XIV. NEUROPHYSIOLOGY*

W. S. McCulloch
F. S. Axelrod
H. A. Baldwin
M. Blum
S. Frenk
R. C. Gesteland
M. C. Goodall
B. Howland
W. L. Kilmer
K. Kornacker
J. Y. Lettvin
Diane Major
L. M. Mendell
Barbara C. Pickard
W. F. Pickard
W. H. Pitts
G. Szekely
A. Taub
P. D. Wall
Barbara G. Wickelgren

A. TOWARD A THEORY OF THE RETICULAR FORMATION†

Throughout the life of the vertebrates, the core of the central nervous system, sometimes called the reticular formation, has retained the power to commit the whole animal to one mode of behavior rather than another. Its anatomy, or wiring diagram, is fairly well known, but thus far no theory of its circuit action has been proposed which could possibly account for its known performance. Its basic structure is that of a string of similar modules, wide but shallow in computation everywhere, and connected not merely from module to adjacent module, but by long jumpers between distant modules. Analysis of its circuit actions, heretofore proposed in terms of finite automata or coupled nonlinear oscillators, has failed. We propose probabilistic automata that handle regular events as proper modules. The behavior of a connected chain of such modules is still under investigation.

Work continues on a precise formulation of the reticular formation model, which will be programmed on a large digital computer during the next quarter.

W. L. Kilmer, W. S. McCulloch

B. A GENERAL THEORY OF OBSERVATION AND CONTROL‡

This reporting period was occupied with heuristic considerations concerning models and representations. The object of the former was to secure realistic assumptions, in particular, the finiteness of channel capacity for continuous channels. In the latter part, the aim has been to connect representations with various formalized languages. Considered together, these approaches have notably helped to bridge the gap between the metrical (probabilistic) and the logical (language) aspects of two-way communication

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between the observer O and a universe U.

1. Models

A nonrelativistic quantum-mechanical N-particle system, with states Σ, in interaction with the electromagnetic (EM) field can be taken as a model in which the input is the EM potential A and the output signal is the particle current J. Such a system can be characterized as a probabilistic automaton in which the next-state and output functions

$$\Sigma' \rightarrow (A, \Sigma)$$

$$J \rightarrow (A, \Sigma)$$

are given implicitly by the wave equation and projection operators, respectively. Such a characterization shows:

(a) For finite channel capacity, all three objects (A, Σ, J) must be quantized fields.

(b) For the same reason, there must be finite bandwidth, hence the restriction in general to the nonrelativistic formalism.

(c) Finding the operator conjugate to the input is an essential step in determining the next-state function. (Because of the preferred role of time, this is the energy conjugate.) The functions themselves appear in the theory as Green's functions (propagators).

(d) The assumption of finiteness suggests approximation by finite probabilistic automata (e.g., discrete finite memory channels) as a fruitful approach.

2. Representations

The object here, in conformity with conclusion (d), is to represent the current history of the channels as a finite structure with conditional probabilities attached. An element of such a representation is a triad, A, R, S (axioms, rules, signals), where S is to be considered as generated by application of R to A. Such elements can be built into a graph G with A's as nodes and R's as connections, where A' is connected to A if it is in the equivalence class $\{A\}_R$. A path ARA'R'... in G represents a signal S^* that is received when A, A', ... (punctuating the null signal) is sent, in the sense that R, R', ... generate the best approximation to S^* in the segments between the A's. A primitive decision theory for the probability $\Pr(R/A, S^*)$ has been given elsewhere.[1] For $\Pr(A'/R, S^*)$ one needs arguments of a higher logical type, that is, equivalence classes $\{R\}_{\mathfrak{R}}$ under some super rule $\mathfrak{R}$.

3. Relation between Model and Representation

A continuous signal segment $A(t, t')$ can be quantized without loss of information (this is essentially a sample data process) thereby giving a discrete version A. In the model, $A(t, t')$ determined a transformation of the internal state Σ and thus the output $J(t)$, which

can also be quantized as a signal S^*. Although there are problems about how this conversion should be made, the possibility of a correspondence here shows that the role of the model should be that of formalizing a decision procedure for Σ. In particular, it shows that models corresponding to open systems in which the particle number N is not conserved will have to be considered.

4. Application to Relativistic Quantum Theory (RQM)

The present theory is known not to be consistent. According to the point of view taken here, it should occupy a unique place among all theories of observation and control. This makes it possible to characterize much more sharply a conjecture previously based on group-theoretic considerations[2]; namely, RQM is characterized by a three-way symmetry between input, output, and state spaces. This 'principle of triality' is known to be associated with certain exceptional continuous transformation groups, in effect, with those that are automorphisms of the octonion plane.[3] A paper on this subject, entitled "Causality, Measurement, Mach's Principle," is in preparation.

5. Problem of Higher Functions in the Brain

A paper with this title was given at the International Biophysics Congress, in Paris, June 24-27, 1964. Three points were emphasized: (i) the necessity of acquiring universal algorithms; (ii) the use of redundancy as a learning mechanism; (iii) the possible role of RNA in the block coding of memory.

M. C. Goodall

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C. RESULTS OF BIOLOGICAL TESTS WITH La^{+++}

In Quarterly Progress Report No. 73 (pages 204-208), we presented the introduction to a new theory of passive ionic fluxes through nerve membrane. The theory has not been submitted to extensive tests, but several predictions have been verified in detail.

1. La^{+++} was expected to act as a super Ca^{++}, binding itself coulombically to the surface of the membrane and neither penetrating nor dislodging to allow other ions to penetrate. In fact it does block nerve membrane quite reversibly in such a way that no

significant cation current can be forced through the membrane. This work was done with Dr. John Moore and Dr. M. Takata at Duke University. A paper describing this research is now in manuscript.

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2. It has been proposed that La^{+++} can replace Ca^{++} on the outer surface of the cell membrane and other closed structures. We have studied the possibility of using La^{+++} as a stain in electron microscopy. Lobster and crayfish nerves have been incubated in $La(NO_3)_3$ and postfixed in gluteraldehyde. A dense band appeared along the outer surface of the membranes.

We synthesized $La(MnO_4)_3$ and used it as a fixative. Material fixed in balanced solutions of this salt differs remarkably from the specimens fixed in $KMnO_4$. The gap substance between unmyelinated axons appears densely stained in crayfish and lobster. A similar staining occurs in the optic fibers of the retina of the frog. The intraperiod line of myelin of the frog sciatic and mouse optic axons is heavily stained.

The space between membranes of the retinal rod outer segment also appears densely stained alternately, as is expected from the folding membrane model. We also suspect that La^{+++} replaces Ca^{++} on the neuraminic acid groups attached to membrane, as well as other ground substances, stabilizing as well as staining them.

This work was done in collaboration with Dr. C. Doggenweiler and Dr. J. D. Robertson at McLean Hospital, Belmont, Massachusetts.

S. Frenk, J. Y. Lettvin, W. F. Pickard

D. RESULTS OF BIOLOGICAL TESTS WITH Cs^+ AND Rb^+

Our insistence that it is the shape, as well as the size and charge of an ion, that determines passage through the nerve membrane led us to compare Cs^+ and Rb^+ with the other alkali cations. Rb^+, for reasons given in Quarterly Progress Report No. 73 (pages 204-208), ought to act as K^+. But Cs^+, having no water of hydration and having the same mobilities in solution and the same interaction radius as hydrated K^+, should not supplant either Na^+ or K^+ in the membrane because it has too rigid a morphe. This prediction was borne out in voltage-clamp experiments on squid axon carried out at Woods Hole, again in collaboration with Dr. John Moore and his co-workers from Duke University. A paper concerning this work will be published in the Proceedings of the National Academy of Sciences.

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E. EXTENSION OF THE MEMBRANE HYPOTHESIS

The membrane hypothesis permits of further, and very drastic extension. The notion that to pass the membrane a molecule must first fit into the lattice of the membrane,

thereby becoming an integral part of it, suggested to us that we ought to consider the equivalence of plastic flow and deformation in the cell membrane. That is, we asked ourselves whether in a two-dimensional lattice there ought to be the equivalent of domain propagation and deformation spread as in the classical cases handled by Bragg. Indeed, it seemed to us that the ionic movements, particularly of Ca^{++}, off and on to the laminar micelle ought to be accompanied by mechanical change. In Quarterly Progress Report No. 64 (page 291) we reported (in collaboration with Dr. Sten-Knudsen) that a twitch of a nerve fiber occurred during the rising phase of a nerve spike. At that time we tried to think of a mechanism for this phenomenon and were unsatisfied with the notion that it was a change in bulk of the axon because of the entry of water with Na^{+}. According to our present notions such a change would be expected when Ca^{++} leaves the membrane on its inner surface. This led us to the notion that a lattice distortion at a point might cause a propagating disturbance throughout the rest of the lattice. We searched for experimental evidence to support this hypothesis and found the following:

1. The Drs. Levinthal informed us that a single molecule of K-colicine turns off all of the oxidative phosphorylation in a single E. Coli when it is adsorbed to the outer surface. If the molecule is washed off, the oxidative phosphorylation returns.

2. A single molecule of botulinus toxin turns off the ability of a nerve terminus to liberate acetylcholine.

3. If a muscle is denervated, the sensitivity to acetylcholine, which is normally specific to the end plate, begins to spread away from the end-plate region until at the end of a few weeks the whole muscle membrane is sensitive to this compound. If the nerve regenerates, the muscle fiber again becomes sensitive to acetylcholine only at the end plate.

4. The entrance of a sperm cell into an ovum, as in Arbacia, causes the membrane forthwith to become impenetrable to other sperm. Touching the egg with a needle produces the same effect.

It is repulsive to think that the action of a K-colicine or of a botulinus toxin molecule is due to its being able to act at a distance. Equally repulsive is the notion that the molecule attracts to itself those parts of the substrate that would ordinarily be fluxing this way and that way through the membrane. An alternative suggestion is that the change of some local process by the adsorbed particle produces a regenerative change that spreads into contiguous regions and so affects that process everywhere. Because of these observations, we think that the surficial spread of defects and distortions over a membrane is consistent with its being as ordered as it appears to be in the electron microscope.

We would expect several types of domain propagation.

1. The setting up of local strain in the membrane lattice, or the relieving of such a strain, institutes a progressive self-powered change at all other points in the membrane. For example, consider the ability of a red blood cell to break and disappear

completely in less than 10 msec, and the behavior of the Arbacia egg.

2. A local change causes adjacent regions to change, but the effect decreases with distance from the local change. For example, the effects of heavy metal ions on a unit membrane are primarily local.

3. A local change in some particular process causes that process and only that process to change everywhere in the membrane. This is similar to a skip propagation for a group of processes of one type. For example, note the action of K-colicine and of botulinus toxin.

If paucimolecular cases are considered instead of monomolecular cases, how is the bulk of neuropharmacology to be explained? Trivially small concentrations of certain toxins and drugs cause enormous changes in nervous behavior. Thus, a small dose of strychnine will kill a man, although it is many orders of magnitude less in concentration than any of the ions or nutrients of the cell. The dose is not metabolized and cannot be supposed to act in competition with ions or nutrients everywhere. At the same time, it has little effect on the various enzyme systems. Indeed, what happens seems to be that the membrane potential, the after-potentials, and the resting impedance of nerve are changed.[1,2] Its poisonous action is attributable solely to these minute shifts. Yet strychnine is in more or less equal concentration throughout the body of a poisoned man. If it acted by virtue of affecting ion passage only by competition, there would not be enough of it to account for the changes observed, if ionic channels were utterly independent of each other everywhere and under all circumstances. Thus we conceive that the essence of explaining the whole corpus of present inexplicable neuropharmacology lies in the realm of showing domain propagation along the membrane arising from drugs on the membrane. At the extremes, we have one botulinus toxin molecule affecting all of a certain sort of microstructure in a cell, and one procaine molecule affecting only its most immediate neighborhood.

This concept also enters importantly into that most difficult of fields – embryology.

The present deplorable micro-Lamarckian tendency (à la Hyden) is to suppose that what occurs in one portion of a cell is somehow transmogrified into a change in RNA structure, which replicating industriously, transmits its information to change another part of the cell. How much more elegant it is to suppose that the very membrane of the cell is, in a sense, its nervous system, whereby influences from various points produce fields spreading over the surface, so as to transmit and combine information. In this case, instead of two mysterious transformations (from the cell structure to RNA code and from RNA code back to cell structure) we have only one, the lateral propagation of influences along a membrane.

J. Y. Lettvin, W. F. Pickard

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F. OLFACTORY PROCESSES

The work on olfactory processes has yielded an extraordinarily varied set of results. Several interactions are observable between electro-olfactograms. We have contrived a single model that explains these interactions and the activity of the single fiber of the olfactory nerve.

We can distinguish two classes of ions by their relation to the membrane potential. One class consists of those species whose chemical potential across the membrane is close to the membrane potential, that is, those whose activity is in the ratio predicted from the measurement of free energy differences across the membrane. The other class consists of those ions whose chemical potential across the membrane is far from that predicted by the membrane potential, that is, the Donnan equilibrium does not apply to these. The first class we call "equilibrium ions" or "shunt species." If we increase the ease with which these ions can cross the membrane, the membrane potential will be little affected, a small net current will flow, and every part of the membrane will be increasingly decoupled from every other part. If any current flows through the membrane, it will flow preferentially through points where this ion species can flow. The second class we call "nonequilibrium ions" or "current-generating species." If we increase the ease with which these ions cross the membrane, current will be generated because the ions will be flowing down a large electrochemical gradient that differs from the membrane potential. The variational resistivity of the membrane changes in the same way as it does for the shunt-species case. Thus the effect of a decrease in resistivity to the current-generating species of ion is also a shunting, but it is accompanied by a current flow. We propose that these two processes occur at receptor sites on the cells of the olfactory mucosa. An odorous stimulus increases the ease with which either class of ions, or both, can move through the membrane. A signal is generated in the olfactory receptor axon if a large enough change in current flow through the axon hillock occurs.

We consider a sheet of densely packed receptor cells with sensitive sites on the input end sticking up into a mucus layer of high conductivity and with axons projecting through the membrane at the bottom around the edges to the mucus on top. We measure the voltage change between the top and bottom of the sheet caused by changes in current

flowing as a result of odors arriving at appropriate receptor sites. We choose the polarity so that increased flow of the current-generating species ion causes a negative voltage transient. A particular receptor cell site can respond several possible ways to odors:

1. It can do nothing.
2. Its permeability to the current-generating species can increase.
3. Its permeability to the shunt species can increase.
4. Its permeability to both current-generating and shunt species can increase.

Consider the patterns of the measured voltages that can be obtained when we have a mucosa made up of receptor cells which can have sites of more than one type under the following assumptions. Each receptor cell must have a relatively small number of receptor sites. Every site that can gate the current-generating species must look like every other electrically, as seen from the axon hillock. The same must also be true for every shunt-species site. The surface resistivity of the epithelium must be low compared with the bulk resistivity of the sheet so that external currents generated by a cell have a space constant large compared with a cell diameter. The excitement of the tissue by an odor will generate extracellular currents flowing between mucus and basement membrane which combined result in an IR drop that is our measured signal. Qualitatively, these voltages can be predicted for the limit conditions:

(a) Let all sites gate the current-generating ionic species; that is, any odor causes the current-generating species ion to flow at a site or has no effect.

The external current flow will increase linearly for increases of odor strength at low concentrations, but at high concentrations will asymptotically approach the limit current acquired when all sites are occupied. Thus there will be additivity for the effects of two puffs of smell at low concentration and occlusion between the effects at high concentration.

(b) Let all sites gate the shunting ionic species; that is, any odor opens the membrane to the shunt-species ion or has no effect.

The phenomena in this case are the same as in (a) but of opposite polarity and much smaller because the resting potential of the membrane is close to the potential of the shunt species.

(c) Let there be two types of cells, one with sites of the current-generating species sensitive to an odor, and the other with shunt-species sites sensitive to the odor.

The voltage transients from stimulating with two odor puffs would add algebraically and be of opposite polarities, the wave from the current-generating species being large and negative, that from the shunting species being small and positive.

(d) Let both types of sites exist on the same cell.

In this case the effect that is due to one type of site activity will be attenuated by activity at the other type of site. Thus if, during an odor causing the voltage swing that is typical of the current-generating species, an odor is delivered which excites the

shunt-species sites on the same cell, there will be a local short circuit, and much of the current from one site will flow back into the cell at the other site rather than through the long external path to the axon hillock. This phenomenon is parallel to the electrical signs of synaptic inhibition seen elsewhere in the nervous system.

The model that we propose, then, allows six possible conditions:

For two stimuli – if both gate the current-generating sites

(i) negative transients add.

(ii) negative transients occlude.

For two stimuli – if both gate the shunt sites

(iii) positive transients add.

(iv) positive transients occlude.

For two stimuli – if they evoke signals of the opposite sign

(v) the negative and positive transients add.

(vi) the negative and positive transients attenuate.each other.

In a series of studies of the electro-olfactograms of the frog's nose obtained with multiple odor stimulation, we have been able to demonstrate each of the six phenomena listed and can find no case that is not included in the list. We suggest that our model is in fact a description of the mechanism by which odorous substances signal their presence at olfactory receptor endings.

In an attempt to verify this model we measured impedance changes across the mucosa caused by an odor. We found an interesting complication. If the measurement is made at low frequencies, that is, near 2 cps, the impedance follows the course predicted by our theory for the slow transients. We have not yet succeeded in devising a scheme for resolving the impedance changes during the faster, positive-going transients because the time course of the phenomena is about the same as the duration of the measuring signal. When we go to the higher frequencies (~25 cps), we measure a most surprising reactance change in the direction opposite to the change in low-frequency impedance and much larger in magnitude. We are now trying to find the cause of this apparent reactance increase, and to resolve the change in resistance during the short positive transient.

R. C. Gesteland, J. Y. Lettvin

G. ENTOPTIC PHENOMENA AND VISUAL ILLUSIONS

Entoptic phenomena are elegantly described and explained by Helmholtz in his Physiological Optics (Chapter 50). They have not been put to very much use, although they form a rather simple way to show most modern visual psychological problems.

1. Purkinje tree. This is the shadow cast on the retina by its own blood vessels. Since any image cast on the retina is shaded by these vessels and the aperture of the

pupil is not large enough to blur them, the question naturally arises, Why we don't see them ubiquitously? The answer is rather simple, we don't and we do. Since these vessels form a fixed image on the retina with respect to the retina, they are not to be seen, since stabilized images disappear. They do form a distributed blind spot in every respect similar to the blind spot where the optic nerve enters the eye, and produce effects very similar to those given by the latter. For example, if you cause a small black disc to pass over the visual field where the optic nerve entrance causes a hiatus, the disc disappears and then reappears. From this you infer that you have a blind spot. In a very similar way edges obscured by the shadow of a blood vessel undergo a sort of wavering that is quite distinctive. Two optical illusions can be used to show this. The simplest one is that given by ordinary extended checkerboard pattern. If you look at the very center of the pattern for a while, you will notice a kind of wavering of checks several degrees in the periphery both above and below your center of gaze. This is particularly marked with strongly colored checks. A more complex one is the illusion given by McKay of the apparent rotation at the periphery of a strongly detailed radial pattern. When you have achieved the seeing of these jitterings you can superpose upon the image in front of you the pattern of the blood vessels in your eye by illuminating through your eyelid and at the orbital margin with a constantly moving source of light, for example, the head of a pencil flashlight held against the orbital margin. Then you will see that the wavering is in fact a sort of constantly moving moiré pattern formed by the interaction of the blood vessels with the image projected into the retina. An interesting subsidiary exercise is to close your eyes and get the image of the blood vessels alone. Then, if you use two pencil flashlights, one above the eye and one below, and turn them on and off alternately, you will see that only the horizontal branches of the tree are clear. On the other hand, if you illuminate alternately the inner and outer corners of the eye, only the vertical branches appear. No more elegant demonstration exists to show how eye movements ordinarily enhance those image boundaries that are orthogonal to the movements. Helmholtz has a lovely description of this particular phenomenon.

2. If you use a cold light source of high intensity such as is obtained by interposing a glass rod with a rounded end between the light and your eye (or alternatively a flexible light pipe) and then move the light about on the rim of your closed eye so as to see the Purkinje tree, you will notice that the tree moves in the direction of the light, as it is expected to if it is due to the shadow of blood vessels. Looking ahead into the far distance of the scene evoked in this way, you see that the tree is moving against a reddish background in the center of which, that is, in the direction of your gaze, there is a pebbly patch the very center of which either moves not at all or in the opposite direction to the Purkinje tree. It is as if you are looking into a valley, keeping your eyes fixed at the bottom and moving from side to side. This area (first noted by Purkinje and properly called "shagreen-like" by Helmholtz) is the shadow of irregularities on the surface of

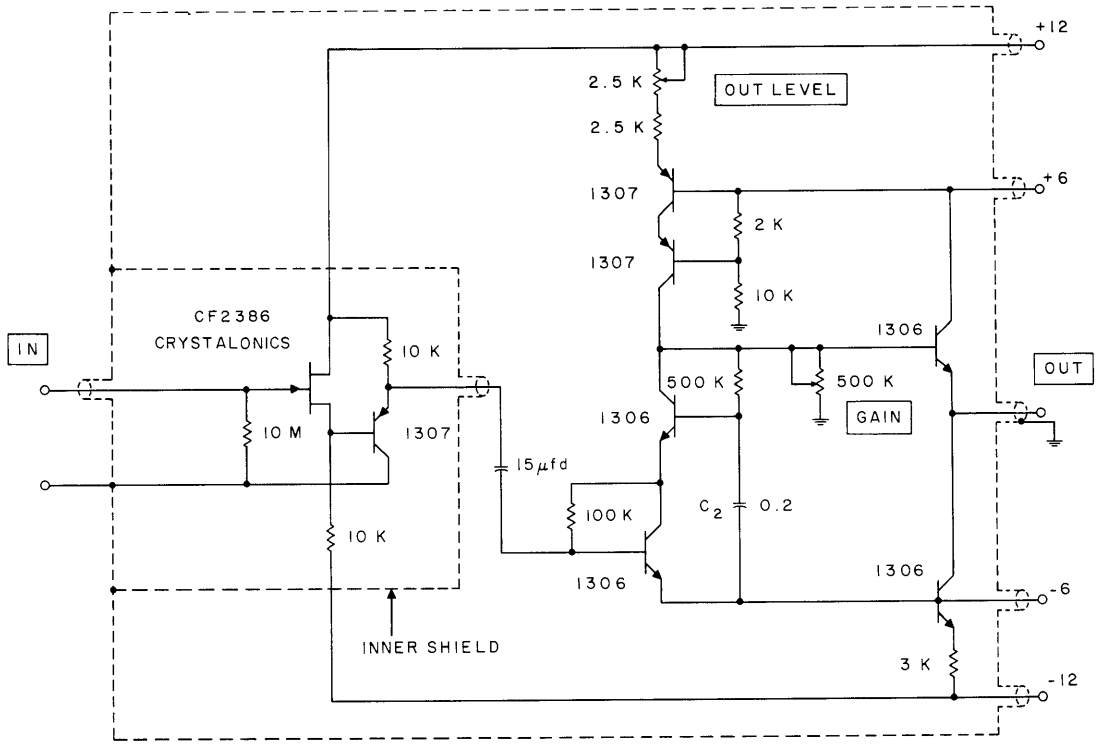
your fovea cast upon the cones beneath and highlights; and shadows arise because of enhancement by the Stiles-Crawford effect. Now, you might think that this is only a curiosity, but very quickly it can be shown that it is not trivial. For, if you look at McKay's radial figure again, and note the constant seeming movement of the center where you look at it and, in a way similar to projecting the Purkinje tree, project this foveal pattern onto McKay's figure, again you will see that that apparent rotation arises as a moiré pattern of interaction between the foveal structure and the image.

3. A very ambitious but rewarding amusement is to train yourself to draw a part of the Purkinje tree on a sheet of paper upon which there is a point of fixation. For, then you can quickly satisfy yourself that those few sketched lines vanish and reappear when you gaze at the fixation point. A more extended discussion of entoptic studies is being prepared for publication.

J. Y. Lettvin

H. PHYSIOLOGICAL AMPLIFIER

Figure XIV-1 shows a very inexpensive AC coupled amplifier for use with high-impedance metal microelectrodes. It is novel in that there is only one stage of gain,



C_2 determines low-frequency cutoff.
The first stage must be completely shielded to get good high-frequency response.

Fig. XIV-1. Physiological amplifier circuit.

and the gain is variable from 0 to 10,000 continuously. It has a flat band from approximately 20 cycles to 20 kc at full gain, and the bandwidth increases as the gain is lowered.

J. Y. Lettvin