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Neuronal coding
Optic nerve
Temporal discharge pattern
Neuronal decoding
Axonal conduction block

Multiple Meaning in Single Visual Units

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The meaning of the message in a neuron has usually been guessed by observing the relations between a stimulus and a change in the number of impulses discharged by the neuron per unit time. In part this has been because a vigorous burst of impulses or a sudden suppression of the maintained activity is so compelling to an observer that he naturally assumes that it is the message. This assumption is derived presumably from several other factors. First, an orderly relationship has been established in a variety of systems between the mean rate of discharge and the stimulus intensity [e. g., MATTHEWS, 1964; FUORTES, 1958; GRÜSSER *et al.*, 1968]. Second, changes in other features of the pulse train are generally accompanied by changes in the mean rate. Although modifications of patterns of pulse intervals such as shifts in the slopes or peaks of pulse interval histograms have often been noted, the significance of such changes has not been emphasized because of the concomitant changes in the average discharge rate [cf. PERKEL and BULLOCK, 1968]. Finally, to transfer increased or decreased mean rates of discharge from cell to cell requires no great complexity from synaptic mechanisms.

Thus, the temptation is to consider the extensive and often irregular variations of interspike interval that are present in a sequential record of the discharges of many neurons to be 'noise' corrupting the important measure of mean discharge rate [STEIN, 1967]. Such an approach has been very useful, not only in tracing the connectivity of neurons, but in discriminating different operations for single neurons of the optic nerve or the visual cortex [e. g., KUFFLER, 1953; HUBEL and WIESEL, 1959; LETTVIN *et al.*, 1959]. As VON UEXKÜLL [1909] points out, however, the meaning of the message transmitted by a neuron is unknown and is indeed the very feature that one attempts to investigate. Thus, the separation of neuronal responses into 'signal' and 'noise' remains arbitrary and begs the questions of what the message is and how the nervous system is designed to handle it.

We consider here the changes in temporal discharge pattern occurring in the dimming fibers of the frog's optic nerve. These changes were found to be interpretable in terms of several characteristics of the stimulus. By noting the aspects of the stimulus leading consistently to changes in temporal discharge patterns, we infer that these patterns can be thought of as messages having multiple meanings; that is, messages that make statements about combinations of several properties of the simulus. In the second part of this paper, we suggest a mechanism by which such meanings can be represented at the teledendron. Other accounts of some of these experiments and the notions regarding the interpretive mechanisms that we are proposing have been given elsewhere [GESTELAND *et al.*, 1967; CHUNG and LETTVIN, 1969; RAYMOND, 1969; RAYMOND and LETTVIN, 1969; LETTVIN *et al.*, in preparation].

Part I: Discharge Patterns of Frog Dimming Fibers

Frogs (*Rana pipiens*) were immobilized by injecting 0.10–0.15 cc tubocurarine in the dorsal lymph sac, and mounted on a corkboard. The skull was opened over the forebrain, which was removed (or sometimes only retracted) to expose the optic nerve leaving the orbit. Since the nerve bundle is encapsulated by a thick membrane, a small slit had to be carefully made with a fine dissection knife to permit the passage of a microelectrode. A modified Dowben-Rose electrode was used for recording. Pipettes were drawn, and the tips were broken to a diameter of 2–5 μ. The pipettes were then filled with an alloy (Cerrolow 136) and a wire lead was embedded in the alloy at the wide end of the pipette [GESTELAND *et al.*, 1959]. The tips were plated first with gold and then with platinum black to make a cap on the tip slightly wider than the tip itself.

Recording was done through a conventional low-noise AC amplifier of bandwidth 10^2–10^4 Hz and with an input resistance of 10 MΩ. The impulses were displayed on one oscilloscope and were monitored over a loudspeaker. Successive pulse-interval durations were exhibited by a 'CLOOGE' (the acronym for Continuous Log Of On-Going Events). This instrument generated an output voltage proportional to the logarithm of the duration of each pulse interval. Interspike intervals from 1 msec to approximately 2 min duration were represented on the vertical axis of a second oscilloscope. The horizontal axis of this same oscilloscope constituted a time sweep. When needed, extremely slow sweeps were generated by coupling the wiper of a motor-driven potentiometer to the horizontal amplifier. A variable neutral density filter of 8 decades range was placed between the light source and one end of a light pipe of 6.3 mm diameter. The other end of the light pipe was placed approximately 1 cm away from the eye. A threshold intensity was defined by measuring the minimum amount of light that elicted 'off' responses from a dark-adapted unit. Unless noted otherwise, the numerical intensities reported in our figures are expressed in decibels with reference to the threshold intensity. Most of the records displayed were obtained from the final 20 of more than 400 units that we have examined.

Results I

Unlike the receptive fields of the units in the mammalian optic nerve, the receptive fields of the dimming fibers in the frog do not exhibit intimate center-surround organization. Most of these units have oval-shaped receptive fields that subtend from 10° to 15° of visual angle. In the light-adapted state, the fiber discharges briskly upon the cessation of illumination or the emergence of a dark object in the field. When the animal is placed in total darkness, the discharge rate changes slowly to reach a stable, steady-state level. The time course of this change, which, under certain conditions, lasts up to 3 h, depends in part on the amount of light that has previously impinged on the retina. The activity of the fibers usually arrives at a steady state within an hour in the dark after the surgery.

A. Three types of dimming fibers. All dimming fibers show continuous discharge in absolute darkness when the retina is dark-adapted. On the basis of the discharge characteristics in the dark, the fibers can be classified into three more or less distinct types, as shown in figure 1.

Type I (upper record) discharges so that two bands, a sharp high-frequency band and a diffuse low-frequency band, appear in the continuous plot of interspike intervals. The presence of only very short and very long intervals is also apparent on listening to the audio monitor which sounds 'bursty': groups of impulses separated by periods of silence. Bursty discharge patterns occur in a variety of cells, such as the cardiac ganglion neurons in *Crustacea* [HAGIWARA, 1961], mammalian hippocampal cells [KANDEL and SPENCER, 1961], certain neurons in *Aplysia* [STRUMWASSER, 1967], and others.

When the retina is well dark-adapted, a type I fiber discharges at an average rate of approximately 60 impulses/min. Type II (middle record) discharges at a faster average rate (240/min) than type I, and unlike type I, does not show empty bands. The record shows well-defined upper and

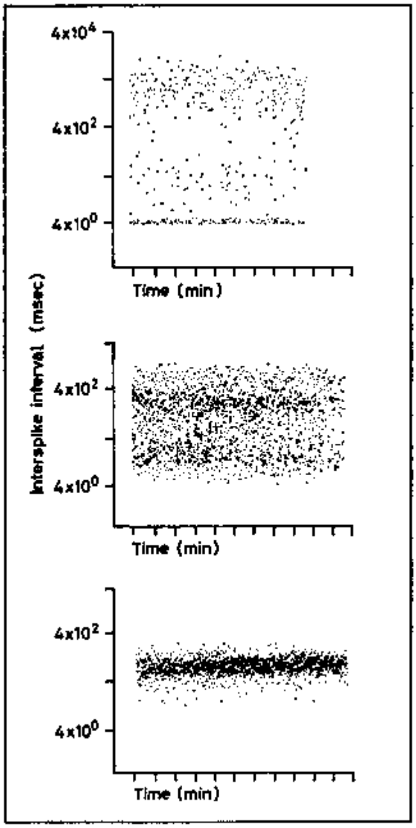


Fig. 1. Three types of dimming fibers. The logarithm of successive interspike intervals is plotted as a function of time. Each dot denotes the occurrence of an impulse, and its vertical displacement gives the duration of the interval between the impulse and the preceding one. The records were obtained from three different units discharging in the dark after the retina was fully dark-adapted.

lower limits of interspike intervals, and all intervals within these limits are represented. A few dimming fibers, type III, fire in a steady and regular pattern (lower record). These fibers discharge more rapidly (600/min) than the first two types, and the majority of these fibers appear to project to the diencephalon.

The first two types comprised approximately 85 % of the dimming fibers, and were encountered equally often in the optic nerve. Less than 5 % of the units were type III. A variety of other types of discharge patterns was occasionally encountered. For example, one type generated bursts of 10–15 spikes. Each burst had a distinct form wherein the longer pulse intervals occurred at the beginning. Progressively shorter intervals followed the first few spikes, and the burst terminated at a relatively high frequency. Another infrequent type exhibited the characteristic discharge pattern of type II in the dark, but also had a sharp high-frequency band outside the broad central distribution. Since the sample sizes of these miscellaneous types are small, we shall consider the alterations in the discharge patterns during different conditions of illumination and different states of adaptation only for the three types shown in figure 1.

B. Modification of discharge patterns by background illumination. With a dim background illumination the average frequency of discharge per unit time can remain essentially unchanged while the temporal pattern of discharge undergoes a drastic modification. Figure 2 shows two examples of such cases. The first segment of the upper record was obtained in the dark from a type I unit. When a dim background light was introduced, the short-interval band characteristic of the dark discharge pattern of type I disappeared. The predominant long-interval band remained almost unchanged. An analogous modification of the discharge pattern during crepuscular illumination was frequently observed in type II fibers. The middle record of figure 2 shows that the broadband interspike interval pattern, characteristic of type II fibers in the dark, was separated into two distinct bands by a dim background illumination. Less conspicuous cases occurred where background illumination would rarefy the density of dots in the center-frequency region between the preferred bands, rather than eliminate such intervals altogether. The effect of a steady illumination on the type III dimming fibers is easier to describe than on types I and II. The firing frequency is lowered when a background illumination is introduced (lower record), and the magnitude of the lowering is directly related to the intensity of illumination. No modification of the discharge pattern can be discerned. Unlike that for the majority of the dimming fibers, the operating range of type III fibers is narrow. At photopic illumination (∾40–50 dB) the fiber abruptly ceases to discharge, thereby suggesting that it is inhibited by cone activity.

The disappearance of the high-frequency band of type I is not an all-or-none phenomenon. As shown in figure 3, the density of spikes in the high-frequency band is rarefied gradually. The successive records in the figure were taken at various intensities of background illumination. The numbers shown with each record indicate the amount of increment in de-

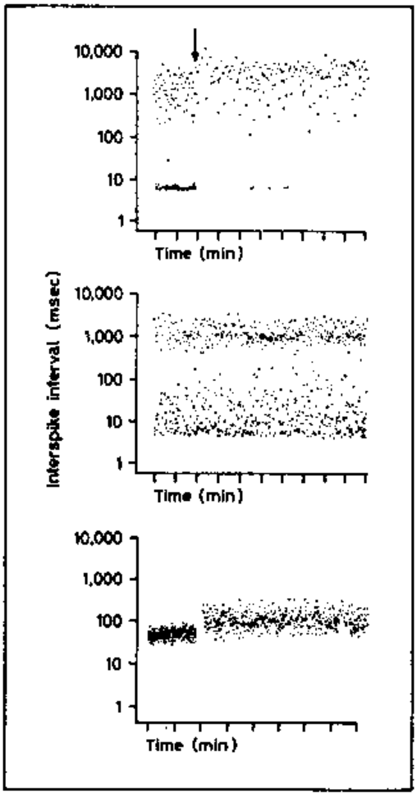


Fig. 2. Modification of discharge patterns during dim illumination. The first segment of the upper record shows the discharge pattern of a type I fiber in the dark. The high-frequency band disappeared when a dim illumination (30 dB) was turned on at the arrow. The middle record is a record of the steady-state activity of a type II unit in the presence of background illumination (30 dB). The background illumination was introduced approximately 5 min before the beginning of the record. The initial transient suppression of the maintained activity is not shown in the record. Compare with records of these units in the dark (fig. 1 middle record, fig. 4 upper record). The first segment of the lower record was obtained from a type III unit in the dark. The presence of a steady background light (20 dB) suppressed the mean discharge rate.

cibels with reference to the control record. Each successive increment of ambient light diminished the probability of occurrence of 'doublets'. At a higher intensity of light (still relatively dim) no doublets occurred and the short interval band vanished completely. A further increment of the background illumination depresses the firing rate, and at a high level of ambient illumination the fiber ceases to discharge.

The sensitivity of type II fibers is higher than that of the other two types of dimming fibers. Although no attempts were made to measure the absolute or differential threshold, casual observations indicate that the sensitivity of these fibers exceeds that of the experimenters. Mention has already been made of the modification of the type II discharge pattern in the dark which happens during dim background illumination. When a bright light (80 dB) is impinging on the receptive field of the fiber, the unit begins to discharge rhythmically. The rhythmicity becomes more and more pronounced as the intensity of the illumination increases. The upper record in figure 4 shows the type II dark discharge pattern. A band appeared with an interval duration of ∾800 msec when the retina became adapted to a bright light (middle record). The band was accentuated when the intensity of illumination was enhanced by another decade (lower record). Thus this class of dimming fibers fired in one characteristic pattern in the dark, and in another very different pattern during bright illumination. It is possible, however, that the modification of discharge pattern described above is not directly due to background illumination itself but arises from objects in the visual field which the illumination reveals.

Similar observations have been made by others. KUFFLER *et al.* [1957] noted that maintained activity in the cat's retinal ganglion cells was present whether the animal was in total darkness or in light. In some of the units that they examined, the average frequency of maintained discharge after a transient shift was found to be approximately constant over a wide range of ambient intensities. They suggested that incoming visual messages are coded by modulation of this maintained discharge. RATLIFF *et al.* [1968] observed that the variation of interspike intervals in the discharge of a dark-adapted *Limulus* eccentric cell is greater than the variation of interval duration in a light-adapted cell discharging at the same frequency. They considered the possibility that the cell could be capable of transmitting two types of information – the light intensity and the state of adaptation of the unit.

C. Second inhibition. To square pulse of light the dimming fibers exhibit a series of oscillatory variations in frequency of discharge. The sequence of this response is shown in figure 5. The initial segment of the record shows the maintained activity of a dark-adapted fiber of type II. A flash of about 45 sec long and an intensity of 80 dB interrupted the darkness. During the stimulus, discharges were completely suppressed. At the cessa-

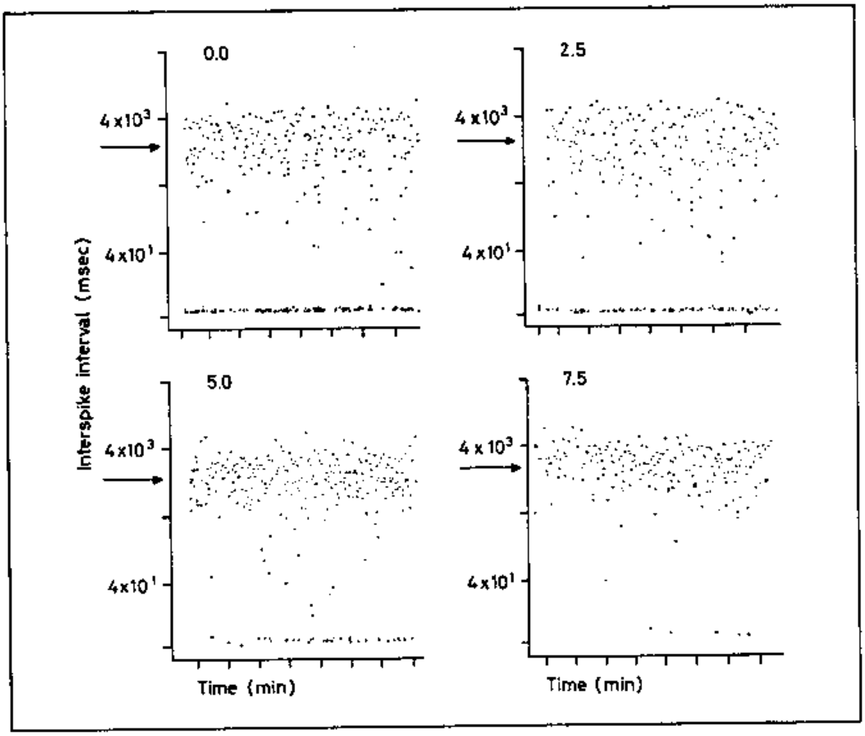


Fig. 3. Rarefaction of the density of the high-frequency band. The number accompanying each of the four records denotes the light intensity in decibels with reference to the control intensity used to obtain the upper left record. The arrows along the ordinates indicate the average interspike interval computed from 5 min of each record. At least 5 min of adaptation at each intensity was permitted before taking the record.

tion of the stimulus a burst of impulses (first excitation) appeared. A brief first inhibition signalled by the single dot near 2nd arrow was followed by a vigorous activity (second excitation) for >1 min. Then there appeared a long period of inhibition (second inhibition) which slowly decreased until the resting level was regained. The time course of each of these processes depends on intensity and duration of the stimulus, as well as on the state of retinal adaptation.

One of the most salient features of the dimming fibers is the prolonged second inhibition, which, under certain conditions, lasts up to 3 h. A slow recovery from the second inhibition can be illustrated with a moder-

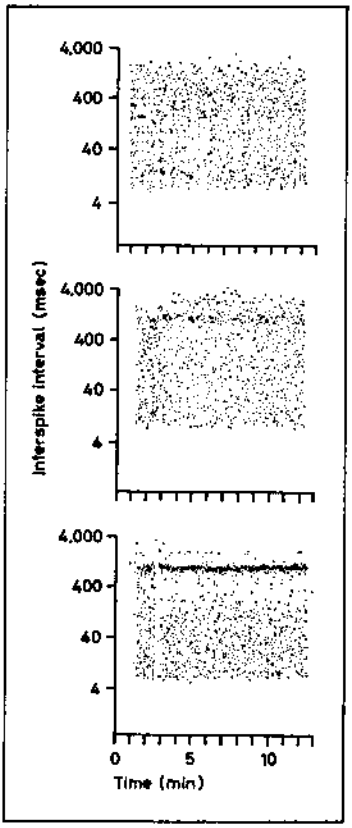


Fig. 4. Discharge pattern of a type II unit under bright illumination. The discharge pattern in dark is given in the upper record. The background light intensity was gradually increased in the course of the experiment, from the threshold level to ~90 dB above the threshold. The middle record was taken when the unit was adapted to 80 dB light. Five min before the lower record was taken, the intensity of the background illumination was increased by another 10 dB. A rhythmic discharge, such as shown in the lower record, can often be elicted from a type II unit.

ately low intensity of light. Figure 6 shows the characteristic inhibition for each of the three types. The upper and middle records in the figure were obtained by presenting a dim light (40 dB) of 2-min duration. The duration of the second inhibition for type II (middle record) is longer than that for type I (upper record), thereby indicating that type II is more sensitive to light than type I. A bright light (80 dB) of the same duration was

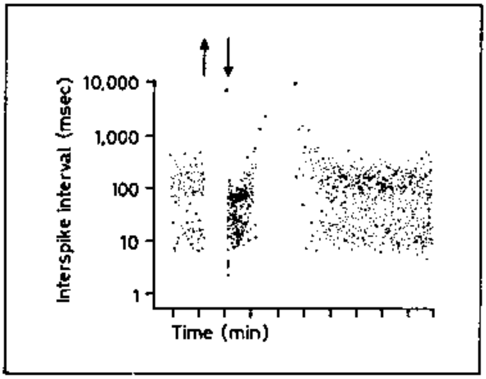


Fig. 5. Responses following a single flash of light. Suppression of the steady-state dark discharge activity occurred after the onset of the stimulus, as shown by the absence of dots after the initial segment of the record. The light (80 dB) was turned on at the upward arrow and off at the downward arrow. Vigorous response after the cessation of the stimulus is shown by the dots at short intervals which occur following the gap. This response lasted <2 min and was followed by another inhibition represented by a period of long interspike intervals. The duration of this second inhibition depended on the brightness of the light. Following the second inhibition, the fiber's activity returned to the steady-state characteristic of type II dark discharges, thus indicating that there is no background illumination. Interspike intervals >10 sec are off scale.

used to obtain the lower record for type III. For all three types of fibers the most reliable indication of the extent of the second inhibition was the upper envelope, an imaginary boundary on the dots representing the longest intervals.

The upper envelope appears to reflect the course of adaptation of the unit. Evidence for this is based on several observations. The recovery process during the inhibition has been shown to be related closely to the sensitivity changes in the dark and to the time course of rhodopsin regeneration in the frog's retina [Chung and Lettvin, 1969]. Furthermore, the recovery duration is a monotonic function of the amount of light that had impinged on the retina, as shown in figure 7. The points in the figure were obtained from a type I fiber exposed to a dim light of various durations. The linearity of the function should not be extrapolated, since only a narrow range of stimulus duration was explored.

D. Post-stimulus intervalgram. Implicit in the preceding discussion is the notion that the number of impulses occurring per unit time is a crude

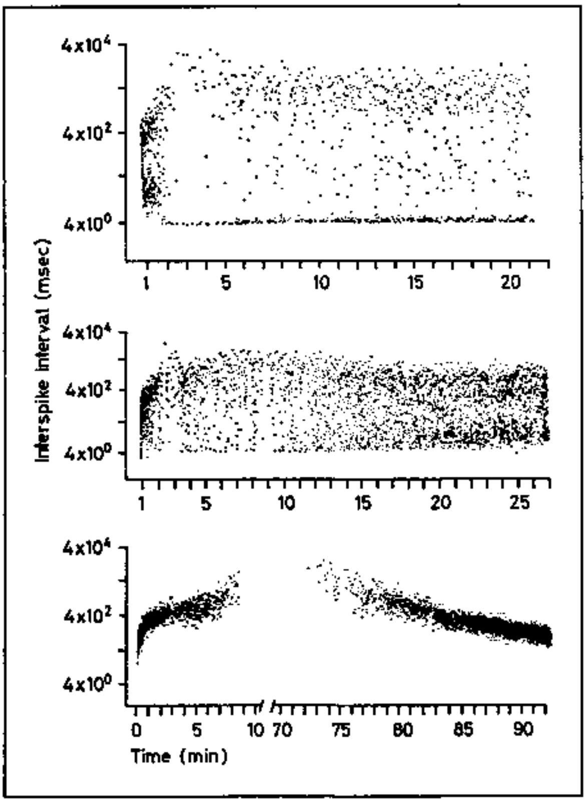


Fig. 6. Second inhibition. The upper and middle records show the responses of type I and type II units following a stimulus (40 dB) of 2 min duration. The lower record was obtained from a type III unit by using a bright light (80 dB) of the same duration. Before the stimulus was introduced, the fibers were completely dark-adapted. The records begin at the left immediately after the cessation of the stimulus. The envelopes formed by the longest intervals are an index of the second inhibition. See text.

'indicant' for stimulus parameters. Another way that this can be illustrated is by constructing post-stimulus intervalgrams such as those shown in figures 8 and 9. The temporal pattern of impulses occurring after a brief flash of light is remarkably regular, and the predominant pattern associated with a specific stimulus intensity becomes gradually more defined as more traces are superimposed. Within 2 sec after the cessation of a single brief flash, the unit shown in figure 8 discharged 10 spikes in clusters of

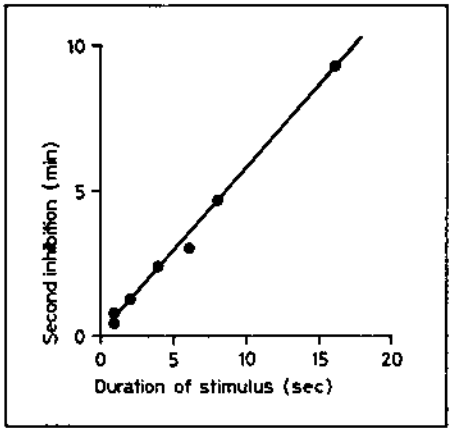


Fig. 7. Response-strength curve for the second inhibition. After a type I unit was dark-adapted, flashes of equal intensity (50 dB) with varying durations were presented. The duration of the second inhibition was determined by measuring the time required for the upper envelope to return to steady state.

2–3 spikes (upper record). The middle record, obtained after 10 flashes of identical intensity to that of the upper record, shows that the fiber fires in very restricted intervals occurring in phased relation to the stimulus. After 100 flashes (lower record) it can be seen that the restrictions on the intervals of some of the spikes are stricter than on others. In many cases they are so severe that dots of one trace exactly overlay dots of preceding traces. Since the photograph does not integrate overlaid dots directly, the record cannot be transformed into a conventional post-stimulus histogram.

Figure 9 shows the changes occurring in the temporal disposition to fire as the intensity of the flash is varied. Each of the records in figure 9 was taken during a series of 100 flashes. The intensity of the flashes in each series is denoted in decibels by a number accompanying each record. It is clear from the figure that the distribution of interspike interval probabilities is reliably related to the intensity of the stimulus. The limits of preferred firing time following a flash of light are fairly constrained, and they change as the intensity of the flash is varied.

Different patterns of post-stimulus interspike intervals can also be obtained by using different visual shapes as stimuli; e. g., presenting horizontal vs vertical stripes. The results of such experiments might be attri-

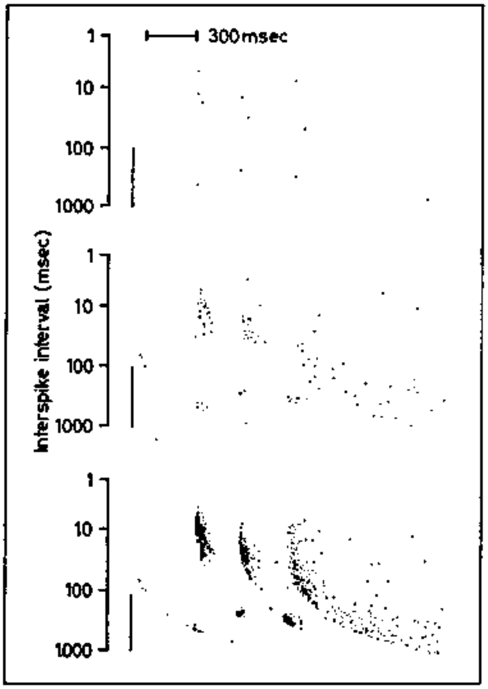


Fig. 8. Post-stimulus intervalgram. The temporal discharge pattern following one of a series of 50-μsec strobe flashes is shown in the upper record. In order to phase the records to the flash, the first interval taken is the one between the flash (denoted by vertical lines at left) and the first spike following the flash. This spike occurred with a rather fixed latency, and after several repetitions can be seen as a cluster in a restricted region. Ten dots, representing various interspike intervals occurred within the 2-sec sweep, which also began at the vertical line. The middle and lower records are superimpositions of the traces following 10 and 100 flashes, respectively. Each flash was separated by 2 sec of darkness. The records were obtained after at least 5 min of continuous flashing in order to allow responses to stabilize. The regularity of the timing of discharges following the flash resulted in exact overlays of some dots. The smooth logarithmic curve at the right-hand side of the lower record indicates two things: (a) that the last spike in the train is not fixed with respect to the spike preceding it, and (c) that a spike almost always occurs at the position characteristic for the penultimate spike. Otherwise, the dots corresponding to the last interspike intervals would not be bounded by a smooth curve.

butable, however, to intensity effects if one assumes that the receptive field of these fibers is not perfectly symmetrical.

E. Resolution of temporal patterns. Reliable and definite alterations in the structure of interspike interval patterns obtained from the dimming fi-

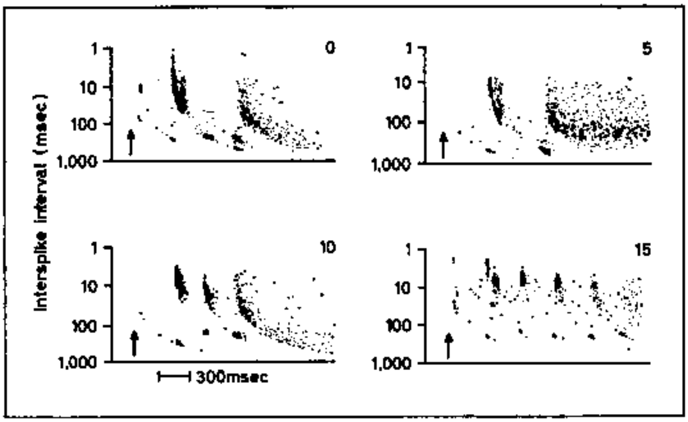


Fig. 9. Variations in shapes of the post-stimulus intervalgram with stimulus intensity. The records are analogous to those displayed in figure 8. A flash of light was given at the beginning of each record (marked by an arrow) and, after the interval between the flash and the first spike, successive interspike intervals are plotted against a regular time base. The records were obtained by superimposing 100 traces. The flash frequency was one per 2 sec. The numbers accompanying the records denote the stimulus intensity in decibels with reference to the intensity used to obtain the upper-left record. If the interval between the flash and the first spike were not fixed, the lower boundary of dots in the intervalgram would form a smooth logarithmic function. Thus the smooth curve formed by dots in the last portion of the lower-left record indicates that the interval between the final and the penultimate spikes is not fixed. Contrast this figure with that in the upper-right record. The predominant sequential patterns associated with different stimulus intensities are revealed by the clustering of dots.

bers are quite apparent to a human observer of the 'CLOOGE' records. For example, it is possible, given the record of interspike intervals shown in figure 5, for an experimenter to determine when a light was turned on, when it was turned off, how intense the light was (i. e. how much it bleached the retina), and whether or not any background illumination was present.

One naturally wonders if there is a mechanism in the nervous system of the frog which would permit it to prehend such changes in interval patterns. Such a system would require a memory of some sort in order for it to 'pay attention' to more than one dot – a definite need in order to abstract a pattern. The existence of interpretable pulse interval patterns has led us to search for indications of how neural processes might be arranged to interpret the meanings in these patterns elucidated by the preceding experiments.

Recent work on branching axons of the dorsal column of cats has indicated that long-term aftereffects of an impulse may alter the distribution of subsequent impulses in the highly bifurcated terminal arborization of axons. We present some of these results here, since we consider it likely that the mechanism responsible for interpreting temporal patterns is the branched axon. Our results support several propositions which we have used in developing a general theory of how the nervous system handles information that is present in pulse interval patterns. A brief account of these experiments is given below.

Part II: Resolution of Temporal Patterns by Axonal Trees

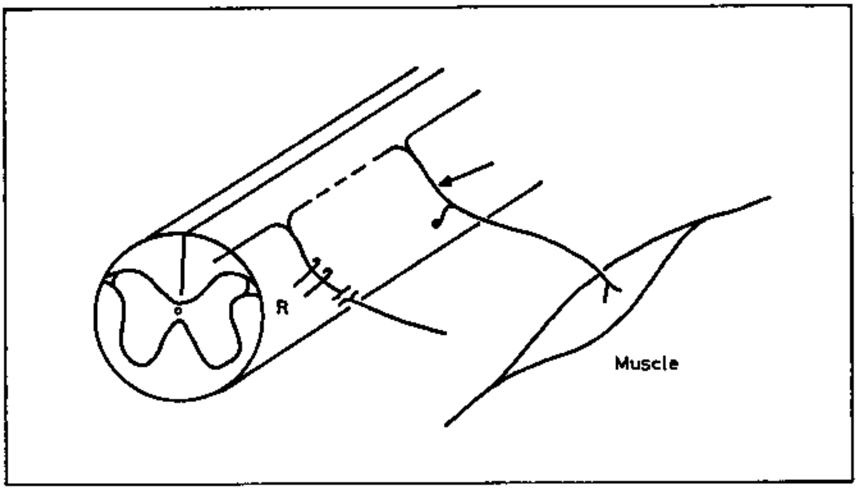
Cats were anesthetized with Nembutal (0.5 cc/kg) and supported by ear bars, hip bars, and clamps on the dorsal spinous processes. Additional anesthetic and Flaxedil (Gallamine Triethiodide, Merck) were administered, when needed, via a cannula inserted in the radial vein of the foreleg. A tracheal cannula was routinely inserted in all animals to permit use of a respirator, if needed. A dorsal laminectomy was made in the lumbar region, and the dura was opened after mineral oil was poured into a cavity formed by the retracted back muscles. Tiny rootlets, usually from L6, L7, or S1 dorsal roots, were gently isolated and were severed near the dorsal root ganglia. The central stretch of one of these rootlets was lifted into the oil on a pair of Ag/AgCl nerve hooks for recording. Some of these bundles appeared to carry impulses from a peripheral receptor. After locating and characterizing the receptive field of such fibers, rootlets near the recorded rootlet were cut until one was found such that cutting it silenced the receptive field. When this rootlet was subsequently stimulated electrically, single fiber discharges again appeared at the recording electrodes on the first rootlet.

Deep body temperature, which was maintained between 38° C and 40° C, was read from a thermometer inserted between the scapula and rib cage. The temperature of the oil bath was kept at 39.5° C by an incandescent lamp.

We repeated all of the experiments reported here in animals prepared under temporary ether anesthesia during which the carotid and vertebral arteries were occluded permanently. All of the essential observations made in these preparations were found to be qualitatively similar to those obtained under barbiturate anesthesia.

Results II

To examine the notion that an impulse traveling along an axon will not invade all of the branches of that axon, we have investigated axonal con-



duction in the primary afferent fibers of cat spinal cord. A few of these fibers are physiologically coupled to specific fibers in other rootlets [BARRON and MATTHEWS, 1935; RAYMOND and LETTVIN, 1969]. Thus, one can record from the central stub of a severed dorsal rootlet and observe impulses originating in a peripheral sense organ. These impulses travel into the cord along an afferent fiber in a nearby uncut rootlet. This situation is shown diagrammatically above. The architecture of the central pathway connecting the recorded rootlet (R) to the rootlet containing the single afferent from the muscle (arrow) is not known and is, therefore, represented by a dashed line. It is reasonably certain, however, that the pathway does not contain a synapse for the following reasons. (a) The delay between electrical stimulation on one rootlet and the response on the other is often too brief to allow for both conduction delay and a synaptic delay. If 0.3 msec is allowed for synaptic delay, the conduction velocity in some cases would have to be greater than 120 m/sec [RAYMOND, 1969]. (b) The pathway conducts impulses equally well in either direction; that is, the stimulating electrodes can be interchanged with the recording electrodes without altering the conduction latency. (c) The fibers can sustain impulse rates greater than 800/sec for several seconds without conduction failure, even during deep barbiturate anesthesia or anoxia.

The strong physiological coupling between single fibers in the two rootlets is apparently the result of a continuous axonal pathway running between them. This conviction has been supported by radiotracer studies showing that the intra-axonal contents of the fibers of one root are in uninterrupted communication with approximately 1 % of the fibers of immediately adjacent neighboring roots [RAYMOND, 1969]. Thus, we suspect that the following results were obtained from a system having only axonal properties such as constrictions or bifurcations. We have termed fibers conducting between rootlets 'ectodromic' fibers, since the impulses they carry travel outward (toward the periphery) on the recorded rootlet. The only other class of impulse transfer between dorsal roots, the dorsal root reflex [TOENNIES, 1938], cannot sustain repetitive activation at rates above 25/sec and is very sensitive to anoxia [HURSH, 1940; TOENNIES, 1939; RAYMOND, 1969].

A. A region of low safety factor in an axonal pathway. The conduction between one rootlet and another is not 100% safe even at low frequencies of stimulation. For example, the lower record in figure 12 is a dot display showing a number of conduction blocks occurring intermittently during continuous natural stimulation of a 1A muscle spindle afferent by stretching the leg. Note that the block lasted considerably longer than the usual interval between the steady rhythmic discharges characteristic of these receptors. The location of the region where blocking occurred is within the spinal cord, for the following reasons. First, stimulation of muscle afferents does not lead to blocking of the sort seen in figure 12. Each impulse set up at a receptor always appears on recording electrodes, provided such electrodes are on peripheral nerve or on an incoming dorsal root distally connected to the receptor [MATTHEWS, 1964]. We have found that the blocks occur only if the impulses travel for some distance along the cord and are recorded from the central stub of a rootlet other than the one carrying the impulses into the cord. Second, the blocking of impulses in ectodromic fibers occurs during electrical stimulation, as well as during natural stimulation of the receptor. Blocking is virtually independent of the magnitude of the electrical stimulus as long as the stimulus exceeds threshold; it occurs at least as often during high-amplitude stimulation as it does when the stimulation intensity is just above threshold. Moving either pair of electrodes along either rootlet does not prevent blocks from occurring as would be expected if the locus of the block was outside the cord. Thus, impulses were arriving at the cord, but were not departing from it.

B. Variation in conduction safety induced by changes in interspike interval. There are important consequences stemming from the existence of a region of low conduction safety in this axonal pathway. One is that once

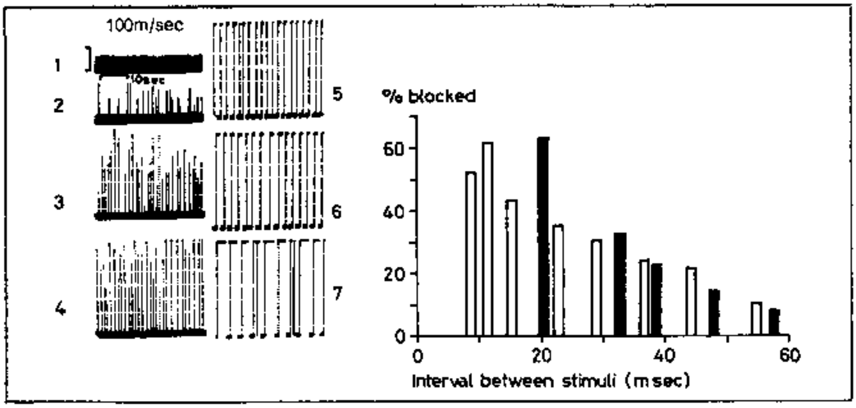


Fig. 10. Interspike interval and conduction block. Each of the left records is a running series of vertical lines whose height gives the time between successive pulses on the fiber. The steady-state frequency is increased in each successively numbered plot. At low-frequency natural proprioceptive stimulation as in (1) no blocks occur. Since the steady-state frequency was varied by changing the static stretch of a muscle spindle, all lines are of nearly equal height because of the regularity of such discharges. These vertical lines show up as a dense baseline bar which has a vertical thickness proportional to the interspike interval (~80 msec). As the frequency was increased, the thickness of the bar decreased. In (2) a few blocks occurred. These are represented by the lines which rise between 1 and 4 times higher than the baseline thickness. These lines correspond to blocks of 1, 2, 3, or 4 spikes. As the frequency increases, more blocks occur, blocks become longer, and the progressively thinner baseline of each graph begins to be interrupted by long gaps. At the highest natural steady-state frequencies (last 3 pictures) the blocks exceed the maximum range of the display and the spot stays at the top of the picture until the first spike of the next period of continuous conduction returns it to the bottom. Note the regularity of the alteration between conduction and block. This regularity was most noticeable in animals anesthetized with Nembutal.

The right record is a graph obtained from an automatic device that detected blocks, measured the duration of each block, and summed these durations over a test period 1 min long. (For design of this device, see Raymond, 1969.) The Y axis gives the per cent of the total test period during which the fiber was blocked at different frequencies of stimulation. The solid bars were obtained during natural proprioceptive stimulation, and the hollow bars were from the same fiber during electrical stimulation.

the safety factor becomes lower than 100 %, the conduction of each spike becomes tenuous and can be prevented or enhanced by slight changes in excitability. Such shifts occur in a nerve fiber as a result of preceding activity, and thus it is not surprising that a strong relationship exists be-

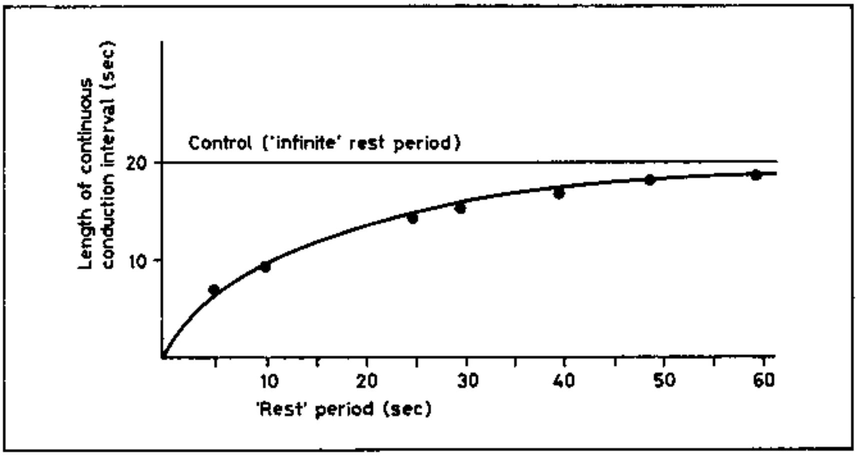


Fig. 11. Long-lasting aftereffects of high-frequency stimulation. Continuous stimulation at 350/sec for 30 sec was applied to one rootlet while responses were monitored on another. Following approximately 20 sec of continuous conduction, conduction block began and soon became essentially complete. After 30 sec, stimulation was stopped for 'rest periods' of varying duration before a second step of continuous stimulation at the same frequency was given as a test. The duration of conduction during stimulation after rest is plotted in seconds on the Y axis. The abscissa gives the length of the rest period in seconds. The line across the top shows the average duration of continuous conduction measured during the initial 30-sec stimulation period. Each 30-sec period was preceded by 4 min of rest with no stimulation.

tween the interspike interval and the safety factor. The graph at the right of figure 10 shows that during continuous stimulation, whether by applying electrical pulses or by stretching a slowly adapting spindle, the amount of blocking depends, in the steady-state, on the frequency of stimulation. When the interspike intervals are short, the fiber is blocked nearly 50 % of the time. When the interspike intervals are long, conduction is nearly continuous with a few spike trains of varied length blocking intermittently. The ramp display of figure 10 shows that not only does blocking increase in degree as the interspike intervals are shortened, it also changes in pattern. As the frequency rises, each block becomes longer. Blocks at high frequency are complete and relatively long. They are followed by periods where a train of spikes is conducted without a single failure. The alteration between conduction and block can be very regular at certain steady-state frequencies.

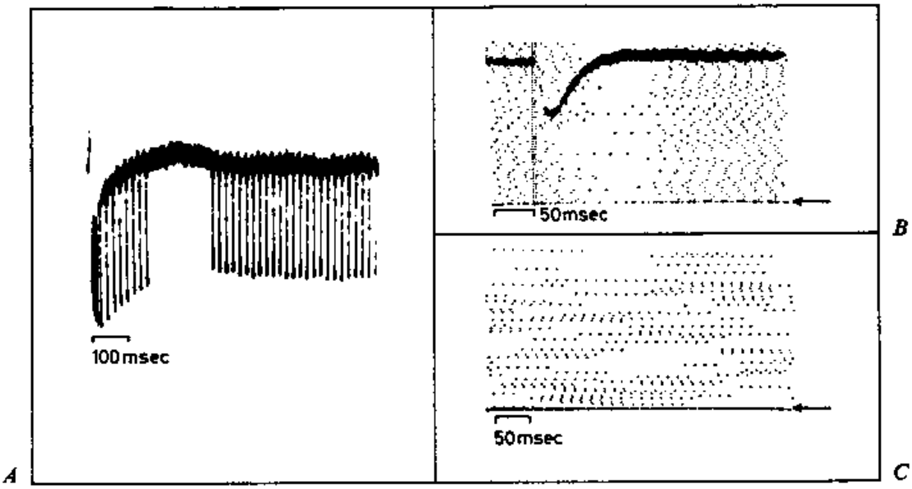


Fig. 12. Dorsal root potentials and the control of ectodromic conduction block. The left trace (A) is a record of the block that occurs on the falling phase of the dorsal root potential. The fiber was connected to a stretch receptor in the left leg; discharges were produced by moving the limb. The animal was paralyzed with Flaxedil. A submaximal shock, which led to the dorsal root potential, was given to the sciatic nerve at the left of the trace. The right photographs (B and C) are dot displays obtained from a different fiber. These displays are not analogous to the 'CLOOGE' records. Instead, a 50 V pulse triggered by each recorded spike is used to intensify the beam of an oscilloscope. The dots produced as the beam sweeps from left to right correspond to the original spikes, but since they have less vertical displacement, many sweeps can be included in the same record merely by moving each successive sweep vertically by the same amount. The test picture (B) immediately above the control (C) shows the time course (DC recording) of the dorsal root potential which resulted from stimulation of a rootlet close to the ectodromic fiber. Superimposed upon the DRP is a dot display of a number of successive traces showing the conduction block occurring in the ectodromic fibers during continuous stimulation. These traces were displaced, one below the other, until at the bottom of pictures B and C (arrows) the migration of the trace was halted to allow several rows of dots to superimpose. Note that a gap occurred in the test picture, but that the control line is essentially continuous. Except for turning off the stimulus applied to the adjacent dorsal rootlet, the conditions of the control experiment were identical to those used in the test display in B. Blocks were present, as shown by the gaps in the rows of dots representing the muscle spindle discharges, but they did not occur at any consistent time with respect to the triggering of the trace.

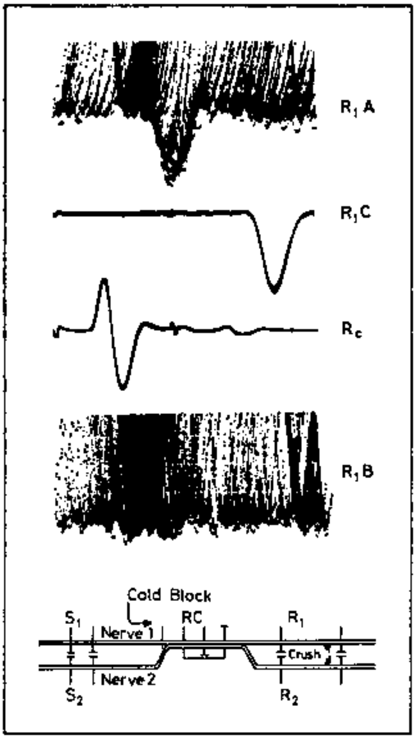


Fig. 13. The effect of a partial block on the interaction of two adjacent nerves. The diagram shows the arrangement of the two nerves. The stimulus at S$_1$ gave rise to a volley in Nerve 1 whose height (negativity downwards) was recorded monophasically from the electrodes at R$_1$, as seen in the trace labeled R$_1$C. The timing of the stimulus at S$_1$ was varied with respect to the stimulus at S$_2$ which was always given to Nerve 2 at the beginning of each sweep. Thus, a series of peaks of the action potentials recorded at R$_1$ could be photographed (R$_1$A, R$_1$B). The clipped peaks shown in the records correspond to about 25 % of the overall height of the action potential. Thus the baseline of trace R$_1$A and R$_1$B is off scale above the picture and is not shown. A partial cold block was applied to Nerve 1 at the designated mark via an Ag/AgCl wire cooled by dry ice. The trace labeled R$_c$ is a record from the R$_c$ electrodes during stimulation S$_1$ and S$_2$. The first large triphasic spike is the action potential of Nerve 2; the small one following the second shock-artefact is a record at R$_0$ of the action potential of the cold-blocked Nerve 1. The variation in the height of the action potential at R$_1$ in record R$_1$A shows that as the stimulus at S$_1$ was given at various delays with respect to S$_2$, the number of impulses getting through the cold block was changed. The peak facilitation occurred when the stimulus at S$_1$ was timed so that the peak negativity of the volley in Nerve 2 arrived at the contiguous zone at the same time that the volley in Nerve 1 was penetrating the cold block. Note that the facilitation is followed by a period of slight inhibition,

The steady-state pattern of blocking at a particular frequency is approached slowly following a change in frequency. The aftereffects of a period of activity on the safety factor can be gauged by the results of an experiment shown in figure 11. After a period of no impulse discharge ('rest'), the ectodromic fibers running between dorsal roots conduct initially without blocking for a much longer time than they do in steady-state. The curve in figure 11 shows that it requires approximately 20 sec of rest following a period of intense activity for a fiber to maximize the duration of this initial period of continuous conduction.

C. Variation in conduction safety induced by activity in adjacent neuronal structures. Shifts in the excitability of a fiber are known to occur in response to impulses traveling in its neighbors [KATZ and SCHMITT, 1940; ARVANITAKI, 1942; MARRAZZI and LORENTE DE NÓ, 1944]. It can be seen from figure 12 that the conduction safety of the dorsal root fibers that we studied was sensitive to discharges in nearby rootlets. The left record shows a conduction block in a continuously stimulated fiber. This block followed an electrical stimulus given to the sciatic nerve. The right records, obtained from a different fiber, shows that the tendency to block was correlated with the stimulation of a neighboring rootlet next to the pair of rootlets containing the fiber that was being recorded. There is a definite time, beginning just after the peak of the long negative wave of the dorsal root potential [DRP 5, LLOYD and MCINTYRE, 1949], during which conduction is usually blocked. The lower record is identical to the middle record, except that no electrical stimulus was given to neighboring rootlets. The control of blocking in one fiber by activity in others was not only observed when these neighbor fibers were stimulated synchronously with an electric shock; variation in the safety factor was also quite pronounced if the hind limb ipsilateral to the recorded rootlet was touched or moved.

The variation in conduction safety observed in ectodromic fibers during activity in their neighbors is an expected consequence of the existence of a region of low safety factor. The induced block need not depend in any way on synaptic mechanisms. In fact we suppose that the dorsal root potential and presynaptic inhibition are not mediated by synapses, but in-

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as would be expected from the geometry of the two nerves. The trace in R_1B was taken a half hour after the cold block was allowed to recover. The region where interaction occurred during cold block was explored carefully for interaction, accounting for the increased blackness of the trace in that region, but no interaction was seen.

stead are derived from the ionic and electrotonic consequences of activity in densely packed neuropil [HOWLAND *et al.*, 1955, RAYMOND, 1969]. The assertion that induced block can stem from electrotonic influences is supported by the following experiment. A model region of low safety factor was created by using a partial cold block applied to the extracted sciatic nerve of a frog *(Rana catesbiana).* Figure 13 shows that in the absence of a region of low safety factor in the test nerve, action currents from an impulse in a neighboring nerve have negligible effects on impulse conduction. When the test nerve is cooled so that impulse conduction is blocked in approximately 50 % of the A fibers, the effects of the action currents in the neighbor are accentuated. Depending on the spatial and temporal relations between the impulses in the two nerves, conduction block can be transiently augmented or reduced according to the sign of the excitability change induced in the test nerve by the current from its neighbor.

Discussion

1. Bifurcations as regions of low safety factor. Evidence that regions of axonal bifurcation are areas of low safety factor for impulse conduction has been adduced by studies on motor axon terminals by KRNJEVIĆ and MILEDI [1959], BITTNER [1968], BITTNER and HARRISON [1969], by previous work on primary afferents of the spinal cord [HOWLAND *et al.*, 1955], and by the blocking of impulses shown here by ectodromic fibers which occurs near a region of extensive branching [RAMÓN Y CAJAL, 1952; SCHEIBEL and SCHEIBEL, 1969]. The invadability of regions of low safety factor seems to be highly dependent on slight excitability shifts. Shifts in membrane potential of a sort that would modify the probability that any one particular impulse will pass a given region can arise from two sources. One source would be the action currents and slow potentials deriving from activity of other elements in the vicinity of the region of low safety factor. The other source would be the long-lasting excitability shifts that follow the activation of the fiber itself whenever impulses pass along its axon. Indications that both of these variables have profound effects on the probability that an impulse will invade a branch can be seen in the variation of ectodromic blocking resulting from changed rates of stimulation and by the capability of an impulse in the fibers of nearby dorsal rootlets to generate a block in the ectodromic fiber (cf. fig. 12). These effects are definite and not small. The importance of changed stimulation rates and polarizing currents to the amount and pattern of blocking occurring in motor axon terminals was also emphasized by Krnjević and Miledi [1959]. Notably, they found that the separate daughter branches of the same parent axon each seemed to fail at different frequencies and with different patterns. Each of the ectodromic fibers that we have studied also failed at characteristic frequencies that differed from the failure frequencies of others.

2. *Axonal branching and impulse conduction.* The characteristics and details of axonal branching have not been emphasized in anatomical studies, although there are enough reports that some general statements can be made. Virtually all axons branch several times before forming their final synaptic articulations. Each of the branches is usually smaller than the branch from which it stems. Thus, the arborizations taper from a trunk or parent axon into branches, branches into twigs, and twigs into fine terminal filaments. Furthermore, a cursory examination of a good Golgi section of axonal arborization shows that branching seems to be asymmetrical. That is, only rarely do both daughter branches have the same size [Ramón y Cajal, 1952; Lorente de Nó, 1933; Scheibel and Scheibel, 1969].

The tapering and asymmetrical characteristics of axonal arborization constitute the anatomical or geometrical basis for the peculiarities of axonal conduction noted in these regions by ourselves and by Krnjević and Miledi [1959]. Not only does conduction velocity depend on axonal diameter but so do the maximum frequency of stimulation that an axon can sustain and the refractory period [Paintal, 1965]. The aftereffects of an impulse include all of the residual variations in excitability that follow the invasion of an axon segment. In very small fibers, each impulse leads to sizable shifts in ionic concentrations, which would be expected to lead to long-lasting excitability shifts if ion pump mechanisms are electrogenic [Rang and Ritchie, 1968]. Lorente de Nó [1947] showed that the metabolic consequences of an impulse could still be detected in peripheral nerve several minutes after stimulation. In tiny terminals, even longer effects may persist, and because of the sensitivity of regions of low safety factor to slight shifts in excitability, the invasion of impulses into individual branches might depend on them. Since the extent and duration of the excitability variations are functions of fiber size, the asymmetry of bifurcations implies that the time course of the excitabilities of two daughter branches will, in general, differ. After an impulse has invaded both branches, the relative excitabilities will depend on the time between the first impulse and a second one. Thus, whether the second impulse invades one or the other or both or neither of the daughter branches will depend on the length of time by which it follows a first impulse.

3. Resolution of temporal patterns into spatial ones. These considerations point to the presence of a kind of memory in axonal trees, which suggests that they might indeed serve to resolve the meanings inherent in pulse interval patterns. The way in which we conceive of this type of operation is outlined below.

First, the entire axonal system of any one fiber is composed of hundreds or thousands of terminals [SCHEIBEL and SCHEIBEL, 1969]. Since an impulse arrives at any one terminal only after passing through a number of branches with low safety factor, only a subset of the available terminals is likely to be activated by any one impulse on the parent axon. Thus, at the outset, we are confronted not by a system having only two states at the output, on or off, but by one having a very large number of possible combinations of active and inactive terminals.

Second, the dependence of the excitability of each of the branches on the rate of activity, when considered over the entire tree, means that whatever subset of terminals is activated by one impulse depends upon the time by which it follows the impulse preceding it. If we take a case in which the parent axon has not fired for a time sufficiently long that rate-dependent processes have all regained steady state, then the first impulse (I_0) to occur on the axon will occupy a subset of terminals which is determined by the geometry of the fiber, by the 1/F noise in the parts of the tree [VERVEEN *et al.*, 1967; POUSSART, 1968], and by whatever activity is present in nearby neuronal structures. A second impulse will follow I_0 by a time interval T_1-T_0. This impulse will encounter at each of the many branches of the axon excitability shifts continuously changing with time as a result of I_0. The particular subset of terminals that is activated by this impulse will thus depend not only on the geometry of the fiber and the activity of its neighbors, but also on the time interval T_1. A third impulse, I_2, will encounter the excitability shifts following I_1 and those still lingering after I_0. Thus, the subset of terminals that it invades will depend on the interspike intervals of the impulses preceding it. If this process is extended, then the distribution of excitability in the terminals of fibers would at any time constitute a record of the relative times between all of the impulses that had previously passed through the parent axon. This follows directly from the notion that the way in which any given impulse distributes in the terminals depends on the distribution of the impulse preceding it and causes changes in the relative excitability of one branch *vis-à-vis* other branches which will affect the distribution of the impulse following it. Thus, the way in which a fiber will distribute its impulses will be expected to depend on previous distributions. The 'statement' of a neuron at any one time (the spatial pattern of its activated terminals) will appear in the context of what it has already 'said'.

In the manner above, the axonal arborizations act to transform the temporal pulse patterns of the parent axon into spatial patterns in its terminals. The spatial distribution of terminals activated by any one impulse embodies in it a statement of the past history of the fiber before that impulse, and each new impulse reveals more about developing patterns.

The records obtained from the dimming fiber can be used to explain the transformation occurring in axonal arborizations by considering separately the roles reserved to postsynaptic cells and to the preterminal arborizations. Imagine that we view the record in figure 5 through a slit so thin that it accommodates only one short interspike interval, and hence, only one dot can be seen at a time as we slowly pass the slit from left to right over the surface of the record. This is analogous to experiencing the original spike train in a system where there is no memory. It is obvious that such a system tells little about the environment. No comparison between successive intervals can be made. As we make the slit wider, however, we notice, as physiologists, that the record gets more and more meaningful, and we can begin to say how each of the bands is changing and to appreciate structure. If we have no way of separating and comparing individual intervals, but instead, measure the frequency of the spike train by integrating the number of impulses occurring within a fixed period, we would lose much of the information that is present in the original picture by smearing away the structure. The operation that we have conceived for the axonal arbors, however, sharpens temporal structure and displays it in spatial terms.

4. The role of secondary cells. The role that we envision for the cells on which axonal arborizations end can be thought of as 'subset picking'. These cells, with their own geometries carefully refined with respect to the spatial distributions of the input, can extract those subsets within the preterminal array that correspond to statements about the recent history of the external world, insofar as the frog is interested in it. One could imagine, then, a cell-afferent coupling designed to select afferent terminal patterns meaning a light has just been turned off and it was very bright but not on too long. The output of secondary neurons would, in turn, have multiple meanings, again reflected in pulse interval patterns and, again, transformed for higher order cells by axonal arborizations. Quite complex, but potentially readable, statements about the world could be compiled by a hierarchical system of such units.

5. Implications. Several important shifts in perspective stem from the recognition of the complexity of the process of axonal conduction in arborizations and the possible significance such conduction has in spatially structuring interspike interval patterns. Among the most obvious is that 'spontaneous' activity and bursty discharge ought not to be regarded as 'noise'. It is not obvious what any neuron is trying to say, and given the possibility that burstiness may itself be meaningful, we have no basis *a priori* to decide what is noise and what is message. To do so would imply a prior knowledge of the intentions of the system and its modes of operation or, to use VON NEUMANN's phrase [1958], 'the language of the brain'.

That areas of low safety factor are very sensitive to extracellular currents raises a second issue. The points of low safety factor present in branched axons imply that neighboring regions in the central nervous system must interact profoundly. The notion that cross talk will degrade the performance of the nervous system is not necessarily true. The degree of interaction that exists suggests that information handling may be aided rather than hampered by cross communication.

Finally, if every pulse arriving at a cell embodies in its spatial distribution an instantaneous statement about the recent history of events, the physiological basis exists for a kind of 'short-term memory'. Moreover, there is the intriguing possibility that the relative diameters of branches might be structurally altered by activity, thereby rendering the system capable of imbedding prior experiences.

Acknowledgment

We are indebted to the late WALTER H. PITTS, whose ideas have shaped the notion presented here. Miss CAROLYN PASS and Mr. WILLIAM SAIDEL provided excellent technical assistance for which we are grateful. This study was supported in part by the National Institutes of Health (Grants 5 RO1 NB 07501-02, 5 P01 GM14940-03) and by a grant from Bell Telephone Laboratories, Inc.

Summary

We have described dimming fibers in the frog's optic nerve which occasionally show drastic modification in the temporal pattern of discharge while the average

number of impulses discharged per unit time remains more or less unchanged. These units appear to be concerned with at least two independent variables: some function of intensity and distribution of light, and the state of adaptation of the eye. We plotted the logarithm of interspike interval versus time, and noted that the intensity of the ambient illumination could be read from the shorter interspike interval bands which are found in such plots. The longer interspike interval band served as an excellent monitor of the state of adaptation of the unit. Either of these two bands could be shifted independently.

The decay of excitation at synapses seems to be too rapid to detect the observed changes of interspike interval, and we have proposed instead that temporal patterns in general are resolved within axon terminals. Evidence was obtained from an apparently continuous single fiber pathway between dorsal roots of the cat that conduction block occurs naturally in an axonal system. This finding is substantiated by the evidence of others from studies of motor axon terminals and spinal afferents which suggest that conduction block occurs near regions of axonal bifurcations. Thus, an impulse traveling along a parent axon is not expected to invade every one of the daugther branches of that axon. Moreover, conduction block in dorsal rootlet afferents depends on interspike intervals and on shifts in excitability associated with activity in nearby elements. The effects of slight shifts of excitability on the probability of invasion past a point of low conduction safety were studied in two adjacent frog sciatic nerves and were found to be substantial. Thus, the probability that a particular impulse will invade a particular branch seems to be conditional on the time lag between that impulse and the ones that preceded it in time or happened to be close to it in space. This implies that the subset of daughter terminals invaded by an impulse can be considered to depend on the temporal relations of the impulse to others in the discharge train of the axon. Temporal patterns such as those found in optic nerve fibers may thus be transformed into spatial ones at axon terminals which can be distinguished by the cells on which these terminals end.

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