Nerve-Model Experiments on Fluctuation in Excitability

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INTRODUCTION

A nerve fibre stimulated with identical electrical rectangular pulses of about-threshold intensity responds with an action potential in a fraction of all trials. This phenomenon, the fluctuation in excitability, viz. the property that in the threshold region the fibre responds to a non-random, fixed, input with a certain probability, reveals the existence of a noise factor in excitation. This is an endogenous property of the fibre, as can be concluded from the mutual independency in reacting of fibres in a two-fibre preparation upon application of the same stimulus (Pecher, 1939).

It was shown (Verveen, 1960, 1961) that upon low frequency stimulation (once per 2 sec) with identical stimuli

(1) the successive reactions have each time the same probability of occurrence, independent of the preceding reactions;

(2) the relation between the probability of response and stimulus intensity approximates the Gaussian distribution function;

(3) both parameters of this function, the threshold (the mean) and the spread (the standard deviation) are dependent on the stimulus duration : the (50 %) stimulation threshold is related to the stimulus duration according to the strength-duration characteristic; the coefficient of variation, the quotient of spread and threshold, called the relative spread (RS), proves to be independent of the stimulus parameters and about equal for short (0.25 msec) and long (2.5 msec) pulses;

(4) the fluctuation in excitability is also present during the recovery period, during a sub-rheobasic current and after the application of strychnine and urethane; only the parameters of the probability-intensity relation undergo a change;

(5) the RS, the measure of the width of the threshold range relative to the value of the threshold, is related to the fibre diameter : the smaller the fibre, the larger the RS (Verveen, 1962).

MODEL EXPERIMENTS

One of the possible sources of threshold fluctuation (*cf.* Frishkopf and Rosenblith, 1958) might be given by local statistical variations of the membrane potential due to

thermal agitation noise (Pecher, 1939 ; Fatt and Katz, 1952). In this case the RS might be a measure of the effective membrane noise potential relative to the threshold membrane potential (Verveen, 1962).

As long as we are not able to study the proper biological noise directly, in the above mentioned case for instance as slight disturbances of the resting membrane potential (Brook *et al.,* 1952), additional information may be obtained in an indirect way, assuming that a voltage noise is responsible for the phenomenon.

To this end model experiments were carried out with a twofold intention. First to gain an understanding of the influence of noise on a triggerable device. Second to develop methods allowing a more effective study of the processes occurring in the nerve fibre.

Work is also in progress on a mathematical model. The central problem is related to the axis-crossing problem, a topic well-known in the field of information and detection theory. For the case in question the difficulty arises in the form of a time-dependent function. In earlier studies on the theoretical interpretation of threshold measurements in the presence of noise of excitable tissue only the amplitude distribution (mostly assumed as Gaussian) of the random function and not the rate of change (the frequency spectrum) of the variable seems to have been at stake (Rashevsky, 1948; Hagiwara, 1954). Recently Viernstein and Grossman (1960) paid attention to the necessity to involve this aspect of the process in computations.

For reasons of simplicity we desired to start with a simple analogue device, general impression at this stage of the study being more valuable than numerical solutions on complex models. More intricate problems, for instance in connection with the local potential and its fluctuation (Del Castillo and Stark, *1952)* are not yet considered either.

This communication is, therefore, not a presentation of a rounded off investigation. We are just gaining some understanding of the behaviour of a triggerable device in the presence of noise.

Harmon's electronic neuron model (Harmon, 1959) provided the triggerable device. The stimulus, delivered by a Tektronix pulse generator, was fed into it via a network transforming the stimulus in the same way as it apparently occurs in an arbitrary functionally isolated single frog node of Ranvier (A-fibre, situated in intact sciatic frog nerve), one of the neural elements investigated in the previously mentioned experiments. This transformation is deduced from the time course of excitability after applying a non-effective constant stimulus of long duration and from the strength duration relation.

The excitability cycle after the application of a constant stimulus at t = 0 is of the form:

$$f(t) = \exp(-t/\tau_1) - \exp(-t/\tau_2) \text{ with } \tau_1 > \tau_2.$$

For a rectangular stimulus of finite duration *T,* starting at *t* = 0, this stimulus-transforming function can be written as

$$f(t) \text{ for } 0 \leq t \leq T,$$
$$f(t) - f(t-T) \text{ for } t > T.$$

The resulting excitability cycle and strength-duration relation of this model are comparable to those of the frog node studied in the situations mentioned above.

The rest of the model consists essentially of a monostable multivibrator. As soon as the voltage at the input reaches a critical value a pulse is given off. On the internal threshold of the device noise of a verifiable quality is superimposed. The noise is initiated in the model via a suitable network and a band-pass filter (Krohn-Hite; max. 20-20,000 c/s; slope 24 db/octave) by a white noise generator (Peekel; 20-20,000 c/s). In the experiments reported hereafter band-limited white noise of an adjustable intensity and frequency spectrum was used.

No recovery period was involved in these experiments, though another version of the model with a supra- and a second subnormal phase in the relative refractory period is ready for further investigation. Intentionally the duration of the recovery period was made much shorter in the model than it is in the fibre, thereby allowing to test the model with higher frequencies (intervals between the stimuli 160 msec). The lengthy recovery period of the nerve fibre requires a stimulation frequency not higher than once per 2 sec. Otherwise cumulative effects will complicate the interpretation of the experimental results.

RESULTS

The first series of observations on the model were limited to noise with a frequency spectrum of 20-1000 c/s. It followed that the behaviour of the model, on the whole, is about equal to that of the nerve fibre (1) the existence of a threshold region (Fig. 1); (2) the relation between probability of response and stimulus intensity, with given stimulus duration, can be approximated by a Gaussian distribution function; (3) both parameters, the threshold and the spread, depend on stimulus duration (Fig. 2). As
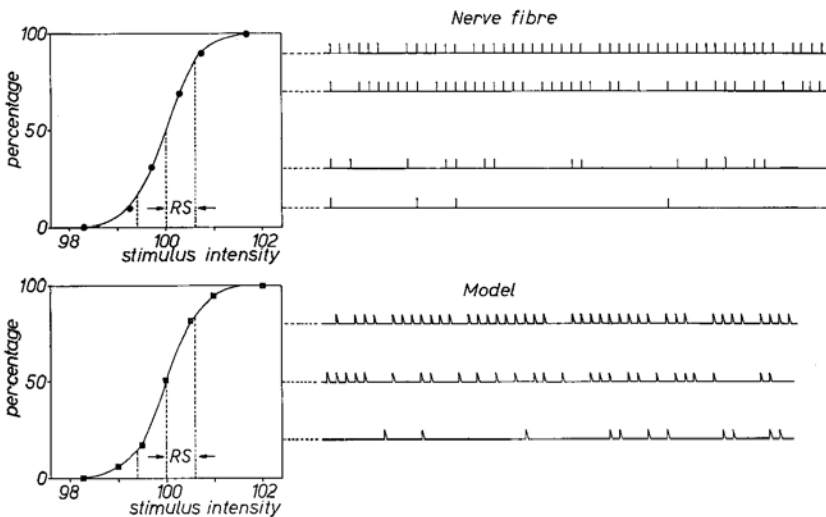

Fig. 1. The relation between probability of response and stimulus intensity, in percentage of the threshold. Stimulus given every 2 sec.

mentioned earlier for the nerve fibre the RS is the same for short and long pulses. For the model this is the case under certain conditions of the noise characteristics only. This property will be discussed later; (4) the relation between probability of response and stimulus duration - for intensities which are different but fixed each
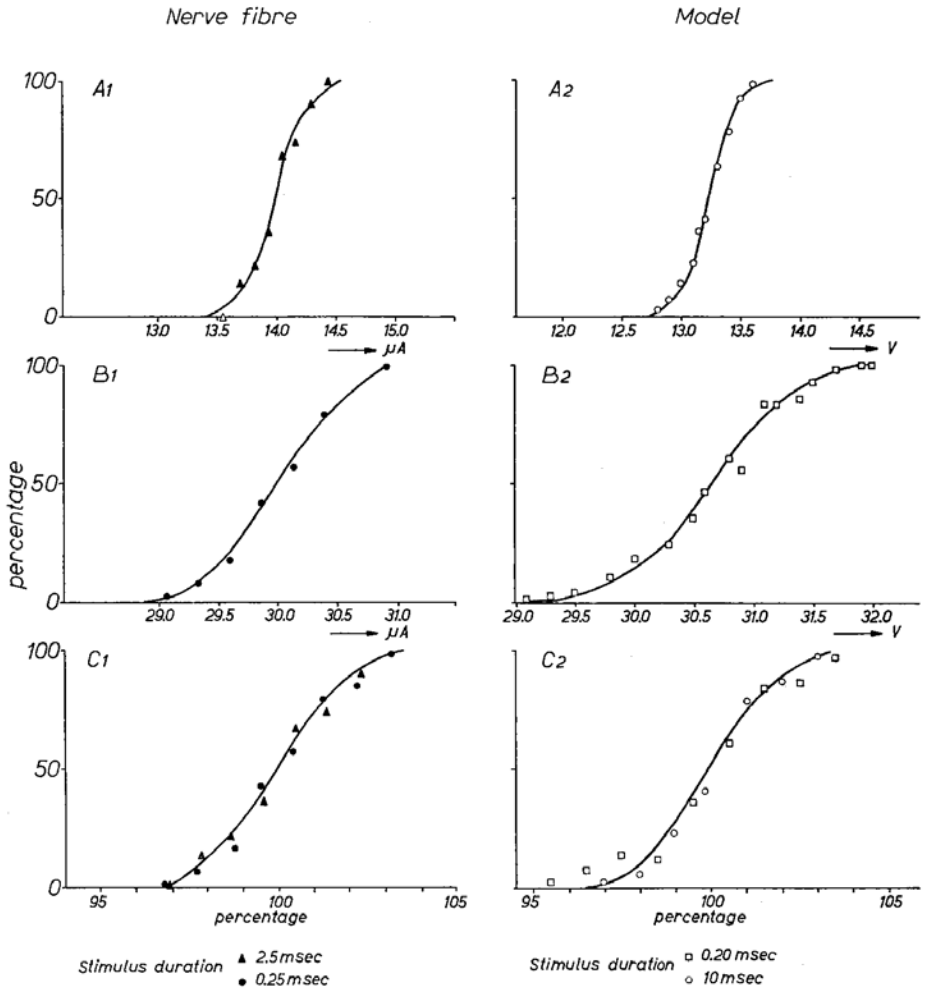

Fig. 2. The relation between probability of response and stimulus intensity for two stimulus durations (A, B) and the same relations after standardisation of the threshold (C).

time - has the same properties (Fig. 3) : the curves are asymmetrical to the right and steeper at higher intensities. At rheobasic stimulus intensities a percentage of 100 is never reached.

It appeared, therefore, that the agreement between the model experiments and our physiological experiments is satisfactory. The question, however, is whether the model can be used as a tool allowing a more effective study of the processes occurring in the nerve fibre.

Together with the fluctuation in excitability a variation is seen in the time interval

between the initiation of the stimulus and the passage of the eventual action potential in the part of the nerve fibre below the recording electrodes. This fluctuation in response time occurs at the point of stimulation as a variation in latency. It is independent
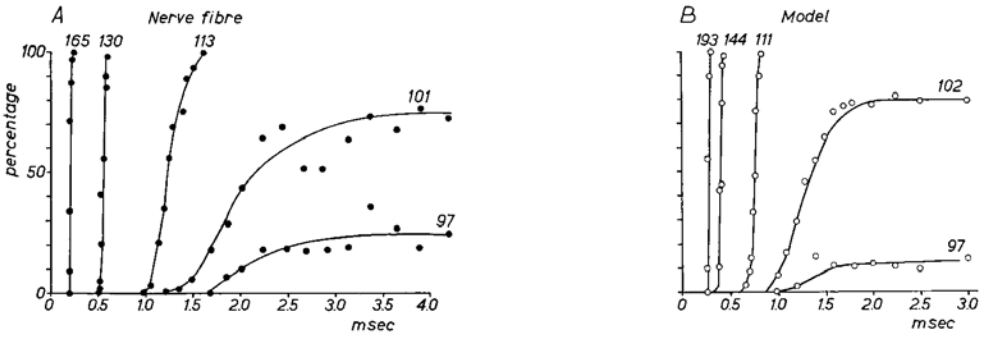

Fig. 3. Duration-probability curves. Stimulus intensity in percentage of the rheobase.

of the site of the recording electrodes on the nerve fibre (Blair and Erlanger, 1933) and probably due to the different instances of time at which the process of
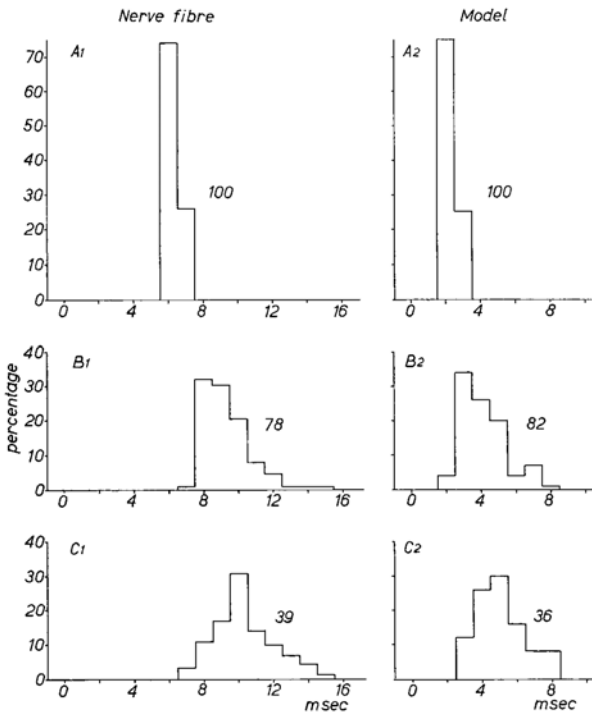

Fig. 4. Latency-distribution histograms. Stimulus intensity in percentage of rheobase: Al : 110.0; B1: 100.3; C1 : 99.7; A2: 103.0; B2: 100.8; C2: 99.8. Numbers beside histograms indicate the per-centages of response. Stimulus durations in all cases 10 cosec. For the nerve fibre the latency includes the time of conduction over a length of 12 cm (frog A-fibre).

excitation, initiated by the stimulus, triggers the nerve, because of its fluctuating excitability (Erlanger and Gasser, 1937).

The same phenomenon is present in the model. An orientating investigation of the latency distributions in the model upon stimulation with a pulse of long duration (10 msec) revealed the following characteristics (Fig. 4). At higher stimulus intensities the mean latency between stimulus and response is shorter and the dispersion is smaller. The histograms are asymmetrical to the right, in particular at low intensities of the stimulus.

Investigation of a frog nerve fibre (also with 10 msec duration pulses) showed that the characteristics predicted by the model are present (Fig. 4).

It will be noted that these latency distributions bear a close resemblance to the interval distributions studied by Buller *et al.* (1953) and by Hagiwara (1954) for the muscle spindle, by Grossman and Viernstein (1961) for slowly adapting, spontaneously discharging neurons of the cochlear nucleus and by Amassian *et al.* (1961) for the spontaneous activity of neurons in the reticular formation of the midbrain.

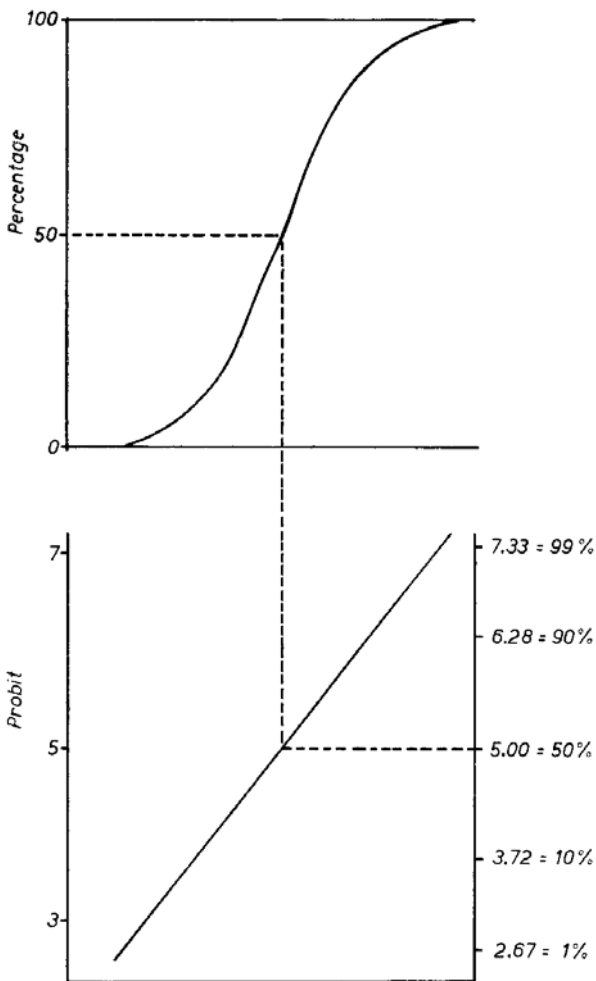It is probable that this phenomenon allows a closer investigation of the noise

Fig. 5. Probit transformation of a Gaussian distribution function (Finney, 1952).

characteristics. As yet no model studies were made on the relations between different modes of noise and the latency distributions.

By way of convenience the probability intensity function was chosen as a means to study the influences exerted by different modes of noise and to compare the behaviour of the model to that of the nerve fibre in this respect. In particular the RS is a surveyable measure.

The procedure used is the probit analysis (Finney, 1952). This analysis is applied to each set of data covering the relation between probability of response and stimulus intensity. The method is based on a transformation of the Gaussian distribution function in such a way that the function is made linear. The manner in which percentages are converted into probits is illustrated in Fig. 5.
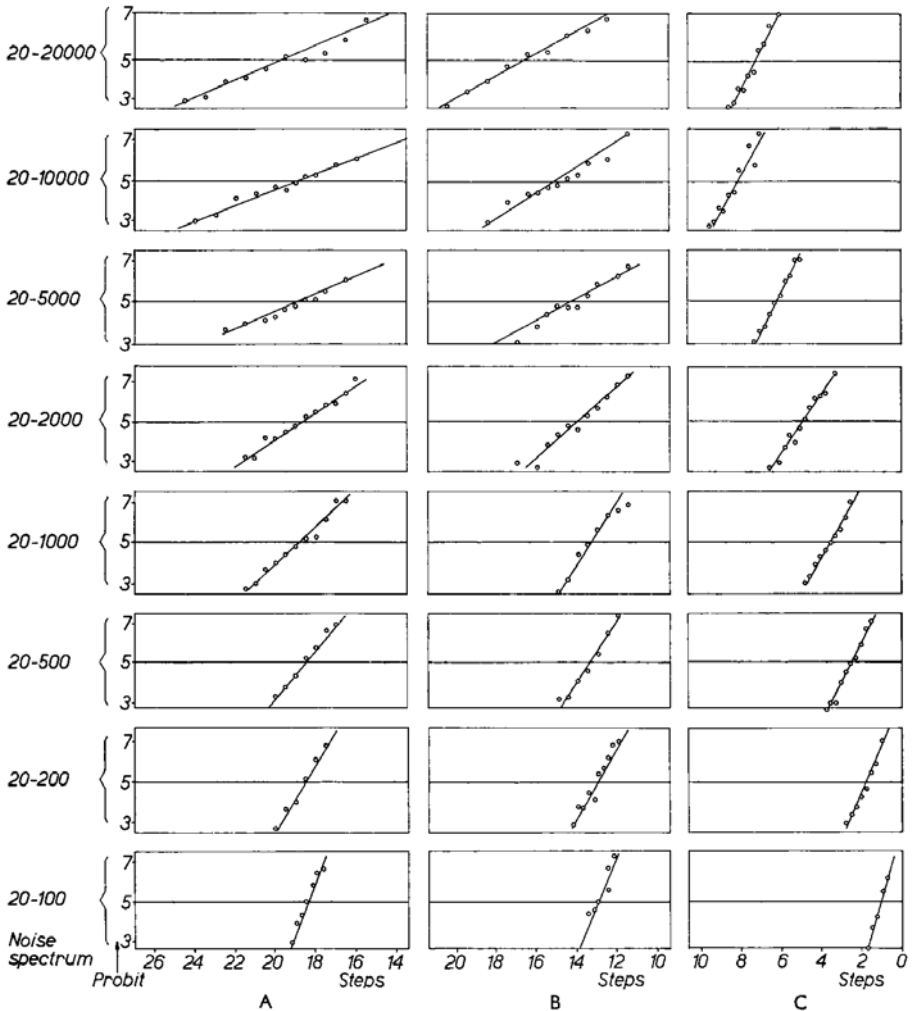

Fig. 6. Probability-intensity relations after the probit transformation. Stimulus durations: 0.2 msec (A), 1.0 msec (B) and 10 msec (C). The value of one step is 1 % of the threshold stimulus intensity. The band width of the noise frequency spectrum is indicated on the left in cps. Stimulus transforming function: $1 - \exp(-t/\tau)$ with $\tau = 0.5$ msec. Standard noise intensity (for explanation see text).

In this transformation the inverse of the standard deviation appears as the slope of the transformed function. Owing to the technique used, viz. plotting the intensity on the abscissa in units of the threshold, the reciprocal of the slope is not an estimate of the standard deviation but of the coefficient of variation, the RS.

Each set of data was obtained in the following way. The stimulus intensity is adjusted to such a value that upon stimulation the model reacts with a probability of about 50 %. This value is then an estimate of the threshold. Hereafter, the stimulus intensity is varied in steps, each step being equal to a given percentage (1 %) of the
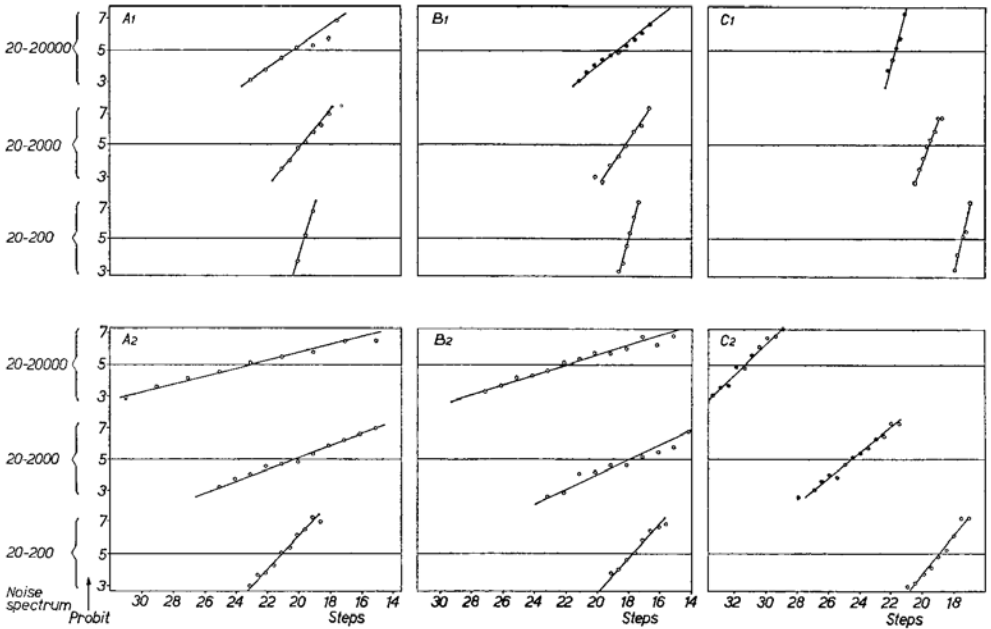

Fig. 7. Probability-intensity relations after the probit transformation. Stimulus durations : 0.2 msec (A), 1.0 msec (B) and 10 msec (C). The value of one step is 1 % of the threshold stimulus intensity. The band width of the noise frequency spectrum is indicated on the left in cps. Stimulus transforming function : $1- \exp(- t/\tau)$ with $\tau = 0.5$ msec. Noise intensity 5 db below (A1, B1, C1) and 5 db above (A2, B2, C2) standard intensity.

threshold value. The threshold range is scanned in this way, while a certain number (100) of stimuli is given at each step; the total number of reactions per step is noted and converted into percentages and probits. After this transformation the estimates for threshold and RS were determined graphically. The estimates obtained for the RS were not corrected for the shift in the (50 %) stimulation threshold following a change of the noise level or the frequency spectrum. This omission does not alter the estimates of the RS significantly (less than 10 %.

The results of the measurements concerning the intensity-probability relations for different noise intensities and noise frequency spectra are presented in Figs. 6, 7 and 8. Figs. 9 and 11 give a graphical summary of the estimates of the RS, while Fig. 10 gives an example of the degree of reproducibility of the measurements. Several values
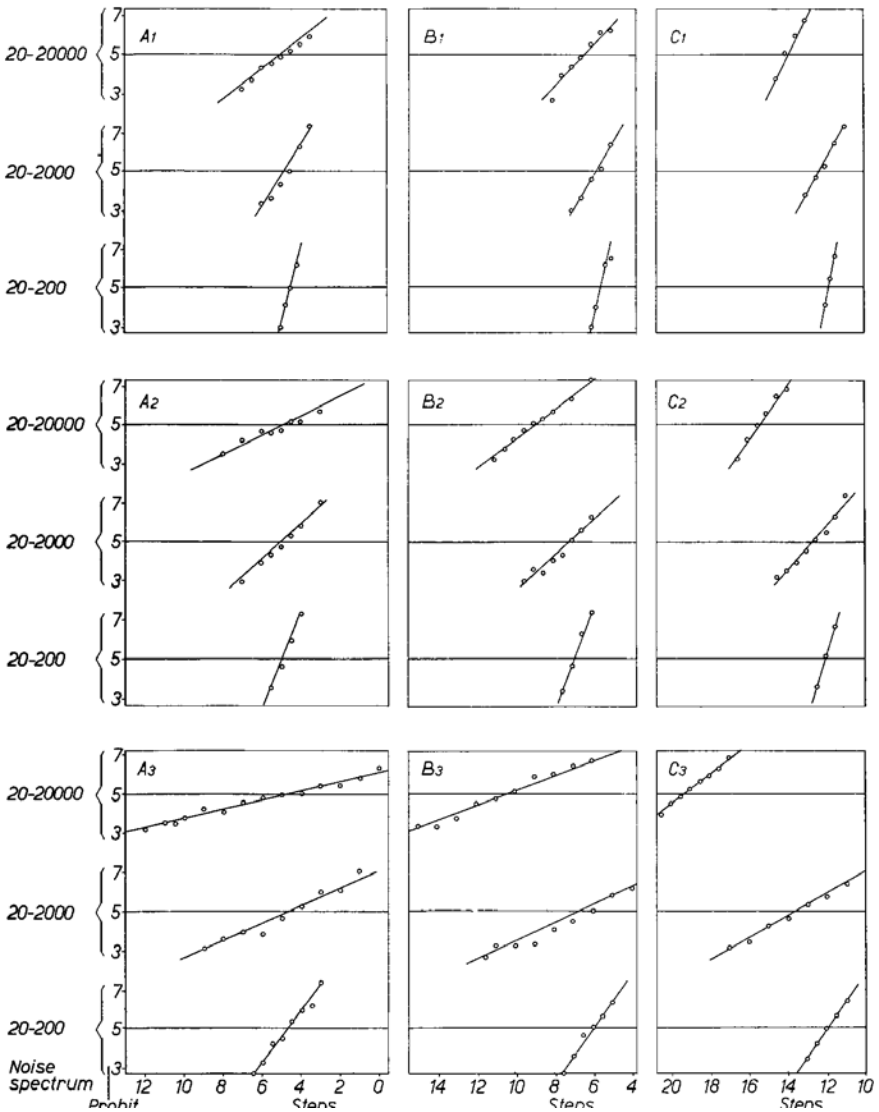
Fig. 8. Probability-intensity relations after the probit transformation. Stimulus durations : 0.2 msec (A), 1.0 msec (B) and 10 msec (C). The value of one step is 1 % of the threshold stimulus intensity.
The band width of the noise frequency spectrum is indicated on the left in cps. Stimulus transforming function : exp (- t/τ_1) - exp (- t/τ_2) with $\tau_1 = 6.7$ msec and $\tau_2 = 0.5$ msec. Noise intensity 5 db below (A1, B1, C1) and 5 db above (A3, B3, C3) standard intensity (A2, B2, C2).

of the upper limit of the noise frequency band width were examined. For ease of survey only the results for 20,000, 2,000 and 200 cps are reproduced in Figs. 9 and 11.

Three intensities of the noise were used : a so-called standard intensity and two other intensities 5 db above and below the first respectively. The root mean square (r.m.s.) value of the noise amplitude relative to the internal threshold is about 0.005 in the case of the standard intensity and for a frequency-band of 20-2,000 cps. The r.m.s. values for the other intensities and for the same frequency band are then 77 %
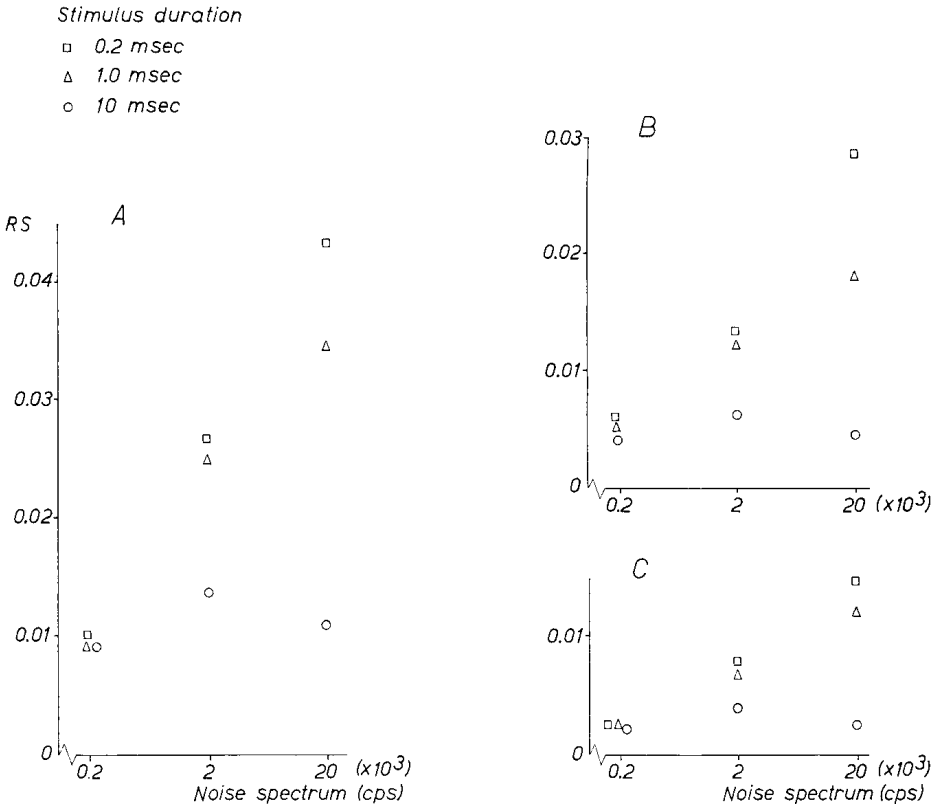
Fig. 9. Relative spread, RS, in relation to stimulus duration, noise intensity and noise frequency spectrum. Stimulus transforming function: 1- exp (- t/τ) with τ = 0.5 msec. Noise intensity 5 db above (A) and 5 db below (C) that of the standard intensity (B).

greater, respectively 44 % less than this value. Three stimulus durations were used 0.2, 1.0 and 10 msec.

Figs. 6, 7, 9 and 10 have been obtained with a stimulus transforming function *f (t)*
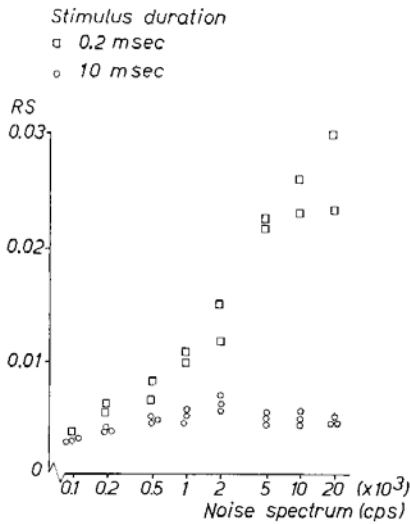

Fig. 10. As Fig. 9B to show the degree of reproducibility.

of the form : 1 - exp (- t/τ) with $\tau = 0.5$ msec. This case, comparable to a non-accommodating nerve fibre, was most extensively used in order to have more easily interpretable results.
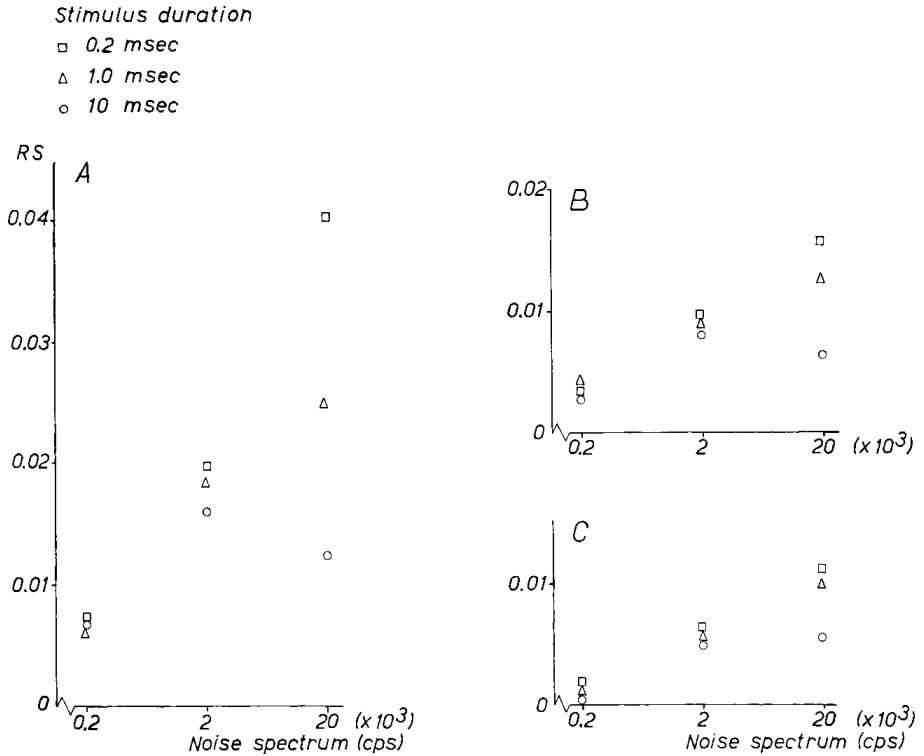

Fig. 11. Relative spread, RS, in relation to stimulus duration, noise intensity and noise frequency spectrum. Stimulus transforming function: exp (- t/τ_1) - exp (- t/τ_2) with $\tau_1 = 6.7$ msec and $\tau_2 = 0.5$ msec. Noise intensity 5 db above (A) and 5 db below (C) that of the standard value (B).

For Figs. 8 and 11 the function $f(t)$ is given by : exp (- t/τ_1) - exp (- t/τ_2), with $\tau_1 = 6.7$ msec and $\tau_2 = 0.5$ msec. This case corresponds with the before-mentioned frog A-fibre.

It can be seen, that changing the upper frequency limit of the band width, the lower being fixed at 20 cps for a stimulus of a fixed duration, has the following influences (1) with increased band width the threshold decreases; (2) the RS increases, at least for lower values of the upper frequency limit of the band width.

When stimuli of different durations are compared it is noted that the decrease of the threshold with increasing band width is more pronounced for long than for short stimuli, whereas the change of the RS is more pronounced for short than for long stimuli. Both effects are more marked for noise of higher than for noise of lower intensity.

It can be concluded that noise of increasing band width and intensity: (1) renders a triggerable unit more excitable, an effect more pronounced for long duration stimuli; (2) increases the width of the threshold region (relative to the threshold), an effect more pronounced for short duration stimuli.

DISCUSSION

The effect of noise intensity on the stimulus threshold and the RS is not demonstrated in the nerve fibre because threshold measurements on the same nerve without fluctuations are impossible. It is conceivable, however, to change the biological noise artificially in a predictable way without altering the fundamental ignition mechanism.

Strychnine is known to increase the threshold range (Erlanger *et al.,* 1941). A study of the influence of strychnine on the fluctuation region of frog A-fibres has revealed that the RS increases, while no influence on the threshold was found (Verveen, 1961).

In this case only short duration stimuli were used (0.12 msec). According to the results of our model experiments one should expect these results and furthermore that upon stimulation with pulses of long duration a decrease of the threshold will be present after treatment with strychnine. Experiments to detect whether or not the strychnine-treated nerve will exhibit this phenomenon upon stimulation with long pulses as predicted by these model experiments are planned.

The independency of the RS of stimulus duration, found for the nerve fibre, gives an indication of the nature of the noise.

From Figs. 9, 10 and 11 it is seen that with certain combinations of noise intensity and noise-frequency band the RS for the model is indeed the same for the three stimulus durations tested, within the experimental and compilation errors. So far as band-limited white noise is concerned, this means that the rate of fluctuation of physiologically effective noise does not exceed 2,000 cps and the upper limit may very well be about 500 cps.

Frishkopf (1956), in his experiments on first order auditory neurons with the use of externally added noise, arrives at a minimal number of 2,000 states per second. Viernstein and Grossman (1960) accepted a number of 1000 states per second in their study on neural discharge patterns.

These values are in agreement with the conclusion reached above from the comparison of our model and nerve fibre experiments. Furthermore, the idea that very brief fluctuations of membrane potential have probably little effect, is advanced by Buller *et al.* (1953).

Until now the lower frequency limit of the noise studied in the model has been kept constant at 20 c/s. Further refinement is possible by changing this lower limit also. This cannot yet be done because there is another, striking but somewhat disturbing, agreement between nerve fibre and model ; a long term instability, or drift, of the threshold. Its causes are not clear. The nerve fibre is a biological preparation and its properties are thereby subject to slow changes in time (metabolic changes, deterioration). The threshold is furthermore sensitive to changes in temperature, so that the experiments should be made in a strictly temperature-controlled environment. The transistors in the model are sensitive to thermal influences too. These were somewhat compensated by working in a thermally stabilised room. A long term drift of the stimulating apparatus may also come into play.

These circumstances make it necessary to work with short samples and consequently, to accept rather large variances in the estimates of threshold and RS. These can be

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reduced by increasing the rate of sampling, which was practicable for the model as described before. It is not possible to do this with the nerve fibre, because of its long recovery period.

Our observations on a simple nerve model with noise superimposed on the threshold and its comparison with the behaviour of the nerve fibre upon stimulation have thus revealed a number of interesting features and problems, warranting a further study on the nerve fibre (and on the model).

SUMMARY

In summarising our work it is concluded that a simple nerve model describes the intensity-probability and duration-probability relations as encountered in the nerve fibre quite satisfactorily. The general characteristics of the latency-distributions as predicted by the model appear to hold for the nerve and they indicate a means of further study of `noise' characteristics in nerve fibres.

Observations on the behaviour of the nerve model with noise of different intensities and frequency band widths revealed that noise of increasing intensity and band width renders a triggerable unit more excitable, an effect more pronounced for long duration stimuli, and increases the width of the threshold region (relative to the threshold), which is more pronounced for short duration stimuli.

The implications of these findings with regard to the actual nerve fibre are discussed.

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