Fluctuation Phenomena in Nerve Membrane

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Abstract - The fluctuations of the voltage across the resting membrane of myelinated nerve fibers have been analyzed. They show a 1/f spectrum and a Gaussian amplitude distribution and are related to the net flow of potassium through the membrane. When the average membrane voltage is made more negative by means of an external current, depolarizing deflections can be observed. They cause an asymmetry in the noise amplitude distribution and a marked increase in the subaudio spectral components of the noise. The depolarizing deflections can be attributed to batch-wise inflow of sodium ions. Possible mechanisms of both types of membrane voltage fluctuations are discussed.

INTRODUCTION

NERVOUS systems can be considered as mainly digital computing systems. Their basic elements, the nerve cells or neurons, can be likened to pulse generators incorporating their own power supplies and delivering uniform output pulses serving as input signals for similar cells. Cells, including neurons, consist of polyphasic systems in which ions and nonelectrolytes are dissolved or suspended in water, surrounded by a membrane about 10 nm thick, consisting of a lipoid layer enclosed in a protein envelope. Functionally, this membrane appears to be porous and exhibits selective permeability toward certain substances.

In the resting state, the ionic composition of the interior of the cell differs greatly from that of the interstitial fluid in which the cell is bathed. Inside the K^+ concentration is about 20 times that in the outside fluid; the Na^+ concentration is about 9 times higher outside than inside; and the Cl^- concentration outside is about 12 times that inside. The resting membrane is permeable to K^+, Na^+, and Cl^-, the approximate ratios of the permeabilities being $P_K : P_{Na} : P_{Cl} = 1 : 0.04 : 0.45$. The resting membrane potential is negative inside and dominated by the difference in K^+ concentration between the inside and the outside of the membrane. It is approximately equal to the Nernst equilibrium potential for K^+. The low concentration of Na^+ is maintained by an active extrusion mechanism. Partial depolarization by the application of an external voltage source causes a sudden, transient increase of sodium conductance as soon as a critical depolarization level is exceeded. This leads to an inrush of Na^+ and a transient reversal of the polarity of the membrane potential. This, in turn, serves to depolarize the adjacent region of the fiber. The process thus is self-propagating. It can be described as the passage along the membrane of a brief wave of outside negativity, the action potential. The membrane behaves like a monostable device exhibiting a transient tunnel diode characteristic. A diagram of one common type of neuron is shown in Fig. 1. It consists of a cell body with a multitude of arborized processes, the dendrites, which serve as inputs, long process, the nerve fiber or axon, which serves as the output. In this type of neuron, the axon is surrounded by a phosphatide-galactolipid layer, the myelin sheath, which is interrupted every 2 mm or so at the Ranvier nodes.

These are the only regions where depolarization occurs and an action potential is generated: a current initiated at one node flows through the extracellular fluid to the next node and back through the axoplasm.

A depolarization can be initiated by applying an external pulse of current. If this is of sufficient amplitude and duration, an action potential will be generated along the fiber in the cathodic region.

Experiments of this kind show the behavior of the membrane to be stochastic. For a given pulse duration, a range of pulse amplitudes can be found for which the probability that an action potential will be generated is an increasing function of pulse amplitude. If the fiber is repeatedly stimulated by identical pulses of an amplitude within this range, it is found that an action potential is delivered in only a fraction of the cases because neither the amplitude nor the duration of the initial local depolarization is identical from trial to trial. If an action potential is generated, its latency is variable (see Fig. 2).

That responses occur to only a fraction of the stimuli upon repetitive pulse stimulation of nerve fibers was observed first by Blair and Erlanger[1] and by Monnier and Jasper[2]. Pecher, however, was the first to study fluctuations in excitability for their own sake. He found that the occurrence or nonoccurrence of a response is completely random for low-frequency stimulation and that the probability of response depends on the stimulus intensity. Both Blair and Erlanger[1] and Pecher[3] showed that these fluctuations are properties of the individual nerve fibers since different axons in a single nerve react independently of each other. These results have been confirmed recently (Verveen[4],[5] and Poussart[6]). The relation between probability of response and stimulus intensity (Fig. 3) follows a Gaussian distribution law for rates of repetitive stimulation that are low enough to ensure statistical independence of successive responses (Verveen[4],[5] and Poussart[6],[7]). Since in frog Ranvier nodes, aftereffects are relatively long lasting, this condition implies repetition rates of one stim-
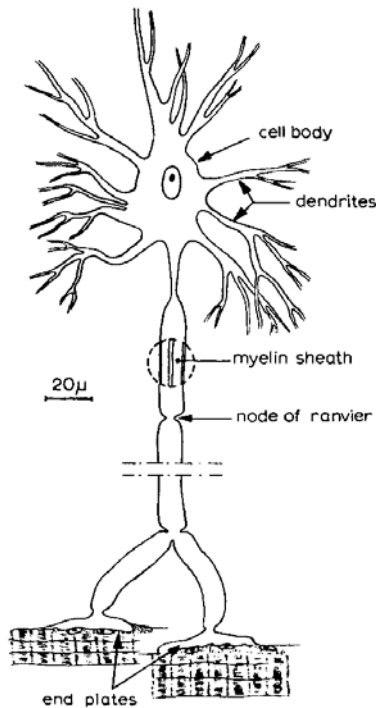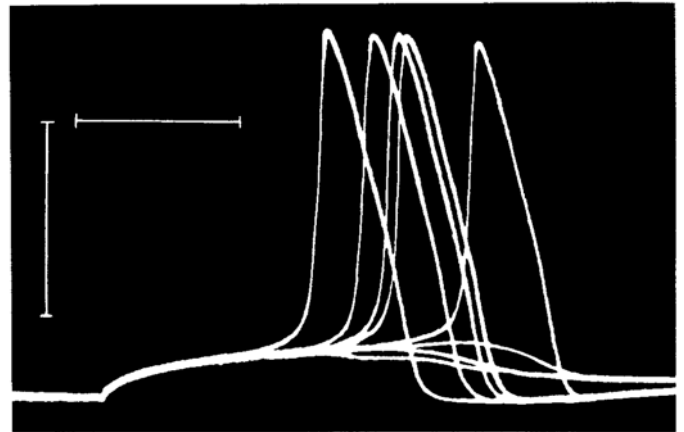
Fig. 1. Schematic representation of neuron

Fig. 2. Response of a Ranvier node to repeated stimulation at threshold intensity. Stimulus duration: 5 ms. Interval between successive stimuli: 2 seconds. Superposition of eight successive sweeps.
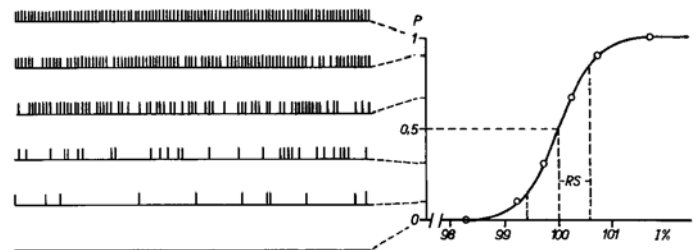

Fig. 3. Relation between stimulus intensity and probability of response. Frequency of stimulation: 0.5 Hz. (From Verveen[4].)

ulus per two seconds. Both the mean of the distribution function (defined as the threshold) and the standard deviation show an approximately hyperbolic relation to stimulus duration. The coefficient of variation (the normalized standard deviation) is constant for a given fiber. The latency distributions exhibit a rather complex dependence on duration and amplitude of the stimulus (Pecher,[8] Horvath et al.,[9] ten Hoopen and Verveen [10]).

For stimuli of long duration (10 ms) only a limited amount of data has been published (Verveen and Derksen[11] and Poussart[6]). The characteristics of the latency distribution can be described as follows (Fig. 4). For stimuli of about threshold intensity the distributions are positively skewed. As the stimulus amplitude is increased, the skewness diminishes and the mean and the standard deviation decrease. The standard deviation is quadratically related to the mean (Fig. 5). The fluctuation phenomena described here may have several origins, such as fluctuations of the critical depolarization level and/or fluctuations of the stimulus-induced depolarization (del Castillo and Stark[12] and del Castillo and Suckling [13]). For subthreshold stimuli of very short duration the amplitude of the depolarizing potentials was found to fluctuate randomly and in a quantal manner (this has been confirmed by Lüttgau[14]). In histograms of peak amplitudes the peaks were distributed regularly with interpeak differences of 0.6 to 1.1 mV (cf. Figs. 1 and 2 of Lüttgau[14]). This result was explained on the assumption that the depolarization potential is composed of a variable number of unit potentials (del Castillo and Suckling[13], the mean number of which depends on stimulus intensity. The action potential might be similarly composed. Quantal jumps in depolarizing potential are too large to account for the response probability function and

the latency distributions. Therefore, fluctuations of the critical depolarization level or of the resting membrane voltage must be involved. Theoretical studies (Landahl;[62] Verveen;[5] ten Hoopen and Verveen;[10] and Weiss[15]) and model experiments (ten Hoopen and Verveen[10] and Weiss [15]) have been made to investigate whether a single noise source could explain the fluctuations in the observed stimulus-response relationship. The central mathematical problem is related to the axis-crossing problem: starting from a given level (the resting membrane potential), a time-dependent function (the stimulus-induced depolarization) crosses a critical level. This event is assumed to determine the time of occurrence of an action potential.

When Gaussian noise of a given intensity and bandwidth is added to either the resting potential or the critical depolarization level, these minimum parameter models indeed reproduce the stimulus-response relationships observed in nerves. However, it is not possible to make a distinction between these two possibilities in this way. Not much information is gained on matters such as the frequency spectrum of the noise involved. In an investigation of response probability functions of axons of different species at room temperature, the following relationship was found to exist between the coefficient of variation, RS, and the axonal diameter d (microns), (Verveen [5]).
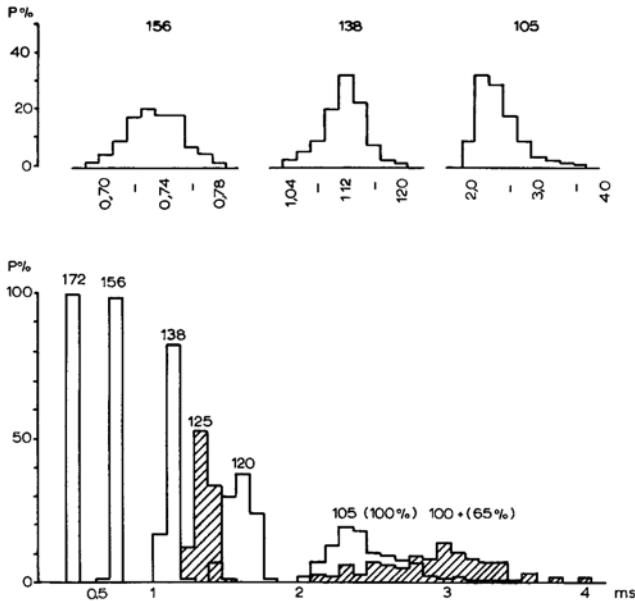
Fig. 4. Latency distributions of action potentials at a node of Ranvier in the frog. Stimulus duration: 5 ms. Interval between successive stimuli 3 seconds. Stimulus intensity in percentage of threshold. Probability of response for low intensity stimuli indicated between brackets. Ordinate percentage of number of latencies per class recorded at a given intensity of stimulation. A few distributions are shown with expanded abscissas to show the shape of the distribution. (From Verveen and Derksen[11].)

$$\log RS = -1.5 - 0.8 \log d.$$

Assuming a value of 20 mV for the difference between resting membrane potential and critical depolarization level, the rms intensity $E(mv)$ of the total noise in the system is

$$\log E = -3.2 - 0.8 \log d.$$

Thermal or Johnson noise has been invoked by several authors (Pecher,[8] Fatt and Katz,[161] Buller *et al.,*[17] and Hagiwara[18]) as a probable source of voltage fluctuations in neural membrane, although both Pecher and Hagiwara doubted that the intensity of thermal noise was sufficient to explain the phenomena observed. From calculations made by Fatt and Katz[16] and by Wijnja [19] on the basis of the Nyquist expression for thermal noise across the membrane resistance, it follows that for a bandwidth of 10 kHz

$$\log E = -4.0 - 0.75 \log d.$$

Both relationships have a similar dependence on axonal diameter, but the rms intensity of thermal noise is too small by an order of magnitude to account for the data. This difference in magnitude might by caused, therefore, by fluctuations of the critical level or might indicate the existence of membrane voltage noise due to additional sources. In the following, results of an investigation of membrane voltage noise are presented.
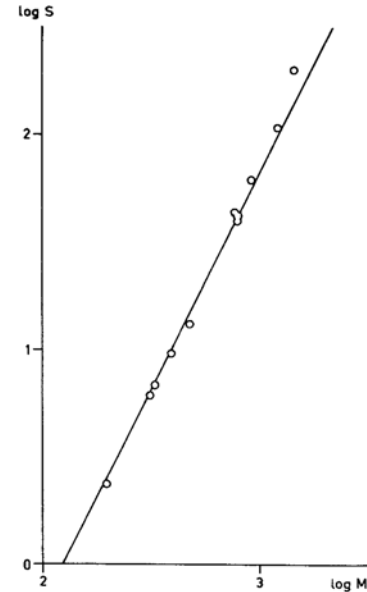

Fig. 5. Log-log representation of the relationship between the mean (M) and the standard deviation (S) of the latency distributions of a frog Ranvier node. Time in microseconds. Twenty-five observations per point. Line drawn with slope 2.

METHODS OF INVESTIGATION

The method devised to investigate fluctuation phenomena in nerve membrane was adapted to the object of investigation, a single nerve fiber of the sciatic nerve of the frog, *Rana temporaria.* Electrical properties of the node of Ranvier in the resting state and of the internodal segments and physical dimensions of both are given in Table I. Dynamic properties of nodal membrane, i.e., its characteristics as a pulse generator, were described by Dodge[20] and by Frankenhaeuser and Huxley.[21] A crude picture of a myelinated axon and its equivalent electric circuit is given in Fig. 6. Because the use of internal electrodes is impossible with this preparation, the only way to measure membrane potential and to modify it through direct-current injection is to use adjacent nodes as input and output terminals. These nodes have to be electrically isolated from the node to be investigated by means of air gaps, flowing sucrose solutions, or insulating jellies combined with electronic guardring systems. In the present investigation a three-terminal arrangement was used. Three nodes of a single axon were placed in fluid-filled compartments as shown in Fig. 7. These compartments were machined in a block of polycarbonate plastic. Two other compartments end in narrow grooves; they contain a salt solution that wets the middle part of the myelin sheaths between the three nodes. This serves to increase the electrical isolation between node pairs by means of a feedback circuit devised by Frankenhaeuser. Fig. 8 shows a top view of the nerve chamber with the single nerve fiber.

TABLE I
SOME DIMENSIONS AND ELECTRIC PROPERTIES OF FROG
MYELINATED AXON

Data given by Tasaki (1955), Tasaki and Frank (1955) for frog myelinated
axons of 12 to 15 μm diameter (myelinated part)

Myelin sheath	
Segment length	2 to 2.5 mm
Thickness	2 to 3 μm
Resistance	290±40 MΩ/mm
Capacitance	1.6±0.2 pF/mm
Axoplasm	15 MΩ/mm
Node of Ranvier	
Diameter	8 μm
Width	0.5 to 1 μm(*)
Surface area	2 to 5 x 10⁻⁷ cm²
Membrane resistance	41±6 MΩ
Membrane capacitance	1.5±0.6 μF

(*) Nodal diameters vary from fiber to fiber between 1 and 10 μm. In this
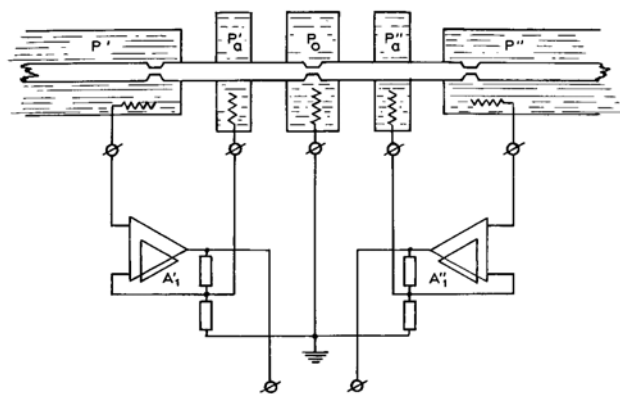investigation axons having node diameters in the order of 4 μm were
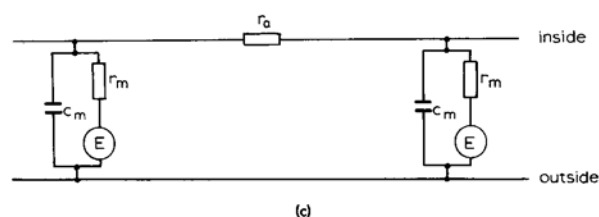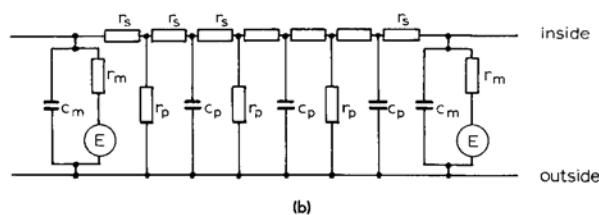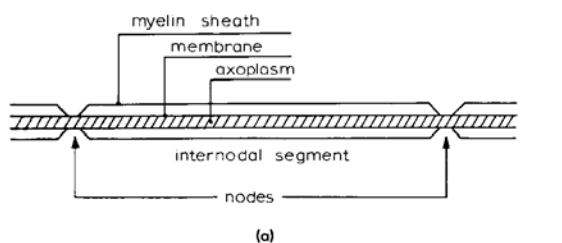selected.

Fig. 6. (a) Axial cross section of myelinated axon segment. (b) Equivalent
electric ladder network. (c) Simplified electric equivalent.

Even without electronic feedback isolation, the seals of
silicone grease that separate the channels have a resistance
of 100 to 500 MΩ. Generally, the compartments containing
the outer nodes are filled with an isotonic KCl solution.
Consequently these nodes are depolarized and their mem-
brane resistance is reduced to roughly 25 percent of its
normal value. The solution bathing the central node flows
at a low rate from a reservoir through the nerve chamber.
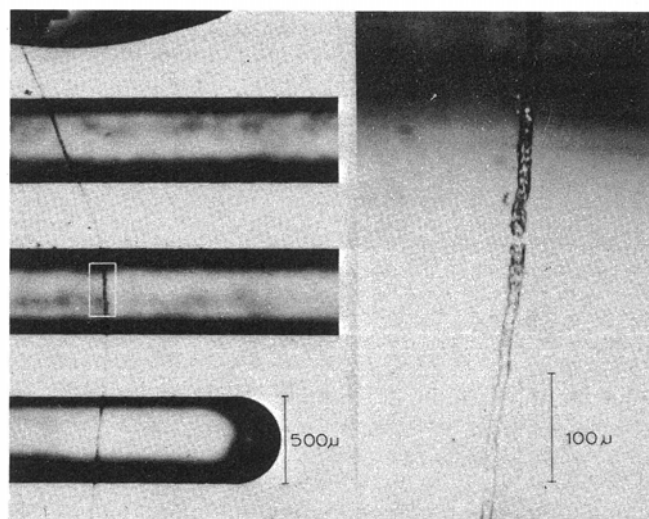The five compartments are connected through KCl-agar

Fig. 7. Three-terminal arrangement, showing nodes in pools P', P₀, and
P". Pools P_a' and P_a" are connected so as to decrease shunt losses along the
myelin sheaths.

Fig. 8. Top view of part of nerve chamber with single nerve fiber.
Insert shows node of Ranvier. (From Derksen.[23])

salt bridges to silver chloride-silver electrodes. These, in
turn, are connected to chopper-stabilized, electrometer
amplifiers. (Moore and Gebhart[22] and Derksen[23].)

Fig. 9 gives the arrangement of the nerve preparation and
amplifiers. The membrane potential of the central node can be
varied by means of dc current injected through a 1000MΩ
series resistor via one of the adjacent nodes.

MEASUREMENT OF NOISE SPECTRA

As the central node is the only common element in the
symmetrical circuit of Fig. 9, its noise voltage appears as a
common component of the output noise of the two
amplifiers. Consequently, multiplication of the output
voltages with each other followed by time averaging will
give a dc voltage proportional to the mean square voltage
across the central node (Derksen[23]). The noise
contributions of the adjacent segments of axoplasm and nodes
of Ranvier, as well as those of the two preamplifiers, were
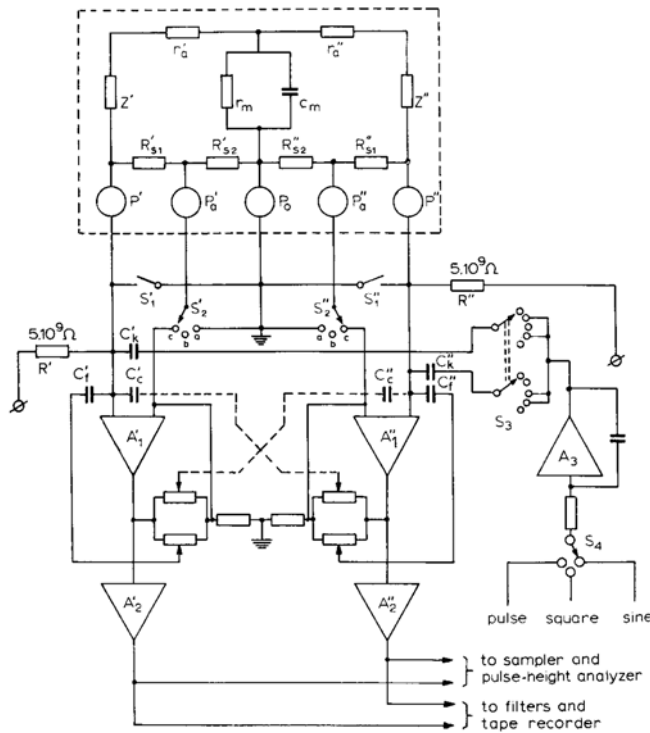reduced in this

Fig. 9. Detailed circuit diagram of three-terminal arrangement. A'_1 and A''_1 are chopper-stabilized electrometer amplifiers. Input capacitance neutralization is through 1 pF capacitors C'_f and C''_f, test signals can be introduced through 1 pF capacitors C_k and C''_k. Dc injection is through 5.10^9 series resistors. By means of a sinusoidal test signal introduced at the right-hand side and measuring ac output voltage of amplifier A'_1 with switch S'_2 in positions a, b, and c; shunt resistance R'_{s1}, R''_{s2}, and nodal resistance r_m can be determined.
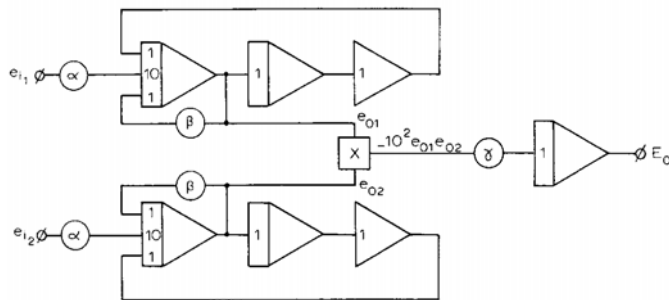

Fig. 10. Analog computer diagram showing bandpass filters, multiplier, and integrator. The integrator was sometimes replaced by a single time constant low-pass filter.

way, of course at the cost of increased integration time. Similar methods have been realized in the domains of radio-astronomy (Blum[24]) and underwater sound detection (Jacobson [25]) and have been suggested for the measurement of low-level light fluxes (Chen and van der Ziel,[26] Wolff, [27] and Pao et al.[28]).

The output voltages of the two amplifiers shown in Fig. 9 were filtered, after further amplification, by means of identical active bandpass filters (Fig. 10), whose center frequencies were between 1 rad•s^{-1} and 2.10^4 rad•s $^{-1}$. Later, a tape recorder was used off-line and analysis for

different frequencies was accomplished by changing the playback speed of the tape recorder. The output voltages of the filters were multiplied by high-speed analog multipliers, the product voltage being integrated over a suitable period of time or smoothed by a single-time-constant RC network and recorded on a servo-recorder. Integration periods and smoothing time constants were chosen to obtain estimates of the spectrum with statistical errors of less than 10 percent.

DETERMINATION OF AMPLITUDE DISTRIBUTIONS

Amplitude distributions were determined from samples of 1.5 seconds duration taken from the output of one of the amplifiers A'_2 or A''_2 in Fig. 9. Generally 100 000 samples were taken at a rate of 1000 samples per second. The sample pulses were sorted out by a 128-channel pulse height analyzer, one channel corresponding to 100 μV at the pre-amplifier input terminal.

The noise band was limited at the low-frequency end by an RC-coupling element having a one-second time constant and at the high-frequency end by the transfer function of the source impedance and amplifier system. From the amplitude distributions obtained in this way the standard deviation (corresponding to the broad-band noise intensity) and the reduced third moment (indicative of the skewness) were calculated. It is relevant to point out here that the calculation of the third moment corresponds to the cube-law rectification of asymmetric waveforms proposed by Bridges,[29] Kemal and Adams,[30] Hooper,[31] and Young.[32] During this investigation the determination of the third moment of the amplitude distributions turned out to be a convenient way to detect the presence of small depolarizing pulses almost hidden in Gaussian noise.

It is evident that the equipment had to be checked for gain, linearity, input impedance, and frequency response. The noise spectrum of the amplifiers was measured with shorted inputs as well as with 100-MΩ resistors as source resistances. Amplifier noise was generally found to be one to two orders of magnitude lower than the nodal membrane noise measured during the experiments. The measurement procedure could be checked by means of a network of resistances (Fig. 11), analogous to the nerve equivalent circuit shown in Fig. 6, with approximately equal parameter values. The criterion was that the measured mean squared noise voltage was equal to that calculated from the Nyquist formula $e^2 = 4kTR$ volt per cycle of bandwidth, R being the value of resistance R_4 in Fig. 11(a) or of R_3 in Fig. 11(b). The worst cases were at the low-frequency end, 0.2 to 100 rad•s^{-1}, because of flicker noise of the preamplifiers and at the high frequency end, from 10^4 to 5×10^4 rad•s^{-1}, where experimental errors were introduced by capacitive cross talk and unequal phase shifts in the amplifier channels. Voltage fluctuations in the electrodes were found to be negligible, which is no surprise in view of their large surface areas and their corresponding low resistance of a few kilohms.

Before each experiment the resting membrane voltage, membrane resistance, and the amplitude and waveform of
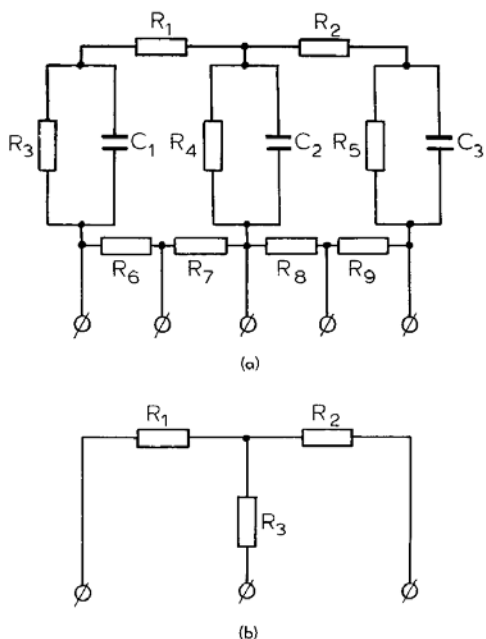
Fig. 11. Test circuits simulating axon; (a) includes nodal capacitances and shunt-leak resistances; (b) is a simple test circuit to check the correlation procedure.

Fig. 12. Log-log plot of noise power per cycle of bandwidth N against frequency ω. Noise spectrum with slope of −1, changing into a white spectrum at about 1000 rad/s. (From Derksen[23])

the nerve impulse were checked. Nodes that gave abnormal values of these variables were rejected.

RESULTS

Measurements of the noise spectra (Verveen and Derksen, [11] Derksen, [32] and Derksen and Verveen [34]) revealed the existence of 1/f noise between 1 and about 10 000 rad•s^{-1} in all 20 nodes investigated. The term 1/f noise is used to denote current or voltage fluctuations with a spectral intensity $e^2 = cf^{\alpha}$ with $a \approx -1$ over several decades of frequency (Fig. 12).

At the high frequencies the spectrum approaches that of white noise as shown in Fig. 12. At low frequencies a decrease of the slope of the log noise power versus log frequency line may occur (Fig. 13). This is to be expected since the total noise intensity would otherwise be infinite. In some cases an increase of this slope did occur, however (Fig. 14), and was found to be associated with the presence of depolarizing noise bursts of the type described by del Castillo and Katz.[35] In experiments reported elsewhere (Derksen [23] and Derksen and Verveen [34]), it was shown that interference with metabolism or with sodium ion transport did not influence the 1/f spectrum but that the intensity of the l/f spectrum was found to be related to the passive flux of potassium ions through the membrane. At the potassium equilibrium potential, with zero flux for the potassium ion, the 1/f component disappears in the thermal noise (Fig. 15). A number of noise voltage amplitude distributions for a single node are shown in Fig. 16. The amplitude distributions are Gaussian for membrane potentials above a certain value and positively skewed for lower values of membrane potential. The skewness increases as the membrane potential becomes more negative. The standard deviations (the wide-band rms intensities mV) of a number of amplitude distributions for another
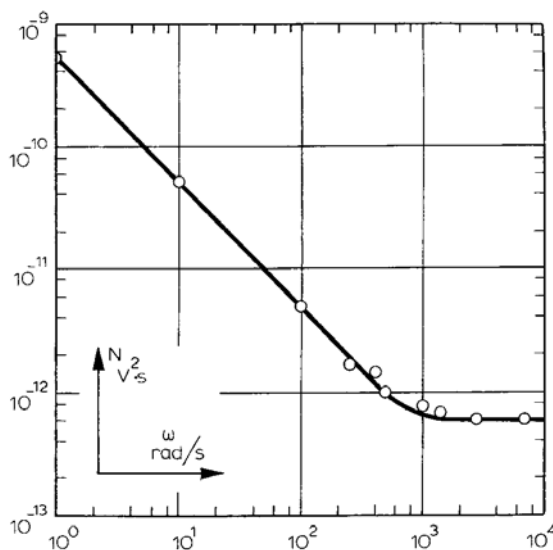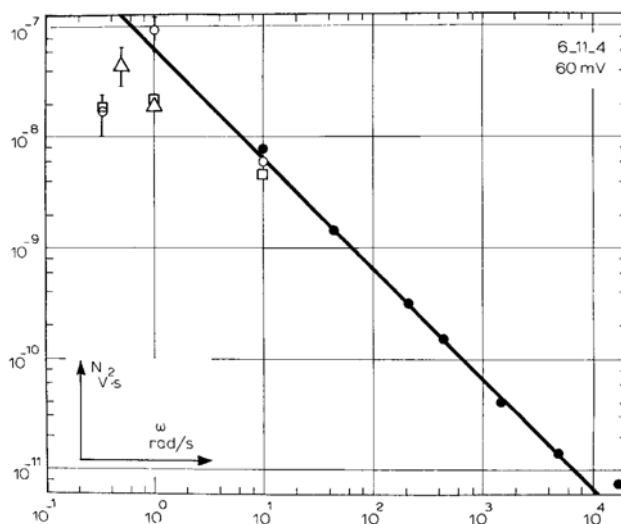

Fig. 13. Noise spectrum showing decrease of negative slope down from 1 rad/s. From Derksen.[23]

node are presented in Fig. 17. For this node the noise changes from Gaussian to positively skewed noise, with the transition occurring at a membrane potential of 75 to 80 mV. Gaussian distributions occur less often with lower levels of membrane potential and are visible only when short-duration sampling intervals are used. When Gaussian distributions only are taken into consideration, the rms intensity is found to be minimal at the potassium equilibrium potential. In experiments to be reported elsewhere the Gaussian noise as well as the 1/f noise is shown to be related to the passive flux of potassium ions through the membrane. Both Gaussian noise and 1/f noise, therefore, originate from the same noise source: passive potassium ion flux through the membrane.

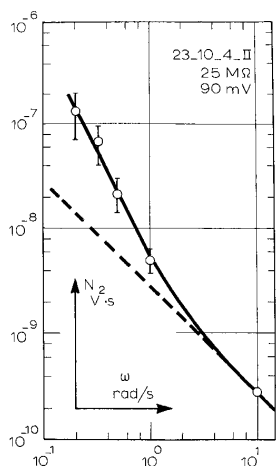Skewed noise is associated with the irregular occurrence

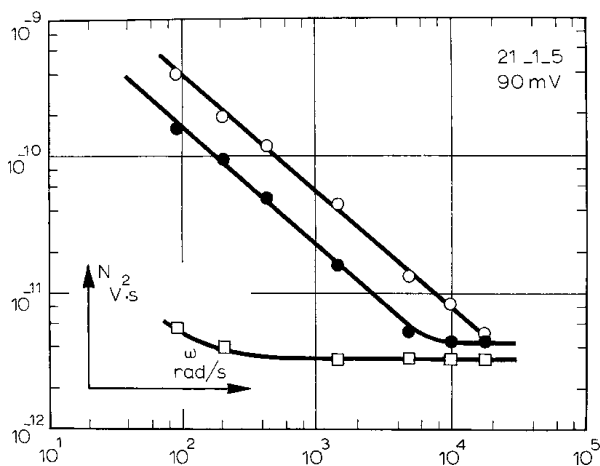Fig. 14.   Noise spectrum showing increase of negative slope down from about 5 rad/s. (From Derksen.[23])

Fig. 15. Power spectra in Ringer's solution (open circles), in isotonic KCl solution (filled circles), and back in Ringer's solution (open squares). (From Derksen.[23])
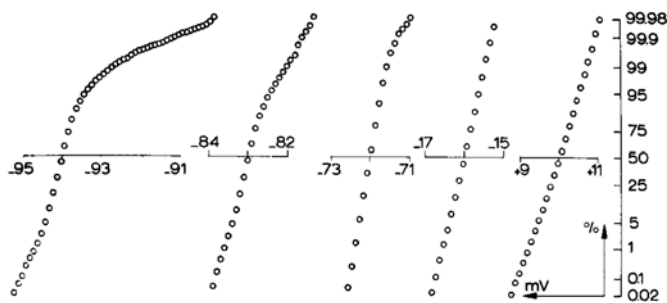

Fig. 16. Cumulative amplitude distributions (in percentage of total number of samples) for different levels of membrane potential, plotted on Gaussian paper. (From Verveen, in preparation.)
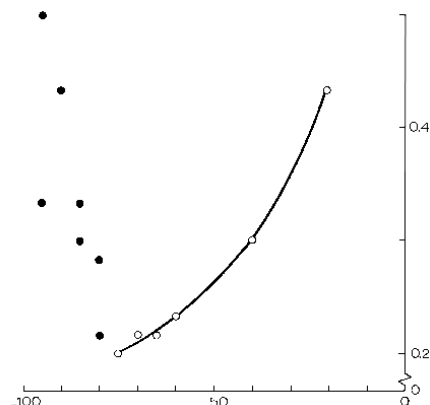

Fig. 17. Standard deviation (ordinate in mV) of membrane noise voltage plotted against membrane potential (abscissa in mV). Open circles Gaussian distributions; filled circles: positively skewed distributions. Length of noise tracks analyzed: 100 seconds. (From Verveen, in preparation.)

of depolarizing noise bursts. These bursts occur only at very low levels of membrane potential and increase in frequency, amplitude, and duration with decrease of membrane potential (Figs. 18 through 20).

Close investigation of the traces with skewed noise shows the existence of miniature depolarizing potentials of approximately triangular shape and with amplitudes and durations of the order of 1 mV and 1 ms, respectively (Fig. 20). The miniature depolarization potentials occur irregularly, both singly and in clusters, forming the noise bursts. Since the miniature depolarizing potentials occur in the range in which sodium inactivation is low, and because of their depolarizing nature, they suggest spontaneous functioning of passive sodium sites in the membrane; they occur for large membrane hyperpolarizations only (membrane potentials less than the resting value), and their frequency increases with a decrease of the membrane potential.

A related conclusion follows from the finding that the position of the transitional range is independent of the actual resting membrane potential recorded in the absence

of dc injection, which suggests that skewed noise is not related to mechanisms that maintain the resting membrane potential. Interference with metabolism did not influence skewed noise, nor did interference with potassium or chloride ion transport. Replacement of sodium ions shifts the range of transition to higher levels by a voltage that is approximately linearly dependent on the amount of sodium replaced. It follows that skewed noise is caused by spontaneous functioning of passive sodium transport sites within the membrane.

DISCUSSION

The measurements of membrane voltage noise were made on nodes of Ranvier in the frog with a diameter of about 4 μm. The wide-band rms intensity of the noise was found to be 200 μV or more (cf. Fig. 17). This is indeed an order of magnitude more than the calculated thermal noise intensity of 32 μV for fibers of this diameter. Since the wide-band rms value found is equal to the total noise rms value calculated from the data obtained from the response probability relationships (208 μV for 4 μ diameter), membrane voltage noise is sufficient to account for fluctuations in the response of sciatic nerve fibers. Effects of "skewed" noise are infrequently encountered in stimulation experiments, since they
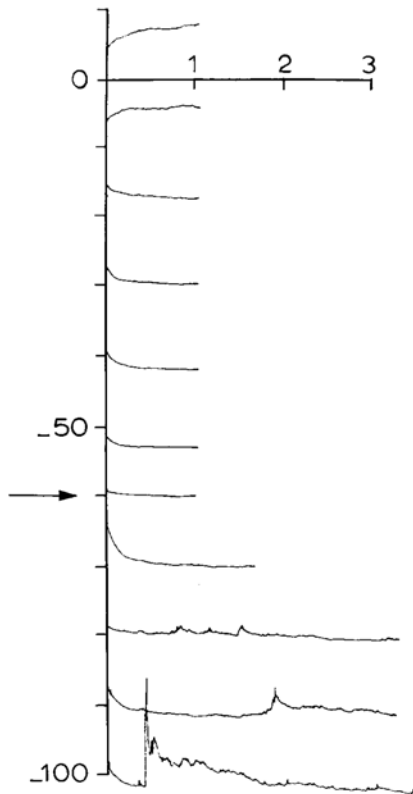
Fig. 18. Time course of membrane potential at different levels. Dc injection; low-pass filter with time constant of 1 second. Note depolarizing nature of noise bursts at hyperpolarized levels (From Verveen, in preparation.) Units: minutes, mV.
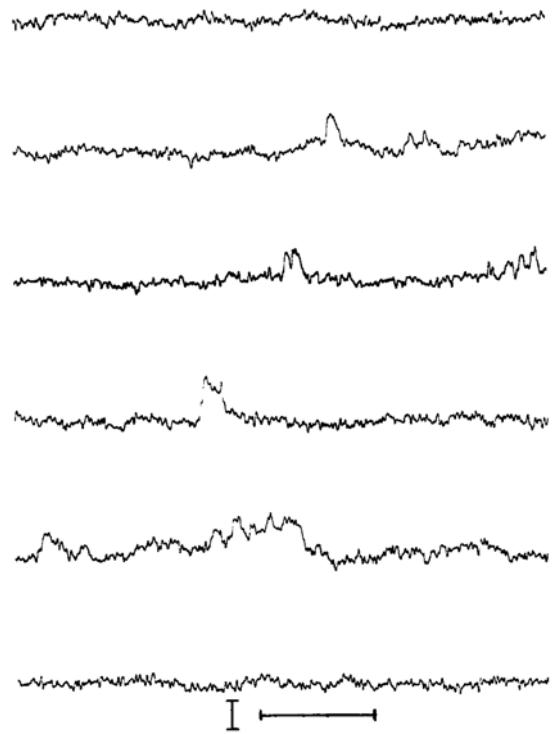
Fig. 20. Membrane noise at a membrane potential of - 90 mV. High pass filter with time constant of 1 second. Units: 1 mV and 10 ms. A single miniature depolarizing potential is visible in the second track. Clusters are present in tracks 3 through 5; the first and the last tracks have Gaussian amplitude distributions. (Front Verveen, in preparation.)

Fig. 19. Membrane noise at different levels of membrane potential. Units: 5 mV and 1 second. High-pass filter time constant: 1 second.

are prominent at levels of membrane potential that are lower than the resting membrane potential.

It has been found that 1/f noise occurs in the electron emission of oxide-coated vacuum tube cathodes (flicker effect), in carbon resistors and carbon microphones, in some metal film resistors, across contacts (excess noise), in bulk semiconductor material, and in thermistors. In all cases the flow of a direct curre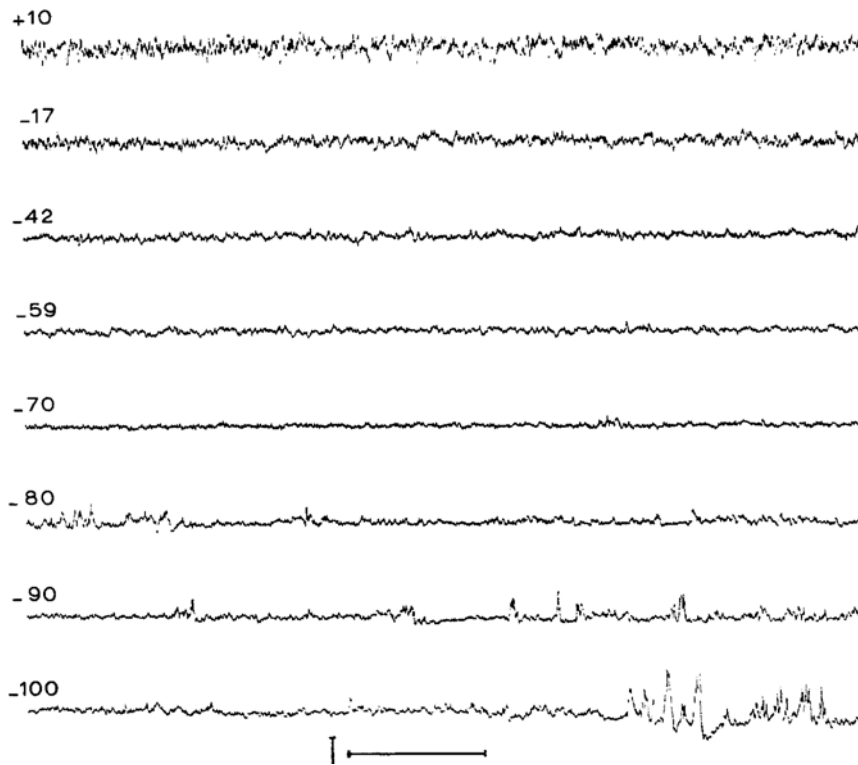nt in the samples appears to be a prerequisite for the existence of 1/f noise. In the present investigation, external currents were used to depolarize or hyperpolarize the membrane. But even in the absence of external current, the resting membrane is not in thermodynamic equilibrium, and several species of ions are transported across it.

So far, no unified theory of the origin of 1/f noise exists, although there exists a great variety of physical systems that exhibit this kind of noise spectrum. The theories developed (van der Ziel,[36]-[38] Richardson,[39] McFarlane,[40] Petritz,[41] Bess,[42] Morrison,[43] McWhorter,[44] Bell,[45] and Sautter[46]) as a rule apply at best to one special case and cannot be extended to cover the others.

It is evident that 1/f noise must result if the noise is produced by a great number of elementary sources whose relaxation times have a hyperbolic distribution. This has been proposed by Du Pre[47] and by van der Ziel[36] and is the basis of one of the best-known theories of noise in semiconductor material, which was developed by McWhorter.[44]

The question is, however, does this model apply to nerve membranes. That such a distribution actually occurs follows from the measurements of McWhorter on the frequency dependence of the conductivity modulation of a sample of semiconductor material upon application of an ac field.

Many of the theories attempting to explain 1/f noise spectra have their counterparts in the theories of dielectric relaxation (Cole[48]). Corresponding to the white noise case in fluctuation theory is the simple dielectric behavior variously described as: Debye, semicircular, single relaxation time, exponential decay or first-order kinetics. In a number of cases, however, deviations from this simple behavior are found, and then the most commonly invoked explanations are based on the assumption of a suitable distribution of exponential decay processes that superpose to produce the observed dispersion. Explicit theories of this type exist (Hoffman,[49] Glarum,[50] and Cole [51]) but may not be applicable to membrane phenomena. Cole[52] suggests an alternative point of view: "The broad range of frequencies in which dielectric or other responses, vary significantly with frequency need not be explained by invoking a spectrum of exponential decay processes. It is possible, and when the range of times is very broad it is far less awkward, to look for an explanation in terms of elementary cooperative processes by which the natural fluctuations of the system lead to decay of correlations which are intrinsically non-exponential in time."

Now if one assumes (Goldman,[53] Fitzhugh,[54] and Schick, in preparation) that membrane permeability, at least for potassium, is controlled by the orientation of polar groups of macromolecules that are part of the lining of membrane pores, dielectric relaxation theory and theories about 1/f noise might have, at least for resting potential fluctuations in nodal membrane, a common base. That means that one should consider an ensemble of electrically coupled dipoles in an orienting field due to membrane potential, each subject to thermal fluctuations and each governing the access of a potassium ion to a transport channel. It remains to calculate the fluctuations in the total potassium ion transport, notably the spectral composition of these fluctuations. To our knowledge no such theory exists and, as far as we can see, developing one is a rather formidable task.

However, experiments on inductors with ferrite cores gave a 1/f spectrum for the voltage fluctuations across the inductor terminal (Brophy[51]). Notwithstanding the differences between a three-dimensional array of coupled magnetic spins and a sheet of coupled electrical dipoles, further investigation of fluctuation phenomena in cooperative processes appears to be the most promising approach to an explanation of 1/f noise in nerve membrane.

The second type of fluctuations was observed during an investigation concerning the course of the noise spectrum at the low-frequency end. One characteristic of 1/f noise is that the relation Nω-) = const., where N is noise power per cycle of bandwidth and co the angular frequency, can hold only over a limited frequency range. In order that the autocorrelation function of a random variable $X(t)$:

$$\overline{X(t)X(t+\tau)} = \frac{1}{2\pi}\int_0^\infty N(\omega)e^{j\omega\tau}\,d\omega$$

converge for all values of τ, including zero, $N(\omega)$ must
  1) decline faster than 1/w at high frequencies, otherwise the integral would diverge at $\tau = 0$,
  2) decline slower than 1/ω at very low frequencies, otherwise it would diverge for all values of τ(van der Ziel[37]).

In the log N versus log ω plot, the negative slope of the spectral intensity curve should thus become lower at low frequencies and increase at high frequencies. Although a decrease in negative slope was indeed found in a few cases, our results show that generally an increase in slope was found in the range of angular frequencies from 0.1 to 10 rad•s^{-1}, and this was always correlated with the occurrence of a number of small (roughly 1 mV, 1 ms) depolarizing deflections in the noise voltage. When this occurred, the amplitude distribution became positively skewed. This occurs rather abruptly when a certain level of membrane potential (generally −80 to −90 mV) is reached. The depolarizing deflections could be ascribed to the inflow of sodium ions. A full report on this phenomenon will be published elsewhere (Verveen, in preparation); a few comments, however, will be made on it now.

A number of investigations (Chandler and Meves[56] and Moore et al,[57] using entirely different methods, point to the existence of sparsely distributed transport sites that under normal circumstances allow for transient sodium inflow during the action potential.

Reasonable estimates are fifteen sites per square micron, each site transporting a batch of one to two thousand sodium ions during an action potential. This explains the quantal nature of the local response following subthreshold excitation, as observed by del Castillo and Katz [35] and by Lüttgau. [14]

The depolarizing deflections observed in the present investigation can be explained by assuming that, in the resting state, sodium transport sites conduct occasionally as a result of thermal motion within the membrane. The order of magnitude of the charge transported through a nodal membrane of 1 pF capacitance during a depolarizing deflection of 0.5 to 1 mV amplitude and 0.5 to 1 ms duration corresponds to that transported by a single site during an action potential. Further, a time series of such pulses results in a markedly asymmetric amplitude probability density function of the baseline when the ratio of the pulse duration to the interpulse duration is, on the average, one or less (Adolph[60]).

A number of interesting problems remain to be investigated in the near future. Substances such as tetrodotoxin and saxitoxin selectively block the sodium channels, while DDT and veratrine cause the channels to remain open for a longer time. These substances might influence either the occurrence or the duration of the depolarizing deflections associated with those fluctuation components characterized by an asymmetric amplitude distribution. On the other hand, tetraethylammonium (TEA) ions abolish the delayed potassium currents in voltage clamp experiments on frog nodal membrane (Hille[61]). If our assumptions are correct, TEA in the bathing solution should reduce or abolish $1/f$ noise. Finally, the influence of divalent cations, primarily Ca^{++}, of pH and of temperature on the properties of the membrane voltage fluctuations can yield important clues as to the mechanism of ion transport through nerve membrane.

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