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Isomorphism, Task Dependence, and the Multiple Meaning Theory of Neural Coding

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Abstract
The neural coding problem is defined and several possible answers to it are reviewed. A widely accepted answer descends from early suggestions that neural activity, in general, is isomorphic with sensation and that the biological signal resident in the axons of neurons, in particular, is given by their frequency of firing. More recent data are reviewed which indicate that the pattern of neural responses may also be informative. Such data led to the formulation of the multiple meaning theory which suggests that neural pattern may encode different information features in single responses. After a period in which attention turned elsewhere, the multiple meaning theory has quite recently been revived and has stimulated novel and careful experimental investigations. A corollary theory, the task dependence hypothesis, suggests that these information-bearing multiple response features are accessed differentially in different behavioral tasks. These theories place stringent temporal requirements on the generation and analysis of neural responses. Recent data are examined indicating that both requirements may indeed be satisfied by the nervous system. Finally, several methods of experimentally testing such coding theories are described; they involve manipulating the biological signals of neurons and observing the effect of these manipulations on behavior.

Neural Coding

The problem of neural coding is straightforward: Given that the biological signals found in nerve cells exhibit complex spatial and temporal characteristics, how is information encoded in the nervous system? What properties of a neuronal signal are meaningful and what epiphenomenal? In the special case of sensory coding, the essence of the neural coding problem can be ostensively defined by pointing to the fact that signals in sensory nerve cells are quite different in form from the environmental stimuli that evoke them, as will be seen in more detail below. Given these facts, what features of bio-electric signals represent information in the nervous system generally? More particularly, what is it that signifies that one sensory signal is conveying that it stands for something that is stronger than another signal? What is it that signifies that one signal represents something faster? Etcetera.

This problem has always required at least a provisional answer, in the sense that any speculation about the nature of the brain would have had to incorporate at least an implicit theory of neural coding. However, the need for a useful scientific answer to the question became quite pressing the moment advancing technique made it possible for bio-electric responses to be recorded from single nerve cells. Adrian [1, 2, 3] was a pioneer in such work. Following the lead of his teacher, Keith Lucas [2, p.vii], Adrian applied the then-new-technique of electronic amplification to the study of the nervous system. Lacking the yet-to-be-invented microelectrode, Adrian investigated cellular responses by dissecting bundles containing single active nerve fibers (axons) from their context. He then used fairly large electrodes to record the extracellular signs of their bio-electric activity.

This technique recorded all-or-none responses from nerve axons. Because of their brevity, these responses are often described as “spikes” or “impulses”. The term “action potential” is sometimes also used to denote the fact that these are active responses of the cell.

The Isomorphism Coding Hypothesis

Adrian recognized that the neural coding problem was an antecedent problem—meaning that any attempt to interpret his cellular data without an answer to the coding problem would guarantee that such an interpretation would be incomplete. The answer he drew from his extensive research was summarized in 1928 in *The Basis of Sensation* [1]; this answer was based on a correlation of behavioral data collected by others with physiological data, namely his own recordings of action potentials in single afferent neurons.

—Insert Figure 1 about here—

The nature of this correlation is illustrated in Figure 1 of the present paper, which has been taken from the final figure of Adrian's 1928 book. This plot does not display raw data; instead it is a schematic which summarized Adrian's studies of many different neural systems. The figure contains four waveforms. Two of these represent observables and two represent inferences: The top trace is the observable amplitude of a sensory stimulus plotted as a function of time, and the third trace is the observable train of spike impulses evoked by this stimulus in an afferent neuron's axon. The second trace represents an inference about the likely form of the excitatory process that probably generated these spikes. This process was inferred to take a graded form which, unlike the all-or-none spikes, gradually varied in amplitude; this amplitude is roughly inversely proportional to the interval between successive spikes. (About two more decades would elapse before the invention of the intracellular microelectrode would conclusively confirm the validity of Adrian's inference about the graded processes that generate axonal spikes. Such graduated generators are now called "receptor potentials" if they occur in sensory receptors, "postsynaptic potentials" if they occur in central neurons, and "endplate potentials" if they occur in muscle cells.)

The bottom trace shows the inference of primary concern at present. This trace was intended as a generic representation of sensations. However, it was mainly derived from Adrian's knowledge of Broca and Sulzer's measurements of the time course of the sensation evoked in a human observer by a visual stimulus. The pattern of the sensation obviously correlates with the patterns of both the observed axonal discharge of spikes and the inferred generator of the spikes. Adrian concluded from this correlation that sensations were intimately connected to the waveforms of cellular responses.

Isomorphism is a term currently used [4] to describe the coding concept that Adrian drew from this correlation, namely that the magnitude of sensation was proportional to the magnitude of the cellular waveform (indexed by either the amplitude of graded potentials or the frequency of action potentials) and that the time course of sensation followed the time course of the cellular waveform.

Development of the Isomorphism Doctrine

This answer to the neural coding question became well established. Its general acceptance was reflected in its early incorporation into standard neuroscience texts [5, pp.111-119]. In more current texts [6, p. 23], this doctrine is often introduced under the rubric of "frequency coding," with accordingly special emphasis on axonal spikes. While this concept has become so well known that it is sometimes only briefly reviewed, certain texts do develop the concept more fully [7, ch.15].

A standard notion has therefore developed, namely that the frequency of a neuron's impulses is the information-bearing biological signal produced by the cell's bio-electric mechanisms. On accepting this notion, investigators probing new systems or new preparations would concern themselves with spike frequency when they were examining axonal signals. And the amplitude of graded potentials would be the index when they were the objects of investigation.

Naturally, the isomorphism concept was regularly rejuvenated by amalgamation with more recent findings about neural coding. Thus, as research probed further into the central nervous system, it became apparent that many—perhaps most—neurons discharged spontaneously in the absence of any apparent input. The existence of inhibitory (i.e., hyperpolarizing) synaptic mechanisms therefore made it possible for decreases as well as increases in firing rate to signal information about the environment [8]. And these axonal patterns had their counterparts in meaningful decreases as well as increases in the amplitude of the graded potentials that generate spikes [9].

It also became abundantly clear that many sensory neurons respond when challenged by stimuli that fall within a large region (called the receptive field) of the sensory surface (e.g., retina, skin, etc.) from which they project [10]. It further became clear that stimuli falling within a cell's receptive field often had to present just the right spatio-temporal pattern of energies or the cell would not respond [11—14]. A stillcontroversial interpretation of these data led to the denotation of the adequate stimulus pattern as the cell's "trigger feature" and a designation of the cell itself as a "feature detector." Updating the isomorphism doctrine to include such results lead to the proposition that "...high impulse frequency in such neurons corresponds to high certainty that the trigger feature is present." [15, p. 371].

Technical factors made the isomorphism doctrine of particular significance in the design and execution of experiments aimed at probing information processing in large-brained animals with complex behavioral repertoires. Intracellular micropipettes—which record all of the biopotentials found in neurons, large or small—are generally not usable in such preparations because of mechanical difficulties. By contrast, large spike potentials are easily recordable with an extracellular microelectrode driven into a large brain. Hence, the vast bulk of what is now known about neural processing in large brains comes from studies in which technical considerations led the investigators to record axonal spikes while the isomorphism doctrine led them to analyse spike frequency.

Problems with the Isomorphism Doctrine

Unfortunately, the isomorphism doctrine was originally based on an illusory correlation of two different temporal variables, one in nerve cells and the other in behavior: Although Adrian had indeed measured the time course of axonal discharges in nerve cells, Broca and Sulzer (as well as other psychophysicists) had not actually measured the time course of sensations—instead they had measured the magnitude of sensations evoked by stimuli of different durations. Much later, when an appropriate comparison of physiology and behavior was made— by examining responses to stimuli of different durations in both domains—a clear and simple correlation was not found [16]. This illusory correlation between time and duration is extremely potent and has a tendency to recur [17].

Hence the antecedent neural coding question had really been left unresolved from the very beginning of cellular research and the door was open for problems to enter. Consequently, the development of coding research has also addressed the inevitable appearance of data which were problematic from the isomorphism point of view. (Adrian himself suggested he was aware of such problems in later publications [3]. Although it was he who promulgated the isomorphism suggestion, it should be understood that its development into a standard doctrine took on a life of its own.)

Problems emerged in both the analysis of responses evoked from the nervous system and in the characterization of the performance of the nervous system when challenged by stimuli. An especially instructive example of the analytic difficulty occurred in the studies of color coding done by Granit, summarized in 1947 [18]. He had been studying the response of optic nerve axons to lights of different color. This is a very difficult problem in the case of species that, like ourselves, have duplex retinae with rod receptors providing colorless information in dim light and cone receptors providing color information in bright light. The problem might be easy if there were different axons connecting each type of receptor separately to the brain. But convergence occurs and, in primates, most afferent visual cells carry spikes that are now believed to signal chromatic information in bright light and achromatic information in dim light [19].

—Insert Figure 2 about here—

Granit found [20], as Figure 2 shows, that the pattern of spikes varied when he changed the color of the stimulus; the pattern also varied when he changed the intensity. In a tantalizing discussion [18, p. 306] which foreshadows much of the multiple meaning theory (to be described below), he offered a theoretical characterization of these pattern variations in terms of what he called dominator/modulator theory. This theory of color coding has now been replaced by another characterization of the same type of data, offered by Svaetichin [9]. Data of the sort seen in Figure 2 are now generally interpreted in terms of the opponent color theory. Further information on the details of color theory in general and on this interpretative shift in particular can be found elsewhere [21].

From our present point of view, attention should be focused on two facts: First, here is a vivid example of the antecedence of the coding problem—Granit's interpretation of the meaning of the patterns in his spike data deflected his theory of color in what now seems to have been an inappropriate direction. This demonstrates that it is necessary to have at least a first approximation to an answer to the coding problem before an investigation of information transfer in the nervous system can be even provisionally completed.

Second, as Figure 2 shows, stimulus modifications obviously changed the pattern of the spikes, not just their frequency. Because of these pattern changes, the response to one color may not be mappable onto the response to any other color by a simple scale change. Hence the information in neural responses can not be fully captured by measuring their frequency.

Parallel problems were being encountered in motor axons in crustacea at about the same time. They appeared when Wiersma revisited incomplete studies which had suggested that pattern might be important in determining neural function in motor systems [22].

An important technique was used here which will be described in detail because it will be repeatedly encountered again below: Trains of very brief electrical stimuli were delivered to axons. The stimulus strength was adjusted so that all of the stimuli were well above the strength required to excite impulses in all of the conditions of the experiment. Since the individual stimuli were also adjusted to be briefer than the axonal impulses which they evoked, the experimenters could produce a train of axonal spikes of any desired pattern by simply adjusting the stimulator appropriately. This technique will here be called the spike driving technique.

—Insert Figure 3 about here—

To return, the endpoint under investigation by Wiersma was the contraction of a muscle synaptically driven by the motor axons which had been brought under experimental control. In some muscles, the contraction was reasonably proportional to the frequency of axonal spikes, as the frequency coding notion predicted.

However, in other cases, changing the pattern of spikes while keeping their frequency constant would produce quite extraordinary, totally disproportionate changes in response, as shown in Figure 3. Here, the frequency of spikes was 20 per second and the train duration was 3 sec. Sometimes the stimulus would therefore produce 60 spikes with an interval between spikes of 50 msec. However, the pattern could be altered by delivering the same 60 spikes with successive spikes arranged in doublets so that (say) one spike would follow another by 5 msec and the next would follow by 95 msec and so forth. Wiersma found that such patterning could increase the contraction by as much as 40 times over that produced by a regular pattern even though the frequency of the two patterns and the total number of spikes was identical.

Similar concepts were explored in yet another arena by Brindley in 1960 [23]. He was not primarily concerned with the neural side of the coding problem. Instead, he focused on the problems created on the psychophysical side when inferences were drawn from experiments wherein observers were asked to make judgements of the identity of one sensory quality in the presence of a difference in another. (For example, consider observers being asked to equate the brightness of two lights that are of different colors.)

Brindley argued that research in this area should be restricted to a consideration of data obtained in experiments wherein the observer acted as a null instrument. That is, according to Brindley, observers can only accurately report on (a) whether a sensation is present or absent or (b) whether two sensations are the same or different. Any other judgements would, according to Brindley, be untrustworthy. And relating physiology to behavior would then become vulnerable to problems on this front.

This line of reasoning has been subject to criticism [24]. However, for the purposes of the present discussion, we need only focus on the essence of Brindley's idea, namely that the reduction of a composite entity (whether it be a sensation or a neural response) to a single attribute (either brightness or frequency) is an activity that merits careful analysis.

Awareness of the incompleteness of understanding of this fundamental issue spread. It eventually lead to the convening of a work session by Perkel and Bullock to focus explicitly on the problem of neural coding; this session was held in 1968 under the auspices of the Neurosciences Research Program [25]. Twenty nine investigators of neural coding came together to discuss coding of impulses and of graded potentials. Their work product included a systematic catalog of the large number of possible neural codes that might be investigated and an analysis of the issues that remained to be addressed. They called these possible neural codes “candidate codes.”

Further scholarly reviews of the problem were given later by Uttal [4, 26]. He suggested the adoption of a strict terminology in which possible representations would be called “signs” while the term “code” would ideally be reserved for a representation that had actually been shown to influence the brain (by being shown to be essential for information transfer between cells); the best showing would be if there were some relation of a putative code with the behavior of the whole organism. As we have already seen (cf. Adrian’s illusory correlation), matching physiology to behavioral endpoints can be problematic, and caution has often been urged therefore [24, 27]. However, such strictures have not always been observed and the current literature contains frequent references to “codes” that would be only “signs” or “candidates” if the nomenclature were more orderly.

The Multiple Meaning Theory

Chung, Raymond, and Lettvin presented the term “multiple meaning” in the title of a seminal paper published in 1970 [28]. They examined the pattern of spike intervals occurring in frog optic nerve fibers as a function of two sensory variables: the intensity of light stimulation and the state of adaptation. Adrian’s early work [2, p.25] had shown that these two input variables are confounded in the cellular output—the same spike frequency may be produced in an optic nerve fiber by a bright light in a light-adapted state or by a dim light in a dark-adapted state. Since the same sort of confounding may be observed in certain aspects of sensation, this confounding need not be a fundamental problem in and of itself.

However, Lettvin’s group was intimately familiar with the prior literature indicating that adaptation and intensity both affected spike variability in visual neurons as well as frequency. They therefore developed a data display that emphasized these effects—it presented each spike as a single dot in a plot of interspike interval as a function of time. Such a dot display directly allows the investigator’s visual system to apprehend the statistical dependencies which are elegantly expressed by the distribution and clustering of dots. Figure 4 shows several dot displays characteristic of the dark activity of three different types of “dimming” fibers (i.e., cells which discharge in the dark and are inhibited by light).

—Insert Figure 4 about here—

This display makes it obvious that the pattern of impulses is very different across cells. The bottom cell gives a metronome-like discharge which can be fairly characterized by its frequency; the heavy band of dots clearly indicates that most spikes occur at about the same interval. But the other two cells give evidence of patterning that is quite compelling: There are bands of dots grouped about at least two quite different time intervals and these bands are quite clearly separated. Hence these cells give bursty discharges.

When these cells were challenged by light flashes, striking changes in discharge pattern could occur. In these dot displays, these pattern changes were often much more impressive than the associated modest changes in frequency. The authors concluded that the records permitted “...an experimenter to determine when a light was turned on, when it was turned off, how intense the light was, ... and whether or not any background illumination was present.” [28, p. 85] This finding led to the inference 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 stimulus.” [28, p. 73]

Note that Lettvin's group did not have to address the behavioral difficulty because they restricted their investigation to purely physiological endpoints; one could say that they characterized various neural signs in visual neurons by the degree to which they produced dot patterns which were distinguishable by the experimenters. It has been therefore said by many observers that such investigations may be about what the frog's eye tells the human brain.

—Insert Figure 5 about here—

These concepts evoked a great deal of initial interest which gradually died away, as indicated by a citation analysis: The Chung, Raymond, and Lettvin paper [28] was heavily cited during the '70s but citations declined to zero by the mid-'80s, as Figure 5 shows. (The data in the figure were collected by counting citations published annually in the *Science Citation Index* [29].) Moreover, the initial extensive discussion mainly consisted of parenthetical remarks as opposed to serious experimental work.

Multiple Meaning Analysis of Receptive Field Maps

Interest in the problem has revived in recent years, as Figure 5 also showed. However, this time, the interest has produced a variety of quite interesting experimental studies which have given us new views of well-established problems. One such problem was already alluded to above, namely the structure of retinal receptive fields. It will be recalled that the receptive field is the region of the sensory surface which can influence the firing of a neuron. Following initial reports [10], it had been found that receptive fields could be subdivided into excitatory and inhibitory subregions [30, 31]. To a first approximation, the map of a retinal receptive field, as indexed by the firing of optic nerve fibers, has often been characterized by two concentric circular regions. The central disc is a relatively small area in which excitatory responses are evoked by light while the surrounding annulus is a generally larger area in which inhibitory responses are evoked. However, in some cells, the response polarities of center and surround are reversed. Functionally, this type of spatial arrangement has often been believed to facilitate the detection of border contrast.

Levine and Zimmerman recently re-examined these maps from the point of view of multiple meaning theory [32]. Accordingly, they systematically investigated the temporal structure of goldfish ganglion cell spike responses as a function of location within the classically-defined center/surround receptive field. In the new spirit, they created a quantitative data display which sensitively indicated the pattern of firing as follows: The relative balance of excitation and inhibition was represented by the angle of a vector. Changes in this balance during the time course of a response were then represented by changes in these vector angles.

—Insert Figure 6 about here—

Using this index of temporal pattern, clusters of responses were found, indicating that some stimuli evoked similar firing patterns. Most importantly, as Figure 6 shows, these temporally-defined clusters were not randomly distributed across the spatially-defined receptive field. Instead, they turned out to represent spatially contiguous subregions within the classically defined receptive field. Even within what would otherwise have been called the center of the receptive field, Figure 6 shows that the response patterns often varied reliably enough to delineate many subregions. The investigators carefully made no claim that this firing pattern information was actually used by the nervous system since the end-point of the study was the investigators' inspections of the quantitative displays of these response patterns.

Multiple Meaning in Cortical Cells

Multiple meanings were further implicated by a series of studies in several central visual structures. The classical picture of the function of such cells has developed from the work of Hubel and Wiesel on processing in visual cortex of cat and monkey [12—14]. They were extending Kuffler's [30] receptive field mapping technique from the retina to the brain. Accordingly, they presented spots of light at different locations in the visual field while recording extracellular spikes from single cells. They found that the receptive field structure changed drastically in primary visual cortex: Instead of circularly symmetric receptive fields, Hubel and Wiesel encountered highly elongated receptive fields.

The important insight they drew from these receptive field maps was the idea of challenging cortical cells with visual stimuli consisting of extended straight edges or bars of light. Prior to this time, of course, the custom had been to challenge nerve cells with physically simple stimuli, such as spatially isolated spots of fixed intensity and duration having a constant spectrum. But when Hubel and Wiesel began to use physically complicated stimuli, they not only found that those cells which had responded to spots responded even more vigorously to elongated stimuli, but they also discovered that there were many cells in cortex which only responded to visual contours but not to isolated spots of light.

Hubel and Wiesel naturally began the task of characterizing the trigger features of the cells they had discovered. They immediately found that the angle of the extended visual contour was critical: Turned so that it paralleled the long axis of the receptive field, a contour could produce a quite vigorous spike discharge. Turned 90°, so that it was perpendicular to the long axis, no response at all might result. Hence, such cells have often been considered feature detectors which signal the orientation of contours in the visual field. Whether this characterization of their function is complete is still a matter under discussion, as will be seen below. What is important is that the brain contains cells which simply do not fire unless they are challenged with appropriate stimuli. Under these circumstances, the brain gives no answer at all unless the investigator asks the right question.

Later research indicated that the firing pattern of cells in visual cortex might be an important variable. Cattaneo, Maffei, and Morrone [33] found that some cortical cells do not exhibit much bursting and so their responses can be fairly characterized by spike frequency measures. However, they also found that other cells exhibit response bursts that are differentially related to stimulus features. In these cells, frequency and bursting give different information about the cell's input.

More recently, the properties of visual cells in primate brain have been revisited by Richmond and Optican's group at the NIH; they have been explicitly pursuing issues raised by the multiple meaning theory. Many structures in primate brain have been investigated by them and a review of these studies has recently been given [34].

The present paper will mainly consider their studies of primate visual cortex [35, 36]; these studies are perhaps the most accessible because of the ready contrast they offer with the classic work of Hubel and Wiesel [12—14]. It should be noted that methodology varied: Hubel and Wiesel anesthetized their animals and paralyzed their eyes while the NIH group used awake animals who were trained to look at the stimuli under reinforcement control. A comparison of the firing rates obtained with these two methods indicates that both evoked and spontaneous responses were much more vigorous in the awake animals. However, as noted above, some degree of temporal patterning had previously been seen even under anesthesia [33]. The role of anesthesia in neural response patterning is important and it will be revisited below.

—Insert Figure 7 about here—

The most recent work follows the multiple meaning tradition in that the spike data are presented in a form that maximizes the clarity of any temporal patterns. The results, some of which are shown in Figure 7, indicate that very pronounced temporal structures pervade visual cortical responses. The figure also shows that these structures vary with the orientation of the stimulus and with its contrast relative to background. Note particularly the fact that the gross and fine temporal structures of the responses to 0° stimuli differ radically when contrast is reversed from white on gray to black on grey. Note further that the response to a 45° stimulus varies from almost purely phasic to almost purely tonic as the stimulus changes from white to black.

These data show that a simple measurement of spike frequency over any interval of time would indicate that the responses of such primary visual cortical cells are ambiguous about stimulus orientation, which is the stimulus feature they are widely believed to detect. This conclusion follows from the showing that different combinations of contrast and orientation produce the same frequency. In order for such cells truly to convey information that signals stimulus orientation, the nervous system would have to have some way of assessing the multiple meanings inherent in the temporal patterns. Under these circumstances, the possibility exists that a single neuron could be conveying information that otherwise would have to be represented by a group of neurons. Complimentarily, it is possible that the activities of groups of neurons, each of which is carrying a different combination of meanings, may have to be consulted to extract unambiguous information.

The Task Dependence Hypothesis

Our own laboratory encountered the full force of the neural coding problem over a decade ago. We had been obtaining microelectrode recordings of the electrical waveforms evoked in single photoreceptors and optic nerve fibers in horseshoe crabs and we were investigating the problem of temporal summation [37—41].

However, we had been sensitized by the coding literature and we immediately found that cellular responses did not display a single form of temporal summation. Instead, different varieties of temporal summation were associated with various neural signs. One sign would exhibit linear energy-dependent summation (wherein responses were determined by the product of stimulus intensity and duration) while another sign would exhibit nonlinear time-dependent summation (wherein changes in duration had a much greater effect than corresponding changes in intensity).

The different summation patterns exhibited by these signs had close correlates in behavioral data obtained using different tasks [42—45]. Because the various signs had clear behavioral correlates, we tentatively labeled these signs as neural codes. Because the differences between these putative neural codes systematically covaried with behavioral task differences, we formulated the hypothesis that the neural code varied with the task. Our hypothesis grew out of the multiple meaning theory, but it is not identical with it, as will be seen below.

We tested this approach by executing cellular investigations of other phenomena. One was the occurrence of time dependent effects in visual masking [46, 47]. These had previously been given a cognitive explanation [48, 49] which held that the processing of the information resident in a neural representation could be interrupted. Our neural coding analysis indicated that these effects could well be a consequence of the time dependent integrative processing that underlies computation in nerve cells. We found that cellular integrative processes could actually interrupt the cellular representation itself.

We extended this research program further by studying other problem areas. One was the problem of sensory quantity [50, 51]. It had long been known that behavioral assessments of sensory quantity could be changed by changing the observer's task; we found that those behavioral changes matched the changes in cellular properties that were produced by changing the code.

A more recent focus has been the problem of perceived duration [52]. That literature contained reports of some behavioral tasks which gave indices of perceived duration that were a direct function of intensity while other behavioral tasks yielded inverse functions. We [53] found that different neural codes exhibited each of the apparently contradictory properties found in the behavioral studies.

—Insert Figure 8 about here—

Two summaries of this research have been published [52, 54]. The core concept of the task dependence hypothesis is illustrated in Figure 8, taken from the more recent review paper. This figure contains graded receptor potentials (RP) whose momentary amplitude is systematically related, albeit in a complex way [55], to the instantaneous frequency of spikes subsequently generated in sensory axons. The figure shows how a single neural response can contain at least four representations of the information resident in a single stimulus. Each of the four panels in Figure 8 contains the same trace; this trace displays the time course of the electrical potential evoked in a single photoreceptor cell by a light flash. But each panel also displays a different way of coding this single response: The upper left-hand panel shows a measurement of the amplitude of the peak of the response; the upper right-hand panel shows a measurement of the integral of the response; the lower left-hand panel shows a measurement of the time that the response stays above a criterion potential; and the last panel shows the time it takes for the response to decline from its peak to a criterion value.

The task dependence hypothesis suggests that these four neural codes are associated with different forms of information processing that are required by four different behavioral tasks. To make this association explicit, the four panels of Figure 8 are labeled with terms that relate to four different behavioral tasks. For example, "detection" represents behavioral tasks in which observers are asked to report whether or not they simply perceive a stimulus; by contrast "identification" represents behavioral tasks in which observers are asked to report on some attribute of a stimulus, such as its shape or extent. "Persistence" and "offset" represent tasks in which observers are asked to report on the termination of a percept—in the former case, the report is of the final disappearance of the percept; in the latter case, the report is of the initial decay of the percept. What we mean by this labeling is that these four codes have been consistently associated with these four tasks across the large number of studies that we described above.

Attaching these four task labels to these four neural codes represents an assertion that performance in these tasks is mediated by these codes. This strong characterization is only a working hypothesis; it is unlikely to be correct in detail because each of these codes is obviously only an exemplar of a family of closely related codes. Moreover, technical constraints have generally led to somewhat different ways of characterizing the patterns resident in trains of all-or-none spike potentials, even though these are generated by graded potentials and related to them in a complex way [55]. Therefore, a weaker, but much more general formulation would be that the neural code is task dependent—we suggest that different features of identical neural responses mediate behavioral performance in different tasks. We do not then claim that we have found the exact codes that may be used.

Hence our hypothesis is based on the multiple meaning theory in that it starts from the notion that information about different aspects of stimuli may be registered in different characteristics of the time series that forms the neural response. We go beyond the multiple meaning theory in suggesting that the demands of different behavioral tasks may lead the observer to access the neural information resident in the multiple meanings of the response in different ways.

Creating Temporal Structures in Neurons

The multiple meaning theory has certain necessary consequences. It is obvious that, if the temporal structure of a cellular response has any meaning, then the nervous system must have a way of creating that response structure. Can the nervous system actually do that? The older literature has long contained data which suggested that the ability to control firing patterns was a fundamental capability of at least certain neurons. For example, Figure 9 shows an example from fish motor system wherein the threshold response is not one spike but two [56]. Here are photographically superimposed traces of the responses to a depolarizing current adjusted to be just at spike threshold. (Data from two cells are shown in the figure; they are electrically connected and the depolarizing current is injected into the cell represented in the upper set of traces. Current spreads to the second cell whose responses accordingly occur somewhat later.) In the textbook case, such a stimulus would sometimes evoke one spike and sometimes no spikes. But in this case, one either gets nothing or one gets two closely spaced spikes. Hence, a system which contained such a rhythmic neuron would exhibit an intrinsic patterning of its discharges.

—Insert Figure 9 about here—

Similarly, intrinsic rhythmicity of cellular discharges has been found in both sensory and motor systems. As noted earlier, the spike driving technique delivers regular clocklike electrical stimuli to an axon and they evoke regular clocklike spike discharges in that neuron. However, obvious patterning has been found when such regular discharges are generated in certain interneurons that synaptically drive motoneurons [57]. In that case, the regular firing of the interneuron produces bursts of spikes in the motoneuron. And the number of spikes in the motoneuron bursts is a monotone function of the frequency of spikes in the interneuron.

Along the same lines, sensory neurons have been found to conduct bursts of spikes in ways that might represent information about the stimulus. An example is found in temperature sensitive fibers coming from the skin. Changing skin temperature changes spike frequency in these cells, as has long been known. However, bursts of spikes can be seen in the discharges of such cells and the number of spikes per burst is a monotone function of skin temperature [58].

More recent work has gone beyond these demonstrations and inquired into the degree of temporal precision of impulses. Can cell potentials be determined very precisely in time? Strehler and Lestienne [59, 60] report data which possibly suggest that that may be so. They examined the recurrences of spike doublets and triplets in data collected from single cells in monkey cortex. They compared these data with a model that assumes spikes are generated at random. Neither the model nor the data analysis were presented in enough detail for me to evaluate their conclusions. However, the authors report that their analyses indicate that spike timing can be determined in single cells to about 0.2 msec precision.

A related way of inquiring into the same issue is to ask if the timing of neighboring cells can be strictly related in time. Gray and Singer [61—63] have reported data which strongly support this notion. Their data emerged from a very specialized investigation, but they have attracted very wide interest and it is likely that these phenomena will be characterized more exactly within a short time. The data come from recordings taken from cells in cat visual cortex which were stimulated by visual contours. Oscillatory field potentials were found whose frequencies were in the 40 to 60 Hz range. These field potentials were related to fairly obvious phase locking of spikes discharges between neighboring cortical cells. This phase locking could extend up to 7 mm across the cortex; at such distances, the receptive fields of two cortical cells need not be overlapping. Hence the effect could be studied by independently presenting two visual stimuli that would engage two separate cortical cells. It could then be demonstrated that the temporal linkage between the two cells was dependent on the spatial linkage between the two stimuli. The cross correlations between responses depended on the similarity of the orientations of the two stimuli and their directions of movement.

Interestingly, global stimulus properties were influential: Two bars of the same orientation and moving in the same direction at the same velocity produced more linkage when the ends of the two bars actually touched so that they formed one long bar than when there was a gap between the ends of the two bars. These data not only demonstrate temporal linking between spike discharges in related cells, but they also demonstrate that the linkage may depend on important properties of the stimulus, just as the multiple meaning theory requires.

The various indices of temporal structure in neural responses under review here have been drawn from quite varied investigational domains. The slower structures (e.g., the classical excitatory and inhibitory responses described above) may well be completely orthogonal to the faster structures (e.g., the 40-60 Hz oscillations). To avoid overinterpretation: these data do indicate that varied temporal structures exist in neurons; it remains for future investigation to determine whether or not these diverse temporal phenomena are components of some deeper mechanism.

Processing Temporal Structures in Neural Responses

A temporal response structure might simply be passed along to downstream neurons with minor modification. Were that the case, it would be very difficult to decide if such a structure were a sign or a code, in Uttal's [26] terminology. For a positive demonstration that a neural response pattern is a true neural code, it is not enough to create a temporal structure in a neuron; both general coding theory and multiple meaning theory lead to a strong interest in the possibility that follower neurons can react differentially to different temporal structures. Does a pattern change critically influence either the activity of subsequent neurons or ultimate behavior? The present paper has already discussed Wiersma's data which indicated that such differential reaction was possible in principle [22]. However, all that was measured in that case was system input and output with little light being shed on mechanism.

—Insert Figure 10 about here—

One possible mechanistic basis would be that temporal summation of synaptic potentials can process temporal patterns of incoming spikes. This type of pattern-sensitive effect has been clearly demonstrated in cells in the visceral ganglion of *Aplysia* [64] and it is illustrated in Figure 10. Here, the spike driving technique was used to deliver trios of electric shocks to an axon which provides synaptic input to the cell in which the recording microelectrode is impaled. Exploiting the spike driving technique, the experimenter can impose patterns on the afferent spikes which in turn impose patterns on the postsynaptic potentials which are what is actually displayed in the figure.

These data demonstrate that varying the input pattern produces a marked variation in the likelihood of an output from this system when the number of spikes and their frequency are held constant. No output spike is produced when S_2 precedes S_3 by a long interval, as in case A. As the interval is shortened, as in cases B and C, then the summated postsynaptic potentials produce progressively larger depolarizations. Finally, when the interval is even shorter, as in case D, synaptic summation triggers an action potential in the postsynaptic cell.

Changes in postspike excitability have also been recognized [64] and the implications of these changes have been pursued further [28, 65]. Of particular recent interest has been the possibility that temporal patterns could be converted to spatial patterns in regions where excitability changes would have a powerful effect. It has long been known that axon bifurcations exhibit such effects. Here the safety factor is often less than 100%, meaning that not every spike which arrives at a bifurcation will propagate successfully past the bifurcation into the daughter branches.

Attention was focused by Lettvin's group on the fact that variations in spike interval affected the safety factor. Also noted was the fact that the influence of neighboring cells can be very profound when the safety factor is low. Finally, the probability of a spike going down both of the daughter branches of a bifurcation must vary because of variations in branch diameters. Since most axons bifurcate considerably, these factors make it possible for a sequence of spikes to be differentially distributed to the various terminals of an axon. Since the terminals extend over space, such an effect would convert the temporal pattern in the spike train into a spatial pattern of active terminals.

—Insert Figure 11 about here—

More recently, these questions have been pursued in the system of giant axons found in the squid [66]. As has often been the case in the history of neuroscience research, use of this preparation makes it possible to obtain direct observation of variables that may only be indirectly inferred in other preparations. Several very relevant findings from this investigation are illustrated in Figure 11. Here the spike driving technique is used to apply a pair of electrical shocks to a bifurcating axon and the interval between shocks is varied. The middle trace in the figure shows extracellular recordings made just prior to the bifurcation—it can be seen that pairs of action potentials are produced at all three interspike intervals, labeled a, b, and c.

These pairs of potentials have the possibility of propagating into both branches after the bifurcation. Accordingly, the upper and lower traces show recordings taken from the corresponding branches. It can be seen that when the interval is 2.7 msec (labeled a), the input pair of spikes produces a pair of spikes in both daughter branches. However, the longer daughter branch fails to produce two spikes at an interval of 2.6 msec (labeled b) while the shorter daughter continues to produce a pair of spikes. Here then is a direct demonstration of how the nervous system might create two different spatial patterns of activity out of two temporal patterns of spiking.

The specific theoretical bases of these axonal effects have been analyzed [67—69]. On a deeper and more general theoretical level, N. Stockbridge [personal communication] has raised an important question, namely that "...away from the primary receptor and the motor output, it may not be possible to look at the output along a single intermediate axon and say how the information is encoded." On his view, an intimate knowledge of the state of all of the processes of a central neuron is needed to avoid having an incomplete understanding of that neuron's function.

This problem extends beyond axonal firing and affects our understanding of other parts of neurons since formally similar effects have been implicated in dendritic arborizations [70]. To the extent that local circuits in the dendrites of intrinsic neurons determine the amount of depolarization of a dendritic presynaptic membrane (and hence the release of synaptic transmitter), to that extent does the potential at each presynaptic site on a dendrite become a neuronal integrator whose function is similar to the integration performed by the axon pacemaker at the axon hillock. It will therefore be appreciated that the problems created here by dendritic geometry are nontrivial.

Experimental Tests of the Multiple Meaning Theory

The multiple meaning theory therefore now stands on an impressive body of converging physiological and anatomical evidence. However, it has still only a minimal connection to behavior, which is the principal product of neural function. It will be recalled that the only behavioral connections mentioned thus far have been those which were made by Adrian and by our laboratory. In both cases, the connections were made by examining correlations. As noted above, correlations can be dangerous and thoughtful warnings have often been issued [23, 24, 27].

What is needed are behaviorally-rooted methods of testing coding theories by experiment rather than by correlation. Fortunately, several such methods of approaching these questions are available which offer the possibility of executing true neural coding experiments. One method relies on the obvious effect of anesthetics on the behavioral state we call consciousness. This approach will be further discussed below.

Another method depends on the fact that certain favorable situations make it possible for one to stimulate neurons in conscious human observers while monitoring their behavior. The pattern of stimulation can be varied to produce neural activity that follows one putative coding system or another. And the behavioral performance produced by the two codes can be recorded. If changing the code reliably changes behavior, one would have a solid experimental, not correlational, basis for concluding that a genuine coding effect had been obtained.

Uttal [26, pp. 321-335] earlier reported coding experiments of this type which exploited the favorable fact that somatosensory afferents in the arm occasionally come close enough to the skin so that they can be stimulated in human volunteers. Using the spike driving technique, patterns of afferent spikes were evoked. The weakest prediction from coding theory is that spike pattern should influence behavior. The observers were therefore interrogated to see if their behavior could differentiate the pattern of the afferent spikes independently of their frequency. For certain patterns and intervals, the answer was yes, indicating that pattern information in a primary afferent is actually capable of altering behavior.

More recently, we have begun to investigate such questions in another favorable preparation, namely nerve deaf patients [41, 71, 72]. These are people who have lost their hearing after damage to their auditory nervous system. In most cases, such loss occurs because of damage to the hair cells , which are the auditory receptors. However, such patients generally have surviving auditory nerve fibers and electrical stimulation of these surviving fibers produces an auditory sensation. By stimulating different axons coming from different places in the inner ear, one can partially reproduce the pitch sensations of normal hearing [73, 74].

—Insert Figure 12 about here—

Recent advances in microsurgical technique and in microelectronics have made it possible to fit such patients with an artificial ear, called a cochlear implant [73]. As shown in Figure 12, such an ear consists of a microphone, a signal processor, and stimulating electrodes; the latter are surgically implanted in or near the cochlea so that they stimulate auditory nerve fibers when sound reaches the microphone. From the coding point of view, the signal processor is an artificial neuron. Its processing scheme can be manipulated to influence perception of sound.

We have thus far examined the weakest prediction one can deduce from coding theory: If neural response pattern *per se* actually does contain coded information, then replicating the pattern produced by natural nerve cells should produce an artificial signal that contains every possible neural code. Controlled experiments were therefore done in which performance was measured when the artificial ear simulated the function of natural hair cells [41, 71, 72, 74]. This was accomplished by processing a digitized representation of the acoustic waveform through an algorithm that executed a standard filter-feedback model of receptor function. Such a model produces graded waveforms that simulate the natural receptor potentials (RP) normally produced in hair cells [75]. With all other conditions held constant, the performance mediated by this neural coding was compared to the control performance; namely the performance produced when the algorithm was changed so that it did not simulate natural function—the control signal waveforms simply followed the acoustic waveforms. The simulated neural coding improved speech discrimination performance in every patient investigated, regardless of age of deafness onset or etiology of deafness.

—Insert Figure 13 about here—

An extreme example of performance improvement is shown in a star patient in Figure 13. In this particular experiment, incomplete sentences were delivered. The sentences were incomplete because they were missing their last word. Two possible last words were displayed as text on a computer screen and the patient pushed a button to chose the word which best seemed to complete the spoken sentence. On this difficult task, even this star patient performed at chance in the control condition in which the waveform of the stimulus was not processed (other than by simple filtration). However, passing the same information through the model that simulated the RPs found in the natural hair cell enabled this particular patient to chose over 75% of the last words correctly. Other patients, who cannot perform above chance on this difficult task, showed corresponding improvements in easier speech discrimination tasks. These results are consistent with coding theory, however, much more needs to be done to determine whether these performance improvements are actually a necessary consequence of the neural coding employed.

This preparation provides the opportunity for stronger tests of coding theory. By varying the model that acts as an artificial nerve cell, one can systematically vary the signals imposed in the afferent neurons of such human patients. By interrogating the behavior of such patients appropriately, one can determine—by experiment rather than by correlation—whether a putative neural code is actually accessible to the brain.

Yet another way of linking neural codes to behavior is by studying anesthesia. As was noted above (in the discussion of visual cortex function), both quantitative and qualitative differences are found in the firing of visual cortical cells in anesthetized animals. Similar neural changes are also related to the changes in consciousness that are part of the normal sleep-waking cycle [76].

The mechanism of anesthesia is incompletely understood. Since Sherrington's work at the beginning of this century (see the review in [77]), it has been known that general anesthetics do not block axonal activity. This led to the presumption that the site of action of general anesthetics would be found in other parts of the neuron; synaptic mechanisms have been particularly considered and synaptic effects of anesthetics have indeed been demonstrated (see [77]). However, multiple meaning theory draws one's attention beyond mere spike generation towards the question of spike patterning. Clearly, if the integrative action of the nervous system (as expressed in behavior) were critically determined by the pattern of neural responses, then anything which disrupted that pattern would be expected to disrupt behavior.

This notion has been tested in experiments on isolated frog sciatic neurons maintained *in vitro.* Hence no systemic influences could affect this preparation. This work has shown that anesthetics do disrupt neural firing patterns at concentrations that are clinically effective [77]. The disruption is mediated by the effect of anesthesia on an interesting mechanism, one which operates even in the absence of anesthesia: Spikes propagating in axons normally leave behind a residual that influences subsequent spikes [78]; the effect is of an increase in the latency and threshold of subsequent spikes. This residual effect gradually builds up and decays away over periods measured in minutes. And the magnitude of this residual effect is modality specific within various types of somatosensory axons.

Anesthetics damp down this activity-dependent change in spike threshold and latency; anesthetics therefore change the normal patterning of spikes by changing the residual effect of one spike on another. A strong and experimentally testable prediction of this hypothesis is "...that agents which disrupt activity-dependent processes in electrically excitable nerve membrane will act as general anesthetics [77]."

Conclusions

This review has shown that several antecedent issues are unavoidable in the study of neural systems. These issues are antecedent because they have to be addressed before any investigator can communicate any empirical results in any form that is more compact than a complete dump of all raw data. These antecedent issues exist for the following reasons: First, complex signal patterns do exist in the nervous system and it is not always possible to characterize such patterns by a single simple measure. Second, nervous systems do contain mechanisms that are able to react, at least partially, to the pattern of these biological signals. Third, these patterns do contain multiple indicators of information about multiple attributes of stimuli. Fourth, evidence does indicate that the brain may actually use such pattern information and that its use of these patterns may be modified by changing the demands of the task at hand. The need then becomes manifest for an empirically-based general answer to the neural coding question. Investigations which proceed without giving attention to the coding question are likely to lead to an incomplete understanding of the problems they address.

Acknowledgements

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FIGURES

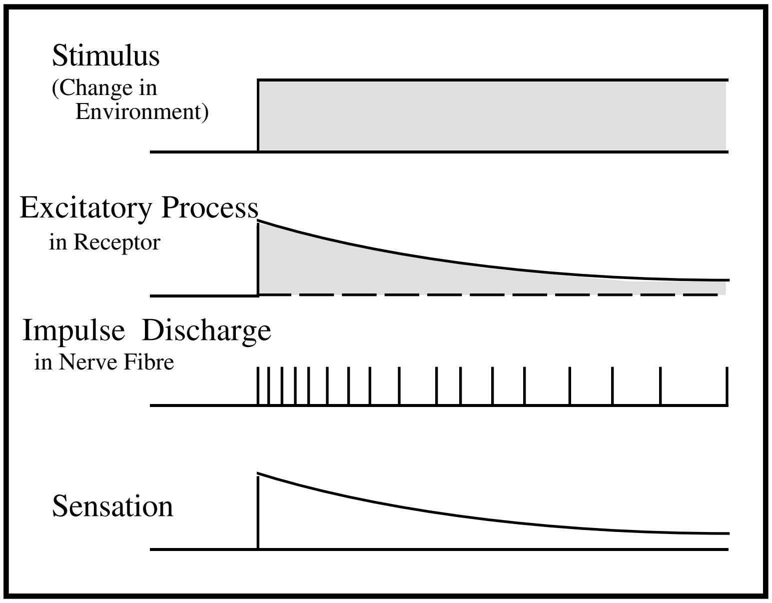

Fig. 1. The isomorphism hypothesis expressed in Adrian's 1928 schematic summary of his early research on sensory coding [1]. The traces show the "relation between stimulus, sensory message and sensation" by plotting the time course of four variables: a stimulus which is suddenly turned on and held at a fixed amplitude thereafter; an inferred excitatory process produced by the stimulus; a measured train of axonal spikes produced by this excitatory process; and the sensation inferred to be correlated with these cellular signals. Isomorphism is expressed by the congruence of the sensation with the biological signals. (After Figure 31 in Adrian [1].)

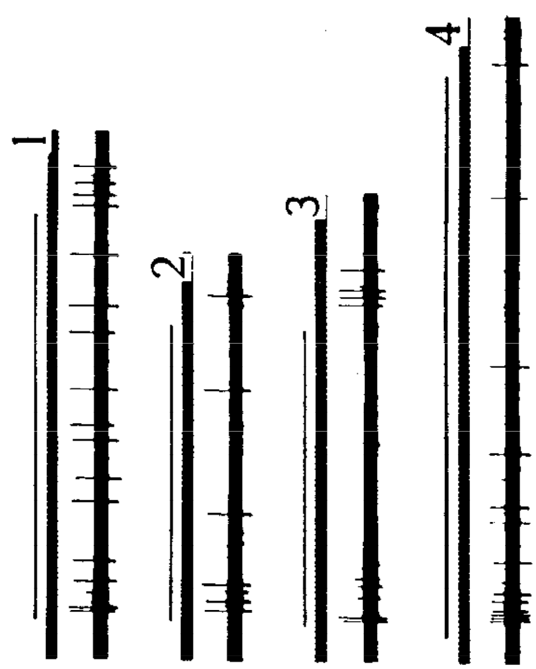

Fig. 2. (rotated 90°) The antecedent nature of the neural coding question is apparent on considering Granit's 1943 recordings of spikes in cat optic nerve fibers evoked by lights of different wavelengths and intensities [20]. Records 1, 2, and 3 are from one cell. In record 1, the wavelength was 620 nm and the relative energy of the light flash was 6.3. Record 2 is the same wavelength at a lower relative energy of 2.3. In record 3, the wavelength was 460 nm and the energy was 2.5. Record 4 is from another cell showing its response to 500 nm light. It is apparent that the firing pattern changes its form as a function of wavelength. Interpretation of such compound effects cannot be done without an appeal to coding theory, as described more fully in the text. (Each record contains three traces: The thin upper trace indicates the presence of the light stimulus. The wavy middle trace is a 50 Hz sine wave. The lower trace presents the spikes recorded in response to stimulations.) (Reprinted by permission of Acta Physiologica Scandinavica.)

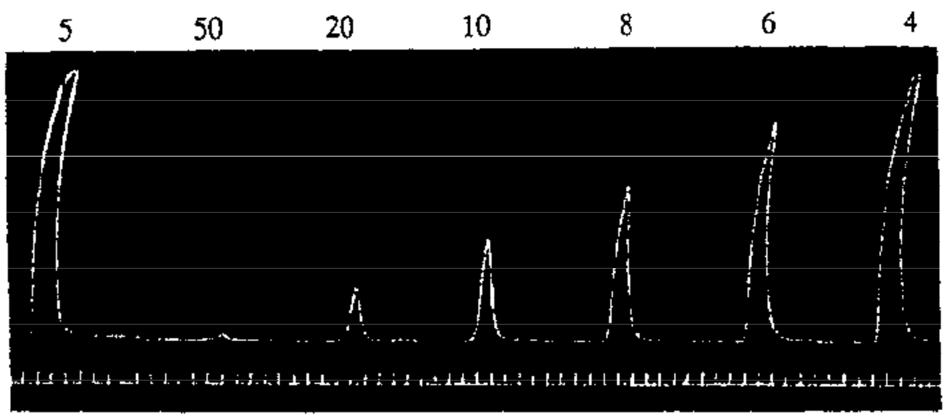

Fig. 3. Evidence that spike pattern is important appeared in Wiersma's measurements [22] which show large changes in the magnitude of crustacean muscle contraction in response to patterning of efferent spikes. Upper trace represents muscle contraction as a function of time. Lower trace gives a 1 sec time marker. Spike frequency is 20 per sec and the spikes are arranged in short interval doublets with longer intervals between doublets. Numbers above the trace give the doublet interval in msec; at 50 msec, the longer interval equals the shorter. It can be seen that the record begins with a large response evoked by a 5 msec doublet. But lengthening the doublet to 50 msec almost eliminates the next response. Progressive shortening of the doublet interval back down to 4 msec produces dramatic increases in response size. (Reprinted by permission of Kluwer Academic Publishers. The contrast of the original data was quite low and so the contrast of this reproduction was enhanced by a digital image processor.)

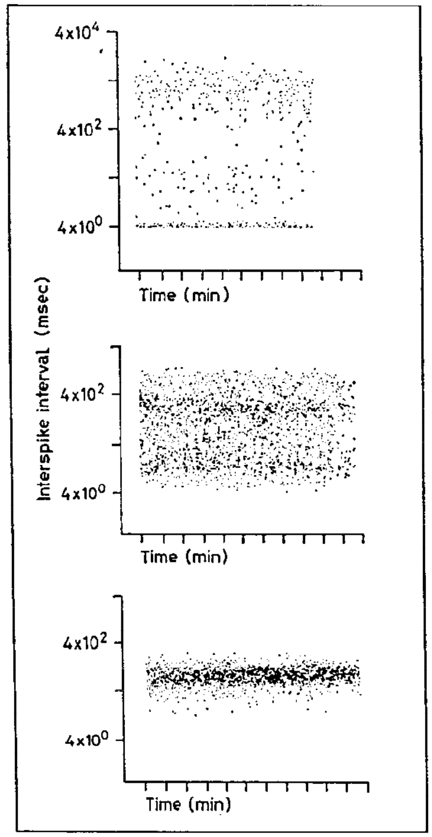

Fig. 4. Evidence that response patterns are prominent in some cells. Dot displays characterize spike patterns in three different frog optic nerve fibers [28]. Each dot represents one spike; it is plotted at a horizontal position that represents the time of occurrence of that spike with its vertical location representing the time interval since the previous spike. Different temporal patterns are evident in the type and degree of banding of the dots: The two upper panels represent "bursty" fibers while the lower represents a fiber with a fairly regular discharge. (Reprinted by permission of S. Karger AG, Basel.)

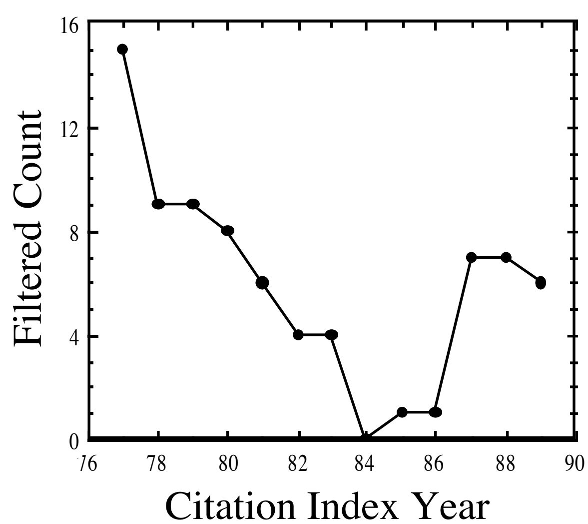

Fig. 5. Decline and recent revival of interest in the multiple meaning theory as indexed by annual citations to the Raymond, and Lettvin paper [28] as logged in the *Science Citation Index* [29]. In order to

show the general trend more clearly, these data were smoothed by a median filter (i.e., each plotted point is the median of the three values for the plotted year and the years just before and after the plotted year). In consecutive order from 1976, the unfiltered counts were: 15, 9, 15, 8, 9, 6, 4, 0, 5, 0, 1, 8, 7, 5, 6.

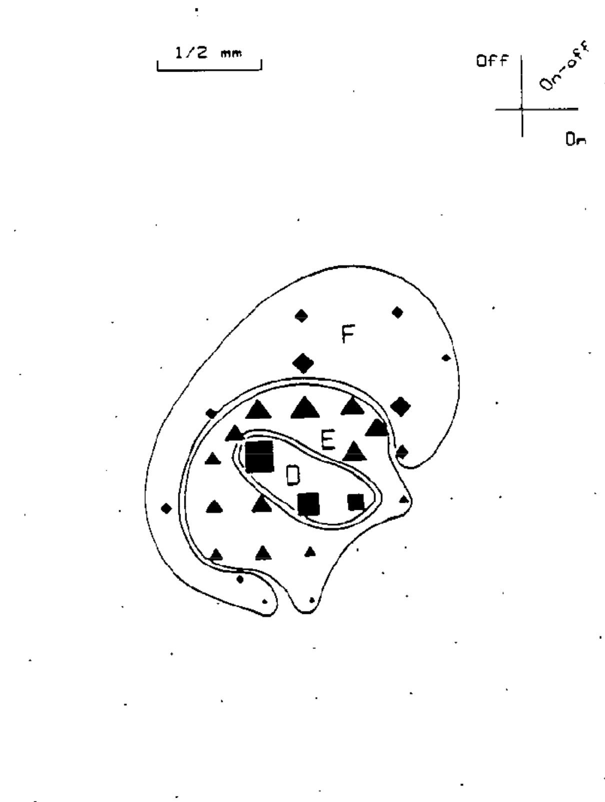

Fig. 6. Evidence that temporal pattern of neural responses may be systematically related to the spatial analysis done by a neuron. The figure shows that the central region of a classical center/surround receptive field of goldfish optic nerve fiber can be subdivided by quantitating the firing patterns exhibited by its spikes [32]. Firing pattern was quantitatively characterized by a vector which represented a cell's On response by its horizontal extent and the same cell's Off response by its vertical extent (with response polarity represented). Hence any particular response could be plotted by a vector from the origin of the two-dimensional space shown in the upper right corner of this figure. A finer assessment of the firing pattern was made by comparing the vector which characterized the response occurring during the first quarter second after stimulus onset or offset with the vector which characterized the same response during the first half second after onset or offset. A cluster analysis of these two vectors indicated that the response firing patterns are grouped into three clearly distinct types. The spatial distribution of these types is, indicated in this figure by three different symbols: triangles, squares, and diamonds. The size of a symbol is proportional to the overall level of firing produced by stimulating that portion of the receptive field. (Reprinted by permission of Cambridge University Press.)

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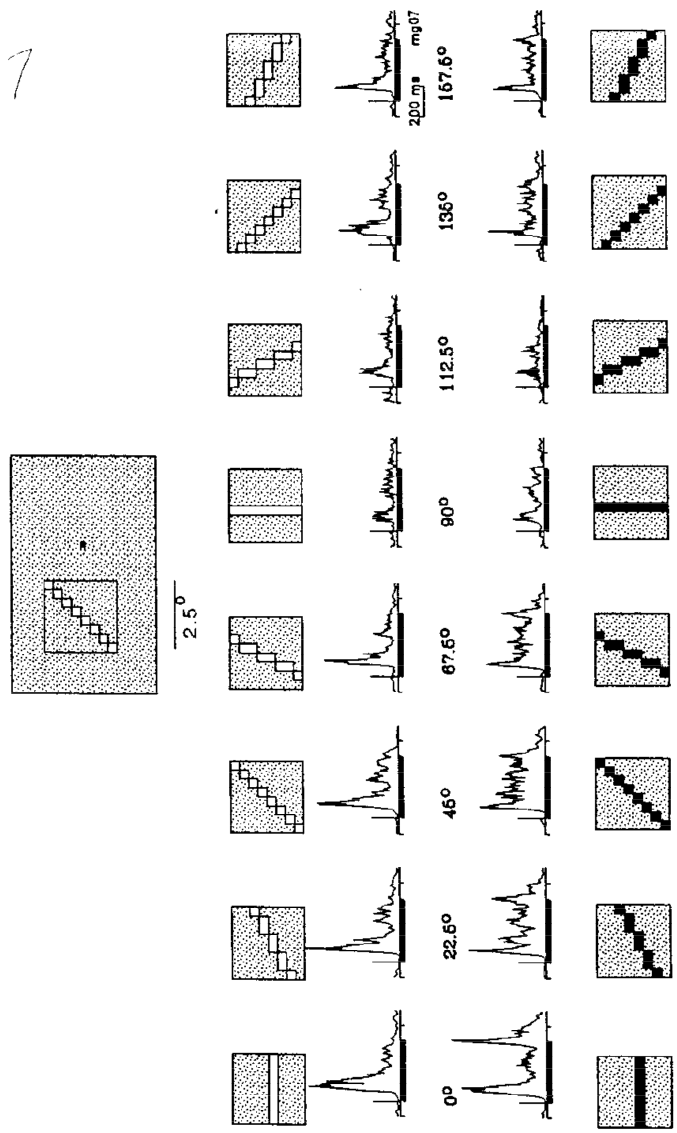

Fig. 7. (rotated 90°) Multiple meaning in the response of a cell in monkey visual cortex to bars of different orientations and different contrasts [35]. Upper row shows the location of the point fixated by the monkey and the position in the visual field of the target stimuli. The next row shows eight different orientations of a target stimulus that is brighter than the background. The next row down shows eight peristimulus histograms describing the responses evoked by these bars. Stimulus duration of 400 msec is indicated by the thick horizontal bar just below each histogram. The thin vertical bar at stimulus onset represents a firing frequency of 100 spikes/sec. The bottom two rows provide corresponding information for bars that are darker than the background. (Reprinted by permission of the American Physiological Society.)

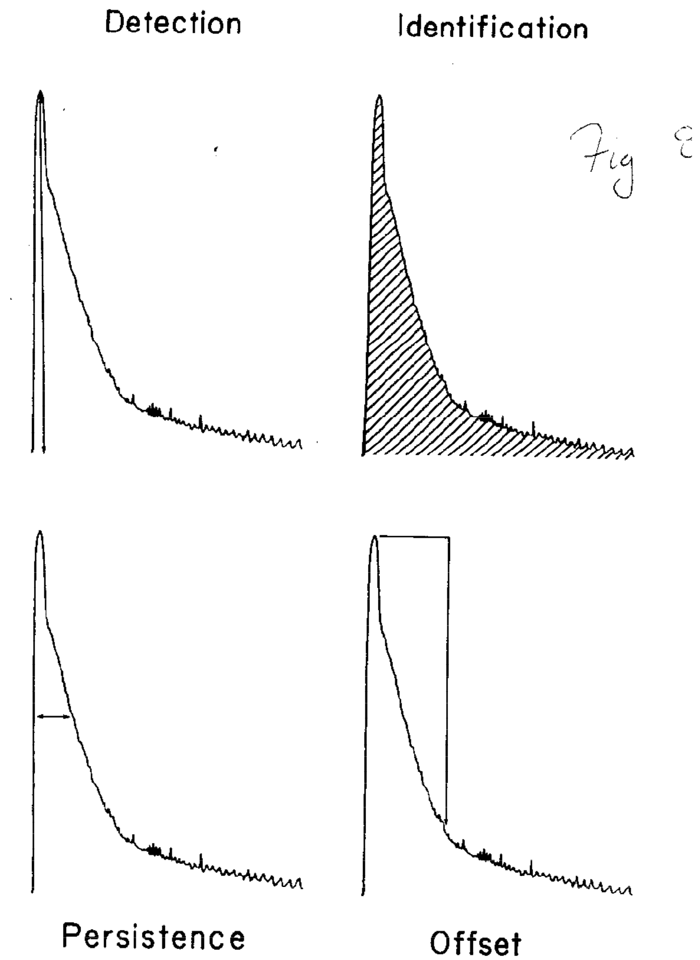

Fig. 8. Summary of the present state of the strong version of the task dependence hypothesis [52]. Each panel contains a reproduction of the identical photoreceptor potential evoked in single photoreceptor by a flash of light. Each of the four panels associates a different feature of the same response with a different behavioral task. The peak correlates with detection, the integral with identification, the time the potential is above a criterion level goes with persistence, and the time it takes to fall from its peak by a criterion amount goes with offset. (The criterion values were allowed to vary over the entire physiological range of these responses. For reference, the peak amplitude of this waveform equals 48 mV and the duration of this trace is 9.8 sec. The small fluctuations on the descending tail of the receptor potential represent potentials occurring in neighboring cells.)

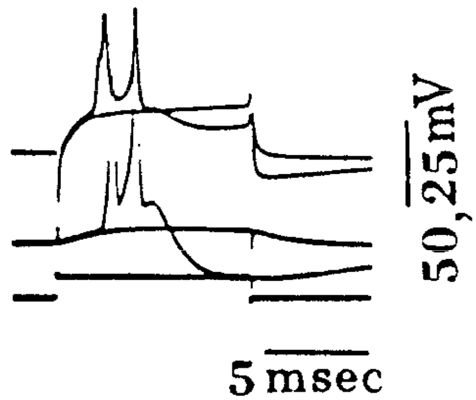

Fig. 9. Patterning of synchronous spike discharges at threshold in two electrically coupled fish motor neurons [56]. Simultaneous intracellular recordings from both neurons yield the two upper sets of photographically-superimposed traces. Each set is composed of a threshold pair of traces which overlap completely until depolarizing current is applied whereupon they diverge, depending on whether or not spikes were produced during that particular trial. The lowest trace marks the application of a 10 msec pulse of depolarizing current to the cell represented by the upper set of traces. Current artifacts are evident on all of the potential recordings at current onset and offset. Note that the threshold response is of two spikes. (Reprinted by permission of the American Physiological Society.)

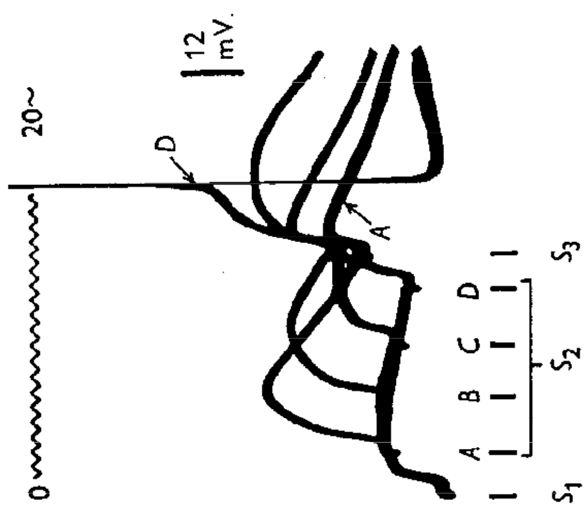

Fig. 10. (rotated 90°) Effect of presynaptic spike pattern on the amplitude of postsynaptic potentials recorded in a neuron in the visceral ganglion of *Aplysia* [64] Trios of spikes arrive at this synapse with the same frequency but with different patterns produced by varying the timing of the second spike, as shown schematically at the bottom of the figure. Pattern D is the only one that is able to evoke a spike in the impaled cell. A sinusoid has been placed at the top of this figure to indicate where zero membrane potential would be for this neuron; time is indexed by the 20 Hz frequency of this sinusoid . (Reprinted by permission of Cambridge University Press.)

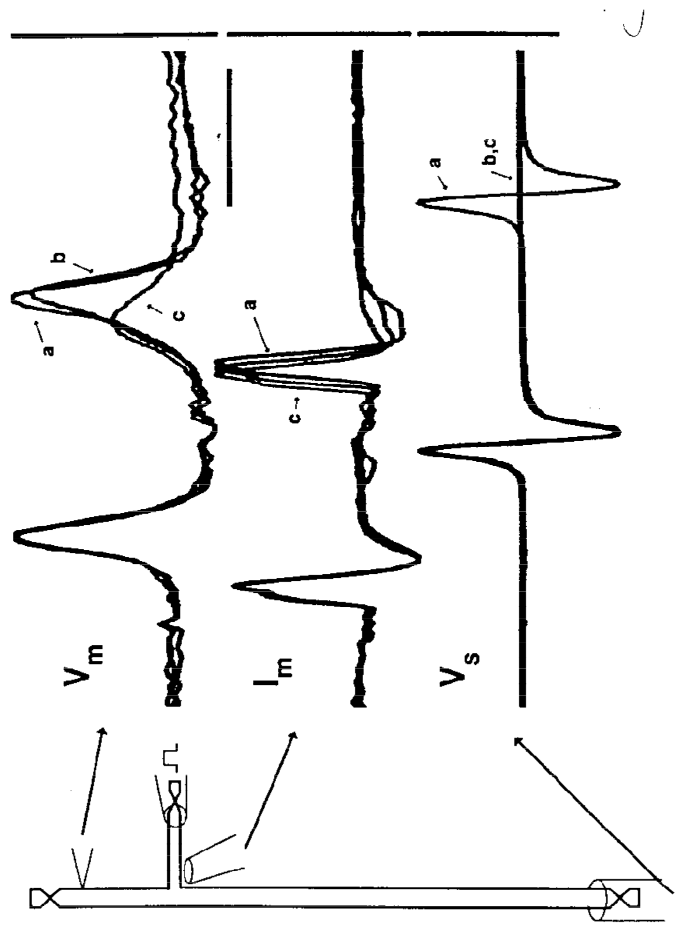

Fig. 11. (rotated 90°) Conversion of a temporal pattern of spikes in the input of a bifurcating axon into a spatial pattern of spikes in the daughter branches after the bifurcation [66]. The axon and its branches are schematically indicated at the left. Stimulation is applied to the input with a suction electrode and spikes are recorded extracellularly just prior to the bifurcation. Intracellular recordings of the spikes in the upper branch are made while those in the lower daughter are recorded with a suction electrode. Three sets of three superimposed traces on the right display the responses obtained at these locations at three different interspike intervals (ISI): a = 2.7 msec, b = 2.6 msec, and c = 2.5 msec. Note that spike propagation into the daughters fails at different ISIs, giving rise to a spatial variation. Calibration bars represent 70 mV in V_m, 1.25 μA in I_m, 20 mV in V_s, and 2 msec. (Reprinted by permission of the American Physiological Society.)

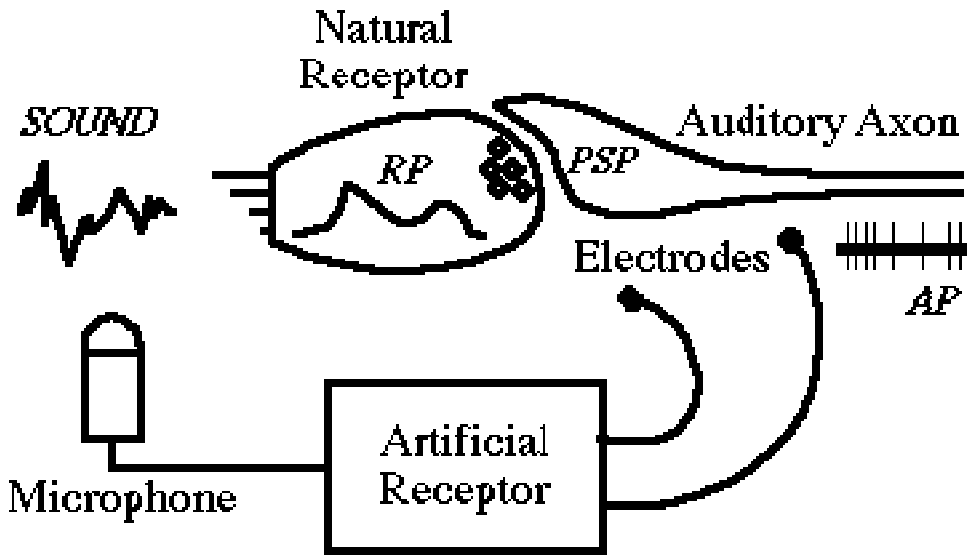

Fig. 12. Schematic display of one method that makes it possible to do experimental tests of theories of neural coding in human patients who have fitted with artificial receptors to overcome nerve deafness [74]. In natural hearing, sound is transduced into graded receptor potentials (RP) by the hair cells of the inner ear, which are first-order neurons. Graded postsynaptic potentials (PSP—not drawn here) are then produced in second-order neurons whose axons form the auditory nerve. The PSPs generate action potentials (AP) in these axons; these APs convey information to the brain. Artificial hearing, by contrast, is mediated by a surgically-installed cochlear implant. Such an artificial ear uses a microphone to record sound signals and it electrically stimulates the production of APs in auditory nerve fibers which lead to auditory perceptions. Hence the electronic portion of a cochlear implant is really an artificial neuron; it particularly is an artificial receptor cell. Variations in the sensory code used by this artificial neuron can be imposed and the effect of these variations on human perception can be studied. (Copyrighted 1992 by the IEEE Computer Society Press. Reprinted with permission of the publisher.)

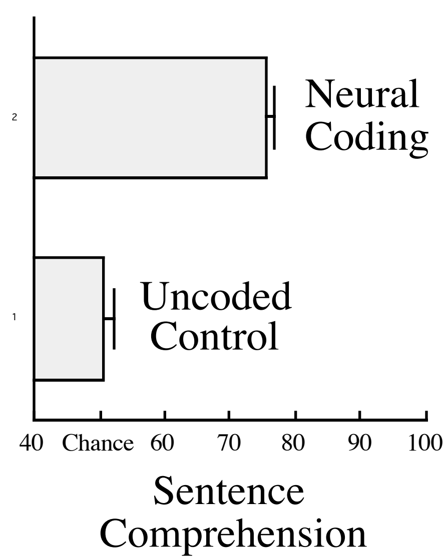

Fig. 13. Performance on a difficult sentence discrimination task by a patient fitted with a cochlear implant when sensory signals either are or are not processed by an algorithm that emulates a neuroreceptor cell. Data taken from [41, 71]. Error bars are 1 SE.

References

1 Adrian ED: The Basis of Sensation. London, Christophers, 1928.

2 Adrian ED: The Mechanism of Nervous Action. Philadelphia, University of Pennsylvania Press, 1932.

3 Adrian ED: The Physical Background of Perception. Oxford, Clarendon Press,1947.

4 Uttal WR: The Psychobiology of Mind. Hillsdale, New Jersey, Erlbaum, 1978.

5 Brazier MAB: The Electrical Activity of the Nervous System. London, Pitman, 1957, p. 111-119, Chap. 11.

6 Kandel ER, Schwartz, JH: Principles of Neural Science. Amsterdam, Elsevier North Holland, 1981, p. 23.

7 Aidley DJ: The Physiology of Excitable Cells. Cambridge, Cambridge University Press, 1971, Chap. 15.

8 Granit R: Receptors and Sensory Perception. New Haven, Yale University Press, 1955.

9 Svaetichin G: Supplement 134. Acta Physiologica Scandinavica 1956;39:1-112.

10 Hartline HK: The receptive fields of optic nerve fibers. American Journal of Physiology 1940;130:690-699.

11 Lettvin JY, Maturana HR, McCulloch WS, Pitts WH: What the frog's eye tells the frog's brain. Proceedings of the Institute of Radio Engineers 1959;47:1940-1951.

12 Hubel DH, Wiesel TN: Receptive fields of single neurones in the cat's striate cortex. Journal of Physiology 1959;148:574-591.

13 Hubel DH, Wiesel TN: Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. Journal of Physiology 1962;160:106-154.

14 Hubel DH, Wiesel TN: Receptive fields and functional architecture of monkey striate cortex. Journal of Physiology 1968;195:215-243.

15 Barlow HB: Single units and sensation: A neuron doctrine for perceptual psychology? Perception 1972;1:371-394.

16 Wasserman GS, Kong K-L: Illusory correlation of brightness enhancement and transients in the nervous system. Science 1974;184:911-913.

17 Wasserman GS: Time and duration: A persistent illusion. Perception and Psychophysics 1991; 50:603-604.

18 Granit R: Sensory Mechanisms of the Retina. New York, Hafner, 1947.

19 Wiesel TN, Hubel DH: Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. Journal of Neurophysiology 1966;29:1115-1156.

20 Granit R: The spectral properties of the visual receptors of the cat. Acta Physiologica Scandinavica 1943;5:219-229.

21 Wasserman GS: Color Vision. New York, Wiley, 1978.

22 Wiersma CAG, Adams RT: The influence of nerve impulse sequence on the contractions of different crustacean muscles. Physiologia Comparata et Oecologia 1950;2:20-33.

23 Brindley GS: Physiology of the Retina and Visual Pathway. Baltimore, Williams & Wilkins, 1960.

24 Teller DY: Linking propositions. Vision Research 1984;24:1233-1246.

25 Perkel DH, Bullock TH: Neural coding. Neurosciences Research Program Bulletin 1968;6:221-347.

26 Uttal WR: The Psychobiology of Sensory Coding. New York, Harper and Row, 1973.

27 Uttal WR: On some two-way barriers between models and mechanisms. Perception and Psychophysics 1990;48:188-203.

28 Chung S-H, Raymond SA, Lettvin JY: Multiple meaning in single visual units. Brain, Behavior, and Evolution 1970;3:72-101.

29 Science Citation Index. Philadelphia, Institute for Scientific Information.

30 Kuffler SW: Discharge patterns and functional organization of mammalian retina. Journal of Neurophysiology 1953;16:37-68.

31 Barlow HB: Summation and inhibition in the frog's retina. Journal of Physiology 1953;119:69-88.

32 Levine MW, Zimmerman RP: Evidence for local circuits within the receptive fields of retinal ganglion cells in goldfish. Visual Neuroscience 1988;1:377-385.

33 Cattaneo A, Maffei L, Morrone C: Patterns in the discharge of simple and complex visual cortical cells. Proceedings of the Royal Society of London 1981;212:279-297.

34 Richmond BJ, Optican LM, Gawne TJ: Neurons use multiple messages encoded in temporally modulated spike

trains to represent pictures; in Kulikowski, JJ, Dickenson, CM (eds): Seeing Contour and Colour. New York, Pergamon, 1989.

35 Richmond BJ, Optican LM, Spitzer H: Temporal encoding of two-dimensional patterns by single units in primary visual cortex: I. Stimulus-response relations. Journal of Neurophysiology 1990;64:351-369.

36 Richmond BJ, Optican LM: Temporal encoding of two-dimensional patterns by single units in primary visual cortex: II. Information transmission. Journal of Neurophysiology 1990;64:370-380.

37 Kong K-L, Wasserman GS: Two linear rules relate the latencies of visual responses to their critical durations. Sensory Processes 1978;2:1-8.

38 Kong K-L, Wasserman GS: Temporal summation in the receptor potentials of the *Limulus* lateral eye: Comparison between retinula and eccentric cells. Sensory Processes 1978;2:9-20.

39 Kong K-L, Wasserman GS: Changing response measures alters temporal summation in the receptor and spike potentials of the *Limulus* lateral eye. Sensory Processes 1978;2:21-31.

40 Wasserman GS: *Limulus* psychophysics: Temporal summation in the ventral eye. Journal of Experimental Psychology: General 1978;107:276-286.

41 Wasserman GS, Wang-Bennett LT, Miyamoto RT: Temporal dispersion in natural receptors and pattern discrimination mediated by artificial receptors (cochlear implants); in Geissler H-G, Müller MH, Prinz W (eds): Psychophysical Explorations of Mental Structure. Toronto, Hogrefe and Huber, 1990, ch 17, pp 211-227.

42 Barlow HB: Temporal and spatial summation in human vision at different background intensities. Journal of Physiology 1958;141:337-349.

43 Hunter WS, Sigler M: The span of visual discrimination as a function of time and intensity of stimulation. Journal of Experimental Psychology 1940;26:160-279.

44 Kahneman D: Time-intensity reciprocity under various conditions of adaptation and backward masking. Journal of Experimental Psychology 1966;71:543-549.

45 Kaswan J, Young S: Stimulus exposure time, brightness and spatial factors as determinants of visual perception. Journal of Experimental Psychology 1963;65:113-123.

46 Felsten G, Wasserman GS: The photoreceptor sensory code for pattern identification during visual masking. Sensory Processes 1979;3:230-239.

47 Felsten G, Wasserman GS: The photoreceptor sensory code for perceived duration during visual masking. Physiological Psychology 1981;9:68-76.

48 Haber RN, Standing L: Direct estimates of the apparent duration of a flash. Canadian Journal of Psychology 1970;24:216-229.

49 Kahneman D, Norman J: The time-intensity relation in visual perception as a function of observer's task. Journal of Experimental Psychology 1964;68:215-220.

50 Wasserman GS, Felsten G, Easland GS: The psychophysical function: Harmonizing Fechner and Stevens. Science 1979;204:85-87.

51 Wasserman GS, Wang-Bennett LT: Unity and diversity of neurelectric and psychophysical functions: The invariance question. Behavioral and Brain Sciences 1989;12:297-299.

52 Nisly SJ, Wasserman GS: Intensity dependence of perceived duration: Data, theories, and neural integration. Psychological Bulletin 1989;106:483-496.

53 Nisly S, Wasserman GS: Perceived duration, visual persistence, and neural integration. Perception and Psychophysics 1987;42:400-406.

54 Felsten G, Wasserman GS: Visual masking: Mechanisms and theories. Psychological Bulletin 1980;88:329-353.

55 Wang LT, Wasserman GS: Direct intracellular measurement of nonlinear postreceptor transfer functions in dark and light adaptation in Limulus. Brain Research 1985:328:41-50.

56 Bennett MVL, Pappas GD, Gimenez M, Nakajima Y: Physiology and ultrastructure of electrotonic junctions: II. Spinal and medullary electromotor nuclei in Mormyrid fish. Journal of Neurophysiology 1967;30:180-208.

57 Gillary HL, Kennedy D: Pattern generation in a crustacean motoneuron. Journal of Neurophysiology 1969;32:595-606.

58 Darian-Smith I, Johnson KO, Dykes R: "Cold" fiber population innervating palmar and digital skin of the monkey: Responses to cooling pulses. Journal of Neurophysiology 1973;36:325-346.

59 Strehler BL, Lestienne R: Evidence on precise time-coded symbols and memory of patterns in monkey cortical neuronal spike trains. Proceedings of the National Academy of Sciences, USA 1986;83:9812-9816.

60 Lestienne R, Strehler BL: Time structure and stimulus dependence of precisely replicating patterns present in monkey cortical neuronal spike trains. Brain Research 1987;437:214-238.

61 Gray CM, König P, Engel AK, Singer W: Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 1989;338:334-337.

62 Gray CM, Singer W: Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proceedings of the National Academy of Sciences USA 1989;86:1698-1702.

63 Singer, W: Response synchronization of cortical neurons: An epiphenomenon or a solution to the binding problem? IBRO News 1991;19:6-7.

64 Segundo JP, Moore GP, Stensaas LJ, Bullock TH: Sensitivity of neurones in *Aplysia* to temporal pattern of arriving impulses. Journal of Experimental Biology 1963;40:643-667.

65 Raymond SA, Lettvin JY: Aftereffects of activity in peripheral axons as a clue to nervous coding; in Waxman SG (ed): Physiology and Pathobiology of Axons. New York, Raven Press, 1978.

66 Stockbridge N, Stockbridge LL: Differential conduction at axonal bifurcations: I. Effect of electrotonic length. Journal of Neurophysiology 1988;59:1277-1285.

67 Stockbridge N: Differential conduction at axonal bifurcations. II. Theoretical basis. Journal of Neurophysiology 1988;59:1286-1295.

68 Stockbridge N: Theoretical response to trains of action potentials of a bifurcating axon with one short daughter branch. Biophysical Journal 1988;54:637-641.

69 Stockbridge N: Theoretical response of a bifurcating axon with a locally altered axial resistivity. Journal of Theoretical Biology 1989;137:339-354.

70 Bras H, Gogan P, Tyc-Dumon S: The dendrites of single brain-stem motoneurons intracellularly labelled with horseradish peroxidase in the cat. Morphological and electrical differences. Neuroscience 1987;22:947-970.

71 Wasserman GS, Miyamoto RT: A receptor-coded cochlear implant: Speech discrimination and comprehension results. Journal of the Acoustical Society of America 1987;82:S71 (abstract).

72 Wasserman GS, Miyamoto RT: Error analysis of cochlear implant consonant discriminations. Journal of the Acoustical Society of America 1988;84:S74 (abstract).

73 Schindler RA, Merzenich MM: Cochlear Implants. New York, Raven Press, 1985.

74 Wasserman GS, Berndt BA, Bresnahan BF: The Purdue artificial receptor; in Hazen PF (dir.): Proceedings of the Johns Hopkins National Search for Computing Applications to Assist Persons with Disabilities. Los Alamitos CA, IEEE Computer Society Press, 1992, pp 33-37.

75 Sellick PM: Recordings from single receptor cells in the mammalian cochlea. Trends in Neurosciences 1979;2:114-116.

76 Livingstone MS, Hubel DH: Effect of sleep and arousal on the processing of visual information in the cat. Nature 1981;291:554-561.

77 Butterworth JF, Raymond SA, Roscoe RF: Effects of halothane and enflurane on firing threshold of frog myelinated axons. Journal of Physiology 1989;411:493-516.

78 Raymond SA, Thalhammer JG, Popitz-Berger F, Strichartz GR: Changes in axonal impulse conduction correlate with sensory modality in primary afferent fibers in the rat. Brain Research 1990;526:318-321.