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A Code in the Nose

Our central notion about receptor cells in the nose of vertebrates and chemosensory structures of invertebrates is that every cell has a different ordering principle or point of view with respect to the space of odors. The olfactory system constructs a space of many dimensions (no more than the number of different cells) but with low resolution in any dimension. This is a somewhat novel way of looking at sensory receptor codes but hardly a new notion. Leibniz in his *Monadology* describes the universe with this sort of a construction. His monads are a particularly apt description of olfactory receptors and perhaps the entire nervous system. Only the word, "cell", need be substituted for "monad". (The optical hologram is a simple example of this sort of an integral transform also. Every point on the photographic record of the diffraction pattern contains information about the entire visual field. Each point looks at the visual field from a different viewpoint and with low resolution.)

The olfactory code is more complicated. It is non-linear. Responses to mixtures cannot be predicted from the separate responses to the elements of the mixture. Further, the response is strongly contingent upon the recent history of the activity of the cell. An example of the kinds of responses we obtain from a few cells follows. We feel that there is a particular relevance of this work to the many current efforts to build electronic models of sensory systems. Most of these efforts pointedly ignore

what are, in our view, the crucial principles of organization of biological sensory systems.

Direct evidence for the complexity of representation of sensory phenomena comes from the olfactory system. This is because we can record the signals from the axons of the receptor cells in response to physiological stimuli, and the cells have no interconnections, hence the signal in each cell is independent of the signals in others. We use a fine-tipped metal microelectrode to record activity from the axons which comprise the first nerve of the frog. The frog is pithed in such a way as to insure vigorous circulation and the only other surgical intervention is to remove part of the dorsal surface of the nasal cavity to expose the receptor surface.

The recording electrode external to the axons will often pick up signals from several cells which are sufficiently close to the tip. The activity of different cells can be separated (as long as only a few are near the tip) by observing the amplitudes of the action potentials. The cell most closely coupled to the electrode signals with the largest spike. In the case of the records shown in Figure 1, three spikes of clearly different amplitudes are distinguishable. Simultaneously we pick up the slow potential from the surface of the mucosa which represents activity of a large number of receptors and add this to the signal from the microelectrode. This produces the base line deflections which are indication of the odor stimulus. The spikes from the single cells are passed through an amplitude selector and brightening circuit in order to produce a reasonably clean display. Variations in the amplitudes of each of the three spike groups are due to the ever present noise of the electrodes. The procedure and instrumentation are described in detail elsewhere (Gesteland, *et al.*, 1965).

Traces of an experimental sequence are displayed in Figure 1. Odors were presented in the order shown and each odor puff lasted for about one second except as noted in the caption. Stimuli were never given more frequently than one a minute. The odor intensity was selected to produce a noticeable slow potential, i.e., about one millivolt. This would be called a weak odor by a human but strong enough to allow identification of the substance. Since the slow potential measures the activity of a large number of cells, appearance of a slow potential means that a significant fraction of the receptor cells are affected by the stimulus. Traces of cell activity in between odor puffs also appear in Figure 1 in order to indicate

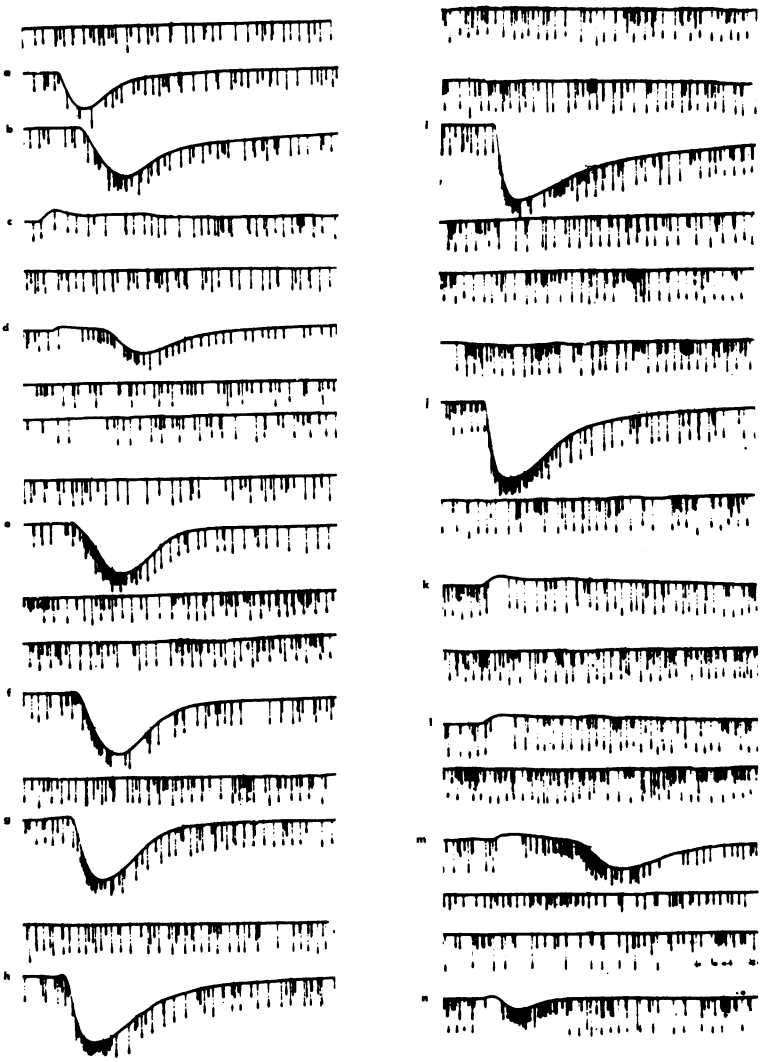

Fig. 1. Responses of single cells in an experimental sequence. Three cells can be distinguished by three different amplitude spikes. Each sweep is 10 seconds long and the base line is deflected to indicate the slow potential recorded with a gross electrode touching the mucosa surface. Lettered traces indicate stimulation with an odorous substance. Others show activity between stimuli. The odors were delivered in the sequence shown with at least one minute between stimuli. Puffs were of less than one second duration except as indicated. a. anisole; b. tetraethyltin; c. methanol; d. pyrrole (2 sec.); e. diethylaminoethanol; f. geraniol; g. limonene; h. menthol; i. camphor; j. menthone; k. methanol; l. methanol; m. pyrrole (4 sec.); and n. pyrrole ($\frac{1}{2}$ sec.).

aftereffects and background activity of the cells. Traces are ten seconds long.

If we look first at the cell whose responses are signalled by the spike with the largest amplitude we find the following behavior. This cell is almost inactive in the absence of a recently delivered odor. It fires once in the first trace and not at all in response to anisole, tetraethyltin, or methanol. It also does not fire at all during and about 20 seconds following a puff of pyrrole. Then begins a prolonged period of irregular activity with an average rate between one and two spikes per second. This now becomes the dominant mode of the cell and remains so for more than a half hour. It may be argued that the cell has been injured by the pyrrole but this seems unlikely since the activity of the other cells underwent no noticeable transition. The firing of this cell is then inhibited by diethylaminoethanol, geraniol, limonene, menthol, camphor, and menthone. There is only a short inhibition caused by methanol, a substance which inhibits firing in a majority of cells. The stimulus is repeated to demonstrate the identity of the response pattern for puffs of the same substance when these puffs are delivered in the same "odor context". There is a great difference between the responses to these two methanol puffs and the response to the puff delivered early in the sequence, before the cell was "turned-on" by pyrrole. The last two stimuli are both pyrrole, the second shorter and weaker than the first. Both are inhibiting, the first with a long aftereffect, the second lasting not much longer than the odor puff.

If we turn our attention to the cell whose response is signalled by the next-to-largest spike amplitude, we find a different ranking of stimuli and different interval patterns within the response. The cell is slightly inhibited by the first odor puff, anisole. It is not much affected by tetraethyltin, slightly inhibited during a puff of methanol and then excited following termination of the puff. It is strongly inhibited by pyrrole, slightly excited by diethylaminoethanol, geraniol, and limonene. Menthol has no effect. Camphor excites it and there are bursts of excitatory response following the puff. Menthone is also excitatory. Methanol is strongly exciting, starting late and lasting long after termination of the stimulus. Again this response repeats accurately in detail when the stimulus puff is repeated. These responses are much like the methanol response early in the series, in contradistinction to the first cell. Responses to pyrrole again demonstrate the importance of the odor context. The early

puff of pyrrole completely inhibited the medium-amplitude spike. The two puffs (long and short) delivered at the end of the series are transiently inhibitory, then strongly excitatory for the remainder of the puff period and for a few seconds following termination of the puff. There appears to be another period of excitation some 20 seconds later but we do not have enough record data to be very sure about the aftereffects in this case.

The cell signalled by the smallest spike also has its own private view of the odor world. Anisole does not affect it at the intensity used. Tetraethyltin excites the cell, methanol inhibits it. Pyrrole causes first, inhibition, then excitation, with the highest spike rate occurring near the peak of the slow potential following termination of the stimulus. Thence follow bursts of activity separated by quiet periods. The response to the two-second long odor puff lasts for minutes. Diethylaminoethanol, geraniol, limonene, menthol, camphor, and menthone all excite the cell. Methanol inhibits the cell during the puff. Turn-off of the odor causes the cell to fire at a rate considerably higher than its resting rate for at least 20 seconds. A second puff of methanol produces the same effect and this is not so different from the methanol response earlier in the series. Pyrrole also produces about the same response late in the series as it did earlier. The pattern preserved independent of odor duration.

We can summarize the results of many such experiments with the following statements (Lettvin and Gesteland, 1965):

1. Every fiber has an irregular base rate at which it fires in the absence of any introduced odor. The instantaneous rate, while varying over a fair range, tends to cluster around a rather low average of at best 1/sec., but usually much less. The fact that we have introduced no odor does not mean that the rate may not be governed by compounds emitted by the animal itself.
2. This noisy instantaneous base rate of firing can be increased (the fiber is exalted) by many compounds, decreased (the fiber is depressed) by many others, and slightly, if at all, affected by still many others. Exaltations and depressions may form a definite sequence when the receptor is exposed to a single odor, so that to characterize properly the response of a fiber we must talk of the sequence.
3. If, to simplify matters, we treat only the initial response as our significant measure, and then we can arrange all odors along a single

axis with respect to any single fiber, from those that exalt it most to those that depress it most.

4. If we have used, say, ten odors in studying a group of fibers seriatim, and for any nine such odors two fibers show the same ordering, it is unlikely that the tenth odor will have the same order position between the two fibers. Put in another way, we are saying that, given any set of stimuli that are ordered the same way by two fibers, it is easy to find an additional stimulus that discriminates the ordering done by the two fibers.
5. These ordering principles for any cell will only apply if the separate stimuli are delivered very far apart in time, since some cells will be affected for a long period following even weak stimulation with certain substances.
6. If we have the response of a fiber to one odor, and the response to another odor, then, whether the responses are different or the same, we cannot predict the response to a mixture of these odors, neither in

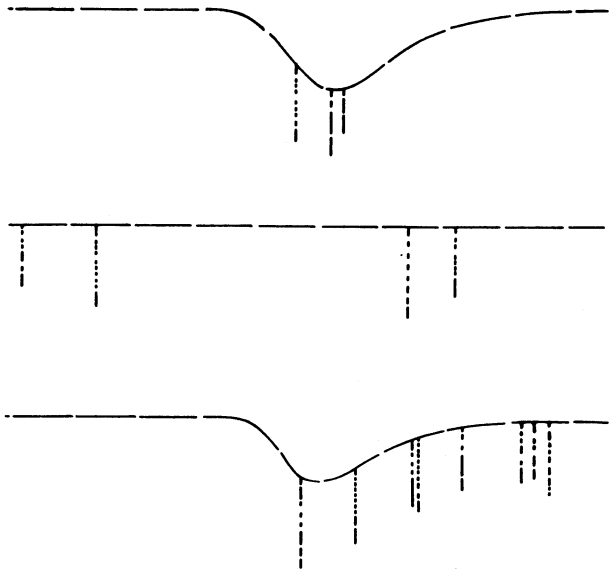

Fig. 2. Response of a single cell to *n*-butanol (top trace), musk xylene (center trace), and to both delivered simultaneously (lower trace).

magnitude nor direction. That is to say, we cannot tell that a fiber will be exalted by a combination of two odors that separately exalt it, or indifferent to a mixture of two odors that separately affect it little if at all. This is illustrated in Figure 2. Here the top trace shows a cell responding weakly to a puff of n-butanol. During the course of the second trace, a strong puff of musk xylene was delivered, producing no response. When the two stimuli are delivered simultaneously, several spikes in rapid succession are evoked.

These qualities that we have found in the olfactory fibers of the frog mirror those found in the "generalist" receptors of the bee by Schneider's group, and those in caterpillars by Dethier's group. When it is possible to say of the same sensory system that the same principles of encoding hold between so widely disparate animal types as bees, moths and frogs, we think it likely that these principles are quite general, and that the results reflect not so much a common incompetence of experimenters who fail to find specific receptors, but rather an unexpected yet legitimate mode of odor representation. The world of odor appears to the brain behind the nose as it is given in the fibers that communicate from nose to brain. There is no other pathway. If the information is given in terms as we just described, that is the informational system we must handle, and not some other that is confected out of odor theories and chosen because the structure is easily represented analytically.

What characterizes the response of an olfactory fiber is that it has a conspectus over the set of all possible odors with respect to which it utters a point of view that is not a measure in any ordinary sense. The most poignant case is when we see that the response to a mixture cannot be predicted well from the response to the components of the mixture given separately. Information so presented by a kind of integral transform is, in turn, unlikely to be handled by simple correlational methods that would only tend to smear, in this case, the resolution between odors. Unless one means by correlation what a judge does on weighing the testimonies of several witnesses, as opposed to what an instrument, marked "CORRELATOR", does on receiving sequences of numbers, we feel that correlation, as well as averaging, can be ruled out except in the first and most general sense. We have no idea how subsequent neurons higher in the nervous system are connected to accomplish this sort of correlation. Psychophysically we know that notions of groups occur and that a rose smells like a rose regardless of context. We should like

to suggest that congenital partial anosmias reflect defects in the second order fibers rather than in the primary receptors, purely by virtue of the sort of coding involved. Some people cannot smell cyanides, others cannot smell butyric acid, etc.; the anosmias being more "sharply tuned" than are receptor cells.

What we have found in the fibers of the olfactory nerve is, in a way, paradigmatic of what we find in most nervous elements. The form stands out most clearly when we handle a system like smell for which we do not have a preconceived mechanism in mind. If we address ourselves to a well-known system we find similarly complex codes in spite of our prejudice against such findings. We take the liberty here of pre-announcing without any supporting data some of the recent findings made by Humberto Maturana, Samy Frenk and two of us (S-H.C. and J.Y.L.) on the optic nerve of frog. From the contingencies crudely described in the original papers on the frog's eye, we were apparently unable to convince most readers of the difficulties in describing the action of even the simplest element in the optic nerve. (Lettvin, *et al.*, 1959.) It is clear that any second- or third-order neuron receives from many other neurons some inputs that inhibit and some that excite. Because of the asymmetrical nature of inhibition and excitation, one cannot sum inhibitors and excitors to explain the firing of the neuron. We may sketch the argument briefly thus: A subsynaptic excitatory patch acts, when it is activated, as a current activator locally introduced (i.e., Na^+-activation). It has an effect on the axon hillock (where firing originates) that depends upon its electrotonic distance from that hillock, for the nerve membrane over the cell and dendrites must be conceived as a nonlinear transmission line that, for small signals such as these, acts almost linearly. But, as Kuffler and Eyzaquirre showed (1955), an inhibitory subsynaptic patch when triggered does not act as a counter-current generator but rather as a shunt (K^+- or Cl^--activation) locally produced across the membrane so as to change the electronic characteristics of the membrane. Thus, the effects of combined excitation and inhibition in the dendrites as exerted upon the axon hillock depend as much upon the placement of excitors and inhibitors with respect to each other as on how many of them are active. One event, the excitatory one, where it occurs, is current generative into a nonlinear transmission line; the other, the inhibitory event, where it occurs, changes the distributed resistance in the line. From these facts alone and from knowledge of the complex anatomy of dendritic trees,

it ought to be possible to see, on a-prioristic grounds, that the transformation from input to output of a neuron is a difficult thing to conceive. We wanted to see what could be said at a minimum.

What we have found is this: any "dimming detector" axon fires at rates such that the intervals between pulses vary from about two milliseconds up to 2000 seconds. (This is significantly different from the rather narrow bandwidth of primary olfactory fibers in which the minimum pulse interval is approximately 100 milliseconds.) Within this dynamic range the firing fluctuates not only as a function of changes of light intensity and absolute light intensity upon the retina, but also according to the previous history of light. We presently have tracked reliably the effect of a bright flash for about two hours. A moving average of the pulse interval displays the measure of some of these parameters. But other functions, notably what we call "envelopes" on a continuous plot of pulse-interval against time, seem to measure not only different combinations of the same parameters but other variables not seen in the averaging. The facts that two or more different operations on the same time series of pulses yield different combinations of information and that some of the operations exclude some of the information while retaining the rest, suggested to us that the fiber was doing a kind of time-sharing multiplexing of the various kinds of information coming to it. We think that the meaning of a pulse interval is not negligible and that its signifficance with respect to the variables being transformed depends on context. Possibly the only analogy we can give here is what would happen if we were to take a similar display of intervals between baseline crossings in uttered speech plotted against time. Here the resulting dot figure would show different preferred interval regions at different times, and these would represent sum- and difference-frequencies, or formant modulations by pitch, as kinds of dotted lines. Such a line we call an envelope. Similar lines, clusterings, tendencies, occur in the firing pattern of the dimming detector, and they change in different ways between themselves according to the different kinds and different sequences of lighting. We are now able to track some of the parameters. It is as if one had a nonlinear oscillator with a kind of distributed control over all the coefficients of the higher order terms that are involved in describing the action of the element. It may be argued that our ability to recover information from a nerve fiber is no guarantee that the information is used by subsequent neurons. Our only reply is that, given the nature of

nervous connectivity, how does one decide what of the information to exclude? Indeed, there is a kind of impiety in holding that information is preserved up to a certain point and then ignored. For to what end would the element be so devised as to waste itself on resolvable ambiguity, frittering away its time with meaningless utterances?

Thus the neuron has a complex point of view and the categories in which it deals are not those that obviously fit the usual simple, time-invariant perceptual models based upon sensory experiences and mathematical conveniences.

ACKNOWLEDGMENT

This work was supported in part by the Bell Telephone Laboratories, Inc. and by the Aerospace Medical Research Laboratories, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio, under Contract AF 33(615)-3885. Dr. Gesteland is supported in part through the National Institutes of Health, Contract Fr-00018-03. Further reproduction is authorized to satisfy needs of the U.S. Government.

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