T. H. BULLOCK. 1963. Unit responses in the frog's tectum to moving and nonmoving visual stimuli. *Science (Washington)*. 141:820.
- HAGIWARA, S., and H. MORITA. 1963. Coding mechanisms of electroreceptor fibers in some electric fish. *J. Neurophysiol.* 26:551.
- HAGIWARA, S., K. KUSANO, and K. NEGISHI. 1962. Physiological properties of electroreceptors of some gymnotids. *J. Neurophysiol.* 25:430.
- HAGIWARA, S., T. SZABO, and P. S. ENGER. 1965 a. Physiological properties of electroreceptors in the electric eel, *Electrophorus electricus*. *J. Neurophysiol.* 28:775.
- HAGIWARA, S., T. SZABO, and P. S. ENGER. 1965 b. Electroreceptor mechanisms in a high frequency weakly electric fish, *Sternarchus albifrons*. *J. Neurophysiol.* 28:784.
- HOWE, D. W., JR., F. I. ERSKINE, and L. P. GRANATH. 1966. Threshold sensitivity of *Sternarchus albifrons* to electric fields. *Amer. Zool.* 6:521.
- HUBEL, D. H., and T. N. WIESEL. 1962. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol. (London)*. 160:106.
- HUBEL, D. H., and T. N. WIESEL. 1968. Receptive fields and functional architecture of monkey striate cortex. *J. Physiol. (London)*. 195:215.
- ISAACS, J. P., and J. C. LAMB. 1969. Complementarity in Biology: Quantization of Molecular Motion. The Johns Hopkins Press, Baltimore, Md.
- JACOBSON, M. 1970. Sensory systems. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- KOGAN, A. B. 1964. Statistical probability principle of the neuronal organization of the functional system of the brain. *Dokl. Akad. Nauk SSSR Biological Sci. Sect. (Transl.)*. 154:139.
- KUFFLER, S. W., R. FITZHUGH, and H. B. BARLOW. 1957. Maintained activity in the cat's retina in light and darkness. *J. Gen. Physiol.* 40:683.
- KUHN, T. S. 1962. *The Structure of Scientific Revolutions*. University of Chicago Press, Chicago, Ill.

- KUIPER, J. W., and J. T. LEUTSCHER-HAZELHOFF. 1965. High-precision repetitive firing in the insect optic lobe and a hypothesis for its function in object location. *Nature (London)*. **206**: 1158.
- LAMB, J. C., and J. P. ISAACS. 1966. Indeterminacy, the synapse, the mnemonic microstate, and the psyche. *Cond. Reflex.* **4**:1.
- LARIMER, J. L., and J. A. McDONALD. 1968. Sensory feedback from electroreceptors to electromotor pacemaker center in gymnotids. *Amer. J. Physiol.* **214**:1253.
- LEVY, M. H., P. J. MARTIN, T. IANO, and H. ZIESKE. 1969. Paradoxical effect of vagus nerve stimulation on heart rate in dogs. *Circ. Res.* **25**:303.
- MARCHIAFAVA, P. L., and G. PEPEU. 1966. The responses of units in the superior colliculus of the cat to a moving visual stimulus. *Experientia (Basel)*. **22**:51.
- MATURANA, H. R., and S. FRENK. 1963. Directional movement and horizontal edge detectors in the pigeon retina. *Science (Washington)*. **142**:977.
- MCCANN, G. D., and J. C. DILL. 1969. Fundamental properties of intensity, form, and motion perception in the visual nervous systems of *Calliphora phaenicia* and *Musca domestica*. *J. Gen. Physiol.* **53**:385.
- MICHAEL, C. R. 1966. Receptive fields of directionally selective units in the optic nerve of the ground squirrel. *Science (Washington)*. **152**:1092.
- MOORE, G. P., D. H. PERKEL, and J. P. SEGUNDO. 1966. Statistical analysis and functional interpretation of neuronal spike data. *Annu. Rev. Physiol.* **28**:493.
- MOUNTCASTLE, V. B. 1967. The problem of sensing and the neural coding of sensory events. In *The Neurosciences: A Study Program*. C. G. Quarton, T. Melnechuk, and F. O. Schmitt, editors. The Rockefeller University Press, New York. 393.
- NICHOLLS, J. G., and D. A. BAYLOR. 1968. Specific modalities and receptive fields of sensory neurons in CNS of the leech. *J. Neurophysiol.* **31**:740.
- OYSTER, C. W. 1968. The analysis of image motion by the rabbit retina. *J. Physiol. (London)*. **199**:613.
- PERKEL, D. H., and T. H. BULLOCK. 1968. Neural coding. *Neurosci. Res. Program Bull.* **6**:221.
- PERKEL, D., J. SCHULMAN, T. H. BULLOCK, G. P. MOORE, and J. P. SEGUNDO. 1964. Pacemaker neurons: Effects of regularly spaced synaptic input. *Science (Washington)*. **145**:61.
- RATLIFF, F., H. K. HARTLINE, and D. LANGE. 1968. Variability of interspike intervals in optic nerve fibers of *Limulus*: Effect of light and dark adaptation. *Proc. Nat. Acad. Sci. U.S.A.* **60**:464.
- REID, J. V. O. 1969. The cardiac pacemaker: Effects of regularly spaced nervous input. *Amer. Heart J.* **78**:58.
- ROBERGE, F. A. 1969. Paradoxical inhibition: A negative feedback principle in oscillatory systems. *Automatika.* **5**:407.
- RUPERT, A., G. MOUSHEGIAN, and R. GALAMBOS. 1962. Microelectrode studies of primary vestibular neurons in cat. *Exp. Neurol.* **5**:100.
- SCHIEBEL, M. E., and A. B. SCHIEBEL. 1970. Elementary processes in selected thalamic and cortical subsystems. The structural substrates. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- SCHOLL, D. A. 1956. *The Organization of the Cerebral Cortex*. John Wiley & Sons, Inc., New York.
- SCHULMAN, J. 1969. Information transfer across an inhibitor to pacemaker synapse at the crayfish stretch receptor. Ph.D. Thesis. Zoology Department, University of California Los Angeles.
- SEGUNDO, J. P., and D. H. PERKEL. 1969. The nerve cell as an analyzer of spike trains. In *UCLA Forum in Medical Sciences No. 11, The Interneuron*. M. A. B. Brazier, editor. University of California Press, Berkeley, Calif. 349.
- SPERRY, R. W. 1963. Chemoaffinity in the orderly growth of nerve fiber patterns and connections. *Proc. Nat. Acad. Sci. U.S.A.* **50**:703.
- STARK, L. 1968. *Neurological Control Systems: Studies in Bioengineering*. Plenum Publishing Corp., New York.

- STEIN, R. B. 1970. The role of spike trains in transmitting and distorting sensory signals. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- STRASCHILL, M., and K. P. HOFFMAN. 1968. Relationship between localization and functional properties of movement-sensitive neurons of the cat's tectum opticum. *Brain Res.* 8:382.
- STRAUSFELD, N., and A. D. BLEST. 1970. Golgi studies on insects. *Phil. Trans. Roy. Soc. London Ser. B. Biol. Sci.* In press.
- STUART, A. E. 1969. Excitatory and inhibitory motoneurons in the central nervous system in the leech. *Science (Washington)*. 165:817.
- SUGA, N. 1969. Classification of inferior collicular neurones of bats in terms of responses to pure tones, FM sounds and noise bursts. *J. Physiol. London*. 200:555.
- SUGA, N. 1967. Echo-detection by single neurons in the inferior colliculus of echo-locating bats. In *Animal Sonar Systems, Biology and Bionics*. R. G. Busnel, editor. C.N.R.S. Jouy-en-Josas, France N.A.T.O. Adv. Study Inst. 1004.
- SWIHART, S. L. 1968. Single unit activity on the visual pathway of the butterfly *Heliconius erato*. *J. Insect Physiol.* 14:1589.
- SZABO, T., and P. S. ENGER. 1964. Pacemaker activity of the medullary nucleus controlling electric organs in high frequency gymnotid fish. *Z. vergl. Physiol.* 49:285.
- SZENTAGOTHAI, J. 1970. Glomerular synapses, complex synaptic arrangements and their operational significance. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.
- TEN HOOPEN, M. 1966. Probabilistic firing of neurons considered as a first passage problem. *Biophys. J.* 6:435.
- TRUJILLO-CENOZ, O. 1965. Some aspects of the structural organization of the intermediate retina of dipterans. *J. Ultrastruct. Res.* 13:1.
- VERBEEK, L. A. M. 1961. Reliable computation with unreliable circuitry. *Proc. Bionics Symp.* Dayton, Ohio, 1960. WADD Tech. Rep. 60-600, Wright Air Development Div., Wright-Patterson A.F.B., Ohio. 83.
- VON NEUMANN, J. 1956. Probability logic and synthesis of reliable organisms from unreliable components. In *Automata Studies*. C. E. Shannon and J. McCarthy, editors. Princeton University Press, Princeton, N. J. 43.
- VOWLES, D. M. 1966. The receptive fields of cells in the retina of the housefly (*Musca domestica*). *Proc. Roy. Soc. Ser. B. Biol. Sci.* 164:552.
- WALD, G. 1965. Determinacy, individuality and the problem of free will. In *New Views of the Nature of Man*. J. R. Platt, editor. University of Chicago Press, Chicago, Ill. 16.
- WALTER, D. O. 1968. The indeterminacies of the brain. *Perspect. Biol. Med.* 11:203.
- WATANABE, A., and K. TAKEDA. 1963. The change of discharge frequency by A. C. stimulus in a weak electric fish. *J. Exp. Biol.* 40:57.
- WATERMAN, T. H., and C. A. G. WIERSMA. 1963. Electrical responses in decapod crustacean visual systems. *J. Cell. Comp. Physiol.* 61:1.
- WIERSMA, C. A. G. 1967. Visual central processing in crustaceans. In *Invertebrate Nervous Systems*. C. A. G. Wiersma, editor. University of Chicago Press, Chicago, Ill. 269.
- WIERSMA, C. A. G., and T. OBERJAT. 1968. The selective responsiveness of various crayfish oculomotor fibers to sensory stimuli. *Comp. Biochem. Physiol.* 26:1.
- WIERSMA, C. A. G., and T. YAMAGUCHI. 1966. Integration of visual stimuli by the crayfish central nervous system. *J. Exp. Biol.* 47:409.
- WILSON, D. M. 1970. Neural operations in arthropod ganglia. In *The Neurosciences: A Second Study Program*. F. O. Schmitt, editor. The Rockefeller University Press, New York. In press.