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Fluctuations of Resting Neural Membrane Potential

Abstract. The membrane potential of myelinated axons in the resting state shows fluctuations for which the power per cycle of bandwidth is inversely proportional to frequency between 1 and 10,000 radians per second. Reduction of potassium ion flux leads to a decrease in noise power.

Statistical analyses of action potential time series recorded from neural elements have furnished important data on spontaneous and induced neuronal activity, and several models have been proposed to explain them. In most models, one or more random processes are invoked. In one aspect, however, the models are arbitrary, for experimental evidence on random processes in neural elements is lacking.

One such process, thermal noise, has been invoked by some neurophysiologists to explain irregular neuronal activity. By thermodynamical arguments, Nyquist has shown (1) that the minimum intensity of the noise voltage in an electrical conductor is given by $N = e^2 = 4 kTR$, where N (in volt² sec) is the noise power per cycle of bandwidth, e' is the open-loop voltage over the resistance R , k is Boltzmann's constant, and T is absolute temperature. When the resistance is independent of frequency the Nyquist noise power is also independent of frequency ("white"

noise). Additional sources of noise are possible for example, in semiconductors.

Fatt and Katz suggested (2) that thermal noise across the resistances of membrane and core of axonal endings might be the cause of spontaneously occurring miniature end-plate potentials. Buller *et al.* (3), Hagiwara (4), and Buller (5) considered the possibility that thermal noise might account for the spontaneous activity of frog muscle spindles and for the irregularities in their discharge under stretch. Hagiwara, however, doubted that the intensity of noise from this source was high enough to explain these phenomena.

Fluctuations in excitability of axons and in the latencies of their responses, first described by Blair and Erlanger (6), and investigated by Pecher (7), were extensively studied by Verveen and co-workers. The statistical properties of these fluctuations (8, 9) could be explained by assuming the existence of a noise voltage over the resting axon membrane (9, 10), with a root-mean-square value on the order of a millivolt for myelinated axons of small diameter and with smaller values for larger axons (11).

Thermal noise, according to Nyquist's theorem, is, however, insufficient to account for these phenomena (compare figure 2 in Verveen, 11). It was, therefore, necessary to acquire direct information on fluctuations in the potential of resting membranes (mem-

brane noise voltage). Because of the influence of membrane noise voltage on signal transmission and data processing in the nervous system, the receptor cell membrane, the presynaptic membrane, the dendritic membrane, and the initial axon segment would be the objects of choice, but technical difficulties preclude this approach at present. This leaves the axon membrane as the object for initial investigations.

Measurements on a nodal membrane-internodal axoplasm-nodal membrane system were published earlier (9). With this two-terminal system it is difficult to evaluate the contribution of the membrane, both because of the necessity for correcting for the noise contributed by electrodes and amplifiers, and because of the difficulty of pinpointing the actual noise source. We now report experiments in which the noise from a single Ranvier node was measured by using a three-terminal arrangement and performing a correlation analysis on the outputs of the two two-terminal arrangements of which it consists (12, 13).

A length of frog sciatic nerve fiber containing three nodes was mounted in a tray with five pools filled with Ringer solution. The middle node lay in the central pool and each of the other nodes in one of the outer pools. The second and fourth pools were used for electronic feedback compensation of the external fluid shunts between adjacent nodes (Frankenhaeuser, 14). The poten-

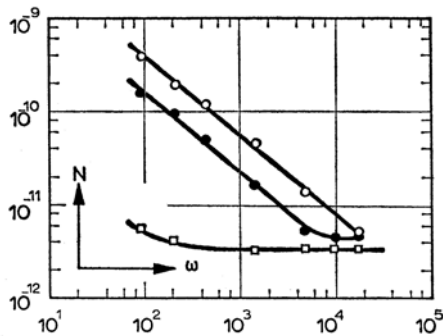


Fig. 1. Noise spectrum of a single frog node of Ranvier. (○) In normal Ringer solution; (■) after replacement of sodium chloride by potassium chloride; (●) back to normal Ringer solution. Noise power N in volt² sec, angular frequency ω in radians/sec.

tial differences between adjacent nodes were amplified separately. Both amplifier outputs were filtered by band-pass filters. The outputs of the two filters were multiplied with each other and the output of the multiplier was time-averaged. Circuit properties in the two channels were equal to within 1 percent. In this way the contributions from additional noise sources (internodal axoplasm, portions of the nerve fiber on either side of and including the outer nodes, electrodes, amplifiers) were eliminated (9, 12), and the power of the noise voltage of the source common to both circuits—the middle node—was measured.

Measurements were made via filter pairs with central angular frequencies ω in the range between 0.2 and 56,000 radians/sec. Between 1 and 10,000 radians/sec a so-called $1/f$ spectrum was found in all cases. In spectra of this

type the noise power per cycle of bandwidth is approximately inversely proportional to frequency: $N = C/\omega^\alpha$, where $\alpha \sim 1$ and C is a constant.

A log-log plot of N against ω gives a straight line with a slope of $-\alpha$. This type of power spectrum is also found in carbon resistors, in vacuum tubes (flicker noise), and in semiconductors carrying direct current, where it increases with increase of current. Deviations from the $1/f$ spectrum were found both at the high-frequency and the low-frequency end of the range covered. At the high-frequency end (usually up from 10,000 radians/sec), the spectrum changes into a white noise spectrum ($\alpha = 0$). At the low-frequency end (usually down from 1 radian/sec), an increase in negative slope of the log N versus log ω line may occur. These deviations will be discussed in a separate report.

In the range between 100 and 20,000 radians/sec, a number of experiments were made to find out whether the $1/f$ component of the noise spectrum is related to fluctuations in membrane ionic conductances and transport (12).

Abolishing sodium inflow, either by replacing the fluid bathing the middle node with a sodium-free Ringer solution (with choline chloride as a substitute) or by addition of urethane, does not result in an immediate change in the noise power spectrum, nor does interference with active sodium transport by addition to the bathing fluid of either 2,4-dinitrophenol or ouabain. It follows that it is most unlikely that the sodium ion plays a direct role in the generation of the $1/f$ component of the spectrum.

Upon replacement of the sodium chloride in the bathing fluid by potassium chloride, the $1/f$ spectrum is immediately, and reversibly, abolished (Fig. 1). This leaves a white spectrum. As a consequence of the membrane depolarization induced by this procedure the passive K^+ and Cl^- flows become zero, as can be predicted (12) on the basis of Frankenhaeuser's verification of the constant-field approximation for the case of myelinated nerve (15). The $1/f$ noise is, therefore, related to the flow of one or both of these ions.

It also follows from Frankenhaeuser's work that the flow of any given ion reduces to zero at its equilibrium potential. The equilibrium potentials of Cl^- (~ -55 mv) and of K^+ (~ -90 mv) lie on either side of the membrane resting potential (~ -70 mv). It follows that if

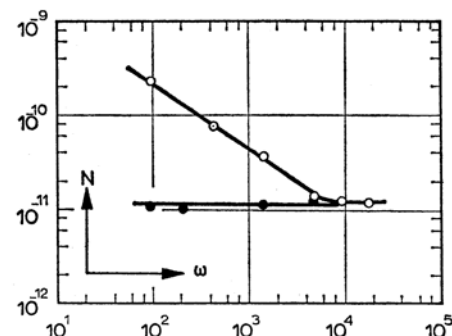


Fig. 3. Influence of current on the spectrum of a single node in normal Ringer solution. (○) Normal frequency spectrum; (●) at 20-millivolt hyperpolarization.

Cl^- should be the ion primarily involved, hyperpolarization of the node bathing in normal Ringer solution should cause an increase in intensity of the $1/f$ spectrum, while depolarization should result in a decrease. The effects should be reversed if the $1/f$ spectrum should be linked primarily to potassium flow. As shown in Fig. 2, depolarization increases the $1/f$ noise (triangles), while it is decreased by hyperpolarization (filled circles). When the membrane potential is made approximately equal to the potassium equilibrium potential, the spectrum changes into a white spectrum (Fig. 3). These phenomena are also reversible. It follows that the $1/f$ component of the membrane noise voltage spectrum is related to the flux of potassium ions.

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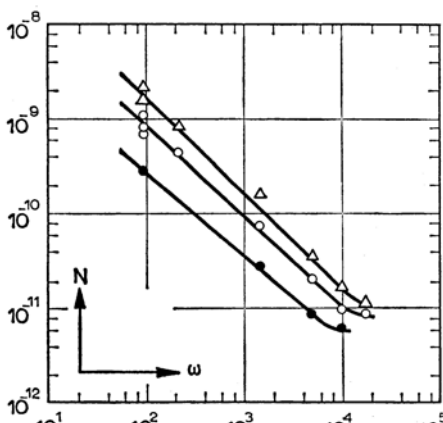


Fig. 2. Influence of current on the spectrum of a single node in normal Ringer solution. (Δ) Ten-millivolt depolarization; (○) no polarization; (●) 10-millivolt hyperpolarization.