Sonderdruck
aus „Kybernetik", 2. Band, 4. Heft, Februar 1965, S. 152–160
Springer-Verlag, Berlin • Heidelberg • New York

Fluctuations in membrane potential of axons and the problem of coding

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With 13 Figures in the Text

Summary. 1. Fluctuations in the resting membrane potential of frog nerve fibers were analyzed in the frequency range from 1 to 10 000 radians per second. The power spectrum follows a $1/f$ law.

2. Latency fluctuations have been measured for different stimulus intensities. The relation between standard deviation and mean follows a quadratic law. It can be shown for a number of different receptors that this relation is in part linear in part quadratic.

Introduction

Fluctuations in excitability were first described by MONNIER and JASPER and by BLAIR and ERLANGER

* Presented at the June 1964 meeting of the "International Organisation for pure and applied Biophysics" in Paris.

(1932). The phenomenon has been investigated further by PECHER (1939). He already thought that these fluctuations would be of importance in sensory nerve endings and in synaptic activity. This has been confirmed in the last decade (cf. HAGIWARA 1954, FATT and KATZ 1952).

The expressions " coding " and " noise " have been introduced into neurophysiology since the advent of information theory. Refined techniques of intra- and extracellular recording as well as statistical analysis of action potential series by means of computers have resulted in a mass of data on spontaneous and externally induced neuronal activity. Models and hypotheses have been put forward in order to organize the data. This report intends to describe one ingredient for future theories: neural noise.

The investigations on fluctuations in excitability and latency pursued by one of us (A.A.V.) since 1957, can be summarized as follows (Fig. 1)

Repetitive application of a rectangular electrical stimulus to an axon results in an action potential in a fraction of all trials, depending on stimulus intensity. The repetition frequency must be low enough to reduce the serial correlation coefficient for successive trials to zero. For frog axons this occurs to repetition frequencies of 0.5 trials/sec or less.

The relation between probability of response and stimulus intensity follows a gaussian distribution law. The mean of this function – the stimulation threshold and the standard deviation *(SD)* – the spread depend both on stimulus duration. The coefficient of variation of the distribution – the relative spread (*RS*) – is independent of the width of the rectangular stimulus[1].)

Different axons in a nerve react to a certain stimulus independently of each other (BLAIR and ERLANGER 1933, PECHER 1939).

When action potentials occur for a given stimulus, the latencies fluctuate. Here, the distribution in general does not follow a gaussian curve.

Another point of interest is the excitability fluctuation during the recovery period following an action potential. For the supranormal period it was found that the *RS* remained the same, although the threshold had a lower value. The *RS*, further, was not measurably influenced by a 15^0 C change of temperature, by a change in the CO_2 concentration of the atmosphere from 0 to 5% or by 1% urethane in the surrounding RINGER'S solution. However, strychnine in a 1:20,000 concentration (ERLANGER et al. 1941) produced an increase in the *RS* of about 50%. From the pattern of the changes in threshold, spread and *RS in* these experiments it was concluded that the *RS is* equal to the quotient of the *SD* σ of the membrane potential fluctuations and the threshold potential difference d.

[1] The moments of the excitability distribution are given other names, to prevent confusion with the moments of the latency distributions and with the terms used in the statistical analyses needed in the investigations. The name (stimulus) threshold is used for the mean in accordance with the arbitrary threshold definitions by BLAIR and ERLANGER (1935/36) and by HODGKIN and RUSHTON (1946). Spread is a synonym for the *SD*.

Theoretical considerations led to the same conclusion.

For axons of the species Rana, Astacus and Sepia it was found that

$$\log RS = -1.50 - 0.80 \log D,$$

where D is the axon or node diameter in microns.

To explain these findings, one might invoke as a cause the thermally generated voltage fluctuations across the membrane resistance (FATT and KATZ 1952, FITZHUGH 1955).

However, the calculations by FATT and KATZ result in the following relation between voltage fluctuations and fiber diameter

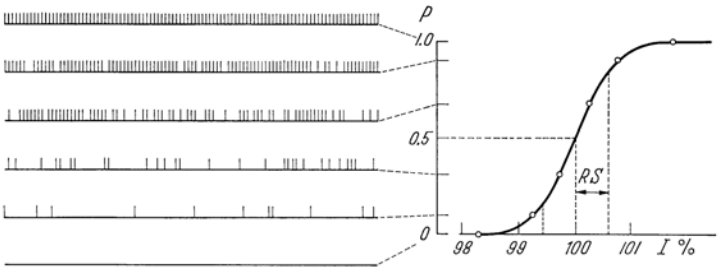

Fig. 1. The relation between response probability and stimulus intensity for a frog nerve fiber. Stimulus intensity in percentage of threshold. Stimulus presented every 2 seconds.
(After VERVEEN 1959)

$$\log \sqrt{v^{-2}} = -4.20 - 0.75 \log D.$$

Although the slopes of these two lines are nearly equal, fluctuation intensities derived from the second expression are much too small (about 10 times) to explain the fluctuations found.

Another discrepancy has been found for the width of the noise spectrum. Starting from the equivalent electrical diagram for frog node one arrives at the conclusion that the membrane time constant (60 μsec) is the limiting factor at the upper end of the spectrum, which leads to a cut off at 2800 c/sec. This problem has been investigated by means of neuron analogs and direct computation by TEN HOOPEN and VERVEEN and by TEN HOOPEN et al. (1963). In these studies the noise was assumed to be white. It was found that the spectrum would fall off between 500 and 2000 c/sec.

The cause of these discrepancies can only be found by means of a more direct approach. The following paragraph describes the result of direct measurements of the membrane potential fluctuations. In the last paragraph the problem of neural noise and coding in receptors is investigated, using knowledge gained from experiments on Ranvier nodes.

Voltage fluctuations in an axon segment

The empirical equations describing ionic currents as functions of membrane voltage and of time, as given by HODGKIN and HUXLEY for squid giant axon and by FRANKENHAEUSER (1957) and DODGE (1961) for frog node do not take into account any fluctuation phenomena, though these were present in the voltage clamp measurements on which the equations are based. Another, and as FITZHUGH pointed out in 1955, related aspect of the equations is that they do not have, at threshold, a discontinuity in the strict

mathematical sense. There is a narrow zone of stimulus intensities where the equations predict responses intermediate in size between subliminal responses and action potentials. However, as a consequence of membrane voltage fluctuations it will be impossible for these intermediates to occur : the noise will throw

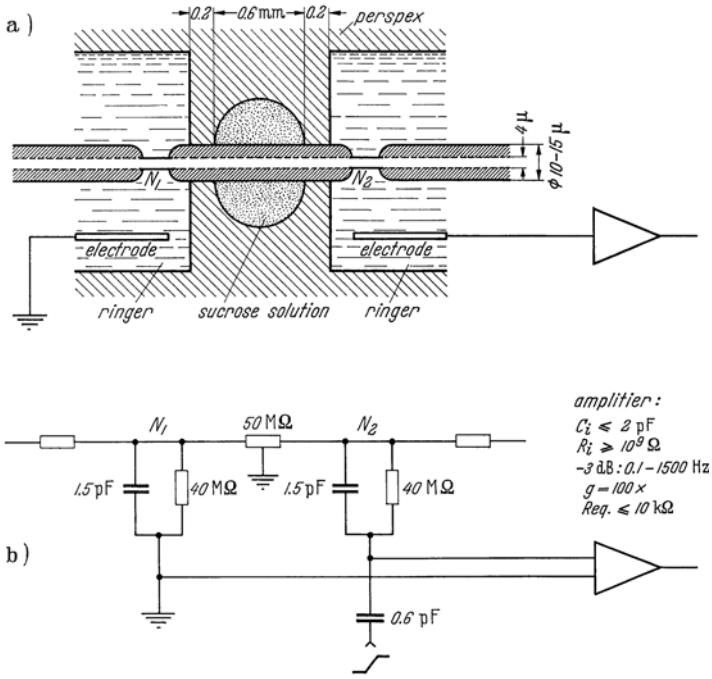

Fig. 2. a Arrangement of the nerve fiber in pools of RINGER'S solution. b Electrical equivalent of the nerve fiber in the resting state. Voltage sources are not drawn

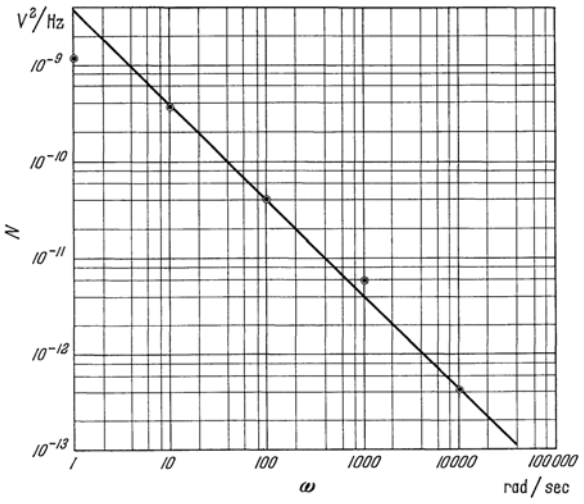

Fig. 3. Noise spectrum of a nerve fiber showing deviation from $1/f$ aw at the lowest frequency

the response of the system into one of the two classes, all or none, with a probability distribution depending on stimulus intensity. This phenomenon has been investigated by PECHER and recently by VERVEEN.

To estimate the magnitude of membrane voltage fluctuations, FITZHUGH (1955), FATT and KATZ (1952), BULLER et al. (1953), HAGIWARA (1954) and several other authors used NYQUISTS formula for the rms voltage fluctuations across the terminals of a metallic electron conductor: $e^2 = 4\,kT\,BR$.

For R the measured value of the membrane resistance was used. Generally this leads to discrepancies with experimental results. From a theoretical point of view NYQUIST'S formula does not apply in this case, for in the resting state already currents of several species of ions flow through the membrane, which leads to shot noise. Adsorption on fixed anions will lead to generation-recombination noise, moreover the total conductance of the membrane might fluctuate.

For these reasons we have tried to measure membrane voltage fluctuations directly. In our first series of experiments we used the well-known arrangement where the internodal segment of a single frog sciatic nerve fiber crosses the gap between two pools of RINGER' S solution (Fig. 2). Internodal isolation was realized either by desiccation or by a small flow of ion free sucrose solution.

The voltage between pools was amplified one hundred times by a specially designed preamplifier, which had to meet the conflicting requirements of very low grid current and high input impedance on the one hand, and low noise and microphonics on the other. After further amplification (1000 times) the signal was fed into a set of five bandpass filters, programmed on a general-purpose analog computer. The resonant frequencies were 1, 10, 100, 1000 and 10,000 radians per second and the bandwidth corresponded to a Q of 10. The narrow band noise voltages at the filter output terminals were squared and than integrated over a period of 5 to 15 minutes.

The noise spectra of the sixteen fibers measured in this way all show over most of the range covered an intensity inversely proportional to the frequency. Our most recent determinations which we believe are the most accurate, all show a deviation from this $1/f$ rule at the lowest frequency of one radian per second (Fig. 3).

At the high end of our spectral range, we sometimes found a transition to a flat power spectrum (Fig. 4).

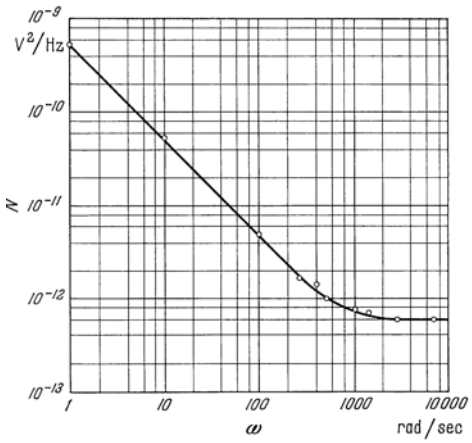

Fig. 4. Noise spectrum of a nerve fiber with low noise intensity, showing deviation from $1/f$ law at high frequencies

Unfortunately the range could not be extended so as to find the two transitions always and on the same preparation. At a given frequency in the 1/*f*-range, the noise intensities vary from fiber to fiber but do not differ more than one order of magnitude, that is somewhat more than a factor three in rms noise voltage.

The results so far obtained suggest that the power spectrum of nerve membrane voltage fluctuation runs flat from zero frequency to about one rad/sec, then follows the 1/*f* relation to a frequency somewhere between 10^3 or 10^4 rad/sec and then remains frequency independent again. At very high frequency it will fall off due to membrane capacitance. This spectrum is shown in Fig. 5 together with the autocorrelation function calculated from it. The shape of the autocorrelation function confirms PECHER'S conclusion that determinations of threshold fluctuations had to be done at stimulus intervals not less than two seconds or so to get independent trials.

The 1/*f* type of power spectrum is well known in physics and technology. It is called by different names such as current noise, flicker noise or excess noise. It is found in carbon resistors, carbon microphones and in some metal films where it originates in the granular structure of the conducting material. It is present in the electron emission of oxide coated cathodes of vacuum tubes, where the most probable cause is the presence of foreign atoms diffusing through the oxide layer and locally modulating the work function of the cathode material. As a final example we may mention the excess noise in semiconductors either in the bulk material or in junctions. It is believed that surface contaminations which trap free carriers cause conductivity fluctuations in this case.

Theoretical analyses for these cases are far from satisfactory. When we try to apply the mechanisms proposed so far to cell membrane physiology only a few approaches remain. The first is derived from MCFARLANE'S theory of 1/*f* noise (1950). Atoms or ions diffusing over the surface of a metal show density fluctuations. For a circular area of the surface the power spectrum of the density fluctuations is roughly proportional to 1/*f* over three decades. We could apply this to a circular cross section of nerve. Here however the area is not bounded by a hypothetical circle but by a circular barrier.

Another possibility would be that ion conduction takes place through channels in the membrane and that a channel could be blocked by adsorption of an ion. It has been argued by BELL (1958) that for an exponential distribution of adsorption times the number of ions waiting for passage would fluctuate and that the spectrum might follow the 1/*f* rule.

The numerical evaluation of these two mechanisms is rather difficult. We are working on it now. What kind, of mechanism will finally be the most plausible we do not know. The main point is that the study of fluctuation processes in nerve can show us something about the ion conduction on a molecular scale. On the experimental side several improvements are now being introduced. We have to expand the frequency range to get the full power spectrum. Further the method just described does not allow of a separation between the contributions of node membrane and internodal segment. The nodes adjacent to the gap are moreover shunted by neighboring fiber sections.

Fig. 6 shows how this has been circumvented. Isolation between nodes is now established by means of electronic feedback, a method introduced by FRANKENHAEUSER. The isolation amplifiers are stabilized, have

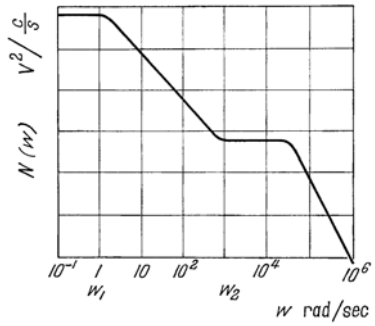

Fig. 5a. Hypothetical noise spectrum of a nerve fiber with a 1/*f* range terminated by flat power spectra at both low and high frequencies. At still higher frequencies the spectrum is supposed to be limited by membrane capacitance. Vertical scale in arbitrary units

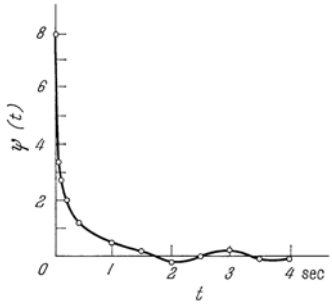

Fig. 5b. Autocorrelation function of the power spectrum of Fig. 5 a. Vertical scale in arbitrary units

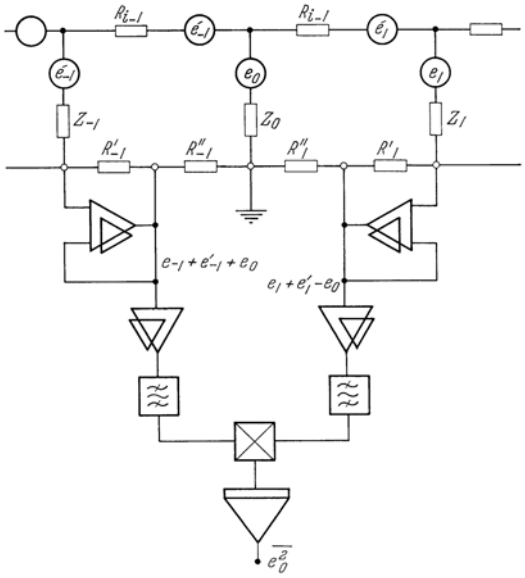

Fig. 6. Experimental arrangement for measuring noise of only one node of RANVIER. The nerve fiber is represented by its electrical equivalent

a grid current below 10^{-12} A, input impedance is 10^{10} Ω, the frequency response is flat from zero to 10 kc/s. The output voltages of the isolation amplifiers are $(e_{-1} - e_0)$ and $(e_0 - e_1)$, respectively, where e_0 is the fluctuating voltage of the middle node membrane and

e_{-1} and e_{+1} are the noise sources to the left and right side of that node.

After further amplification the output voltages are supplied to bandpass filters having identical tuning frequencies and bandwidths. The two narrow band noise voltages are multiplied with each other and so we obtain

$$e_{-1}e_0 - e_{-1}e_1 - e_0^2 + e_o e_1.$$

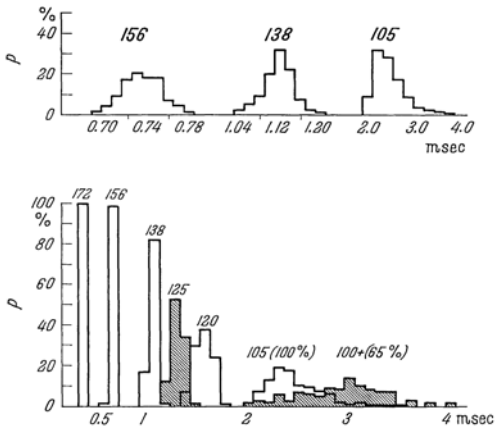

Fig. 7. Latency distributions of a frog node of RANVIER upon stimulation with long duration rectangular currents. Abscissae: time in msec. Ordinates: percentage of total number of latencies recorded. Stimulus intensity in percentage of absolute threshold. Latency distributions at stimulus intensities of 105, 138 and 156 % are also plotted on expanded abscissae to show shape of the distribution

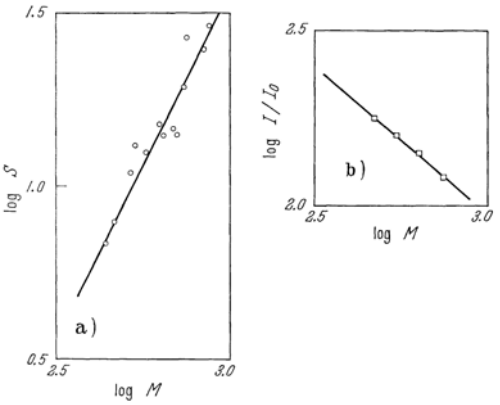

Fig. 8 a. Log-log representation of the relation between the mean M and the standard deviation D of the latency distributions of a frog node of RANVIER. Time is measured in microseconds. Each point is calculated from 25 meas-urements. The best fitting line with a slope of 2 is drawn

Fig. 8b. Log-log representation of the relation between the mean M and the percentage intensity of the stimulus

After integration the only term remaining is $\overline{e_0^2}$, the mean square of the fluctuating voltage across the middle node. This we can relate to the nodal membrane impedance and to fluctuations in excitability and latency.

Membrane noise and coding

Upon stimulation of an excitable membrane the existence of membrane noise becomes manifest by a fluctuation in its excitability, and, if an action potential is generated, by a fluctuation in its latency: the interval of time between the onset of the stimulus and the beginning of the action potential.

The threshold range is rather narrow in thick axons (the *RS* is small) and the safety factor is large, so one might ask whether the experiments mentioned in the introduction do give much information relevant to the problem of "coding and neural noise". However, thin elements may exhibit an impressive degree of neural noise (FATT and KATZ 1952, VERVEEN 1962). And, even for elements with not much noise (with a small *RS),* the fluctuations will always become manifest as fluctuations in latency, also for high intensity stimulation.

In this paper the preliminary result of experiments on latency fluctuations of isolated nodes of RANVIER will be communicated.

Fig. 7 gives an impression of the different latency distributions obtained for different stimulus intensities

At stimulus intensities about the threshold range, the distributions are broad and skewed to the right. With increased intensity of stimulation the distributions shift to the left – their mean value decreases –, they become much narrower and they also lose their asymmetrical appearance. The upper distributions shown, except the one at the far right, can be regarded as symmetrical, as has already been pointed out by HORVATH et al. (1961). In Fig. 8a a log-log plot is shown of the *SD S* versus the mean *M* of the latency distributions. The points characterizing these distributions move down with increase of the intensity of stimulation. The slope of the regression line is about 2. This is a striking phenomenon: when the mean decreases the *SD* decreases quadratically. This is a consistent property of the latency distributions. In Fig. 8b a log-log plot of the mean *M* of these distributions versus relative stimulus intensity is given. The impression is that the slope of this relation is about minus 1. If we take the reciprocal of the mean interval and express this as a "rate" of firing in impulses per second, this result indicates that the "firing rate" is linearly related to the intensity of the stimulus. A phenomenon that has been described for many receptors, for non-accommodating axons (cf. BULLOCK 1953) and, recently, for motoneurons (GRANIT et al. 1963).

One might perhaps ask at this point, what information with regard to our topic is given by these experiments. To this end both the latency fluctuations of the Ranvier node to external stimulation and the interval fluctuations of the sequence of action potentials generated by receptors are considered from the same point of view (BULLOCK 1953).

The properties involved are listed in the set, visualized by Fig. 9 (Related models were suggested or used by BLAIR and ERLANGER 1935/36, LANDAHL 1941, RASHEVSKY 1948, VERVEEN 1961, VIERNSTEIN and GROSSMAN 1961, TEN HOOPEN et al. 1963 a and b, and WEISS 1964).

1. Due to some mechanism or influence the membrane depolarizes. By first approximation the depolarization is exponential, asymptotically tending to some ultimate depolarization level U, with a time constant τ.

2. The starting level of this "activation depolarization" is at the resting potential in silent elements. In

active elements the process is supposed to start at the end of the refractory period.

3. When the depolarization crosses a critical level, an impulse will be produced. The difference between the starting level and the critical level is the threshold potential difference *d*.

4. The noise in the system is gaussian, with a *SD* σ. For ease of calculations its mean is set at the critical level d, which is, therefore, fluctuating.

5. It is assumed that no correlation exists between the respective noise amplitudes at successive crossings of the critical potential (HAGIWARA 1954, BISCOE and TAYLOR 1963, HORVATH et al. 1961).

For ease of presentation the effects of adaptation, accommodation and the refractory period are not taken into consideration in this paper.

The type of the interval distributions generated in this system (Fig. 9) is related to the size of the ultimate depolarization level U considered with regard to the threshold potential difference *d*:

1. For *U* smaller than *d* the distribution of intervals is exponential. We may visualize the process as the negatively sloped intersections of the fluctuating critical level with a horizontal line, indicating U, below d. At each intersection an action potential will be generated.

2. When *U* is about equal to *d* the distribution shows a substantial gap at its beginning, due to the fact that we must take account of the change in time of the activation process.

3. With *U* larger than *d* the locus of the points of intersections of the activation process with the critical range is curved. The distributions are about symmetrical, because of the fact that a crossing later in time can occur only if no earlier crossing has occurred.

4. When *U* is much larger than *d* the locus is linear and very steep. In this case the resulting distributions are Gaussian.

For this family of distributions the relations between the *SD S* and the mean *M* are

$$\log S = \begin{cases} \log M, \text{ for } U < d & \text{exponential distribution.} \\ 2 \log M + \log k, \text{ for } U > d & \text{symmetrical distribution.} \\ \log M + \log \sigma/d, \text{ for } U > d & \text{Gaussian distribution.} \end{cases} \quad (1)$$

The second part of this relation could be derived only by histogram evaluation (cf. the histograms published by TEN HOOPEN et al. 1963). Some uncertainty exists, therefore, about the exact value of the coefficient 2. On the basis of this result, however, an expression for the constant k could be derived

$$k = c/\tau \bullet \sigma/d \text{ , with } 2.08 < c < 4. \quad (2)$$

It will be noted that the *RS (= σ/d)* plays an important role in these equations.

Because of the same reasons no equations were found for the relation between the mean *M* and the ultimate depolarization level U. The mean *M* decreases with the increase of U. The authors have the impression that, for *U> d,* the mean *M* is hyperbolically related to *U,* while for *U< d* the error function comes into the equation.

In Fig. 10 the behavior of the *SD S* versus the mean M is pictured in a log-log plot. For increasing values of U the point characterizing the distribution moves from a position at the far right, on the " exponential" segment (with slope 1), via the segment with slope 2 onto the lower " Gaussian " segment with again a slope

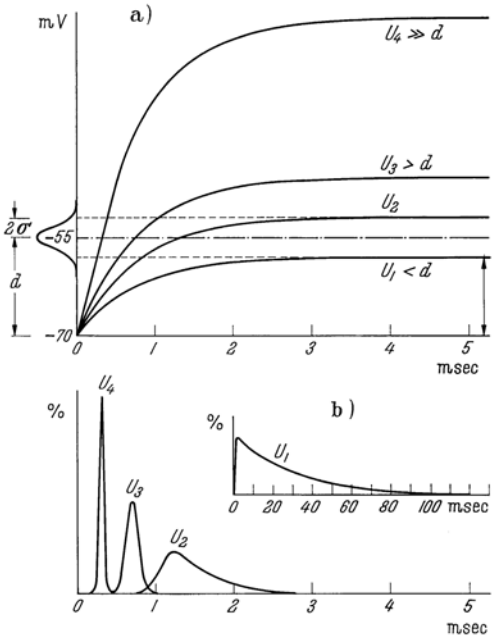

Fig. 9. a: representation of the model; b: schematic drawing of the resulting interval distributions. For explanation of symbols see text

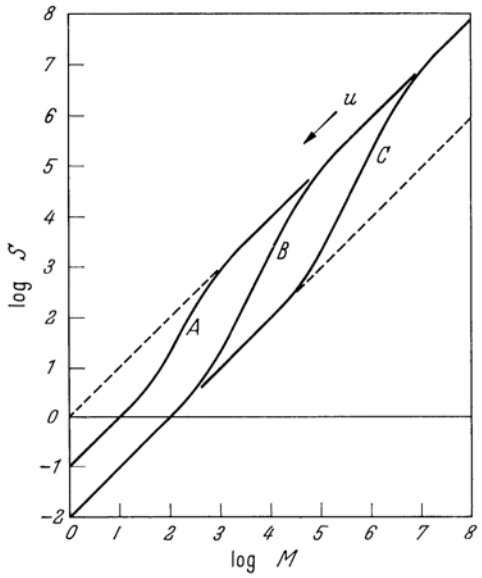

Fig. 10. Theoretical relations between mean *M* and standard deviation *S*. Both are expressed in log (microseconds). The values of the *RS* and of τ (msec) are for *A :* 0.1 and 1, for *B :* 0.01 and 1 and for C : 0.01 and 10

of 1. The middle segment of the relation will be called the "quadratic " segment, for obvious reasons. The influence of the amount of noise in the system is pictured by the relations *A* and *B*. For the first one the *RS* is 0.1, the second *(B)* has a *RS* of 0.01. The other properties of the element are equal. It is clear that an increase of the noise shifts the quadratic segment to the left and the lower segment upwards. The "exponential" segment remains in its place, but it becomes longer to the left. The upper part of this

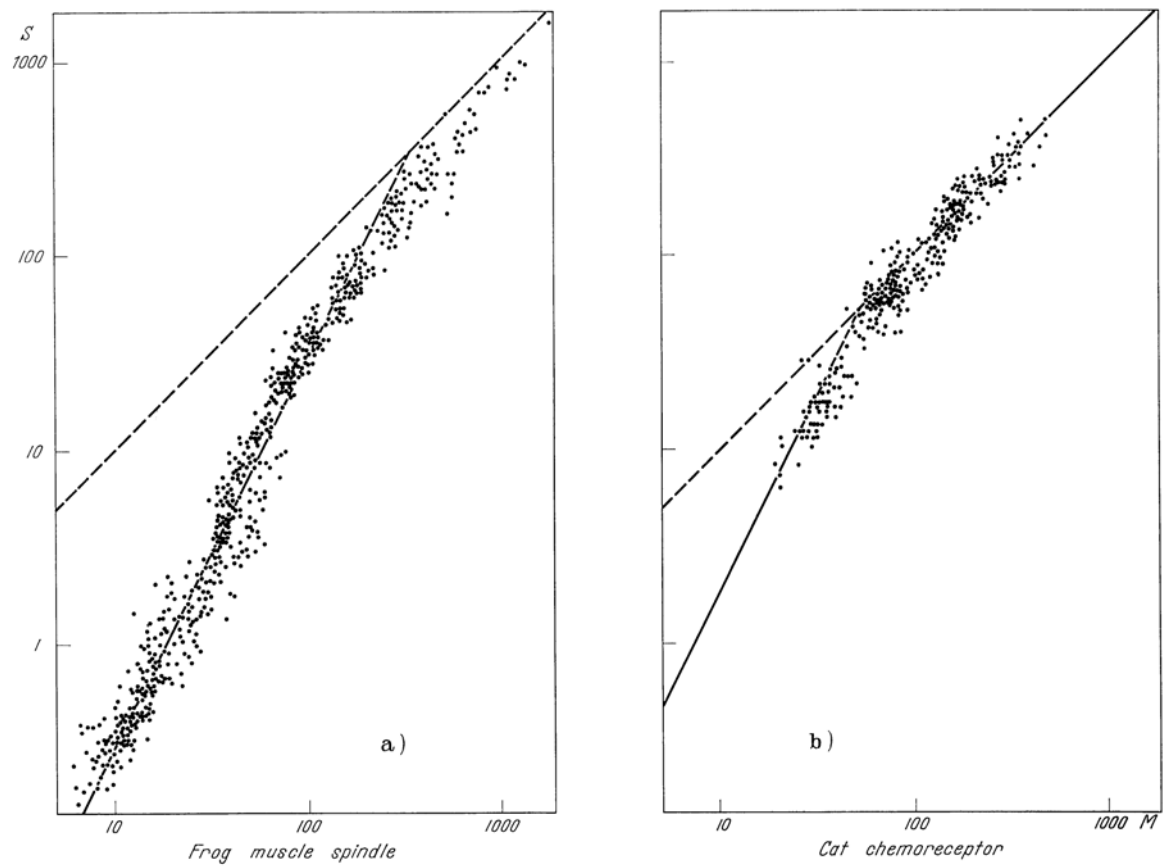

Fig. 11. The moments of the interval distributions of frog muscle spindle and of cat chemoreceptor, redrawn respectively after BULLER et al. (1953) and BISCOE and TAYLOR (1963). M and S are expressed in milliseconds. The quadratic line at the right side is drawn by the authors

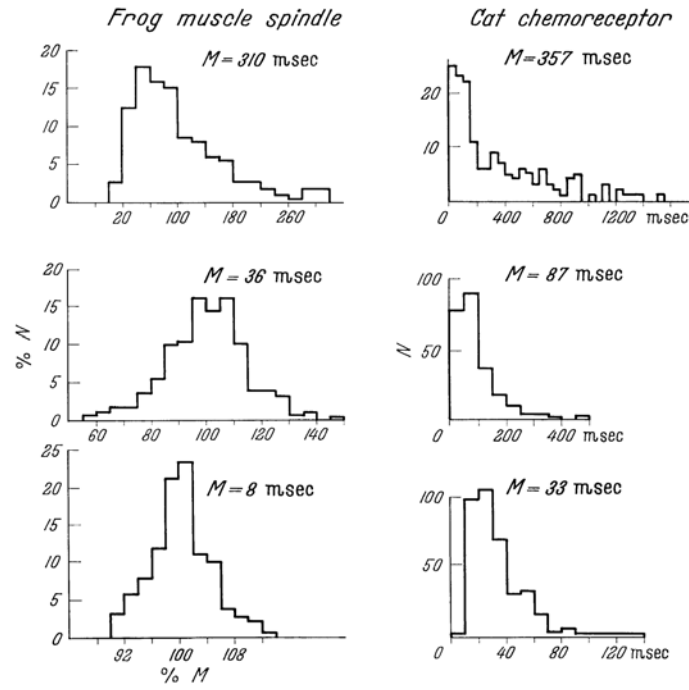

Fig. 12

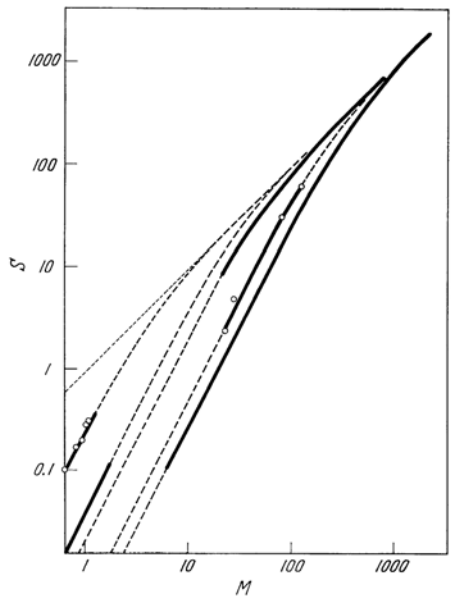

Fig. 13

Fig. 12. Interval distributions of frog muscle spindle (left) and of cat chemoreceptor (right), redrawn respectively after BULLER et al. (1953) and BISCOE and TAYLOR (1963). - Fig. 13. Coding ranges found for (from left to right) : a model (random step function TEN HOOPEN et al. 1963), an isolated node of RANVIER (only the upper part is shown), the cat chemoreceptor (BISCOE and TAYLOR 1963), the infrared receptor (calculated from BULLOCK and DIECKE 1956) and the frog muscle spindle (BULLER et al. 1953). M and S are expressed in milliseconds

type considered. If only the time constant is changed, increased in this case (Relations *C* and *B),* than the position of the "quadratic" segment is changed, it is shifted to the right. When we look at the upper two segments of relations *B* and *C* only, it is clear that the effect of an increase of the time constant is comparable with a decrease of the noise.

The relationships between the *SD S,* the mean *M* and the shape of the distributions (their third moment) specify the pattern of impulses for any ultimate depolarization level *U*. In other words : they specify the code. Because of their particular properties these distributions will be called "coding distributions of the one-two-one type ". They are first order coding distributions, because, due to the primary influence of membrane noise, one has to look for these distributions at the primary fibers, in receptors. Of course, membrane noise is only one kind, although important, of the different kinds of noise (fluctuations) one may distinguish in the nervous system.

Receptor patterns have been analyzed for the properties of their interval distributions by BULLER et al. 1953, HAGIWARA 1954 and BISCOE and TAYLOR 1963. Fig. 11 gives the relations between *SD S* and mean *M* for carotid body chemoreceptors in the cat, as determined by BISCOE and TAYLOR. Most points are located on the "exponential" segment. With more activity a downward shift is seen, indicating the approach of the "quadratic" relation. The figure also shows the relation, as found by BULLER and co-workers, for the frog muscle spindle. Here most points are located on the "quadratic" segment (its slope is 2,03), while for higher values of the mean a tendency to approach the "exponential" segment is visible. The shape of these distributions is as expected from their positions on the *S–M* graph : At the right side of Fig. 12 the interval distributions of the cat chemoreceptors (BISCOE and TAYLOR 1963) are shown. For high values of the mean the distribution is exponential. For smaller means the tendency to become less asymmetrical is apparent. Histograms published by BULLER et al. (1953), also shown on Fig. 12, and by HAGIWARA (1954), continue the trend: asymmetrical for larger means, symmetrical for smaller means.

In the last graph (Fig. 13) a summary of the findings is given. From left to right the coding ranges are shown in the *S–M* representation for: a model; the frog node of RANVIER; the cat chemoreceptor; the infra-red receptor of the rattle snake (these points are calculated from interval distributions published by BULLOCK and DIECKE 1956) and the frog muscle spindle. The discharge patterns of all these elements follow the one-two-one type coding distribution.

At the first center of integration, which may be located peripherally, the situation may change. If only coincidence is required and no inhibition is present, the coding range may show a related shape. General equations for these distributions have been developed by TEN HOOPEN and REUVER (1964). If complications occur, and also after the second integration things will probably become more complex. Work on the pattern of higher order distributions has been done by KUFFLER, FITZHUGH and BARLOW (1957), VIERNSTEIN and GROSSMAN (1961), AMASSIAN et al. (1961, 1962), MOUNTCASTLE et al. (1962, 1963), BISHOP et al. (1964) and by GERSTEIN, KIANG and coworkers (1960, 1961, 1962, 1964).

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Verveen, A. A. and Derksen, H. E. 1965. Fluctuations in membrane potential of axons and the problem of coding.
Biological Cybernetics, **2**, 152-160

Druck der Universitätsdruckerei H. Stürtz AG., Würzburg