THE CHARACTERISTICS AND THE IMPLICATIONS OF ELECTRICAL ACTIVITY WITHIN THE NERVOUS SYSTEM

by

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CONTENTS

Appendix: Reprints of personal publications, and of publications reporting other work which was facilitated by the work described here.

PREFACE

Many of the characteristica of the electrical activity of the nervous system can be studied by amplifying and recording fluctuations in electrical potential which are associated with the activity and are known as action potentials. In some cases, implications of the activity can be deduced from the study of the action potentials, especially when the electrical activity is in response to controlled stimulation of a sense-organ by light, sound, deformation, etc.. Another way in which the implications may be studied is by producing electrical activity in some part of the nervous system by electrical stimulation, and observing responses such as muscle twitches, or electrical activity evoked elsewhere in the nervous system. The two main methods of investigation, then, are the electrical excitation of nerve, and the amplification and recording of action potentials.

In Part 1, mathematical theory and experimental findings are presented which relate to the first of these methods, the electrical excitation of nerve. Part 2 illustrates the other method of investigation, for it is an account of a study of the electrical activity of a part of the nervous system of the frog, by the amplification and recording of action potentials.

In Parts 3, 4 and 5, three different methods are discussed for the analysis and interpretation of observations on the electrical activity of the nervous system. Part 3 is a discussion of the applications of Information Theory to Neurophysiology, with an original contribution to the mathematical theory by which the maximum information-carrying capacity of a nerve fibre can be estimated. Since the function of the nervous system is to convey information, it is reasonable to suppose that Information Theory might be of value in trying to understand the working of the system. In actual fact, Information Theory has proved much less fruitful than most people expected, both in its applications to biology and in its applications to artificial communication systems. Its possible applications to the nervous system have not been exhausted, however, as will be seen from the discussion in Part 3.

In Parts 4 and 5, further methods for the analysis and interpretation of experimental observations are discussed. These methods are of a more empirical nature than the applications of Information Theory discussed in Part 3. Observations of electrical phenomena associated with nervous activity can be divided into three main types. Part 4 contains contributions to the development of techniques for the analysis of observations of one of these types; Part 5 is a description of methods of analysis of another of the types. The analysis of observations of the third type is not discussed here because I have made no contribution to it, and it has received a great deal of attention elsewhere.

The three categories of observations are as follows :-

(a) Records from electrodes which are not in contact with the nervous tissue. Records of this sort are obtained in electroencephalography (EEG) in which the recording electrodes are placed on the intact head of a human subject. One of the great advantages of the EEG over other methods for examination of the brain is that the EEG involves no surgical interference with the subject. The usefulness of the method is however limited by the fact that only the potential field at the surface of the volume conductor formed by the head is accessible for examination. Part 4 is a discussion of the applicability of electrical potential theory to the interpretation of EEG records, and a solution of a problem in potential theory which has a bearing on EEG interpretation.

(b) Records from electrodes which are intimately associated with nervous tissue in such a way that the record consists of a series of brief pulses ("action-potential spikes") due to the activity of a single nerve-cell (or a single nerve-fibre, which is part of a nerve-cell). Part 5 deals with methods for the analysis of records of this sort, and particularly with methods for drawing the graph of impulse-frequency against time without the need for tedious measurements from the photographic records of the action-potentials.

(c) Records from electrodes which are in contact, or nearly in contact, with nervous tissue, but which are influenced by the activity of a large number of nerve cells. Methods for the analysis of these records are not discussed in detail here, though brief mention is made in Part 4 of a method which was devised by Pitts, and applied by the research group headed by Dr. Warren McCulloch to the analysis of records from electrodes inserted in the spinal cord of the cat.

In Parts 6, 7 and 8, the design of apparatus for the investigation of the electrical activity of the nervous system is discussed. These sections are partly devoted to the description of items of apparatus which have been developed and used in the Physiology Department. They also contain a number of contributions to the theory of design of electronic apparatus, of which the most significant is perhaps the section on the design of difference-amplifiers in Part 6.

It will be clear from the list of contents that I have been particularly interested in applications of physics, mathematics and electronics to physiology. This is appropriate, since the study of physiology must always depend on an understanding of physical principles, and modern neurophysiology depends almost completely on electronic techniques. Nevertheless, I should perhaps explain that my experience and training, before embarking on the work herein described, were as a physicist with a particular interest in electronics. My degree is in Natural Philosophy and Mathematics, and before graduating I was employed in the Radio Dept. of the Royal Aircraft Establishment for 18 months, and with Messrs. Welwyn Electrical Laboratories, Ltd. for a further period of 18 months. My decision to work on physiology after graduating was largely due to a desire to help to advance medical science - a desire which was vague and idealistic then, but whose consequences I certainly do not regret.

The largest piece of work I have carried out on a purely physiological problem is reported in Part 2. This work was carried out while I was spending 18 months in the Massachusetts Institute of Technology at the invitation of Dr. Warren McCulloch. During that time I was able to give my whole attention to the problem, since matters of apparatus design or mathematical theory were handled by other members of the McCulloch group. While in Glasgow I was never able to ignore questions of apparatus design for long. In fact, I never really wished to be able to ignore tham, since electronics is one of my primary interests. Nevertheless, it was very valuable to me to be able to concentrate, for a time, on a purely physiological problem. I intend to continue with the investigations which were begun while I was with Dr. McCulloch's group.

Work which is claimed as original

All the work described is my own, except where it is clearly stated that another source is quoted, and with the following exceptions :-

Part 2. The results of the experiments on cats are not claimed as my own. The results obtained on frogs are my own, but I received a great deal of guidance from Dr. J.Y. Lettvin and Dr. P.D. Wall. Many of the microelectrodes I used were made for me by Dr. Lettvin, and the discussion of the choice of type of electrode for different applications is mainly an account of his recommendations.

Part 4. The mathematical solution in the general case was obtained independently by me, but had actually been published elsewhere at the time I obtained it.

Part 5. The general principle of the pulse-interval meter was evolved in discussions between Dr. T.D.M. Roberts and myself, and it is impossible to say who was mainly responsible. I am wholly responsible for the detailed design and development of the instrument.

Part 6. The pre-amplifier design conforms fairly closely to a design which was suggested by Professor Ritchie of St. Andrews.

ACKNOWLEDGEMENTS

I am indebted to Professor R.C. Garry for his guidance, interest and encouragement in the work reported here and in the preparation of this account of it, and to Dr. T.D.M. Roberts for guidance and encouragement and for giving me, some years ago, elementary instruction in neurophysiology. I am enormously indebted to Dr. Warren McCulloch for giving me the opportunity to carry out the work described in Part 2, and to his colleagues, particularly Dr. J.Y. Lettvin and Dr. P.D. Wall, for constant guidance and encouragement during the time I spent with them.

In connection with the preparation of this thesis, I am greatly indebted to Professor T. Ferguson Rodger, who has permitted the postponement of many of our plans for experimental work in his department, in order that I might have time to work on my thesis. I am indebted to numerous friends for encouragement in my task, notably Miss Joyce Mann, who also did some of the typing.

I have received valuable assistance from the technical staff of the Physiology Department, particularly Mr. Donald McAllister and his assistant Mr. Hugh Rodger, who cheerfully undertook a vast amount of photographic work.

PART 1

THE ELECTRICAL EXCITATION OF NERVE

Part 1(a). Stimulation with least power : theoretical treatment.

Part 1(b). Study of accommodation.

PART 1 (a). STIMULATION WITH LEAST POWER : THEORETICAL TREATMENT

Much research, and a great deal of theoretical speculation, has been directed towards a specification of the "threshold" conditions which an electrical stimulus must fulfil in order to produce excitation of a nerve. Several mathematical theories have been put forward; that of Hill (1936a) is the best known. None of the theories has accounted for all of the observed data, but in view of the widespread acceptance of Hill's theory there can be no doubt that it represents a reasonable approximation to the true properties of nerves. Some of its deficiencies will be examined later.

Offner (1946) has applied Hill's theory to the problem of finding the waveform which a stimulating current should have in order to produce excitation with a minimum amount of electrical energy. This waveform will not be the most desirable under all circumstances where electrical excitation is required, for in experiments the minimisation of stimulus artefact in the recording circuits, or the selective stimulation of one type of nerve fibre rather than another, may be of more importance than the minimisation of the electrical energy. In other cases it may be necessary to use short pulses to ensure precise control of the time of stimulation, and sometimes special waveforms are used in order to investigate the properties of nerves. However, in cases where the stimulating current may cause damage to tissue through which it flows, it is reasonable to suppose that the damage depends on the power dissipated, and in such cases it is desirable that the energy in each stimulating pulse be minimised.

Offner also points out that, according to the theoretical treatment of nerve conduction due to Rashevsky (1933), the action current which stimulates a point in the length of the axon, in the course of normal conduction of an impulse, is of the form which has been found to give stimulation with least energy. Hence Offner's result may be of theoretical as well as practical importance.

Offner's results show the forms which electrical stimuli must have to stimulate with least energy, both for the case where the stimulating current is limited to a given time, and for the case where the duration is not restricted. He has also derived an expression for the optimum duration of a rectangular stimulating pulse and has compared its stimulating efficiency with that of the optimum waveform. The rectangular pulse of optimum duration requires only 22% more power to stimulate than does the optimum waveform. The rectangular pulse is much more easily produced, and Offner concludes that it is a good form of stimulus to use.

It will be shown here that triangular pulses, consisting of a linear rise of current followed by an abrupt drop, can stimulate with an amount of energy only 3·3% greater than is contained in the optimum stimulus. An expression for the optimum duration for the triangular pulse will be derived.

Before triangular pulses are considered, a short review will be made of the main results of Offner's theory. The validity of the assumptions he makes about the properties of nerves will be discussed later.

Offner's Theory

The electrical energy which is supplied by a stimulating current is given by

$$H = a\int_{0}^{t_0} I^2\,dt \qquad (1)$$

where I is the current at any time t, and t_0 is the interval during which current flows. a is a constant.

Offner represents the excitation process by the differential equation

$$dE/dt = KI - kE \qquad (2)$$

where k and K are constants of the nerve. E represents an excitatory state, and excitation occurs when E reaches a certain value E_0.

Integration of equation (2) gives the condition for excitation

$$E_0 = K\,e^{-kt_0}\int_{0}^{t_0} I\,e^{kt}\,dt \qquad (3)$$

Offner applies the method of the calculus of variations to find how the current I must vary during the interval from $t = 0$ to $t = t_0$ in order that the energy H in equation (1) should be a minimum, subject to the condition that equation (3) must be satisfied. He finds that the current should have the waveform:-

$$I = 2\,k\,E_0\,e^{kt}/\,K\,(e^{kt_0} - e^{-kt_0}) \qquad (4)$$

$$\text{for } 0 \leq t \leq t_0$$

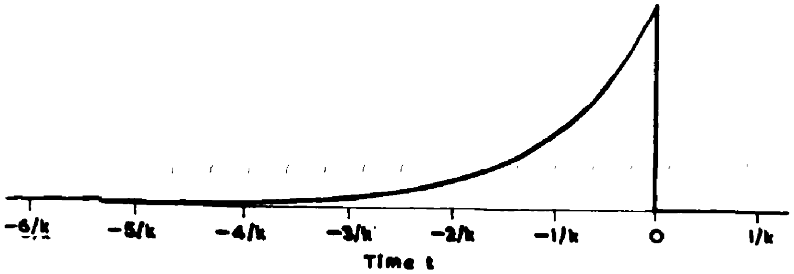


Fig. 1.1. Optimum stimulating waveform, according to Offner's theory.

Equation (4) represents the form the current must have when the current flow is restricted to a time interval of length t_o. Offner shows, further, that when there is no limitation on the duration of current-flow, the least energy is expended if the current flow occupies an infinite time. In that case, ($t_o = \infty$), the most convenient expression for the form of the current is given by taking the moment at which the excitation is achieved to be the time zero. (In previous equations the time of excitation was $t = t_o$).

For a current of infinite duration, and with a shift of the time scale so that excitation occurs at $t = 0$, equation (4) becomes

$$I = 2\,k\,E_o\,e^{kt}/K \qquad \text{for } t \leqslant 0 \qquad (5)$$

$I = 0$ for $t > 0$, since there is no point in dissipating further energy once excitation has been achieved. Equation (5) is Offner's expression for the optimum current waveform to achieve excitation with least energy. The energy expended is in fact equal to

$$H_{min} = 2\,a\,k\,E_o^2 / K^2 \qquad (6)$$

The current waveform represented by equation (5) is shown in Fig. 1.1. There is an exponential rise of current, and a sharp fall to zero at the moment excitation is achieved.

Stimulation with rectangular pulses.

The waveform represented by equation (5) cannot be produced in practice since it starts at time $t = -\infty$. An approximation could be made, starting at a finite time before the moment of excitation, or the waveform represented by equation (4) could be produced, but the waveforms are all inconvenient ones to produce electronically. Since rectangular pulses are commonly used for nerve excitation, Offner compares their efficiency of stimulation with that of the optimum stimulus of equation (5).

There is an optimum duration for a rectangular pulse to stimulate with least energy. The duration is shown by Offner to be

$$t_r = 1{\cdot}257/k \tag{7}$$

and the energy expended is

$$H = 2{\cdot}44\ a\ k\ E_0^2 \ / \ K^2 \tag{8}$$

From equations (6) and (8) it is seen that the

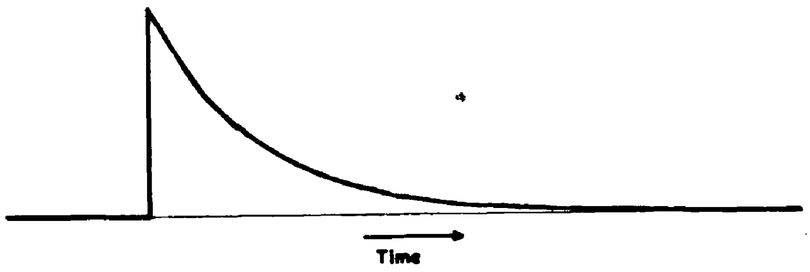


Fig. 1.2. Condenser-discharge waveform.

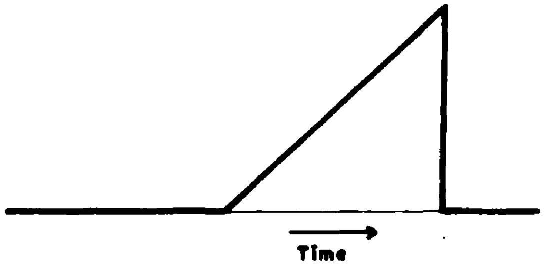


Fig. 1.3. Triangular pulse.

rectangular pulse of optimum duration requires 22% more energy to excite than does the optimum waveform of equation (5).

Offner also calculates the efficiency of exponentially falling current pulses, or condenser discharges (Fig. 1.2) and finds that the most efficient current of this form requires 85% more energy to excite than does the optimum form of stimulus, and 51% more than does the optimum rectangular pulse. Offner concludes that rectangular pulses should generally be used in preference to condenser discharges.

Extension of the theory to stimulation with triangular pulses.

Offner rightly concludes that rectangular pulses provide a simple practical way of stimulating with low power. A further possibility which he has not considered is that of stimulation with triangular pulses. (Fig. 1.3). Triangular pulses can be generated conveniently in electronic circuits.

It will now be shown that the optimum duration for a triangular pulse is

$$t_t = 2{\cdot}15/k \tag{9}$$

and the energy is only 3·3% more than for the optimum waveform.

The proof of these properties is as follows:-

Suppose that the pulse is of duration t_o , and lasts from $t = 0$ to $t = t_o$. Let the current during the pulse be

$$I = \alpha t \tag{10}$$

Then the energy in the pulse is

$$H = a \int_0^{t_o} I^2\, dt$$

$$= a \int_0^{t_o} \alpha^2 t^2\, dt = a\, \alpha^2 t_o^3 / 3 \tag{11}$$

The condition for excitation is

$$E_o = K e^{-kt_o} \int_0^{t_o} I e^{kt} dt \tag{3}$$

$$= K e^{-kt_o} \int_0^{t_o} \alpha\, t\, e^{kt}\, dt$$

$$= K \alpha \left\{ \frac{t_o}{k} - \frac{1}{k^2} + \frac{1}{k^2} e^{-kt_o} \right\}$$

$$\alpha = \frac{E_o}{K} \frac{1}{\frac{t_o}{k} - \frac{1}{k^2} + \frac{1}{k^2} e^{-kt_o}}$$

$$= \frac{E_o k^2}{K} \frac{1}{kt_o - 1 + e^{-kt_o}} \tag{12}$$

Substituting for a in equation (11) gives

$$H = \frac{a}{3} \frac{E_0^2 k}{K^2} \frac{(kt_0)^3}{(kt_0 - 1 + e^{-kt_0})^2} \tag{13}$$

To find the value of t_0 which gives a minimum value of H, the derivative of equation (13) with respect to (kt_0) is equated to zero, and the condition for a minimum is found to be

$$3 - kt_0 = (3 + 2\,kt_0)\,e^{-kt_0} \tag{14}$$

By a method of successive approximations, the appropriate root of equation (14) is found to be

$$kt_0 = 2{\cdot}15$$

$$\text{or} \quad t_0 = 2{\cdot}15\,/k \tag{15}$$

which is the result already quoted in equation (9).

Substituting the above value for kt_0 in equation (13) gives

$$H = 2{\cdot}066\,a\,k\,E_0^2\,/\,K^2 \tag{16}$$

By comparing equation (16) with Offner's expression (equation 6) for the energy of the optimum stimulus:-

$$H_{min} = 2\,a\,k\,E_0^2\,/\,K^2$$

it is seen that the optimum triangular pulse requires 3·3% more energy to stimulate than does the optimum waveform.

Relationship between Offner's k, Hill's k and chronaxie.

The expressions which have been given for the optimum durations of the two forms of pulses (equation 7 for rectangular pulse; equation 9 for triangular pulses) both express the durations in terms of the constant k. This is a constant of the nerve. Unfortunately the symbol k as used by Offner, and as used here, does not have the same meaning as the same symbol as used by Hill (1936a). The symbol as used here is in fact the reciprocal of Hill's time-constant of excitation.

It can be shown that if the excitation process conforms to Offner's assumptions as expressed by equation (2), the chronaxie of the nerve is given by

$$\text{Chronaxie} = \log_e 2 \;/\; k = 0.693/k$$

Hence equation (9) can be written :-

$$t_t = \text{optimum duration for a triangular pulse}$$

$$= \frac{2{\cdot}15}{0{\cdot}693} \times \text{chronaxie}$$

$$= 3{\cdot}1 \times \text{chronaxie}$$

Similarly, Offner's result for the optimum duration of a rectangular pulse can be expressed as a multiple of the chronaxie :-

$$t_r = \text{optimum duration for a rectangular pulse}$$

$$= 1{\cdot}257\,/k$$

$$= \frac{1{\cdot}257}{0{\cdot}693} \times \text{chronaxie}$$

$$= 1{\cdot}82 \times \text{chronaxie}$$

<u>Comparison between the use of triangular and rectangular pulses, and the use of optimum stimuli restricted to the same durations.</u>

The amounts of energy required to excite when rectangular and triangular pulses were used has so far been compared with the energy required for that form of stimulus which has been shown to be optimum when no restriction is placed on the duration. Offner's theoretical treatment gives an expression for the form of stimulus which is optimum when the duration is limited (equation 4). It can be shown further, that the optimum stimulus restricted to duration t_o contains an amount of energy given by

$$H = \frac{2\ a\ k\ E_0^2}{K^2} \cdot \frac{1}{1-e^{-2kt_0}} \tag{17}$$

From this it can be calculated that the optimum stimulus, restricted to the duration of the optimum triangular stimulus ($t_o = 2{\cdot}15/k$ or $3{\cdot}1 \times$ chronaxie) contains 1·35% more energy than the optimum unrestricted stimulus. This can be compared with the optimum triangular stimulus itself, which, as has been seen, contains 3·3% more energy than the optimum unrestricted stimulus.

The optimum stimulus restricted to the duration of the optimum rectangular pulse ($t_o = 1{\cdot}257/k$ or 1·82 × chronaxie) contains 8·1% more energy than the optimum unrestricted stimulus. This can be compared with the optimum rectangular stimulus itself, which, as has been seen, contains 22% more energy than the optimum unrestricted stimulus.

DISCUSSION

The use of triangular pulses for stimulation appears to be indicated when it is important to dissipate as little power as possible in the tissues. The validity of the whole theoretical treatment depends, however, on the extent to which the behaviour of a nerve is accurately represented by equation (2). This will be discussed. Offner's conclusion for rectangular pulses, that the duration giving stimulation with least energy is 1·82 times the chronaxie, can be compared with the statement by Lapique (1926, quoted by Medlicott, 1948) that excitation is produced with the least electrical energy when the duration of the electrical pulse is equal to or below one chronaxie.

The findings of Offner and Lapique are not in exact agreement but the discrepancy is not sufficient to invalidate Offner's theory.

The theory due to Offner, and its extension to triangular pulses, have been presented here as based on Hill's (1936a) theory of nerve excitation. However, the basic assumptions made by Offner, and embodied in equation (2), can be derived from any of a number of mathematical theories of nerve excitation. The mathematical theories due to Hill (1936a) and Rashevsky (1933), as well as the theory put forward by Lapique in 1907 and discussed and extended by Blair (1936) are all equivalent to one another except in the way in which they take account of accommodation. If no account is taken of accommodation these theories can all be represented by equation (2). The theory of Monnier (1934), discussed by Katz (1939, p.52), also leads to equation (2) if one of the time-constants is assumed infinite.

The first criticism which can be made of Offner's theory, then, is that it takes no account of accommodation. This is not a serious objection when the stimulating pulses are fairly short; when the optimum triangular or rectangular stimulating pulses are considered, the time-constant of accommodation is then long compared to the duration of the pulses. The duration of the pulses in these cases is of the same order of magnitude as Hill's time-constant of excitation, which he represents by the letter k. The duration of the optimum rectangular pulse is 1·257 times the value of Hill's time-constant k, and the duration of the optimum triangular pulse is 2·15 times it. The time-constant of accommodation (Hill's λ) is at least 7 times the value of Hill's time-constant of excitation, and is generally much more, according to Solandt (1936) and the discussion by Katz (1939, p. 53).

If accommodation were taken into account in the determination of the form of the optimum stimulus (Fig. 1.1), this would be of a somewhat different form, with less current flowing in the early part of the stimulus and more in the later part. The optimum stimulus would then approximate more closely a triangular pulse than does Fig. 1.1. Probably the efficiency of the optimum triangular stimulating pulse would come even closer to that of the optimum stimulus if accommodation were considered.

The question must now be considered whether, apart from accommodation, the excitation process can be accurately represented by equation (2) :-

$$dE/dt = KI - kE$$

or the equivalent equation obtained by integration :-

$$E_t = K\int_0^t I e^{-k(t-\tau)} d\tau \qquad (18)$$

There is abundant evidence that for extremely short electrical stimuli, the quantity of electricity required to excite is independent of the form of the pulse. In other words, for brief stimuli, the condition for stimulation is

$$\int I\,dt = \text{threshold value} \qquad (19)$$

where the integration is over the duration of the stimulus. This appears to be almost the only aspect of nerve excitation about which all workers are agreed. Hill (1936a, p. 317) quotes the results of numerous workers in support of this proposition. Among these are Fabre and Swyngedauw (1933) and Fabre, Quesnoy and Bertreaux (1934), who are also quoted by Tasaki (1950). Tasaki finds that the constant-quantity relationship is in agreement with his results for single-fibre preparations. Hill (1936b) has obtained further support for it from very precise experiments on the stimulation of nerves with condenser discharges. The subject is also discussed by Katz (1939).

The constant-quantity relationship expressed by equation (19) does not hold for shocks of longer duration or for a number of brief shocks separated in time. It is found that these are less effective in stimulation than they would be if their effects were additive. It therefore appears that the effect produced by a shock decays with time. It is therefore reasonable to suppose that the condition for excitation may be of the form

$$\int_0^t I \ \phi \ (t - \tau) \ d\tau \ = \ \text{threshold value}$$

which is equivalent to the form

$$E \ = \ K \int_0^t I \ \phi (t - \tau) \ d\tau \tag{20}$$

with excitation occurring when E reaches a threshold value E_0.

$\phi (t - \tau)$ is some function of $(t - \tau)$ and represents the decay of the effect which a brief shock produces in the nerve. The quantity E may be termed "excitatory state". Equation (20) reduces to the form used by Offner (equation 2) in the special case where

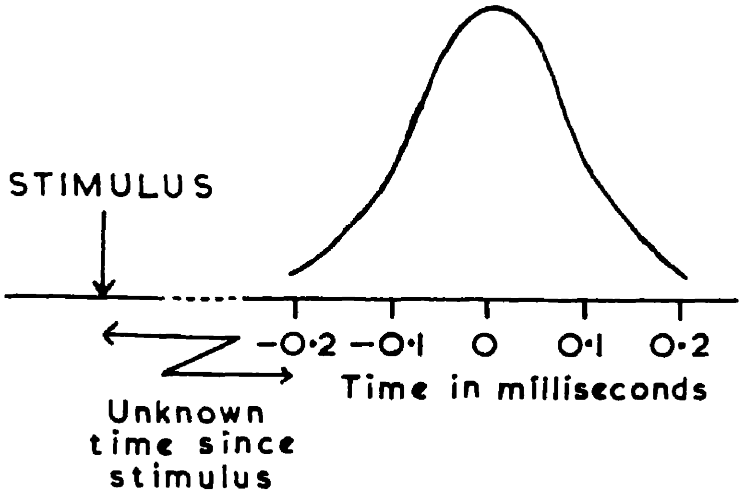


Fig. 1.4. Variation in excitatory state following a brief stimulus, according to Tasaki.

$$\phi(t - \tau) \equiv e^{-k(t-\tau)} \tag{21}$$

that is to say, when the excitatory state decays exponentially.

There is, however, quite a lot of experimental evidence that the excitatory state does not always decay exponentially.

Evidence for non-exponential decay.

Tasaki (1950) has studied the excitation of single fibres of toad nerves using his "bridge-insulator" technique. He states that, so long as stimuli of duration shorter than 0·3 msec are being considered, an equation of the form of equation (20) (but expressed in terms of stimulating voltage, not current) gives a satisfactory explanation of his findings. He states quite definitely, however, that the variation of excitatory state following a brief shock is not in the form of an exponential decay as required by equation (21). Instead, he finds that the excitatory state must rise to a maximum and then fall away at about the same rate as it rose, as shown in Fig. 1.4. If Tasaki's interpretation of his experimental findings is to be accepted, Offner's theoretical treatment of nerve stimulation must be modified.

It is difficult to reconcile Tasaki's findings with those of other workers, particularly Katz (1937a and b). Katz has shown, using a frog sciatic-gastrocnemius preparation, that the decay of excitatory state following a brief stimulus is approximately exponential provided the initial stimulus is less than about 50% of threshold. If the initial stimulus is stronger, the decay of excitatory state is less rapid; there is a "hump" superimposed on the exponential decay. The hump is attributed to the local response of a small region of nerve. This agrees with a suggestion of Rushton (1937a and b) that, to initiate a propogated disturbance, the excitation condition must be met over a certain minimum length of nerve. Katz tested the excitability of the nerve at various intervals after a subthreshold conditioning shock. In this way he was able to graph the difference between threshold shock at various times, and the threshold shock required to excite a resting nerve. This difference in thresholds is proportional to the level of excitatory state remaining as a result of the conditioning shock.

Katz's findings agree remarkably well with the theoretical predictions of Rushton (1937a), based on the cable-like structure of nerve. According to Rushton's theory, the decay of excitatory state should be exponential so long as it has not reached more than $\sqrt{h}$ of threshold, where h is a constant of the nerve which typically has a value of 0·75. Hence $\sqrt{h}$ is typically $\sqrt{0{\cdot}75} = 0{\cdot}87$. According to Rushton's theory, therefore, the decay of excitatory state should be exponential provided the stimulus is less than about 87% of threshold. Katz actually finds the departure from exponential decay with much smaller stimuli than this, but otherwise his experimental curves are strikingly similar to the theoretical curves shown by Rushton.

It is difficult to reconcile Tasaki's findings with those of Katz. Perhaps the great difference in the condition of the nerve in the two sets of experiments produced a difference in properties; Tasaki's experiments were on an isolated nerve fibre stimulated at one node of Ranvier, whereas Katz worked with intact sciatic nerves. It seems very unlikely, however, that even this great difference in the conditions would produce such a fundamental difference in the properties of the nerve.

It is possible that Katz's findings give a clue to a way in which Tasaki's results might be explained. Tasaki's interpretation of his results, and his derivation from them of the form which $\phi(t - \tau)$ must take (equation 20) depend on the assumption that $\phi(t - \tau)$ is the same function whatever level of excitatory state has been reached. Katz's findings appear to indicate that this assumption is not permissable under the conditions of Katz's experiments; in his experiments the decay is exponential for small stimuli, but of another form for near-threshold stimuli. It is possible that Tasaki's experimental findings could be interpreted differently by assuming that in this case also, $\phi(t - \tau)$ represents exponential decay for weak stimuli, but a slower decay for near-threshold stimuli. However, if in Tasaki's experiments the form of the decay depends on the level of excitatory state, the effect cannot be explained by Rushton's theory. Rushton's theory is not applicable when the stimulation is at a single node of Ranvier. If the form of the decay depends on the level of excitatory state reached, in Tasaki's experiments, it must be because of a non-propogated response occurring at the node itself.

The existence of a non-propogated "local potential" in nerve has been discussed by Blair (1938), Hodgkin (1937, 1938), Kato (1950) and Katz (1939, pp. 108 - 110). Hodgkin gives direct evidence, from electrical recording, for a non-propogated response in crustacean nerve. Nevertheless, Blair, while admitting Hodgkin's result for crustacean nerve, does not agree that there is a local response in frog nerve. This is not very significant in itself, however, since he used intact nerves, and Hodgkin was not able to detect a non-propogated response in intact crab nerve either, but only in single axons.

Blair accounts for Katz's results, not by postulating a local response, but by postulating that the variation of excitatory state following a brief stimulus is of a form similar to that suggested by Tasaki (Fig. 1.4), and is proportional in amplitude to the strength of the stimulus. Blair's argument in fact, is exactly the reverse of the one I have used in suggesting that Tasaki's response might be due to a local response; Blair suggests, on the contrary, that the kind of interpretation given by Tasaki can account for the results which Katz interprets as evidence for a local response. Blair's argument appears to be satisfactorily refuted by Katz (1939, p. 109), who states "At long intervals, the after-effect of a nearly liminal shock may be about twenty times greater than that of a two times weaker shock, and actually outlasts the latter for a considerable period. This cannot be fitted into Blair's present schemes but is easilt explained by the presence of a local response."

Kato (1950, p.63) also opposes the idea of a non-propogated response to stimulation, partly on the grounds of the absence of a refractory period following subthreshold stimulation, and partly on the grounds of the absence of a detectable electrical response. As evidence for the absence of an electrical response he quotes Erlanger and Blair (1931a) whose results are not conclusive since they were obtained on intact nerve. The absence of a refractory period does not prove there is no non-propogated response, and in any case Lorente de Nó (1947, part II, p.101) states that there <u>is</u> a period of subnormal excitability (relatively refractory period) following a subthreshold cathodal shock.

The bulk of the evidence, then, favours the occurrence of a non-propogated response. Lorente de Nó (1947, part II, p.100) in fact, states that "nerve fibres do not act as passive conductors when shocks of any magnitude or of either polarity are applied to them", so he appears to consider that there is a "local response" to any electric current applied to a nerve.

Another kind of departure from the exponential decay of excitatory state is described by Monnier (1952, quoting Monnier and Coraboeuf, 1948) who describes cyclical fluctuations of excitability following a subthreshold shock. Another departure is the observation by Lorente de Nó, already quoted, of a phase of subnormal excitability following the period of enhanced excitability after a cathodal shock. Monnier's results can be disregarded for the present purpose since they were obtained on nerve under abnormal (decalcified) conditions. The observations of Lorente de Nó cannot be so easily put aside, however.

Conclusions

The discussion shows that equation (2), on which Offner's theory and its extensions here are based is not a completely accurate representation of the properties of nerve. In the first place, it takes no account of accommodation. Also, it assumes an exponential decay of the excitatory state, and this certainly does not always occur. It is difficult

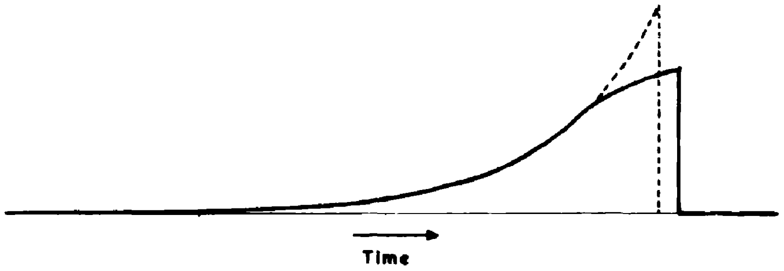


Fig. 1.5. Approximate shape of the optimum waveform when modified to take account of Katz's finding of non-exponential decay. The waveform according to Offner is shown as a broken line.

to say how Offner's conclusions and their extension here would be modified by taking into account the departure from exponential decay described by Lorente de Nó. The chief departure is a period of subnormal excitability following a subthreshold shock. The effect is not observed with other than extremely brief stimuli, so it can perhaps be ignored for the present purpose.

Katz's results indicate that the decay is exponential so long as the excitatory state does not reach more than 50% of threshold. Thus, if Katz's results are accepted, the conclusions reached about the efficiencies of different waveforms are applicable to the early part of the waveform, i.e. the part which raises the excitatory state to 50% of threshold. If Katz's results were taken into account in the derivation of the optimum stimulus, the result would be something like the waveform of Fig. 1.5. The first part of the waveform is identical with that derived by Offner (Fig. 1.1). After achieving an excitatory state which is 50% of threshold, however, advantage would be taken of the fact that the decay is less rapid than is assumed in the

derivation of Offner's result. The advantage would be gained by keeping the current lower in value in this later part of the stimulus, since power varies as the square of the current. The time taken to raise the excitatory state from 50% to 100% of threshold would consequently be slightly increased, as shown in Fig. 1.5.
It is interesting to note that taking Katz's findings into account brings the optimum waveform closer to the triangular one of Fig. 1.3.

The way in which the optimum waveform would differ if accommodation were taken into account has already been discussed. There would be less current flowing in the early part of the stimulus and more in the later part. This change, also, makes the optimum stimulus approach the triangular form more closely.

The modifications of the theory to take account of accommodation and of Katz's results make it appear that the triangular stimulus is probably an even closer approximation to the optimum than was indicated by the extension of Offner's theory. It therefore appears that triangular stimuli can be used with advantage when the stimulating power must be minimised.

There are, however, many complicating factors. One of these is the fact that nerve is usually shunted by other tissues when it is being stimulated electrically, and since the nerve presents a complex and non-linear impedance, the waveform of the current through the nerve may differ from the waveform of the current applied by the stimulator. Also the theory depends on the assumption (implicit in equation 1) that the stimulating current is passing through a pure and constant resistance, and in practice this will not be strictly true. It is probably most nearly true in cases where the nerves which react to the current form only a small part of the tissue through which the current passes, and where it is required to minimise the power dissipated in the whole mass of tissue.

Application to E.C.T.

The problem of stimulation with minimum power is of particular interest in connection with electro-convulsive therapy, and Offner had this in mind when he considered the problem. My own interest has also been mainly on account of the possible application of the results to E.C.T. The standard E.C.T. technique involves the passage of alternating current of mains frequency through the head of the patient. The voltage applied is between 70 and 130 volts, the current between 200 and 1600 milliamperes, and the duration from one tenth to half a second (Kalinowsky and Hock, 1946, quoted by Kouwenhoven, 1949). A considerable amount of electrical energy is supplied by such a shock, and tissue damage might easily result. By the use of efficient stimulating waveforms instead of sinusoidal alternating current, the amount of electrical energy needed to produce a convulsion can be greatly reduced. Liberson (1944 and 1945) has found that in rabbits and guinea pigs he could produce convulsions by the use of brief pulses, with 1/10 to 1/30 of the energy required by the classical technique. By the use of triangular pulses it may be possible to reduce the energy still further. The use of brief stimuli for E.C.T. is reviewed by Medlicott (1948).

Medlicott mentions one disadvantage of the use of low energy shocks for electro-convulsive therapy. The low-energy shock causes less interference with memory than does the standard technique, and a patient who has received a shock may retain an unpleasant recollection of the shock which will make him apprehensive the next time he goes for treatment. However, this objection to the use of low-energy shocks will presumably not apply when the shock is given under general anaesthesia, as is now the usual practice.

Nevertheless, theories of nerve excitation should certainly be applied with great caution in connection with E.C.T., since the mode of action of E.C.T. is far from being understood. Kouwenhoven (1949) remarks "There is no universally accepted theory which explains the value of electric shock in therapy. Some speak of profound physiochemical changes in nerve cells while others believe that the shocks form an acceptable punishment which relieves the patient of guilt". The "acceptable punishment" theory can presumably be rejected since it is equally effective whether it is applied to an anaesthetised or a conscious patient. Nevertheless it is true that the mode of operation of E.C.T. is little understood, and though it is very probable that nerve excitation is what is needed to produce the therapeutic effect, even this is not entirely certain.

PART 1 (b). STUDY OF ACCOMMODATION.

In part 1(a), no detailed account was taken of the effects of "accommodation". It is easily shown that nerves are much more readily excited by a current which begins abruptly than by one which rises slowly to the same final value. This is usually explained by saying that when the current rises slowly the nerve is able to "accommodate" to the current during the time of current rise. The word (in German "Akkommodation") appears to have been first applied to the description of properties of nerve by Nerst (1908).

Granit (1955, p. 26) defines accommodation differently, by saying it is "a purely formal description of the fact that each impulse in the nerve is succeeded by a process of restitution which counteracts the setting up of a fresh impulse".

The usual meaning of "accommodation" is certainly not as defined by Granit; in the mathematical theory of excitation due to Hill (1936a), accommodation is taken into account although the theory deals only with the changes leading up to the initiation of an impulse, and takes no account of changes following the initiation. Thus in Hill's use of the word, accommodation is a reaction to the stimulus or to a non-propogated response to it, and not, as in Granit's definition, a reaction to the initiation of a propogated impulse. In this thesis, the word will be used in Hill's sense, which is the commonly accepted one.

Hill's theory of excitation.

In the development of Hill's theory it is assumed that the nerve has an "excitatory state" V, which obeys a differential equation of the form of equation (2). Using Hill's notation, this can be written: -

$$\frac{dV}{dt} = bI - \frac{V - V_o}{k} \qquad (22)$$

where V_o is the resting value of V, and b and k are constants of the nerve.

Excitation occurs when V reaches a threshold value U. To take accommodation into account, U is assumed not to be a constant but to start to rise from its resting value U_o as soon as V rises above its resting value V_o. U is assumed to obey the differential equation

$$\frac{dU}{dt} = \frac{V - V_o}{\beta} - \frac{U - U_o}{\lambda} \qquad (23)$$

where β and λ are constants of the nerve, and excitation occurs when $V = U$.

Hill makes the further assumption that when a steady current I flows for a sufficient time, U and V reach equilibrium values U_1 and V_1 which are such that

$$U_1 - V_1 = U_o - V_o \qquad (24)$$

that is to say, the threshold stimulus needed to excite a "fully accommodated" nerve is the same as that needed to excite it in its resting state. The results obtained by not making this assumption will be discussed later.

It can readily be shown, from Equation (23) that the condition imposed by equation (24) is equivalent to the condition

$$\beta = \lambda \qquad (25)$$

Hence, instead of the three time-constants k, β and λ, which occur in equation (22) and (23), only k and λ are needed, since β is equal to λ. k is the time-constant of excitation and λ the time-constant of accommodation.

Other theories of excitation.

The theory of nerve excitation due to Rashevsky (1933) depends on equations fairly similar to equations (22) and (23), namely (in Rashevsky's notation) :-

$$\frac{de}{dt} = KI - k(e-e_0) \qquad (26)$$

$$\frac{di}{dt} = MI - m(i-i_0) \qquad (27)$$

with excitation occurring when e = i.
Equation (26) corresponds exactly with equation (22), and e in equation (26) may be termed "excitatory state". If i is taken to correspond to Hill's U, however, the difference between the two theories becomes evident, for whereas in Hill's theory the changes in U are determined by the excitatory state V, in Rashevsky's theory the changes in i are determined by the current I.

There appears to be little evidence on which to decide which type of theory is to be preferred. Hill (1936a), in developing his theory, states "Excitation is caused by a sufficient rise in the 'local potential' V: it is natural, therefore, to suppose that 'accommodation' is caused, not directly by I, but also by the rise of V." Hill's argument is not entirely convincing, but what experimental evidence there is suggests that Hill's way of taking account of accommodation is to be preferred to Rashevsky's. Blair (1936) considers that, following the start of a constant-current stimulus, the changes due to accommodation do not commence until a certain time has elapsed. Such a finding is closer to the predictions of Hill's theory than to those of Rashevsky's theory.

The theory of nerve excitation due to Monnier (1934) is discussed by Hill in his paper and shown to be equivalent to Hill's theory.

The criteria stated by Tasaki (1950) for excitation by a slowly varying voltage form a further theory of nerve excitation which takes account of accommodation, though without explicitly

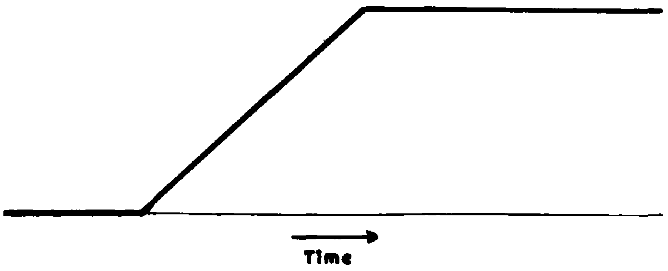


Fig. 1.6(a). Linearly-rising current waveform, used for measurement of accommodation.

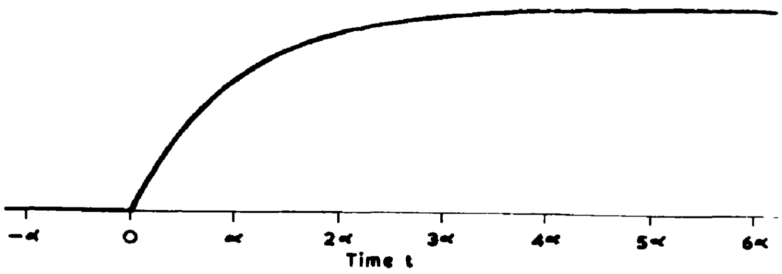


Fig. 1.6(b). Exponentially-rising current waveform, used for measurement of accommodation.

referring to it. Tasaki's criteria take a form entirely different from the other theories. His theory appears less satisfactory than the others since he requires different theories to account for excitation by brief shocks and for excitation by slowly varying voltages.

The measurement of accommodation.

The property of accommodation of a nerve can be investigated by applying stimulating currents with varying degrees of abruptness of rise of current. If the nerve accommodates well, the current slowly rising to a value which is just sufficient to excite will be much greater in magnitude than the abruptly-rising current which is just sufficient to excite;if the nerve shows little accommodation the magnitudes of the currents will not differ greatly.

The gradually-rising current used to investigate accommodation may rise linearly, as shown in Fig. 1.6(a), or may be of the form

$$I = I_0(1 - e^{-\frac{t}{\kappa}}) \tag{28}$$

as shown in Fig. 1.6(b). This second type of rise is referred to as "exponential rise". Linearly rising currents have been used by Skoglund (1942) and Kugelberg and Skoglund (1946). Exponentially rising currents have been used by a number of workers, including Solandt (1936), Kugelberg (1944) and Wigton and Brink (1944). It is usual to graph the value of the current I_o required for threshold stimulation against the time-constant α of the rise of current; such a graph is termed the "accommodation curve" for the nerve.

The procedure of testing by use of exponentially-rising currents, and drawing the "accommodation curve" as described above, has come to be the classical method for investigation of accommodation. This is mainly because Hill (1936a) has shown that, according to his theory of nerve excitation, the accommodation curve drawn in this way should be approximately a straight line, and if the rheobase is taken as the unit of current the gradient of the line is $1/\lambda$, where λ is the time-constant of accommodation in Hill's theory. Hence, testing with exponentially-rising currents, and drawing the accommodation curve, is the usual way of evaluating λ.

The value of λ for a given nerve can be greatly altered by changing the composition of the fluid bathing the nerve. In particular, the accommodation becomes very weak (λ long) if the fluid is deficient in calcium. Hence, Wigton and Brink (1944) were able to correlate changes in accommodation in human nerves with blood-calcium deficiency due to parathyroid deficiency. Accommodation in human nerves can be readily investigated by stimulating with electrodes on the skin.

The Exponential Stimulator

To investigate changes in accommodation of nerves, a special stimulator has been developed (Andrew 1952a). This gives exponentially-rising currents, and is primarily designed for the stimulation of human nerves through the skin. It can readily be adapted for other conditions of stimulation. For stimulation through the skin it is important that the stimulating current and the time-constant of rise of current should be independent of the resistance presented by the subject.

These requirements have been met by making the stimulator a servo-device, having a large amount of current-negative-feedback applied to the output stage. The general principle is due to Rushton (1949), but the exponential stimulator differs from Rushton's circuit in several important ways, one of them being in the use of a direct-coupled amplifier and feedback path instead of a capacitance-coupled amplifier as used by Rushton. This feature is essential in a stimulator used to provide accurately-controlled stimulating wave forms of long duration.

The design of the stimulator will be discussed more fully in Part VII of this thesis.

Results of experiments on stimulation with exponentially-rising current.

Stimulation through the skin. The stimulator has been used to study the accommodation of the ulnar nerves of human subjects, by placing a small electrode over the nerve at either the wrist or the elbow, and a large neutral electrode on the forearm. Current from the stimulator was passed between these electrodes, the smaller one being the more negative. The threshold current was taken as the smallest which would give a particular sign of excitation, such as a twitch of the fourth and fifth fingers, or flexion at the wrist detectable by palpation

The first investigation to which the exponential stimulator was applied was one begun by Dr. J.B. Gaylor and Dr. S. Renfrew, to find whether there was a connection between nerve accommodation, the Chvostek sign, and certain E.E.G. abnormalities usually associated with epilepsy. (The Chvostek sign consists of a twitch of the corner of the mouth produced by tapping the side of the face over the facial nerve; when present it is thought to show that the subject's facial nerve is more easily excitable than is usual).

This investigation has not been carried to a stage where definite conclusions can be stated, but it seemed clear from tests on twelve students, and on a number of patients, that the Chvostek sign co-exists with poor nerve accommodation (a flat "accommodation curve", or high value for the time-constant of accommodation, λ).

Dr. J.A. Simpson has used the stimulator (with, initially, assistance from the writer and Dr. T.D.M. Roberts) to investigate changes in nerve accommodation in patients suffering from hypoparathyroidism, hyperparathyroidism, and one patient whose body temperature was very low. The results in the cases of hyperparathyroidism (Simpson, 1954) and low temperature (Simpson, 1955) have been published with acknowledgements made to the present writer, and reprints are included in the appendix to this thesis. In the work on hyperparathyroidism, measurements of nerve accommodation showed a higher value for λ than is usual, as might be expected from the increased blood calcium level in this condition. Simpson considers that the deafness which is associated with the condition probably results from the changes in the properties of the nerves.

In the case of low body temperature (hypothermia), the value of λ was found to be unusually high (accommodation poor). This agrees with the finding of Solandt (1936) that cooling frog nerves increases the value of λ for them. Simpson 's results indicate that the muscular rigidity seen in hypothermia may be due to changes in the properties of the nerves, and hence similar to the tetany produced by a low blood-calcium level.

In the mathematical theories of nerve excitation, it is usually the stimulating current rather than voltage which is represented in the equations. However, in experiments based on these theories, it is frequently the stimulating voltage which is known or controlled. Also, even in many cases where the current supplied to the preparation is known, the nerve is shunted by a low-resistance path through other tissues, and it is probably the voltage between two points on the nerve, rather than the current passing through the nerve, which is of the same form as the applied current. In particular, when human nerves are stimulated through the skin the stimulating current is shunted through other tissue.

Stimulation of nerves directly. It is therefore of interest to stimulate nerves and to examine their properties under conditions where the shunting due to other tissues and fluid is kept to a minimum, and to find to what extent the properties are different when a low-resistance shunt is intentionally introduced. Some experiments of this sort have been carried out. Under the conditions of minimum shunting, the source of the stimulating current was the exponential stimulator, used with a resistance network to reduce the amount of stimulating current applied to the preparation. This network was needed because the range of currents available from the stimulator is much higher than the range needed to stimulate isolated nerve. Since the resistance network was used, the extremely high output impedance of the exponential stimulator was not utilised. The output impedance of the resistance network was, in some experiments, 330,000 ohms, and in others 2.2 megohms. With values as high as these, the stimulus can be regarded as a "constant-current" one.

For comparison, a stimulus from a low-impedance source was obtained by shunting the

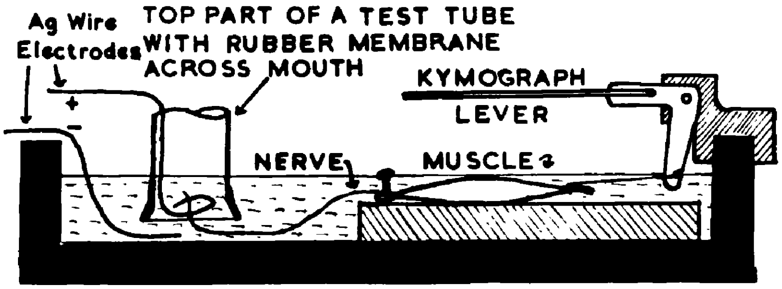


Fig. 1.7. Apparatus used for experiments on stimulation of nerves directly.

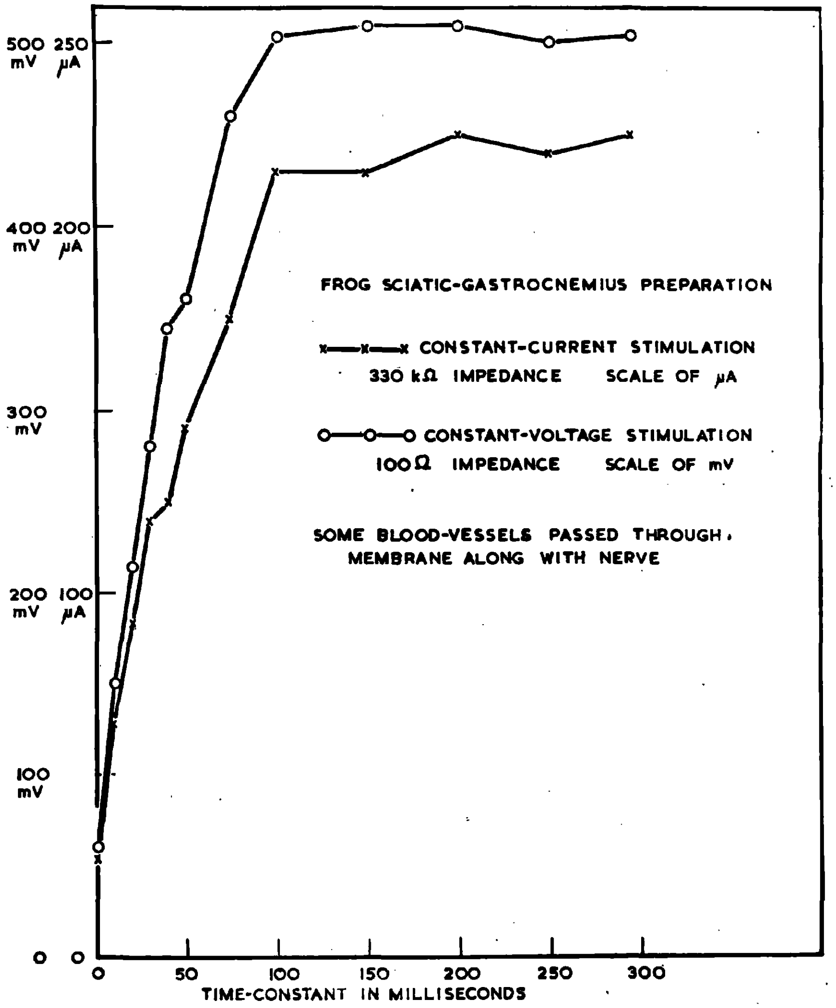


Fig. 1.8.

Accommodation curves for frog nerve. The terms "constant-voltage" and "constant-current" are used in their engineering sense to mean voltage and current not affected by circuit resistance; they do not imply values invariant with time.

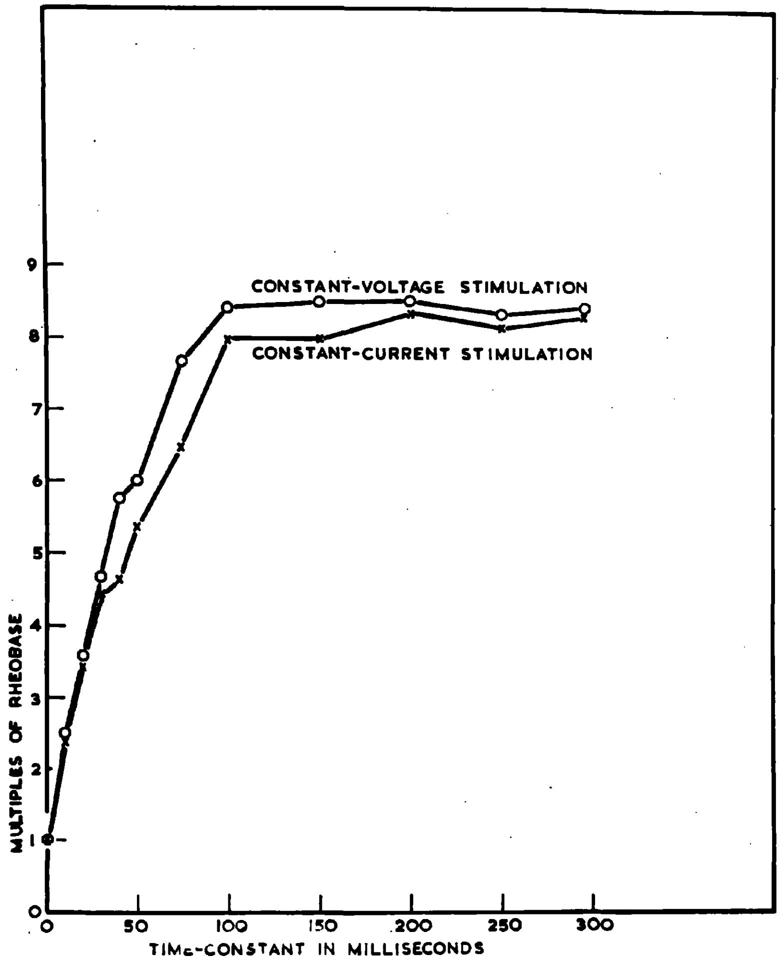


Fig. 1.9.

The same curves as Fig. 1.8, replotted with the rheobasic values taken as the units of current and voltage.

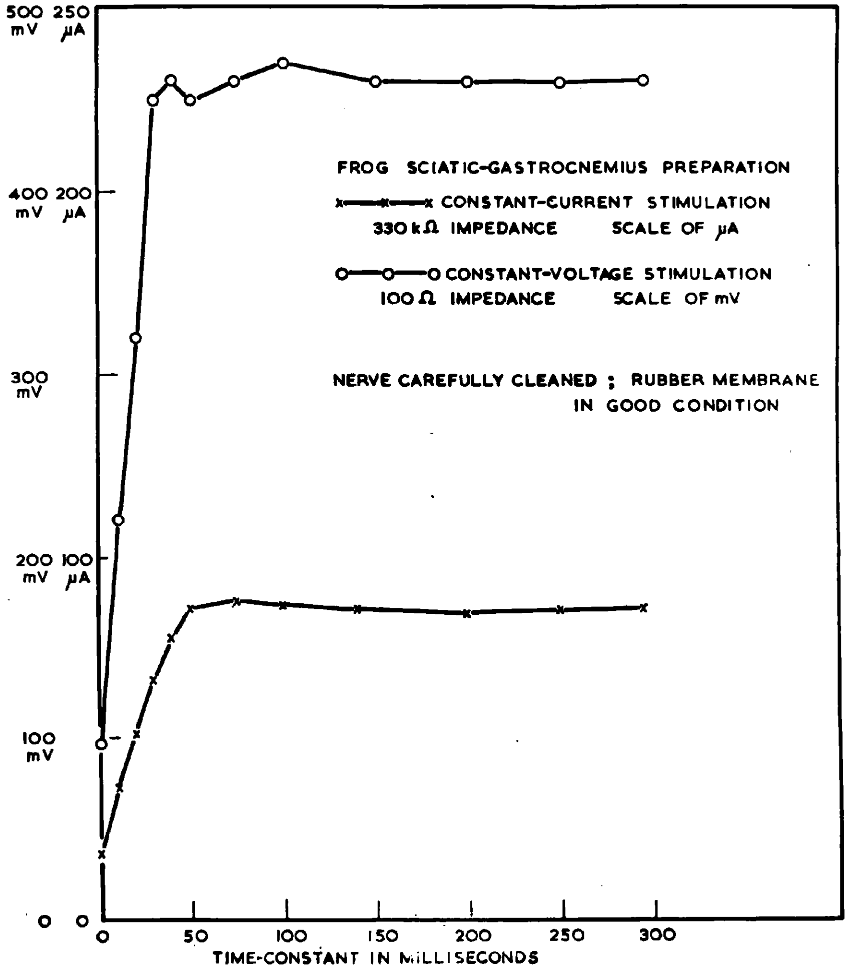


Fig. 1.10.

Accommodation curves for frog nerve.

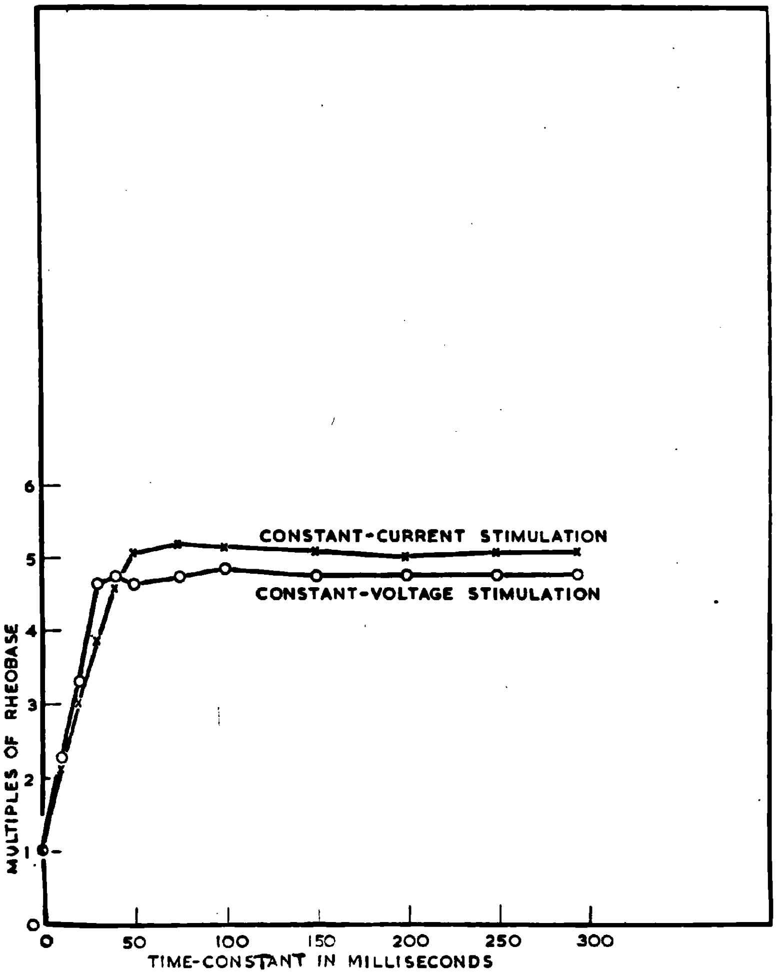


Fig. 1.11.

The same curves as Fig. 1.10, replotted with the rheobasic values taken as the units of current and voltage.

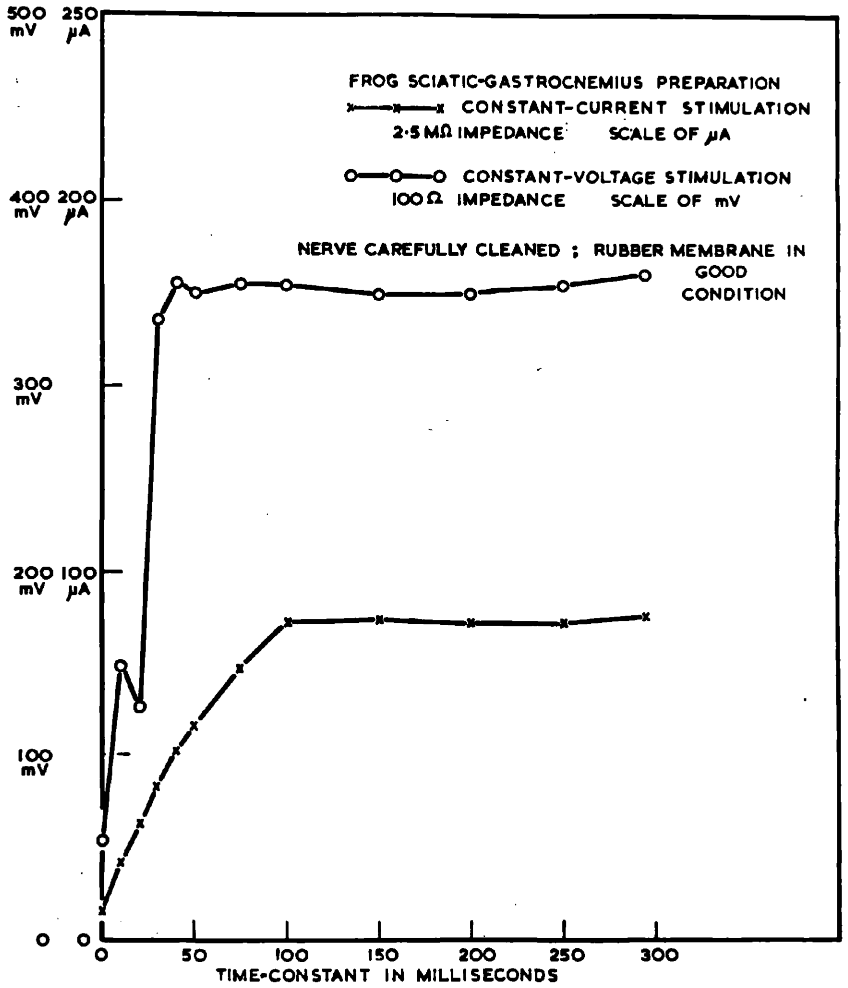


Fig. 1.12.

Accommodation curves for frog nerve.

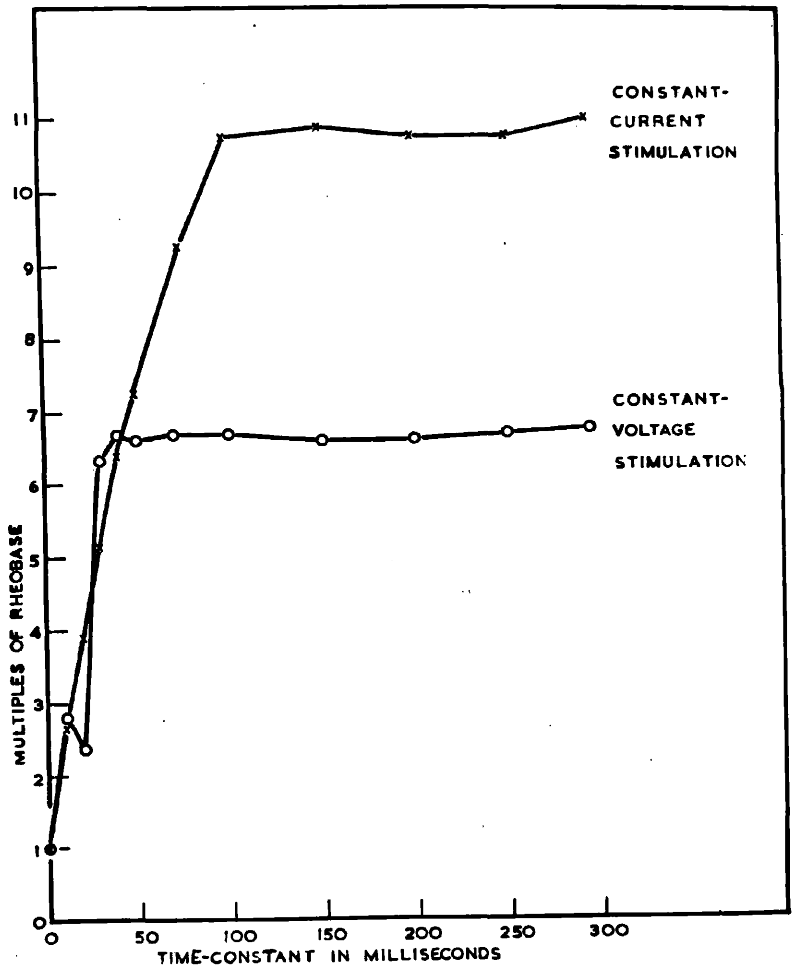


Fig. 1.13.

The same curves as Fig. 1.12, replotted with the rheobasic values taken as the units of current and voltage.

exponential stimulator with a resistance of 100 ohms. The stimulus was then effectively a "constant-voltage" one.

In these experiments the sciatic-gastrocnemius preparation from frogs was used. The muscle was connected to the type of lever normally used to record muscle contractions on a kymograph, but no record was made. A just-perceptible movement of the writing lever was used as the index of excitation.

To apply the stimulating current to the nerve with minimum shunting, a rubber membrane electrode was used. This was similar in principle, though of different form, to that used by Garry and Wishart (1951). The type of electrode used is shown in Fig. 1.7.

The results are shown in Figs. 1.8 - 1.13. In Figs. 1.8, 1.10 and 1.12 the currents and voltages are plotted in conventional units. In Figs. 1.9, 1.11 and 1.13 the curves are re-plotted, with the stimulating currents and voltages expressed as multiples of the rheobasic values.

It can be seen that in every case the

threshold value of current or voltage increases with increasing value of time-constant until a point is reached, beyond which an increase in time-constant produces no further increase in threshold. In other words, there is a certain current or voltage value which will stimulate, however slowly the voltage or current rises. Bernhard, Granit and Skoglund (1942) and Granit (1947, p. 8) speak of "breakdown of accommodation" as taking place where the curve becomes horizontal.

In the curves of Figs. 1.8 and 1.9, the "breakdown of accommodation" occurs at the same time-constant whether the stimulation is of the constant-voltage or constant-current type. In fact, the two curves in Fig. 1.9 are not significantly different. This is not surprising in view of the fact that in this experiment a blood vessel passed through the rubber membrane along with the nerve, so the constant-current stimulus was shunted by a low resistance, and so became effectively a low-impedance or constant-voltage stimulus so far as the nerve was concerned.

In the experiments of Figs. 1.10 and 1.11

the nerve was carefully cleaned and the rubber membrane was in good condition. The two curves in Fig. 1.11 are not greatly different, but it can be seen that with constant-voltage stimulation, "breakdown" occurs at a smaller time-constant than with constant-current stimulation. The difference in the time-constants at which "breakdown" occurs is more pronounced in Figs. 1.12 and 1.13, which also show results obtained with a clean nerve.

In all of these experiments the constant-current tests were carried out first, and then the constant-voltage tests. However, the difference between the two curves in Fig. 13 cannot be explained as being due to a change in the properties of the nerve in the time which elapsed between the two sets of tests, for additional constant-current tests were made after the constant-voltage tests had been completed, and these agreed well with the earlier constant-current results.

The occurrence of "breakdown" at a shorter time-constant with constant-voltage stimulation than with constant-current stimulation is surprising. Since the nerve presumably presents a capacitive impedance, a constant-current stimulus of a given time-constant of rise should be equivalent to a constant-voltage stimulus rising more slowly. Hence, a phenomenon such as "breakdown" should be expected to occur with a shorter time-constant of rise when constant-current stimulating conditions apply, than when constant-voltage conditions apply. As has been seen, however, the experimental results indicate the opposite effect - "breakdown" occurs at a shorter time-constant under constant-voltage conditions. No explanation is offered for this finding.

The Form of the Accommodation Curve

The form of the accommodation curves shown in Figs. 1.8 - 1.13 is not in accordance with Hill's theory. To conform to the theory the curves should be almost straight lines, except for slight curvature at the lower ends. Curve 4 in Fig. 1.14 shows the form of a curve conforming to Hill's theory. It never becomes horizontal as the experimental curves frequently do. In other words the "breakdown" of accommodation is not accounted for by the theory.

Although the phenomenon of "breakdown" and the failure of Hill's theory to account for it, have been discussed at length by Bernhard, Granit and Skoglund (1942) and Granit (1947), it does not appear to have been realised that Hill's theory can readily be modified to take account of "breakdown of accommodation". It is possible, however, that the possibility of extending Hill's theory may have been realised, but rejected because the extended theory does not fit very well with observations on electrotonic changes of excitability, such as those of Skoglund (1945). The mathematical treatment which follows was worked out before Skoglund's results (which are in a rather little-known journal) had been seen. It is thought to be worth reporting, in spite of Skoglund's findings, since it accounts for "breakdown of accommodation" rather elegantly, and may not be entirely irreconcilable with Skoglund's results.

THE MODIFIED HILL'S THEORY

To produce a modified form of Hill's (1936a) theory, which takes account of "breakdown of accommodation", it is only necessary to refrain from making one of the simplifying assumptions which Hill makes in developing his theory. This is the assumption which Hill introduces as follows:- "We shall assume, therefore, for simplicity, that in a nerve 'fully accommodated' to the passage of a constant current the excitability is the same as it was originally, i.e. that the *extra* current required to excite is the same as the original rheobase." By making this assumption, Hill greatly simplifies his mathematics, but he plainly considers that the assumption is a weak point in the theory, for he states elsewhere in his paper:- "The statement given above of the two time-factors in electric excitation is the simplest possible one, and it is realised only too clearly that in certain respects it is inadequate. Its chief weakness is that it deals only with 'normal accommodation', in which, after full 'accommodation' to a constant current, (U - V) attains its original value ($U_0 - V_0$). It takes no account, therefore, of electrotonic changes of excitability along a nerve in which current is flowing: these are regarded as secondary, for conditions are known in which they do not occur. This weakness will often make it impossible in experimental work to obtain exact quantitative agreement with the formulae given above, for electrotonic changes of excitability will have set in during the passage of the current considered."

The differential equations which, according to Hill's theory, describe the behaviour of a nerve with respect to electrical stimulation, are: -

$$\frac{dV}{dt} = bI - \frac{V - V_0}{k} \qquad (22)$$

and

$$\frac{dV}{dt} = \frac{V - V_0}{\beta} - \frac{U - U_0}{\lambda} \qquad (23)$$

where V is the "local potential" or "excitatory state", with resting value V_0, and U is the threshold (with resting value U_0) which V must reach to produce propogated excitation. The quantities b, k, β and λ are constants of the nerve, and all except b have the dimension of time.

At any instant, the quantity $(U - V)$ may be regarded as the amount by which the nerve fails to be excited, and the additional stimulus required to excite is proportional to this quantity. The assumption made by Hill is that if a steady current, say I_1, flows for a long time, the final equilibrium values U_1 and V_1 reached by U and V are such that

$$U_1 - V_1 = U_o - V_o \qquad (24)$$

That is to say, the additional stimulus required to excite the nerve when there is a steady current flowing through it is the same as the stimulus required to excite the resting nerve.

It can be shown from equations (22), (23) and (24) that if the above assumption is made, the two constants β and λ are equal. Hill is therefore able to dispense with the constant β, and takes k and λ as the two time-constants of excitation.

Equations (22) and (23) can be integrated as follows (assuming $U = U_o$; $V = V_o$ when $t = 0$):-

$$V - V_o = b\, e^{-\frac{t}{k}} \int_{\theta=0}^{\theta=t} I_\theta\, e^{\frac{\theta}{k}}\, d\theta \tag{29}$$

$$U - U_o = \frac{e^{-\frac{t}{\lambda}}}{\beta} \int_{\theta=0}^{\theta=t} (V_\theta - V_0)\, e^{\frac{\theta}{\lambda}}\, d\theta \tag{30}$$

where the suffix θ denotes that V is a function of θ.

Exponentially rising currents, as used experimentally to determine the accommodation curve, are represented by

$$I_t = I_2 (1 - e^{-\frac{t}{\alpha}}) \tag{31}$$

where α is the time-constant of rise of current and I_2 is the final current value reached.

Hence, for exponentially rising current

$$V - V_o = b\, e^{-\frac{t}{k}} \int_0^t I_2 \left(1 - e^{-\frac{\theta}{\alpha}}\right) e^{\frac{\theta}{k}}\, d\theta \tag{32}$$

and Hill integrates this expression to obtain

$$V - V_o = b\, k\, I_2 \left[1 - \frac{e^{-\frac{t}{k}}}{1 - \frac{\alpha}{k}} - \frac{e^{-\frac{t}{\alpha}}}{1 - \frac{k}{\alpha}} \right] \tag{33}$$

Substituting this value for $(V - V_o)$ in equation (30) and integrating yields the expression

$$U - U_o = \frac{\lambda}{\beta} b\, k\, I_2 \left[1 - \frac{e^{-t/k}}{(1-\frac{\lambda}{k})(1-\frac{\alpha}{k})} - \frac{e^{-t/\alpha}}{(1-\frac{\lambda}{\alpha})(1-\frac{k}{\alpha})} - \frac{e^{-t/\lambda}}{(1-\frac{k}{\lambda})(1-\frac{\alpha}{\lambda})} \right] \qquad (34)$$

which, in Hill's case, is simplified by omitting the term λ/β, since according to his assumptions $\lambda/\beta = 1$.

Hill simplifies equations (33) and (34) by omitting the last term in the bracket in each case. He shows that this is permissible when, as is usual, $k \ll \lambda$, and the utilisation time is not less than about five times k. Equations (33) and (34) become

$$V - V_o = b\, k\, I_2 \left[1 - \frac{e^{-\frac{t}{\alpha}}}{1 - \frac{k}{\alpha}} \right] \qquad (33')$$

$$U - U_o = b\, k\, I_2 \left[1 - \frac{e^{-\frac{t}{\alpha}}}{(1-\frac{\lambda}{\alpha})(1-\frac{k}{\alpha})} - \frac{e^{-\frac{t}{\lambda}}}{(1-\frac{\alpha}{\lambda})(1-\frac{k}{\lambda})} \right] (34')$$

The conditions for threshold stimulation are

$V = U$ and $dV/dt = dU/dt$

Applying the second of these conditions to equations (33') and (34'), Hill finds, for the utilisation time t_1 (i.e. the time, measured from the start of the stimulating current at $t = 0$, at which the conditions for excitation are satisfied):-

$$\frac{t_1}{\alpha} = \frac{\log\left(\frac{\alpha - k}{\lambda - k}\right)}{\alpha/\lambda - 1} \tag{35}$$

which, if k is small compared with α and λ, becomes

$$\frac{t_1 - k}{\alpha} = \frac{\log \frac{\alpha}{\lambda}}{\frac{\alpha}{\lambda} - 1} \tag{35'}$$

Then, putting $U = V$ and inserting the value of t_1, simplifying and putting $U_0 - V_0 = b\,k\,I_0$, Hill obtains

$$\frac{I_2}{I_0} = \left(1 - \frac{k}{\lambda}\right)\left(\frac{\alpha - k}{\lambda - k}\right)^{\frac{\frac{\alpha}{\lambda}}{\alpha/\lambda - 1}} \tag{36}$$

If $\frac{k}{\alpha}$ and $\frac{k}{\lambda}$ are small, this becomes

$$\frac{I_2}{I_0} = \left(\frac{\alpha}{\lambda}\right)^{\frac{\alpha/\lambda}{\alpha/\lambda - 1}} \tag{36'}$$

This is the equation given by Hill to represent the "accommodation curve" for values of α greater than about 10 × k. The form of the curve represented by equation (36') is shown as curve 4 of Fig. 1.14.

To extend Hill's theory by refraining from making the assumption that $\beta = \lambda$, the equation corresponding to equation (34') must include the term λ/β which appears in equation (34) :-

$$U - U_0 = \frac{\lambda}{\beta}\, b\, k\, I_2 \left[1 - \frac{e^{-t/\alpha}}{\left(1 - \frac{\lambda}{\alpha}\right)\left(1 - \frac{k}{\alpha}\right)} - \frac{e^{-t/\lambda}}{\left(1 - \frac{\alpha}{\lambda}\right)\left(1 - \frac{k}{\lambda}\right)} \right] \qquad (34'')$$

The expression obtained for the utilisation time, corresponding to equation (35') is

$$\frac{t_1 - k}{\alpha} = \frac{\log \dfrac{1}{1 - \beta/\lambda + \beta/\alpha}}{\alpha/\lambda - 1}$$

$$= - \frac{\log\left(1 + \frac{\beta}{\alpha} - \frac{\beta}{\lambda}\right)}{\alpha/\lambda - 1} \qquad (35'')$$

From equations (33'), (34'') and (35'') and the relation U = V, and making the assumption that k is small compared to the other time-constants, the expression for the accommodation curve is found to be

$$\frac{I_2}{I_0} = \frac{1}{1 - \frac{\lambda}{\beta} + \frac{\lambda}{\beta}\left(1 + \frac{\beta}{\alpha} - \frac{\beta}{\lambda}\right)^{\frac{\alpha}{\alpha - \lambda}}} \qquad (36'')$$

It is easily verified that for $\beta = \lambda$ this expression reduces to Hill's expression, given in Equation (36').

Breakdown of Accommodation. Breakdown of accommodation is readily accounted for by the extended form of Hill's theory. Consider a nerve, to which is applied a steady current I_1. Then we may write down the two basic equations of Hill's theory

$$dV/dt = b\,I_1 - (V - V_o)/k \tag{37}$$

$$dU/dt = (V - V_o)/\beta - (U - U_o)/\lambda \tag{23}$$

When the nerve is "fully accommodated", that is to say, when the current has been flowing for a long time and U and V have come into equilibrium, $dU/dt = dV/dt = 0$ and therefore

$$b\,I_1 = (V - V_o)/k$$

$$\text{or} \quad V - V_o = b\,k\,I_1 \tag{38}$$

$$\text{and} \quad (U - U_o)/\lambda = (V - V_o)/\beta = b\,k\,I_1/\beta$$

$$\text{or} \quad U - U_o = b\,k\,\lambda\,I_1/\beta$$

From equations (38) and (39),

$$U - V = (U_o - V_o) + b\,k\,I_1\,(\lambda/\beta - 1)$$

$$= b\,k\left\{I_o - I_1(1 - \lambda/\beta)\right\}$$

where I_o is the rheobase.

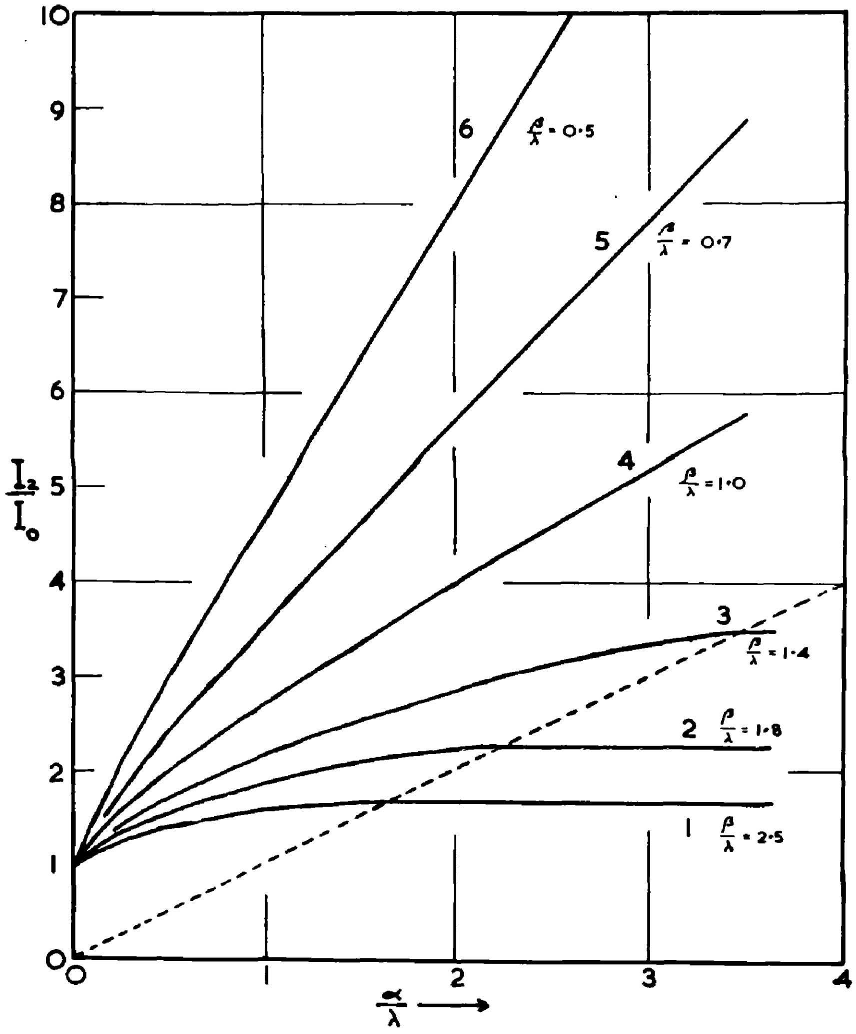


Fig. 1.14. Theoretical accommodation curves according to the extended Hill's theory.

Breakdown of accommodation occurs when the value of I_2 (the "final value" of the exponentially-rising current, as defined by equation 31) is sufficiently great that when the nerve is fully accommodated to it, the condition for excitation is satisfied. That is to say, when the nerve is fully accommodated to this current, $U - V = 0$. Breakdown must then occur, for the conditions of excitation are satisfied, no matter how slowly the current has risen to the value I_2.

Hence, breakdown occurs when

$$I_0 - I_2(1 - \lambda/\beta) = 0$$

$$\text{or } I_2 = \frac{I_0}{1 - \frac{\lambda}{\beta}} \qquad (40)$$

From equations (36) and (40) it can be shown that the value of the time-constant α at which breakdown occurs is given by

$$\frac{\alpha}{\lambda} = \frac{I_2}{I_0} = \frac{1}{1 - \frac{\lambda}{\beta}} \qquad (41)$$

Fig. 1.14 shows the form of the accommodation curves represented by equation (36''), with breakdown occurring where the curves meet the straight line whose equation is

$$\alpha/\lambda = I_2/I_0 \text{ (from equation 41).}$$

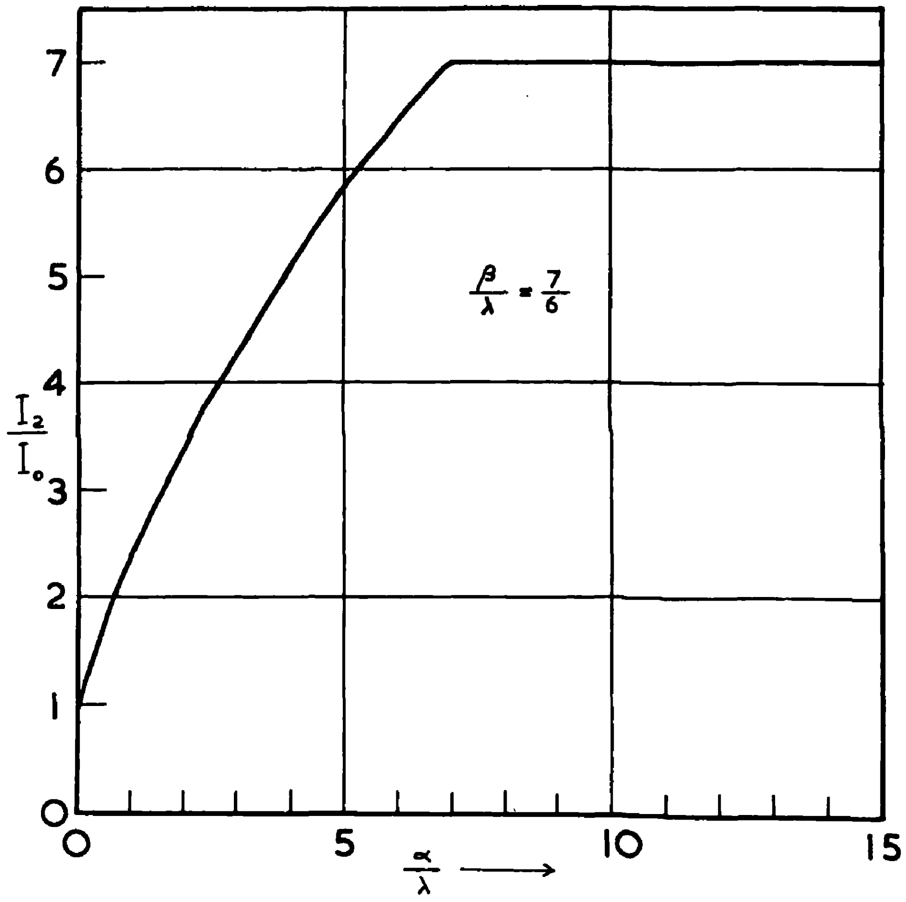


Fig. 1.15. Theoretical accommodation curve according to the extended Hill's theory.

Curve no. 4 in Fig. 1.14 corresponds to $\beta/\lambda = 1$, and therefore to the case considered by Hill. Curves 4, 5 and 6 correspond to $\beta/\lambda \leqslant 1$, and there is no breakdown of accommodation in these cases.

None of the curves of Fig. 1.14 resembles the experimental curves in Figs. 1.8 - 1.13, but the theoretical curves corresponding to values of β/λ only slightly greater than unity are very similar to the experimental curves. Fig. 1.15 shows a theoretical curve for $\beta/\lambda = 7/6$ and the agreement with the experimental curves is very close.

Curves 2 and 3 of Fig. 1.14 are similar to the experimental accommodation curves obtained by Wigton and Brink (1944) for the human ulnar nerve. Thus there is good agreement between the curves derived from the modified form of Hill's theory, and experimental curves obtained both with frog nerve and with human nerve.

It should be mentioned that Katz (1937b) published curves showing the theoretical variations of the quantities U and V following the start of a constant current, and considered the case of $\lambda \neq \beta$.

Katz thus made a first step towards extending Hill's theory as has been done in the foregoing. However, he did not point out that the"breakdown of accommodation" can be accounted for by the extended theory. At the time of publication of Katz's paper, "breakdown" had not been discussed widely, and possibly had not been discovered at all.

Other theories of excitation. The theory of nerve excitation due to Rashevsky (1933) can also account for "breakdown of accommodation". Rashevsky's equations are

$$\frac{de}{dt} = K I - k(e - e_0) \qquad (42)$$

$$\frac{di}{dt} = MI - m(i - i_0) \qquad (43)$$

with excitation occurring when $e = i$.

e_0 and i_0 are resting values of the variables e and i, and $e_0 < i_0$; K, M, k and m are constants of the nerve.

I is the applied current.

If the nerve is allowed to become fully accommodated to a current I_1, the following relations hold when the current has been flowing for a sufficiently long time: -

$$0 = K I_1 - k(e - e_0)$$

$$0 = M I_1 - m(i - i_0)$$

$$e = e_0 + \frac{K}{k} I_1$$

$$i = i_0 + \frac{M}{m} I_1$$

Excitation can occur if $e \geqslant i$

$$e_0 + \frac{K}{k} I_1 > i_0 + \frac{M}{m} I_1$$

$$\left(\frac{K}{k} - \frac{M}{m}\right) I_1 > i_0 - e_0$$

Hence if $(\frac{K}{k} - \frac{M}{m})$ is positive, excitation can occur for a steady current of value

$$I_1 = \frac{i_0 - e_0}{\frac{K}{k} - \frac{M}{m}} \qquad (44)$$

no matter how slowly the current rises. Thus there is "breakdown of accommodation" at this current value.

Rashevsky does not give this explanation of "breakdown" in his paper, for he states as a basic principle of his theory that "very slowly rising currents do not excite", which is equivalent to saying breakdown cannot occur. Because his theory must conform to this principle, Rashevsky states that $(\frac{K}{k} - \frac{M}{m})$ must be negative $(M/m > K/k)$, but as has just been shown, it is possible to account for breakdown of accommodation if $(\frac{K}{k} - \frac{M}{m})$ is positive.

No attempt has been made to decide whether the phenomenon of breakdown is better represented by the extended form of Hill's theory or by the slightly modified form of Rashevsky's theory, described above. It is unlikely that the results obtained by applying the two theories would be sufficiently different to make it possible to choose between them.

According to Tasaki's (1950) theory about the conditions for excitation by slowly-varying voltages, breakdown of accommodation cannot possibly occur since a certain minimal voltage gradient must be attained before excitation occurs, whatever the current amplitude. It must be remembered that Tasaki's results are for nerve under the special conditions of the single-fibre bridge-insulator preparation. Also, in Tasaki's experiments the nodes of Ranvier adjacent to the one under investigation were in pools of cocainised Ringer, and it has been shown by Frankenhaeuser (1952) that the properties of the nerve are different if the cocaine is not used.

Criticisms of the extended Hill's theory

Hill's theory has been extended by refraining from making the simplifying assumption that $\beta = \lambda$. This assumption, when it is made, is equivalent to the assumption that there are no electrotonic changes in excitability. Since the modified theory allows electrotonic changes in excitability, it is of interest to compare the changes calculated according to the theory with those obtained experimentally. It is found that the agreement between theory and experiment is poor, and this is a serious criticism of the extended Hill's theory.

To find what excitability changes would conform to the theory, consider once more a nerve to which is applied a steady current I_1 (the current producing electrotonus). The equations for U and V are

$$\frac{dV}{dt} = bI_1 - \frac{V - V_o}{k} \qquad (37)$$

$$\frac{dU}{dt} = \frac{V - V_o}{\beta} - \frac{U - U_o}{\lambda} \qquad (23)$$

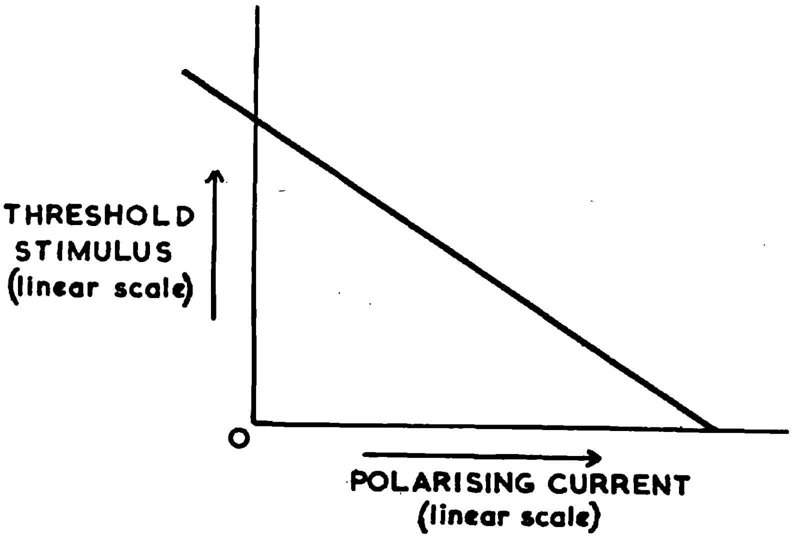


Fig. 1.16. Electrotonic changes in excitability conforming to the extended Hill's theory. (Cathodal stimulus and polarising current).

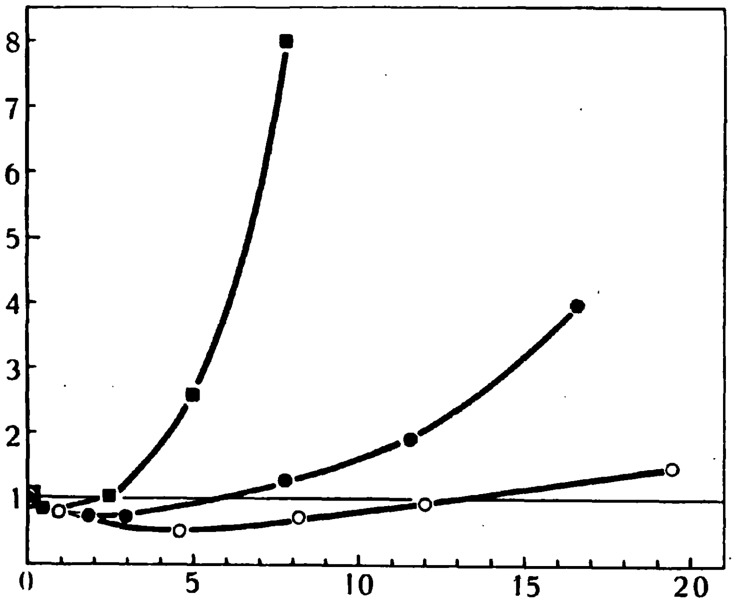


Fig. 1.17. Electrotonic changes observed by Skoglund. See caption of Fig. 1.18.

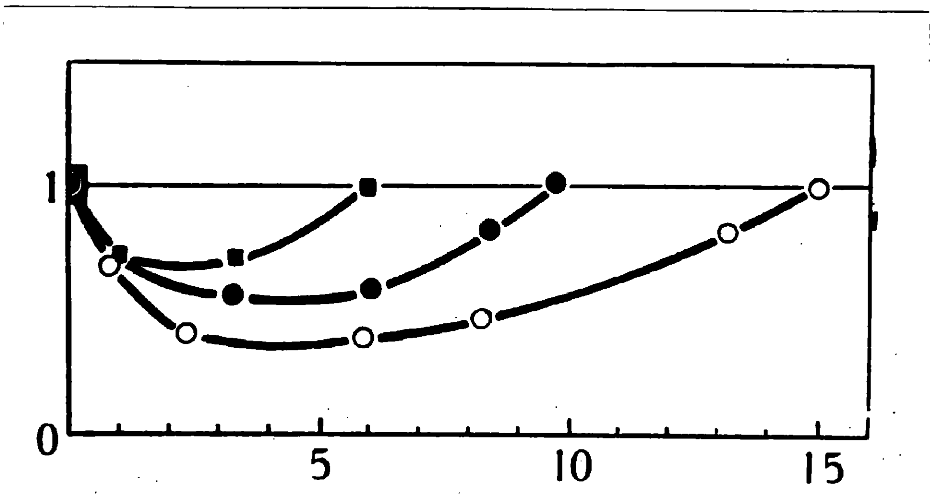


Fig. 1.18. Electrotonic changes in excitability observed by Skoglund. Both Fig. 1.17 and Fig. 1.18 are from Skoglund (1945). Both show results for the frog sciatic nerve, the index of excitation being half-maximal amplitude of the nerve action-potential. In both diagrams, the filled circles show results for freshly-excised nerve in Ringer, the open circles show results obtained after treatment of the nerve with citrate, and the squares are for nerve after treatment with calcium-rich Ringer.

and it is easily shown that for the fully accommodated nerve,

$$U - V = bk \left\{ I_0 - I_1 \left(1 - \frac{\lambda}{\beta}\right) \right\}$$

The magnitude of the threshold stimulus at any time is proportional to (U - V), and hence in this case is proportional to

$$I_0 - I_1 \left(1 - \frac{\lambda}{\beta}\right)$$

where I_0 is the rheobase and I_1 the polarising current.

It follows that the graph of threshold stimulus against polarising current I_1 should be, according to the theory, a straight line as in Fig. 1.16.

There is a good deal of evidence in the literature to show that the experimental graph is not in fact a straight line. The most thorough examination of the electrotonic changes of excitability is that by Skoglund (1945). Figs. 1.17 and 1.18 are from his paper, and show the graphs of threshold stimulus against polarising current for frog nerve under three different sets of conditions. The curves are certainly not linear, but they are clearly for a nerve which does not show "breakdown" under any of the conditions of the experiment. If it did, the corresponding curve in Figs. 17 and 18 would meet the x-axis (threshold stimulus = zero) for the value of polarising current producing breakdown. Hence, the experimental curve under conditions producing "breakdown" might not differ very seriously from Fig. 1.16, over the range of cathodal polarising currents between zero and the current producing breakdown of accommodation. This is the range of current which is important for the extended Hill's theory. In cases where breakdown occurs, therefore, the extended Hill's theory may be a reasonable approximation to the true behaviour of nerve, but not in other cases. Further experimental work is indicated here, to obtain curves corresponding to Skoglund's for nerves under conditions which produce "breakdown of accommodation". It is hoped to attempt this in the future.

Further evidence that the changes in threshold are a non-linear function of the polarising current is provided by Erlanger and Blair (1931b). They show a graph of a quantity proportional to the reciprocal of threshold stimulus, against polarising current. The graph is approximately represented by the equation

$$y = x - b e^{ky} \tag{45}$$

where y is proportional to the reciprocal of threshold stimulus (and hence is directly proportional to the excitability) and x is the polarising current. b and k are constants, having no connection with the same symbols used in Hill's theory. Equation (45) does not lend itself to simple mathematical treatment, but it can readily be seen that it represents a very non-linear relationship between the size of the threshold stimulus and the polarising current, and therefore is not in accordance with the modified Hill's theory. However, the experiments of Erlanger and Blair also were on nerves which did not show "breakdown of accommodation".

Tasaki (1950) considers that the main effects of electrotonus is to alter the value of the minimum voltage gradient required to excite. His findings are difficult to relate to the modified Hill's theory. His theory about the conditions for excitation by slowly-varying voltages does not admit the possibility of "breakdown of accommodation".

Rosenblueth (1941a and b) has also examined the effects of d.c. currents on the excitability of nerve, and has obtained results which are much too complex to fit into any simple theory. He states (1941a) "There may be an increase or a decrease of excitability at the anode or the cathode during or after the passage of d.c." He finds that application of d.c. not only affects the rheobase, but also the value of Hill's time-constant k. However, the outstanding change produced by d.c. was in the rheobase.

It is clear from the findings of Skoglund, Tasaki and Rosenblueth that the extended form of Hill's theory does not account for the changes in nerve excitability produced by passing d.c. through the nerve. However, in view of the good agreement between the experimental accommodation curves and those derived from the theory in cases where "breakdown of accommodation" occurs, it is possible that the extended theory provides a reasonable approximation to the behaviour of nerve in these cases, over a certain range of applied current. It is possible that some of the experimental evidence on electrotonic changes of excitability is not applicable to the analysis of the accommodation curve because of the difference in the duration of current flow in the electrotomic and accommodation experiments.

APPENDIX TO PART I (b)

The exponential stimulator: the possibility of an additional factor in stimulation.

A defect in the exponential stimulator was recently noticed by Mr. Alan Cairnie. It was found that, at the moment of initiation of the desired stimulating current, a brief spurious pulse of current was delivered by the stimulator. The spurious pulse was extremely brief, and consequently had not previously been observed when the output waveform of the stimulator was examined on an oscilloscope. The way in which the spurious pulse was produced, and how the stimulator can be modified to eliminate it, will be discussed in Part 7. The pulse was produced because of a property of gas - discharge tubes which was not appreciated at the time the stimulator was built. This property of gas-discharge tubes has since been investigated in a different connection (Andrew, 1952c) and will be discussed in Part 8.

Although the spurious pulse was brief, it may have influenced the experimental results obtained using the stimulator, In particular, the observation of "breakdown of accommodation" may possibly have been due to this spurious pulse, and not to a genuine property of the nerve. The amplitude of the spurious pulse depended on the output-current setting of the stimulator. Hence, the apparent "breakdown of accommodation" may have been caused by the spurious pulse becoming large enough to excite the nerve by itself. An apparent "breakdown" would then have been observed because excitation would have been obtained at the same current-setting for all longer time-constants of rise of the main part of the current.

It is by no means certain however, that the apparent "breakdown of accommodation" seen in the experimental results can be dismissed as an artefact due to the spurious pulse. It is clearly necessary to repeat the experiments to make sure. In any case, the phenomenon of "breakdown" has been reported by other workers. The extension of Hill's theory to take account of "breakdown" may therefore have applications apart from the experimental results quoted here.

PART 2

EXPERIMENTS ON THE OPTIC LOBES OF THE FROG

From a photograph by W.T. Davidson in Photography (Ziff-Davis Publishing Co., New York), March 1952. The original photograph is one of a series, in colour.

PART 2. EXPERIMENTS ON THE OPTIC LOBES OF THE FROG

In the frog, the superior colliculi (optic lobes) offer a convenient site for the study of visual function. They can be fairly easily exposed, and the electrical activity, in response to light stimuli, can be explored using a micro-electrode.

The Function of the Superior Colliculi

In a variety of animals, the superior colliculi (usually termed optic lobes or optic tectum in the case of birds, amphibia and fish) have been shown to be associated with vision. In amphibia, they appear to be the main part of the central nervous system dealing with vision. A point-to-point representation of the retina on the superior colliculus has been reported by Apter (1945) in the cat, by Cooper, Daniel and Whitteridge (1953c) in the goat, and by Hamdi and Whitteridge (1953 and 1954) in the goat, rabbit and pigeon. A representation of the retina on the optic lobes of fish has been reported by Buser and Dusardier (1953), and there is evidence from the work of Sperry (1944) that such representation also exists in the frog. Sperry's evidence comes from ablation experiments. He destroyed parts of the optic lobes in frogs and then noted the responses to a lure held in different parts of the visual field. He found there was no response to a lure held in a forward part of the visual field of one eye when the anterior part of the contralateral optic lobe had been destroyed. Similarly, removal of the posterior part of a lobe interfered with backward vision, and removal of the ventral part with vision in the lower part of the visual field. These results strongly suggest a point-to-point representation of the retina on the optic lobe. The work here described provides further evidence for this representation in the frog, though it has not been mapped in detail.

Besides the above-mentioned evidence that the superior colliculi are concerned with vision, there is evidence from the work of Apter (1946) that in the cat the superior colliculi play a part in directing the animal's eyes. Apter placed a small quantity of strychnine on the surface of one superior colliculus and found that, in response to diffuse illumination of the whole visual field, the animal's eyes would turn towards the point in the field corresponding to the point on the colliculus to which the strychnine had been applied. There is also evidence, discussed by Hamdi and Whitteridge (1954), that the optic lobes of birds are concerned with reflex movements in response to visual stimuli, and in particular with directing the eyes in this case also. In birds, the direction of the eyes is determined mainly by the position of the head, and it has been found that stimulation of the optic tectum, either electrically or by strychnine, produces head movements. Akert (1949), quoted by Hess (1954, p. 55), describes experiments on trout which indicate that here, also, stimulation of the optic tectum produces both eye and body movements which combine to direct the gaze in a particular direction. It appears that in a wide variety of animals the superior colliculi are concerned with directing the gaze, by means of both eye and body movements.

In the case of monkeys (macacus sinicus and rhesus), however, it has been shown by Ferrier and Turner (1901) that oculo-motor action is retained after complete ablation of the superior colliculi. Nothnagel (1889) discusses the symptoms of disease of the corpora quadrigemina in man and states that ophthalmoplegia is not always observed in patients with disease of these bodies. He gives the opinion that ophthalmoplegia, when it does occur, is not a direct result of the disease of the quadrigeminal bodies, but is due to involvement of neighbouring structures. It is possible that in the primates most of the function of the superior colliculi has been taken over by the cerebral cortex. However, the observations of Ferrier and Turner and of Nothnagel only show that co-ordinated eye movements are possible without the superior colliculi; they do not show that the superior colliculi play no part in directing the eyes.

Experiments involving ablation of the superior colliculi of cats have been described by Keller and Stewart (1932) and Magoun (1935), but these workers do not report whether or not the eye movements were affected. They do report that the pupillary light reflex was unaffected, so it appears the superior colliculi are not essential for this reflex to occur.

My investigations of the superior colliculi were at first directed toward obtaining information about the influence of the superior colliculi on posture and motion. I was invited by Dr. Warren McCulloch to spend a year at the Massachusetts Institute of Technology working on this problem. The evidence reviewed above shows that the superior colliculi are concerned with directing the eyes. There is no direct evidence that in the higher animals they influence head movements since, in the experiments of Apter (1946), the head was held steady by the apparatus. It is reasonable to suppose that the colliculi may affect posture and motion in all animals, perhaps via a colliculo-spinal tract, so attempts were made to verify this.

COLLICULO-SPINAL PATHS

Work on frogs

Experiments were begun on the optic lobes of the frog. The frogs used in all experiments described in this part of this thesis were of the same size as rana temporaria, the species commonly used in Britain. Most of them were of the species rana pipiens. The others were not definitely identified, but were probably rana palustris.

A micro-electrode was inserted at points throughout the optic lobes of anaesthetised frogs and electrical stimuli were given by passing current between the micro-electrode and one of the pins securing the frog to the frog-board. Current pulses of one millisecond duration, with a repetition frequency of 40 per second were generally used, though other durations and frequencies were also tried. A special stimulator with very high output impedance was used, and the current strength required to produce an effect was in the region of 0·2 mA. Except for the head, the frog lay on a sheet of wet glass, and therefore movements of the limbs met with very little frictional resistance. Eye or limb movements resulting from the electrical stimulation were noted.

In all such preparations the only response which occurred with reasonable consistency was retraction and closing of the eyes. When only one eye responded in this way, it was invariably the one on the same side as the stimulating electrode. This response may not have been due to collicular activity at all, since the stimulation was monopolar and consequently its effect was not very well localised. The electrode used was a silver one of the same kind as was used for recording from the optic lobes, which will be described.

Other responses observed included extension of the limbs, more commonly of the hind limbs than of the fore limbs, with fanning of the toes. More rarely, flexion occurred, and on one occasion stimulation of the middle of the right colliculus at a depth of 0·5 mm caused flexion of the left leg and extension of the right.

Stimulation at a depth of 1•5 mm frequently caused powerful limb movements, often amounting to struggling, sometimes with acceleration of the breathing and croaking. Since the thickness of the optic lobes is only about 1•5 mm, the electrode was presumably stimulating deeper structures when this occurred.

Except for the eye retraction and closing, which could be elicited with the stimulating electrode in any part of the colliculus, no clear patterns of response to collicular stimulation emerged. This is surprising in view of the findings of Akert (1949), quoted by Hess (1954, p. 35), who stimulated the optic tectum of fish (trout) and obtained characteristic movements of eyes and body. Akert used an unusual anaesthetic (MS 222 Sandoz) which is stated to be exceptionally well-suited to cold-blooded animals (Rothlin, 1932). The experiments described here were tried under a variety of conditions of anaesthesia but the one used by Akert was not used. Some of this anaesthetic has now been obtained and I plan to repeat the experiments using it.

Anaesthesia for frogs. In the above-mentioned experiments, the frogs were usually anaesthetised by injecting urethane (3% solution, the quantity determined as described below) into the lymph space of the back, and then exposing to ether vapour for approximately 60 secs. By this means a very light urethane anaesthesia was produced. The amount of urethane injected was insufficient to induce anaesthesia by itself, but maintained it when the effect of the ether had worn off. The amount of urethane required varied widely from frog to frog, but was fairly constant within a particular batch. The amount which had to be injected when using the above (urethane plus ether) procedure was about 2/3 of the amount needed to induce anaesthesia in another frog of the same batch when urethane was used alone. This amount varied from 4·5 ml of 3% solution for very lively frogs, to 1·2 ml for frogs which had been stored a long time. The corresponding amounts when used in conjunction with ether were 3 ml and 0·8 ml.

Urethane anaesthesia induced by immersion was also tried, but it is difficult to standardise and usually results in deeper anaesthesia than does the urethane-ether method. When ether was used alone, it was difficult to maintain a steady level of anaesthesia. Nembutal was also tried as an anaesthetic (injected as a dilute solution into the lymph space of the back) but was quite unsuitable since the frog was quickly killed by a quantity only slightly greater than that which allowed it to remain apparently conscious.

Stimulation with implanted electrodes

In an attempt to observe the effects of collicular stimulation in an unanaesthetised frog, two ways of implanting electrodes were devised. The electrodes were implanted under ether anaesthesia, from which the animal was allowed to recover. Then the optic lobes of the unanaesthetised frog were stimulated through flexible leads while it swam in a small tank. The first type of implanted electrode tried consisted simply of a steel needle insulated except at the tip and pushed through the skull. Stimulating current was passed between the electrode and the water in which the frog swam. With such electrodes, it was found with one frog that stimulation in the region of the posterior part of the left optic lobe caused the frog to swim in a tight circle, clockwise. Stimulation in the posterior part of the right optic lobe caused the frog to sink to the bottom.

A type of bipolar electrode was developed which could be placed in contact with the exposed optic lobe and then cemented in place by filling the hole in the skull with dental cement. With these electrodes the stimulus was more accurately localised in the optic lobes, and the earlier results did not reappear. The bipolar electrodes were successfully implanted in two frogs. In one the connection was between the left and right lobes. In the other the connection was across the posterior lateral part of the right optic lobe. In each frog, the response to stimulation was a general "panic" reaction, in which the frog darted rapidly and seemingly randomly. The strength of the stimulus was continuously variable, and no effects were observable at strengths lower than that which caused the "panic" effect.

Experiments on Cats

Experiments on cats were conducted as part of the project to investigate the effect of the superior colliculi on posture and motion. This part of the work was mainly carried out by Dr. J.Y. Lettvin and Dr. P.D. Wall of the Massachusetts Institute of Technology, with my assistance. The results of three of these experiments will be briefly described here, though I do not claim them as my own.

Projection of the superior colliculus on the spinal cord in cats.

A test was made for projection of the colliculus on the sixth cervical segment of the spinal cord, by antidromic stimulation. An exposure of one superior colliculus was made by removing the occipital cortex of a cat under fairly deep Dial anaesthesia. Recording electrodes were placed on the colliculus. The spinal cord was exposed at the level of the sixth cervical segment, and six bipolar microelectrodes were inserted in turn and made to advance through the cord along six separate tracks. The electrodes were advanced 0·15 mm at a time, and a stimulating current was passed at each halt. From none of these stimuli was any response observed at the superior colliculus, although at the same time good responses were obtained from an electrode in the pyramids, due to antidromic stimulation of corticospinal fibres.

From the histological findings of Rasmussen (1936), some response at the colliculus should have been expected in the above experiment, since Rasmussen reports a tectospinal tract in the cat, arising wholly in the superior colliculus, and ending "conspicuously about the motor nuclei in the lower region of the medulla oblongata and ventral horn cells of the upper seven cervical segments of the spinal cord". Hence there are fibres which connect the superior colliculus with the sixth cervical segment. The probable explanation of the negative result in the experiment is that the proportion of fibres reaching the sixth segment is small, and the effect produced at the superior colliculus by stimulation at the sixth segment was too small to be detected.

Projection of the superior colliculus on the cerebellum in cats.

A preliminary test for a projection of the superior colliculus on the cerebellum gave negative results. This test was made on a cat under Dial anaesthesia. Since clear cerebellar responses were obtained in the later experiment described below, it appears that the cerebellar response is abolished by Dial anaesthesia. The cat appeared to be in good condition when the negative result was obtained, so the anaesthesia is the most probable explanation.

A later experiment, conducted in such a manner that the preparation was free from anaesthesia when the observations were made, showed a definite projection of the superior colliculus on the cerebellum. A cat was

SHADED AREAS - GOOD RESPONSES WERE OBTAINED ON COLLICULAR STIMULATION

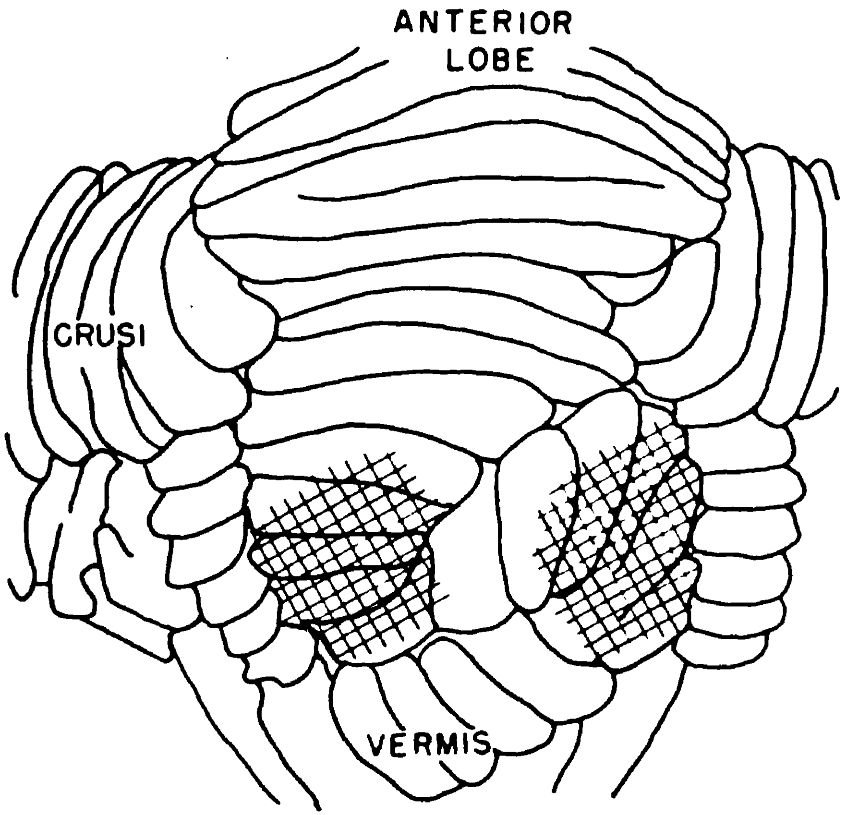


FIG. 2.1. DIAGRAM OF CEREBELLUM, AFTER SNIDER

anaesthetised with ether and spinalised. The cerebral cortex was remove bilaterally, and the thalamus destroyed. No further ether was given, so the animal was free from anaesthetic when the experiment began. A concentric bipolar electrode was placed on the left colliculus and another was used to explore the cerebellum.

The anterior portion of the left colliculus was stimulated, and responses were recorded from numerous points on the exposed surface of the cerebellum. An interesting feature of the response of the cerebellum is that two small shocks with a separation in time of 3 msec, applied to the colliculus, gave a much greater cerebellar response than was produced by a single shock of greater amplitude.

Good cerebellar responses were obtained from the areas shown shaded in Fig. 2.1. These areas approximately coincide with two of the three areas from which Snider and Stowell (1944) obtained good responses when flashing a light before the right eye. The third of the areas described by Snider and Stowell was outside the region of the cerebellum exposed in our experiment. The shortest latency observed for these responses was 3 msec.

No electrical response could be detected at the colliculus when the cerebellum was stimulated. From this it appears that the pathways from superior colliculus to cerebellum go through synapses.

Since the pattern of cerebellar activity resulting from stimulation of the left superior colliculus is similar to that resulting from photic stimulation of the right eye, it is possible that the cerebellum receives visual stimuli only through the superior colliculi. The existence of pathways from the superior colliculus to the cerebellum makes it appear likely that any effect which the superior colliculi have on posture and motion is at least partly produced through the cerebellum.

STUDY OF VISION IN THE FROG

The procedure which has been evolved for exposing the optic lobes of the frog and inserting a micro-electrode, provides a very convenient way of studying visual function. Electrical activity in response to visual stimulation has been picked up by micro-electrodes and suitably amplified and displayed on the cathode-ray oscilloscope.

Action potentials from the frog optic lobes in response to light stimulation have also been recorded by

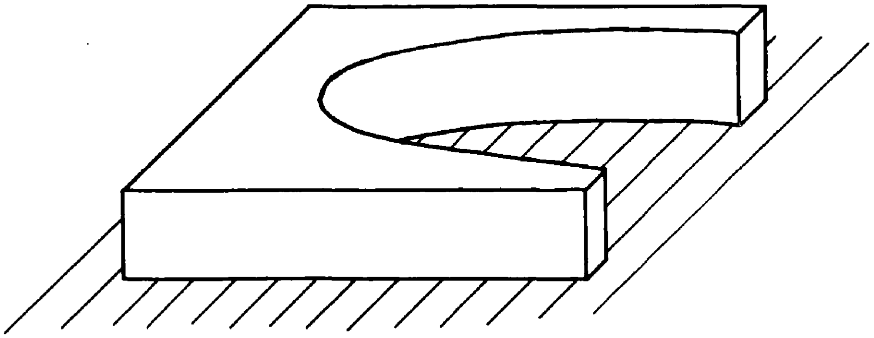


Fig. 2.2. "Dry dock" cut from 1/4" rubber sheet, used to support head of frog with minimum interference with breathing.

Beritoff and Tzkipuridze (1943). Their results will be discussed later.

Methods

In the earlier experiments the frogs were anaesthetised by the urethane-ether procedure already described. Good responses to visual stimulation were obtained from frogs anaesthetised in this way, but the procedure is difficult to use, since a very small amount of over-anaesthetisation can abolish the responses. Furthermore, there is no guarantee that the collicular activity under anaesthesia is similar to the activity in the absence of anaesthesia. The later experiments were therefore conducted without anaesthesia. The spinal cord, in these experiments was cut at the level of the shoulders or just below it, and the experiment proceeded with.

The frog was pinned down to a rubber or cork baseboard by a pin through the nose and one on each side immediately in front of the tympanic membrane. To make sure there was no interference with breathing, the underside of the head was not laid on the flat surface, but was supported round its periphery by resting on a shaped piece of 1/4" rubber sheet, as shown in Fig. 2.2. Also a small slip of wood (part of a toothpick) was inserted in the mouth like a horse's bit. It was found that the frog breathed more freely with this in place. In hot weather the body of the frog was covered with cotton wool which was kept wet.

To expose the optic lobes, a small area of skin was first removed from above the dome of the skull. Before the necessary opening could be made in the skull, some muscles had to be pushed backwards out of the way. This was done with the top end of the handle of a metal-handled scalpel. Any bleeding which started from the muscles was stopped by cauterisation with a miniature electric soldering iron. Two blood-vessels coming back from the eyes were also cauterised. Care was taken to have the soldering iron in contact with the skull for only very short periods of time.

A hole about 3/16" square was made in the skull, by running the tip of a pointed scalpel (no. 11 blade) along the sides of the square until the grooves were deep enough to allow the square to be prized out. Sometimes the square came out in one piece; at other times part of it came out at first and the remainder was picked out with forceps. The hole in the skull can if necessary be enlarged by using a fine pair of Spencer-Wells forceps as rongeurs, but there is a serious danger of starting severe bleeding when this is done. It is therefore best to make the hole large enough at the beginning.

The dura was generally removed so that the electrode could penetrate easily. The lobes were covered with liquid paraffin to prevent drying. The dura was punctured before the liquid paraffin was applied, using fine forceps and a fine hook made from the eye-end of a fine sewing needle. It was difficult to puncture the dura after the paraffin had been applied. After the paraffin was applied the puncture was extended until the surface of the optic lobes was clear of dura.

The micro-electrode was brought into position by a micro-manipulator giving movement in three dimensions. The vertical movement, by which the electrode was finally inserted into the optic lobe, was finely controlled by a micrometer head.

Electrodes

The electrodes consisted of a metal core coated with glass. Sometimes the metal was platinum, sometimes silver and sometimes antimony. Electrodes of this sort, having a platinum core, have been described by Pitts (1952). The platinum electrodes consisted of a platinum wire, 10 microns in diameter, coated with glass to an overall diameter of about 15 microns, and sharpened to a conical tip. The silver electrodes were similar, except that the wire had a diameter of 15 microns, and the overall diameter was about 20 microns. In making the platinum and silver electrodes the wire was not drawn out; it remained at its original diameter of 10 or 15 microns. In the antimony electrodes, on the other hand, the antimony was softened and drawn out when the electrode was drawn. Very fine electrodes, having an overall diameter of 2 or 3 microns at the tip, were produced in this way.

The choice of antimony as an electrode material may seem strange. The drawing-out of metal in glass to make very fine electrodes is not easy, and breaks frequently occur in the column of metal. The physical properties of antimony are such, however, that electrodes can be drawn fairly readily when antimony is used. Other low-melting-point and medium-melting-point metals and alloys have been tried without much success. Antimony was originally tried as a micro-electrode material by Dr. J.Y. Lettvin, for a special application in which the electro-chemical properties of antimony led to its choice. This was an application in which a micro-pH-electrode was wanted for intracellular use.

An antimony electrode~~s~~ was used when an electrode was required of smaller diameter than the silver or platinum electrodes. Antimony electrodes were therefore used to look for single-unit responses, though these could also be observed sometimes with a platinum electrode.

When an electrode other than an antimony one was used, the choice between silver and platinum depended on what features of the potential variations were of interest. The electrical potential changes in the frog optic lobes contain both slow and fast components. It is best to use a silver electrode when the slow components are of interest, since the silver electrode has lower impedance than the platinum one at low frequencies and therefore introduces less low-frequency thermal noise into the record. However, if the fast components are of most interest, the amplifier can be set to have a short time-constant and therefore to be relatively insensitive to low frequencies. In this case a platinum electrode is preferred since its impedance is lower than that of a silver one at high frequencies.

Reference has been made in the foregoing to the electrical impedance of the silver and of the platinum electrodes. The part of the impedance which is due to the resistance of the metal of the electrode is entirely negligible; the significant part of the impedance is that which occurs at the interface between the metal and the tissue fluid with which it connects. This impedance is complex and when measured with sinusoidal a.c. current it is found to decrease in magnitude with increasing frequency. The rate of decrease depends on the metal of the electrode and on the composition of the electrolyte with which it is in contact. An extensive investigation of the impedance of different types of metal micro-electrode has been carried out by Dr. J.Y. Lettvin and Bradford Howland of M.I.T., but the results are as yet unpublished. There appears to be no satisfactory physical theory to account for the observations on electrode impedance.

The micro-electrode was, in every case, connected by a short length of unscreened wire to a cathode-follower unit similar in principle to the one described in section 6 of this thesis. The valve in the cathode-follower unit was selected for low grid-current. The output from the cathode-follower unit was amplified by a pre-amplifier which was similar in principle to the one described in section 6 of this thesis. A step signal was then added to the amplified signal to show the times of commencement and termination of the visual stimulus, and the combined signal was displayed and recorded on a cathode-ray oscillograph.

Apparatus for visual stimulation

A Sylvania glow-modulator tube type R1130B was used to give a controlled source of light for visual stimulation. This source was chosen because its light may readily be modulated by varying the current through the tube, and the light output responds extremely rapidly to a change in current. It gives a fairly powerful light output which is blue-white in colour. The colour depends somewhat on the amount of current passing through the tube, becoming reddish at very low currents.

The glow-modulator tube was connected to an electronic circuit which supplied an adjustable current of up to 55 mA. The circuit could be set to give brief flashes of light, or to switch the light on for several seconds, then off for the same time, and so on; thus distinct "on" and "off" physiological responses could be observed alternately. This latter mode of operation gave the most interesting results. The transitions from off to on and vice versa were synchronised with the time base of the recording oscillograph, so "on" and "off" responses were displayed on alternate sweeps. The time-base could be triggered from a push-button, or from an oscillator which could be set to any repetition frequency within a wide range, with a slowest rate of one sweep in 30 seconds. By the use of such a slow rate it was possible to ensure that the frog's visual system had plenty of time in which to recover from the previous stimulation.

When diffuse stimulation of the whole visual field of one eye was required, a small diffusing screen (of "onion-skin" paper) about 3/4 inch diameter, was mounted 2 inches in front of the end of the glow-modulator tube. The assembly was then placed so that the diffusing screen was very close to the frog's eye and occupied almost all of the visual field. The glow-modulator tube was always covered by a metal screening-can which had a hole of 1/4" diameter in the top to let the light through. A further metal tube was mounted on top of this to carry the diffusing screen when required.

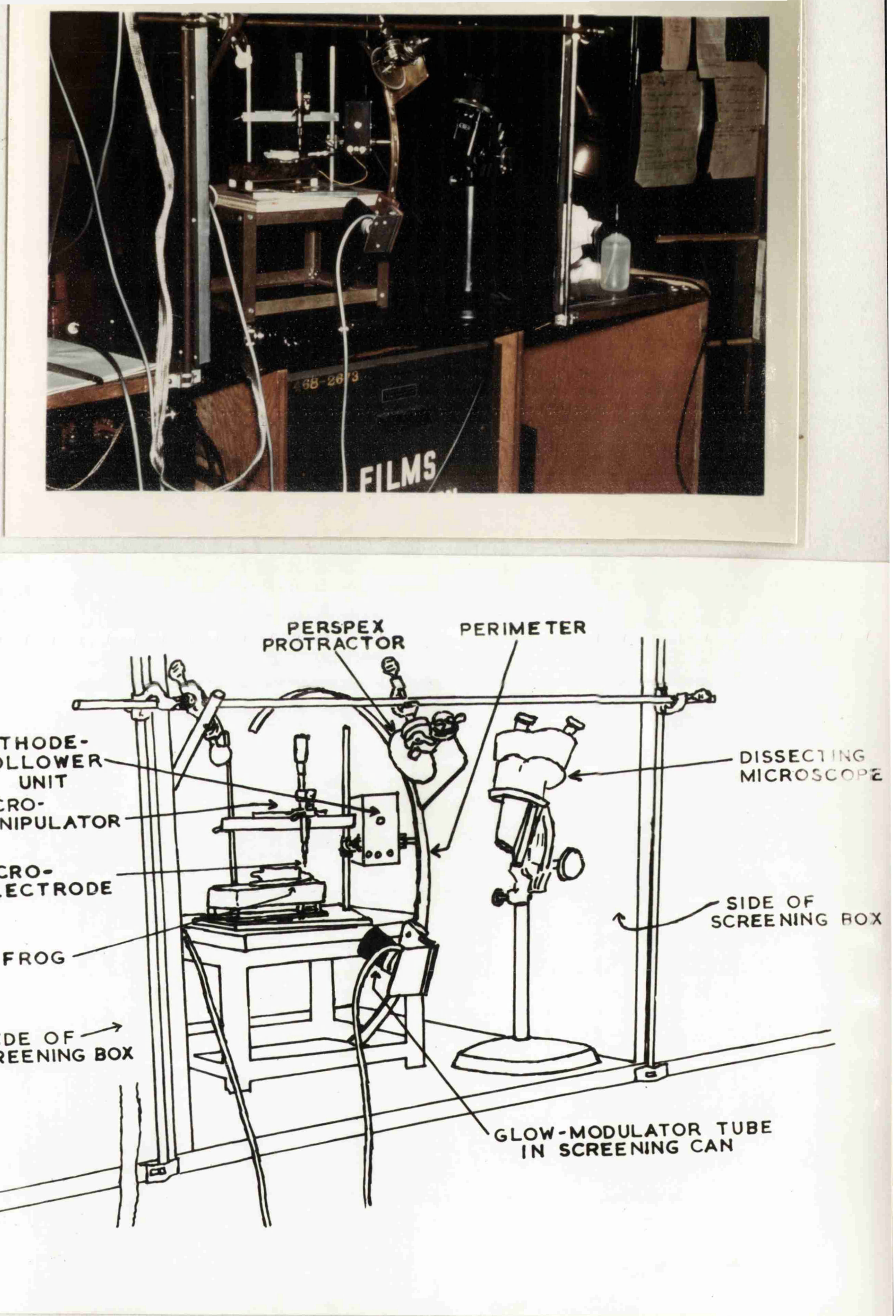


Fig. 2.3. Perimeter arrangement with glow-modulator tube. See also Fig. 2.8.

When the requirement was for light impinging from a particular direction, the glow-modulator tube was used without the diffusing screen. The light source was then 0.056 inches in diameter, and therefore subtended 0.3° of angle when held or mounted 10" from the eye. The light from a glow-modulator tube is fairly well collimated, and lights up a circle of about 2½" diameter at 10" from the tube. It is therefore necessary to have the tube directed fairly accurately towards the eye of the frog.

So that the glow-modulator tube could be moved to different parts of the visual field, while still at a constant distance (10 inches) from the frog's eye, and always directed towards the eye, the tube was mounted on a strip of metal bent into an arc, constituting a perimeter as used in clinical testing of vision. The arrangement is shown in Fig. 2.3. The tube could be moved to different positions along the perimeter, and the whole perimeter could be rotated.

This arrangement was used to investigate the response of the colliculus to movement of a spot of light in the visual field. The glow-modulator tube was moved by hand along the perimeter to give radial

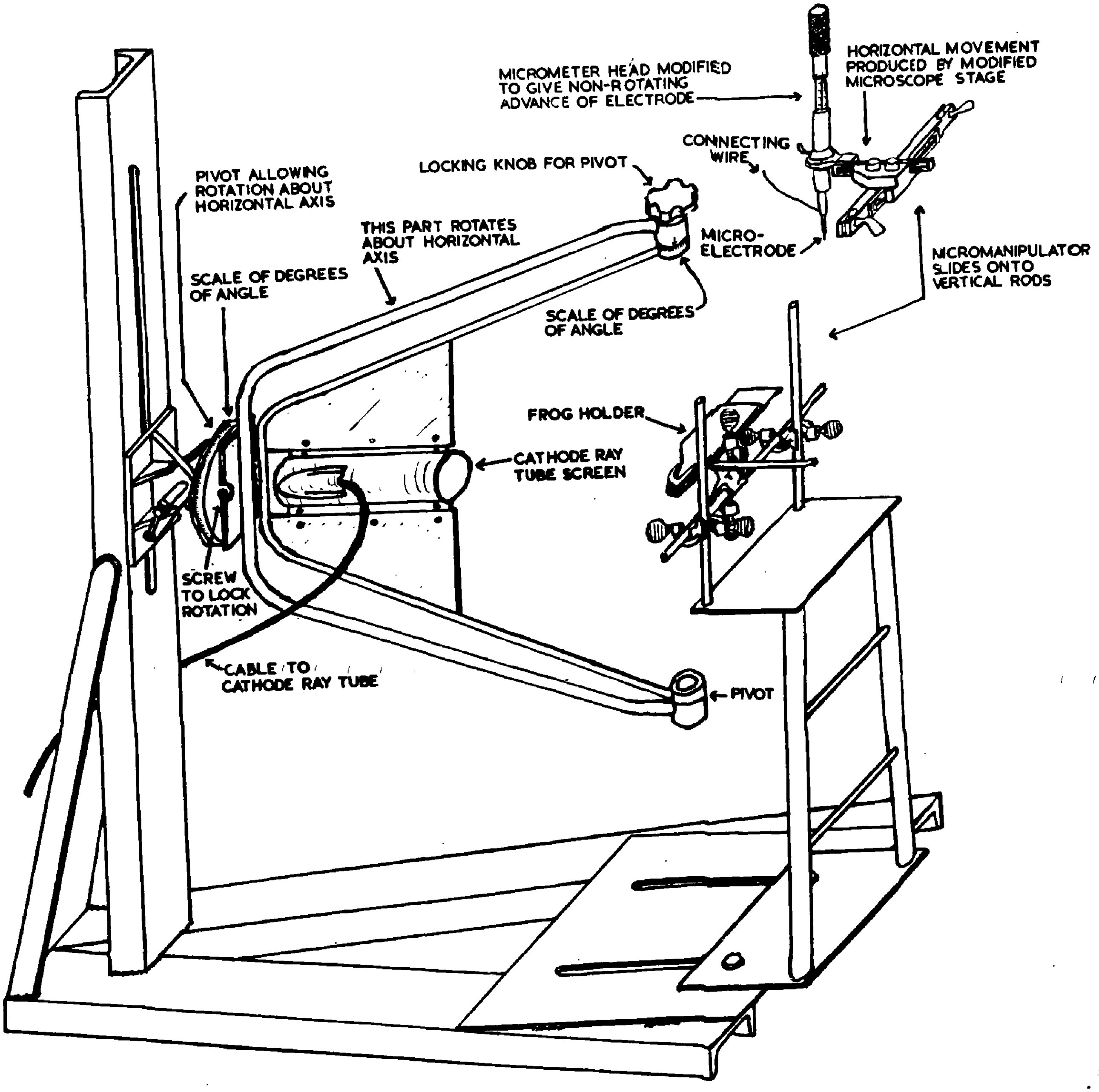


Fig. 2.4. Mechanical arrangement for positioning cathode-ray tube in frog's visual field.

movement, or the whole perimeter was rotated to give circumferential movement. It was impossible to control the speed of movement with any accuracy, however, so, for later experiments, a small cathode-ray tube was used as the light source, and the spot of it could be made to travel across the screen at a selected speed. The cathode ray tube was mounted in a mechanical arrangement which allowed it to be placed anywhere in the visual field of one eye of the frog. The mechanism ensured that the cathode-ray tube was always directed towards the frog's eye and the screen was at a distance of 10 inches from the eye. The mechanism was equivalent to the perimeter arrangement used with the glow-modulator tube (Fig. 2.3) but was devised so that no sliding action was involved; the action depended entirely on pivots (Fig. 2.4). It would have been difficult to design a sliding mechanism which would carry the necessary weight and still slide freely.

The cathode-ray tube had a blue phosphoresence (Du Mont phosphor type P11) with negligible afterglow.

The mechanical arrangements for supporting the glow-modulator tube and the cathode-ray tube were both made so that the source of light was 10 inches from the frog's eye. This distance was chosen mainly for convenience; a greater distance would have made the apparatus very cumbersome, and a smaller distance would have allowed the light source to collide with the micrometer head used to advance the micro-electrode. Ideally, the light source should be at such a distance that the frog's eyes are focussed at that distance.

The focussing of the frog's eyes.

Some early workers have reported that the frog eye has no power of accommodation (Hirschberg, 1882, Beer, 1898) and this is quoted by Holmes (1927, p.348), who states "The lens cannot either be changed in form or brought nearer to or further from the retina, so that only objects are in focus which are at a particular distance from the eye. ... In the air the frog is myopic .... In the water it is hypermetropic." Hirschberg found that in air the frog is myopic to the extent of 5 to 7.5 dioptres. Beer agrees with this for the usual range of degree of myopia, and gives figures for frogs of different species. If Hirschberg's result is accepted, it appears the light source should be from 13 to 20 cm (5 to 8 ins.) from the eye of the frog.

Hirschberg's result does not agree with the observations of Dr. P.D. Wall and myself, nor with modern published observations by Young (1950) and Walls (1942). Dr. Wall and I used a standard ophthalmoscope to observe the fundus of the eyes of both conscious and anaesthetised frogs. We employed the Direct Method of Ophthalmoscopy in which the observer's eye and ophthalmoscope are placed close to the eye under examination. We found that a clear view of the fundus was obtained when the ophthalmoscope was set to its "zero dioptres" position; that is to say, when no correction of the visual system was introduced by the ophthalmoscope. This result is incompatible with the finding of Hirschberg that the frog's eye is always myopic to the extent of 5 to 7.5 dioptres, since the eyes of Dr. Wall and myself are certainly not hypermetropic to that extent.

Young (1950 p.332) does not agree with the statement that the frog has no power of accommodation. He states "Accommodation is effected by protractor lentis muscles attached to the fibres by which the lens is supported." Walls (1942, pp.266-7) also discusses the mechanism of accommodation in amphibian eyes, and states "Frogs are emmetropic in air, Under water, they of course become strongly hypermetropic, and are quite unable to compensate therefore with their limited range of forward lens-movement. No amphibian has as much as five diopters of accommodation."

Since the modern authoritative works of Young and Walls both discuss the accommodation of the frog's eye, there can be no doubt that the eye does in fact have the power of accommodation. The discrepancy between the observations by Wall and myself on one hand, and those of Hirschberg and Beer on the other, can be partly attributed to some difference in technique which caused the eyes to be in different states of accommodation when examined. The discrepancy, however, is too large to be completely explained in this way if it is true that the eyes have less than five dioptres of accommodation.

Since the frog's eyes have the power of accommodation, there is no simple way of knowing where they are focussed during an experiment. Probably they focus at the distance of the stimulating light (10 inches),

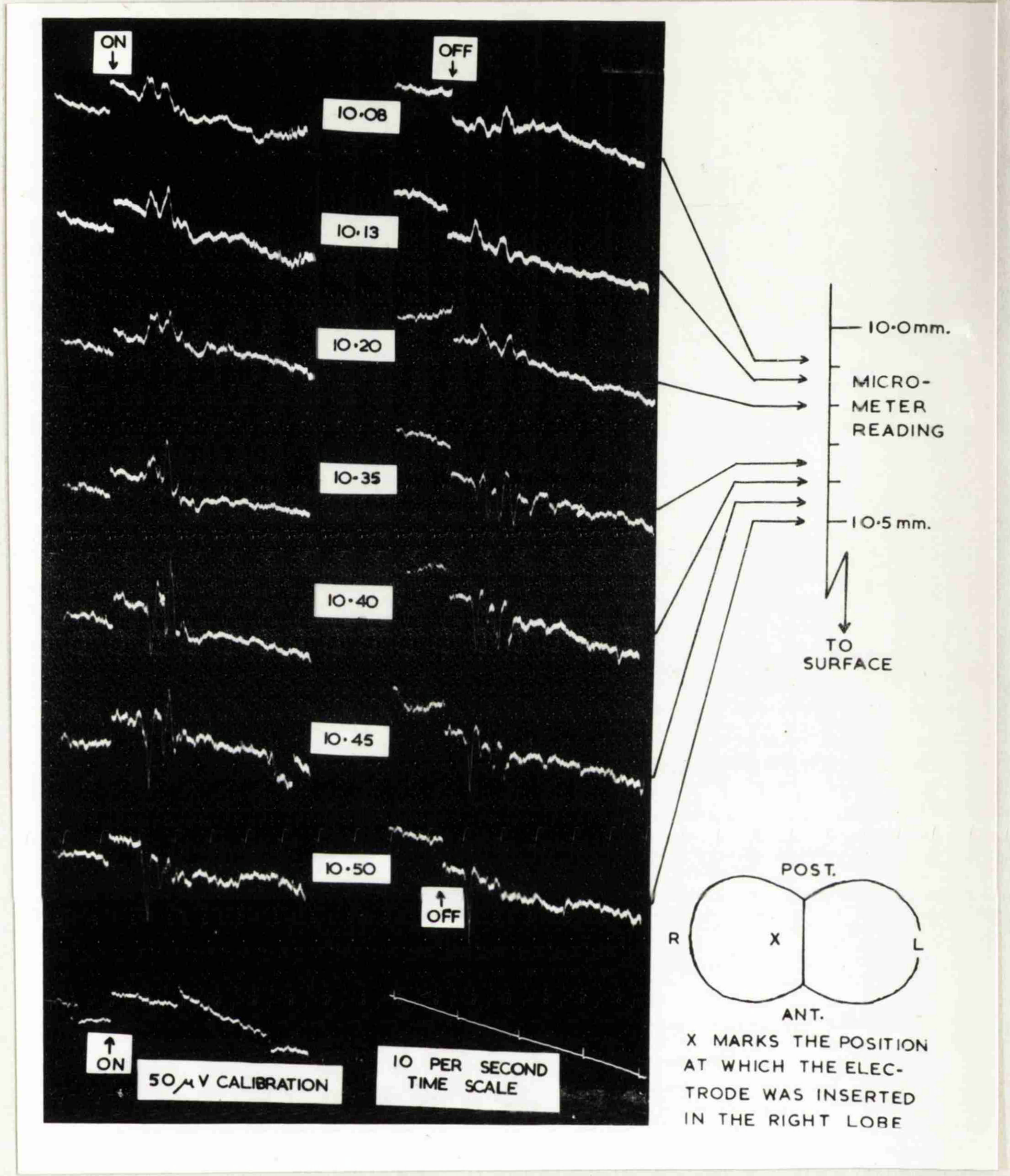


Fig. 2.5. On- and off-responses at different depths in one optic lobe, showing "phase-reversal" of the two peaks in the on-response. The records at the top of the figure are from deeper in the lobe than those at the bottom. In these records, positive potential at the micro-electrode is represented by upward deflection of the trace (contrary to the usual convention). Some of the traces have been slightly retouched.

but it is not possible to be sure of this.

Results

Responses to diffuse illumination.

Fig. 2.5 shows responses of the right optic lobe of a frog to diffuse illumination of the visual field of the left eye. The frog had been anaesthetised by the urethane-ether procedure using, in this case, 2 ml of 3% urethane solution.

Records are shown of the on-response and off-response at various depths at the position in the left lobe indicated in the diagram. The difference in depth between the different recording sites can be obtained from the micrometer readings corresponding to the different depths. In this case the absolute depth below the surface is not known exactly. These records were obtained using a long amplifier time-constant (and hence good low-frequency response) as can be seen from the calibration signal.

The most prominent feature of the on-response is the two peaks at about 70 msec after the turning-on of the light. These are features of the on-response obtained from any part of the lobe. In the records shown in Fig. 2.5, it can be seen that these peaks

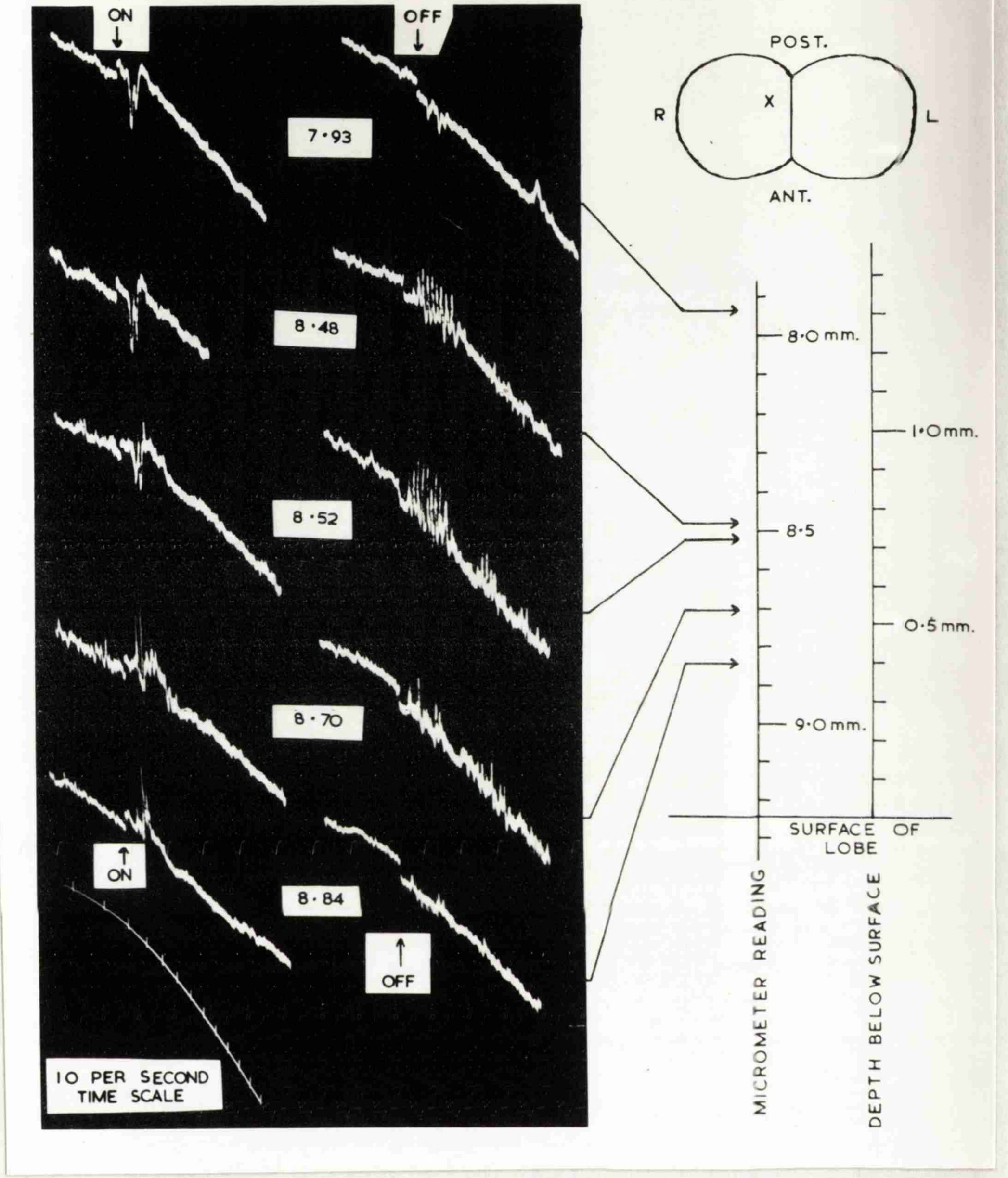


Fig. 2.6. On- and off-responses at different depths in one optic lobe, showing "phase-reversal" of the two peaks in the on-response. The records at the top of the diagram are from deeper in the lobe than those at the bottom. In these records, positive potential at the micro-electrode is represented by downward deflection of the trace (conforming to the usual convention). Some of the traces have been slightly retouched.

are upward (positive) in the records from the deeper sites in the lobe, but are downward (negative) in the records from sites nearer the surface. Thus there is a phase-reversal as the electrode passes a certain depth. This shows that the nervous activity producing this component of the response takes place at this depth.

The phase-reversal method of determining the depth of the activity which causes a particular component of the response is of general applicability.

Fig. 2.6 shows a set of records at various depths, similar to those of Fig. 2.5, and here again the two peaks in the on-response undergo phase-reversal, this time at a depth of about 0.6 mm.. In this case also, the frog was anaesthetised by the urethane-ether method, using 2 ml of 3% urethane solution. The electrode was inserted in the right optic lobe at the point shown in the diagram, and the visual field of the left eye was illuminated by the glow-modulator tube.

With diffuse illumination of the visual field it was usual to obtain both on- and off-responses from a recording site. Almost always the off-response was

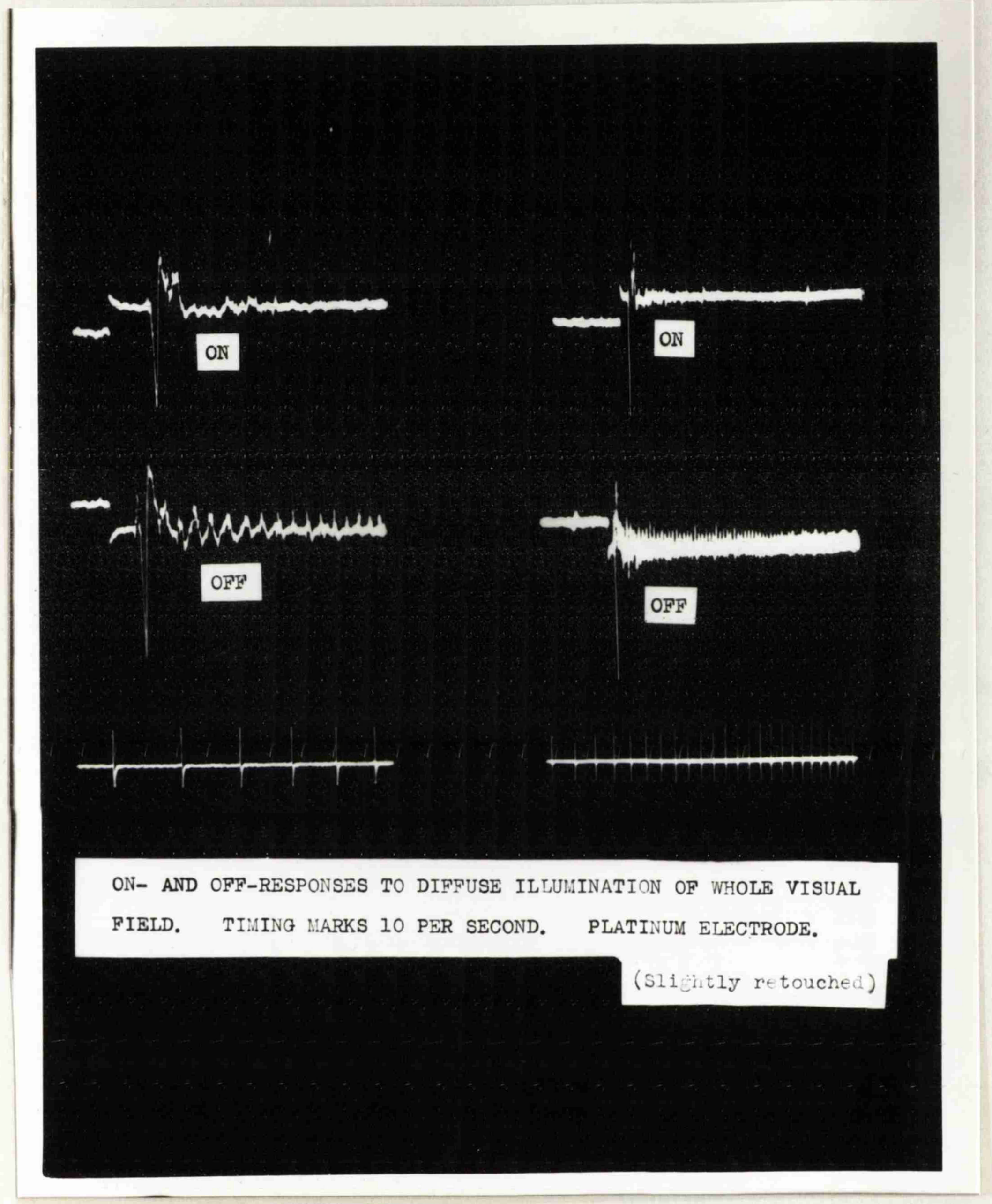


Fig. 2.7. Responses from left optic lobe (electrode position approximately as in Fig. 2.9) to diffuse illumination of visual field of right eye, showing long-lasting off-response. Recorded with short amplifier time-constant. Height of timing marks above base-line corresponds to 200 µV voltage calibration.

larger and had a lower threshold of light-intensity than the on-response. The latency of the off-response was generally shorter. Typical values were 30 and 50 msec respectively. Beritoff and Tzkipuridze (1943) have also examined electrical responses of the frog optic lobes to the turning on and off of illumination of the whole field. They found that both the optic lobes and the optic nerve reacted more strongly at a darkening than at an illumination.

No maintained response to steady illumination has been seen. Hence the on-response in the optic lobes differs from the discharge in the on-fibres of the optic nerve as described by Hartline (1938) and by Granit (1947, Ch. 5). These fibres continue to fire as long as the illumination remains.

Sometimes the off-response continued for a very long time. One preparation, using an unanaesthetised frog, gave off-responses of more than 40 seconds duration from a particular electrode position and depth. Fig. 2.7 shows a long-lasting off-response, recorded from an unanaesthetised frog (though the phenomenon occurred also with anaesthetised frogs). These records were taken with a short amplifier

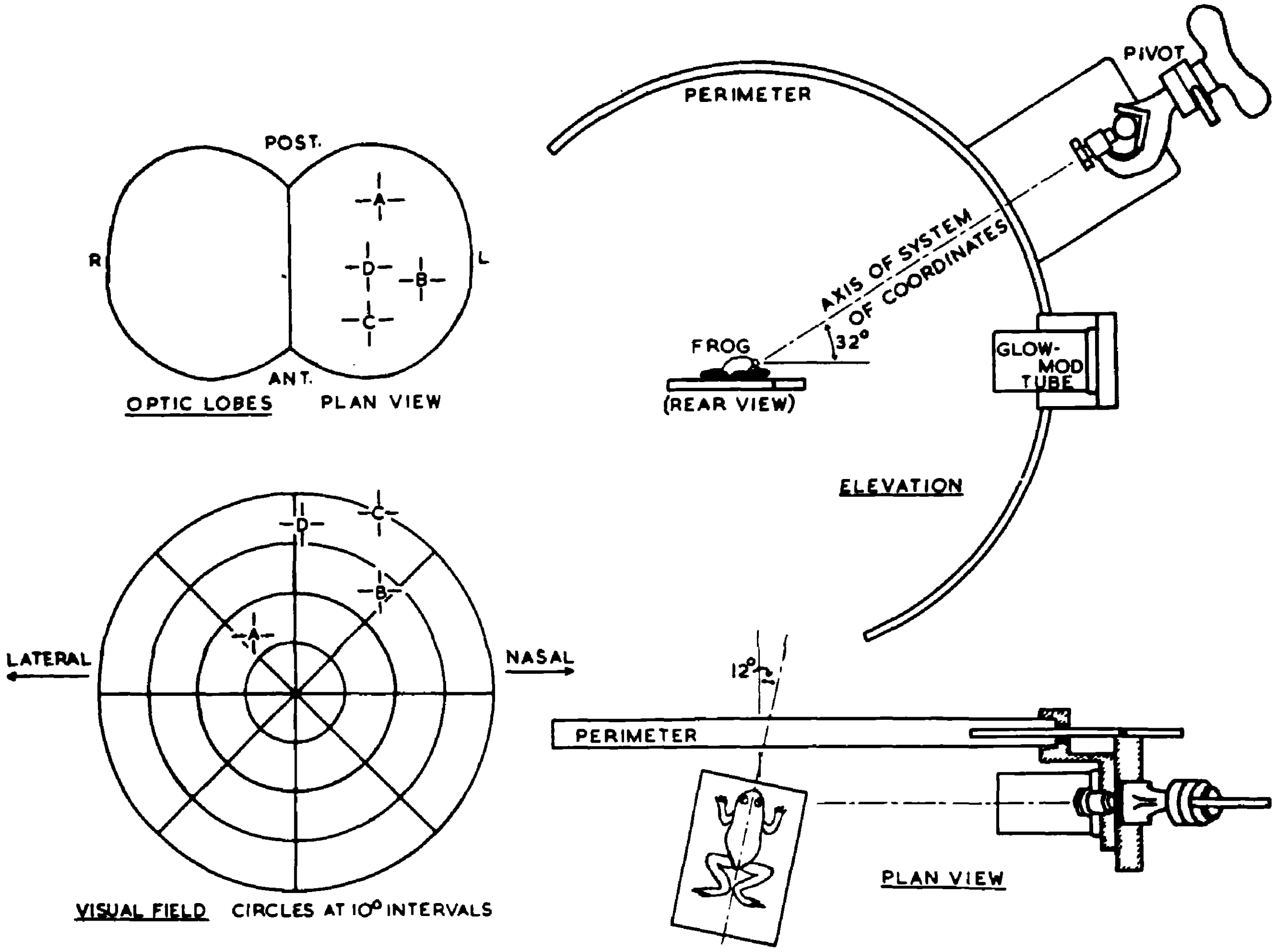


Fig. 2.8. Experiment on mapping of the visual field on one optic lobe. The experimental arrangement is shown on the right (see also Fig. 2.3) and results are shown on the left.

time-constant (3 msec) in order to emphasize the faster components of the signal, which arise from nervous activity near the electrode.

Mapping of retina on optic lobes.

Fig. 2.8 shows the result of one experiment in which an attempt was made to map the visual field of the right eye on the area of the left optic lobe. Four electrode positions are shown on the diagram of the optic lobes, and the points in the visual field which produced responses at these positions are shown on polar coordinates.

In this experiment the frog was anaesthetised by the urethane-ether procedure, using 2 ml of 3% urethane solution. The glow-modulator tube, mounted on the perimeter (Fig. 2.3) was used to produce stimuli in different parts of the visual field.

The perimeter was mounted with its axis at an angle of 32° to the horizontal, and in such a way that its projection on a horizontal plane made an angle of 12° with a line perpendicular to the body axis of the frog (see diagram). This orientation of the perimeter was chosen with the object of making its axis approximately coincident with the optic axis of the eye of the frog. The direction of the optic axis was not determined in any exact way, however.

At each of the electrode positions shown on Fig. 2.8, the electrode depth was adjusted until a good response was obtained to diffuse illumination of the whole visual field. Then the electrode was left at that depth and a search was made, with the glow-modulator tube mounted on the perimeter, for that point in the visual field which would produce the largest responses at the electrode. Only four points were successfully mapped in this way before the preparation deteriorated.

The results are in general agreement with those of Sperry (1944) who found that ablation of the anterior part of the optic lobe destroyed forward vision, ablation of the posterior part destroyed backward vision, and of the medial part destroyed vision in the upper part of the visual field.

Response to a moving spot of light.

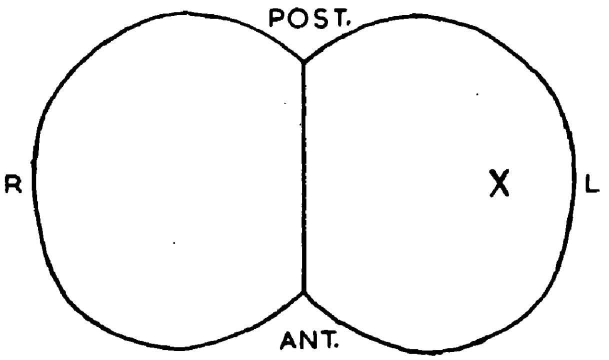
The first observations of the response to a moving spot of light were made with the glow-modulator tube mounted on the perimeter, the movements being produced by hand. No photographic records were made of the responses evoked by this means, as it was not possible to standardise the conditions of stimulation. It was observed, however (with both anaesthetised and unanaesthetised frogs) that, for a particular electrode-position in the colliculus, a point in the visual field could often be found such that, in a region of the field round it, movement of a spot of light *away* from the point, in any direction, gave a greater response at the electrode than did movement *towards* the point. The point in the field which had this property usually coincided with the point at which a light-source had to be placed to produce the largest on- and off-responses at the electrode.

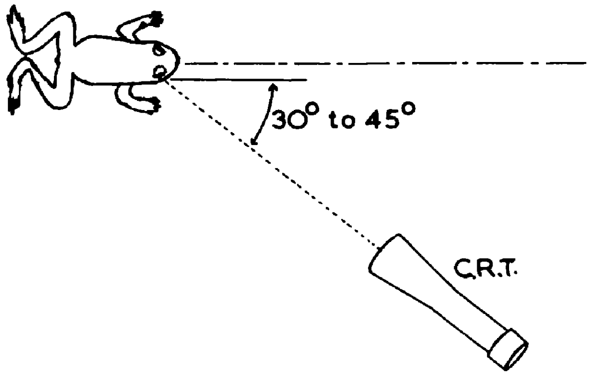
In many of the experiments in which the above effect was observed, the responses to movement were what might have been expected as a summation of on- and off-responses at points in the path. When the light spot moved *away* from the point mentioned above, the response contained an off-response from that end of the path at which the responses were greatest, combined with an on-response from that end of the path at which the responses were least. When the spot moved towards the point the response contained an off-response from the end of the path at which responses were least, and an on-response from the end at which responses were greatest. Since the off-responses were generally greater than the on-responses under the same conditions, it is not surprising that movement away from the point mentioned above should have produced a larger response than movement towards it.

However, although in many cases the response to movement could be accounted for as a summation of on- and off-responses, there were also cases in which it could not be so explained. The responses to movement were sometimes markedly different for opposite directions of movement along the same path, even though there was no significant difference in the on- and off-responses at points along the path.

When the movements were produced by hand with the glow-modulator tube and perimeter, however, it was impossible to be sure that movements in opposite directions were at the same speed. The later experiments were therefore made with the cathode-ray tube as the light source.

Responses obtained using the cathode-ray tube as





Above - Fig. 2.9. Approximate position of the microelectrode in the left optic lobe for all the records in Figs. 2.11 to 2.15.

Below - Fig. 2.10. Showing range of positions of the cathode-ray tube for the records in Figs. 2.11 to 2.15.

light source are shown in Figs. 2.11 to 2.15. All of these records were obtained with electrodes in approximately the position shown in Fig. 2.9. The position is fairly far lateral on the left optic lobe, and roughly midway between the anterior and posterior poles of the lobe. This electrode position was used because the part of the visual field in which the cathode ray tube then had to be placed to evoke responses was a convenient one with the particular experimental arrangement used. The cathode-ray tube had to be well forward in the visual field, making an angle of 30° to 45° with the axis of the frog's body, and slightly above the level of the eye (see Fig. 2.10). The best position was found by trial.

The tip of the electrode was passed into the substance of the lobe to a depth of not more than ½ mm. Responses ~~worked~~ evoked by diffuse illimination were observed as the electrode was moved in, and the depth was adjusted until good responses were seen.

In Figs. 2.11 to 2.15, movement of the spot of the stimulating cathode-ray tube is represented by upward or downward deflection of the trace of the recording cathode-ray oscillograph. In the records

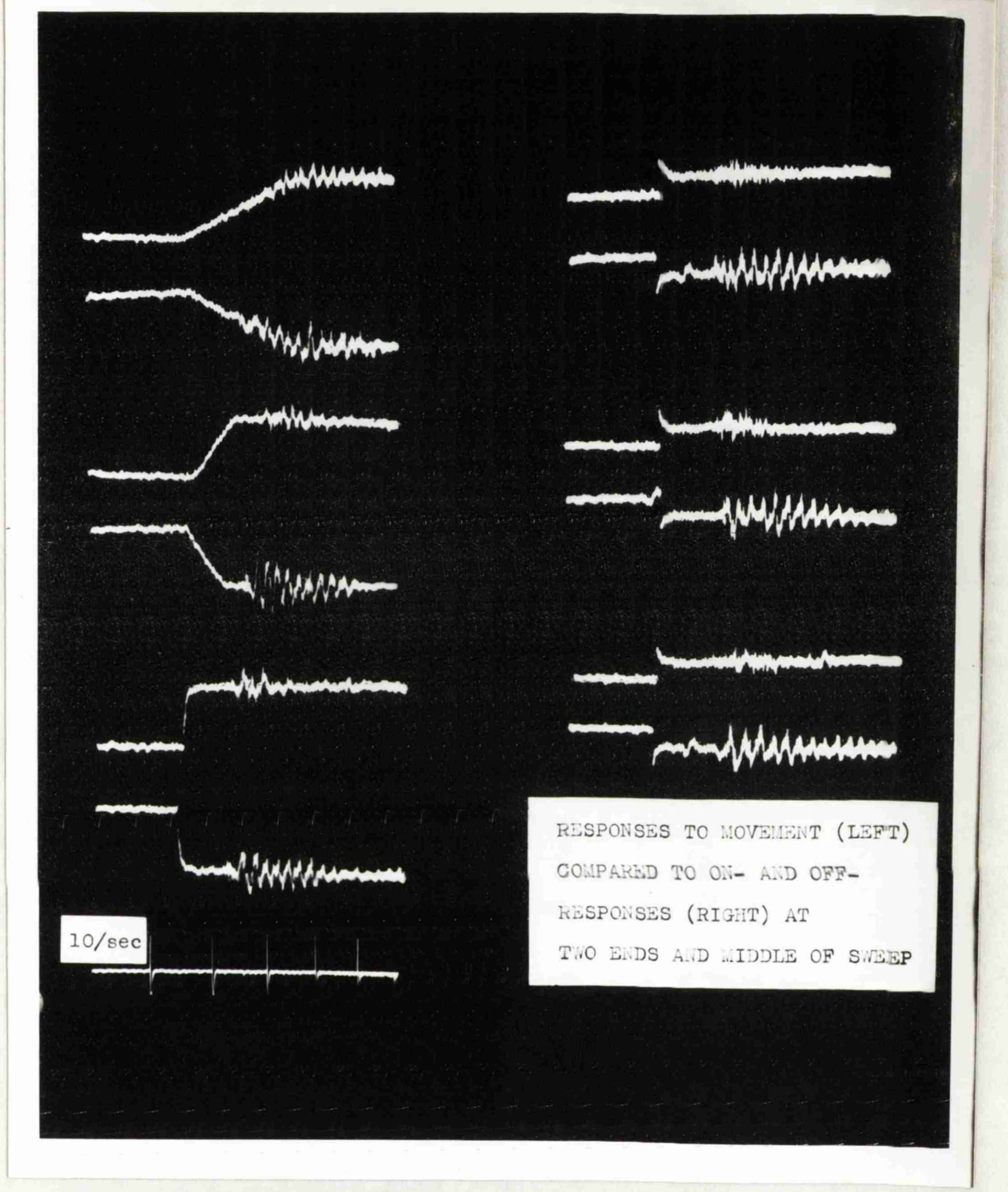


Fig. 2.11. Responses to movement of the cathode-ray tube spot along a circumferential (approx. vertical) path. Records on left show responses to movement; upward deflection of recording spot represents upward deflection of stimulating spot. Records on right show on- and off-responses, at the top end, middle and lower end respectively, of the previous path of movement. The height of the timing marks above the base-line corresponds to 200 μV calibration.

to the left of Fig. 2.11, for instance, upward movement of the recording spot represents upward movement of the stimulating spot, and the physiological responses are superimposed on this movement signal. The movement of the stimulating spot was not strictly linear, as it was controlled by a sweep voltage obtained by charging a capacitor through a resistor. In the records of Figs. 2.11 to 2.15 the stimulating sweep looks more linear than it really was, because its non-linearity is to some extent compensated in the record by the non-linearity of the recording sweep (which can be judged from the timing trace). The stimulating sweep is non-linear since it is very difficult to devise a time-base circuit which gives a linear sweep and can be relied upon to give precisely similar sweeps in opposite directions.

Fig. 2.11 shows responses to movement, both upward and downward, along a circumferential (approx. vertical) path. It is clear that downward movement produces a much larger response than does upward movement. The different responses cannot be accounted for as summations of on- and off-responses at points passed by the spot, for the records on the right side

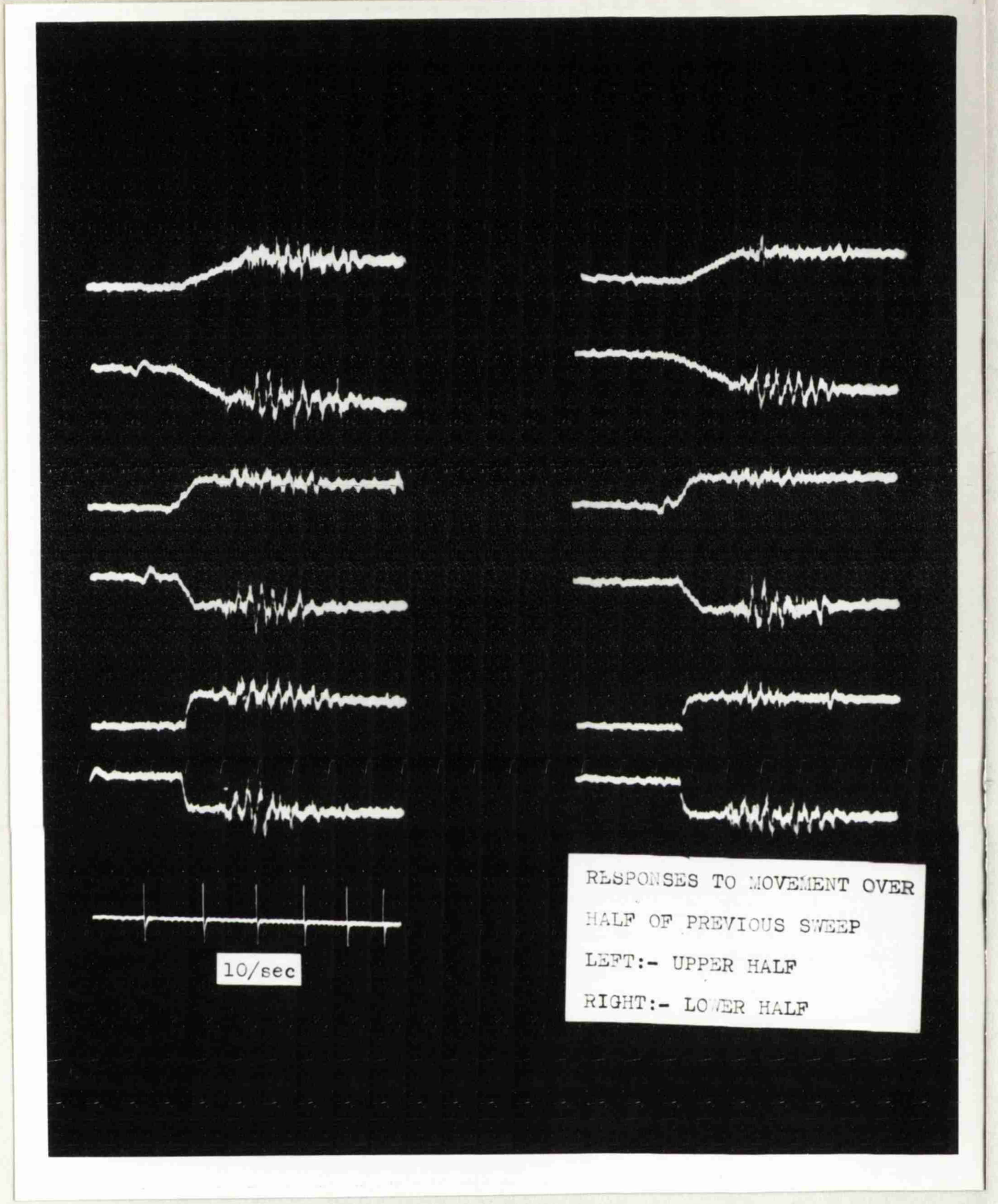


Fig. 2.12. Responses to movement obtained under the same conditions as those of Fig. 2.11, except that the movement of the spot was over half the distance of the previous sweep.

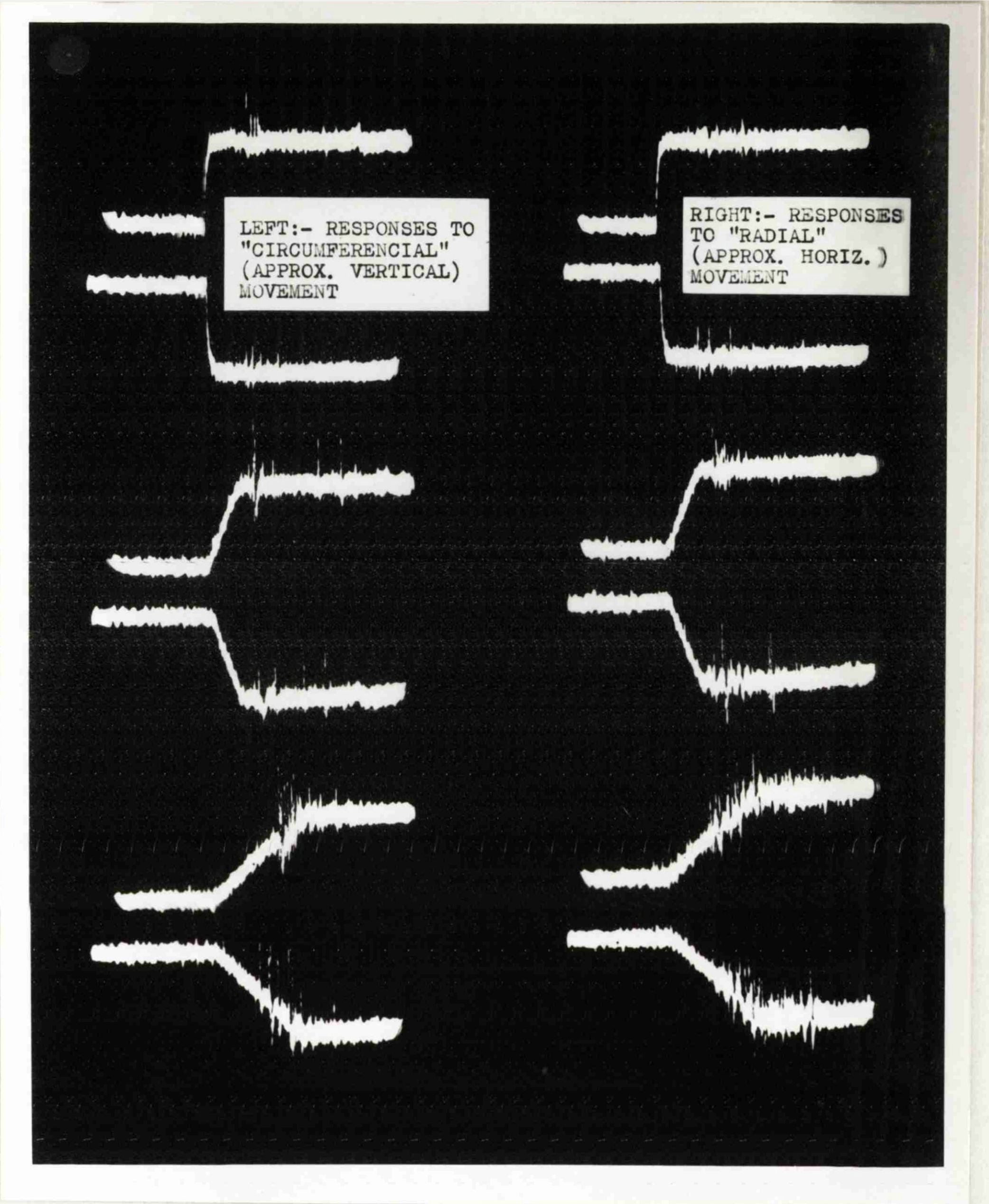


Fig. 2.13. Responses to movement of the cathode-ray tube spot both radially and circumferentially, showing that in this case the response was greatest when the spot was moving relatively slowly. In the four records at the top of the figure, the stimulating spot moved practically instantaneously. (The record does not appear to represent instantaneous movement. This is because the movement of the recording spot was slowed by a capacitor used to introduce the action-potential signal.)

of the figure show that the on- and off-responses are similar at points along the path of the spot.

Fig. 2.12 shows more records from the same preparation, under the same conditions, except that here the stimulating spot is traversing only half the distance previously covered. The records on the left were produced by the spot travelling over the upper half of the previous sweep; those on the right were produced by it travelling over the lower half. It is clear that for the reduced paths also, downward movement produces a bigger response than does upward movement.

The movements were on the face of a 2" cathode-ray tube, and in producing the records of Fig. 2.11 the spot travelled across almost the full width of the screen. The distance from the eye was 10 ins. The angle subtended at the eye by the movement was therefore about 11°, and for the records of Fig. 2.12 it was about 5½°.

Fig. 2.13 shows responses to movement with no obvious difference according to the direction of movement. These records are interesting because slow movements produce a bigger response than do fast

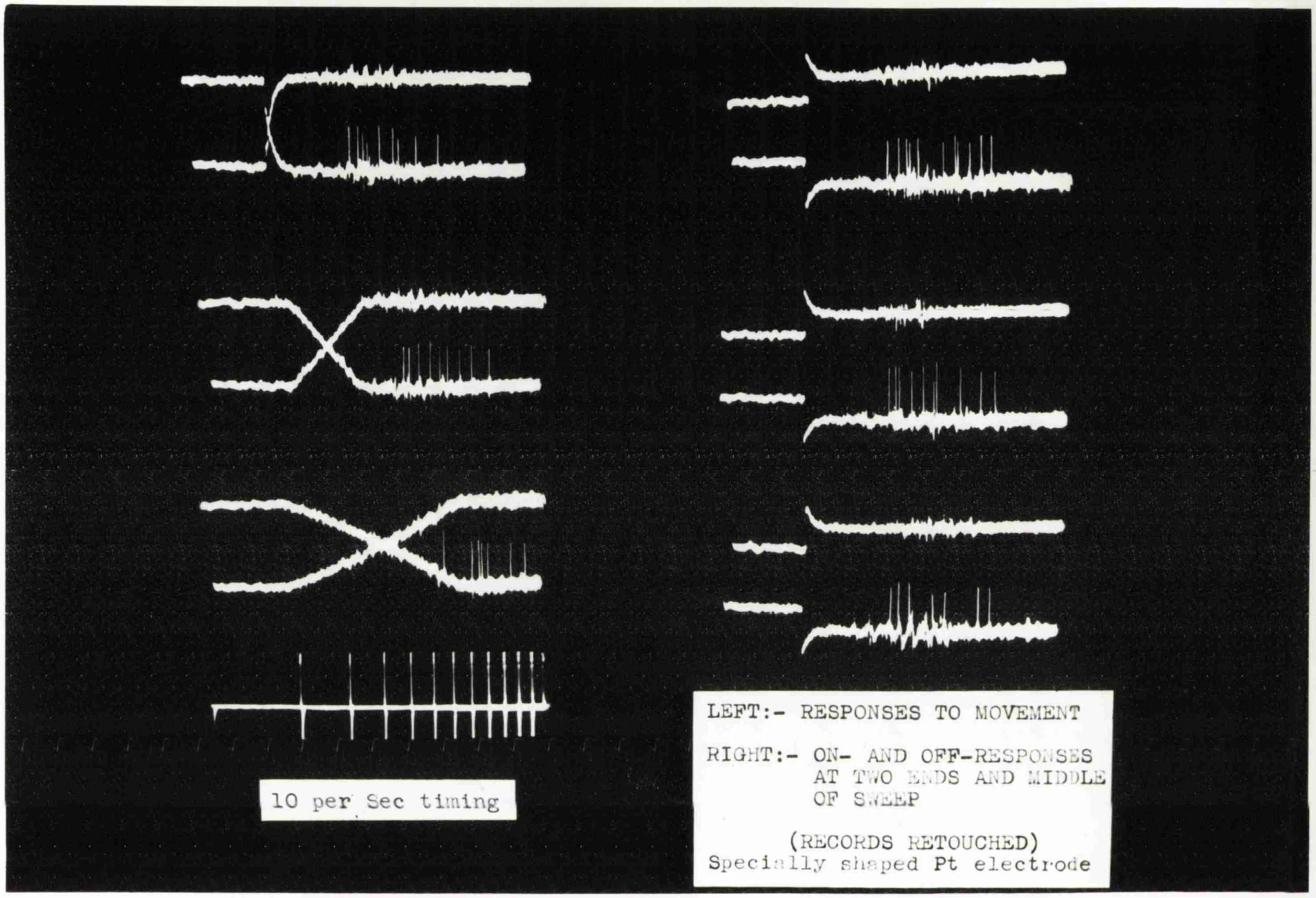
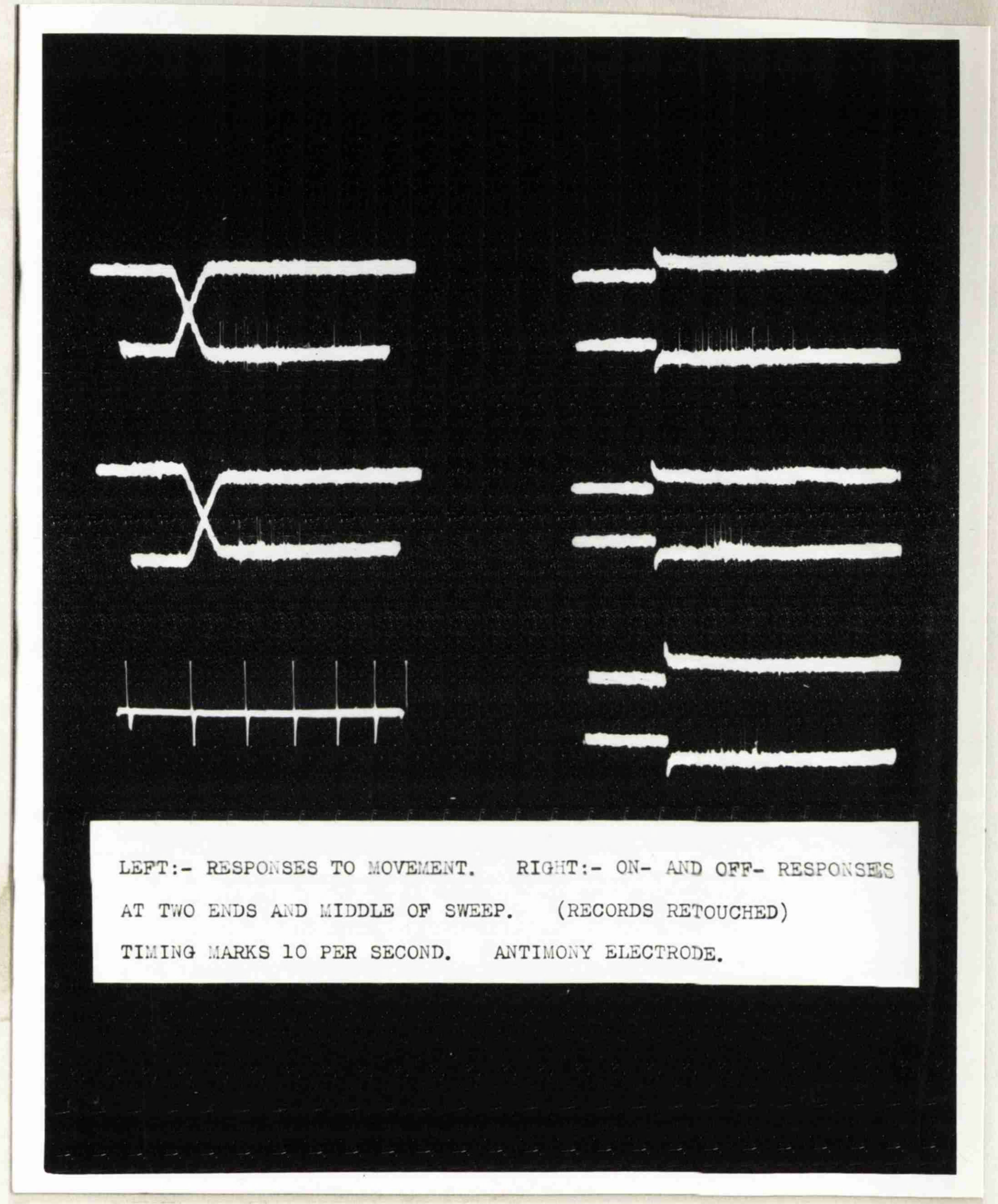


Fig. 2.14. Responses to radial (horizontal) movement of the cathode-ray tube spot. Records on left show responses to movement; downward deflection of the recording spot represents forward movement of the stimulating spot. The upper left-hand pair of records show responses to spot movements which were practically instantaneous. The height of the timing marks above the base-line corresponds to 200 μV calibration.

movements. Probably the explanation is that light at a point in the middle of the sweep gave larger off-responses than did light at either end of the sweep. Larger responses were therefore produced when the light passed over this point slowly than when it passed over it quickly. Unfortunately the on- and off-responses were not recorded at points in the path of the spot. Before this could be done the frog moved and the position of the electrode was altered.

The records of movement-response which have been discussed up to now have all been recorded with a short amplifier time-constant (3 msec) in order to emphasize the faster components of the response. These records do not, however, show the responses of single nerve units. By very careful adjustment of the electrode depth, and by the use of very fine (antimony) electrodes or specially shaped (stubby tip) platinum electrodes, it is possible to obtain records which are either from single units or from a very small number of units.

Fig. 2.14 shows a set of results similar to those of Fig. 2.11, but showing the response from a single unit, or a very small number of units. In



LEFT:- RESPONSES TO MOVEMENT. RIGHT:- ON- AND OFF- RESPONSES AT TWO ENDS AND MIDDLE OF SWEEP. (RECORDS RETOUCHED) TIMING MARKS 10 PER SECOND. ANTIMONY ELECTRODE.

Fig. 2.15. Responses to circumferential (approx. vertical) movement of cathode-ray tube spot, recorded for one speed of movement only. As in Fig. 2.14, pairs of records of movement-response have been superimposed. The records on the right show on- and off-responses obtained by turning the spot off and on when stationary at the upper end, middle and lower end respectively of the previous path of movement.

this case the stimulating spot was moving horizontally, and downward deflection of the trace represents forward movement of the stimulating spot. In the records on the left, the records of responses to movements in opposite directions have been superimposed. In all cases, forward movement produces a response, whereas backward movement does not.

It is apparent that the three off-responses do not contain exactly the same number of impulses. Nevertheless these records show that the responses to movement are not a summation of the on- and off-responses, for in the top left-hand record there is no response when the spot moves practically instantaneously from the outermost to the innermost position, although an off-response is obtained when the spot is simply turned off in the outermost position.

Fig. 2.15 shows another case in which there is no response to movement in one direction, even though an off-response can be obtained by extinguishing the stationary spot at either end or in the middle of the sweep.

DISCUSSION

It appears from the experiments that there is a point-to-point representation of the retina on the optic lobes in frogs, but it has not yet been mapped in any detail.

The evidence for a characteristic response to movement is important because it provides some information about the way in which visual images are analysed by the central nervous system. To understand this analysis of visual information it will be necessary to know what qualities of the image are abstracted and at what level in the system. The results described here suggest that movement is abstracted at an early stage.

It has been suggested by Mr. Walter Pitts, of the Massachusetts Institute of Technology, that the finding has philosophical significance, since the philosophy of Kant, Locke and Hume is largely concerned with the impressions received from the senses and what qualities are abstracted from them. There has been very little previous work on responses to movement in the visual field. Wang and Lu (1936) have recorded, in mammals, action potentials in the visual cortex and superior colliculi in response to movement of a shadow across the visual field. These workers found that a response could be produced by a shadow movement against a background which was so dimly illuminated that no response was produced by turning the background illumination on or off. Barlow (1953b p. 83) discusses the probable response of retinal elements in the frog when there is a moving object in the visual field, but he has not carried out experiments with moving objects.

Beritoff and Tzkipuridze (1943) have recorded action potentials from the optic lobes of the frog, including potentials evoked by movements of an object or a shadow in the visual field. They do not appear to have controlled or measured the velocity of movement, but have simply moved small objects, such as a finger, in the visual field. They state that the response to movement is always weaker than the response to illumination. The illumination referred to appears to have been diffuse illumination of the whole visual field. The responses obtained by these workers were not of the single-unit type and appear as rather disorganised activity, something like the responses shown in Figs. 2.11 and 2.12.

Evidence for a characteristic reaction in the retina to movement in the visual field has also been obtained by Motokawa (1953). His experiments were of an entirely different nature from the others discussed here. In his experiments a narrow band of yellow light was made to sweep across the visual field of a human subject. The state of the retina at different parts of its area was then examined by illuminating the appropriate part of the field briefly with white light, and then, at some later instant, applying an electric shock to the eye. By following this procedure repeatedly, Motokawa found the threshold strength of electric shock required to produce the sensation of a flash of light. The graph of threshold shock-strength against time elapsed since the white-light illumination varied for different positions in the area of the visual field swept by the band of yellow light.

Further work on the frog optic lobes may provide some explanation of the unexpected result obtained by Sperry (1944 1951). Sperry operated on frogs to sever the optic nerve on one side and to turn the corresponding eye upside-down. The other eye was excised. The cut ends of the optic nerve were placed near each other and allowed to regenerate. (In amphibia, the central nervous system is capable of regeneration). When the nerve had regenerated, the frog's vision was tested by waving a lure in different parts of the visual field. The tests showed that the frogs had recovered their vision, for they would make snapping movements in response to the lure. Their visual impressions were apparently inverted, however, for they would snap at the lower part of the visual field when the lure was in the upper part, and vice versa.

The frogs whose eyes were inverted showed no sign of learning from experience to snap in the correct direction. Their only reaction which could perhaps be ascribed to experience was to become less willing to snap in response to the lure than were the control frogs whose eyes had not be rotated. It may be noted in passing that these findings are in contrast to the observations on humans and a monkey whose vision was inverted by an arrangement of lenses in front of one or both eyes. Stratton (1896 and 1897) covered one of his eyes and mounted an arrangement of lenses before the other, so as to invert the visual image. After several days he adapted to a considerable extent and could move around fairly freely. Ewert (1936 and 1937), however, reviews experiments of this kind by himself and several other workers, and states that a person never becomes completely adapted to the inversion, and never achieves a feeling of naturalness while wearing the inverting spectacles. Foley (1940) attached inverting spectacles to a rhesus monkey, and found that it apparently adapted to the new conditions to some extent, since its ability to move around and to pick up objects progressively improved during the seven days of the experiment.

Sperry's finding is surprising, since the fibres of regenerating nerves are generally thought to join up more or less randomly, though Hooker (1930), in experiments on regeneration of the spinal cord of amphibian embryos, found that the fasciculi on one side of a section tended to join up with the corresponding fasciculi on the other side even when a segment of cord had been rotated by 90° or 135°. It is possible that random connections could lead to full recovery of vision, provided the nervous system was permitted to adapt itself to the new conditions. In fact, it has been suggested by Ashby (1952) and others that a large part of the nervous system is originally connected in a fairly random fashion, and only functions usefully when it has adapted itself so as to do so. However, the recovery of vision in Sperry's frogs cannot be due to adaptation or re-education, for if it were the frogs would see right-way-up when vision returned. Sperry's conclusion is that the fibres do not join up randomly, but that there is some similarity between the connections after regeneration and those before section of the nerve. If this is so, there must be some way in which a regenerating fibre is guided to join up with an appropriate fibre on the other side of the section. This implies that the different fibres in the optic nerve are distinguishable by chemical or other means.

This last conclusion is so revolutionary that it should not be accepted without first considering any possible alternatives. It may be that some of the information which goes from the retina to the optic lobes is recoded in the ganglion layers of the retina into a form which still gives information about the position of an object in the visual field when the fibres of the optic nerve have been sectioned and then reconnected randomly. Recording from the optic lobes with micro-electrodes as described here may produce evidence for such a process of recoding.

From the fact that the response to a moving spot of light is different from a summation of on- and off-effects at points passed by the spot, it follows that there is some form of interaction between the different areas of the retina. If the complete system of interactions were known, the response evoked by a moving spot of light could presumably be accounted for in terms of the interactions. The result shown in the top left-hand trace of Fig. 2.14 can readily be expressed in terms of interactions by saying that the off-response which would normally appear as the spot disappeared from the outermost end of the sweep is inhibited by the simultaneous appearance of the spot at the innermost end of the sweep. (When this record was obtained, the movement of the stimulating spot was practically instantaneous. The movement of the recording spot, however, was slowed down because of a capacitor used to combine the action-potential signal with the movement signal).

Interactions between retinal areas have been reported by Kuffler (1952 and 1953) for the cat, and by Barlow (1953 a and b) for the frog. These workers recorded from ganglion cells in the retina itself. It is clear that the complete system of interactions is very complicated. Kuffler and Barlow illuminated or extinguished different points on the retina simultaneously and found that under some conditions the stimuli were additive in their effect at a ganglion cell; under other conditions one stimulus could inhibit the effect of another. Before the results of this type of experiment can be related to experiments with moving lights or objects it will be necessary to perform a variety of further experiments. For instance, it will be necessary to know how the turning-on of illumination of one area interacts with the extinction of illumination of another area.

The preparation used in these experiments is a convenient one for the investigation of many aspects of visual function. An obvious extension of the work described here would be to study the response evoked by movement of a dark spot against a light background. In fact, since the frog normally pays attention to flies which are dark in colour, the dark spot would have been tried in preference to the light spot if the apparatus requirements had been equally easily met. The responses to coloured lights may prove interesting, and it should be possible to look for inhibition and facilitation of the response from one retinal area by simultaneous stimulation of another. There are numerous other possibilities.

In some ways, the experimental technique I have used is crude compared to those of Kuffler and Barlow. In particular, with the arrangements I have used to provide visual stimuli it is impossible to know exactly what image is formed on the retina, for it is not known at what distance the eyes are focussed, nor whether the eyes are being moved slightly by the ocular muscles. Any eye movements which did occur were not great enough to be seen by the experimenter, but the possibility of their occurrence cannot be ruled out. On the other hand, the method I have used to apply the visual stimuli has the advantage over that of Barlow that it is used with the eye intact and therefore with the retina receiving its normal blood supply. Barlow worked with excised retinas. The method I have used also has the great advantage over those of both Kuffler and Barlow that a wide variety of forms of visual stimulus can readily be produced. The facility of using a cathode-ray tube as the light source is particularly valuable. Further work using the technique seems likely to be fruitful.

The Histology of the Optic Lobes.

In all of the experiments described here in which action potentials were recorded from the frog optic lobes, the electrode was passed into the substance of the lobe to a distance which never greatly exceeded 1 mm. Slides showing sections of the optic lobes have been prepared in the Histology Division of the Physiology Dept. These show layers of nerve cells and fibres alternating with one another. So far, no attempt has been made to correlate the nature of the response with the site of the electrode within the lobe.

In future work the histology of the optic lobes will be taken into account, and an attempt will be made to decide from which layer the electrode is recording at any time.

A large amount of information about the histology of the optic lobes of the frog is available in the literature. There is also information about the optic lobes of other animals, which are somewhat similar in structure to the frog optic lobes. In particular, the literature on the histology of the optic lobes of birds has been reviewed by Hamdi and Whitteridge (1954) and a very complete description has been given by P. Ramón y. Cajal (1943).

The histology of the frog optic lobes is discussed by S. Ramón y. Cajal (1955, vol.2, pp.215-217) and by Kappers, Huber and Crosby (1936, vol.2 pp.942-946).

In order to form a picture of the way in which the activity aroused by retinal stimulation passes through the optic lobes, it will be necessary to know what parts of the lobes receive fibres from the optic tract. This aspect of the problem is complicated by the fact that there is not one bundle of optic fibres arriving at each lobe, but three. Kappers, Huber and Crosby (1936, vol. 2, pp.946-953) give a description of the major fibre connections in the tectal region in amphibians, and state "Three optic bundles have been recognised in various amphibians. Thus, in the frog, Wlassek ('93) identified, behind the optic chiasma (1) a superficial or marginal optic bundle which follows the surface of the diencephalon dorsocaudalward to its termination in the stratum album of the tectum (2) an axial bundle which runs more deeply, passing through both the nucleus anterior superior corporis geniculati thalami of Bellonici ('88) and the corpus geniculatum thalami of Gaupp ('89) on its way to the tectum, and finally (3) a basal optic bundle which passes caudalward to a nucleus in the base of the midbrain just in front of the level of the oculomotor nerve and undoubtedly comparable to the nucleus of the basal optic root of reptiles."

The references to Wlassek (1893), Bellonici (1888) and Gaupp (1889) are included in the references at the end of this thesis. It is clear that a great deal of attention must be given to the histology and connections of the optic lobes, but I have not yet undertaken their serious study because of limited time.

University of Glasgow

Session 1956-57

HIGHER DEGREES AND SPECIAL STUDY AND RESEARCH

SUMMARY OF FEES*

Research Student			
	Matriculation fee	2½	gns.
	Research fee	9	,,
	Laboratory fee, where applicable, annually	12	,,
Post-Graduate Diploma or Certificate, for Proficiency in a Special Subject			
	Matriculation fee, annually	2½	gns.
	Tuition fee, annually	7	,,
	Examination fee	3	,,
D.Mus.			
	On submission of thesis, or on entry for examination	15	,,
D.Litt. **D.Sc.** **D.Sc. in Public Health** **Ph.D.** **M.D.S.**	on submission and on re-submission of thesis	15	,,
M.D. **Ch.M.**	on submission of thesis	20	,,
	on re-submission of thesis	5	,,

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* These Fees are under review.

GENERAL INFORMATION

Higher Degrees

The University awards the higher degrees of Doctor of Letters (D.Litt.) and Doctor of Music (D.Mus.) in the Faculty of Arts, Doctor of Medicine (M.D.), Master of Surgery (Ch.M.) and Master of Dental Surgery (M.D.S.) in the Faculty of Medicine, Doctor of Science (D.Sc.) in the Faculties of Science and Engineering, and Doctor of Philosophy (Ph.D.) in all Faculties.[1]

The regulations governing these degrees are printed below. Candidates for any higher degree are required to submit a thesis embodying original work ; candidates for the degrees of Doctor of Medicine, Master of Surgery and Doctor of Music are also required to submit to examination and candidates for any other higher degree may be required to do so. For the degrees of Doctor of Medicine and Master of Surgery only Bachelors of Medicine of this University, and for the degree of Doctor of Science in Public Health only Bachelors of Science in Public Health of this University, may be candidates, and no residence is required for these degrees. The degree of Master of Dental Surgery is open to Bachelors of Dental Surgery of this University, and to Bachelors of Medicine or of Science of this University who hold a registrable dental qualification. The degrees of Doctor of Letters and Doctor of Science are open both to graduates in Arts or Pure Science or Engineering with Honours of this University, of whom no further residence is required, and to other graduates of this University, or graduates of other Universities, who have spent a prescribed period as Research Students in this University. The degree of Doctor of Music is open both to Bachelors of Music with Honours of this University, of whom no further residence is required, and to Bachelors of Music of other Universities who have spent a prescribed period as Research Students in this University. The degree of Doctor of Philosophy is open to graduates of this University or of other Universities ; all candidates are required to spend a prescribed period as Research Students in this University.[2]

The conditions under which candidates are admitted to the status of Research Student are printed below, pp. 505 *et seq.* The basic fee payable by Research Students, in addition to the normal matriculation fee of £2 12s. 6d. a year, is £9 9s. a year with a supplementary fee of £12 12s. a year where laboratory facilities are given.

Enquiries regarding admission to the status of Research Student should be addressed to the Clerk of Senate.

Diplomas and Certificates for Post-graduate Study

Graduates and other advanced students may be candidates for the Diploma and the Certificate of Proficiency awarded for special study in the Faculty of Arts. The Diploma is intended for Honours graduates who have pursued advanced study of a special subject under the direction of a Professor or Lecturer, the Certificate for others who have attended one of the regular advanced courses provided in the Faculty. The minimum period of study required either for the Diploma or for the Certificate is one year ; in addition to the normal matriculation fee, candidates are required to pay a tuition fee of seven guineas a year and an examination fee of three guineas. The regulations are printed in the syllabus of the Faculty of Arts.

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[1] The Regulations for the Degree of Bachelor of Letters appear in the Syllabus of the Faculty of Arts.

[2] An Ordinance instituting a Higher Degree in Law is at present being made.

The Regulations for the Diploma in Public Health are printed in the syllabus of the Faculty of Medicine.

I. DEGREE OF DOCTOR OF LETTERS

The Degree of Doctor of Letters is awarded under Ordinance XXVI (Glasgow No. 7), which came into force on 26th September, 1908. The following are the relevant provisions of the Ordinance.

VII. Graduates who have obtained any degree in the University of Glasgow, and who have either before or after graduation passed the Examination in an Honours Group for the Degree in Arts, or the Final Science Examination for the degree in Pure Science or in Engineering with Honours may offer themselves for the degree of Doctor of Letters (D.Litt.) after the expiry of five years from the date of their graduation.

VIII. Research Students as aforesaid, who have prosecuted in the University of Glasgow some special study under Ordinance No. 61 (General, No. 23—Regulations for the Encouragement of Special Study and Research, and for the appointment of Research Fellows), may offer themselves for the degree of Doctor of Letters ; provided—

(1) That they have obtained a degree in any Scottish University, or a degree in another University specially recognised by the University Court for the purpose of this section, which the Senatus shall deem to be equivalent to the corresponding degree in the University of Glasgow ; and provided that candidates who have obtained any such degree in a University outside the United Kingdom so recognised may be required if the Senatus think fit, before beginning their course as Research Students with a view to the degree of Doctor of Letters, to pass an examination equivalent to an Honours Examination in a group of subjects cognate to their line of work as Research Students.

(2) That they have spent not less than two terms in each of two academical years, or an equivalent period, as Research Students in the University of Glasgow, and produce to the Senatus evidence of satisfactory progress in the special study undertaken by them during that period.

(3) That a period of not less than five years shall have elapsed from the date of the graduation required in sub-section (1) of this section.

IX. All candidates for the degree of Doctor of Letters shall present a thesis or a published memoir or work, which shall be an original contribution to learning in relation to literature or to philosophy, to be approved by the Senatus on the recommendation of a Special Committee appointed by the Senatus ; provided that, if required by the Senatus, a candidate shall also be bound to pass such an examination, conducted orally or otherwise, on the subjects of his special study, or his thesis, or memoir or work, as may from time to time be determined. The thesis or memoir or work shall be accompanied by a declaration signed by the candidate that it has been composed by himself. If the thesis has not already been published, it shall be published by the candidate in such a manner as the Senatus shall approve, and a copy thereof shall be deposited by the candidate in the University Library.

X. Notwithstanding, and in supplement of the provisions of Ordinance No. 13 (General, No. 8—Regulations as to Examinations), Sections

XIV and XV, the Senatus shall appoint such Professors or Lecturers in the University as it may think suitable to examine the theses and to conduct the examination of candidates who may offer themselves under the provisions of Ordinance No. 12 (General, No. 7, Regulations for Degrees in Science) or of Ordinance No. 23, Glasgow No. 2—Regulations for Degrees in Engineering, Science or of this Ordinance, for the degree of Doctor of Letters ... ; and the University Court shall, after consultation with the Senatus, appoint one or more additional Examiners to act along with them in adjudicating on the merits of the candidates. Every such additional Examiner shall be a person of recognised eminence in the subject of the thesis or memoir or work which is to be submitted for approval, and may be a Professor or Lecturer in any Scottish University other than the University of Glasgow. The result of the examination and adjudication shall be reported to the appropriate Faculty or Special Committee of Senatus, who shall if they think fit make a recommendation thereon to the Senatus ; and no candidate shall be approved for the degree unless the Senatus is satisfied that his work is of distinction as a record of original research undertaken by himself, or of important engineering work designed by himself and actually carried out, or as an original contribution to learning.

SUPPLEMENTARY REGULATIONS

1. The thesis should be presented in the form of a single memoir or writing containing a connected account of the candidate's research or work. Detached papers under various headings will not be regarded as a sufficient substitute, unless they are accompanied by a separate statement, composed by the candidate, giving a full account of the methods, results and conclusions of the research or work on which his candidature is based.

Along with this thesis each candidate must submit a résumé of it, stating what is claimed as original in it, and a bibliography.

2. Candidates who have been awarded a Certificate of Proficiency in the subjects of an Honours Group will be regarded as having " passed the Examination in an Honours Group " for the purpose of proceeding to the degree of D.Litt.

3. Each candidate must submit two copies of his thesis : both copies, whether the thesis is approved for the degree or not, shall become the property of the University.

2. DEGREE OF DOCTOR OF MUSIC

The Degree of Doctor of Music was instituted by Ordinance CLXXIII (Glasgow No. 42) ; the following are the sections of that Ordinance which govern the award of the Degree.

XI. (1) Bachelors of Music of the University of Glasgow, who have taken Honours either before or after graduation, may offer themselves for the degree of Doctor of Music (D.Mus.), after the expiry of five years from the date of their graduation.

(2) Bachelors of Music of other Universities recognised for the purpose by the University Court after consultation with the Senatus may offer themselves for the degree of Doctor of Music, after the expiry of

five years from the date of their graduation, provided they have spent not less than three years as Research Students in the University of Glasgow, under Ordinance No. 61 (General, No. 23), and produce to the Senatus evidence of satisfactory progress in the special study undertaken by them during that period.

XII. The Degree shall be given in three Departments, and candidates may present themselves in one or more of these Departments.

The Departments shall be those of:

(*a*) Composers;
(*b*) Executants;
(*c*) Theorists or Historians.

Composers

XIII. (1) Candidates for the Degree of Doctor of Music as Composers shall submit a prescribed number of original works in accordance with regulations to be prescribed by the Senatus.

Compositions must be accompanied by a declaration signed by the candidate that they are his own unaided work, and that no portion has been submitted previously to any University.

(2) Candidates in this department shall also be examined in the following subjects:

(*a*) Eight-part Harmony and Counterpoint;
(*b*) Canon and Double Counterpoint in four parts, and Fugue in five parts;
(*c*) Scoring for full Orchestra;
(*d*) Historical Knowledge.

Executants

XIV. (1) Candidates for the Degree of Doctor of Music as Executants shall be required to pass a test of a wide repertoire of concert works in accordance with regulations to be prescribed by the Senatus.

(2) Candidates in this department must also qualify for the optional subject set forth in VI (8) p. 276 (Degree of Bachelor of Music), and may also be required to pass an examination in any or all of the subjects prescribed for candidates for the Degree of Doctor of Music as Composers in accordance with regulations to be prescribed by the Senatus.

Theorists or Historians

XV. (1) Candidates for the Degree of Doctor of Music as Theorists or Historians shall present, in accordance with regulations to be prescribed by the Senatus, one or more treatise on Theoretical or Historical subjects. Such treatises must be the result of original thought and research, not merely abstracts or compilations of existing works.

Each treatise must be accompanied by a declaration signed by the candidate that it is his own unaided work and that it has not been submitted to any other University.

(2) Candidates in this department may also be required to pass an examination in any or all of the subjects prescribed for candidates for the Degree of Doctor of Music as Composers, in accordance with regulations to be prescribed by the Senatus.

SUPPLEMENTARY REGULATIONS

1. **Executants, Theorists and Historians.** All candidates in these categories will be examined in the following four subjects :

(*a*) Harmony and counterpoint in not more than eight parts.

(*b*) Canon and Double and Triple counterpoint in not more than three parts, and Fugue in not more than five parts.

(*c*) Scoring for full orchestra.

(*d*) The History of music from 1500 A.D. to the present day.

2. **Executants.** Each candidate must submit, not later than six weeks before the examination, an extensive list of works which he professes ; if the list is approved, he will be informed, a month before the examination, of not more than four works which he will be required to perform. Violinists and violoncellists must include one or more of the unaccompanied sonatas or suites of J. S. Bach ; candidates who profess instruments other than pianoforte, violin, violoncello or organ must include concertos and chamber works ; vocalists must include rôles in opera and oratorio.

3. **Theorists and Historians.** Before submitting a treatise, candidates must submit a précis indicating its scope and general character ; a treatise may not be submitted until the précis has been approved.

3. DEGREE OF DOCTOR OF MEDICINE

The following regulations for the award of the degree of Doctor of Medicine are contained in Ordinance XXXI (Glasgow No. 9).

XXII. (1) Subject to the conditions hereinafter specified, the Degree of Doctor of Medicine may be conferred on any candidate who has obtained the Degrees of Bachelor of Medicine and Bachelor of Surgery of the University of Glasgow, and is of the age of twenty-four years or upwards, and has produced a certificate showing that, after having received the degrees of Bachelor of Medicine and Bachelor of Surgery, he has been engaged for at least one year in attending the Medical Wards of a Hospital or in scientific work bearing directly on his profession, such as is conducted in the Research Laboratories of the University, or in the Naval, Military, Colonial, or Public Health Medical Services, or has been engaged for at least two years in Practice other than Practice restricted to Surgery.

(2) Each candidate for the degree of Doctor of Medicine shall be required to pass an examination in Clinical Medicine or in such special department of Medical Science or Practice professed by the candidate as the Senatus, on the recommendation of the Faculty of Medicine, may approve ; and he may be admitted to the examination at such time, not sooner than one year after he has received the degrees of Bachelor of Medicine and Bachelor of Surgery, as the Senatus may appoint for the purpose.

(3) Each candidate for the degree of Doctor of Medicine shall submit for the approval of the Faculty of Medicine a thesis on any branch of knowledge, comprised in the several divisions of the Examination for the degrees of Bachelor of Medicine and Bachelor of Surgery, which he

may have made a subject of special study, excepting a subject that is exclusively surgical; and the thesis, accompanied by a declaration signed by the candidate that the work has been done and the thesis composed by himself, shall be lodged with the Dean of the Faculty of Medicine on or before a date to be fixed by the Senatus. The Faculty may, if it sees fit, before approving the thesis, require the candidate to present himself for oral or other examination on the subject-matter thereof. If the thesis is, in the judgment of the Faculty, of special merit, the Senatus may, on the recommendation of the Faculty, exempt the candidate from the whole or part of the examination prescribed in sub-section 2 of this Section.

(4) A Bachelor of Medicine and Bachelor of Surgery, who produces to the Senatus satisfactory evidence of his intention of entering within twelve months after obtaining such degrees on the practice of his profession in a British Possession or Colony, or in a Foreign Country, may, under such conditions as the Senatus may from time to time prescribe, be admitted to the examination in Clinical Medicine or in a special department of Medical Science or Practice prescribed in sub-section 2 of this Section at such time after he has received such degrees as the Senatus may appoint for the purpose: provided always that in special circumstances the Senatus may, if it sees fit, on the recommendation of the Faculty of Medicine, exempt him from the whole or part of the Examination; but the degree of Doctor of Medicine shall not be conferred on him unless he shall produce a certificate showing that, after having received the degrees of Bachelor of Medicine and Bachelor of Surgery, he has been engaged for at least one year in attending the Medical Wards of a Hospital or in scientific work bearing directly on his profession, such as is conducted in the Research Laboratories of the University, or in the Naval, Military, Colonial or Public Health Medical Services, or for at least two years in Practice other than Practice restricted to Surgery, and unless his thesis, in the judgment of the Faculty of Medicine, is of special merit.

SUPPLEMENTARY REGULATIONS

1. To comply with the conditions prescribed in sub-sections 2 and 3 above, a candidate, after submitting a thesis, may be required to present himself before the examiners for interview or for further examination on the subject-matter of his thesis and related subjects. When a candidate is required to undergo further examination, this examination may be a written, or oral, or practical test, or any combination of these, as the examiners think fit.

2. One copy only of a thesis is required. It must be typewritten on paper of crown quarto size (10 inches by 7½ inches), bound in cloth with stiff boards, and have its title and the name of the author printed in block letters on the outside binding. The thesis should be lodged with the Dean of the Faculty of Medicine not later than 15th September, or 15th December, or 15th March, for adjudication during the Martinmas, Candlemas, and Whitsun terms respectively.

3. A thesis will not be approved unless it gives evidence of original observation, or, if it deals with the researches of others, gives a full statement of the literature of its subject with accurate references and critical investigation of the views or facts cited: mere compilations will in no case be accepted.

4. A thesis submitted for the degree must be a dissertation written for the purpose, provided that the results of original observations already published in medical or scientific journals or in the transactions of learned societies or otherwise may be accepted in place of such a dissertation.

5. Three grades of distinction may be awarded for the excellence of theses submitted for the degree—Commendation, High Commendation and Honours.

6. The copies of theses submitted by candidates, whether the theses are approved for the degree or not, shall become the property of the University.

4. DEGREE OF MASTER OF SURGERY

The following regulations for the award of the degree of Master of Surgery are contained in Ordinance XXXI (Glasgow No. 9).

XXIII. (1) Subject to the conditions hereinafter specified the degree of Master of Surgery may be conferred on any candidate who has obtained the degrees of Bachelor of Medicine and Bachelor of Surgery of the University of Glasgow, and is of the age of twenty-four years or upwards, and has produced a certificate showing that, after having received the degrees of a Bachelor of Medicine and Bachelor of Surgery, he has been engaged for at least one year in attending the Surgical Wards of a Hospital or in scientific work bearing directly on his profession, such as is conducted in the Research Laboratories of the University, or in the Naval, Military, or Colonial Medical Services, or has been engaged for at least two years in Practice other than Practice restricted to Medicine.

(2) Each candidate for the degree of Master of Surgery shall be required to pass an examination in the following subjects: Surgical Anatomy, Operations upon the dead body, and Clinical Surgery or such special department of Surgery professed by the candidate as the Senatus, on the recommendation of the Faculty of Medicine, may approve; and he may be admitted to the examination at such time, not sooner than one year after he has received the degrees of Bachelor of Medicine and Bachelor of Surgery, as the Senatus may appoint for the purpose.

(3) Each candidate for the degree of Master of Surgery shall submit for the approval of the Faculty of Medicine a thesis on any branch of knowledge, comprised in the several divisions of the Examination for the degrees of Bachelor of Medicine and Bachelor of Surgery, which he may have made a subject of special study, excepting a subject that is exclusively medical; and the thesis, accompanied by a declaration signed by the candidate that the work has been done and the thesis composed by himself, shall be lodged with the Dean of the Faculty of Medicine on or before a date to be fixed by the Senatus. The Faculty may, if it sees fit, before approving the thesis, require the candidate to present himself for oral or other examination on the subject-matter thereof. If the thesis is, in the judgment of the Faculty, of special merit,

the Senatus may, on the recommendation of the Faculty, exempt the candidate from the whole or part of the examination prescribed in sub-section 2 of this Section.

(4) A Bachelor of Medicine and Bachelor of Surgery who produces to the Senatus satisfactory evidence of his intention of entering within twelve months after obtaining such degrees on the practice of his profession in a British Possession or Colony, or in a Foreign Country, may, under such conditions as the Senatus may from time to time prescribe, be admitted to the examination in the subjects specified in sub-section 2 of this Section, at such time after he has received such degrees as the Senatus may appoint for the purpose : provided always that in special circumstances the Senatus may, if it sees fit, on the recommendation of the Faculty of Medicine, exempt him from the whole or part of the examination ; but the degree of Master of Surgery shall not be conferred on him unless he shall produce a certificate showing that, after having received the degrees of Bachelor of Medicine and Bachelor of Surgery, he has been engaged for at least one year in attending the Surgical Wards of a Hospital or in scientific work bearing directly on his profession, such as is conducted in the Research Laboratories of the University, or in the Naval, Military, or Colonial Medical Services, or for at least two years in Practice other than Practice restricted to Medicine, and unless his thesis in the judgment of the Faculty of Medicine is of special merit.

SUPPLEMENTARY REGULATIONS

1. To comply with the conditions prescribed in sub-sections 2 and 3 above, a candidate, after submitting a thesis, may be required to present himself before the examiners for interview or for further examination on the subject-matter of his thesis and related subjects. When a candidate is required to undergo further examination, this examination may be a written, or oral, or practical test, or any combination of these, as the examiners think fit.

2. One copy only of a thesis is required. It must be typewritten on paper of crown quarto size (10 inches by 7½ inches), bound in cloth with stiff boards, and have its title and the name of the author printed in block letters on the outside binding. The thesis should be lodged with the Dean of the Faculty of Medicine not later than 15th September, or 15th December, or 15th March, for adjudication during the Martinmas, Candlemas, and Whitsun Terms respectively.

3. A thesis will not be approved unless it gives evidence of original observation, or, if it deals with the researches of others, gives a full statement of the literature of its subject with accurate references and critical investigation of the views or facts cited : mere compilations will in no case be accepted.

4. A thesis submitted for the degree must be a dissertation written for the purpose, provided that the results of original observations already published in medical or scientific journals or in the transactions of learned societies or otherwise may be accepted in place of such a dissertation.

5. Three grades of distinction may be awarded for the excellence of theses submitted for the degree—Commendation, High Commendation and Honours.

6. The copies of theses submitted by candidates, whether the theses are approved for the degree or not, shall become the property of the University.

5. DEGREE OF DOCTOR OF SCIENCE

The degree of Doctor of Science is awarded under Ordinance XXVI (Glasgow No. 7), which came into force in September, 1908. The following are the relevant provisions of that Ordinance, with the amendments made in subsequent Ordinances.

I. Graduates who have obtained any degree in the University of Glasgow, and who have either before or after graduation passed the Examination in an Honours Group for the degree in Arts, or the Final Science Examination for the degree in Pure Science or in Engineering with Honours, may offer themselves for the degree of Doctor of Science (D.Sc.) after the expiry of five years from the date of their graduation.

II. Research Students within the meaning of Ordinance No. 61 (General No. 23—Regulations for the Encouragement of Special Study and Research and for the Appointment of Research Fellows), who have prosecuted in the University of Glasgow (or in a College affiliated thereto) some special study or research under that Ordinance, may offer themselves for the degree of Doctor of Science : provided :

(1) That they have obtained a degree in any Scottish University, or a degree in another University specially recognised by the University Court for the purpose of this section which the Senatus shall deem to be equivalent to the corresponding degree in the University of Glasgow ; and provided that candidates who have obtained any such degree in a University outside the United Kingdom so recognised may be required, if the Senatus think fit, before beginning their course as Research Students with a view to the degree of Doctor of Science, to pass an examination equivalent to an Honours or to a Final Science Examination in a group of subjects cognate to their line of work as Research Students.

(2) That they have spent not less than two terms in each of two academical years, or an equivalent period, as Research Students in the University of Glasgow (or in a College affiliated thereto), and that they produce to the Senatus evidence of satisfactory progress in the special study or research undertaken by them during that period.

(3) That a period of not less than five years shall have elapsed from the date of the graduation required in subsection (1) of this section.

III. All candidates for the degree of Doctor of Science shall present a thesis or a published memoir or work, to be approved by the Senatus on the recommendation of the Faculty of Science ; provided that, if required by the Senatus, the candidate shall also be bound to pass such an examination conducted orally or practically, or by written papers, or by all of these methods, on the subjects of his special study or of his thesis, memoir, or work, as may from time to time be determined. The thesis shall be a record of original research in relation to science undertaken by the candidate, or of some important engineering work designed by the candidate and actually carried out, and shall be accompanied by a declaration signed by him that the work has been done and the thesis composed by himself. If the thesis has not already been published, it shall be published by the candidate in such manner as the Senatus shall approve, and a copy thereof shall be deposited by the candidate in the University Library.

X. Notwithstanding, and in supplement of the provisions of Ordinance No. 13 (General, No. 8—Regulations as to Examinations), Sections XIV and XV, the Senatus shall appoint such Professors or Lecturers in the University as it may think suitable to examine the theses and to conduct the examination of candidates who may offer themselves under the provisions of Ordinance No. 12 (General, No. 7—Regulations for Degrees in Science) or of Ordinance No. 23 Glasgow, No. 2—Regulations for Degrees in Engineering Science, or of this Ordinance, for the degree of Doctor of Science . . . ; and the University Court shall, after consultation with the Senatus, appoint one or more additional Examiners to act along with them in adjudicating on the merits of the candidates. Every such additional Examiner shall be a person of recognised eminence in the subject of the thesis or memoir or work which is to be submitted for approval, and may be a Professor or Lecturer in any Scottish University other than the University of Glasgow. The result of the examination and adjudication shall be reported to the appropriate Faculty or Special Committee of Senatus, who shall if they think fit make a recommendation thereon to the Senatus ; and no candidate shall be approved for the degree unless the Senatus is satisfied that his work is of distinction as a record of original research undertaken by himself, or of important engineering work designed by himself and actually carried out, or as an original contribution to learning.

SUPPLEMENTARY REGULATIONS

1. Candidates who have been awarded a Certificate of Proficiency in the subjects of an Honours Group will be regarded as having " passed the Examination in an Honours Group " for the purpose of proceeding to the degree of D.Sc.

2. Each candidate must submit two copies of his thesis : both copies, whether the thesis is approved for the degree or not, shall become the property of the University.

3. In addition to making the declaration required under Section III of the Ordinance a candidate must, if the whole or any part of the subject-matter of the thesis submitted by him has been included in a thesis already approved for a degree in this or another University, make a declaration to that effect, and must lodge together with his thesis either a copy of such previously approved thesis or a precise statement of its scope.

4. Before acceptance for adjudication, a thesis, or an important part of it, shall have been published either as a book or in periodicals of recognised standing. The thesis may be presented in the form of a single memoir or writing containing a connected account of the

candidate's research or work. Published papers under various headings may be submitted in lieu of a single thesis provided that they are accompanied by a statement showing the relationship between the various studies and placing the whole work critically into perspective with the general state of knowledge in the field of investigation to which the candidate's researches are related. The thesis should also be accompanied by two copies of a separate summary (500–1000 words) which must be an adequate and informative abstract of the work, suitable for publication by the University.

6. DEGREE OF DOCTOR OF SCIENCE IN PUBLIC HEALTH

The regulations for the award of the degree of Doctor of Science in Public Health are contained in Ordinance VI (Glasgow No. 2), which came into force in May, 1903. The relevant provisions of the Ordinance are :

X. Graduates who have held the degree of Bachelor of Science in Public Health from the University of Glasgow for a term of five years, may offer themselves for the degree of Doctor of Science in Public Health in the said University.

XI. Each candidate for the degree of Doctor of Science in Public Health shall present a thesis or a published memoir or work to be approved by the Senatus, on the recommendation of the Faculty of Science, and shall also be required to pass an examination in Public Health, and in such of its special departments as the Senatus, with the approval of the University Court, by regulations framed from time to time, shall determine.

The thesis, or published memoir or work, shall be a record of original research undertaken by the candidate, and shall be accompanied by a declaration, signed by him, that the work has been done, and the thesis or memoir composed, by himself.

XII. The Senatus Academicus shall appoint such Professors or Lecturers as it may think suitable to conduct the examination of candidates who may offer themselves under the provisions of this Ordinance for the degree of Doctor of Science, and the University Court shall, after consultation with the Senatus Academicus, appoint such additional Examiners as they deem necessary to act along with them. Such additional Examiners shall be persons of recognised eminence in the subject of the thesis, or memoir, or work which is to be submitted for approval, and may be Professors or Lecturers in any Scottish University other than the University of Glasgow.

XIII. The thesis, memoir, or work submitted by a candidate for the degrees of Doctor of Science shall in each case be examined by the additional Examiner to be appointed by the University Court, as well as by the Examiners to be appointed by the Senatus under the provisions of Section XII of this Ordinance.

XIV. The result of the examination of the thesis, memoir, or work submitted by a candidate, as well as the result of the Examination prescribed under Section XI of this Ordinance, shall be reported to the Faculty of Science.

7. DEGREE OF DOCTOR OF PHILOSOPHY

The degree of Doctor of Philosophy was instituted by Ordinance LXXIV (Glasgow No. 21), which came into force in October, 1919. The relevant provisions of the Ordinance are as follows :

II. Research Students within the meaning of Ordinance No. 61 (General No. 23), who have prosecuted in the University of Glasgow, or in a College affiliated thereto, a course of special study or research in accordance with the provisions of that Ordinance, may offer themselves for the degree of Doctor of Philosophy, under the following conditions, namely—

(1) That they have obtained a degree in any Scottish University, or in another University or College specially recognised for the purpose of this Section by the University Court on the recommendation of the Senatus : provided always that a diploma or certificate recognised in like manner as equivalent to a degree may be accepted in place of a degree.

(2) That they have prosecuted a course of special study or research during a period of three academical years as Research Students in the University of Glasgow, or in a College affiliated thereto, and that they produce to the Senatus evidence of satisfactory progress in the special study or research undertaken by them during that period : provided always that the Senatus shall have power, in exceptional cases, to reduce the period to two academical years, and to permit a Research Student during part of the period to prosecute elsewhere his special study or research.

III. All candidates for the degree of Doctor of Philosophy shall present a thesis to be approved by the Senatus on the recommendation of a Special Committee appointed by the Senatus. The thesis shall embody the results of the candidate's special study or research, and shall be accompanied by a declaration signed by the candidate that it has been composed by himself. The Special Committee shall always include the Professor or other Head of a Department who has been appointed by the Senatus to supervise the candidate's work as a Research Student.

The University Court may, on the recommendation of the Senatus, appoint one or more additional Examiners to act along with the Special Committee in adjudicating on the merits of the thesis. The Senatus may, on the recommendation of the Special Committee, require the candidate to present himself for oral or other examination on the subject-matter of his thesis. A copy of the thesis, if approved, shall be deposited by the candidate in the University Library.

SUPPLEMENTARY REGULATIONS

1. Except in the case of members of the teaching staff of the University, the Senatus will not recognise Research Students as candidates for the degree of Ph.D. in the Faculties of Arts, Medicine, Science and Engineering unless they are able to devote the major part of the day during term-time to the object of their research.

2. In submitting a thesis a candidate must state, generally in the preface and specifically in the notes, the sources from which his information is derived, the extent to which he has availed himself of the work of others, and the portions of the thesis which he claims as original.

3. A candidate must submit two copies of the thesis and in addition two copies of a separate summary of the thesis. The separate summary (250–750 words) must be an adequate and informative abstract of the work, suitable for publication by the University. Both copies of the thesis, whether approved for the degree or not, become the property of the University.

8. DEGREE OF MASTER OF DENTAL SURGERY

The following regulations for the award of the degree of Master of Dental Surgery (M.D.S.) are contained in Ordinance CCXLI (Glasgow No. 56) which was approved by His Majesty in Council on 26th January, 1948.

XXII. Subject to the conditions hereinafter specified, the Degree of Master of Dental Surgery may be conferred on any candidate who has obtained the Degree of Bachelor of Dental Surgery of the University of Glasgow ; or, having obtained the Degrees of Bachelor of Medicine and Bachelor of Surgery, or the Degree of Bachelor of Science, of the University of Glasgow, holds in addition a Registrable Dental Qualification. The candidate must have produced certificates showing that, after having received his Registrable Dental Qualification, he has been engaged for at least one year in attending a Dental Hospital or the Dental Department of a General Hospital approved by the University Court, after consultation with the Senatus, or in the Naval, Military, or Public Health Services, or in practice in Dental Surgery.

XXIII. Each candidate for the Degree of Master of Dental Surgery shall be required to pass a clinical examination in Dental Surgery, and he may be admitted to that examination at such time, not sooner than one calendar year after he has received his Registrable Dental Qualification, as the Senatus may appoint for the purpose : provided always that in special circumstances the Senatus may, if they see fit, on the recommendation of the Board of Studies in Dentistry and the Faculty of Medicine, exempt a candidate from the whole or part of such examination.

XXIV. Each candidate for the Degree of Master of Dental Surgery shall submit for the approval of the Faculty of Medicine a Thesis on any branch of knowledge in the Second, Third, or Fourth divisions of the examination for the Degree of Bachelor of Dental Surgery, which he may have made a subject of study, excepting those subjects which are exclusively medical or surgical ; and the Thesis, accompanied by a declaration signed by the candidate that the work has been done and the Thesis composed by himself, shall be lodged with the Dean of the Faculty of Medicine on or before a date to be fixed by the Senatus. The Faculty may, if it sees fit, before approving the Thesis, require the candidate to present himself for oral or other examination on the subject-matter thereof.

9. DEGREE OF DOCTOR OF VETERINARY MEDICINE

By Ordinance CCLXI (Glasgow No. 66) which was approved by His Majesty in Council on 26th June, 1950, the Degree of Doctor of Veterinary Medicine (D.V.M.) may be conferred.

Regulations governing the award of the Degree have not yet been drawn up.

10. DEGREE OF MASTER OF VETERINARY SURGERY

By Ordinance CCLXI (Glasgow, No. 66) which was approved by His Majesty in Council on 26th June, 1950, the Degree of Master of Veterinary Surgery (M.V.S.) may be conferred.

Regulations governing the award of the Degree have not yet been drawn up.

RESEARCH STUDENTS

The following are the provisions of Ordinance No. 61 (General No. 23), by which the admission of Research Students is controlled :

I. It shall be in the power of the Senatus Academicus in each University, with the approval of the University Court, to make regulations under which graduates of Scottish Universities or of other Universities recognised by the University Court for the purposes of this Ordinance, or other persons who have given satisfactory proof of general education and of fitness to engage in some special study or research, may be admitted to prosecute such study or research in the University [or in a College affiliated thereto [1]].

II. It shall be the duty of the Senatus Academicus in each University :

(1) To receive and decide upon all applications for admission to prosecute special study or research ;

(2) To prepare a list of all persons so admitted (hereinafter referred to as Research Students) ;

(3) To make regulations for the supervision of their work ;

(4) To satisfy themselves from time to time that the Research Students are carrying on their work in the University in a satisfactory manner ;

(5) To suspend or exclude from any course any student whose conduct or progress is unsatisfactory.

III. Every applicant for admission must send in to the Senatus Academicus a written application stating any degree or other distinction which he has already obtained, the line of study or research which he

[1] Added by Ordinance XXXIX (Glasgow No. 12).

wishes to prosecute, and the probable period of its duration, together with evidence as to his character, capacity, and general qualifications.

IV. Any application for admission shall be in the first instance referred by the Senatus Academicus to the appropriate Faculty, or to a Committee appointed by the Senatus ; one member of the Committee shall always be a Professor or Lecturer within whose department the proposed line of study or research falls. No applicant shall be recommended by the Faculty or the Committee who has not satisfied them by examination or otherwise that he is qualified to prosecute the proposed line of study or research, and further:

(*a*) That his proposed line of study or research is a fit and proper one ;

(*b*) That he possesses a good general education ;

(*c*) That he is of good character ;

(*d*) That he proposes to prosecute his studies or research during a period to be approved by the Senatus Academicus.

The Faculty or the Committee shall make a report to the Senatus Academicus upon each application. It shall also be their duty, subject to the regulations of the Senatus Academicus, to provide for the supervision of the Research Student's work, and to report at least once a year to the Senatus as to his progress and conduct. The Senatus shall then determine whether he shall remain a Research Student.

V. Every Research Student shall be required to matriculate each year, paying the ordinary fee.

VI. Research Students shall have access to and the use of the University Laboratories and Museums, under such conditions as to payment and otherwise as the University Court, after consultation with the Senatus Academicus, may determine.

VII. The title of Research Fellow may be conferred by the Senatus Academicus, with the approval of the University Court, on Research Students who have shown special distinction. Such title shall not of itself confer any right to stipend, but it shall be in the power of the University Court to provide a stipend of such amount and for such period as it may think fit to any Research Fellow, under the powers of Section XI, sub-section 8, of Ordinances numbered 25 and 27, Section X, sub-section 8, of Ordinance numbered 26, and Section IV, sub-section 2, of Ordinance numbered 46.

VIII. (1) The Research Fellows shall be appointed as aforesaid after consideration of the report or reports submitted in terms of Section IV hereof.

(2) The title of Research Fellow may be conferred either at the commencement of the Research Student's course of study or research, or at any time during its progress, as the Senatus Academicus may determine.

(3) Research Fellows shall retain their title and stipend, if any, for the period during which they are engaged in special study or research in the University, and no longer.

(4) Research Students who have been appointed Research Fellows shall continue to be subject to the conditions above prescribed as to the supervision of their work, and the reports to be made thereon.

IX. Nothing herein contained shall prejudice the right of Research Students to such Fellowships, Scholarships, or prizes as may be open to them by Ordinance or Deed of Foundation.

X. The University Court may, subject to the provisions of Section XI, sub-section 8, of Ordinances numbered 25 and 27, Section X, sub-section 8, of Ordinance numbered 26, and Section IV, sub-section 2, of Ordinance numbered 46, provide such sums as it may think fit in aid of the expenses of special study or Research.

SUPPLEMENTARY REGULATIONS

1. Application for admission to the status of Research Student must be made to the Clerk of Senate on the prescribed form.

2. A Research Student may be required at the discretion of the Head of the Department to report his attendance to the supervisor of his research, or to the Clerk of Senate, at least once a week in term-time, except during periods when, with the permission of the Senatus, he is prosecuting his special study or research elsewhere than in the University or in a College affiliated thereto.

3. A Research Student may, with the sanction of his supervisor, attend classes in the University as a Private Student but he shall not be eligible for prizes in classes so attended and his attendance shall not qualify for graduation.

4. All papers arising out of work done in a department shall be submitted before publication to the Professor in charge of the department, and in all such papers, when they are published, a due recognition of the department shall be inserted.

CARNEGIE TRUST FOR THE UNIVERSITIES OF SCOTLAND

ENDOWMENT OF POST-GRADUATE STUDY AND RESEARCH

The regulations governing the award by the Trust of Scholarships, Fellowships and Grants in aid of research, are printed below. Nominations for Scholarships or Fellowships must be lodged not later than 15th March with the Secretary of the Trust, Merchants' Hall, Hanover Street, Edinburgh, from whom forms may be obtained. All Scholarships and Fellowships awarded in any year will normally date from 1st October.

A student who has not graduated but expects to take a degree at the summer or autumn graduation may be nominated for a Scholarship or apply for a Research Grant in the preceding March, but will not be eligible to receive either until he has graduated.

I. SCHOLARSHIPS

I. The Executive Committee are prepared to consider annually applications for Carnegie Scholarships in Science and Medicine and in History, Economics, English Literature and Modern Languages.

II. The number of Scholarships for annual award is limited. Applicants for Scholarships in Science, more especially where the proposed research is in Physics or Chemistry, are requested to note that, in consideration that maintenance allowances for training in research are available from public funds administered by the Department of Scientific and Industrial Research, the Executive Committee must reserve to themselves the right to give preferential treatment to applicants ineligible to receive allowances from the above-named source.

III. Scholarships will be of the annual value of £300. They will be tenable for one year in the first instance and, subject to satisfactory reports, be renewable for a second year. They may, in exceptional circumstances, be extended to a third year. Unless with the express consent of the Executive Committee the holder will be expected to devote his whole time to the purpose for which the Scholarship is awarded.[1]

IV. Applicants for Scholarships must be graduates of a Scottish University.[2] The standard required for applicants holding Degrees in the Faculties of Arts and Science is First Class Honours.

V. Applicants for Scholarships must be nominated by a Professor, Reader or Lecturer in a Scottish University, or by a Teacher in Scotland recognised for purposes of graduation by a Scottish University. In assessing the suitability of applicants for Carnegie Scholarships nominators will be expected to take into account the awards obtainable for research from such bodies as the Department of Scientific and Industrial Research, the Medical Research Council and the Agricultural Research Council.

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[1] In the event that applicants are not considered sufficiently advanced to warrant the award of the full Scholarship of £300, the Executive Committee may award a Minor Scholarship of £200 for one year.

[2] *Note.*—For the time being the Executive Committee will be prepared to consider applications from students who expect to graduate within a short time of making their application.

VI. The Executive Committee may, at their discretion, supplement Bursaries. Scholarships and Fellowships gained by graduates of the Scottish Universities. Applicants for such supplements must furnish a certificate from the Secretary or Registrar of their University showing the title, value and length of tenure of the Bursary, Scholarship or Fellowship gained, and will be required to conform to the regulations framed by the Executive Committee for holders of the full Carnegie Scholarships.

VII. Scholars will be required to work under a supervisor who need not be the Professor, Reader or Lecturer nominating them. Quarterly reports will be expected from the Scholars and their supervisors. Payments of the Scholarships will be made quarterly, the second and subsequent quarterly payments being dependent on the receipt of satisfactory reports.

2. SENIOR SCHOLARSHIPS

I. The Executive Committee are prepared to consider annually applications for a restricted number of Senior Scholarships in Science and Medicine, and in History, Economics, English Literature and Modern Languages.

II. The Senior Scholarships will be of the annual value of £350 together with a sum not exceeding £100 for fees, books and any necessary travelling expenses. They will be tenable for one year in the first instance but may be renewed for a second and, in exceptional circumstances, a third year. Payment will be made in quarterly instalments.

III. Applicants must be graduates of a Scottish University and be able to adduce proof of successful research for a period of at least three years prior to the application. Applications are not confined to those who have previously held Carnegie Scholarships of £300 per annum.

IV. Applicants must be nominated by a University Professor, Reader or Lecturer in a Scottish University, and must submit the names of two authorities, other than the nominator, to whom reference may be made if deemed necessary. Successful applicants will work under the general direction of a supervisor from whom, twice annually, a certificate will be required attesting satisfactory progress. The Senior Scholar will himself furnish reports twice annually on the progress of his work. He will be required to give his full time to the purpose for which the Senior Scholarship is awarded unless with the express sanction of the Committee.

3. FELLOWSHIPS

I. The Executive Committee are prepared to consider applications for Carnegie Fellowships in Science and Medicine and in History, Economics, English Literature and Modern Languages.

II. The applicant must be a graduate of a Scottish University or a member of the staff of one of the Universities or Colleges in Scotland receiving grants from the Trust.

III. The number of Fellowships will be limited. Their annual value will not, normally, exceed £800 per annum together with a sum not exceeding £50 for expenses in instances in which such grant is considered necessary. The period of tenure will, normally, be one year but special periods may be arranged.

IV. Nominations of persons holding posts in one or other of the Scottish Universities will be made by the appropriate University Authority ; nominations of graduates not so employed will be made by a Professor, Reader or Lecturer in a Scottish University. Arrangements will be made where necessary to maintain the employer's contribution to the Federated Superannuation System for Universities or similar scheme.

V. The Carnegie Fellows will undertake to give full time to the programme of research in respect of which the applications are made, but may, at the discretion of the Committee, engage in a limited amount of higher teaching or instruction associated with the special nature of their research work. They will come under an obligation to furnish a report once in each year on the progress of their work.

SPECIAL AWARDS

The Executive Committee are prepared to consider applications for special awards to be made for the execution of particular research projects which may not fall within the scope of the foregoing Regulations.

4. GRANTS IN AID OF RESEARCH

I. An applicant for a Research Grant must be a Scottish University Graduate resident in Scotland, or an actual member of the staff of one of the Universities or Colleges in Scotland receiving Grants from the Trust.

II. Applications must be made on a form which can be had from the Secretary of the Trust.

III. Applicants proposing to engage on research must furnish information on the following points at the time of making a first application.

(1) Their experience in research, with copies of or references to any published papers ; or, if they have no papers to offer, with references to two or more authorities who are acquainted with their qualifications for research.

(2) The nature of the research in which they desire to engage, and the results expected to follow therefrom.

(3) A statement of special requirements for the proposed research, with a detailed estimate of the cost.

(4) Whether they have received, or are receiving, any grant from any other source for the same object ; and if so, what results have already ensued from their investigations.

NOTE.—*Second or subsequent applications need not be accompanied by copies of published papers.*

IV. By accepting a Grant applicants come under an obligation to pursue the programme of research which has been approved, and to send to the Executive Committee a report containing (*a*) a brief statement (not necessarily for publication) showing the results arrived at, or the stage which the inquiry has reached ; (*b*) a statement of the expenditure incurred ; and (*c*) copies of or references to any papers in which results of the research have been printed.

The Executive Committee expect that in every case the results of the research will be published in some form. Copies of the published records of all work carried out with the aid of a Grant must be forwarded to the Offices of the Trust without delay.

V. A Research Grant is not intended (1) to take the place of such provision as should be made by the University Courts out of the Grants for Permanent Equipment under the Scheme of " Grants for five years to the four Universities of Scotland," or (2) to provide minor apparatus or research materials or instruments which should form part of the equipment of a Laboratory appropriate to the investigation.

VI. Grants are not applicable to the payment of salaries, wages, or honoraria, except in so far as they may be assigned for a specific purpose, as, for example, the cost of preparing necessary illustrations as specified in the application and approved by the Executive Committee. Such illustrations may include drawings, photographs, or maps.

VII. Applicants for guarantees against loss on the publication of books must, at the time of application, submit such MSS. as will enable the Trust's advisers to arrive at a recommendation in regard to the application.

VIII. Grants in aid of illustration to an amount not exceeding three-fourths of the estimated cost may be applied towards the preparation of process blocks or other means of reproduction, and of the actual printing of the illustration, including any special paper necessary for the purpose. Grants are not applicable to the cost of printing and publishing the letterpress of the publication unless, in exceptional cases, special tabular matter is required. Applicants for such grants in aid must, at the time of application, submit either an off-print of the publication or such MSS. as will enable the Trust's advisers to arrive at a recommendation in regard to the application.

Note :—Certain grants in aid of the publication of papers on the *Transactions*, *Proceedings* or *Journals* of learned societies in Scotland are now paid direct to the society and not to the individual contributor.

IX. Applications for Grants in aid of Laboratory research, or of the adequate publication of its results, must be made by the individual workers concerned, and Grants made for specific purposes to one worker cannot be utilised by another (whether in the same Laboratory or not) without the express consent of the Executive Committee.

X. An application for a Grant to be used by two or more collaborators in the same research must be signed by each ; but they shall appoint one of their number who shall be responsible for furnishing the report, for receiving and disbursing the money, and in general, for the conduct of the research.

XI. Instruments of permanent value purchased by means of the Grant shall remain the property of the Trust, but at the conclusion of the research, or at such other time as the Executive Committee may determine, they shall be placed under the care and at the disposal of the institution in which the research has been conducted, provided that the Executive Committee may, if they see fit, request their return.

5. TRAVEL AND MAINTENANCE ABROAD ON RESEARCH

I. In extension of its existing Research Scheme, the Trust proposes, as a tentative measure in the first instance, to invite applications from members of the staff of a Scottish University who wish to pursue research abroad for a limited period.

II. The essential object of the scheme is to give an opportunity to advanced investigators in Science and Medicine and in History, Economics, English Literature and Language and Literature other than English to pursue their particular research work abroad for such periods as may seem advantageous.

III. Normally the period for which application is made shall be not less than three or more than twelve calendar months.

IV. The amount of the award shall be such as may be found requisite having regard to the expense to be incurred in travel and additional maintenance, but shall, in no case, exceed £600.

V. The number of awards to be made in any one academic year will depend upon the nature and extent of the applications received but should not, normally, exceed 10, not more than 4 of which will be tenable in the United States of America.

VI. Members of the staff of a Scottish University shall be nominated by the Principal of the University. Full details of the proposed investigation together with the estimated cost thereof must be forwarded with the nomination.

VII. Successful applicants will be responsible for making all arrangements for travel and for residence abroad. The Trust will supply what information is required to enable the applicants' bankers to make the necessary representations to the Bank of England but cannot undertake to arrange details of the journey and residence.

VIII. Upon their return applicants will be required to furnish a report to the Trust giving, *inter alia*, such details as will be useful to the Executive Committee in their future consideration of this scheme as a whole.

IX. Special forms of application can be had on request from the Secretary and Treasurer at Merchants' Hall, 22 Hanover Street, Edinburgh, and must be returned to him not later than 1st February in each academic year.

X. Applicants must be not less than 30 years of age at the time of application.

THE CHARACTERISTICS AND THE IMPLICATIONS OF ELECTRICAL ACTIVITY WITHIN THE NERVOUS SYSTEM

by A.M. Andrew.

VOLUME 2

comprising Parts 3, 4, 5, 6, 7, and 8,

and the list of references.

PART 3

APPLICATIONS OF INFORMATION THEORY TO NEUROPHYSIOLOGY

PART 3. APPLICATIONS OF INFORMATION THEORY TO NEUROPHYSIOLOGY

The idea that information might be treated as a physical quantity, which can be measured in suitable units, is generally attributed to Hartley (1928). Modern Information Theory, which represents a considerable extension and modification of Hartley's work, is based on the work of Shannon (1948). An elementary account of it has been written (Andrew, 1953) and a reprint is included in the appendix of this thesis.

Information theory depends on the fact that information, in a certain sense of the word, can be treated as a physical quantity and expressed in units. The kind of "information" which can be treated in this way is not quite the same as what is meant by information in everyday usage. The word will be used here in its information-theory sense. In this sense, the amount of information in a message is a measure of the difficulty of transmitting the message from place to place, or of storing it, not of its significance.

The Unit of Information

A message may be of either of two types. It may consist of a sequence of symbols (e.g. letters, spaces and punctuation marks) or of a sequence of values of some continuously variable quantity (e.g. the instantaneous amplitude of the waveform representing a speech sound). Information theory is applicable to both kinds of message, but for the purpose of defining the unit of information only the type of message consisting of discrete symbols will be considered.

For this kind of message, the origination of the message is a process of selection. The individual symbols are selected in turn from the set of possible symbols, and any message is a selection from the set of possible messages, a set which is finite if the message length is limited.

The smallest number of possibilities from which a selection can be made is two. An obvious choice, therefore, for a unit of information is the amount required to indicate a choice between two possibilities which were equally likely to be selected. (The average amount of information is smaller when the probabilities are not equal.) A choice from four equiprobable possibilities involves two such units of information, for the possibilities may be represented by 00, 01, 10, 11 and then the choice from the four may be resolved into a choice from two equiprobable possibilities for the first digit, plus a similar choice for the second digit.

Proceeding in this way, it can be seen that three units of information corresponds to eight possibilities, four units to 16 possibilities, and so on. It is clear that if n, the number of possible and equiprobable messages, is a power of two, then H, the amount of information per message, is given by :-

$$H = \log_2 n$$

The unit of information is called a "bit", the word being a contraction of "binary digit". If it is required to represent a message by a sequence of binary digits, it will be found that a message containing H bits of information, H being an integer, can be represented by a sequence containing H binary digits.

Applications to Biology

I have been interested in Information Theory because of its possible application to neurophysiology and psychological medicine. It has been suggested, particularly in connection with the subject of Cybernetics (Wiener, 1948) that Information Theory should be useful in connection with biological problems. Information Theory does in fact have biological applications, though it has not proved so fruitful as was expected. The higher animals contain a complex communication system, in which information is transmitted along nerve fibres, and by the circulation of hormones in the blood. It is reasonable to suppose that Information Theory might have some application to the study of this system.

The ideas of Information Theory have proved useful when considering certain aspects of biological communication in a general way, without making any exact or detailed calculations about information rates or channel capacities. For example, Rushton (1950) makes use of the idea of information as a physical quantity in discussing the passage of information from eye to brain, to show that only part of the information received by the retina is actually conveyed along the optic nerve.

Hick (1950 and 1952) has made an application of Information Theory to psychology which, in contrast to the above, is strictly quantitative but takes no account of actual nervous pathways. Hick has found a relation between the responses of a human subject and the stimuli he is given, with no attempt at present to explain the mechanism. The relation gives an explanation, or at least a systematisation, of numerous experimental findings in reaction-time experiments.

In Rushton's application of the theory, actual neural pathways are considered but information rates and channel capacities are not estimated with any exactness. In Hick's application the details of the nervous pathways are ignored. In addition to the kinds of application typified by these, however, there have been attempts to apply Information Theory with exactness to the detailed study of the nervous system. A first step in this direction was made by MacKay (1952, also MacKay and McCulloch, 1952), who attempted to evaluate the maximum rate of information flow along a nerve fibre.

The Information-Carrying Capacity of a Nerve Fibre

MacKay's calculation is for a nerve fibre ending at a synapse, or splitting up into collateral fibres ending at separate synapses. Every nerve fibre (or axon) is an outgrowth (or process) of a nerve cell (or neuron). A synapse is a region in which the end of a fibre of one neuron comes close to the cell body or dendrites of another neuron; the arrival of a propogated impulse along the fibre affects the second neuron and may be sufficient to excite it so as to produce a propogated impulse in the nerve fibre which comes from it.

Generally there is more than one synapse on a neuron, and a corresponding number of fibre connections from other neurons. In order that a neuron may be excited so as to produce a propogated impulse along its axon, it may be necessary for impulses to arrive at several synapses on it more or less simultaneously. Lorente de Nő (1939) has shown that impulses arriving at different synapses on the same neuron are usually additive in their effects if their separation in time is less than 0•15 msec. He states "When two volleys of impulses are delivered to different synapses on a motoneuron, the statistical chances of effective summation are greatest if the volleys are delivered simultaneously or at intervals of less than 0•15 msec. They decrease rapidly when the volleys are separated by progressively increasing intervals of time, because some impulses fail to summate when they have arrived at intervals of over 0•15 - 0•2 msec. Finally, the chances of effective summation disappear when the separation between volleys becomes 0•5 msec."

In order to estimate the information-carrying capacity of a nerve fibre it is necessary to know with what accuracy time-intervals can be resolved by the arrangement of synapses to which the fibre delivers its information. MacKay decides that 0•05 msec. is a reasonable approximation to the minimum difference in interval which can be resolved (represented by ΔT). This value is chosen initially by consideration of the random variations which occur in the synaptic delay (i.e. the delay between the arrival of impulses at a group of synapses, and the initiation of the propogated impulse in the neuron on which the synapses are made). The value of 0·05 msec. is finally justified by comparison with the data of Lorente de Nó. MacKay states "It is known (Lorente de Nó, 1939, p. 422) that the period of latent addition of two converging impulses, over which their relative arrival-time may vary without appreciable effect, is of the order of 0·15 msec. This might seem to suggest that our scale unit of time ΔT should be of the same magnitude, or even twice this, since the relative delay may be of either sign. But the index of latent addition falls off very sharply over a few hundredths of a millisecond when the relative delay exceeds 0·15 msec. As a time resolving instrument, therefore, such a summation mechanism can in principle detect coincidence to much finer limits (as may be seen by imagining a constant delay of 0·15 msec to be introduced into one signal path), so that it is not obvious that the operational value of ΔT merits much increase."

The minimum interval between successive impulses in a nerve fibre has been variously estimated at values between 1 and 4 msec, depending on the particular nerve studied. The refractory period of the nerve fibre itself precludes values very much shorter than a millisecond.

The Information Rate under Binary Pulse-Code Modulation

Using the approximate data discussed above, MacKay estimates the capacity of a nerve fibre to transmit information, for three different ways of coding the information. The first which he considers is binary pulse-code modulation (binary PCM). When this kind of modulation is used the message time is divided into a large number of equal intervals, and in each interval of time an impulse may or may not occur. If the minimum possible interval between successive impulses is 1 msec, the maximum number of intervals into which one second of message time can be divided is 1000. In each interval of time one binary digit, or "bit" of information is conveyed along the fibre. Hence, using binary PCM, if the minimum possible interval between pulses is 1 msec, the maximum possible rate of flow of information is 1000 bits per second. Similarly, if the minimum interval is 4 msec, the maximum rate is 250 bits per second.

Other kinds of modulation

MacKay then goes on to consider two other kinds of modulation which could be used to send information along a nerve fibre, and he finds that the information rates which can be achieved using these forms of modulation are much higher than can be attained using binary PCM. It is not very surprising that binary PCM can be improved upon, for in binary PCM the intervals between successive pulses can only be integral multiples of the intervals into which the message time is divided. If these intervals are of 1 msec duration, the intervals between successive pulses are restricted to the values 1, 2, 3, ... msec. But the synapses to which the information is conveyed are able to discriminate the time of arrival much more accurately than is needed to measure the pulse-interval to the nearest millisecond, for it appears that a shift of pulse-position of about 0·05 msec can be detected. Hence it is not surprising to find that a higher information rate can be achieved using a system of modulation which allows the pulse-intervals to have values other than those to which they are restricted in binary PCM.

One of the main purposes of MacKay's paper is to point out that binary PCM is of no special merit for conveying information along nerve fibres. This point is important because the view seems to have arisen that the nervous system should be expected to work on a binary system. This view is a result of attempts to draw an analogy between the central nervous system and digital electronic computers, for which a binary system of operation has been found to be best. Wiener (1948, p. 137), for instance, discusses computing machines and the nervous system in the same chapter, and mathematical theory is put forward by McCulloch and Pitts (1943) which is intended to be applicable both to computers and to the nervous system. It is now generally agreed that there is no close analogy between the working of a digital computer and the working of the nervous system, and MacKay's conclusions serve to emphasize this.

The two other modulation systems which MacKay considers are pulse-position modulation (PPM) and pulse-interval modulation (PIM). Pulse-position modulation will not be discussed in detail here, since it is really a special case of pulse-interval modulation, with certain restrictions placed on the duration of interval which can occur at any time. In fact, all forms of pulse modulation which do not involve variation of the amplitude or form of the individual pulses are special cases of pulse-interval modulation. Since this is so, the information rate which is found for pulse-interval modulation, with the optimum distribution of pulse-intervals, must be greater than, or equal to, the best rate which can be obtained with pulse-position modulation. It is not clear from MacKay's papers whether he has appreciated this fact.

THE INFORMATION RATE UNDER PULSE-INTERVAL MODULATION

To estimate the maximum possible rate of flow of information along a nerve fibre, then, it is necessary to consider what MacKay calls pulse-interval modulation, or PIM. This is simply the type of modulation in which each interval between pulses is separately determined by the message to be transmitted. Each pulse-interval is in effect a separate transmitted symbol, in much the same way as the letters of the alphabet are symbols in a written message. This type of modulation of the nerve impulses imposes no restriction whatever on the time-patterns of impulses which can be produced, and hence it is the kind of modulation which should be considered in order to estimate the maximum possible rate of flow of information. (In binary PCM the time-patterns of pulses are restricted by the fact that the pulse-intervals must be integral multiples of some fixed interval longer than 1 msec or so; in PPM, the time-patterns are restricted by the fact that the message-time is divided into equal intervals, and one nerve impulse always appears somewhere in each of these intervals).

MacKay makes an estimate of the information capacity under PIM, but the method he uses is admitted by him to be approximate. An approximate estimation was sufficient for MacKay's purpose of showing that a higher information rate is generally possible with PIM than with binary PCM. The rate under PIM has, however, been rigorously determined by the writer (Andrew, 1952b), and the following is an account, first of MacKay's approximate estimation, and then of the exact solution.

MacKay's calculation of the rate under PIM

Following MacKay, let Δt be the smallest difference in duration of a time-interval which can be resolved by the synapses which receive information from the nerve fibre. Suppose that after sending a pulse the transmitter must wait for a minimum relaxation time t_r before sending another pulse. The interval between two pulses is denoted by t_s, where $t_s \geqslant t_r$.

It is convenient to take Δt as the unit of time and to write $t_r/\Delta t = r$; $t_s/\Delta t = s$.

MacKay assumes there will be some maximum duration which a pulse-interval can have, and he denotes this by t_m, and lets $t_m/\Delta t = m$. The pulse-durations which can occur, according to MacKay's assumptions, range from a minimum of t_r to a maximum of t_m. Since the smallest time-difference which can be resolved is Δt, it follows that the number of distinguishable interval-durations in this range is $(t_m - t_r)/\Delta t = (m - r)$. Hence each pulse-interval represents a choice among $(m - r)$ possibilities. Each pulse-interval therefore conveys an amount of information $\log_2(m - r)$ bits, if all the possibilities are equally probable.

MacKay assumes that the system of coding is such that all the possibilities are in fact equally probable, and under this assumption the mean value of the pulse-to-pulse interval t_s will be $(t_m + t_r)/2$, and the mean pulse-rate will be $2/(t_m + t_r)$, or $2/(m + r)\Delta t$ per second. The average number of bits transmitted per second, or informational capacity of the fibre, is therefore given by

$$C_T = \left[2/(m + r)\Delta t\right] \cdot \log_2(m - r) \qquad (1)$$

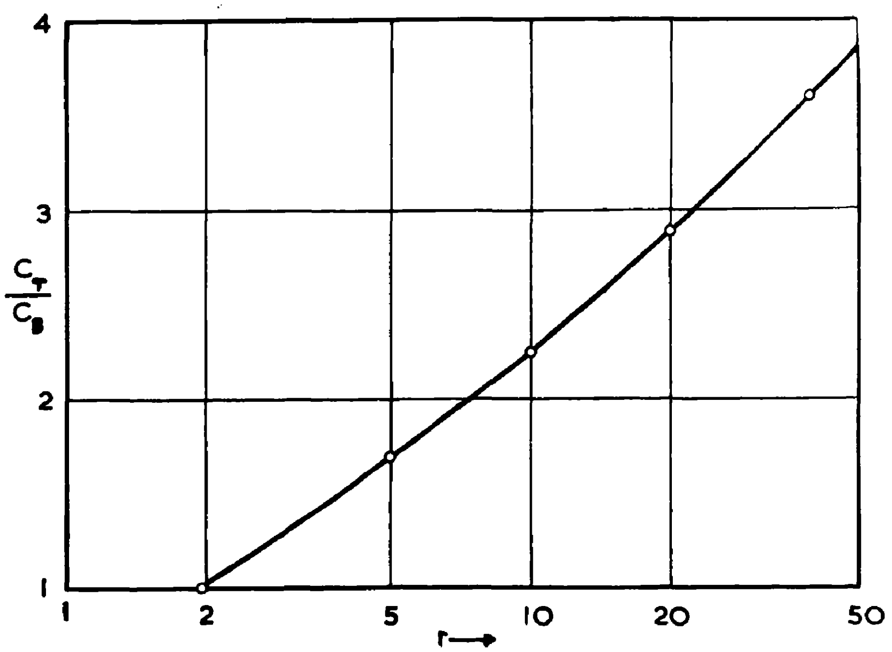


Fig. 3.1. MacKay's approximate evaluation of the ratio C_T/C_B, as a function of r.

C_T = maximum information rate under Pulse-Interval Modulation.

C_B = information rate under binary Pulse-Code Modulation.

r = $t_r/\Delta t$, where t_r is the minimum possible interval between pulses, and Δt is the minimum resolvable difference in pulse-interval duration.

By differentiation with respect to m it is found that the maximum value of C_T for a given r is given by the value of m satisfying the equation

$$(m + r)/(m - r) = \log_2(m - r) \qquad (2)$$

MacKay has solved this equation (presumably either graphically or by a method of successive approximation) for various values of r, and has graphed the solution against r.

For a given value of r, the optimum value of m can be substituted in equation (1), and then C_T can be evaluated if some value is taken for Δt. MacKay does not evaluate C_T itself, but the ratio C_T/C_B, where C_T is, as above, the capacity under PIM, and C_B is the capacity under binary PCM, given simply by $C_B = 1/t_r = 1/r\Delta t$. It has been seen that C_B may be from 250 to 1000 bits/second, depending on the particular nerve whose properties are taken.

MacKay's final result is shown in Fig. 3.1. It can be seen that PIM may be nearly 4 times as efficient as binary PCM when r = 50.

MacKay's solution as outlined above is admitted by him to be only an approximate one, since the distribution of pulse-interval durations assumed by him is not the optimum distribution. The exact solution of the problem, in which the optimum distribution of pulse-interval durations is found, is as follows.

The exact calculation of the rate under PIM

The problem of finding the informational capacity under PIM, in the case where the optimum distribution of values of t_s is employed, can be solved by utilising a result obtained by Brillouin (1951).

Under PIM, t_s may in effect take the values $(r + j)\Delta t$, where $j = 0, 1, 2, 3 \ldots\ldots\ldots$

Let $t_j = (r + j)\Delta t$. Brillouin has shown that for symbols of duration t_j, and probability p_j, the most efficient coding is achieved if, for every value of j, $\log p_j = -\beta t_j$, where β is a constant.

For convenience, let the logarithms be taken to base 2. Let each pulse, and the interval preceding it, be regarded as a symbol of the message. Then for most efficient coding,

$$\log_2 p_j = -\beta t_j \qquad (3)$$

i.e. $$p_j = 2^{-\beta t_j} = 2^{-\beta(r+j)\Delta t}$$

To evaluate β, we make use of the relationship

$$\sum_{j=0}^{\infty} p_j = 1$$

i.e. $$1 = \sum_{j=0}^{\infty} 2^{-\beta(r+j)\Delta t}$$

$$= \frac{2^{-\beta r \Delta t}}{1 - 2^{-\beta \Delta t}} \text{ since } 2^{-\beta\Delta t} < 1 \qquad (4)$$

Let $\alpha = 2^{-\beta\Delta t}$

Then equation (4) can be written

$$\alpha^r + \alpha - 1 = 0$$

Hence $\beta = -(\log_2 \alpha)/\Delta t$, where α is the positive real root of the equation

$$x^r + x - 1 = 0 \qquad (5)$$

The average amount of information per symbol is given by (Shannon and Weaver, 1949, p. 19) :-

$$H = -\sum_{j=0}^{\infty} p_j \log_2 p_j$$

The average duration of a symbol is given by

$$\overline{t}_j = \sum_{j=0}^{\infty} p_j t_j$$

The informational capacity of the system is given by

$$C_T = \frac{H}{\overline{t}_j} = \frac{-\sum_{j=0}^{\infty} p_j \log_2 p_j}{\sum_{j=0}^{\infty} p_j t_j}$$

$$= \frac{-\sum_{j=0}^{\infty} p_j(-\beta t_j)}{\sum_{j=0}^{\infty} p_j t_j}, \text{ by substituting from equation (3)}$$

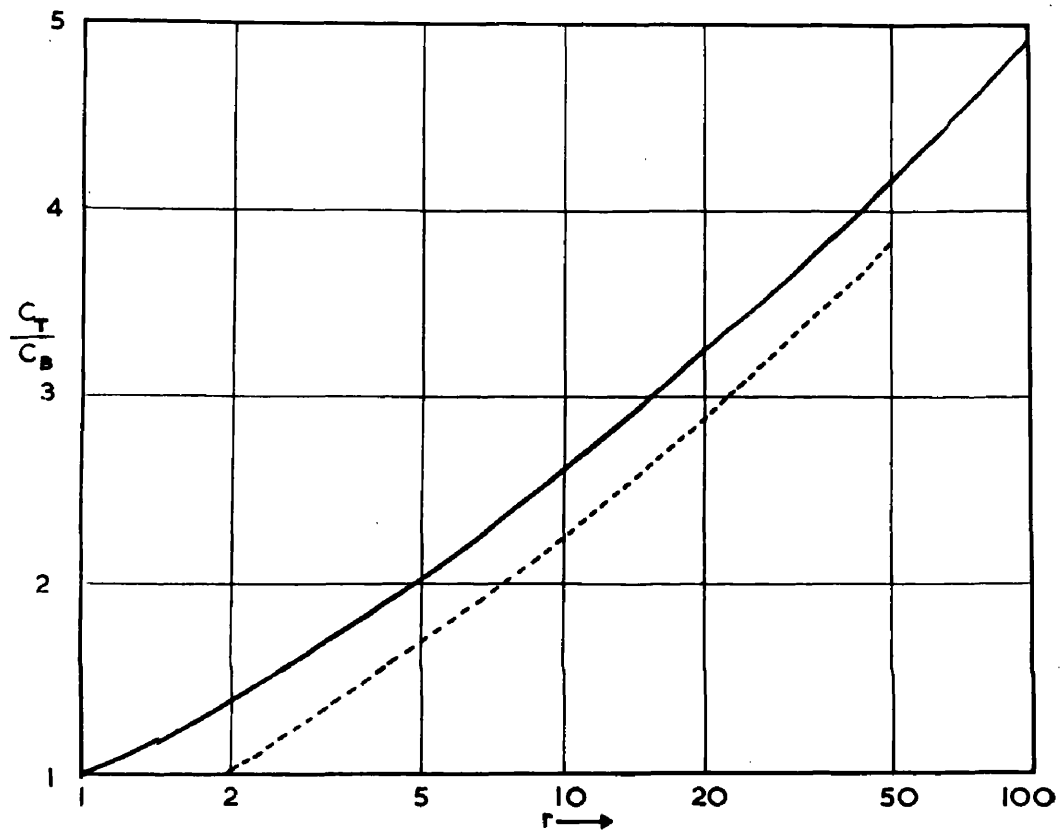


Fig. 3.2. Solid line :- The exact evaluation of C_T/C_B as a function of r (see caption of Fig. 3.1).

The broken line shows MacKay's result, as in Fig. 3.1, for comparison.

$$= \beta$$

$$= -(\log_2 \alpha)/\Delta t \qquad (6)$$

where α is the positive real root of equation (5).

This result can also be derived by a method described by Shannon and Weaver (1949, p. 8).

Fig. 3.2 shows the values of C_T/C_B calculated from equation (6), plotted against r. This graph can be compared with the approximate graph shown in Fig. 3.1, which is taken from MacKay's paper, and is shown as a broken line for comparison in Fig. 3.2.

The results obtained above and embodied in Fig. 3.2 do not affect the qualitative conclusions reached by MacKay in his paper. In fact, they support his conclusions even better than do his own results.

It is interesting to note that when $r = 1$, that is to say, when the minimum pulse interval equals the minimum distinguishable difference in interval, the capacity under optimal PIM equals the capacity under binary PCM. It can also be shown that the statistical distribution of pulse intervals is the same under binary PCM as under optimal PIM when $r = 1$. In fact, in this limiting case the two modulation systems are equivalent.

DISCUSSION

The above theory makes it possible to estimate a maximum rate at which information can be conveyed along a nerve fibre. Observations on the nervous system appear to indicate, however, that nerve fibres do not convey information at the maximum rate or anything approaching it. Pitts has pointed out, in the mathematical appendix of a paper by Wall, Lettvin, McCulloch and Pitts (1955) that if the nerve fibres were conveying information at the maximum possible rate the mean pulse frequency would be in the region of 620 per second according to MacKay's theory, and 735 per second according to the exact theory. In fact, pulse frequencies in peripheral nerves are generally lower than 100 per second.

MacKay does not claim that his theory shows that the nervous system works, or ought to work, in any particular manner. He would presumably explain the fact that the pulse-frequency is generally only about 50 per second by saying that the theory is applicable only to the calculation of a maximum possible rate, and that in fact this rate is not utilised. This conclusion may be correct, and is discussed further below.

Pitts' explanation of the low pulse-frequencies observed in nerves

Wall, Lettvin, McCulloch and Pitts (1955) have suggested another possible explanation for the low pulse-frequencies which are actually found in nerves. The experiments of these workers on the cat spinal cord have shown that, in the spinal cord, the conduction of a nerve impulse is not such an infallible process as it is generally assumed to be. A proportion of the impulses which enter the cord at a dorsal root are not conducted to the end of the axon in which they are travelling. The greater the frequency of impulses in a fibre, the greater is the proportion which is "lost" in this way. Activity in neighbouring fibres also increases the probability of impulses being "lost".

Pitts has shown, in the mathematical appendix of the above paper that, if the proportion of impulses which are "lost" is taken to be a particular function of the pulse frequency in the fibre, the optimum conditions for the transmission of information are altered in such a way that a lower pulse frequency is optimal. There is experimental justification for the form of relationship taken by Pitts to exist between the pulse frequency and the proportion of impulses "lost". By this teleological argument Pitts accounts for the low pulse-frequencies which occur in nerve fibres.

Pitts' argument is open to question because there is no way of telling whether the failure of some impulses to be transmitted in the spinal cord should be regarded as an imperfection of the system imposed by physical limitations of nerve fibres, or whether it should be regarded as a useful stage in the processing of information which leads to the normal reactions of the nervous system. At least one of Pitts' colleagues, namely Dr. J.Y. Lettvin, is of the opinion that the failures in conduction probably should not be regarded as an imperfection of the system.

Another explanation of the low pulse-frequencies observed in nerves

In the nervous system, the rate at which information is required to be conveyed along any pathway will generally be far from constant, since both sensation and motor activity are intermittent. It is not possible to level out the information rate by means of storage of information (i.e. a memory) at the transmitting end, since the nervous system is required to transmit most of its information without appreciable delay.

It would therefore be surprising if nerve fibres <u>were</u> found to be transmitting information at the maximum possible rate at all times. In fact, it seems likely that this rate will only be achieved under very unusual conditions, either because of exceptionally violent motor activity, or exceptionally intense sensation. It is reasonable to suppose that when the nervous system is not having exceptional demands made on it, the system of coding of information will be such that the pulse-frequencies are kept low to economise in metabolism.

As already mentioned, MacKay considers that his theory (and mine) lead merely to a limiting value for the rate of flow of information along a nerve fibre, and there is no reason to believe that this rate is approached in fact. My argument above is that the maximum rate may be approached under exceptional conditions but is never approached normally. This view is supported by the findings of Galambos and Davis (1943), who report that in a fibre of the auditory nerve of the cat the response to acoustic stimulation may contain impulses with only 1 msec separation. The highest repetition rate measured over a series of several impulses was about 500 per second, and the maximum sustained rate when the ear was adapted to a continuous tone was about 200 per second. Enroth (1952) reports frequencies as high as 750 per second for single retinal elements of the cat's eye; in this case also the very high frequency was not maintained for more than a few impulses.

Information Theory is not readily applicable to communication systems in which account must be taken of the delay in transmission. Nevertheless, it may prove possible to develop a theory which will indicate what is the optimum way of coding information for transmission along a nerve fibre when only a very small delay is permissible. It would be interesting to compare the results of such a theory with what is known about the nervous system. I hope to try to develop such a theory in the future.

PART 4

THE ELECTRIC FIELD OF A CURRENT DIPOLE IN A HOMOGENEOUS CONDUCTING SPHERE

PART 4. THE ELECTRICAL FIELD OF A CURRENT DIPOLE IN A HOMOGENEOUS CONDUCTING SPHERE

The mathematical problem of calculating the electrical field over the surface of a homogeneous conducting sphere containing a dipole has been considered because it has some application to electroencephalography. In the interpretation of E.E.G. records it is frequently desirable to try to decide whether some feature of the record can be attributed to a local electrical disturbance somewhere in the head, and if it can, to decide in what part of the head the disturbance is situated. Doing this is termed "localisation of a focus". The local disturbance, or focus, may be either physiological or pathological.

The suggestion that the local disturbance might take the form of a current dipole has been made by Brazier (1949), Walter (1949), Shaw (1954) and Shaw and Roth (1955). What is generally meant by a "current dipole" is a source and a sink of current extremely close together; Walter, however, considers the case where the source and sink are separated by a finite distance.

The limitations of potential theory in the interpretation of E.E.G. records

In any attempt to make use of electrical potential theory in the interpretation of E.E.G. records, it is important to realise that, if the head is regarded as a volume conductor, the positions of sources and sinks of current within its volume cannot be inferred with certainty from measurements of potential at points on the surface. The surface distribution of potential does not define a unique system of generators (or of sources and sinks of current) within the volume. In fact, Pitts (1953) has stated that for a conductor in the form of an ellipsoid or sphere or any other round shape with no edges or spines, any given surface distribution of potential can be attributed to a sufficiently complicated electrical disturbance at any one point in the volume. An electrical disturbance at a point may contain an infinity of components, including a point source or sink of current, a dipole (i.e. a source and a sink extremely close together), a quadripole (two opposed dipoles extremely close together), an octopole (two opposed quadripoles extremely close together) and higher multipoles. Pitts contends that by suitably choosing the strengths and orientations of these components of the electrical disturbance at any given point, any surface distribution of potential can be produced.

I have not seen a complete proof of this statement by Pitts. However, in a personal communication, Pitts has indicated roughly how the proof would go. In any case, when the statement is made by a mathematician of the standing of Pitts, there can be little doubt that it is correct.

The main argument of Pitts' (1953) lecture was that, because of the foregoing considerations, the E.E.G. can never yield definite information about the location of electrical activity in the brain, and that the only way in which information can be obtained about the precise site of electrical activity anywhere in the central nervous system is by recording with micro-electrodes from a large number of points in the volume of nervous tissue, and analysing the results in a particular fashion. The procedure, as applied to the spinal cord, has been described by Pitts (1952) and by Howard, Lettvin, McCulloch, Pitts and Wall (1955).

The technique developed by Pitts et al. is no substitute for E.E.G. as a clinical procedure. For one thing, one of the great merits of E.E.G. is that its use involves no surgical interference with the patient. Even if it were permissible to insert the micro-electrodes, however, there would be great difficulties in applying the technique of Pitts et al. to the brain. It is necessary, in order to apply the technique, to take records from a very large number of points in the substance of the tissue. In the work on the spinal cord these records could be taken serially, since they were records of the response to an applied stimulus, and it was found that the responses were the same to successive stimuli. On the other hand, the electrical activity in brain tissue (in the cerebral cortex, at least) is non-repeating, even when it is in response to identical stimuli, so the method of serial recording cannot be employed. It would be necessary, instead, to take simultaneous records from a very large number of points, probably at least one hundred, and at present this does not seem to be feasible.

Since the micro-electrode technique of Pitts and colleagues cannot be used in the brain, and since surface recordings (E.E.G.) apparently cannot give positive information about the location of electrical activity, it might appear that electrophysiological techniques are of no value in determining the location of electrical activity in the brain. It is found, however, that E.E.G. records do in fact yield useful information about the sites of brain tumours and epileptic foci (see, for instance, Renfrew, Cameron and Haggar, 1953).

The statement by Pitts shows that measurements of potential on the surface of the head cannot yield information about the location of a focus in the case where the focus may consist of any combination whatever of sources and sinks of current. The fact that useful information can in fact be obtained from a study of the surface potentials must be due to the fact that there are limitations on the form which an electrical disturbance in the brain can take. It is extremely difficult to say exactly what the limitations are, or even to see how to determine them. Fortunately, it is not essential to be able to state the precise limitations on the form of the disturbance in order to evolve impirical ways of treating E.E.G. records so as to obtain information about location of foci.

Standard methods for the location of foci

The standard methods for the location of foci are qualitative rather than quantitative, except insofar as they involve a rough comparison of the amplitudes in the different recording channels of those components of the record which are thought to be due to activity at the focus. The three main principles used in location are as follows :-

(a) The focus is probably in that part of the head from which records are obtained which show with the largest amplitude the components which are due to the focus. (Assuming the spacing between electrodes is the same in the different areas).

(b) Suppose three electrodes A, B and C are in a straight line on the head, in that order. If a feature of the record of the kind under investigation appears as a fluctuation of the potential difference (A - B), and simultaneously appears, but with reversed polarity, as a fluctuation of the potential differance (B - C), then the focus is thought to lie in the vicinity of a plane through B, at right angles to the line AC. This is the principle of location by "phase reversals" described by Walter (1949).

(c) Walter also states that an indication of the depth of a focus below the surface can be obtained by comparing the amplitude of the record from two electrodes close together on the surface with that from two widely-spaced electrodes on the surface. If the focus is deep, the widely-spaced electrodes will pick up larger fluctuations of potential difference than are picked up by the closely-spaced electrodes. For a shallow focus, closely-spaced electrodes over the focus will pick up larger fluctuations than will widely-spaced electrodes.

These rules for location of foci, put forward by Walter, are based on his assumption that an abnormal focus can always be represented by an equivalent dipole, by which he means a source and a sink of current, not necessarily extremely close together.

Attempts to evolve precise methods of location

Various workers have felt that there should be some way of treating the E.E.G. records quantitatively so as to obtain more precise information about location than can be obtained by the foregoing classical methods. In particular, the problem has recently been considered by Shaw (1953, also Shaw and Roth, 1955). By making careful measurements on conventional E.E.G. records, Shaw has studied the potential field which existed on a subject's head at different instants in time. The potential field has also been studied by Rémond and Offner (1952) who used an automatic device to do much of the tedious work which was performed manually by Shaw.

Shaw, however, subjects his measurements to a form of analysis which was not used by Remond and Offner, which he terms "normalisation".

THE FIELD DUE TO A DIPOLE

Since attempts have been made to locate foci, on the assumption that the foci consist of dipoles, it is of interest to compare the potential fields found to exist on the surface of the head with those which could be produced by a dipole in the substance of the brain. The field due to a dipole can be determined using a model of the "electrolytic tank" type, or it can be calculated. The electrolytic tank method has much to commend it, since it can take account of the exact shape of the head, which does not readily lend itself to mathematical treatment. (A rough electrolytic model, made of saline-soaked cotton-wool, is used in the Burden Neurological Institute for instructional purposes.)

Since the shape of the head does not lend itself to mathematical treatment, the field due to dipole in a sphere of homogeneous conducting material has been calculated as an approximation. The calculation was carried out after the publication of Shaw's 1953 paper and after discussion of the general problem with Shaw. I worked out the solutions to the problem which are given here, before I discovered that the problem has been solved in the most general case by Frank (1952) whose final answer is almost identical with mine. Also, a much more cumbersome solution has been published by Wilson and Bayley (1950). These solutions are for the general case in which the dipole is located at any point in the sphere, with its axis in any direction.

For the special case of the dipole at the centre of the sphere the result is given by Canfield in an appendix to a paper by Craib (1927).

The special case in which the dipole is not in the centre of the sphere, but its axis lies along a diameter, has been solved and published by Brazier (1949), but unfortunately an error was made in the preparation of that diagram of her paper in which the formula appears, and the formula as it appears is incorrect (personal communication).

The ways in which I solved the problem in the two special cases, as well as in the general case, are given in the following. These solutions were obtained before the papers of Frank (1952) and Wilson and Bayley (1950) had been found. The solutions do not contribute any information which is not contained in the other papers; the expression I have derived for the general case is similar to that derived by Frank, and very much less cumbersome than the expression derived by Wilson and Bayley. The method I have used in solving the problem in the general case is somewhat different from that given by Frank, and may be somewhat simpler.

Case 1. Dipole at centre of sphere.

The kind of dipole which has been considered in connection with E.E.G. is a current dipole, consisting of a source and a sink of current very close together. It can be shown that there must always be a charge dipole, consisting of a positive and a negative charge extremely close together, coincident in position and orientation with any current dipole.

Let m be the moment of the charge-dipole which co-exists with the current-dipole.

It is convenient to define

$$M = m/k \qquad ((1)$$

where k is the dielectric constant of the medium.

It can be shown that

$$m = \frac{k\rho}{4\pi} s \qquad (2)$$

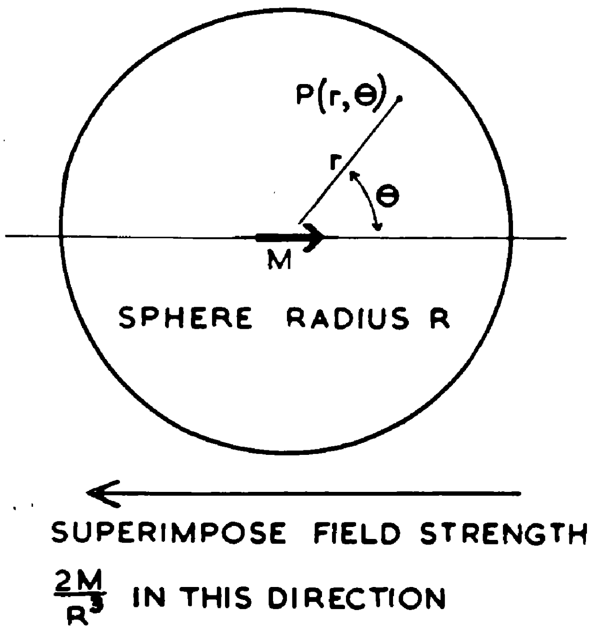


Fig. 4.1. The dipole at the centre of the sphere (Case 1).

where s is the moment (in current units x length units) of the current dipole, and ρ is the resistivity of the medium.

Hence $M = \dfrac{\rho}{4\pi} s$ (3)

To derive the field due to a dipole at the centre of a sphere, let the axis of the dipole be the principle axis of a system of spherical polar coordinates, with the centre of the sphere as origin (see Fig. 4.1).

If the dipole were in an unbounded medium, instead of in a sphere, the potential at any point P (r, θ) would be given by

$$V = \frac{M \cos\theta}{r^2} \tag{4}$$

and at distance R from the dipole by

$$V = \frac{M \cos\theta}{R^2} \tag{5}$$

When the dipole is at the centre of an insulated sphere of radius R, the potential field inside the sphere must satisfy Laplace's equation, and also the two boundary conditions :-

(a) There must be the right number of lines of force entering and leaving the dipole.

(b) Over the surface of the sphere, $\dfrac{\partial V}{\partial n} = 0$. This condition may also be written

$$\left(\frac{\partial V}{\partial r}\right)_{r=R} = 0$$

since the centre of the sphere is the origin.

For the field which would be produced by the dipole in an infinite medium,

$$\left(\frac{\partial V}{\partial r}\right)_{r=R} = \left(-\frac{2M\cos\theta}{r^3}\right)_{r=R} = -\frac{2M\cos\theta}{R^3}$$

Suppose that there is superimposed on this field a uniform field of strength $2M/R^3$ in the direction shown in Fig. 4.1.

$$\text{Then } V = \frac{M\cos\theta}{r^2} + \frac{2M}{R^3}r\cos\theta + K \qquad (6)$$

where K is an arbitrary constant. For this potential field,

$$\left(\frac{\partial V}{\partial r}\right)_{r=R} = -\frac{2M\cos\theta}{R^3} + \frac{2M\cos\theta}{R^3} = 0$$

Hence boundary condition (b) is satisfied, since $\frac{\partial V}{\partial n} = 0$ over the surface of the sphere. Also, boundary condition (a) is satisfied, because the uniform field makes no difference to the number of lines of force entering and leaving the dipole. The field satisfies Laplace's equation, since it is a summation of a uniform field and the field produced by a dipole in an infinitely extended medium.

Hence the field represented by equation (6) is the correct solution for the potential field inside the sphere.

The distribution of potential over the surface is given by

$$V = \frac{3M \cos\theta}{R^2} \qquad (7)$$

This potential distribution is the same, except for multiplication by a factor of 3, as the distribution of potential over the spherical surface when in an unbounded medium, represented by equation (5).

The result for the potential anywhere in the sphere (equation 6) is given, except for the arbitrary constant, by Duchosal and Sulzer (1949, p. 24), who derive it from the result obtained by Canfield (see Craib, 1927). Canfield's result is not actually for a dipole, but for two small spherical electrodes of radius a, separated by distance 2b, at potentials $+V_o$ and $-V_o$ respectively. For two such electrodes situated on either side of the centre of the conducting sphere, Canfield obtains the expression for the potential field inside the sphere

$$V = 2 V_o a b \cos\theta \left[\frac{1}{r^2} + \frac{2r}{R^3} \right] \qquad (8)$$

Equation (6) can be derived from Equation (8) by taking account of the fact that the resistance between the spherical electrodes is given by (Jeans, 1941, p. 352):-

$$\frac{\rho}{4\pi}\left(\frac{2}{a} - \frac{1}{b}\right)$$

provided b >> a.

Hence, the potential difference between the electrodes = $2V_o$ = $i\frac{\rho}{4\pi}\left(\frac{2}{a} - \frac{1}{b}\right)$

where i is the current flowing between the electrodes.

Substituting for $2V_o$ in equation (8) gives

$$V = i\frac{\rho}{4\pi}\left(\frac{2}{a} - \frac{1}{b}\right) a\ b \cos\theta \left[\frac{1}{r^2} + \frac{2r}{R^3}\right]$$

Letting a → 0, since the source and sink of current in the dipole are point-sources, the expression tends towards

$$V = 2\ b\ i\ \frac{\rho}{4\pi} \cos\theta \left[\frac{1}{r^2} + \frac{2r}{R^3}\right]$$

Now let b → 0. Then 2bi represents the moment of the current dipole s. But from equation (3), $M = \frac{\rho}{4\pi} s$.

Hence the expression becomes

$$V = M \cos\theta \left[\frac{1}{r^2} + \frac{2r}{R^3}\right]$$

which is the same as equation (6), except for the arbitrary constant.

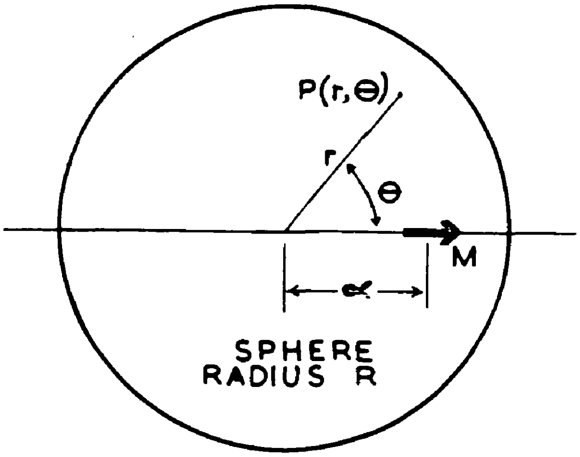


Fig. 4.2. The dipole situated with its axis along a diameter (Case 2).

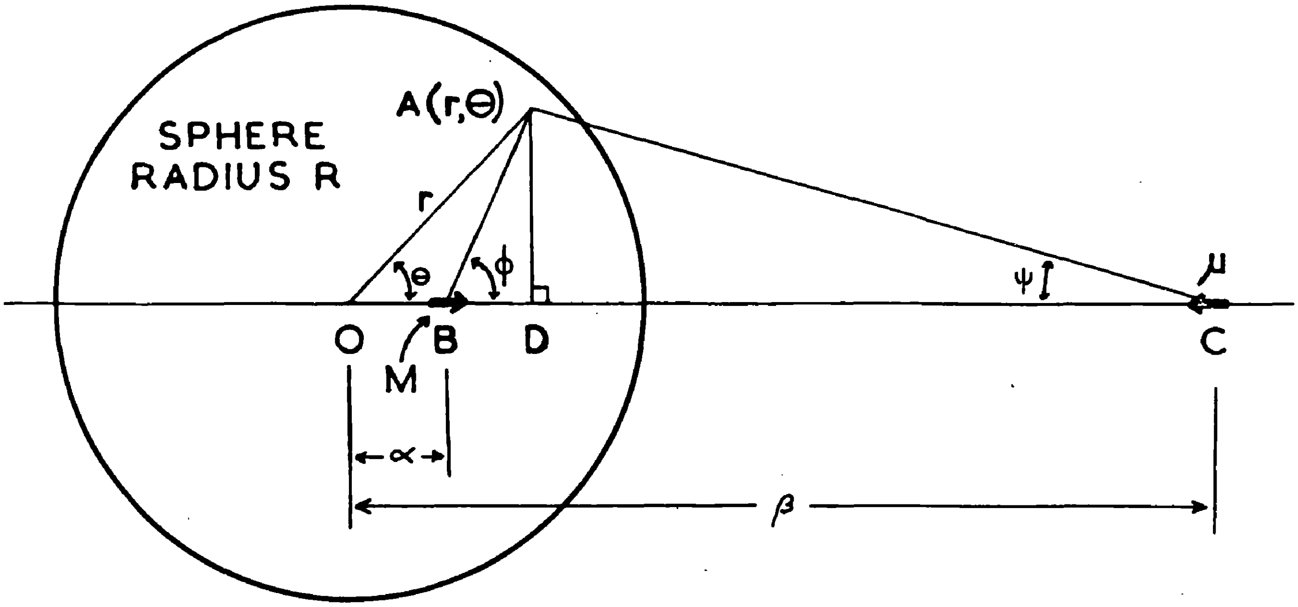


Fig. 4.3. The dipole situated with its axis along a diameter, showing the image dipole μ.

Case 2. Dipole not at the centre, but with its axis lying along a diameter of the sphere.

Let the diameter on which the dipole lies be the principal axis of the system of spherical polar coordinates, with the centre of the sphere as origin. Let α be the distance from the centre of the sphere to the dipole, as shown in Fig. 4.2.

The method of solution is to superimpose on the field due to dipole M the field of an "image" dipole μ, which must be outside the sphere. If values can be found for the moment and position of μ, such that the combined field conforms to the boundary conditions, then the combined field is the required solution for the potential field inside the sphere. Let us try placing μ on the same diameter of the sphere as M is on (the diameter produced, that is) and let its direction be as shown in Fig. 4.3. Let its distance from the centre of the sphere be β.

At any point $A(r,\theta)$ (see Fig. 4.3), the potential due to dipole M is equal to

$$\frac{M\cos\phi}{AB^2}$$

Now $\cos\phi = \dfrac{BD}{AB} = \dfrac{OD - OB}{AB} = \dfrac{r\cos\theta - \alpha}{\sqrt{\alpha^2 + r^2 - 2\alpha r\cos\theta}}$

and $AB^2 = \alpha^2 + r^2 - 2\alpha r\cos\theta$

∴ Potential at A(r,θ) due to dipole M

$$= \frac{M\,(r\cos\theta - \alpha)}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{3/2}}$$

Similarly, at A(r,θ) the potential due to dipole μ

$$= \frac{\mu\cos\psi}{AC^2}$$

Now $\cos\psi = \frac{DC}{AC} = \frac{OC - OD}{AC} = \frac{\beta - r\cos\theta}{\sqrt{\beta^2 + r^2 - 2\beta r\cos\theta}}$

and $AC^2 = \beta^2 + r^2 - 2\beta r\cos\theta$

∴ Potential at A(r,θ) due to dipole μ

$$= \frac{\mu\,(\beta - r\cos\theta)}{(\beta^2 + r^2 - 2\beta r\cos\theta)^{3/2}}$$

∴ Potential at point A(r,θ)

$$= \frac{M\,(r\cos\theta - \alpha)}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{\frac{3}{2}}} + \frac{\mu(\beta - r\cos\theta)}{(\beta^2 + r^2 - 2\beta r\cos\theta)^{\frac{3}{2}}}$$

$$= \frac{M(r\cos\theta - \alpha)}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{\frac{3}{2}}} - \frac{\mu\,(r\cos\theta - \beta)}{(\beta^2 + r^2 - 2\beta r\cos\theta)^{3/2}} \qquad (9)$$

By differentiating the above expression with respect to r, and equating to zero, it can be shown that the condition that $\frac{\partial V}{\partial n} = \left(\frac{\partial V}{\partial r}\right)_{r=R}$ should vanish is

$$M\,\frac{\alpha R\,(3 + \cos^2\theta) - 2\cos\theta\,(\alpha^2 + R^2)}{(\alpha^2 + R^2 - 2\alpha R\cos\theta)^{5/2}} = \mu\,\frac{\beta R(3 + \cos^2\theta) - 2\cos\theta(\beta^2 + R^2)}{(\beta^2 + R^2 - 2\beta R\cos\theta)^{5/2}}$$

Let us try making $\beta = R^2/a$, i.e. $a\beta = R^2$. Then the condition becomes

$$\frac{M}{\mu} = \left(\frac{\alpha^2 + R^2 - 2\alpha R\cos\theta}{\beta^2 + R^2 - 2\beta R\cos\theta}\right)^{\frac{5}{2}} \frac{\beta R(3+\cos^2\theta) - 2\cos\theta(\beta^2+R^2)}{\alpha R(3+\cos^2\theta) - 2\cos\theta(\alpha^2+R^2)}$$

$$= \left(\frac{\alpha^2\beta + R^2\beta - 2\alpha\beta R\cos\theta}{\alpha\beta^2 + R^2\alpha - 2\alpha\beta R\cos\theta}\cdot\frac{\alpha}{\beta}\right)^{\frac{5}{2}} \frac{\alpha\beta R(3+\cos^2\theta) - 2\cos\theta(\alpha\beta^2+\alpha R^2)}{\alpha\beta R(3+\cos^2\theta) - 2\cos\theta(\alpha^2\beta+\beta R^2)}\cdot\frac{\beta}{\alpha}$$

$$= \left(\frac{\alpha}{\beta}\right)^{\frac{3}{2}}\left(\frac{R^2(\alpha+\beta) - 2R^3\cos\theta}{R^2(\alpha+\beta) - 2R^3\cos\theta}\right)^{\frac{5}{2}} \frac{R^3(3+\cos^2\theta) - 2R^2\cos\theta(\alpha+\beta)}{R^3(3+\cos^2\theta) - 2R^2\cos\theta(\alpha+\beta)}$$

using the substitution $\alpha\beta = R^2$

$$= \left(\frac{\alpha}{\beta}\right)^{\frac{3}{2}}$$

i.e., $\mu = M\left(\frac{\beta}{\alpha}\right)^{\frac{3}{2}} = M\left(\frac{R^2}{\alpha^2}\right)^{\frac{3}{2}} = M\left(\frac{R}{\alpha}\right)^3$

and we had $\beta = R^2/\alpha$

With these values for μ and β, the potential field defined by equation (9) satisfies the boundary conditions, and it can easily be deduced from physical considerations that it conforms to Laplace's equation. It is therefore the required solution.

Making the substitutions for μ and β in equation (9) gives

$$V = \frac{M(r\cos\theta - \alpha)}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{\frac{3}{2}}} - M\frac{R^3}{\alpha^3}\cdot\frac{\left(r\cos\theta - \frac{R^2}{\alpha}\right)}{\left(\frac{R^4}{\alpha^2} + r^2 - 2\frac{R^2 r}{\alpha}\cos\theta\right)^{3/2}}$$

$$= M\left\{\frac{r\cos\theta - \alpha}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{3/2}} - \frac{R^3(\alpha r\cos\theta - R^2)}{\alpha\,(R^4 + \alpha^2 r^2 - 2R^2\alpha r\cos\theta)^{3/2}}\right\} \tag{10}$$

At the surface of the sphere, where $r = R$, equation (10) reduces to

$$V = M \frac{R^2 - \alpha^2}{\alpha(\alpha^2 + R^2 - 2\alpha R \cos\theta)^{3/2}} \qquad (11)$$

Equations (10) and (11) are the required solutions for the potential field. Strictly, both equations should include an arbitrary constant. An arbitrary constant should appear in every expression representing potential in this section; the arbitrary constants have, however, been omitted for simplicity.

It is not possible to derive the expressions for the field produced by a dipole at the centre of the sphere (equations 6 and 7) from equations (10) and (11) by letting $\alpha \to 0$. The expressions for the potential in equations (10) and (11) become infinite when $\alpha = 0$.

It is, however, permissible to let the "arbitrary constant" in equations (10) and (11) take the form of a function of α such that, as α varies, the "equator" of the sphere (i.e. the circle $r = R$, $\theta = \pi/2$) remains at zero potential. It is permissible to do this because the "arbitrary constant" need only be a constant insofar as it is independent of r and θ.

When the additional term is included in equation (10), the new expression for the potential throughout the sphere (with "equator" at zero potential) is

$$V = M\left\{\frac{r\cos\theta - \alpha}{(\alpha^2 + r^2 - 2\alpha r\cos\theta)^{3/2}} - \frac{R^3(\alpha r\cos\theta - R^2)}{\alpha(R^4 + \alpha^2 r^2 - 2R^2\alpha r\cos\theta)^{3/2}} - \frac{R^2-\alpha^2}{\alpha(\alpha^2+R^2)^{3/2}}\right\} \tag{12}$$

and for the distribution of potential over the surface of the sphere

$$V = M\left\{\frac{R^2-\alpha^2}{\alpha(\alpha^2+R^2-2\alpha R\cos\theta)^{3/2}} - \frac{R^2-\alpha^2}{\alpha(\alpha^2+R^2)^{3/2}}\right\}$$

$$= \frac{M(R^2-\alpha^2)}{\alpha}\left\{(\alpha^2+R^2-2\alpha R\cos\theta)^{-\frac{3}{2}} - (\alpha^2+R^2)^{-\frac{3}{2}}\right\} \tag{13}$$

It can be shown that the expressions for the potential in equations (12) and (13) tend towards the expressions already found for the case of the dipole at the centre of the sphere (equations 6 and 7) as $a \rightarrow 0$.

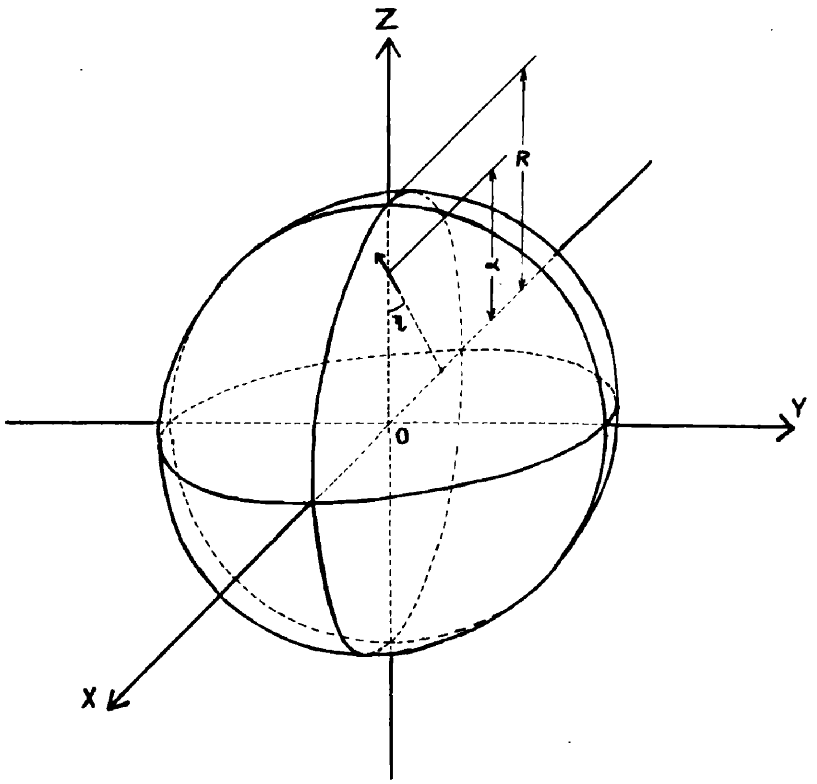


Fig. 4.4. The general case of a dipole in a sphere (Case 3).

Case 3. The general case of a dipole in a sphere.

In a conducting medium, there is no accumulation of charge except at a boundary between media of differing conductivities, or where there is a source or a sink of current. Hence the field inside the conducting sphere is a summation of the field due to the charge-dipole which corresponds in position and orientation with the current-dipole, and the field due to a distribution of charge over the surface of the sphere. The total field must be such that, over the surface of the sphere

$$\frac{\partial V}{\partial n} = 0$$

$$\text{or} \quad \frac{\partial}{\partial n} V_s = -\frac{\partial}{\partial n} V_d$$

where V_s is the part of the potential due to the surface charge, and V_d is the part of the potential due to the dipole.

Let the sphere be of radius R, and let the dipole be distance a from the centre. Let the axes be chosen so that the origin is at the centre of the sphere and the dipole is on the z-axis, and the dipole axis lies in the x-z plane. Let the angle between the dipole axis and the z-axis be η.

If a point P is distance d from the dipole, and if a line joining the dipole to P makes an angle Θ with the dipole axis, the component of potential at P which is due to the dipole is given by

$$V_d = \frac{M \cos \Theta}{d^2} \qquad (14)$$

Let the point P have spherical polar co-ordinates (r, θ, ϕ) and therefore Cartesian co-ordinates $(r \sin\theta \cos\phi,\ r \sin\theta \sin\phi,\ r \cos\theta)$.

The dipole has Cartesian co-ordinates $(0, 0, a)$. Hence the square of the distance from P to the dipole is given by

$$\begin{aligned} d^2 &= r^2\sin^2\theta \cos^2\phi + r^2\sin^2\theta \sin^2\phi + (r\cos\theta - a)^2 \\ &= r^2 - 2\, r\, a \cos\theta + a^2 \end{aligned}$$

The direction cosines of the dipole axis are $(s, 0, c)$

where $s = \sin\eta$; $c = \cos\eta$.

The direction cosines of the line from the dipole to P are

$$\left(\frac{r \sin\theta \cos\phi}{d}, \frac{r \sin\theta \sin\phi}{d}, \frac{r\cos\theta - a}{d}\right)$$

$$\therefore \cos\Theta = \frac{sr \sin\theta \cos\phi}{d} + \frac{c\,(r\cos\theta - a)}{d}$$

The values which have been obtained for d and for $\cos \Theta$ can now be substituted in equation (14).

$$V_d = \frac{M \cos \Theta}{d^2}$$

$$= \frac{M(s r \sin\theta \cos\phi + c r \cos\theta - \alpha c)}{d^3}$$

$$= \frac{M(s r \sin\theta \cos\phi + c r \cos\theta - \alpha c)}{(r^2 - 2 r \alpha \cos\theta + \alpha^2)^{3/2}}$$

$$= M \cos\eta \frac{r\cos\theta - \alpha}{(r^2 - 2r\alpha\cos\theta + \alpha^2)^{3/2}} + M \sin\eta \frac{r\sin\theta\cos\phi}{(r^2 - 2r\alpha\cos\theta + \alpha^2)^{3/2}} \quad (16)$$

(The first term in equation 16 is the field due to a dipole of moment M cos η whose axis lies along the diameter. The second term is the field due to a dipole whose axis is perpendicular to the diameter. In effect, the original dipole has been resolved into two component dipoles at right angles. It would be possible to deal with that component dipole whose axis lies along the diameter, by simply substituting the result obtained for Case 2. The following method, using Spherical Harmonics, need only be applied to the second term of equation 16. However, the method using Spherical Harmonics will be applied to both components.)

Let $\alpha/r = \beta$, $\cos\theta = \mu$, and as before, $\sin\eta = s$,

$\cos\eta = c$.

Then equation (16) becomes

$$V_d = \frac{Mc}{\alpha^2} \cdot \frac{(\mu - \beta)\beta^2}{(1 - 2\beta\mu + \beta^2)^{3/2}} + \frac{Ms}{\alpha^2} \cdot \frac{\beta^2 \sin\theta \cos\phi}{(1 - 2\beta\mu + \beta^2)^{3/2}} \quad (17)$$

If $\beta < 1$ (as it is, near the surface of the sphere)

$$\frac{1}{(1 - 2\beta\mu + \beta^2)^{1/2}} = \sum_{n=0}^{\infty} \beta^n P_n(\mu) \tag{18}$$

where $P_n(\mu)$ is the Lengendre Polynomial of degree n. Equation (18) is, in fact, a statement of the definition of the Legendre Polynomials (see MacRobert, 1947, p. 72).

Differentiating equation (18) with respect to β gives :-

$$\frac{\mu - \beta}{(1 - 2\beta\mu + \beta^2)^{3/2}} = \sum_{n=0}^{\infty} n\,\beta^{n-1}\, P_n(\mu) \tag{19}$$

Differentiating equation (18) with respect to μ gives :-

$$\frac{\beta}{(1 - 2\beta\mu + \beta^2)^{3/2}} = \sum_{n=0}^{\infty} \beta^n P_n'(\mu) \tag{20}$$

From equations (17), (19) and (20),

$$V_d = \frac{M_c}{\alpha^2}\sum_{n=0}^{\infty} n\,\beta^{n+1} P_n(\mu) + \frac{M_s}{\alpha^2}\sum_{n=0}^{\infty} \beta^{n+1} \sin\theta \cos\phi\, P_n'(\mu)$$

$$\frac{\partial}{\partial r} V_d = \frac{d\beta}{dr} \cdot \frac{\partial}{\partial \beta} V_d$$

$$= -\frac{\alpha}{r^2}\left\{\frac{M_c}{\alpha^2}\sum_{n=0}^{\infty} n(n + 1)\, \beta^n P_n(\mu) + \frac{M_s}{\alpha^2}\sum_{n=0}^{\infty} (n + 1)\, \beta^n \sin\theta \cos\phi\, P_n'(\mu)\right\}$$

(since $\frac{d\beta}{dr} = -\alpha/r^2$)

To find $\frac{\partial}{\partial n} V_d$ at the surface of the sphere, it is necessary to put $r = R$; $\beta = \alpha/R$.

$$\frac{\partial}{\partial n} V_d = -\frac{\alpha}{R^2}\left\{ \frac{M_c}{\alpha^2} \sum_{n=0}^{\infty} n(n+1)\left(\frac{\alpha}{R}\right)^n P_n(\mu) + \frac{M_s}{\alpha^2} \sum_{n=0}^{\infty} (n+1)\left(\frac{\alpha}{R}\right)^n \sin\theta \cos\phi \, P_n'(\mu)\right\}$$

$$= -\sum_{n=0}^{\infty} \left\{ \frac{M_c}{R^2\alpha} n(n+1)\left(\frac{\alpha}{R}\right)^n P_n(\mu) + \frac{M_s}{R^2\alpha} (n+1)\left(\frac{\alpha}{R}\right)^n \sin\theta \cos\phi \, P_n'(\mu)\right\}$$

$$= -\frac{\partial}{\partial n} V_s \text{ , since } \frac{\partial}{\partial n} V_s = -\frac{\partial}{\partial n} V_d$$

$$\therefore \frac{\partial}{\partial n} V_s = \sum_{n=1}^{\infty} \left\{ \frac{M_c}{R^2\alpha} n(n+1)\left(\frac{\alpha}{R}\right)^n P_n(\mu) + \frac{M_s}{R^2\alpha} (n+1)\left(\frac{\alpha}{R}\right)^n \cos\phi \, T_n^1(\mu)\right\} \qquad (21)$$

$$\text{where} \quad T_n^m(x) = (1 - x^2)^{\frac{1}{2}m} \frac{d^m}{dx^m} P_n(x)$$

(In equation 21 the summation is taken from $n = 1$ to $n = \infty$, instead of from $n = 0$ to $n = \infty$, since the term for $n = 0$ is zero).

Each term in the summation in equation (21) is a surface spherical harmonic of degree n. The summation is, in fact, in a general form given by MacRobert (1947, p. 141, equation 41).

V_s is the potential due to a distribution of charge on the surface of the sphere of radius R. Hence for all values of r less than R, V_s must conform to Corollary 2 on p. 149 of MacRobert (1947) :-

"If all the attracting matter lies outside the sphere with the origin as centre and r as radius,

$$V = Y_0 + rY_1 + r^2Y_2 + \dots\dots\dots$$

where Y_n is a surface harmonic of degree n."

Let $V_s = Y_0 + rY_1 + r^2Y_2 + \dots\dots\dots$

Then $\frac{\partial}{\partial r} V_s = Y_1 + 2rY_2 + 3r^2Y_3 + \dots\dots\dots$

$$\frac{\partial}{\partial n} V_s \text{ at surface } = Y_1 + 2RY_2 + 3R^2Y_3 + \dots\dots\dots$$

$$= \sum_{n=1}^{\infty} n R^{n-1} Y_n \qquad (22)$$

where each term of the series is a surface harmonic of degree n.

But in equation (21) we already have an expansion of $\frac{\partial}{\partial n} V_s$ as a series of surface harmonics. There is a theorem (Jeans, 1941, p. 214) which states that the expansion of an arbitrary function of position on the surface of a sphere as a series of rational integral harmonics is unique. Hence, corresponding terms in equations (21) and (22) can be equated.

Equating the terms of degree n gives

$$n R^{n-1} Y_n = \frac{Mc}{R^2\alpha} n(n+1)\left(\frac{\alpha}{R}\right)^n P_n(\mu) + \frac{Ms}{R^2\alpha}(n+1)\left(\frac{\alpha}{R}\right)^n \cos\phi\, T_n'(\mu)$$

$$Y_n = \frac{M(n+1)\alpha^{n-1}}{R^{2n+1}}\left\{c\, P_n(\mu) + \frac{s \sin\theta \cos\phi\, P_n'(\mu)}{n}\right\}$$

$$V_s = Y_o + \sum_{n=1}^{\infty} r^n Y_n$$

$$= Y_o + \sum_{n=1}^{\infty} \frac{M(n+1)\alpha^{n-1}}{R^{2n+1}}\left\{c\, P_n(\mu) + \frac{s \sin\theta \cos\phi\, P_n'(\mu)}{n}\right\} r^n \tag{23}$$

where Y_o is an arbitrary constant.

The problem has now been solved, since the potential anywhere in the sphere is given by

$$V = V_d + V_s$$

where V_d can be obtained from equation (16) and V_s from the above equation (23). The solution is not yet in a convenient form, however, since equation (23) contains an infinite series. The next step is to sum the infinite series.

For simplicity, before summing, R will be substituted for r in equation (23). Consequently, the final expression will give only the potential over the surface of the sphere, and not the potential throughout the volume. This is done merely for simplicity; the general method used here could also be used to derive an expression for the potential throughout the volume of the sphere if this were needed.

On putting r = R, and breaking up the infinite series into two parts which will be summed separately, equation (23) becomes :-

$$V_s = Y_0 + \frac{M_c}{R\alpha}\sum_{n=1}^{\infty}\left(\frac{\alpha}{R}\right)^n (n+1)\, P_n(\mu)$$

$$+ \frac{M_s \sin\theta \cos\phi}{R\alpha}\sum_{n=1}^{\infty}\left(\frac{\alpha}{R}\right)^n\left(\frac{n+1}{n}\right)P_n'(\mu) \quad (24)$$

The two infinite series occurring in equation (24) will be considered in turn. The first of them is equal to

$$\sum_{n=1}^{\infty}\left(\frac{\alpha}{R}\right)^n (n+1)\, P_n(\mu)$$

$$= \sum_{n=1}^{\infty} z^n (n+1)\, P_n(\mu) \qquad \text{where } z = \alpha/R$$

$$= \sum_{n=1}^{\infty} z^n \left\{ P_{n+1}'(\mu) - \mu P_n'(\mu) \right\}$$

[see equation 36 on p. 99 of MacRobert, 1947, which states $P_{n+1}'(\mu) - \mu P_n'(\mu) = (n+1)\, P_n(\mu)$]

$$= \frac{1}{z}\sum_{n=1}^{\infty} z^{n+1} P'_{n+1}(\mu) - \mu \sum_{n=1}^{\infty} z^{n} P'_{n}(\mu)$$

$$= \frac{1}{z}\sum_{n=2}^{\infty} z^{n} P'_{n}(\mu) - \mu \sum_{n=1}^{\infty} z^{n} P'_{n}(\mu)$$

$$= \left(\frac{1}{z} - \mu\right)\sum_{n=1}^{\infty} z^{n} P'_{n}(\mu) - \frac{1}{z}\, z\, P'_{1}(\mu)$$

$$= \left(\frac{1}{z} - \mu\right)\frac{\partial}{\partial \mu}\, \frac{1}{(1 - 2\mu z + z^{2})^{1/2}} - 1$$

from definition of Legendre polynomials and fact that $P'_1(\mu) = 1$.

$$= \frac{1 - \mu z}{z} \cdot \frac{z}{(1 - 2\mu z + z^{2})^{3/2}} - 1$$

$$= \frac{1 - \frac{\alpha}{R}\mu}{\left(1 - 2\mu\frac{\alpha}{R} + \frac{\alpha^{2}}{R^{2}}\right)^{3/2}} - 1$$

$$= R^{2}\, \frac{R - \alpha\mu}{(R^{2} - 2\alpha R\mu + \alpha^{2})^{3/2}} - 1$$

The first of the two infinite series in equation (24) has now been summed. The second series is equal to

$$\sum_{n=1}^{\infty} z^{n} \left(\frac{n+1}{n}\right) P'_{n}(\mu)$$

$$= \frac{\partial}{\partial z}\sum_{n=1}^{\infty} \frac{z^{n+1}}{n} P'_{n}(\mu)$$

$$= \frac{\partial}{\partial z}\, z \sum_{n=1}^{\infty} \frac{z^{n}}{n} P'_{n}(\mu)$$

$$= \frac{\partial}{\partial z}\, z \int_{0}^{z} \sum_{n=1}^{\infty} \xi^{n-1} P'_{n}(\mu)\, d\xi$$

$$= \frac{\partial}{\partial z}\, z \int_0^z \frac{1}{\xi} \sum_{n=1}^{\infty} \xi^n P_n'(\mu)\, d\xi$$

$$= \frac{\partial}{\partial z}\, z \int_0^z \frac{1}{\xi}\, \frac{\partial}{\partial \mu}\, \frac{1}{(1 - 2\mu\xi + \xi^2)^{\frac{1}{2}}}\, d\xi$$

from the definition of Legendre polynomials

$$= \frac{\partial}{\partial z}\, z \int_0^z \frac{1}{(1 - 2\mu\xi + \xi^2)^{3/2}}\, d\xi$$

$$= \frac{\partial}{\partial z}\, z \left[\frac{1}{1-\mu^2} \cdot \frac{\xi - \mu}{(1 - 2\mu\xi + \xi^2)^{1/2}} \right]_0^z$$

$$= \frac{1}{1-\mu^2}\, \frac{\partial}{\partial z}\, z \left\{ \frac{z - \mu}{(1 - 2\mu z + z^2)^{1/2}} + \frac{\mu}{1} \right\}$$

$$= \frac{1}{1-\mu^2}\, \frac{\partial}{\partial z} \left\{ \frac{z(z-\mu)}{(1 - 2\mu z + z^2)^{1/2}} + \mu z \right\}$$

$$= \frac{1}{1-\mu^2} \left\{ \frac{z^3 - 3z^2\mu + z(2+\mu^2) - \mu}{(1 - 2\mu z + z^2)^{3/2}} + \mu \right\}$$

$$= \frac{1}{1-\mu^2} \left\{ \frac{\alpha^3 - 3\alpha^2 R\mu + \alpha R^2(2+\mu^2) - R^3\mu}{(R^2 - 2\alpha R\mu + \alpha^2)^{3/2}} + \mu \right\}$$

The summations of the two infinite series can now be substituted in equation (24) to give :-

$$V_s \text{ on surface} = Y_0 + \frac{Mc}{R\alpha}\left\{R^2\frac{R-\alpha\mu}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}} - 1\right\}$$

$$+ \frac{Ms\sin\theta\cos\phi}{R\alpha\,(1-\mu^2)}\left\{\frac{\alpha^3-3\alpha^2R\mu+\alpha R^2(2+\mu^2)-R^3\mu}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}}+\mu\right\}$$

$$= K + \frac{Mc}{R\alpha}\left\{R^2\frac{R-\alpha\mu}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}}\right\}$$

$$+ \frac{Ms\sin\theta\cos\phi}{R\alpha\,(1-\mu^2)}\left\{\frac{\alpha^3-3\alpha^2R\mu+\alpha R^2(2+\mu^2)-R^3\mu}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}}+\mu\right\} \quad (25)$$

where $K = Y_0 - \frac{Mc}{R\alpha}$ = an arbitrary constant

(since Y_0 was arbitrary).

Substituting R for r in equation (16) gives

$$V_d \text{ on surface} = Mc\,\frac{R\mu-\alpha}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}} + Ms\,\frac{R\sin\theta\cos\phi}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}} \quad (26)$$

The potential on the surface is now found by adding equations (25) and (26).

$$V \text{ on surface} = V_s + V_d$$

$$= K + \frac{Mc}{R\alpha}\cdot\frac{R^2(R-\alpha\mu)+R\alpha(R\mu-\alpha)}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}}$$

$$+ \frac{Ms\sin\theta\cos\phi}{R\alpha\,(1-\mu^2)}\left\{\frac{\alpha^3-3\alpha^2R\mu+\alpha R^2(2+\mu^2)-R^3\mu+R^2\alpha(1-\mu^2)}{(R^2-2\alpha R\mu+\alpha^2)^{3/2}}+\mu\right.$$

Substituting $\sin^2\theta$ for $(1 - \mu^2)$, and simplifying, gives the final result :-

$$V \text{ on surface} = K + \frac{Mc}{\alpha} \cdot \frac{R^2 - \alpha^2}{(R^2 - 2\alpha R\mu + \alpha^2)^{3/2}} + \frac{Ms\cos\phi}{R\alpha\sin\theta}\left\{\frac{\alpha^3 - 3\alpha^2 R\mu + 3\alpha R^2 - R^3\mu}{(R^2 - 2\alpha R\mu + \alpha^2)^{3/2}} + \mu\right\} \tag{27}$$

where $\mu = \cos\theta$

$c = \cos\eta$

$s = \sin\eta$

and K is an arbitrary constant.

DISCUSSION

The foregoing theory was worked out before the paper of Frank (1952) had been seen. Frank obtains an expression which is equivalent to equation (27) except in that he has not introduced an arbitrary constant. The expression given by Frank is, in his notation :-

$$V = \frac{p}{4\pi\gamma R b}\left\{\cos\psi\left[\frac{1-f^2}{(1+f^2-2f\mu)^{3/2}}-1\right]\right.$$

$$\left.-\frac{\sin\psi\cos\phi}{\sin\theta}\left[\frac{3f-3f^2\mu+f^3-\mu}{(1+f^2-2f\mu)^{3/2}}+\mu\right]\right\}$$

p is the moment of the current dipole, and γ is the conductivity of the medium. Hence $\frac{p}{4\pi\gamma}$ corresponds to M in my notation.

b, in Frank's notation, corresponds to a in my notation and f = b/R, corresponding to a/R.

The angle ψ in Frank's notation corresponds to (180° - η) in my notation; hence cos ψ corresponds to cos η , or c, in my notation, but sin ψ corresponds to - sin η , or - s, in my notation. This accounts for the appearance of a minus sign between the terms of Frank's expression where a plus sign appears in mine. My expression is exactly equivalent to that of Frank if the arbitrary constant K is given the value $\frac{-h \cos\psi}{4\pi\gamma R b}$

The method used by Frank to derive his expression makes use of Spherical Harmonics, and is roughly equivalent to my method though the actual equations and steps in the calculation are considerably different. The consequences of some of Frank's results when applied to electrocardiography are discussed by Frank and Kay (1953). In another paper, Frank (1953) calculates the field produced by, not merely a single dipole in a sphere, but a hemispherical double-layer of dipoles in a sphere.

The arbitrary constant which I have included in my equation (27) is necessary if the solution is to be strictly correct. The constant is, however, of no practical importance since, in practical E.E.G. recording, what is amplified and recorded is a difference between two potentials, both of which include the constant K. This is so, even when the system of recording is what is termed "monopolar recording", for in that case the potentials are always compared with some reference potential, which is either an average of the potentials of all the head electrodes, or is taken from some point on the head or body. In either case, the constant K is included in the reference potential, and its effects cancel out.

As was mentioned in the discussion of Case 2, the term K need only be a constant insofar as it is independent of r, θ and ϕ; if the dipole moment M varies with time, K may vary with it. Nevertheless, what has been said above is still true; the value of K is of no practical importance. (In conventional E.E.G. recording, the effects of a dipole of constant strength would not be detected by the capacitance-coupled amplifiers. Hence, M must vary with time if its effect is to be observed in a conventional E.E.G. record.)

The results obtained here for the potential distributions have been expressed only as formulae, though for comparison with experimental findings in E.E.G. records, graphical representations of the field would be more convenient. I have not yet made any attempt to compare the theoretical potential distributions with actual E.E.G. findings. Some tentative steps in this direction have been taken by Shaw, but it is not yet possible to say whether the potential distribution produced by an E.E.G. focus approximates the theoretical distribution due to a dipole. Shaw and Roth (1955) have published graphical representations of the potential distribution due to a dipole in a sphere, both for the case in which the dipole axis lies along the diameter on which the dipole lies, and for the case in which the dipole axis is perpendicular to the diameter on which the dipole lies. Reprints of the papers by Shaw and Roth are included in the appendix of this thesis.

PART 5

METHODS FOR INDICATING IMPULSE - FREQUENCY IN NEUROPHYSIOLOGICAL EXPERIMENTS

PART 5. METHODS FOR INDICATING IMPULSE-FREQUENCY IN NEUROPHYSIOLOGICAL EXPERIMENTS

Since the working of the nervous system depends on the conduction of impulses along nerve fibres, detailed investigation of the system is only possible by recording and studying the sequences of impulses in single nerve fibres. Techniques have been evolved for making such records, and the impulses in sensory nerve fibres, in particular, have been studied by Adrian (1928), by Granit (1947) for the optic nerve, by Lowenstein and Roberts (1949) for a nerve supplying the labyrinth, by Boyd and Roberts (1953) for a nerve supplying proprioceptors in the knee-joint, and by many other workers.

As an aid in the analysis of these records from single fibres, Lowenstein and Roberts used an electronic device to indicate the pulse repetition-frequency at any time. This operated on the same principle as a " counting-rate meter" as used in conjunction with Geiger counters. Circuit techniques used in counting-rate meters have been reviewed by Smith (1952).

In the Physiology Department it was decided to build a device to indicate pulse-frequency, for use in experimental projects involving single-fibre records, particularly the work of. Boyd and Roberts (1953, also Boyd, 1954) on proprioceptors in the knee-joint of the cat. A device of the counting-rate meter type was designed and constructed. It later became clear that a counting-rate meter has an inherent limitation when used in neurophysiological experiments, since it necessarily incorporates some kind of integrating or smoothing circuit and is therefore sluggish in its response to any change in pulse-frequency which takes place in a time which is not extremely long compared to the intervals between pulses. This limitation of the counting-rate meter is not a disadvantage when the meter is used with a Geiger counter, for in that case the impulses to be counted occur randomly, and what is wanted is an average rate over a time.

Because of this limitation of the counting-rate meter, it was eventually superseded for our purposes by the pulse-interval meter (Andrew and Roberts, 1954). A brief account of the design of the counting-rate meter is given here, however, especially since an interesting (but unwanted) phenomenon was seen in one circuit which was tried out in the course of its development.

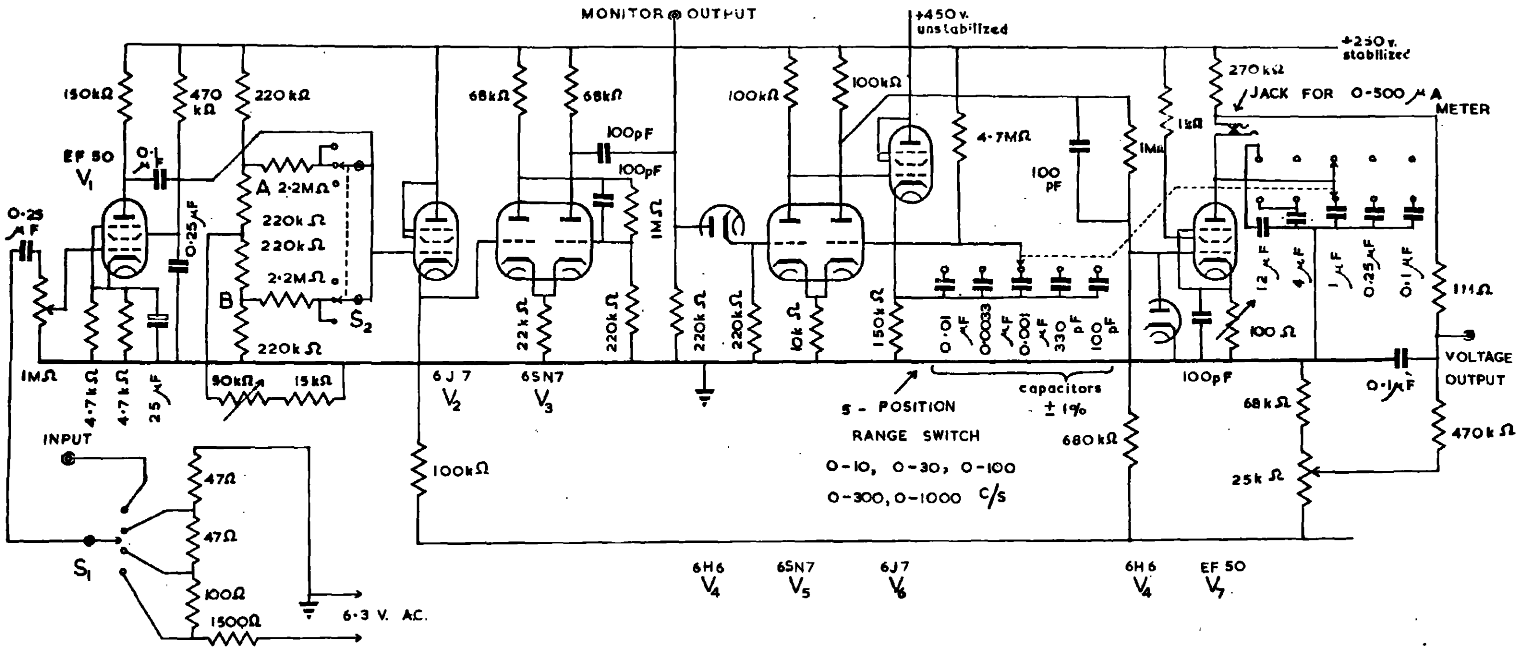


Fig. 5.1. Circuit of the counting-rate meter.

The Design of a Counting-Rate Meter

The circuit of the counting-rate meter is shown in Fig. 5.1. V_1 provides a straightforward stage of amplification, whose input, selected by S_1, may be either the impulses whose frequency is to be determined, or a 50 c/s sinusoidal signal for calibration and setting-up of the instrument. The potentiometer in the grid circuit of V_1 is a sensitivity control which can be set to determine the size of impulse to which the instrument will respond. V_2 is a cathode follower, from whose output the signal is applied to the Schmitt trigger circuit V_3. Pulses of either polarity, whose voltage excursion causes the input to V_3 to pass through its critical range, cause V_3 to produce triggering pulses of standard amplitude which trigger the monostable multivibrator consisting of V_5 and V_6 .

In the grid circuit of V_2 is the 3-position switch S_2, connected to a netwoek of resistors. The setting-up procedure is to turn this switch to its middle, or "test" position. Then the grid leak of V_2 consists of the two 2•2 MΩ resistors in parallel, and is effectively returned to a potential intermediate between the potentials of points A and B. This intermediate potential is then adjusted by means of the "trigger level" preset potentiometer, until the Schmitt trigger can be triggered by the smallest possible sinusoidal input to the instrument. Once this adjustment has been made, it follows that when the grid leak of V_2 is returned to the intermediate potential, the mean potential of V_2 cathode is in the middle of the critical range of potential of the Schmitt trigger circuit.

When the instrument is in use, the three-position switch is in one of its outer positions, so that V_2 has its grid leak returned to either A or B. In the position in which the leak is returned to A, the mean potential of V_2 cathode is more positive than the critical range of potential of the Schmitt trigger circuit. Hence, in order that the input to the Schmitt trigger circuit should pass through its critical range, a negative pulse is required at V1 anode. With S_2 in this position, therefore, the instrument responds to positive pulses at the input (since the pulses are inverted by V_1). Conversely, when the switch is in its other outer position, the grid leak of V_2 is returned to point B, and the instrument responds to negative pulses at its input.

The output from the Schmitt trigger circuit triggers the monostable multivibrator consisting of V_5 and V_6 . The two sections of V_5 are the main valves of the multivibrator, with the right-hand section conducting when in the stable state. V_6 is included as a cathode follower coupling the anode of the left-hand section to the coupling capacitor which goes to the right-hand grid. The purpose of the cathode follower V_6 is to speed up the recovery of the multivibrator after it has been made to operate. (Methods for obtaining fast recovery of multivibrators are discussed by Sayre, 1949, p. 185.)

V_7 is notmally biassed beyond cut-off, and only conducts while the multivibrator (V_5 and V_6) is in its quasi-stable state. The multivibrator is flipped into its quasi-stable state by the arrival of an impulse at the input of the instrument (via V_1, V_2 and V_3), and it remains in that state after each impulse for a time which depends on the capacitance value selected by the 5-position range switch. Thus the fraction of the total time for which V_7 is conducting is proportional to the frequency of the incoming pulses. The intermittent current conducted by V_7 is smoothed by a capacitor between V_7 anode and earth, and the smoothed current represents the indication of pulse-frequency given by the instrument. Both voltage and current outputs are provided, as shown. The magnitude of the current which flows in V_7, during those periods when it is conducting, can be adjusted by means of the 100 Ω variable resistor in the cathode circuit of V_7. To adjust this variable resistor, a signal of known frequency 50 c/s is applied to the input of the instrument, which is turned to its 0 - 100 c/s range. Then the variable resistor is adjusted so that the meter in the anode circuit of V_7 gives half of its full-scale deflection (since 50 c/s is half of 100 c/s).

The circuit of Fig. 5.1 is a fairly conventional circuit for a counting-rate meter, except in the way in which it is made to respond to either positive or negative pulses, according to the position of the switch S_2. This feature is believed to be novel, and is incorporated also in the pulse-interval meter, to be described later.

Smoothing the output of the counting-rate meter

One further feature of the design merits discussion, however. The meter indicating the output reading of the instrument is connected directly in the anode circuit of V_7. It is therefore necessary that V_7 is able to conduct sufficient current to produce full-scale deflection of the meter. Hence the anode resistor of V_7 cannot be much larger than the value shown (270 kΩ), for a higher value would require too high a voltage to make the current needed for full-scale deflection pass through it.

The smoothing of the output, however, depends on the time-constant determined by this anode resistor and the capacitor (different in value for different ranges of the instrument) between V_7 anode and earth. Since the resistor must not be too large, the necessary time-constant must be obtained by using a sufficiently large capacitor. For the lowest frequency-range of the instrument it was necessary to use a total of 16 μF, which is an inconveniently large value to provide in paper capacitors.

The smoothing could have been done with a smaller capacitance value by using a more sensitive meter, so that a larger resistance value could be connected in the anode circuit, or by interposing a valve stage between the smoothing circuit and the meter. However, neither of these alternatives was favoured, because a more sensitive meter would have been less robust than the one which was in fact used, and a valve stage would

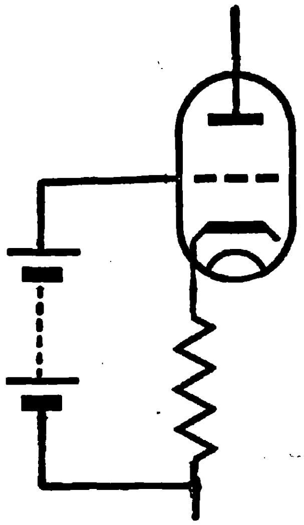


Fig. 5.2. (Above). Circuit having high differential-resistance.

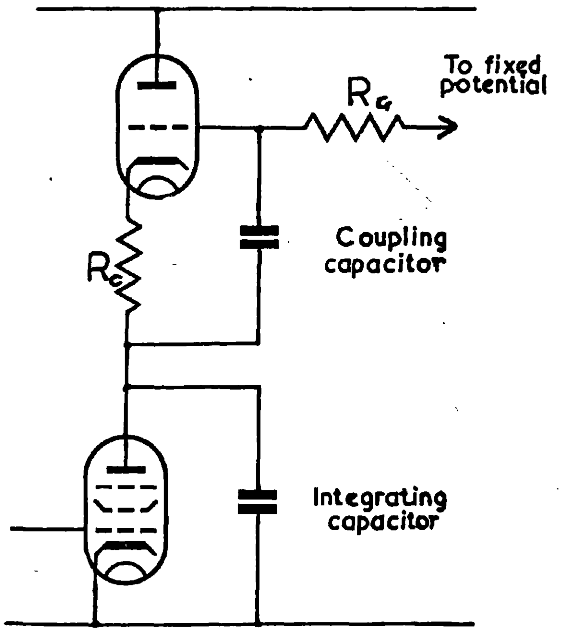


Fig. 5.3. (Above). The upper valve is incorporated in a modified form of the circuit of Fig. 5.2.

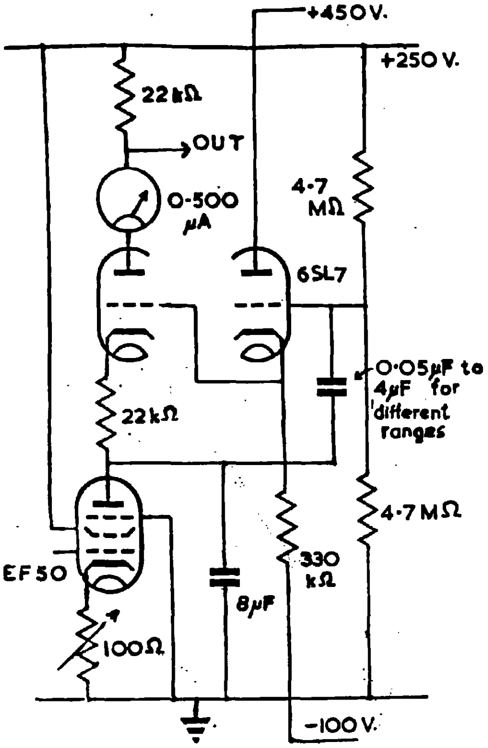


Fig. 5.4. (Left). Practical form of the circuit of Fig. 5.3.

have introduced the need for a zero-setting adjustment, and possibilities of drift and non-linear response.

The possibility was considered of using a valve circuit having high differential-resistance in place of the resistor in the anode circuit of V_7. A circuit having high differential-resistance is shown in Fig. 5.2, incorporating a triode with current negative-feedback (Hughes and Walker, 1949, p. 266). This circuit was not considered suitable, however, partly because it contains a battery, and partly because the triode with current feedback approximates a constant-current device, and will have a relatively low differential-resistance when the current falls below a certain minimum value. It appears that what is needed is a circuit which has a high impedance to rapid fluctuations in current, but allows slow changes in current to take place. A circuit having these properties is shown in Fig. 5.3, where the direct coupling by means of the battery is replaced by a resistance-capacitance coupling. The pentode valve in Fig. 5.3 corresponds to V_7 of Fig. 5.1.

The practical form of the circuit as tried out incorporated yet another valve, as shown in Fig. 5.4. The extra valve (the right-hand triode section) is simply a cathode follower, included to eliminate certain

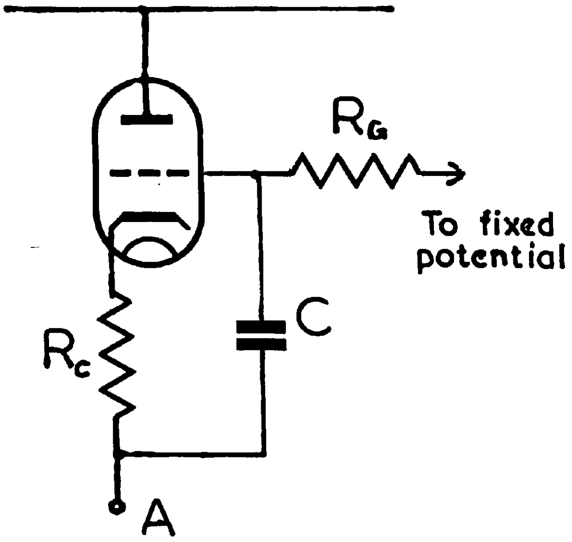


Fig. 5.5. Smoothing impedance as shown in Fig. 5.3.

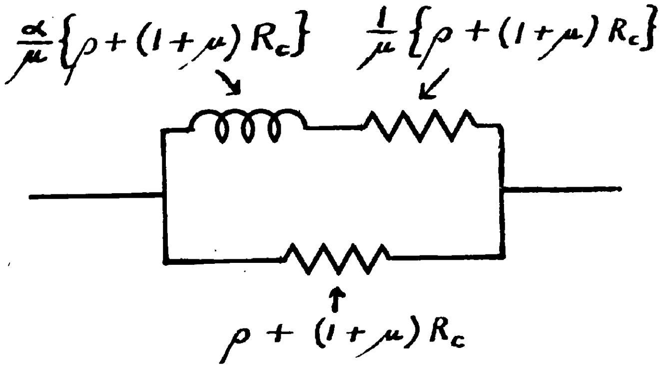


Fig. 5.6. Inductive impedance to which the circuit of Fig. 5.5 is equivalent.

effects which, it was anticipated, might occur if the left-hand triode section passed grid current. The general principle of the circuit is not affected by the inclusion of this extra valve.

When this circuit was tried out, it was found to be unsuitable for our purpose, because the indication of frequency would go into a damped oscillation following an abrupt change in input pulse-frequency. The reason for the oscillation was eventually worked out, and the circuit was modified to that shown in Fig. 5.1. It can be shown by A.C. circuit analysis that, in the circuit of Fig. 5.3, the anode load of V_7 consists of the capacitor shown connected to earth, in parallel with what is effectively an inductance, as will be shown. The capacitor and inductance in parallel constitute a tuned circuit, and it was this tuned circuit which went into oscillation.

The circuit which was between the anode of V_7 and the H.T. line is shown by itself in Fig. 5.5. It will be shown that this circuit is effectively an inductance. Let v be the variations in the potential difference across the whole circuit, so that the potential fluctuations of point A are represented by $-v$. Let the variations of current through the circuit be i. The current through

C and R_G is negligible, so i represents the current fluctuations through the valve.

Potential fluctuations at the valve cathode are given by

$$v_C = -v + i R_C$$

Potential fluctuations at the grid are given by

$$v_G = -v \frac{R_G}{R_G + \frac{1}{j\omega C}} = -v \frac{j\omega C R_G}{1 + j\omega C R_G}$$

The fundamental equation for a triode valve is

$$i = \frac{1}{\rho}(v_a + \mu v_g) \qquad (1)$$

where ρ and μ are constants of the valve, and v_a represents variations in anode-to-cathode voltage, and v_g represents variations in grid-to-cathode voltage.

In this case, $v_a = -v_C$

$$= v - i R_C$$

$$v_g = v_G - v_C$$

$$= -v \frac{j\omega C R_G}{1 + j\omega C R_G} + v - i R_C$$

Substituting for v_a and v_g in equation (1), and simplifying, gives for the impedance of the circuit :-

$$z = v/i$$

$$= \frac{1}{\dfrac{1}{\rho + (1+\mu)R_c} + \dfrac{1}{\frac{1}{\mu}\{\rho + (1+\mu)R_c\} + j\omega\frac{\alpha}{\mu}\{\rho + (1+\mu)R_c\}}} \quad (2)$$

where $\alpha = CR_g$

Equation (2) is also the impedance of an inductance of value $\frac{\alpha}{\mu}\{\rho + (1 + \mu) R_C\}$ in series with a resistance of value $\frac{1}{\mu}\{\rho + (1 + \mu) R_C\}$, the two connected in parallel with another resistance of value $\rho + (1 + \mu) R_C$, as shown in Fig. 5.6. This circuit is equivalent to the circuit of Fig. 5.5, and shows why the counting-rate meter incorporating the circuit of Fig. 5.5 gave an oscillatory response.

The equivalent tuned circuit was damped by the resistance elements shown in Fig. 5.6, but nevertheless had a sufficiently high Q-value to produce chains of damped oscillations. Various possible ways of damping the tuned circuit beyond critical damping were considered, but no satisfactory way was found. This type of circuit was therefore abandoned in favour of the simple smoothing arrangement shown in Fig. 5.1.

The foregoing theory shows that a circuit can be designed, incorporating only resistance, capacitance, and a valve, which behaves as an inductance. The possibility exists of using this principle to design filters and oscillators incorporating only resistance, capacitance and valves, but which are exactly equivalent to familiar types of filters and oscillators which incorporate inductors. The advantage of the resistance-capacitance filters and oscillators is that they can readily be adapted to operate at very low frequencies, at which the inductors required for the conventional circuits would be unwieldy and expensive. Resistance-capacitance oscillators and filters of the kinds which can be evolved by the use of the foregoing theory turn out to be similar to those described by Schneider (1945).

The Pulse-Interval Meter

Mention has been made of the unsuitability of an instrument of the counting-rate meter type for indicating the repetition rate of nerve impulses. Such an instrument is sluggish in its response to any change in repetition frequency which occurs in a time which is not extremely long compared with the pulse intervals.

The instrument which has been termed the "pulse-interval meter" was developed to facilitate the analysis of the patterns of activity in nerve fibres, particularly in sensory nerves. It is free from the limitation of counting-rate meters, since it effectively measures every interval between successive pulses and gives an indication of frequency derived from each pulse-interval. It may find application in fields other than physiology. The frequency range covered by the present instrument is from zero to 100 pulses/second, which is sufficient for most neurophysiological applications.

Other work on interval-meters

A simple pulse-interval meter is mentioned by Enroth (1952, p. 14) and termed an "interval recorder". This device is suitable for cathode-ray oscillograph recording, but does not produce a continuous voltage varying with frequency, in a form suitable for reading on a moving-coil meter, or recording with an ink pen-writer. The recorder mentioned by Enroth consists simply of a time-base or scanning generator which makes the spot of the oscilloscope travel across the screen in a direction perpendicular to the direction of motion of the recording film. The spot is returned to its starting-point whenever an impulse is received at the input to the instrument, so the distance the spot travels across the screen is a measure of the interval between pulses.

Electro-mechanical devices for recording the intervals between successive events are commercially available (Palmer, 1953, p. 50), and the use of one has been described by Gaddum and Kwiatkowski (1938). These devices, however, are quite unsuitable for the pulse frequencies which occur in nerve fibres.

The pulse-interval meter was demonstrated to the Physiological Society in July 1953 (Andrew and Roberts, 1953). During the time which elapsed between this demonstration and the publication of the full account (Andrew and Roberts, 1954) it was learned that a somewhat similar instrument was being developed for a different purpose in the Applied Psychology Research Unit at Oxford. Details of this instrument were published (Dawe and Deutsch, 1955) shortly after our publication of the full description of our pulse-interval meter. The instrument developed by Dawe and Deutsch is intended for the study of speech, and operates over a higher range of frequencies than does our pulse-interval meter. The principle of operation of the two instruments is the same, however, and although the two were developed independently there is remarkable similarity between the circuits employed.

Haapanen and Skoglund (1955) have produced a device which records information about pulse intervals in a condensed and convenient form. Their device is intended for use in neurophysiology, but does not produce a graph of pulse-frequency against time as our pulse-interval meter does. Their device also suffers from the disadvantage that it can only be used to make cathode-ray oscillograph records.

Interval-recording devices have also been employed to make continuous records of heart-rate. These have generally been similar in principle to the interval recorder described by Enroth, with the difference that the heart-rate recorders could be used with a pen recorder, while that described by Enroth was suitable only for use with a cathode-ray oscillograph because of its greater speed of operation.

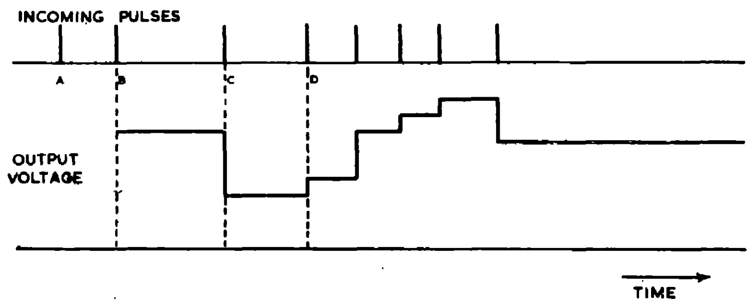


Fig. 5.7. Incoming pulses and resulting output voltage where the output voltage at any instant is determined by the duration of the previous pulse-interval.

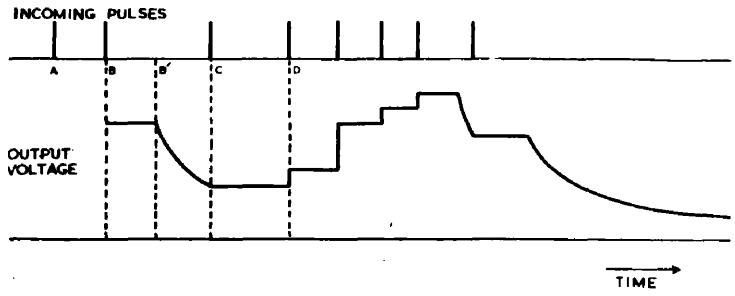


Fig. 5.8. Incoming pulses and resulting output voltage of the pulse-interval meter, in which the output voltage at any instant is determined either by the duration of the preceding pulse-interval, or by the duration which the current interval has already attained, whichever is the longer.

Principle of Operation of the Pulse-Interval Meter.

Each interval between pulses is measured electronically and determines an output voltage. The output voltage is an approximately linear function of the reciprocal of interval duration. Hence an oscilloscope or moving-coil meter connected to the output of the pulse-interval meter gives an indication of frequency on an approximately linear scale.

The series of output voltages determined by successive intervals has to be combined to give a continuous indication of frequency. A way in which this might have been done is illustrated in Fig. 5.7. The instrument could have been designed so that the output voltage determined by each interval was given as output during the succeeding interval. In Fig. 5.7 the interval AB is short and therefore corresponds to a high frequency; hence the output voltage is high during the interval BC. The interval BC is longer and corresponds to a lower frequency, so the output voltage is lower during CD, and so on. This mode of operation may be described by saying that the output at any instant is determined by the duration of the preceding pulse interval.

A serious disadvantage of an instrument operating as described above would be that if the pulse repetition-frequency fell to zero the instrument would not give an indication of zero frequency, but would continue indefinitely to indicate the frequency corresponding to the duration of the interval between the last two pulses. This property is illustrated at the right-hand end of Fig. 5.7.

The mode of operation actually employed is slightly different. The output voltage at any instant is determined either by the duration of the preceding pulse-interval or by the duration which the current interval has already attained, whichever is the longer. This mode of operation is illustrated in Fig. 5.8. When the pulse repetition-frequency becomes zero the output voltage falls asymptotically towards the value corresponding to zero frequency.

Definition of Frequency

When pulses are occurring somewhat irregularly, the most practical definition of frequency appears to be as the reciprocal of the interval between two successive pulses. Using this definition, the instrument responds to a change in frequency as rapidly as is physically possible. If an interval is shorter than the preceding

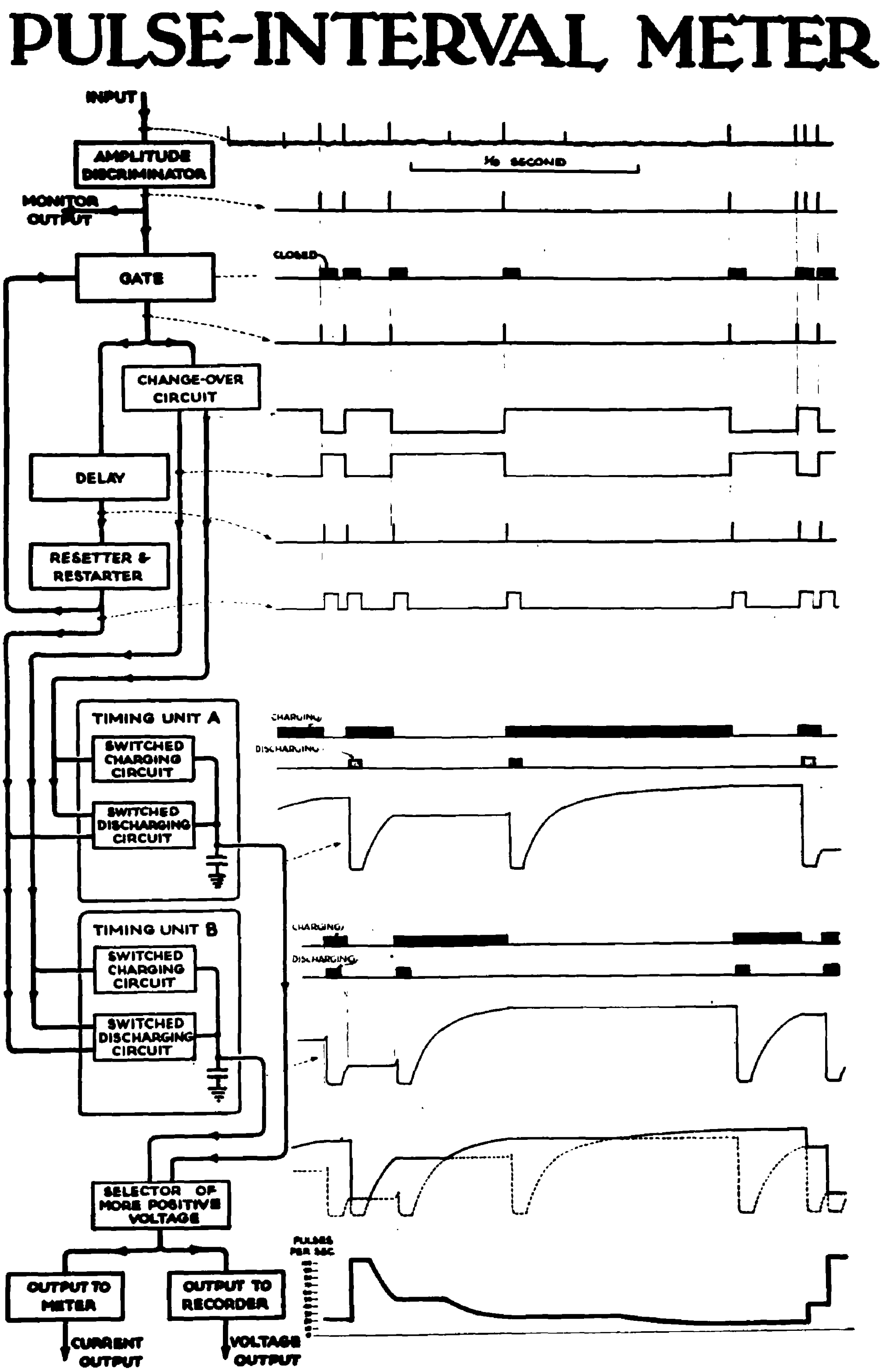


Fig. 5.9. Block diagram of the pulse-interval meter, with associated waveforms.

one the higher value for the frequency is indicated as soon as the interval is completed. If an interval is longer than the preceding one the instrument does not wait until the end of the interval before indicating the reduction in frequency. For instance, in Fig. 5.8 the indication begins to fall away at B', where BB' = AB.

Arrangement of the Instrument

Fig. 5.9 shows a block diagram of the instrument, with associated waveforms. The incoming pulses are applied to an amplitude discriminator, which is triggered only by pulses of greater than a certain amplitude. Pulses from the discriminator then reach a gate circuit, which is closed to further pulses for a time after a pulse has passed through. The moment of reopening of the gate is controlled from further on in the circuit. Its purpose will be discussed later.

The timing of the pulse-intervals is done by two timing units which come into play alternately. To produce the alternate operation, pulses which come through the gate are made to operate a "changeover circuit" which consists of an Eccles-Jordan trigger circuit or bistable multivibrator. Of the two outputs which are taken from this circuit one is always positive and one negative, and they change over every time a pulse comes through the gate.

Each timing unit has two possible states during any pulse-interval; it may operate to "measure" the pulse-interval or it may hold the capacitor charge which represents a measure of the duration of the preceding interval. The voltages developed across the capacitors of the timing units are combined to give the output voltage of the instrument by the circuit termed "selector of more positive voltage". This arrangement gives the mode of operation illustrated in Fig. 5.8. Had it been desired to make an instrument operating as illustrated in Fig. 5.7, the selector of more positive voltage would have been replaced by an electronic switch so arranged that the output voltage was derived from whichever of the timing units was in the "holding" state. The output voltage of the selector of more positive voltage is effectively the output voltage of the instrument.

Circuit Details

A complete description of the instrument has been published (Andrew and Roberts, 1954) and a reprint of the paper is included in the appendix of this thesis.

The circuit is rather complicated. Some of the complication could perhaps be avoided in some applications of the instrument, if it could be assumed that there would never be two pulses at the input within about 7 msec of each other or closer. As is explained in the reprint, it would be difficult to predict the response of the instrument to pulses arriving as close together as this, were it not that rather elaborate precautions are taken to ensure that the instrument simply fails to respond to the second of the two pulses (the "gate" is closed to the second pulse). Hence an "overload" of the instrument by a pulse frequency greater than about 140 pulses/second leads simply to frequency division, so that an input of pulses at 150 per second produces the same output from the instrument as does an input of 75 pulses/second. If the use of the instrument were restricted to applications in which the response to a frequency outside the normal range was of no consequence, a considerable simplification of the circuit would be possible. It was, however, thought to be best to take the precaution of including the "gate" in the present instrument.

Results

The pulse-interval meter was put into use in the Neurophysiology Laboratory and has proved to be convenient and reliable. Its main use has been by Dr. I.A. Boyd in connection with proprioceptors in the knee-joint of the cat. Unfortunately the instrument was not developed until a fairly late stage in Dr. Boyd's work. Had the instrument been available sooner it would have saved a great deal of tedious work involved in measuring pulse-frequencies from photographic records of the nerve action potentials, and manually drawing graphs of frequency against time. The use of the pulse-interval meter is mentioned by Boyd (1954), but most of the experimental results he reports were obtained before it was available.

In more recent work on the cat knee-joint, however, a large number of records has been obtained using the pulse-interval meter. These have been valuable in the attempts which have been made to find a mathematical relationship between the impulse frequency at any instant from a proprioceptor, and the position and motion of the knee-joint. A great deal of work has been done on this mathematical problem, mainly by Mr. Alan Cairnie, and an account of it will probably be published.

PART 6

AMPLIFIER REQUIREMENTS AND DESIGN

PART 6. AMPLIFIER REQUIREMENTS AND DESIGN

The great advances which have been made in neurophysiology in the last decade or two have been made possible by the use of electronic amplification. It is perhaps an exaggeration to say that "a neurophysiologist is only as good as his amplifier", but it is certainly true that greater understanding of the nervous system can be expected to follow from improvements in amplifier design.

The number of stages of amplification between the electrodes which connect with the biological preparation, and the recording or indicating device, is usually from three to six. It is usual to have the early stages grouped together to form the "pre-amplifier" and the other stages form the "main" amplifier. The number of stages in the pre-amplifier is usually from one to three.

The main requirements in a biological amplifier are the following :-

(a) Low level of noise and microphonic effects and of 50 c/s interference (and, in a D.C. amplifier, of drift).

(b) Good rejection of in-phase voltages at the input.

(c) A level frequency response, extending both high enough and low enough to show the required signals without distortion. Also sufficient gain to show the waveforms suitably.

(d) High input-impedance and low grid current.

(e) In the case of capacitance-coupled amplifiers, freedom from "blocking" following a large transient.

Of the above five requirements, three depend entirely or almost entirely on the pre-amplifier. These are (a), (b) and (d). Since these three are usually the requirements which are most difficult to meet, the design of the pre-amplifier is more critical than that of the later stages of amplification.

In setting up the Neurophysiology Laboratory at Glasgow, both pre-amplifiers and main amplifiers were designed and built. This equipment has been used by Boyd and Roberts (1953, also Boyd, 1954) and Roberts (1954) as well as for other investigations not yet published, and for student use. Also, a pre-amplifier similar to the type to be described here was built for the work on the frog optic lobes reported in Part 2.

Design of Amplifiers for the Neurophysiology Laboratory

Design of the "main" amplifiers

The "main" amplifiers, which receive their input from a pre-amplifier and deliver their output to a cathode-ray tube or other recording device, are fairly straightforward push-pull amplifiers about whose design

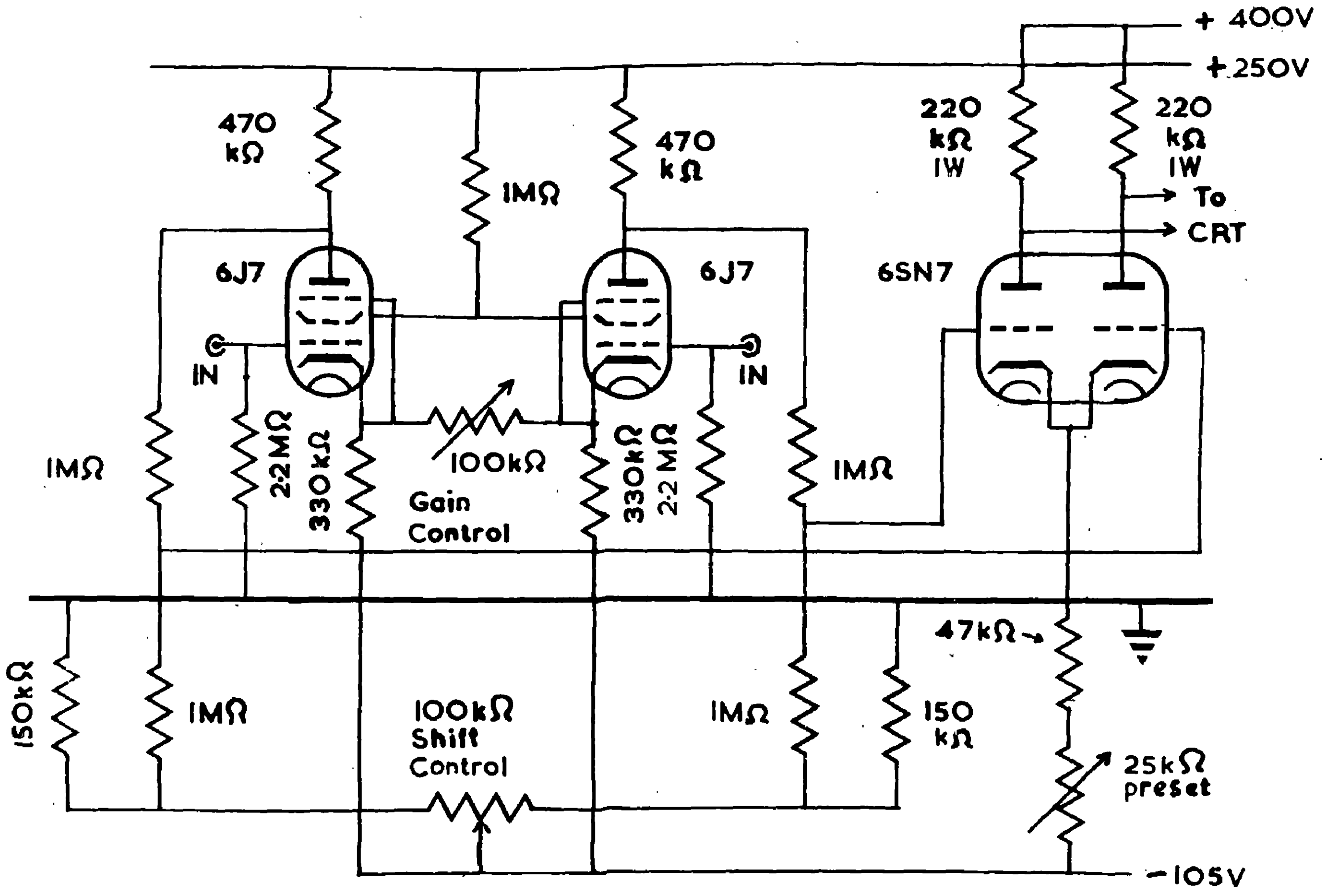


Fig. 6.1. "Main" amplifier for use with cathode-ray tube.

little need be said. When the amplifier was required for use with a cathode-ray tube the circuit used consisted of a pentode stage followed by a triode stage, as shown in Fig. 6.1. This circuit gave a sufficiently large output to give full-screen deflection of either a cathode-ray tube type VCR 97, or a Cossor double-beam tube type 89, with an E.H.T. supply of 2000 volts in each case. When the type 89 tube was used, the signal was taken from one anode only of the double triode, since the double-beam tube does not accept a balanced input.

The main amplifiers are direct-coupled. This is partly so that they can be used with a direct-coupled pre-amplifier when it is necessary to have a recording system direct-coupled throughout, and also because capacitance coupling in these stages would lead to serious "blocking" following large transients. Requirement (e) would not be met if capacitance coupling were used.

A disadvantage of the circuit shown in Fig. 6.1 is that the triode stage receives its input from a high-impedance source. Consequently, the high-frequency response of the amplifier is reduced owing to the input capacitance of the triode stage, which is of the order of 50 pF, owing to Miller effect. An improvement could be made by using pentodes in the output stage so as to

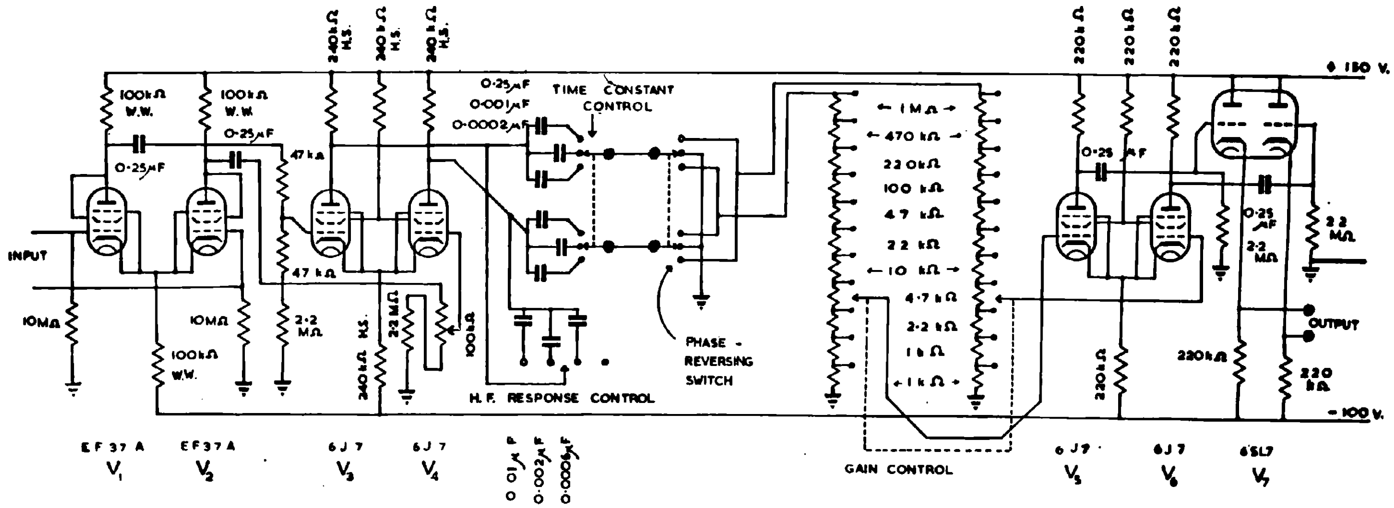


Fig. 6.2. Pre-amplifier circuit. The potentiometer in V_4 grid circuit gives adjustment for in-phase rejection.

reduce its input capacitance. Alternatively, a cathode-follower stage can be interposed between the two stages of amplification. This has in fact been done in the two amplifiers (one for each beam of a double-beam tube) in the display unit which is generally used in the Neurophysiology Laboratory. The circuit as shown, however, has a frequency response which is acceptable for most requirements.

Design of the pre-amplifiers

The pre-amplifiers which have been built are also fairly straightforward in design. The circuit used is shown in Fig. 6.2. There are three stages of push-pull amplification, and an output cathode-follower stage. All of the voltage-amplifying valves are pentodes, but the two in the first stage are connected so that they are effectively triodes. They are connected in this way because triodes are known to have a lower noise level than pentodes.

The valves in the first stage are of type EF 37A, because this type has a low noise level and also low microphony. The two later stages employ valves type 6J7. This is simply because the 6J7 (especially when purchased ex-government) is less expensive than the EF 37A, so is used where the requirements are less stringent than they are in the first stage.

As a further means of reducing the noise level, the resistors in the first stage are all wirewound, because wirewound resistors produce only the thermal agitation noise in accordance with the measurements made by Johnson (1928) and the theory due to Nyquist (1928). They are free from the additional noise ("carbon resistor noise") generated when current flows in a carbon resistor, as discussed by Christensen and Pearson (1936). The resistors used in the second stage are carbon resistors, but are of the "high stability" type. Resistors of this type introduce very much less carbon resistor noise than do carbon composition resistors. The final stage of amplification incorporates ordinary carbon composition resistors.

The first two stages are mounted on a small sub-chassis which is supported by resilient rubber mountings. This form of mounting is used to reduce microphonic effects. The arrangements for controlling gain, etc., all come between the second and third stages. The only control associated with the first two stages is the potentiometer used to balance the amplifier so as to reject in-phase voltage fluctuations at the input. This potentiometer is mounted on the same sub-chassis as the first two stages of amplification.

The coupling capacitors are shown in Fig. 6.2 as 0·25 μF. For most applications in which action potential "spikes" from single nerve or muscle units are recorded, a smaller value could be used for the capacitors - say 0·1 or 0·05 μF. On the other hand, when the signals contain low-frequency components, as in E.E.G., an amplifier with larger coupling capacitors, say 1 μF, is preferable. The amplifier as shown, with 0·25 μF coupling capacitors can, however, be used for E.E.G. without introducing very serious distortion, and represents a good compromise for a general-purpose amplifier. The capacitance values shown in the "H.F. response" and "time constant" controls are also merely typical values. The actual values used are chosen to suit the application of a particular amplifier.

If 1 μF capacitors of the metal-cased "block" type are used as coupling capacitors, the cases must be isolated from earth. Otherwise, the high-frequency response of the amplifier is very poor, owing to the stray capacitance between the plates of the capacitor and

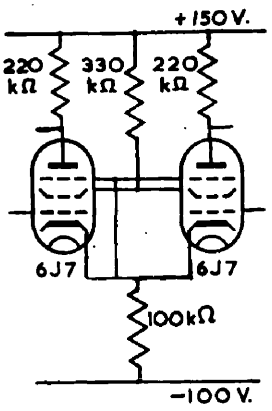


Fig. 6.3. Improved circuit for the second and third stages of the pre-amplifiers.

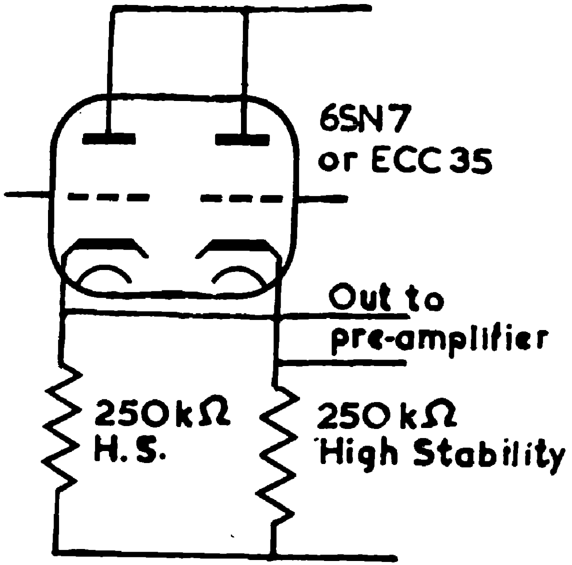


Fig. 6.4. Cathode follower unit.

the case. It has been found that when the capacitor cases are earthed, the high-frequency response of the amplifier is substantially level only to about 2 kc/s. With the cases isolated from earth, it is substantially level to about 10 kc/s. In fact, the high-frequency response of this amplifier circuit is rather poor however it is constructed, because the anodes of the pentode valves operate at a very high impedance, and therefore the high-frequency response is seriously impaired by only a small amount of stray capacitance. Nevertheless, the frequency-response has proved sufficient for the investigations mentioned.

The gain of the amplifier is about 10^4. This is rather less than might be expected from a triode stage and two pentode stages, and in fact a higher value for the overall gain can be obtained by redesigning the pentode stages as shown in Fig. 6.3. The overall gain is then about 10^5. However, most of the pre-amplifiers in the Department have not been modified to make the pentode stages similar to Fig. 6.3, because there is a tendency to oscillation when the higher gain is achieved, and the supply lines must be decoupled to earth at the amplifier, with 1 μF capacitors. The circuit of Fig. 6.2, on the other hand, has never shown any tendency to oscillate.

Design of a cathode-follower unit

The grid current of the first stage of the pre-amplifier is low, since EF 37A valves are very good in this respect, and are suitably biassed in the circuit used. The pre-amplifier has rather high input-capacitance, due to Miller effect, but there is little point in trying to reduce this since the amplifier is usually some distance from the preparation and connected to it by a screened cable which introduces a large amount of capacitance to earth anyhow. Whenever it is important to have a really high impedance connected to the electrodes, a cathode-follower unit, having the circuit shown in Fig. 6.4, is mounted close to the preparation, and the pre-amplifier receives the signal via a screened cable from the output of the cathode-follower unit.

General considerations

The power supplies to the pre-amplifiers and cathode-follower unit must be free of 50 c/s ripple and other fluctuations. The 6-volt heater supply has always been obtained from accumulators, and the + 150 and - 100 volt supplies have been obtained either from dry batteries or from a specially-designed power supply unit which will be described in Part 8.

It is clear from the foregoing that the amplifiers described can be improved upon. The pre-amplifiers in particular, in their present form, do not make full use of the amplification which can be obtained from the pentode valves, and have a high-frequency response which is poorer than is desirable.

Furthermore, the rejection of in-phase voltage fluctuations at the input depends on the adjustment of a balancing control. The adjustment ought to be repeated at intervals to compensate for changes in valve characteristics as the valves age. Recent work on differential-amplifier design has indicated that it should be possible to design an amplifier to have good in-phase rejection without the need for adjustment (Offner, 1947; Andrew, 1955; Klein, 1955).

The amplifiers have, however, been described in some detail because their limitations have not proved serious in use, and they have made possible the work which has been carried out in the Neurophysiology Laboratory. They also provide a basis for future development. Because the amplifiers satisfied the immediate requirements when they were built, there has been no great urgency attached to the development of better designs. There has therefore been time to consider different aspects of the problem. Attention has been given to the problem of achieving good rejection of in-phase voltage fluctuations, or in other words to making a good differential amplifier or difference-amplifier. Work has also been done on the design of an amplifier to have very high input impedance, as is necessary for work with micro-electrodes.

The Design of Difference-Amplifiers

Amplifiers for biological use almost always have two input connections, and the effects which are of interest appear as fluctuations of the difference in potential between these two leads. Unwanted fluctuations such as 50 c/s interference are usually similar in the two leads, so it is highly desirable that the amplifier should respond strictly to the difference between the potentials, and be little affected by fluctuations which are the same in both leads (termed in-phase fluctuations). In other words, a biological amplifier is required to be a good differential amplifier, or difference-amplifier. (The term "differential amplifier" is the more commonly used of the two, but "difference-amplifier" should perhaps be preferred. The word "differential" is ambiguous since it suggests differentiation in the sense of

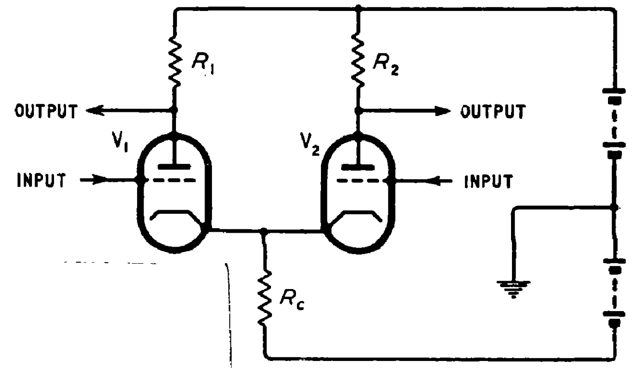


Fig. ~~6.15.~~ 6.5 Usual arrangement of the first stage of a biological amplifier.

the differential calculus, which is not what is intended in the present connection).

The first stage of a biological amplifier is usually of the form shown in Fig. 6.5, where the input is applied to the two grids and outputs are taken from the two anodes. In-phase fluctuations are not amplified greatly because of the degeneration (negative feedback) due to the cathode resistor R_c. For an anti-phase or balanced push-pull signal the resistor R_c does not introduce degeneration, since there is little variation in the total current through it (since, when one valve passes more current, the other passes less current).

The need for a balancing control

The resistor R_c may be replaced by a pentode valve (Johnson, 1947) or some other arrangement having high differential resistance. In the limiting case where R_c is replaced by a true constant-current device (differential resistance infinite) there can be no fluctuations in the total current through the valves. In this case, in-phase voltage fluctuations can have no effect whatever on the outputs if the circuit is completely symmetrical.

In practice, however, the circuit will not be strictly symmetrical since there will be differences between the characteristics of the two valves.

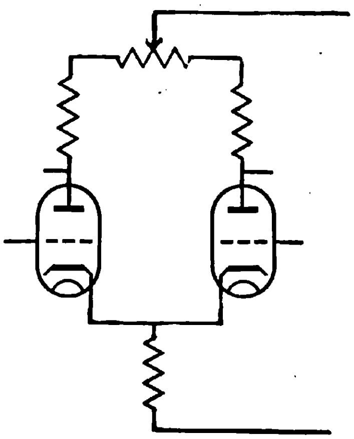


Fig. 6.6. Common type of balancing control.

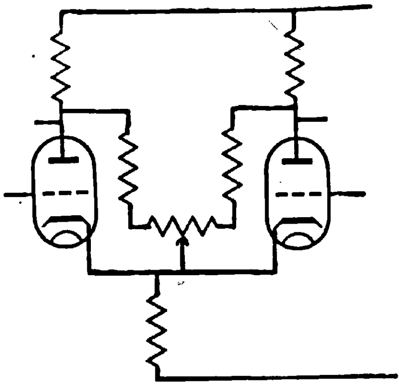


Fig. 6.7. Balancing control due to Parnum.

Fig. 6.8. (Below). Balancing control of Ediswan E.E.G..

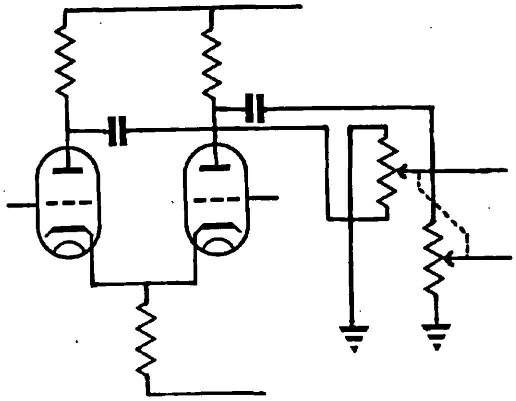
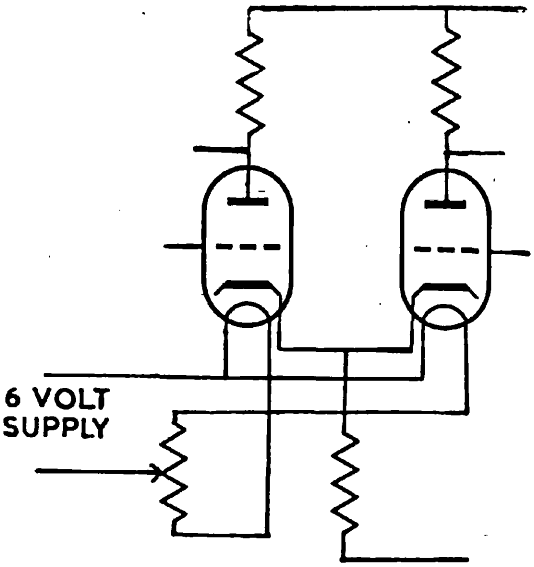


Fig. 6.9. (Below). Balancing control due to Aitchison.



Parnum (1950) has shown that when there is a difference between the values of the "amplification factor" μ of the two valves, an in-phase input to the stage can produce an anti-phase output. This is true, even when the resistor R_c is replaced by a perfect constant-current device. Unless something is done to eliminate the effects of the unbalance, the amplifier output will be affected by in-phase signals at the input.

Frequently the amplifier incorporates some form of balancing control which can be adjusted to compensate for the assymetry introduced by valves and other components. Fig. 6.6 shows a form of adjustment which is often used. Parnum suggests the arrangement of Fig. 6.7. An adjustment of the kind shown in Fig. 6.8 is used in the Ediswan electroencephalograph, and, in a modified form, in the pre-amplifier already described herein (Fig. 6.2). Aitchison (1955) finds that if the D.C. conditions of the two valves are equallised by an adjustment of the heater voltages as shown in Fig. 6.9, the valves are automatically close to symmetry in all important respects. Attree (1953) has described a differential input-stage of a different type, also incorporating a balancing control. The amplifier described by Johnson (1947) does not include a balancing control, but Parnum (1950) has shown that

Johnson's amplifier cannot be relied upon to give really good rejection of in-phase signals.

If an amplifier could be built which could be relied upon to give good rejection of in-phase signals without the need for a balancing adjustment, there would be other advantages besides that of convenience. The amplifier would show good in-phase rejection at all times, whereas amplifiers which require adjustment can drift out of adjustment during use, owing to changes in valve characteristics. Also, in an amplifier which does not require adjustment, the in-phase rejection should remain good, even when the in-phase fluctuations are large enough to drive the valves onto parts of their characteristic curves where the values of the valve "constants" are different from normal. Attree (1953) has drawn attention to the fact that many difference-amplifiers have much poorer in-phase rejection for large than for small in-phase fluctuations. The in-phase rejection of an amplifier which does not require a balancing adjustment should be less readily impaired by large fluctuations than is that of a conventional amplifier.

The theories of Offner and Parnum

It might be supposed, from the fact that most of the published circuits incorporate a balancing control, that good rejection of in-phase voltages can only be obtained when a balancing control is incorporated. On the other hand, theory put forward by Offner (1947) indicates that when in-phase negative-feedback is applied to an amplifier, it should be possible, by the application of sufficient feedback, to make the amplifier reject in-phase voltages to any desired degree.

In the circuit of Fig. 6.5, the cathode resistor R_c causes in-phase negative feedback to be applied to the stage. If Offner's theory were applicable, it would be possible to make the in-phase rejection as near to perfect as desired, simply by increasing the value of R_c sufficiently (or by sufficiently increasing the differential resistance of a valve circuit used in place of R_c). It should be possible to obtain good in-phase rejection in this way, even when the two valves had different characteristics.

On the other hand, Parnum has shown, by a full analysis of the circuit of Fig. 6.5, that even when R_c is effectively infinite, the rejection is not perfect unless the value of the amplification factor μ is the same for each of the two valves.

There is a discrepancy between Parnum's result and the apparent consequences of Offner's theory. The explanation of the discrepancy is that Offner's results are not applicable to the circuit of Fig. 6.5. It is of interest to examine the reason why Offner's theory is not applicable, and to try to find ways of modifying the circuit so that the theory becomes applicable. This has been done and the conclusions published (Andrew, 1955).

The reason Offner's theory is not applicable to the circuit of Fig. 6.5 is as follows. The variations in cathode potential due to the inclusion of R_c produce a change in the grid-to-cathode potential-difference of each valve, and also a change in the anode-to-cathode potential-difference. When R_c is regarded as introducing in-phase negative feedback, only its effect on the grid-to-cathode potential-difference is being taken into consideration. The application of Offner's theory therefore produces an incorrect result.

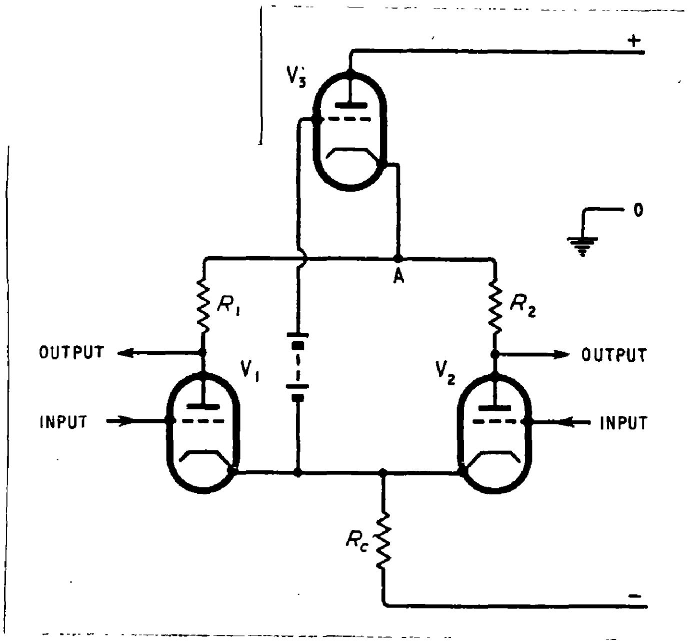


Fig. 6.10. Modification of the circuit of Fig. 6.5 by the addition of a cathode-follower.

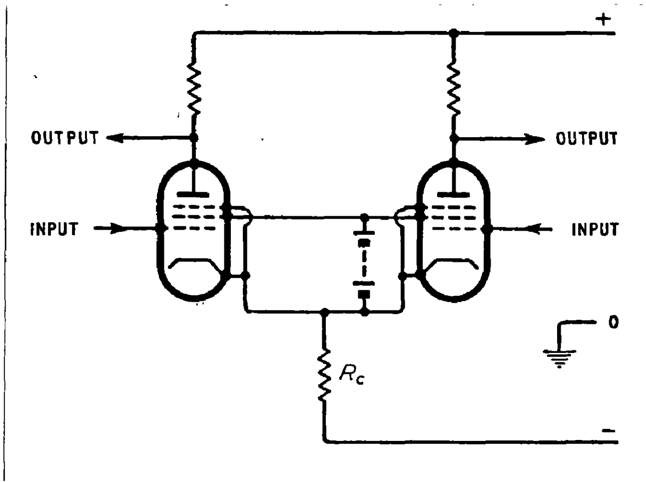


Fig. 6.11. Modification of Fig. 6.5 by suitable use of pentodes.

Circuits with no balancing control

Three modifications of the circuit of Fig. 6.5 can be made so that Offner's theory becomes applicable, or nearly applicable. The three modified circuits are shown in Figs. 6.10, 6.11 and 6.12. When R_c is made effectively infinite, each modified circuit provides a way of obtaining good in-phase rejection without the need for a balancing control.

The circuit of Fig. 6.10 shows one way in which it is possible to ensure that voltage fluctuations at the cathode do not affect the anode-to-cathode voltage. In the ideal case where the cathode-follower has unity gain, the fluctuations in potential of point A are the same as those of the cathode. In this case, if it is further assumed that R_c is effectively infinite, the circuit is completely insensitive to in-phase fluctuations at the input, if the output voltages are measured relative to point A. When the output voltages are measured relative to earth, rather than to point A, the in-phase fluctuations at the input produce in-phase fluctuations of equal magnitude at the output; they do not, however, produce anti-phase voltages at the output. Hence, although the circuit is not entirely unaffected by in-phase components of the input fluctuations, it does

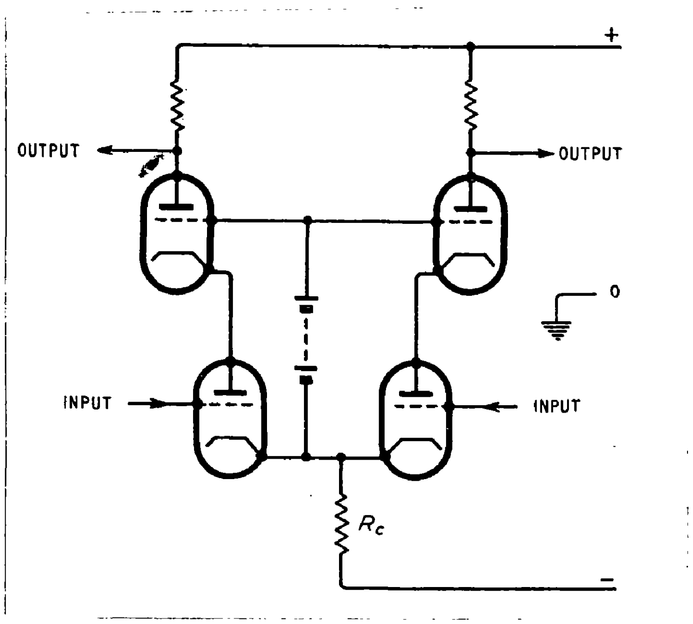


Fig. 6.12. Modification of Fig. 6.5 by the use of cascode pairs.

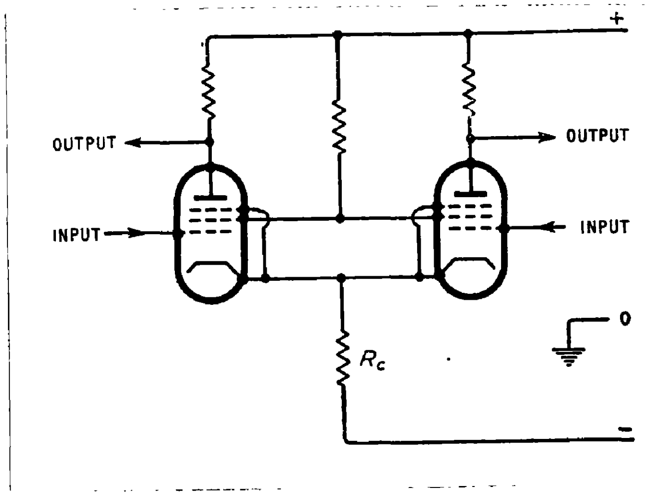


Fig. 6.13. Input stage using pentodes, but which does not have the desirable properties of Fig. 6.11.

not amplify them, and does not allow them to produce anti-phase components in the output.

In the circuit of Fig. 6.11, the variations in cathode potential still affect the anode-to-cathode voltages, but since the valves are pentodes, the variations in anode-to-cathode voltage have little effect on anode current. The anode currents would be much more readily affected by variations in the screen-grid-to-cathode voltage, but this is kept constant by the battery.

This circuit has been tried out and compared with other circuit arrangements, and has been found to give much better rejection of in-phase signals than do either the circuit of Fig. 6.5 or the circuit of Fig. 6.13, using the same valves. The results of the tests on these circuits are described in full in the published paper (Andrew, 1955) of which a copy is included in the appendix of this thesis.

The circuit of Fig. 6.12 uses pairs of triodes in cascode connection instead of the pentodes of Fig. 6.11. A cascode pair is similar to a pentode in that the anode current is very little affected by variations in the total anode-to-cathode voltage (i.e. the potential difference between the anode of the upper valve of a pair, and the cathode of the lower valve).

The circuits of Figs. 6.10 and 6.12 have not been tried experimentally by me; they have only been considered theoretically. Shortly after my paper (Andrew, 1955) was published, I learned that another paper on difference-amplifiers had been written by Dr. G. Klein of Philips Research Laboratories, Eindhoven, Netherlands. This paper (Klein, 1955) was in the press at the time mine was published. It has turned out that the circuits of Figs. 6.11 and 6.12 were devised independently by both Dr. Klein and myself. Dr. Klein has tried out both of these circuits experimentally, and has confirmed that by their use it is possible to achieve good in-phase rejection without the need for a balancing control. He has also devised a further modification of these circuits which eliminates the need for a battery.

A practical difficulty

There is a practical difficulty in achieving an extremely high differential resistance in place of R_C in these circuits. There is no difficulty in designing a valve circuit, consisting of a constant-current pentode or a pair of triodes in cascode connection, to have a differential resistance of 10 or 20 megohms or more. Unfortunately, in practice this high differential resistance is shunted by the heater-cathode leakage and heater-cathode capacitance of the two amplifying valves. In the tests I made of the circuit of Fig. 6.11, the effects of heater-cathode leakage and capacitance were avoided by using a well-insulated battery to supply the heater current. Klein does not appear to have taken any special precautions to overcome the effect of heater-cathode leakage; he quotes the remarkably high value of 60 megohms as being the lowest value of heater-cathode insulation (measured while the valve was heated by a 6-volt supply) found in a large number of valves tested. The valves used by Klein thus appear to have been exceptionally good in this respect.

Future developments

In spite of Klein's data on heater-cathode leakage, it would probably be best not to rely on having such good insulation as this between heater and cathode. In any case, even if the insulation were perfect, capacitance would still be present, and therefore the high impedance in the cathode circuit would be shunted at high frequencies. Klein found that the in-phase rejection of his circuits deteriorated at high frequencies, probably for this reason.

It should be possible to avoid the need for a very high impedance in the cathode circuit by applying feedback from a later stage of amplification, instead of relying on the large differential resistance in the cathode circuit to provide the necessary feedback.

It seems possible a circuit could be devised, as a development of the circuit of Fig. 6.10, in which the feedback would be applied from a later stage instead of by R_c, and would be applied to the anode circuit as well as to the cathode circuit. (The application of the feedback also to the anode circuit would be equivalent to what is done by the battery and cathode-follower in Fig. 6.10.) There is also a way in which the circuit might be made to reject in-phase signals completely, unlike the circuit of Fig. 6.10, which allows in-phase signals to pass through to its output, though without amplifying them or unbalancing them. I hope to do further work on this very soon, and it seems possible the present approach may lead to a complete solution of the problem of how to design a practical difference-amplifier with no need for a balancing adjustment.

Achieving High Input-Impedance

In most applications of electronic amplification in neurophysiology, the amplifier is connected to the biological preparation by electrodes. It is desirable that the current passing through the electrodes should be kept to a very low value, especially when micro-electrodes are used. If the micro-electrode is of the micro-pipette type (as distinct from types having a metallic conductor inside), its resistance may be as high as 100 megohms. An amplifier which receives its input through a resistance of this magnitude must pass very little grid current, and must have an extremely high input-impedance over the whole range of signal frequency which is of interest.

To keep the grid current low, the input valve must be suitably chosen. Electrometer valves can be used, but they are expensive, so it is usual to employ other types which have been found to be suitable. Acorn valves have been found to have very small grid current when used under suitable conditions (Nielsen, 1946) and high-impedance input stages for amplifiers, using acorn valves, have been described by Graham, Harkness and Thode (1947), Bishop (1949b) and Harris (1951).

Nielsen has shown that, for a given anode voltage, the lowest grid currents obtainable with acorn valves are obtained by using a pentode acorn valve and using the third grid (g_3) as the control grid. Graham, Harkness and Thode, as well as Harris, use the third grid as the control grid, but Bishop uses the first grid (g_1). Bishop prefers to use g_1 as the control grid because when so doing he can use the valve as a cathode follower, and this is not possible when g_3 is used as the control grid. Using the valve as a cathode follower has several advantages. The input capacitance of the valve itself is greatly reduced when it is used as a cathode follower, and furthermore it is possible to reduce the effective capacitance of a screened lead connecting the amplifier to the preparation, by connecting the screening to the cathode of the cathode follower, as described by Attree (1949a). Also, in a cathode-follower stage, the fluctuations in grid potential which constitute the signal do not cause much variation in the grid-to-cathode voltage, so this voltage can be held at a value which gives low grid current.

The use of a cathode-follower circuit is a simple way of aplying negative feedback to the first stage of amplification. All the advantages listed above for the cathode-follower circuit can also be obtained by applying negative feedback in other ways. It is possible to devise circuits in which this is done and in which g_3 of a pentode acorn valve is used as the control grid. The arrangement described by Harris is an example of a circuit in which the first-stage valve is an acorn pentode with g_3 used as the control grid, and negative feedback applied.

Harris's circuit, however, is not suitable for recording action potentials in neurophysiological work, because its high-frequency response is deliberately cut down by the insertion of capacitors in order to achieve stability of the feedback loop. Also, the circuit requires the biological preparation to be "floating" since the negative feedback is applied via the indifferent electrode. In neurophysiological experiments it is not always possible to have the preparation "floating" (that is to say, isolated electrically from earth).

In the amplifier described by Graham, Harkness and Thode, negative feedback is applied to the low-impedance end of the input grid-leak resistor. This is roughly equivalent to applying it to the indifferent electrode in the case of an amplifier connected to a biological preparation.

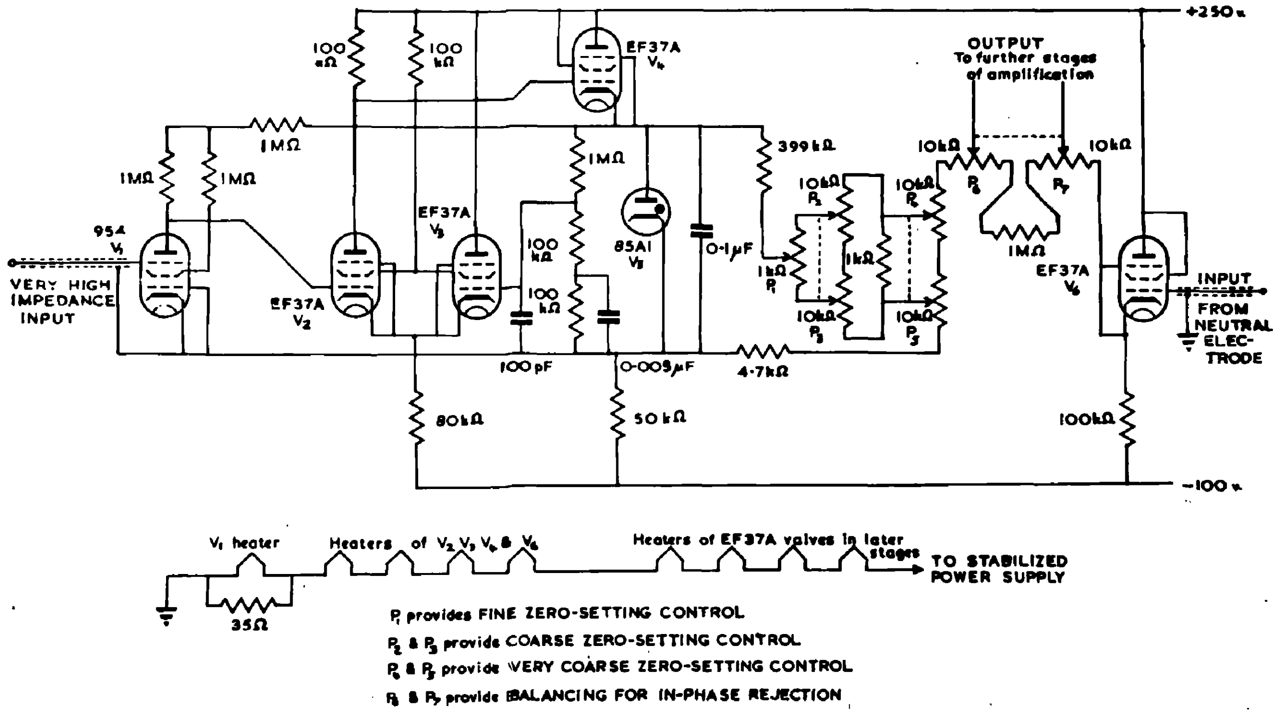


Fig. 6.14. Amplifier having extremely high input-impedance.

An attempt has therefore been made to develop an amplifier having good high-frequency response, which uses an acorn pentode type 954 as the first-stage valve, with g_3 as the control grid, and with negative feedback applied in a way which does not necessitate a "floating" preparation. The voltage fed back can be applied also to the screening of the input lead, so as to obtain low input-capacitance in a manner similar to that described by Attree (1949a). In this way it is hoped to obtain an extremely low value of input-capacitance for the amplifier. If further reduction of the capacitance proves necessary, a negative-capacitance circuit of the kind described by Attree (1949b) could be added.

Practical circuit

The circuit which has been tried is shown in Fig. 6.14. V_1 is the first-stage valve, and is an acorn pentode type 954, with g_3 used as the control grid. This stage obtains its H.T. supply from the 85 volts developed across the stabilizer tube V_5. The whole system containing V_1 and V_5 can be raised and lowered in potential by the signal applied to the grid of the cathode-follower V_4.

V_2 and V_3 provide a second stage of amplification,

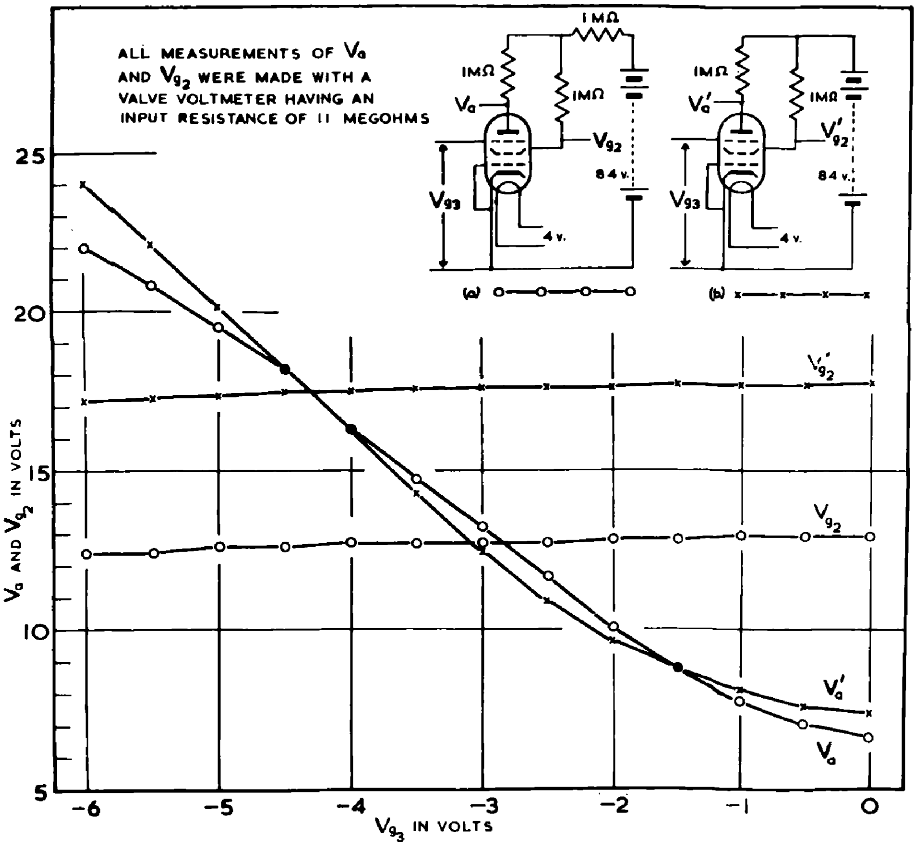


Fig. 6.15. Characteristics of two types of amplifier circuit using a 954 pentode.

and the output from V_2 anode is applied to the cathode-follower V_4. Hence the fluctuations in potential at the anode of V_2 are applied to the first stage of the amplifier, and this provides the required negative feedback.

The output from this part of the amplifier is taken from a rather elaborate potential-dividing network (to provide the zero-setting adjustments) connected across the 85A1 stabilizer tube V_5. The network of potentiometers and resistors is designed to give independent adjustments of in-phase rejection, and zero-setting. The acorn input tube, V_1 and its input lead are enclosed in a metal screen which is connected to the line which is common to the cathodes of V_1 and V_5.

In use, the input lead which goes to the third grid of V_1 would be connected to a micro-electrode. There would generally be an indifferent electrode placed near the micro-electrode. This electrode would be connected to the simple cathode-follower V_6.

Although the acorn valve in Fig. 6.14 is run from an H.T. supply of 85 volts, the voltages on its electrodes are quite low. Fig. 6.15 shows, in the curves applicable to circuit (a), the variations of anode and g_2 voltages with variation of g_3 voltage, for a 954 acorn valve connected to an 84 volt supply through megohm resistors in the way V_1 is connected in Fig. 6.14. These curves are drawn for one particular valve; there is a great deal of variation from valve to valve. In the circuit of Fig. 6.14, it is necessary to insert different 954 valves until one is found which develops 3 or 4 volts bias. Some samples of this type of valve develop only 0·6 volts bias in this circuit, and it is unlikely that the grid current is particularly low with only this amount of bias.

The circuit of Fig. 6.14 was designed on the assumption that the characteristics of the acorn valve V_1 would conform to Fig. 6.15. The circuit was designed to bring the anode voltage of the acorn valve to about 13 volts, which is also the voltage of g_2 according to the curve shown in Fig. 6.15. This is a higher anode- and g_2-voltage than was used by Nielsen, who used voltages from 3·8 to 7·4. However, Harris has found that electrode voltages somewhat higher than those used by Nielsen are permissible. Harris states "Using g_3 injection and 30 k-ohm anode load and 4·5v cathode bias, the anode current at 20v H.T. was 110 µA and the stage gain 0·7. These potentials are higher than those recommended by Nielsen, but the grid current was certainly not more than 10^{-13} amp."

In my circuit, the electrode voltages are lower than those used by Harris, and the anode current is much lower than his. Hence the grid current should not be greater than the value he found. It can be seen from Fig. 6.15 that my circuit, owing to the use of high resistance values, has a stage gain of 3 or 4, compared to 0·7 obtained by Harris.

The network of resistors and capacitors in the grid circuit of V_3 (Fig. 6.14) was needed to avoid high-frequency oscillation of the circuit. The network was found by trial and error.

The experimental amplifier which was built according to the circuit of Fig. 6.14 has never been entirely satisfactory, and further work on it is needed. It had an extremely high noise level. The source of the noise has not been tracked down, and it is possible that one of the wirewound resistors is faulty. Work on the circuit was laid aside because of pressure of other work, but it will be resumed, especially since the micro-pippette type of micro-electrode may be required in future work on the frog optic lobes (see Part 2).

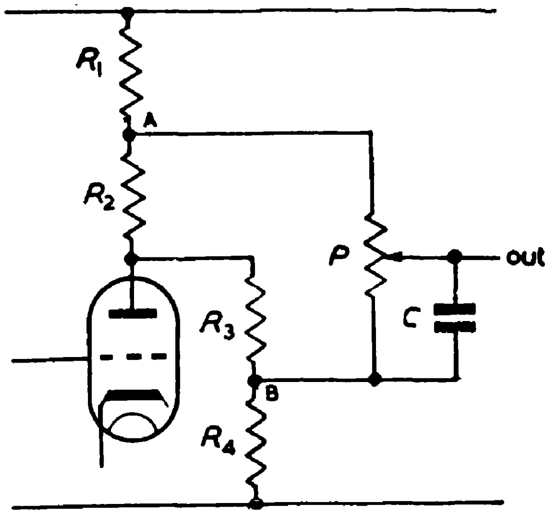


Fig. 6.16. Stage of amplification incorporating shift control with no effect on gain.

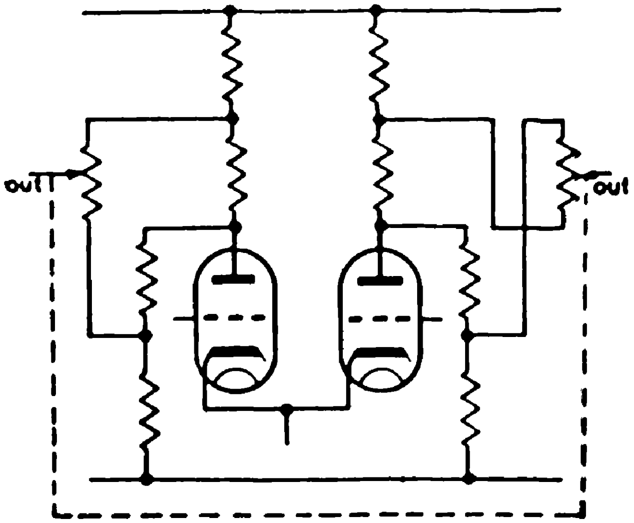


Fig. 6.17. Push-pull stage incorporating shift control with no effect on gain.

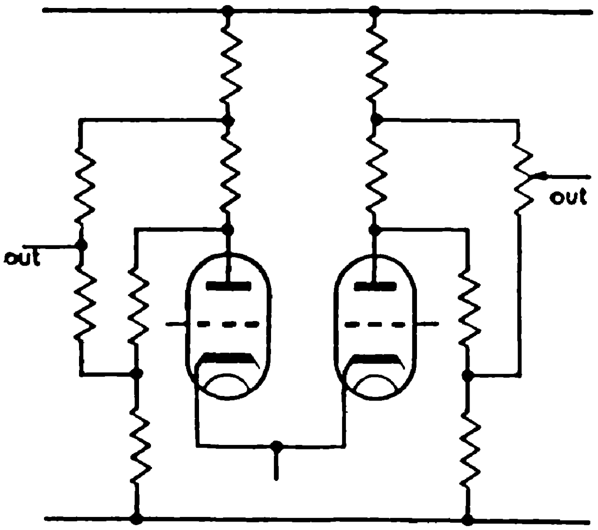


Fig. 6.18. Alternative push-pull stage incorporating shift control with no effect on gain.

A Shift Control with no Effect on Gain

In designing direct-coupled amplifiers, it is frequently necessary to provide a control which will shift the D.C. level of the output of the amplifier, and it is desitable that adjustment of this control should not affect the gain. To achieve this result, I have frequently made use of a principle which does not seem to be widely known, and may be novel. An account of it has been published (Andrew, 1956). The principle has not been used in any of the amplifier circuits discussed hitherto; it was, however, used in an earlier design of "main" amplifier, which was superseded by the circuit shown in Fig. 6.1.

The way in which the shift control can be introduced into the circuit so as to have no effect on gain is shown in Fig. 6.16, where the following relation holds among the resistance values :-

$$R_1/R_2 = R_4/R_3 \qquad (1)$$

but it is not necessary that $R_1 = R_4$ nor that $R_2 = R_3$. The output is connected to a valve grid, so is not appreciably loaded.

To show that there is no change in gain when potentiometer P is adjusted, suppose first that potentiometer P and capacitor C are omitted. Then since equation (1) holds, the fluctuations in potential of point A due to the signal on the valve anode are equal to the fluctuations in potential of point B. So far as the fluctuations are concerned, therefore, Thévenin's theorem shows that the potentiometer is, in effect, connected to a generator of zero e.m.f.. Hence, no fluctuating current flows in the potentiometer. There is, however, a steady potential difference between its ends. The potentiometer therefore provides a shift control with no effect on gain.

If P has a high resistance value, it may be advantageous to include the capacitor C to ensure that the high-frequency response is not unduly impaired by stray capacitance when the wiper of P is not near one end.

The circuit can be used with a cathode-follower instead of with a conventional stage as in Fig. 6.16, and it is not necessary for R_1 and R_4 to go to the H.T. line and to earth; they may go to any two fixed potentials, so long as suitable operating conditions are provided for the valve. In the form in which it is used with a cathode-follower, the circuit is used in the pulse-interval meter (Andrew and Roberts, 1954; the circuit appears in Fig. 5, between V_{23} and V_{24}).

The principle can be applied to push-pull circuits, either by the use of a ganged potentiometer as in Fig. 6.17, or by making the adjustment on one side only, as in Fig. 6.18.

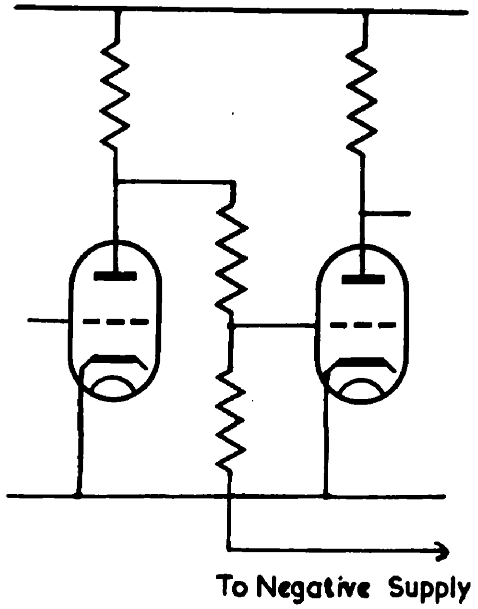


Fig. 6.19. Method of coupling used in D.C. amplifiers.

The Use of Gas-Discharge Tubes for Coupling in D.C. Amplifiers

In successive stages of D.C. amplification it is convenient to have the cathodes of the valves at about the same potential. When the cathodes are at much the same potential, however, the anode of one stage cannot be connected directly to the grid of the following stage, for this would make the second grid positive with respect to its cathode. Some form of interstage coupling must be employed, such that the fluctuations in potential at the anode produce corresponding fluctuations at the following grid, but the mean potential of the grid must be considerably more negative than the mean potential of the anode. Where a negative supply line is available, the interstage coupling can be by a simple pair of resistors as shown in Fig. 6.19. The fluctuations at the grid are then smaller than the fluctuations at the anode; some of the gain of the amplifying stages is lost in the interstage couplings.

The loss of gain in the interstage couplings can be reduced by replacing the lower resistor with a device having high differential-resistance, or by replacing the upper resistor with a device having low differential-resistance, or by doing both of these. The first possibility, that of replacing the lower resistance with a device of high differential-resistance, has been described by Bishop (1949a), who used a constant-current pentode in this position. The second possibility has also been employed, notably by Miller (1941) who used a gas-filled stabilizer tube in place of the upper resistor in the interstage coupling arrangement.

A remarkable feature of Miller's use of gasfilled tubes is that he uses them with a current of only a few microamperes passing through them, although the manufacturer's data on the tubes states that the minimum current for stable operation is 5 mA. Graham, Harkness and Thode (1947) amd Harris (1951) also use stabilizer tubes in the interstage couplings of their D.C. amplifiers, and use them in such a way that they pass only a minute current.

There is a large discrepancy between the current of 5 mA stated by the tube manufacturers to be necessary for stable operation, and the much smaller amount of current found by Miller, and by Graham, Harkness and Thode, and by Harris, to be sufficient.

An explanation of the discrepancy, with some experimental evidence in support of it, has been put forward by me (Andrew, 1953b). The explanation is fairly obvious when the phenomena of the direct-current gas discharge, as described by Shelton and Wade (1953) are considered.

When the tubes are operated at the low currents of 10 or 20 µA used by Miller, the discharge which occurs is presumably what is termed a corona discharge. Larger currents, in excess of 5 mA, produce another type of discharge, termed a cathode-glow discharge. A substantially constant voltage over a range of current values can result from either type of discharge, but if this explanation is correct there will be a range of current somewhere between 20 µA and 5 mA over which the voltage falls sharply with increasing current.

I have made a few tests on stabilizer tubes which tend to support these conclusions. Some tests were made with VR 105 tubes since these have been used in D.C. amplifiers by Graham, Harkness and Thode and by Harris. A used tube of this type, of American manufacture, had the expected characteristics. The voltage across it was approximately the ignition voltage from zero current to about 0·3 mA. At this current a bright spot appeared on the cathode (at lower currents a faint glow was seen near the anode) and the voltage fell to a value in the region of the normal running voltage.

On the other hand, two new tubes type VR 105, of British manufacture, were found to have an ignition voltage very close to the running voltage, and no abrupt voltage change was observed between zero current and the normal operating current. In these tubes it was not possible to observe the discharge as the mica end plates were not sufficiently transparent.

The expected behaviour was shown very clearly by tubes type 7475, in which the critical current for the change from corona to cathode-glow discharge was about 10 μA. These observations are of value for the design of D.C. amplifiers for they show that, although very small currents produce stable behaviour of the tubes, and so do much larger currents, there is an intermediate range of currents which must be avoided.

PART 7

STIMULATOR REQUIREMENTS AND DESIGN

PART 7. STIMULATOR REQUIREMENTS AND DESIGN

In most neurophysiological experiments, some form of stimulation is employed, and the response of the preparation to the stimulus is examined and usually recorded. The stimulus may be mechanical, as in the work of Boyd and Roberts (1953) on proprioceptors in the knee-joint, or it may be visual, as in the work on the frog optic lobes described in Part 2 of this thesis. In many cases, electrical stimulation of a nerve is required, as for instance in the experiments on accommodation of nerves reported in Part 1(b) of this thesis, or the experiments of Garry and Gillespie (1955, also Gillespie, 1955) on the innervation of the colon, or the work of Brown (1954), which will be discussed later.

Stimulator Requirements

In neurophysiological experiments involving electrical stimulation of nerve, it is usual to stimulate with brief pulses of current, having a duration of one millisecond or less. (The word "brief" is of course relative. In physiology a millisecond is regarded as a brief space of time, though in other fields of science electrical pulses of one microsecond duration are common and millimicrosecond pulses are coming into use.)

There are two reasons for the use of brief pulses. The first is that they stimulate with less power than do longer pulses, according to the theory discussed in Part 1(a). More important in many experiments is the fact that when the stimulus is brief, the moment of nerve excitation is accurately determined, so measurements can be made of conduction times in nerves, or of the latency of any activity resulting from the stimulation.

Rectangular pulses are commonly used for stimulation, since they are easily generated and have been shown by Offner (1946) to be a fairly efficient form of stimulus when of optimum duration, as discussed in Part 1(a).

Stimulating pulses of fairly long duration may be required when the properties of nerve or muscle are to be investigated by electrical stimulation. The exponential stimulator, whose use was described in Part 1(b), provides pulses of 3 seconds duration, with a special waveform required for investigation of the property of "accommodation" in nerve. For the determination of the rheobase and chronaxie of a nerve or muscle it is necessary to apply rectangular pulses of various durations, as discussed by Walter and Ritchie (1945). For this purpose, pulses of up to 100 msec duration are needed.

A stimulator for use in neurophysiology will generally be made so that it can be set to give pulses of any duration within a certain range. The facility of a variable pulse-duration allows the possibility of preferentially stimulating one group of fibres in a mixed nerve, by using pulses of the duration which is optimum for that group. It also permits the study of some properties of the nerve, as mentioned above. The shortest pulse-duration likely to be wanted is about 10 or 20 μsec, and the longest (for rectangular pulses) about 100 msec.

Pulse-amplitude

The amplitude of the stimulating pulses delivered by a stimulator must be variable, since widely differing values are required under different experimental conditions. The experimental results presented in Part 1(b) of this thesis show that under suitable conditions an excised nerve may be stimulated with currents of less than 50 μA, or voltages of less than 100 mV. Under other experimental conditions, however, the stimulator may be required to deliver as much as 10 or 20 mA at 60 volts. The stimulation of human nerve or muscle through the skin may require a stimulus as powerful as this, at the shorter pulse-durations.

Output impedance

Usually the current supplied by the stimulator will pass through other tissue besides the nerve it is required to stimulate. The strength of the stimulus reaching the nerve will depend on the amount of resistance in series with the stimulator, and on the extent to which the nerve is shunted by parallel current-paths through tissue or fluid. These conditions are unlikely to be the same from experiment to experiment, or even from minute to minute, so it is desirable that the current reaching the nerve should be as little dependent on them as possible.

This last consideration determines whether a high-impedance or a low-impedance output from the stimulator is preferable. A low-impedance output is best where the main source of variability is shunting of the stimulating circuit. Thus, when using an electrode of the kind described by Garry and Wishart (1951), it is probably best to use a low-impedance stimulator in the case where a blood-vessel is drawn through the membrane along with the nerve, but a high-impedance stimulator might give more consistent results in the case where a clean nerve is drawn through a very small hole in the membrane.

A high-impedance stimulator will be the best when there is a high and unpredictable resistance in series with the stimulator output. A high-impedance stimulator can be expected to give more consistent results than would a low-impedance stimulator when stimulating human nerves through the skin, since in this case the resistance of the skin is directly in series with the stimulator. For this reason the exponential stimulator was made to have an extremely high output-impedance.

There is one disadvantage associated with the use of a high-impedance stimulator for stimulating through the skin. If the electrodes do not make good contact with the skin, the stimulator develops a large voltage and the skin may actually be burned under the electrodes. Stimulators used for clinical purposes therefore generally have a low-impedance output.

The influence of the output-impedance of the stimulator on the effect produced by the stimulus is actually rather more complicated than has been indicated above. The impedances which shunt the stimulating current, and those which come in series with the stimulator, are not purely resistive, but have a capacitive component also. Consequently, they affect the waveform as well as the amplitude of the stimulus reaching the nerve, and in the foregoing discussion only the effect on the amplitude was discussed. The conclusions reached are probably correct nevertheless.

Stimulators are more commonly built to have low output-impedance than high. This is partly because it is much easier to design a low-impedance stimulator whose output is continuously variable from zero volts, than it is to design a high-impedance stimulator with similar control of output current.

Polarity of output

The output of a stimulator is delivered at two terminals, for connection to the preparation. Usually, one of the terminals is earthed. If a nerve is stimulated *in situ* in the body, stimulation generally takes place near the electrode which is not earthed, since it is usually in the neighbourhood of this electrode that the current-density in the tissue is greatest. It is best, under these conditions of stimulation, to let the non-earthed electrode be the one which goes <u>negative</u> during the stimulating pulse, since nerves are more readily stimulated by a cathodal than by an anodal electrode.

On the other hand, if the requirement is the stimulation of excised nerve, or nerve of which a part has been dissected free, it is often preferable to let the non-earthed electrode be the one which goes <u>positive</u> during the stimulus. When using a rubber membrane electrode of the kind described by Garry and Wishart (1951), the nerve is in contact with fluid inside the chamber and with fluid outside. It is clearly convenient to have the outside fluid earthed, but it is also desirable that the outside fluid should make the cathodal connection to the nerve. If the inside fluid made the cathodal connection it is possible that nerve impulses initiated by cathodal stimulation inside the chamber might be stopped by "anodal block" just outside the chamber. With this type of electrode, then, the earthed connection should be the cathodal one, so the non-earthed electrode must go <u>positive</u> during the stimulus. Similar considerations apply when an excised nerve is stimulated in a nerve chamber for the measurement of its conduction velocity; the stimulating electrode which is nearer the recording electrodes should be the cathodal one, to ensure that the nerve impulses do not meet with anodal block, and it is desirable that this electrode also be the earthed one.

The type of stimulator which is best of all in this respect is one which gives a "floating" output, of which neither side is earthed. If the output circuit is really earth-free, with negligible leakage or capacitance to earth, such a stimulator is very desirable in experiments which involve electrical recording of nerve action-potentials as well as nerve stimulation. Since the stimulating circuit is earth-free, the current which enters the preparation through one stimulating electrode is exactly the same as that which leaves through the other stimulating electrode. Consequently, if the two stimulating electrodes are close together, there is no great spread of stimulating current to other parts of the preparation, and little interference with the recording circuits.

A fairly well-isolated "floating" stimulus is often obtained by passing the output of an ordinary stimulator through an isolating transformer. The transformer secondary winding always has capacitance to earth, however. When more complete isolation from earth is needed, a radio-frequency link can be used, as described by Schmitt and Dubbert (1949).

Range of Frequency

The range of repetition frequencies which may be required for the stimulating pulses is very wide. In some experiments the response of the preparation to a single stimulating pulse is studied; in these cases very low repetition rates, down to one pulse every 10 or even every 30 seconds may be required in order that after responding to one stimulus the preparation may have time to settle to its normal state before the next is delivered.

At the other end of the range, repetition frequencies up to 1000 pulses per second may be required to elicit effects which depend on having a rapid succession of stimuli. Garry and Gillespie (1955), for instance, tested the sensitivity of their preparation of the colon at repetition rates up to 1000 per second, and found optimum frequencies for each of the two types of nerve to which the stimuli were applied.

A further requirement

It is essential that the stimulator output circuit be absolutely quiescent in the intervals between stimulating pulses. If it is not, and if the stimulator is used in experiments in which action potentials are recorded, it is possible the spurious activity in the stimulating circuit may cause interference in the recording circuit which would be mistaken for a physiological response.

It is safest to arrange that the output valve of the stimulator is cut off by a large negative bias during the intervals between pulses. It is best to use a pentode with a short grid-base, such as the CV 173 (Mullard EF 55) as the output valve rather than a beam tetrode such as the 6V6, which requires a very large negative bias to cut it off completely.

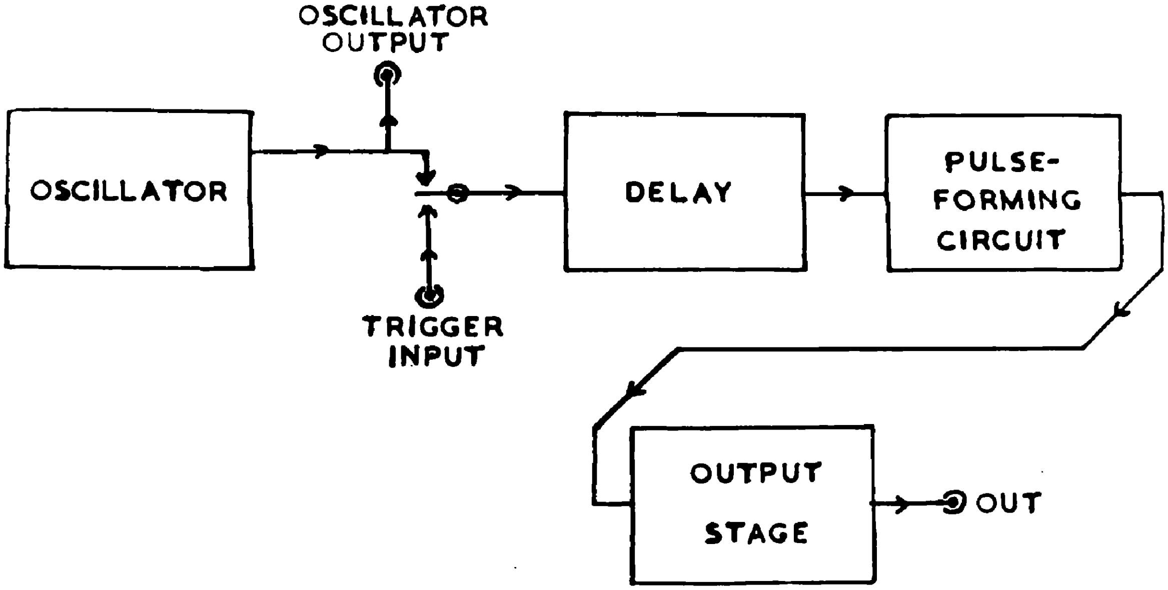


Fig. 7.1. Block diagram of the general-purpose stimulator with delay.

A General-Purpose Stimulator with Delay

A stimulator has been designed for general use in neurophysiological experiments. This is the type which was used by Garry and Gillespie. A block diagram of the stimulator is shown in Fig. 7.1. It will be seen that the stimulating pulses can be initiated (after a delay) by triggering impulses from another piece of apparatus, or, if the switch is in its other position, by pulses from the oscillator which is incorporated in the stimulator itself.

Purpose of the Delay

The incorporation of a circuit giving an adjustable delay, in the position shown in Fig. 7.1, serves two purposes. In some experiments, nerve action-potentials occurring in response to the stimulating pulse are displayed on a cathode-ray oscilloscope. The time-base of the oscilloscope can be triggered either from the "Oscillator Output" or from the same source as supplies the input pulses to "Trigger Input", depending on which way the stimulator is being used. Because of the delay circuit incorporated in the stimulator, the stimulating pulse is not delivered until the oscilloscope sweep has progressed a short distance. This feature of the stimulator is valuable when the time-base is such that it does not start to produce a linear sweep until a short time after it is triggered.

The other purpose which is served by the delay circuit is to make it possible to apply pairs of pulses to a preparation, the two pulses being applied by separate electrodes, and the time-relationship between them variable at will. To achieve this result it is necessary to use two stimulators. The delay circuits of the two may be connected to the same external source of triggering pulses, or both may be connected to the oscillator incorporated in one of the stimulators. By adjusting the delay circuits the stimulating pulses may be made to occur in either order, and separated by any desired time-interval less than a certain limit set by the design of the delay circuits. This sort of arrangement could be used to discover whether and in what way the occurrence of one of the stimuli facilitated or inhibited responses evoked by the other stimulus, for various time-relationships between them.

Facilities provided

The stimulator provides rectangular pulses whose duration is adjustable from 20 μsec to 1·4 seconds. The delay time is adjustable over the same range.

The voltage of the output pulses is adjustable from zero to about 130 volts on open circuit; the output-impedance depends on the setting of the output-amplitude control, and is never greater than 2,500 ohms. One of the output terminals is earthed, and the arrangement is such that the non-earthed electrode becomes negative during the stimulating pulse. The range of repetition frequency provided by the built-in oscillator is from 1 pulse in 100 seconds to 1400 pulses/second.

The range of pulse-duration, and also the range of delay, have as their upper limit the time of 1·4 seconds. It was stated in the section on "requirements" that a pulse-duration of 100 msec is the maximum likely to be required. It is unlikely that a delay time of anything like 1·4 seconds will be wanted for either of the purposes which have been mentioned for the delay. In fact, the upper limits of these ranges are longer than are likely to be required when the stimulator is used for stimulation of nerve or muscle. The stimulator, however, is a versatile instrument whose output can operate relays or light lamps, and the availability of the longer delays and pulse-durations increases its versatility for miscellaneous sequence-timing applications.

The ranges of repetition-frequency and output voltage are what are required in order to conform to the requirements already discussed, plus a little extra for good measure. The output-impedance of 2,500 ohms or less is sufficiently low to place the stimulator in the "low-impedance" class.

The output of the stimulator does not "float", although the advantages of a floating output were discussed in the "requirements" section. Neither an isolating transformer nor a radio-frequency coupled unit is incorporated in the stimulator, but either of them can be connected to it externally. It is not desirable to incorporate either of them as part of the standard circuit, since no reasonably-priced transformer would properly handle the longest pulses produced by the stimulator, while a radio-frequency unit, if of the pattern described by Schmitt and Dubbert, could not handle the maximum output power available from the existing stimulator.

The stimulator was made to give negative output pulses, because at the time it was designed, the type of experiment in which this is preferable was being considered. It now appears, however, that positive pulses are preferable for some purposes. Taking the output from the anode circuit of a valve, as is done when negative pulses are wanted, has the advantage that the output terminals of the stimulator can be short-circuited without any risk of damage to the stimulator. When positive pulses are wanted they are frequently obtained from a cathode-follower output stage, and it could prove harmful to short-circuit this.

Limitation of the pulse-duration and the delay-time

The pulse-duration and the delay-time must always be set to values shorter than the repetition-period of the pulses from the oscillator, otherwise frequency-division occurs in the delay circuit or in the pulse-forming circuit. In fact, for proper operation of the stimulator, neither the pulse-duration nor the delay-time should be longer than about half the repetition-period. This is because the multivibrators used in the delay and pulse-forming circuits require a certain time to recover after each operation.

If the pulse-forming circuit is set to give a pulse-duration of, say, 3/4 of the repetition period, a curious alternate-pulse effect is seen; the pulse-duration is normal for the first pulse, but this leaves insufficient recovery-time before the second pulse. Consequently, the second pulse is shortened, so there is more time for the circuit to recover before the third pulse, which is therefore of about normal duration. The third pulse then leaves insufficient recovery time Before the fourth, which is short. In this way, pulses of two different durations are produced alternately. A similar effect can give rise to unequal spacing of the output pulses if the setting of delay-time is too great a fraction of the repetition-period.

Methods for achieving rapid recovery of multivibrators are discussed by Sayre (1949, p. 185), but none of his recommendations has been incorporated in the stimulator, since it is not normally necessary to have pulse-durations or delay-times greater than half the repetition-period.

Perkins (1955) describes a type of mechanical interlock which can be fitted between the repetition-frequency control and the pulse-duration control of a stimulator to prevent the selection of unsuitable pulse-durations. Attree (1950) describes a "mark space ratio alarm" intended to serve the same purpose.

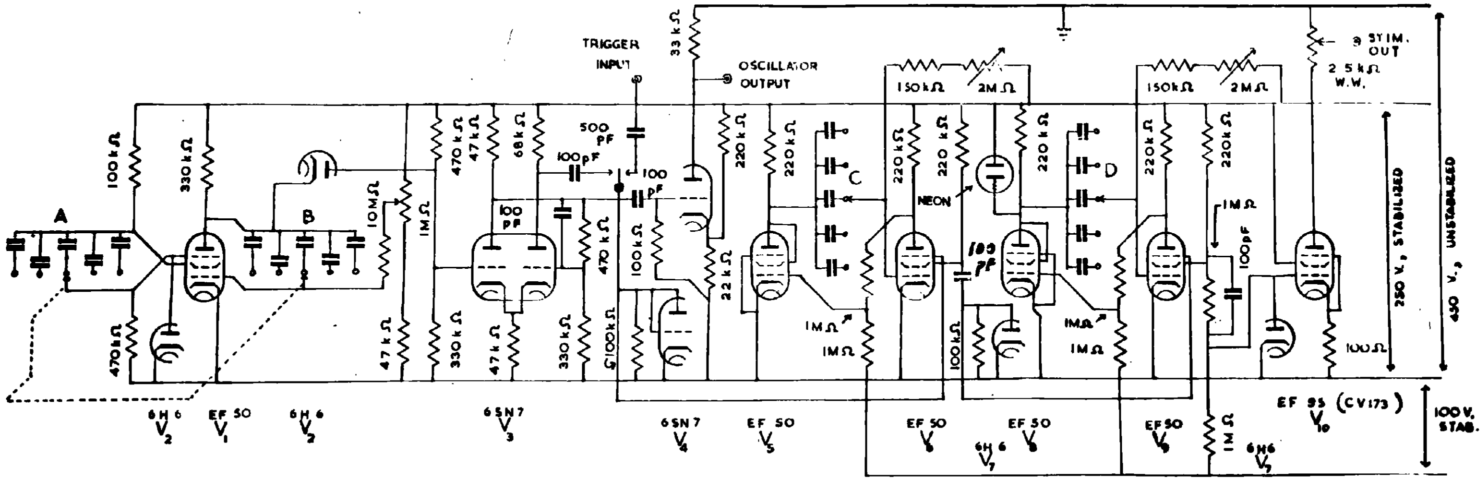


Fig. 7.2. General-purpose stimulator with delay. Each of the banks of capacitors, A, B, C and D contains capacitors of the following values :- 1 µF, 0.1 µF, 0.01 µF, 0.001 µF, 100 pF.

Circuit Details

A circuit diagram, omitting only the power pack, is shown in Fig. 7.2. The arrangement is similar to that described by Attree (1950).

The oscillator shown in Fig. 7.1 consists of that part of the circuit of Fig. 7.2 which contains V_1, V_2 and V_3. V_1 is the actual oscillator valve, in a circuit of the kind known as a Miller transitron oscillator, or as an astable screen-coupled phantastron. Five frequency ranges can be selected by the 5-position switch, and the potentiometer allows continuous adjustment of frequency within each range. V_3 is a Schmitt trigger circuit used to produce sharp pulses from the oscillator output. Attree uses a "scale of two" bistable multivibrator in this position; the Schmitt trigger circuit is somewhat simpler.

The delay circuit consists of the monostable multivibrator containing V_5 and V_6. Five ranges of delay are available by selecting different capacitors from the capacitor bank C. Attree uses a transitron type of circuit to produce the delay, but I have not obtained consistent results from a similar transitron circuit, so the monostable multivibrator is preferred.

The pulse-forming circuit consists of a further monostable multivibrator containing V_8 and V_9, and similar to the multivibrator used for the delay. Both of these multivibrators are similar to the circuit used by Attree as a pulse-forming circuit.

The output valve is V_{10}. A high-slope pentode valve is used because it can be cut-off with a moderate amount of negative bias. Because of the unusual arrangement of power supply lines, it is possible to take the output directly from the anode circuit of V_{10}.

The stimulator differs from that of Attree in the following respects :-

(a) Fewer facilities are provided. Only one delay-unit and pulse-output is provided, whereas in Attree's stimulator these are duplicated. Also, no provision is made for driving a relay to provide "condenser-discharge" stimuli, nor for synchronising the oscillator to the 50 c/s mains. These facilities were not thought to be worth the extra complication they involve; the facility of having "condenser-discharge" stimuli available is only of value when stimuli containing an accurately-known amount of energy are wanted, and no work was contemplated in this department which would necessitate this. The double-output facility of Attree's stimulator can be provided by connecting together two of the present stimulators.

(b) The supply voltages in the present stimulator are lower than in Attree's atimulator. Attree's stimulator is intended to derive its power from a large power unit (Attree, 1948) which also supplies other pieces of apparatus. On the other hand, the stimulators of the type described here are entirely self-contained and can be used in any place where the 50 c/s mains is available. In order that the built-in power unit need not be too heavy and bulky, the stimulator works from supply voltages of + 250 and - 100, and also makes use of an unstabilised supply of + 450 volts. Attree's stimulator uses stabilised supplies of + 400 v. and - 280 volts. At the time when our stabilisers were built, it was quite usual for the mains voltage to fall to 200 volts from a nominal value of 250 volts. A stabilised power unit to supply 400 volts at about 90 mA under these conditions would have been extremely heavy and bulky.

(c) Attree's stimulator delivers positive output pulses from a cathode-follower output stage, whereas the stimulator described here delivers negative pulses from the anode circuit of the output valve. The advantages and disadvantages of these two methods have been discussed.

In order that the output can be taken from the anode circuit without introducing possible distortion of the pulse by the use of a capacitor or a transformer, it is necessary that the positive side of the power supply be earthed. The power supplies are therefore unconventional in the stimulator described here, and the supply voltages quoted under (c) (+ 250 volts and - 100 volts, stabilised, + 450 volts unstabilised) are not the true voltages relative to earth, but are the voltages relative to a supply rail which is itself at - 450 volts relative to earth.

(d) In some parts of the circuit, the details of the circuits used are different from Attree's. The main differences have already been mentioned in the outline which was given of the working of the stimulator.

The stimulator has proved useful. It could be made more versatile in a future version by making provision for outputs of either polarity, and of either high or low impedance as required; an earth-free "floating" output would be advantageous.

The Exponential Stimulator

The stimulator described in the foregoing supplies rectangular pulses of current, since this form of stimulating pulse is suitable for most purposes, and has been shown by Offner (1946) to be an efficient form of stimulus when the duration is suitably chosen. For special purposes, however, other waveforms are sometimes required. For the investigation of accommodation in nerve it is useful to be able to apply a stimulating current which obeys the law

$$I = I_0 (1 - e^{-t/\alpha}) \qquad (1)$$

A stimulator has been developed (Andrew, 1952a) which produces a current varying according to Equation (1). Its use was discussed in Part 1(b). A copy of the published paper on this stimulator is included in the appendix of this thesis.

The stimulator was designed primarily for stimulation of human nerves through the skin. In this type of stimulation a high and unknown resistance is directly in series with the stimulator output. In such a case, when an accurate control of stimulus strength is required, a stimulator with high output impedance is indicated. It is highly desirable that the stimulating waveform be independent of the resistance in the external circuit.

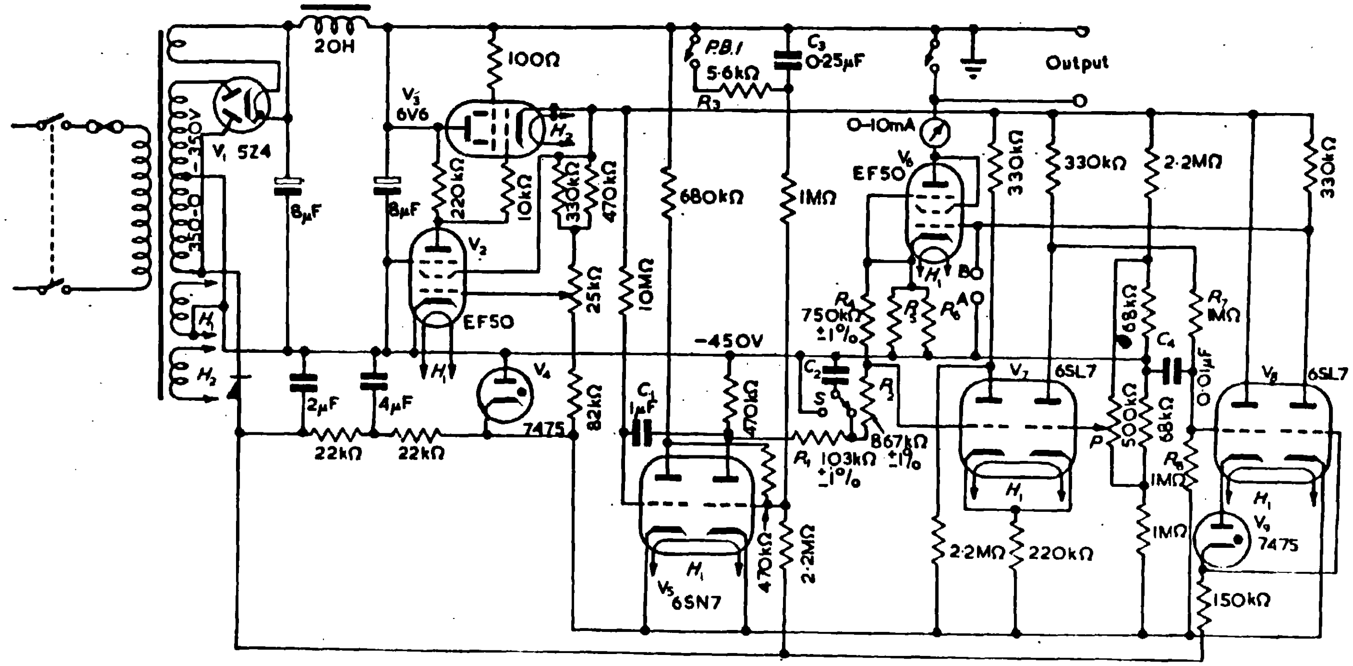


Fig. 7.3. The exponential stimulator.

Some arrangements which have been used for exponential stimulation did not meet the last-mentioned requirement, and the time-constant of rise of current could only be calculated by taking into account the resistance of the biological preparation, as was done by Solandt (1936).

The requirements of high output-impedance and of having the stimulating waveform independent of external circuit resistance have been met by the use of a servo-stimulator arrangement. A servo-stimulator has been briefly described by Rushton (1949), but the design of the exponential stimulator is considerably different from that due to Rushton.

Fig. 7.3 shows a circuit diagram of the exponential stimulator. Valves V_1, V_2, V_3 and V_4 are included in the power pack. V_6 is the output valve, and V_5 is connected to form a flip-flop which has to do with generating a "reference" voltage waveform, with the time-constant of rise determined by R_1 , R_2 and C_2. A voltage proportional to the output current of the stimulator is developed across R_4 , R_5 and R_6 in parallel, and this voltage is compared with the reference voltage by means of the potential divider R_2 , R_4 . The "error" voltage appearing at the junction between R_2 and R_4 is amplified by a D.C. amplifier containing V_7 , V_8

and V_9, and the output of this amplifier is connected to the grid of the output valve V_6. In this way the output current is controlled so as to be proportional to the reference waveform generated by the circuit containing V_5.

Resistors R_5 and R_6 are variable in steps (arranged to be equal steps of conductance), and their settings determine the final value of the output current (I_o in Equation 1). The capacitor C_2 is variable in steps and is used to set the required time-constant of rise (a in Equation 1).

Results obtained using the stimulator have been discussed in Part 1(b).

A defect of the Exponential Stimulator

The exponential stimulator was recently shown to have a defect, in that a brief spurious pulse of current was produced at the moment of initiation of the required waveform. The cause of the trouble appears to have been coupling between the flip-flop incorporating V_5, and the D.C. amplifier incorporating V_7, V_8 and V_9. The coupling was due to the impedance of the stabiliser tube V_4.

At the time the exponential stimulator was built I was not aware that the impedance of gas-filled stabiliser tubes is much greater at high frequencies than at low frequencies. I later discovered this property of the tubes (Andrew, 1952c), which will be discussed more fully in Part 8.

When the flip-flop incorporating V_5 was triggered there was an abrupt change in the amount of current drawn from the negative supply rail which comes from V_4 cathode. Because of the relatively high impedance of V_4 at high frequencies, the abrupt change in the current caused a brief fluctuation in the voltage across V_4. This fluctuation affected the D.C. amplifier and produced the brief pulse at the output of the stimulator.

The trouble has been cured by replacing V_4 with two separate gas-filled stabiliser tubes, receiving their current from the rectifier through separate resistors. The cathodes of V_5 are connected to one of these stabiliser tubes, and the other stabiliser tube is connected to everything else which was previously connected to V_4 cathode.

The effect which the defect in the stimulator may have had on some of the experimental results obtained by its use is discussed in an Appendix to Part 1(b).

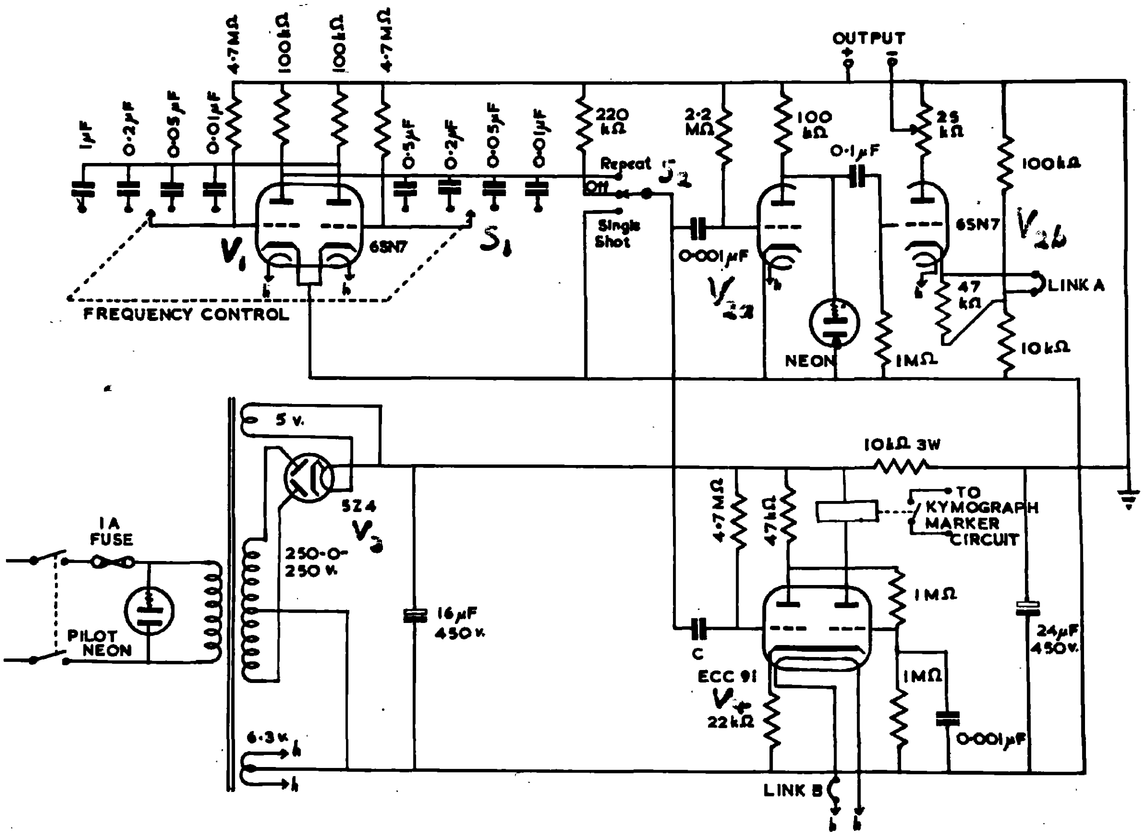


Fig. 7.4. Simple stimulator giving 1 msec pulses, with simultaneous kymograph marking if required. The relay may be either a 4,000 ohm high-speed type, or a 1,000 ohm Post Office type. In the former case, capacitor C has the value 0·001 μF; in the latter case it is 0·005 μF.

Small Stimulator giving Millisecond Pulses

A small, simple stimulator was designed and constructed for use in a student experiment on stimulation of the exposed frog's heart (Experiment 111 in the Experimental Physiology Course). The stimulator is described here because, as well as serving the purpose for which it was intended, it has proved useful as a general-purpose stimulator in experiments where it was not necessary to trigger an oscilloscope in synchrony with the stimulus. In particular, it was used by Brown (1954) in studies of muscle-tone and excitability of nerves under anaesthesia and under the effects of relaxant drugs.

The circuit of the stimulator is shown in Fig. 7.4. The power supply, using resistance smoothing, is conventional, except in that the positive side of its output is earthed.

V_1 is a free-running multivibrator, with four nominal frequencies of 1/4, 1, 4 and 16 pulses per second, of which one is selected by the 4-position switch S_1. From one of the anodes of V_1 an output is taken to one contact of the 3-position switch S_2. The central position of S_2 is the "off" position in which no stimuli are produced. When the operating lever of S_2

is pushed upward to the "repeat" position, stimulating pulses are produced repetitively at the frequency of the multivibrator. In this position of the switch, one anode of the multivibrator is connected through a capacitor to the grid of V_{2a}. V_{2a} is normally conducting, but is cut-off for a short while following each time the potential of the multivibrator anode changes in a negative direction. The time during which V_{2a} is cut-off depends on the time-constant of the resistance and capacitance in its grid circuit, and is in fact about one millisecond for the values shown. A positive pulse of 1 msec duration appears at the anode of V_{2a}, which is coupled to the grid of V_{2b}. V_{2b} is normally cut off, and conducts during this positive pulse, so producing the output pulse of the stimulator.

When the switch S_2 is depressed from the "off" position to the "single shot" position there is an abrupt change of potential of the switch contact. This causes V_{2a} to be cut off for one millisecond, and so one output pulse of 1 msec duration is produced for each depression of the switch.

In the cathode circuit of V_{2b} is a resistance of 47 kΩ, which can be short-circuited by link A. With the link in position, the range of output voltage of the stimulator, on open circuit, is from zero to about 120 volts. When the link is removed, the maximum output voltage is about 1/3 of this, and consequently a finer adjustment of output voltage can be made, in experiments where the full output is not needed.

In some experiments it is useful to have a kymograph marker operating to mark the times of occurrence of the stimulating pulses. When this facility is required, link B is inserted in the heater circuit of V_4, and this valve receives a heater supply and becomes operative. The left-hand section of V_4 is normally conducting, but is cut off for a time by the same voltage swings as cut off V_{2a} and thereby produce the output stimulating pulses. When the left-hand section of V_4 is cut off, its right-hand section conducts and the relay closes. The relay contacts are brought out to terminals which can be connected to the kymograph marker circuit. When the marker is not required, the link B can be removed so as to avoid the noise of the relay operating, and to save wear of the moving parts of the relay.

In his work on anaesthesia and relaxant drugs, Brown generally used the stimulator to stimulate the ulnar nerve at the elbow, passing the current through the skin. From observations made during a procedure for anaesthesia using nitrous oxide, oxygen and ether, Brown decided that the threshold stimulus for the ulnar nerve during the first and second planes of anaesthesia is not significantly different from the value of threshold stimulus for the fully conscious patient. In the third plane of anaesthesia there is a rise of threshold of about 15%, and the threshold in the fourth plane is about 10% higher than the value in the third plane.

From tests made when a relaxant drug was administered, Brown decided that "A slight rise in the threshold to nerve stimulation is usually an indication of a level of curarisation satisfactory for surgery." This finding is of considerable theoretical interest, for it shows that relaxation can be produced by a level of curarisation which does not interfere seriously with the myoneural junction. (Brown was using a muscle twitch as his index of stimulation.) Hence the relaxation due to curare must be largely a central effect.

PART 8

DESIGN OF AUXILIARY APPARATUS

PART 8. DESIGN OF AUXILIARY APPARATUS

The design of amplifiers and stimulators for physiological use has been discussed in Parts 6 and 7. Other items of electronic apparatus required in neurophysiological experiments include temperature regulators, time-base generators for use with cathode-ray oscilloscopes, and power supply units. Some contributions to the design of these will be described here.

Temperature Regulator for Decerebrate Animals

Experiments on the nervous system are frequently carried out on decerebrate animals. The usual procedure is to decerebrate the animal under ether anaesthesia, and then to discontinue the application of ether. The animal is kept breathing, if necessary by the application of artificial respiration, and the ether it has absorbed is eliminated in the expired air. The spinal cord and peripheral nervous system are then available for experiment, uncontaminated by anaesthetic.

The decerebration destroys the animal's ability to regulate its own temperature, so the temperature must be maintained artificially. This is usually done by having one or two electric light bulbs under the operating table. The power supplied to these is often regulated with a Simmerstat.

In some experiments the temperature of the animal, or of a particular part of it, must be closely controlled. In the experiments of Boyd (1954, p. 24) it was important to control the temperature of the paraffin pool in which the articular nerve was immersed. Two infra-red lamps were mounted above the preparation and directed toward the paraffin pool. A thermistor (temperature-sensitive resistor) was immersed in the pool of paraffin. The thermistor was connected to an electronic control unit which switched the infra-red lamps on or off according to the temperature of the paraffin. In this way the temperature of the paraffin was kept close to a fixed value.

A temperature-regulating device employing a thermistor has been described by B.L. Andrew (1947). The regulator to be described here is not greatly different from that described by B.L. Andrew, but has the advantage of being entirely mains-operated. It can also be expected to be less affected by mains voltage variations than B.L. Andrew's regulator, because it uses a series arrangement of two triode valves in the first stage of amplification, to give compensation for heater-voltage changes. It is also slightly more versatile than the regulator due to B.L. Andrew, as it is designed to work in either of two different ranges of temperature.

Both the regulator made by B.L. Andrew, and the one to be described here, provide simple on-off control of the heating power. This form of control is not ideal when the regulator is used in conjunction with sensitive amplifiers, since the switching of the heating power produces interference. In the arrangement of infra-red lamps used in Boyd's experiments, the lamps were run on A.C., and consequently 50 c/s interference was produced while they were switched on. It is clear that a temperature-regulator for use in neurophysiological experiments should, ideally, provide smooth, continuous regulation of D.C. power to the heating element. Dickinson (1949) describes a regulator which provides a continuously-regulated supply of D.C. power, but only supplies a maximum of 10 watts of heating power, which is not enough for the infra-red lamps. In principle it is possible to build a regulator to supply enough D.C. power to operate the infra-red lamps, but it would be large and expensive. The regulator which has been developed therefore gives simple on-off control, and the interference has to be tolerated. (The infra-red lamps can be disconnected altogether for a short time to ensure freedom from interference while records are being taken.)

It has been mentioned that the regulator can work in either of two temperature ranges. It can be set to regulate to a temperature in the region of 37°C required for mammalian physiology, or it can be set to regulate to a temperature in the region of 0°C. This latter facility was provided because it was sometimes necessary to circulate sea-water at a temperature in the region of 0°C, in connection with experiments by Dr. T.D.M. Roberts on the excised eye of the cuttlefish. When regulating to a temperature in the region of 37°C, the regulator will generally be controlling a heater; when regulating to a temperature in the region of 0°C it will normally be controlling a refrigerating unit.

The thermistor is a particularly convenient type of temperature-sensitive element for this application. It has an advantage over a thermocouple in that, in a suitable circuit, it gives a much greater change in output voltage for a given change in temperature, and is therefore more suitable for use with electronic amplification in an automatic regulator. It is preferable to any other type of resistance thermometer because its temperature-coefficient of resistance is much higher. On the grounds of compactness, and because it does not produce electrical interference, it is to be preferred to temperature-sensitive devices employing a bimetallic strip and electrical contacts, or the contact between a wire and a column of mercury.

The thermistor employed in the present regulator is type F 1512/300, made by Standard Telephones and Cables, Ltd.. This is supplied in the form of a glass tube 4 mm in diameter and 70 mm long, with the temperature-sensitive material sealed into the glass at one end, and the connecting wires issuing at the other end. The thermistor can conveniently be inserted so as to respond to the animal's rectal temperature.

Design Considerations for the Regulator

It is stated by the makers of the thermistors that the resistance of a thermistor varies with temperature according to the relationship

$$R = a e^{b/T} \qquad (1)$$

where R is the resistance of the thermistor, T is the absolute temperature, and a and b are constants.

The thermistor type F 1512/300 has a nominal resistance of 100 kΩ at 20°C and of 100Ω at 300°C. Substituting these values in equation (1) and solving for a and b gives

$a = 0{\cdot}0726\,\Omega$ and $b = 4142°K$.

Then at the temperature of 37°C, or 310°K, the resistance is given by

$$R = 0{\cdot}0726\ e^{4142/310}$$

$$= 46{,}140\,\Omega \qquad (2)$$

and the temperature coefficient is given by

$$-\frac{b}{T^2} = -\frac{4142}{(310)^2}$$

$$= -\,0{\cdot}043 \qquad (3)$$

When the thermistor is in use, some electrical power is necessarily dissipated in it, producing a rise in its temperature above that of its surroundings. The amount of this rise depends on the intimacy of contact of the thermistor with its surroundings, so an error in the temperature measurement could result if this rise in temperature were appreciable. To keep the rise in temperature to a low value, the amount of power dissipated in the thermistor must be small.

According to the manufacturer's data, when the thermistor is in air, a rise in temperature of 1°C is caused by the dissipation of 0·62 mW of electrical power. The temperature regulator has been designed so that the power dissipated in the thermistor is approximately

0•1 mW. For temperatures in the region of 37°C, the thermistor resistance is in the region of 40,000 Ω (equation 2). The permissible voltage to be applied to the thermistor in this range of temperature is 2 volts, since this gives 0•1 mW in 40,000Ω.

With 2 volts appearing across the thermistor, the voltage change for a 1°C temperature change would be 2 x 0•04 volts if the thermistor were in series with a constant current device (since the temperature coefficient is approximately 0•04). In the actual circuit used, (Fig. 8.1), the thermistor is not in series with a constant-current device, but with a resistor of 399 kΩ. Hence the change in voltage per degree C is less than 2 x 0•04 volts, and is about 70 mV. The amplifier circuit has been designed to make the relay operate for a change of voltage of about one tenth of this.

For operation at 0°C, the thermistor resistance is calculated to be 224,000Ω , and in this case it is permissible to have 4 volts developed across the thermistor. At this temperature the regulator is more sensitive than at 37°C, for not only is a higher voltage applied to the thermistor, but also the temperature-coefficient of resistance is higher at the lower temperature.

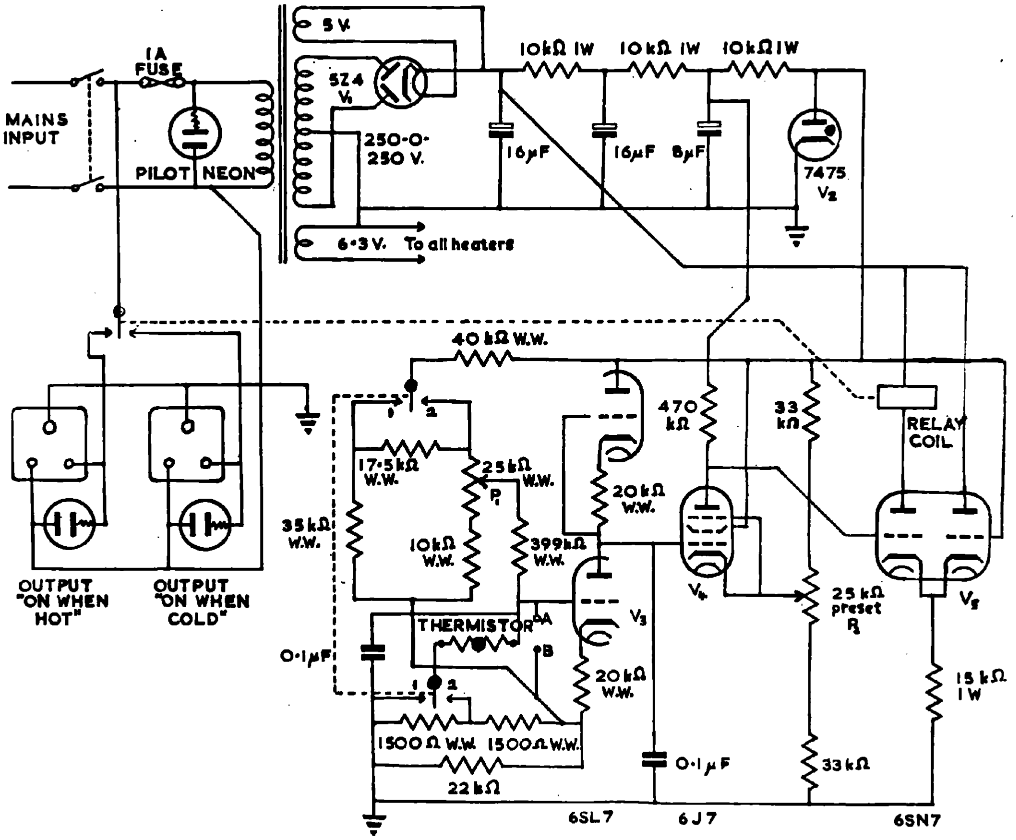


Fig. 8.1. Temperature regulator for decerebrate animals (and for cuttlefish eyes).

Thermistors are sometimes incorporated in A.C. bridge circuits, but in this regulator (as in those of B.L. Andrew and of Dickinson), only D.C. is applied to the thermistor because A.C. might cause interference with the recording of action-potentials.

Circuit details

The circuit of the regulator is shown in Fig. 8.1. The thermistor is incorporated in a network of resistors which is effectively a Wheatstone bridge whose out-of-balance voltage appears between points A and B. The two-pole, two-position range switch selects one of the two temperature ranges. When the switch is in position 1, the device regulates to a temperature in the region of 0°C, the exact value being determined by the setting of potentiometer P_1. With the switch in position 2 the device regulates to a temperature in the region of 37°C.

To ensure that the relay changes over as the output of the Wheatstone bridge passes through zero, the preset potentiometer P_2 is set by the following procedure. Points A and B are connected together, and then P_2 is adjusted to a point as near as possible to that at which the relay changes over.

The first stage of amplification in the regulator contains the two sections of the double triode V_2, of which one section is the amplifier valve and the other is its anode load. This type of amplifying stage is suggested by Artzt (1945) as one way of providing compensation for changes in heater voltage in D.C. amplifiers.

In the anode circuit of V_4 is the relay which controls the heater (or refrigerator). It consists of the coil and armature of a Post Office type relay of 2000 ohms resistance, but instead of the usual contacts of a Post Office relay, it is made to operate a Burgess micro-switch. The rating of the micro-switch is 5 A at 250 volts, so the regulator can be made to control more than a kilowatt of power. The A.C. mains is switched by the micro-switch to one or other of two outlets, labelled respectively "On when hot" and "On when cold". A heater (e.g. the infra-red lamps already mentioned) is connected to the "On when cold" outlet, and a refrigerating unit would be connected to the "On when hot" outlet.

The temperature regulator has proved satisfactory in use, except in that the infra-red lamps introduce interference in the experiments. No difficulty is anticipated in modifying the design to give a smoothly regulated D.C. supply to the lamps, but, as already mentioned, this has not been done because it would necessarily involve making a large and expensive regulator.

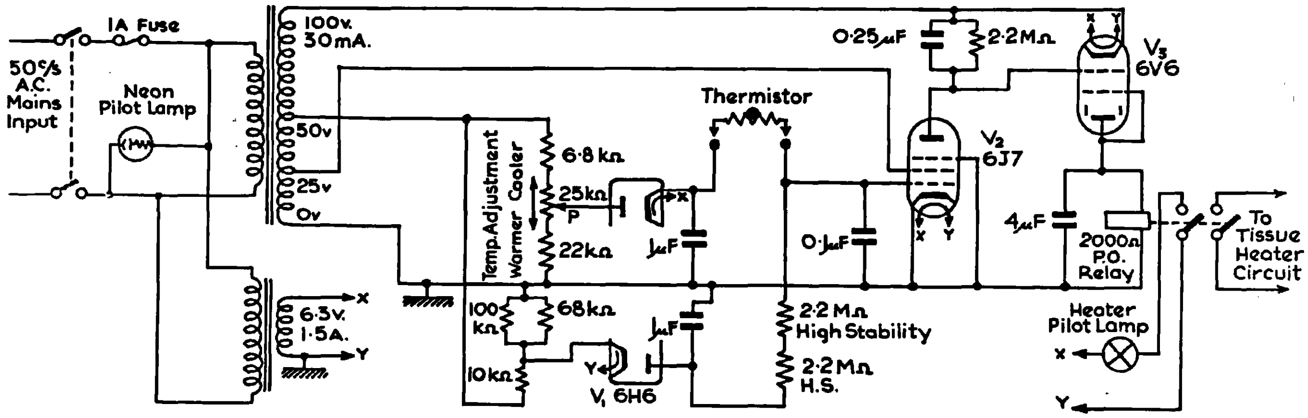


Fig. 8.2. Temperature-regulator for freeze-drying. Circuit used for the temperature range of -45°C to -28°C.

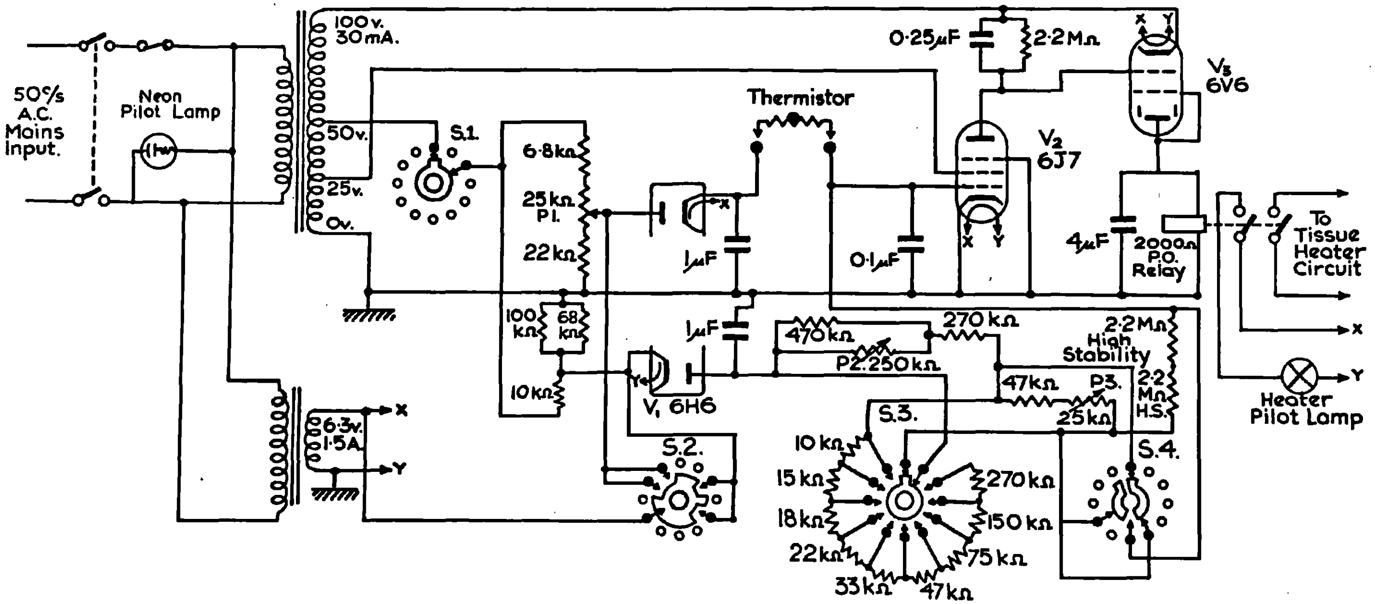


Fig.8.3. Complete circuit of the temperature-regulator for freeze-drying. The switch sections S.1 to S.4 are ganged.

Temperature Regulator for Freeze-Drying

A temperature regulator was required as part of an apparatus for the freeze-drying of tissues for histological purposes. In this case regulation to a temperature in the region of - 40°C was required for the main part of the freeze-drying process. Less precise regulation at temperatures in the range of - 15°C to + 15°C was also required so that the temperature of the tissues could be raised gradually through that range of temperature. An electronic temperature-regulator incorporating a thermistor proved satisfactory in this application also (Andrew and Hale, 1953, 1954).

The regulator was originally designed and constructed to operate at temperatures in the region of - 40°C only. The circuit was that of Fig. 8.2. The facility of regulating at temperatures in the range of - 15°C to + 15°C was a later modification which involved no new principles. As can be seen from Fig. 8.3, the modification increased the complexity considerably, by introducing a 4-bank, 12-position switch to alter the voltage applied to the thermistor circuit and to insert different resistance values for the different temperatures required. In one position of the 12-position switch the circuit is effectively the same as that of Fig. 8.2. This is the switch position which is used when regulation is required at a temperature in the region of - 40°C. The other 11 positions correspond to 11 fixed temperatures in the range of - 15°C to + 15°C.

To avoid undue complication in the description, the regulator will be discussed in its original form; that is to say, only regulation to a temperature in the region of - 40°C will be described. No new principles are involved in the modification to regulate at other temperatures in addition. A full description of the regulator has been published (Andrew and Hale, 1954) and a copy is included in the appendix of this thesis.

Design Considerations

The thermistor is again used with only D.C. flowing in it. An A.C. bridge could have been used in this case, since there is no question of interference with sensitive amplifiers, but the use of a D.C. circuit has the advantage that no account need be taken of stray capacitance, which could be troublesome in an A.C. circuit. Stray capacitance would certainly be troublesome in an A.C. circuit utilising such high resistance values as are used in the present one; the resistance values could, however, be kept lower by making a different choice of type of thermistor.

The thermistor used is of the same type as was used in the regulator for decerebrate animals, namely type F 1512/300. Making use of equation (1), the resistance of the thermistor at - 40°C is calculated as 3·8 MΩ, and the temperature coefficient as - 0·076.

Dissipation of 0·62 mW in the thermistor has been allowed. This is the power which causes 1°C rise in temperature when the thermistor is in air. The rise in temperature under working conditions in the freeze-drying apparatus is difficult to estimate, but is probably not much greater than 1°C.

Allowing 0·62 mW dissipation, the permissible applied voltage for a resistance of 3·8 MΩ is 49 volts. If the thermistor were connected in series with a resistance so large that the current through the two was substantially constant in spite of varying thermistor resistance, the voltage change per degree Centigrade would be 49 x 0·076 volts, or about 3·7 volts. In the practical circuit the series resistance is roughly equal to the thermistor resistance, so the voltage change per degree is roughly half the above value, or about 1·9 volts at - 40°C.

Circuit details

Fig. 8.2 shows the circuit used to give regulation to a temperature in the region of - 40°C. The range of temperatures obtainable is from - 45°C to - 28°C, and the temperature is set by adjustment of potentiometer P_1. The two halves of V_1 act as half-wave rectifiers to provide voltages positive and negative with respect to earth. Alteration of the setting of P_1 alters the positive voltage, and so alters the value of thermistor resistance necessary for balance.

The component values in Fig. 8.2 resulted in the very useful temperature range of - 45°C to - 28°C. In building another regulator it may be found necessary to adjust the limits of the range by altering R_1 and R_2, as the characteristics of individual thermistors differ somewhat.

The output voltage of the thermistor circuit is applied to the grid of V_2. V_2 and V_3 form a D.C. amplifier whose output operates a relay which controls the power supplied to a small heater placed beneath the tissue in the freeze-drier. (A heater is required to bring the tissue to - 40°C because the part of the apparatus in which it is contained is immersed in liquid nitrogen at - 195°C).

The D.C. amplifier used is of a very little-known type. It is convenient in the present application because it does not require a D.C. power supply. The principle of operation is described by Henney (1937, p. 80), who attributes it to Shepard (1935). A charge is produced on the capacitor in V_2 anode circuit, by V_2 acting as a half-wave rectifier. The potential difference across the capacitor depends on the amount of current passed by V_2 during the half-cycles in which it conducts, and hence on the control-grid potential of V_2. The anode current of V_3, which flows during the other half-cycles, depends on the p.d. across this capacitor, and the relay is energised when V_3 conducts sufficiently.

The relay changes over when the control-grid of V_2 is about 3 volts negative.

Performance

To test the performance of the regulator, particularly its susceptibility to errors due to variations in mains voltage, it was disconnected from the thermistor and connected to standard resistors. The resistance values for switching the heater-circuit on and off were as shown in the following table.

Resistance Values for Switching Heater On and Off

Line voltage (volts)	Potentiometer setting	Resistance values (megohms)	
		On	Off
250	Max. temp.	2•229	2•216
200	Max. temp.	2•213	2•183
250	Min. temp.	5•445	5•424
200	Min. temp.	5•418	5•402

At the maximum temperature-setting, the calculated resistance-change per degree is 120 kΩ and at the minimum temperature-setting it is 450 kΩ. The resistance values show that the temperature difference between switching off and on is less than 0•3°C. The change in controlled temperature when the line voltage falls from 250 volts to 200 volts is also less than 0•3°C.

The regulator has been incorporated in the freeze-drying equipment, which has been used routinely in the preparation of tissue for histological investigations. An account of some investigations carried out using the freeze-drying equipment is given by Hale (1954). Some further investigations using it are described by Hale (1955 and 1956).

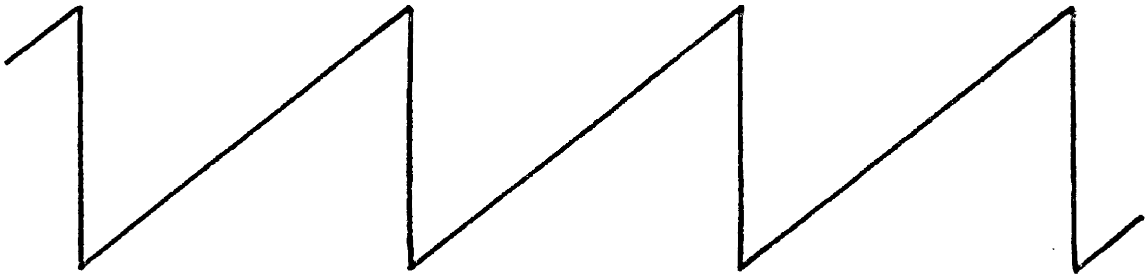
A New Triggered Time-Base

In many physiological experiments, information is displayed on a cathode-ray oscilloscope. A commercial oscilloscope (e.g. Cossor type 1049) is often used. Several "display units", which are in fact oscilloscopes, have been constructed in the Physiology Department, and some problems of oscilloscope design had to be met. In particular, a new time-base circuit was put into use.

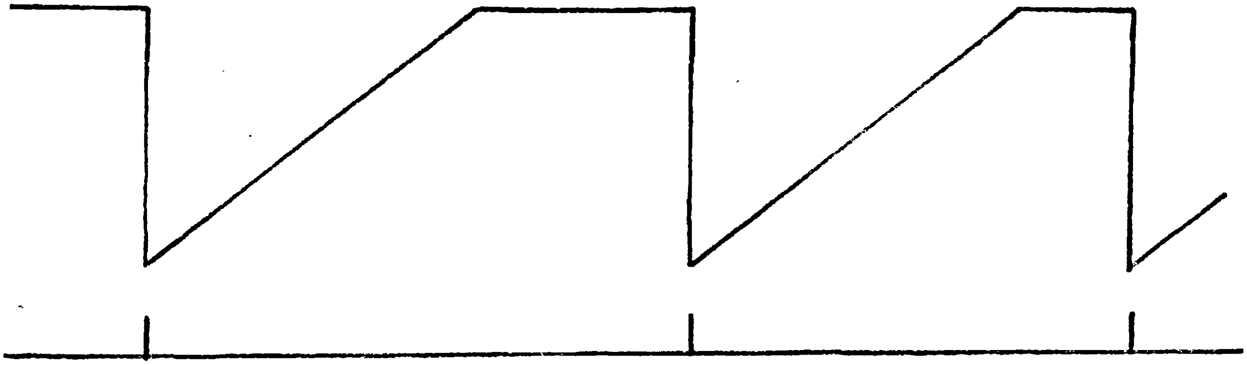
Types of time-base operation

An oscilloscope time-base may operate in any of three ways. These are as follows :-

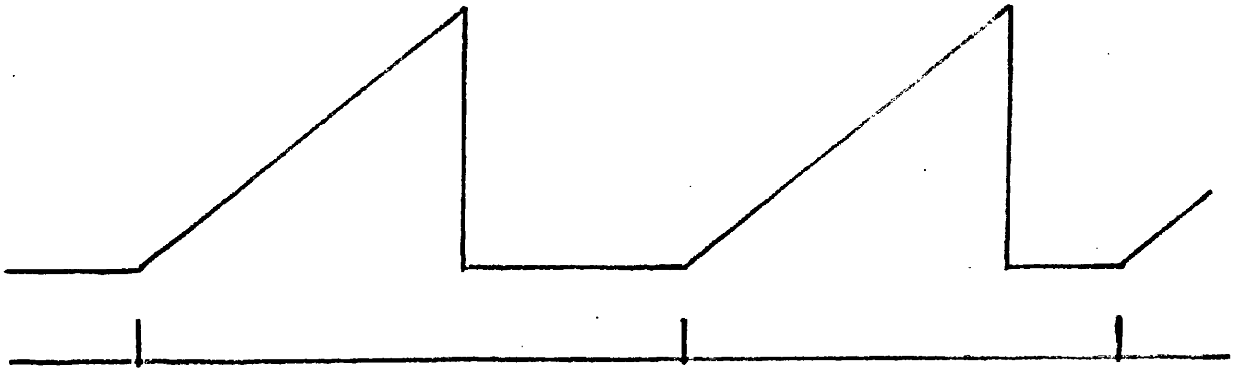
(a) The time-base may be of the "free-running" type. That is to say, when the spot has completed one sweep across the face of the tube it flies back to its starting-point and immediately begins its next sweep. The output-waveform of the time-base, which is also a graph of horizontal spot-deflection against time, is as follows :-



(b) The time-base may be of the "triggered fly-back" type. In this type, the spot travels to the end of its sweep and becomes stationary there, until a triggering impulse is received from an external source. When the triggering impulse is received the spot flies back to its starting position and begins another sweep. The output waveform of the time-base is as follows :-



(c) The time-base may be of the "triggered sweep" type, in which the spot travels to the end of its sweep and then flies back to its starting position, where it remains until a triggering impulse is received. The output waveform is as follows :-



Since a free-running time-base is required in some experiments, and triggered operation is required in others, it is convenient to use a time-base circuit which can be switched at will to give either triggered or free-running operation. In other words, the time-base should be capable of operating according to (a), and also according to either (b) or (c).

Type (c) operation is preferable to type (b) operation, since the fly-back is never quite instantaneous, and consequently, with type (b) there is a slight delay between the arrival of the triggering impulse and the start of the sweep. However, either type of triggered operation is acceptable for most purposes. The delay in sweep-initiation with type (b) operation is of no consequence whatever if the triggering impulses can be made to precede by a suitable interval the events to be displayed on the oscilloscope. This can usually be arranged if the type of stimulator used incorporates a delay circuit (see Part 7).

Puckle's time-base

One of the best-known time-base circuits is that due to Puckle (1952) which was originally devised in 1933. Puckle's time-base is a free-running one.

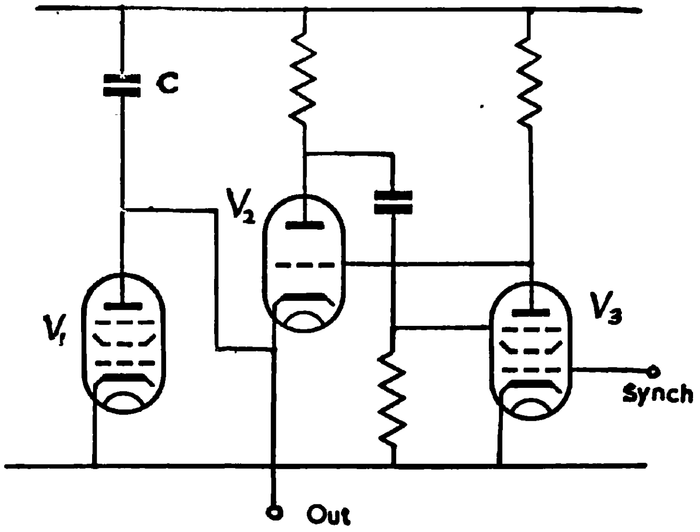


Fig. 8.4. Puckle's time base.

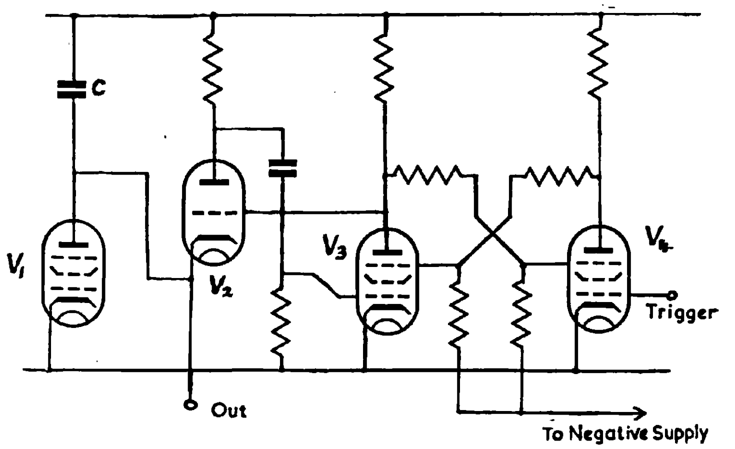


Fig. 8.5. McMullan's modification of Puckle's time base.

The circuit of Puckle's time-base is shown in Fig. 8.4, omitting arrangements for supplying the grids of the constant-current pentode V_1, and the screen grid of V_3.

At the beginning of a sweep, capacitor C is almost completely discharged, so the potential of the cathode of V_2 and of the output terminal is almost that of the H.T. line. C receives charge at a steady rate through the constant-current pentode V_1, and the potential of the output terminal becomes steadily more negative. This steady change of potential produces the linear sweep of the oscilloscope spot.

V_3 has its grid at earth potential, and has a large anode resistor, so its anode potential is well negative compared to the H.T. line. Therefore the grid of V_2 is also well negative with respect to the H.T. line. V_2 does not conduct until the potential of its cathode falls to a value close to that of its grid.

When V_2 starts to conduct, its anode potential falls, and this fall in potential is conveyed by a capacitance coupling to g_3 (or g_1) of V_3. The anode of V_3 goes positive, leading to more current flow through V_2. A cumulative action takes place, coming to an end when C is almost completely discharged, so that no further current can flow through V_2. The rapid discharge of C causes the fly-back of the oscilloscope spot, and then the sweep starts again. A synchronising signal can be applied to g_1 (or g_3) of V_3.

McMullan's modification of Puckle's time-base

A modified form of Puckle's time-base, which gives either triggered or free-running operation at will, has been described by McMullan (1946). This gives type (c) operation when switched so as to work as a triggered time-base. As already mentioned, this is the preferred mode of operation

When switched to give free-running operation, McMullan's circuit is effectively the same as Puckle's circuit (Fig. 8.4). When switched to give triggered operation, the circuit is as shown in Fig. 8.5. Here the valve V_3 of Fig. 8.4 is replaced by a bistable multivibrator, or Eccles-Jordan circuit, consisting of V_3 and V_4.

Suppose that initially the bistable multivibrator is in the state where V_4 conducts and V_3 is cut off. Since V_3 anode, and therefore V_2 grid, are at approximately the potential of the H.T. line, V_2 is conducting, so C cannot be charged. When a negative triggering impulse arrives at the grid of V_4, the bistable multivibrator

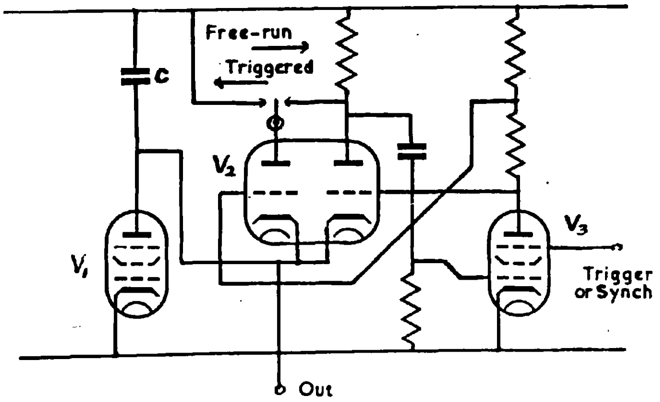


Fig. 8.6. Andrew's modification of Puckle's time base.

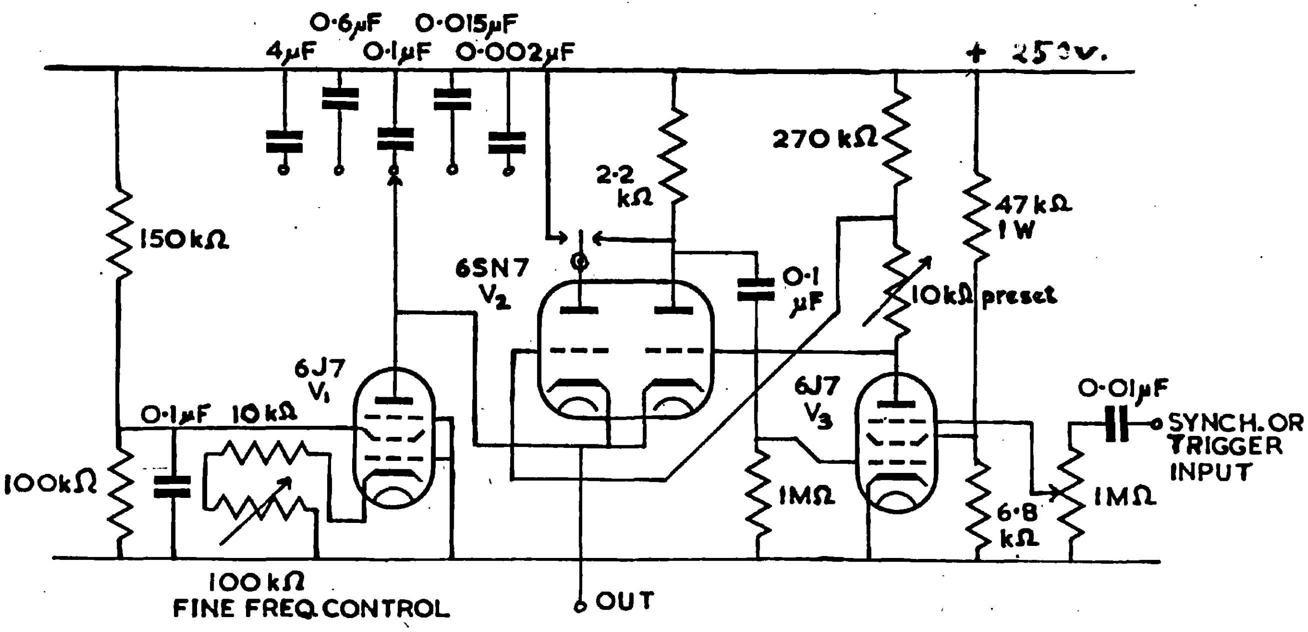


Fig. 8.7. Practical form of the above.

changes over so that V_3 conducts. V_3 anode becomes negative with respect to the H.T. line, taking V_2 grid with it. V_2 ceases to conduct, and the capacitor C is charged linearly through V_1. Then the time-base sweep takes place, until V_2 cathode reaches a potential sufficiently negative for V_2 to conduct.

When V_2 conducts, its anode potential falls, and the fall is conveyed to the grid of V_3. The bistable multivibrator is thus flipped over to the condition wherein V_3 is cut off. V_3 anode goes positive, and V_2 conducts to discharge capacitor C, and remains conducting to hold C discharged until the next triggering pulse is received at V_4 grid.

An alternative modification of Puckle's time-base

The alternative modification of the Puckle time-base, which I have devised, is shown in Fig. 8.6. This gives type (b) operation when switched to work as a triggered time-base. As already mentioned, this is not the preferred mode of operation, but is acceptable for most purposes.

In Fig. 8.6, the discharging valve V_2 of Fig. 8.4 is replaced by a double triode. The potentials of the two grids depend on the anode potential of V_3, but the grid of the left-hand section is a little more positive than the grid of the right-hand section. Hence, when C is charged through V_1, the left-hand section of V_2 begins to conduct before the right-hand section does.

In the "free-running" position of the switch, the two anodes of V_2 are connected together. When the capacitor is charged sufficiently to allow current to flow in the left-hand section of V_2, this current produces a fall in the common anode potential of V_2. The fall is conveyed to the grid of V_3 by the capacitance coupling, V_3 anode goes positive, and C is discharged in the same way as in Puckle's original circuit (Fig. 8.4). The discharging of C produces the fly-back of the spot of the oscilloscope, and then the sweep starts again as C is again charged through V_1.

With the switch turned to the "triggered" position, when the capacitor C is charged sufficiently for the left-hand section of V_2 to start conducting, the current through this section of V_2 prevents C from charging to the voltage where the right-hand section of V_2 would conduct. Current through the left-hand section does not initiate the cumulative discharging action as there is no coupling from the anode of this section to the grid of V_3. When a negative triggering pulse is applied to

g_3 of V_3, however, V_3 anode becomes sufficiently positive for both sections of V_2 to conduct. The current in the right-hand section produces the fall in potential of V_3 grid, needed to produce a cumulative discharging action, and C is discharged, the discharging current being shared by the two sections of V_2. After the discharging of C, it is again linearly charged by the current through V_1.

A practical circuit for the time-base is shown in Fig. 8.7. The variable resistance in V_3 anode circuit is preset to the minimum resistance value which will prevent the circuit from free-running when switched to the "triggered" position. Undesired free-running operation is most likely to occur when the fine frequency control is set to give the maximum frequency in one of the frequency ranges. Hence, the pre-set control connected to V_3 anode should be set when the fine frequency control is fully clockwise (i.e., minimum resistance in V_1 cathode circuit).

The circuit has the advantage of not requiring a negative supply rail. It is also simpler than other circuits which give optional triggered or free-running operation. Apart from these, it has no advantages over McMullan's circuit or other published circuits such as that of Attree (1949c). Because of these two advantages, however, the circuit has been used in the display units built in the Physiology Department.

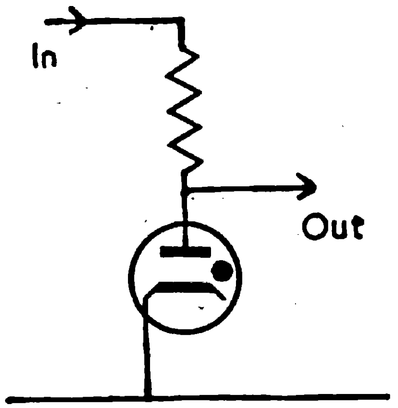


Fig. 8.8. Simple voltage stabilizer.

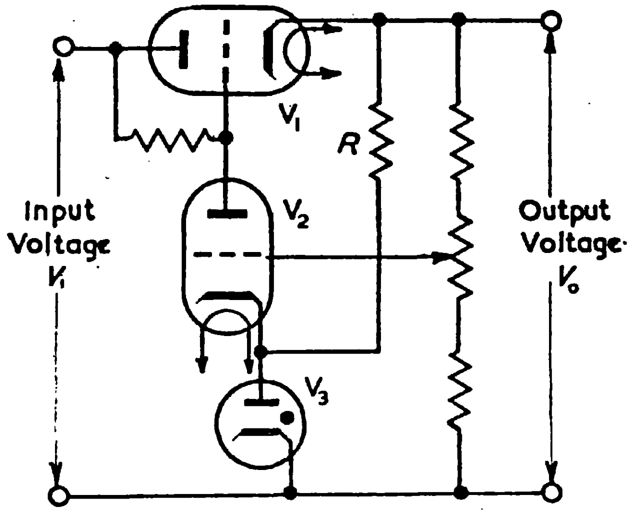


Fig. 8.9. Voltage stabilizer incorporating thermionic valves.

Design of Stabilized Power Supplies

Modern electronic apparatus generally obtains its H.T. supply from a stabilized power unit. The advantages of a good stabilized supply are :-

1. Constancy of voltage in spite of variations in the mains supply voltage.
2. Lower level of 50 c/s and 100 c/s ripple than can readily be obtained by the use of inductance-capacitance filters.
3. Low output impedance of power supply unit, giving freedom from interstage coupling through the H.T. line.

The simplest type of voltage-stabilizing circuit is that shown in Fig. 8.8, using only a resistor and a gas-discharge tube. Much better stabilization can be obtained, however, by using a stabilizer circuit incorporating thermionic valves.

Most voltage stabilizers incorporating thermionic valves have essentially the circuit of Fig. 8.9. A source of unstabilized D.C. power is connected to the input terminals on the left of the diagram, and the load is connected to the terminals at the right hand side. Valve V_1 is in series with the load. The voltage between earth and V_2 grid is a fraction of the output voltage;

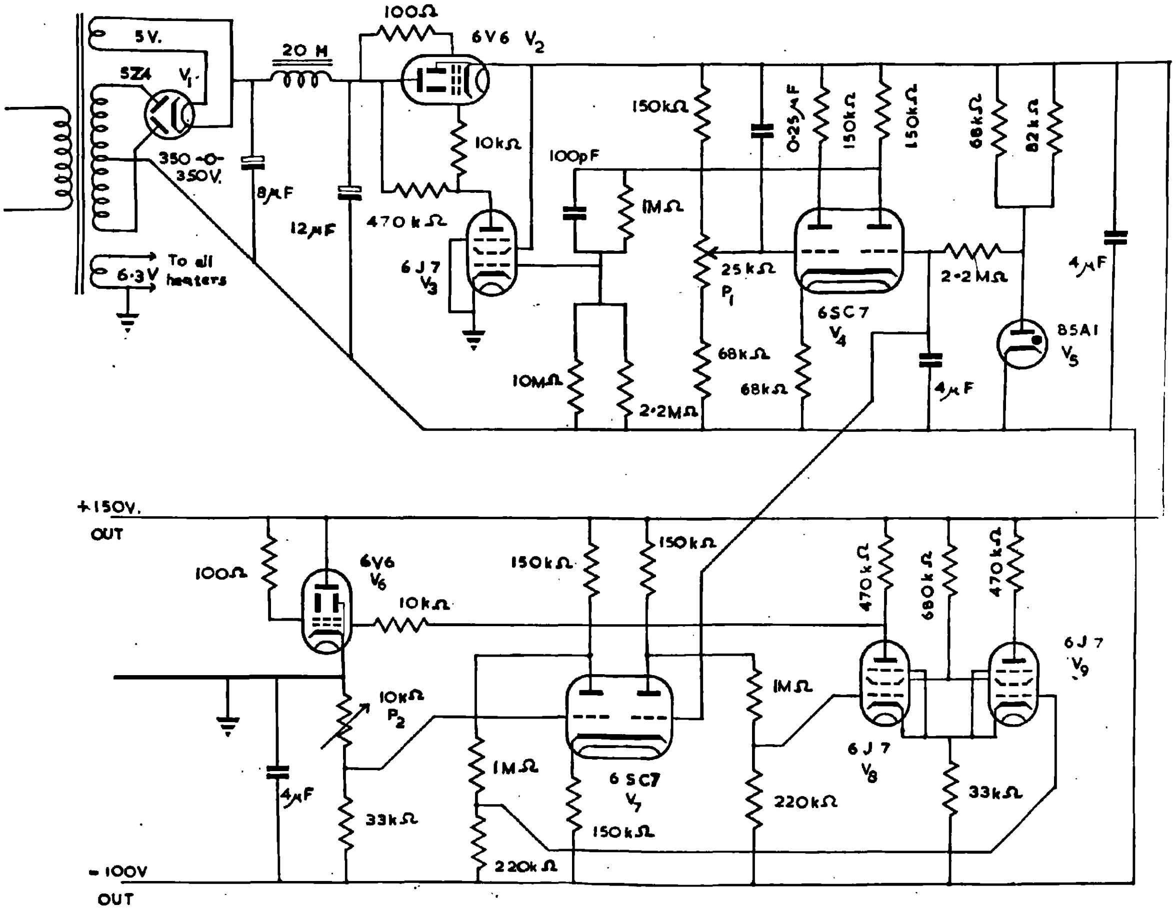


Fig. 8.10. Stabilized power supply unit giving + 150 volts and - 100 volts to supply pre-amplifiers.

there is a fixed voltage between V_2 cathode and earth, since V_3 is a gasfilled stabilizer tube. The grid-to-cathode voltage of V_2 is therefore the difference between a fixed voltage, and a fixed fraction of the output voltage. Any variation in the output voltage produces a corresponding variation in the grid-cathode voltage of V_2. This variation is amplified by V_2 and applied to V_3 grid in such a way as to oppose the variation in output voltage. In this way the output voltage is kept close to some desired value.

Power unit used with pre-amplifiers

In some stabilizers, the simple amplifying stage consisting of V_2 in Fig. 8.9 is replaced by two or more stages of amplification. Fig. 8.10 shows the stabilized power unit used to supply + 150 volts and - 100 volts to pre-amplifiers of the type described in Part 6. The rectifier V_1 produces an unstabilized D.C. supply, which is stabilised to provide a voltage of 250. A fraction of the output voltage of this part of the unit is applied to one grid of V_4, and thereby compared with the reference voltage developed across V_5 and applied to the other grid of V_4. The difference between the voltages on the two grids of V_4 is amplified by V_4 and V_5 and controls the grid potential of V_2, which is the series valve corresponding to V_1 of Fig. 8.9. The potentiometer P_1 is adjusted to bring the output voltage of this part of the unit to exactly 250 volts.

Since the requirement is for supply lines at + 150 volts and - 100 volts, a further stabilizer, consisting of V_6, V_7, V_8 and V_9 is used to provide a stabilized voltage of 100 volts between earth and the negative side of the supply. This stabilizer also uses the reference voltage provided by V_5. The first stage of amplification is given by V_7, and the second by V_8 and V_9. V_6 is the series valve in this stabilizer.

A current of 15 mA can be taken from this stabilizer, and the stabilization will hold for wide fluctuations of input mains voltage. A greater current could be drawn if a transformer with an H.T. winding of higher voltage were used. A current of 15 mA is sufficient for the present purpose, since the pre-amplifiers in use at present require only about 2 mA of current each, so the power unit could supply seven amplifiers at once. The output of the power unit is sufficiently free from hum and noise that when it is used to supply the pre-amplifiers there is no detectable increase in their noise-level above what is seen when batteries are used to supply H.T. power.

The High-Frequency Impedance of Gas-Filled Stabilizer Tubes

A contribution to the design of stabilizers of the type shown in Fig. 8.9 has been made by pointing out (Andrew, 1952b) that the gas-filled stabilizer tube V_3 may present a high impedance at high frequencies. The manufacturer's data on gas-filled stabilizer tubes generally states that they have a differential resistance of 200 to 400 ohms. It is not generally realised (and is not stated by the manufacturers) that the value quoted is applicable at low frequencies only, and at higher frequencies the impedance of the tube is very much greater.

My interest in the high-frequency impedance of stabilizer tubes arose because I have sometimes observed high-frequency oscillation taking place in voltage stabilizers whose circuit was essentially that of Fig. 8.9. It was discovered by my former colleague, Mr. P. Denes, that the oscillation could be stopped by connecting a capacitor of 0·01 to 0·1 μF in parallel with V_3. However, although Denes found a cure for the oscillation he did not explain it. It was not until later that I realised that since the remedy for the oscillation was to by-pass V_3 with a small capacitor, the valve used as V_3 probably had a high impedance at

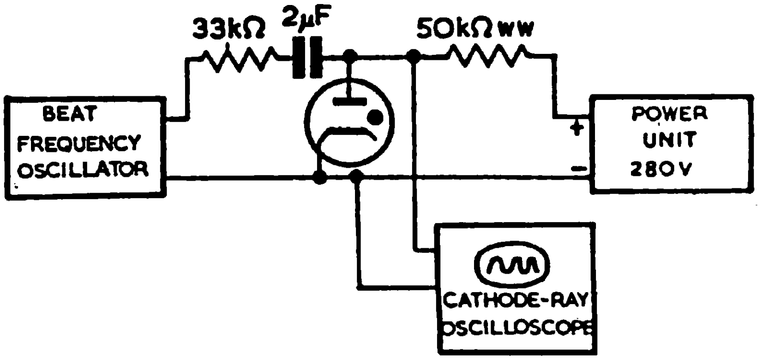


Fig. 8.11. Circuit used for tests on gas-discharge tubes.

high frequencies (at which the capacitor is an effective by-pass), and the high impedance was probably responsible for the oscillation.

Following the publication of a letter by Pocock (1952) in which he described another kind of oscillation which can occur with circuits of this sort, I made some simple tests to find whether the impedance of gas-filled stabilizers did in fact become large at high frequencies. I found that the impedance did rise with frequency, and published a short note on these results (Andrew, 1952b).

The tests were carried out using the circuit of Fig. 8.11. With a tube type 7475 it was found that when the output of the beat-frequency oscillator was 10 volts r.m.s. at 50 c/s, the A.C. voltage across the tube was 0·1 volt peak-to-peak. At 10 kc/s and 20 kc/s, with the same oscillator voltage, the peak-to-peak A.C. voltages across the tube were 2 volts and 3 volts respectively. With a tube type 85A1, the peak-to-peak voltage at 50 c/s was 0·25 volts, and at 20 kc/s was 1·9 volts.

Before I made these tests, I was not aware that the impedance of stabilizer tubes did increase with frequency. A certain amount of information had previously been published about the impedance variations with frequency, however. Benson (1950, p. 50) gives some information about the impedance of the Stabilivolt type of stabilizer tube at frequencies up to 6 kc/s. Other measurements were made by Hunt (1952) and by Iannone and Baller (1946) for VR tubes. Information about the high-frequency impedance of a gas-discharge tube has also been given by Williams (1952), but he worked with a type of tube used for surge suppression, and not actually a stabilizer tube. The results of all of these workers show that the impedance of gas-filled tubes increases with increasing frequency, but at the time of publication of my letter there was no quantitative information for most of the stabilizer tubes in common use.

Since my note on the subject was published, an extensive series of impedance measurements on stabilizer tubes has been reported by Benson and Mayo (1954 and 1956). In addition to these tests on commonly-used stabilizer tubes, Benson and Bental (1955) have made measurements on specially-made experimental gas-discharge tubes.

It appears that Benson and Mayo were stimulated to make measurements on stabilizer tubes by the publication of my note. They begin their 1954 paper :- "It has been pointed out by several investigators that the A.C. impedance of a glow-discharge voltage-regulator tube at high frequencies is considerably greater than the value which is quoted in data sheets for low frequencies. Andrew has drawn attention to this fact and mentions a few interesting experiments on 7475 and 85A1 tubes over the frequency range 50 to 20,000 c/s. He states that it would be useful to have information about the nature of the impedance, which he thinks may well be complex."

The impedance measurements reported by Benson and Mayo are for tubes of the types 85A1, 85A2, 7475 and S130 in the 1954 paper, and for types 90C1, 150B2, QS70/20, QS75/60, QS83/3, QS92/10, QS105/45 and QS150/15 in the 1956 paper. There appear to be two rather serious omissions in their work, for although they have made measurements over a wide range of frequencies, they have not indicated how the high-frequency impedance varies according to the magnitude of the D.C. current passing through the tube. The results of Iannone and Baller, for VR tubes, as well as those of Benson and Bental for experimental tubes, have shown that the variation of high-frequency impedance with D.C. current is considerable.

Also, Benson and Mayo have made no recommendation as to what amount of capacitance, or what network of capacitance and resistance, should be connected in parallel with any type of stabilizer tube in order to obtain a low impedance at all frequencies. There is therefore further work which can profitably be done on this subject.

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