1/f Membrane Noise Generated by Diffusion Processes in Unstirred Solution Layers*

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Abstract. A mathematical treatment is given for $1/f$ noise observed in the ion transport through membranes. It is shown that this noise can be generated by current or voltage fluctuations which occur after step changes of the membrane permeability. Due to diffusion polarization in the unstirred solution layers near the membrane these fluctuations exhibit a $1/\sqrt{t}$ time course which produces noise with a $1/f$ frequency dependence. The spectral density of $1/f$ noise is calculated for porous membranes with random switches between a finite and zero pore permeability. A wide frequency range and a magnitude of $1/f$ noise are obtained which are compatible with experimental data of $1/f$ noise reported for nerve membranes.

Key words: $1/f$ Noise — Nerve membrane — Membrane pore — Single file transport.

Introduction

In the state of thermodynamic equilibrium the source of electrical noise is the Brownian movement of charge carriers. The noise from non-equilibrium ionic systems is larger than this thermal noise level. The spectral density of this "excess noise" decreases at increasing frequencies f and varies in many cases approximately inversely to f over a wide frequency range. This explains the term "$1/f$ noise" which was reported in current or voltage fluctuations at semiconductors and at various biological and artificial membranes (Verveen and DeFelice, 1974). For this widely occuring kind of noise no generally accepted theory is available at present. A superposition of relaxation processes with a certain distribution of time constants can yield a $1/f$ spectrum (Kingston and McWhorter, 1956; Halford, 1968), but no mechanism has been described which generates this particular distribution. Offner (1970, 1972) has claimed to obtain a $1/f$ noise by random walk of charge carriers across a potential barrier. However, Bird (1974) pointed out that such a process does not give a $1/f$ dependence over a wide frequency range. Coupling between parameters of ion pulses passing through the membrane may cause $1/f$ noise (Heiden, 1969; Schick, 1974), but the origin of this coupling remains unclear. Finally an empirical formula for the spectral density of $1/f$ noise was proposed by Hooge and Gaal (1971) which, however, is not in agreement with excess noise measured at artificial membranes (Dorset and Fishman, 1975).

In this contribution a theoretical interpretation of $1/f$ membrane noise is presented. It is shown that diffusion polarization in the unstirred solution layers

near the membrane causes a decrease of the current through the membrane which is proportional to $1/\sqrt{t}$ at sufficiently long times t after a change of the membrane permeability. This time dependence is known to yield $1/f$ noise (Schönfeld, 1955). In order to explain the $1/f$ noise measured at nerve membranes we investigate the time course $I(t)$ of the current through a membrane pore which switches randomly between two permeability states. It is found that $I(t)$ can be represented as superposition of current pulses which are generated at each permeability change and which decay proportional to $1/\sqrt{t}$ during the whole lifetime of the pore. With pore parameters taken from the literature we then calculate a frequency range and spectral density of $1/f$ membrane noise which are compatible with experimental data reported for nerve membranes.

Some results of this work were presented at the Vth International Biophysics Congress 1975 (Abstract P 483).

Results

1/f Noise Generated by Processes with $1/\sqrt{t}$ Time Dependence

In theoretical noise analyses fluctuating quantities normally are approximated by rectangular step functions or represented by random occuring pulses decaying exponentially. For the latter case a single event is described by

$$g(t) = \begin{cases} 0 & t < 0 \\ \exp(-t/\tau) & t \geqslant 0, \end{cases} \tag{1}$$

where g is the fluctuating variable (voltage, current etc) and τ the time constant of the exponential decay.

The Fourier transform

$$G(f) = \int_{-\infty}^{\infty} g(t) \exp(-2\pi i f t) \, dt \tag{2}$$

of $g(t)$ is

$$G(f) = \frac{\tau}{1 + 2\pi i f \tau}. \tag{3}$$

If the events $g(t)$ occur at random at the average rate λ, the spectral density $S(f)$ of the associated noise power spectrum can be calculated by applying Carson's theorem (van der Ziel, 1970):

$$S(f) = 2\lambda \mid G(f) \mid^2 \tag{4}$$

The result is the well known Lorentzian spectrum

$$S(f) = \frac{2\lambda \tau^2}{1 + (2\pi f \tau)^2} \tag{5}$$

which is constant at low frequencies $f \ll 1/2\pi\tau$ and decays proportional to $1/f^2$ at high frequencies $f \gg 1/2\pi\tau$.

The normalization factor of the spectrum (5) is in agreement with the condition

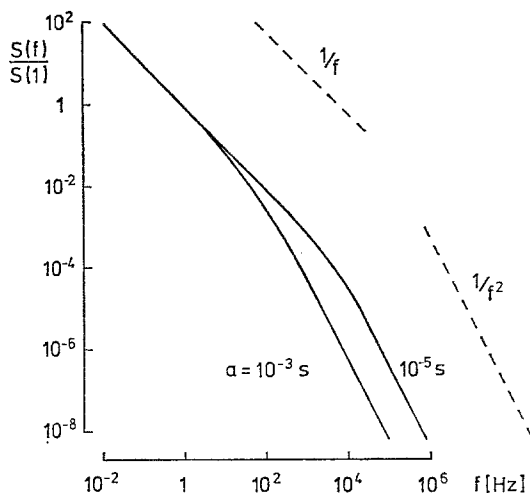$$\int_0^\infty S(f) \, df = \; <g^2(t)> , \tag{6}$$

Fig. 1. Power spectrum $S(f)$ of events $g(t)$ defined in Eq. (8) for the parameters $a = 10^{-3}$ s, 10^{-5} s. $S(f)$ is normalized at $f = 1$ Hz

where

$$< g^2(t) > = \frac{1}{2} \lambda \tau \tag{7}$$

is the variance of $g(t)$.

Exponentially decaying variables thus yield a Lorentzian noise spectrum. Accordingly, a superposition of mutually independent events decaying exponentially with different time constants will result in a spectrum which is the sum of the individual Lorentzian functions. In this way, therefore, no spectrum can be obtained which decays proportional to $1/f$ within a wide frequency range (Hill and Chen, 1972).

We now want to compute the noise spectrum of events $g(t)$ which decay proportional to $1/\sqrt{t}$ at $t > a > 0$:

$$g(t) = \begin{cases} 0 & t < a \\ 1/\sqrt{t} & t \geqslant a. \end{cases} \tag{8}$$

The Fourier transform $G(f)$ of $g(t)$ can be expressed in terms of Fresnel integrals (Schönfeld, 1955) or computed numerically. Fig. 1 shows the noise spectrum obtained from our computations for two values of the parameter a.

For frequencies $f < 1/2 \pi a$ the spectrum turns out to be proportional to $1/f$, at higher frequencies $S(f)$ decays as $1/f^2$. Thus for sufficiently low values of a, a wide frequency range is obtained with a $1/f$ dependence of the spectral intensity $S(f)$. In the extreme case $a = 0$, $S(f)$ would be proportional to $1/f$ at all frequencies (Verveen and DeFelice, 1974).

Since the computed spectrum is proportional to $1/f$ for all frequencies $f < 1/2 \pi a$, $S(f)$ diverges in the low frequency limit $f \to 0$ and no finite value for the variance of $g(t)$ would be obtained from Eq. (6). This divergence is caused by the time course (8) of $g(t)$ which was postulated to be proportional to $1/\sqrt{t}$ at times $t > a$. A superposition of an unlimited number of such single events occuring
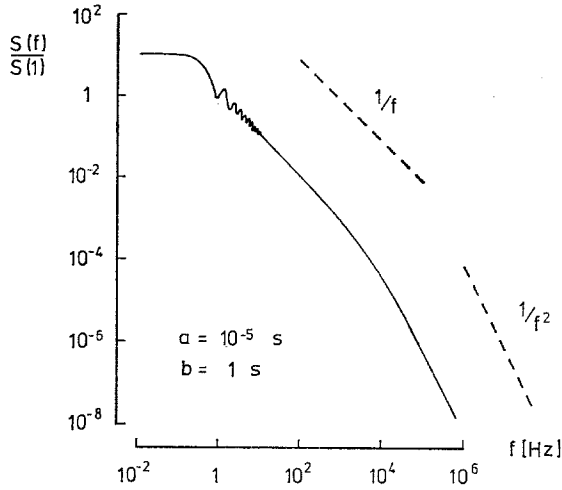
Fig. 2. Power spectrum $S(f)$ of events $g(t)$ defined in Eq. (9) for the parameters $a = 10^{-5}$ s, $b = 1$ s. $S(f)$ is normalized at $f = 1$ Hz

randomly would yield an infinite amplitude thus explaining the divergence of $S(f)$. Therefore, it is more realistic to investigate the noise spectrum of events $g(t)$ which decay proportional to $1/\sqrt{t}$ within a limited time range $a < t < b$:

$$g(t) = \begin{cases} 0 & t < a \\ 1/\sqrt{t} & a \leqslant t \leqslant b \\ 0 & t > b \end{cases} \qquad (9)$$

In this case the $1/f$ dependence of $S(f)$ is restricted to frequencies f with $1/2\pi b < f < 1/2\pi a$ as can be seen from Fig. 2. At low frequencies $f \ll 1/2\pi b$ $S(f)$ assumes the constant value

$$S(f) = 8\lambda (\sqrt{b} - \sqrt{a})^2 \qquad (10)$$

and at high frequencies $f \gg 1/2\pi a$ the spectrum falls off as $1/f^2$ as in Fig. 1.

The small oscillations between $f = 1$ and 10 Hz which are superimposed to the $1/f$ dependence in Fig. 2 are generated by the fixed pulse length $b - a$ of the events (9) yielding oscillations with the period $1/(b - a)$ in the noise spectrum. For pulses (9) with a small scatter of the pulse length, a pure $1/f$ spectrum would be obtained in the frequency range $1/2\pi b < f < 1/2\pi a$. This $1/f$ dependence is independent of the pulse amplitude $g(t)$ between $t = 0$ and $t = a$. In Eq. (9) vanishing values were assumed in this time region. But the same $1/f$ spectrum in the frequency range $1/2\pi b < f < 1/2\pi a$ is obtained if $g(t)$ assumes nonzero values for $0 < t < a$.

For random occuring events (9) and frequencies f with $f \gg 1/2\pi b$ and $f \ll 1/2\pi a$ the spectral intensity $S(f)$ can be approximated by a very simple expression which coincides with the numerical results in this frequency range. The Fourier transform $G(f)$ of $g(t)$

$$G(f) = \int_a^b \frac{1}{\sqrt{t}} \exp(-2\pi ift)\, dt \qquad (11)$$

can be written as

$$G(f) = \frac{1}{\sqrt{2\pi f}} \int\limits_{2\pi fa}^{2\pi fb} \frac{\exp(-iz)}{\sqrt{z}} \, dz \tag{12}$$

by introducing the new variable $z = 2\pi ft$. Lower and upper integration limits then can be replaced by 0 and ∞ respectively:

$$G(f) = \frac{1}{\sqrt{2\pi f}} \int\limits_{0}^{\infty} \frac{\exp(-iz)}{\sqrt{z}} \, dz \tag{13}$$

and the result is:

$$G(f) = \frac{1-i}{2} \cdot \frac{1}{\sqrt{f}} \tag{14}$$

Carson's theorem (4) finally yields:

$$S(f) = \lambda \cdot \frac{1}{f} \quad . \tag{15}$$

The expression (15) is valid for frequencies $1/2\pi b \ll f \ll 1/2\pi a$ and confirms the $1/f$ dependence of the spectral intensity $S(f)$ in this frequency range which already was obtained above by numerical computations. Pulses decaying proportional to $1/\sqrt{t}$ thus give a $1/f$ noise spectrum. It will be shown in the next section that the relaxation of various diffusion processes follows such a time course.

Diffusion Processes in Unstirred Solution Layers give $1/\sqrt{t}$ Time Dependence

If current flows through a membrane, the charge carriers have to move from the bulk of the solutions across the unstirred solution layers near the membrane. Thus the charge carrier concentration in the solutions will decrease at one membrane surface and increase at the other. This gives rise to a membrane potential opposite to the externally applied voltage so that the current will decrease with time. This phenomenon, which is called diffusion polarization, is well known from electrode kinetics and has been observed in the transport of hydrophobic ions across lipid bilayer membranes (LeBlanc, 1969). In a theoretical treatment it has been shown that the current decrease due to diffusion polarization at lipid bilayer membranes is proportional to $1/\sqrt{t}$ at sufficiently long times and that this time course is in agreement with experimental results (Neumcke, 1971; Läuger and Neumcke, 1973). Thus diffusion processes in the unstirred solution layers near lipid bilayer membranes exhibit a time dependence which yields $1/f$ noise.

Our main objective of this investigation is to describe the $1/f$ dependence of the spectral intensity of current and voltage fluctuations at nerve membranes and other biological systems. In these cases the ion flux through the membrane is not uniform but very likely occurs through ion selective channels (Ulbricht, 1974). Thus the one-dimensional treatment of diffusion polarization at lipid bilayer membranes (Neumcke, 1971) cannot be applied to the diffusion of ions in the unstirred solution layers around membrane pores. Instead ions in the solutions will flow at different angles towards a highly conductive pore. Following Hille (1968) who calculated the maximal ion flux through pores in nerve membranes, we idealize this situation by assuming spherical symmetry in infinite extended unstirred solution layers around a cylindrical pore of radius r_0. Our aim is to calculate
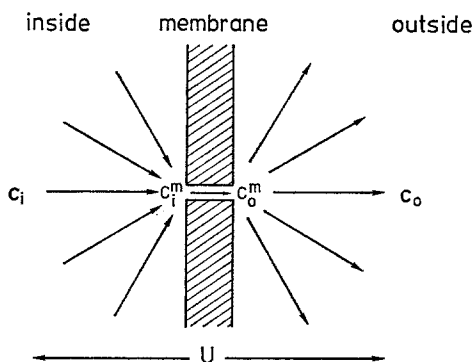
Fig. 3. Illustration of spherical ion flux in the unstirred solution layers around a membrane pore

for a fixed externally applied voltage U across the membrane the time dependence $I(t)$ of the current I through a single membrane pore which at time $t = 0$ switches from a closed to an open state. To simplify the mathematics, the following additional assumptions are made:

1. The pore only is permeable for one univalent cation species (e.g. K^+ or Na^+).

2. The aqueous phases contain a high concentration of an inert electrolyte. In this case the electrical potential is almost constant in the solutions and the drop of the externally applied voltage occurs entirely within the membrane phase.

3. In the unstirred solution layers there are no interferences between the ion fluxes of neighbouring membrane pores.

4. Space charges in the pore are negligible.

The validity of the assumptions 2. and 3. will be estimated in the Appendix.

Fig. 3 illustrates the spherical ion flux in the unstirred solution layers around a membrane pore and shows the notations for the concentrations of the permeant cations in the bulk of intra- and extracellular solutions and at the inner and outer ends of the pore.

According to assumption 2. there are no electrical driving forces for the ion transport in the unstirred solution layers. Therefore, the concentration $c(r)$ of permeant ions at a distance r from the pore end satisfies the time dependent diffusion equation in polar coordinates:

$$\frac{\partial c}{\partial t} = D \left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r} \frac{\partial c}{\partial r} \right). \tag{16}$$

D is the aqueous diffusion coefficient which is assumed to be the same in the intra- and extracellular solution.

The initial concentration values are:

$$c(r, t \leqslant 0) = \begin{cases} c_i & \text{(intracellular solution)} \\ c_o & \text{(extracellular solution)} . \end{cases} \tag{17}$$

At the pore ends $r = r_o$ we have

$$
\Phi = \begin{cases} 2\,\pi\,r_0^2\,D\left(\dfrac{\partial c}{\partial r}\right)_{r=r_0} & \text{(inner pore end)}, \\[2ex] -\,2\,\pi\,r_0^2\,D\left(\dfrac{\partial c}{\partial r}\right)_{r=r_0} & \text{(outer pore end)} \end{cases} \tag{18}
$$

where Φ (expressed in moles/s) is the spherical influx of ions from all possible directions through the surface of the half sphere of area $2\,\pi\,r_0^2$ into the pore or the corresponding outflux at the opposite pore end.

Since the exact molecular structure of pores in nerve membranes and other biological membranes is still unknown, we idealize the actual potential profile in the interior of the pore by a main energy barrier in the center of the pore. The ion flow through the pore then can be described by an ion jump over this single barrier. If space charges in the pore are negligible (assumption 4) it is at any time (Läuger and Neumcke, 1973):

$$
\Phi = \pi\,r_0^2\,P\,[c_i^m\,e^{u/2} - c_0^m\,e^{-u/2}]. \tag{19}
$$

P (expressed in cm/s) is the pore permeability coefficient which is a function of pore parameters (pore length l, diffusion coefficient in the interior of the pore etc). An upper limit of P is reached if the ions in the pore behave as in free solution. Then:

$$
P = \frac{D}{l}. \tag{20}
$$

The normalized voltage u is defined by

$$
u = \frac{F}{RT}\,U \tag{21}
$$

with F: Faraday constant, R: gas constant, T: absolute temperature. At 25° C $u = 1$ corresponds to a voltage of approximately $U = 25$ mV. The ion concentrations c_i^m, c_0^m at the inner and outer pore ends are connected by the symmetry relation

$$
c_i^m + c_0^m = c_i + c_o \tag{22}
$$

because an increase of the ion concentration in one unstirred solution layer must be balanced by a corresponding decrease at the image point in the opposite solution layer. For unequal diffusion coefficients in the intra- and extracellular solutions this symmetry would no longer hold. Eliminating the flux Φ in Eqs. (18), (19) and combining the result with Eq. (22) yields the following boundary condition at the pore ends $r = r_0$:

$$
c\,(r = r_0) - \varkappa\left(\frac{\partial c}{\partial r}\right)_{r=r_0} = \varrho \tag{23}
$$

with

$$
\varkappa = \frac{D}{P}\,\frac{1}{\cosh\,(u/2)} \tag{24}
$$

and

$$
\varrho = \begin{cases} (c_i + c_0)\cdot\dfrac{1}{1 + e^u} & \text{(inner pore end)} \\[2ex] (c_i + c_0)\cdot\dfrac{e^u}{1 + e^u} & \text{(outer pore end)}. \end{cases} \tag{25}
$$

The diffusion Eq. (16) together with the conditions (17) and (23) can be integrated by employing the method of Laplace transformation. The end result for the current $I = F\Phi$ through a single pore is

$$I(t) = 2\pi F D \frac{c_i e^u - c_0}{1 + e^u} \cdot \frac{r_0^2}{r_0 + \varkappa} \cdot \left\{ 1 + \frac{r_0}{\varkappa} \exp\left(\frac{t}{\tau}\right) \mathrm{erfc}\left(\sqrt{\frac{t}{\tau}}\right) \right\} \qquad (26)$$

with

$$\tau = \frac{1}{D}\left(\frac{r_0 \varkappa}{r_0 + \varkappa}\right)^2 \qquad (27)$$

and where erfc denotes the complement error function:

$$\mathrm{erfc}\,(y) = 1 - \frac{2}{\sqrt{\pi}} \int_0^y \exp\,(-u^2)\,du\ . \qquad (28)$$

At $t = 0$:

$$I(0) = 2\pi F D \frac{c_i e^u - c_0}{1 + e^u} \cdot \frac{r_0^2}{\varkappa} \qquad (29)$$

and in the stationary state:

$$I(\infty) = 2\pi F D \frac{c_i e^u - c_0}{1 + e^u} \cdot \frac{r_0^2}{r_0 + \varkappa}\ . \qquad (30)$$

Diffusion polarization in the unstirred solution layers near the pore thus causes a current drop by the amount $I(0) - I(\infty)$. As an example we take a pore radius $r_0 = 2$ Å, a pore length $l = 50$ Å, a diffusion coefficient $D = 10^{-5}$ cm² s⁻¹ for the ion movement in the solutions and in the pore, equal bulk concentrations $c_i = c_0 = 100$ mM in the intra- and extracellular solution, and a normalized membrane voltage $u = 4$ (corresponding to $U \approx 100$ mV). With these values $\varkappa = l/\cosh(u/2) = 13.3$ Å, $I(0) = 1.76 \cdot 10^{-12}$ A, $I(0) - I(\infty) = 0.23 \cdot 10^{-12}$ A. For a shorter pore length $l = 10$ Å we obtain $\varkappa = 2.66$ Å and the initial current and the current drop become $I(0) = 8.79 \cdot 10^{-12}$ A, $I(0) - I(\infty) = 3.77 \cdot 10^{-12}$ A.

To estimate the magnitude of the characteristic time τ we insert Eqs. (24) and (20) into (27). This gives

$$\tau = \frac{1}{D}\left(\frac{r_0 l}{r_0 + l}\right)^2 \qquad (31)$$

for voltages $|u| < 1$. With $D = 10^{-5}$ cm² s⁻¹, $r_0 = 2$ Å, and $l \gg r_0$ we obtain $\tau = 4 \cdot 10^{-11}$ s. In the following Eq. (26) will be applied at times $t \gg \tau$ only. Using the relation

$$\exp\,(y^2) \cdot \mathrm{erfc}\,(y) = \frac{1}{\sqrt{\pi} \cdot y}\ ; \qquad (y \gg 1) \qquad (32)$$

(Carslaw and Jaeger, 1959, appendix II) we then obtain:

$$I(t) = I(\infty) \cdot \left\{ 1 + \frac{r_0}{\varkappa} \sqrt{\frac{\tau}{\pi t}} \right\}\ ; \qquad (t \gg \tau). \qquad (33)$$

Thus the current drop towards the stationary state is proportional to $1/\sqrt{t}$ at large times.

Using Eqs. (27) and (30), the expression (33) can be written in the form:

$$I(t) = I(\infty) + \delta I(t) \qquad (34)$$

with

$$\delta I(t) = 2F \frac{c_i e^u - c_0}{1 + e^u} \cdot \frac{r_0^4}{(r_0 + \varkappa)^2} \sqrt{\frac{\pi D}{t}}\ . \qquad (35)$$
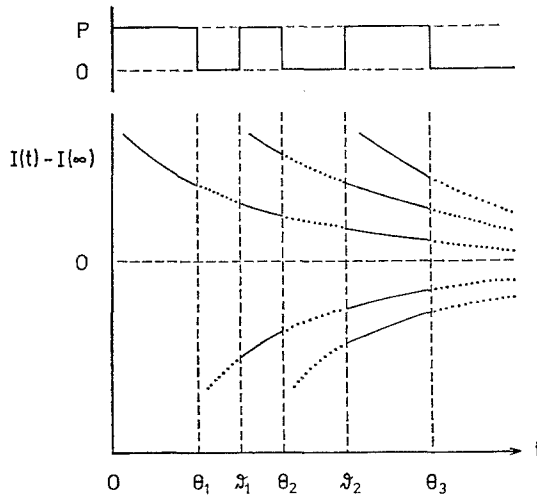
Fig. 4. Illustration of the superposition of current pulses δI in Eq. (36). Upper part: Step changes of the pore permeability between the values P and 0. Lower part: Positive current pulses generated at each pore opening and negative current pulses at each pore closing. $I(t) - I(\infty)$ for an open pore is obtained as superposition of all pulses from previous pore openings and closings. For a closed pore: $I(t) = 0$. Examples: If the pore is closed at $t < 0$, $I(t) - I(\infty)$ is equal to one positive pulse for $0 < t < \theta_1$, $I(t) = 0$ for $\theta_1 < t < \vartheta_1$, $I(t) - I(\infty)$ is obtained as the sum of two positive and one negative pulse for $\vartheta_1 < t < \theta_2$, $I(t) = 0$ for $\theta_2 < t < \vartheta_2$ etc.

Eq. (33) gives the time dependence of the current through a single pore which is closed at times $t < 0$, assumes a finite permeability P at $t = 0$ and remains open at $t > 0$. We now want to study the more general case that the pore is closed at $t < 0$ and switches between open and closed positions at times $t > 0$. This situation is indicated in the upper part of Fig. 4.

During times t with $\theta_\nu < t < \vartheta_\nu$ ($\nu = 1, 2 \ldots$) the pore is closed and the current through this particular pore vanishes. At $t = \vartheta_\nu$ the pore opens again and the current declines towards the stationary value $I(\infty)$ until the pore closes at $t = \theta_{\nu+1}$. Since the two permeability states are of finite duration, the concentration in the unstirred solution layers at $t > 0$ never reaches the stationary state nor does the concentration assume the uniform density which existed for $t < 0$. Therefore, it is necessary to take into account the actual concentration profile at $t = \vartheta_n$, if one wants to calculate the current $I(t)$ between $t = \vartheta_n$ and $t = \theta_{n+1}$. The integration of the diffusion Eq. (16) together with the boundary condition (23) and the appropriate initial concentration values in the unstirred solution layers gives for $\vartheta_n < t < \theta_{n+1}$:

$$I(t) = I(\infty) + \delta I(t) + \sum_{\nu=1}^{n} \delta I(t - \vartheta_\nu) - \left(\frac{r_0 + \varkappa}{\varkappa}\right) \sum_{\nu=1}^{n} \delta I(t - \theta_\nu) \qquad (36)$$

$I(\infty)$ is the stationary current given by Eq. (30) and the pulse function $\delta I(t)$ is defined by Eq. (35). $\delta I(t - \vartheta_\nu)$ and $\delta I(t - \theta_\nu)$ are the same pulses except for a translation along the time axis by the times ϑ_ν and θ_ν, respectively. Similar to relation

(33) the validity of Eq. (36) is restricted to times $(t - \vartheta_n) \gg \tau$ e.g. for times after the opening of the pore which are large compared with the characteristic time τ. In the lower part of Fig. 4 a representation of the current decay $I(t) - I(\infty)$ as superposition of the tails of all previous currents is illustrated. It is obvious that a term $\delta I(t)$ does not only contribute to the current during one particular permeability state but occurs in the expressions $I(t) - I(\infty)$ of all subsequent open states. This unlimited time course of $\delta I(t)$ is essential for the frequency range of the associated $1/f$ noise spectrum as will be shown in the following section.

1/f Noise from Porous Membranes

We start with the simple case of a membrane pore with a time independent finite permeability P during its life time b. It was shown in the preceding section that the initial current through this pore has a finite value and that the current decay towards the stationary state is proportional to $1/\sqrt{t}$ for times after the opening of the pore which are large compared with a characteristic time $\tau \approx 10^{-11}$ s. If an average number N of such pores are open at a given moment, the rate of pore creation will be $\lambda = N/b$. Combining Eqs. (15) and (35) then yields the following expression for the density $S_I(f)$ of the $1/f$ noise spectrum resulting from the current fluctuations due to diffusion polarization in the unstirred solution layers:

$$S_I(f) = \frac{N}{b} q^2 \cdot \frac{1}{f} \tag{37}$$

with

$$q = 2 F \sqrt{\pi D} \frac{r_0^4}{(r_0 + \varkappa)^2} \frac{c_i e^u - c_0}{1 + e^u} . \tag{38}$$

According to the derivation of Eq. (15) the $1/f$ dependence of $S_I(f)$ is restricted to the frequency range $1/2\pi b \ll f \ll 1/2\pi\tau \approx 10^{10}$ Hz.

$S_I(f)$ is the $1/f$ noise spectrum of current fluctuations under voltage clamp conditions. In general the power spectrum $S_U(f)$ of voltage fluctuations under constant current is related to $S_I(f)$ through (Verveen and DeFelice, 1974; Wanke, DeFelice and Conti, 1974)

$$S_U(f) = |Z(f)|^2 \cdot S_I(f) . \tag{39}$$

$Z(f)$ is the complex membrane impedance at the frequency f. If $|Z(f)|$ is constant for the range of frequencies studied, it can be replaced by the reciprocal of the conductance g. Thus: $S_U(f) = S_I(f)/g^2$.

Predictions of formulas (37) and (39) are now compared with the intensity of $1/f$ noise measured at nerve membranes under current and voltage clamp conditions. For nodes of Ranvier (Siebenga, Meyer, Verveen, 1973), for lobster axons (Poussart, 1971) and for squid axons (Fishman, 1973; Conti, DeFelice, Wanke, 1975) very pronounced $1/f$ spectra were reported which could be related mainly to the flux of potassium ions through the membrane. A further common feature of the noise spectra of all preparations is the range of the $1/f$ frequency dependence which is extended down to frequencies of the order of 1 Hz. Therefore, the life time b of individual membrane pores must be higher than 1 s if formulas (37) and (39) are applicable. From measurements of the membrane shot noise the number of potassium channels in the node of Ranvier was estimated to be about

$N = 10^4$ (Siebenga *et al.*, 1973). The potassium concentrations in the intra- and extracellular solutions in contact with frog nerves are approximately $c_i = 120$ mM, $c_o = 2.5$ mM. We further need values for the radius r_o and length l of the potassium channels in the nerve membrane. According to Bezanilla and Armstrong (1972) and to Hille (1973) the narrowest part of the K channel in squid axon membranes and in myelinated nerves is about 3 Å in diameter and the channels have a wide inner mouth. We, therefore, assume that the cylindrical tunnel of the potassium channel has an average radius of $r_o = 2$ Å and a length of the order of $l = 10$ Å. At $U = -70$ mV ($u = -2.8$) we then obtain $\varkappa = 4.65$ Å using Eqs. (24) and (20). With $D = 10^{-5}$ cm² s^{-1} Eq. (38) yields $q = 1.77 \cdot 10^{-19}$ A s$^{1/2}$. Taking $g = 10^{-7}$ S for one single node (Siebenga *et al.*, 1973) and $b > 1$ s we finally arrive at an intensity $S_U(1) < 3.1 \cdot 10^{-20}$ V² s of the *1/f* noise spectrum of voltage fluctuations at $f = 1$ Hz. In contrast to this calculated value the measured intensity is $S_U(1) \approx 10^{-10}$ V² s (Siebenga *et al.*, 1973, Fig. 2).

The same discrepancy occurs for the *1/f* noise at squid axon membranes. Taking the experiments of Fishman (1973) we have $c_i = 500$ mM (potassium concentration of the internal perfusate), $c_o = 10$ mM, $\varkappa = 4.65$ Å at the resting potential which is assumed to be $U = -70$ mV, and $q = 7.5 \cdot 10^{-19}$ A s$^{1/2}$. Using a value of $50\,\mu$m^{-2} for the density of potassium channels on the squid axon membrane (Conti *et al.*, 1975), there are $N = 5 \cdot 10^5$ potassium channels in an isolated membrane patch of 10^{-4} cm². Under these conditions a resistance $1/g$ of 3.5 MΩ and a *1/f* noise density of approximately 10^{-11} V² s at $f = 1$ Hz were measured (Fishman, 1973). However, using Eqs. (37), (39) and $b > 1$ s gives $S_U(1) < 3.4 \cdot 10^{-18}$ V² s. Consider also the *1/f* spectrum of current fluctuation under constant voltage at squid axon membranes (Conti *et al.*, 1975). These authors isolated a membrane area of about 0.38 cm² (20 mm axon length, 600 μm axon diameter) and measured a *1/f* density of about 10^{-21} A² s at $f = 10$ Hz and $U = -56$ mV (Conti *et al.*, 1975, Fig. 1). Instead $S_I(10) < 1.3 \cdot 10^{-28}$ A² s is obtained from Eqs. (37), (38) with the values $c_i = 410$ mM, $c_o = 10$ mM, $\varkappa = 5.9$ Å, $q = 8.4 \cdot 10^{-19}$ A s$^{1/2}$, $N = 1.9 \cdot 10^9$, and $b > 1$ s.

These large deviations between measured and calculated *1/f* noise densities indicate that our theory does not describe the observed *1/f* noise at nerve membranes if permanently open potassium channels are assumed. Therefore, we consider fluctuations of the permeability between the values P and 0 as indicated in the upper part of Fig. 4. The resulting time course of the current $I(t)$ through an open pore is given by Eq. (36). According to this relation $I(t) - I(\infty)$ can be represented as the superposition of positive pulses $\delta I(t)$, $\delta I(t - \vartheta_\nu)$ from previous pore openings and negative pulses $-(r_o + \varkappa)/\varkappa \cdot \delta I(t - \theta_\nu)$ from previous pore closings. Thus $I(t)$ depends on the duration t of permeability fluctuations, but the individual pulses contributing to $I(t)$ are always the same and independent of the time t. Since we assumed statistical switches between the two permeability states, the noise of such randomly occuring pulses can be calculated from Carson's theorem [Eq. (4)]. To obtain the pulse frequency λ we introduce the average time periods τ_o and τ_c of open and closed states of an individual pore. The rate of switches from a closed to an open state then becomes $\lambda = 1/(\tau_o + \tau_c)$. Since the current pulses are interrupted during closed states (compare Fig. 4), the Fourier transforms of the individual pulses have to be multiplied by the fraction

$\tau_o/(\tau_o + \tau_c)$ of time at which the pore is open. Thus Eq. (15) yields for the density $S_I(f)$ of the $1/f$ current noise spectrum:

$$S_I(f) = \frac{N}{\tau_o + \tau_c} \left(\frac{\tau_o}{\tau_o + \tau_c}\right)^2 \left[1 + \left(\frac{r_o + \varkappa}{\varkappa}\right)^2\right] q^2 \cdot \frac{1}{f} . \qquad (40)$$

N is the number of membrane pores which are assumed not to interact with each other, and the expression q is defined by Eq. (38). The time course of the single contributions $\delta I(t)$ in Eq. (36) is not limited by the period τ_o of an open pore but only restricted by the finite lifetime of the pore or by the time range during which no significant changes of the aqueous bulk ion concentrations occur due to ion accumulation or depletion in finite diffusion regions around the pores. Since these times can be several seconds or even longer, the low frequency limit of the $1/f$ spectrum can lie below 1 Hz in accordance with the experiments. The upper frequency limit $1/2 \pi \tau$ of $S_I(f)$ is determined by the characteristic time $\tau \approx 10^{-11}$ s of pore opening and is outside the range of measured noise spectra.

To simplify Eq. (40) we approximate $(r_o + \varkappa)/\varkappa$ by 1 and assume equal periods τ_o and τ_c of open and closed pores. Then

$$S_I(f) = \frac{N}{4 \tau_o} q^2 \cdot \frac{1}{f} . \qquad (41)$$

Thus the lifetime b in formula (37) simply has to be replaced by $4 \tau_o$ to obtain the $1/f$ noise spectrum of pores with random permeability switches. If the time period τ_o of an open state is much smaller than the parameter b, much higher densities S_I follow from Eq. (41) than it would be calculated from Eq. (37) without taking permeability switches into account. The discrepancies found between predictions from Eq. (37) and measured $1/f$ noise densities at nerve membranes now can be resolved by choosing appropriate low values for the period τ_o in Eq. (41). To obtain spectral densities of $1/f$ noise which are compatible with measurements at myelinated nerves (Siebenga et al., 1973), τ_o has to be in the order of 10^{-10} s. The $1/f$ spectrum of voltage fluctuations at squid giant axons (Fishman, 1973) and the $1/f$ current fluctuations at the same preparation (Conti et al., 1975) are in agreement with our theory with $\tau_o \approx 10^{-7}$ s.

Discussion

It was shown in the Results section that the calculated spectral densities of $1/f$ noise only reach the size of measured $1/f$ noise at nerve membranes if there are random switches between two pore permeability states. However, a determination of pore parameters from $1/f$ noise densities is not possible at present for the following reasons: $1/f$ noise probably is not only generated by the flux of potassium ions as it was assumed in the previous section, but there are considerable contributions of sodium and leakage currents to this kind of noise (Conti et al., 1975). Furthermore, no reliable values are available for the size and the density of ion selective channels on nerve membranes. Thus the value $\tau_o \approx 10^{-7}$ to 10^{-10} s for the period of an open pore estimated from Eq. (41) has to be considered as a very rough estimate. However, τ_o is definitely shorter than any time constant of the Hodgkin-Huxley formalism describing the activation and inactivation of sodium currents and the activation of potassium currents in voltage clamp experiments. Therefore, conventional "gating" of the ionic currents is not responsible for the

generation of $1/f$ noise at nerve membranes. A possible alternative interpretation of rapid switches of pore permeabilities with time constants of the order of τ_0 is single file transport of K^+ ions through the potassium channels (Hodgkin and Keynes, 1955; Heckmann, 1972). An influx of ions from the unstirred solution layer into the channel then would be possible only if there is a free site at the entrance of the pore. Otherwise the pore would be closed. The rate $1/\tau_0$ then has to be interpreted as the frequency of transitions between a free and occupied site. These random permeability switches due to single file transport could be the basis of $1/f$ noise at nerve membranes. As a demonstration we refer to the model experiment of Schick and Verveen (1974). These authors investigated the flow of small grains through an hourglass and found a $1/f$ frequency dependence for the fluctuation of the grain density.

Poussart (1971) and Conti *et al.* (1975) have shown that the spectral density of $1/f$ noise is proportional to the square of the potassium current through the nerve membrane. This relation is in accordance with our theoretical description of $1/f$ noise since the parameter q and the stationary ion flux $I(\infty)$ exhibit the same voltage dependence [compare Eqs. (30) and (38)] and the spectral density of $1/f$ noise is proportional to q^2. The temperature dependence of $1/f$ noise cannot be examined easily because almost all parameters of our model will vary with temperature. It could be that an increase of the frequency $1/\tau_0$ and the diffusion coefficient D at increasing temperature is compensated by a slight decrease of the pore radius r_0 such that the $1/f$ density becomes practically temperature independent as observed in the experiments (Conti *et al.*, 1975).

Appendix: *Validity of the Assumptions 2) and 3)*

If Δx and $\Delta\varphi$ are thickness and voltage drop in the Debye Hückel solution layers in front of the membrane, the electrical driving force in this layer gives the contribution

$$I_e = \pi r_0^2 F \, D \, c \, \frac{\Delta\varphi}{\Delta x} \qquad (42)$$

to the current through a single pore. c is a mean concentration of the permeant ion which is of the order of the corresponding bulk concentration. The magnitude of I_e has to be compared with the current arising from the ion flux along the concentration gradient in the unstirred solution layers. For equal bulk concentrations $c_i = c_o = c$ in the intra- and extracellular solutions Eq. (30) gives

$$I(\infty) = 2\,\pi\,F\,D\,c \, \tanh\,(u/2) \, \frac{r_0^2}{r_0 + \varkappa} \qquad (43)$$

and the current ratio between I_e and $I(\infty)$ becomes

$$\frac{I_e}{I(\infty)} = \frac{r_0 + \varkappa}{2\,\Delta x} \cdot \frac{\Delta\varphi}{\tanh\,(u/2)} \,. \qquad (44)$$

This relation was derived under the assumption that the pore radius r_0 is small compared with the Debye Hückel length Δx. Otherwise the half sphere of radius r_0 around the pore ends would include the Debye Hückel solution layer and electrical driving forces could be neglected in the calculation of the ion flux in the unstirred solution layers for pore distances $r < r_0$.

For ion selective channels in nerve membranes the condition $r_o < \Delta x$ is fulfilled and the Eq. (44) applicable. In physiological solutions the Debye Hückel length Δx is of the same order as the sum $r_o + l$ of pore radius r_o and pore length l, whereas at voltages $|U| < 100$ mV ($|u| < 4$) the voltage drop $\Delta\varphi$ in this layer is small as compared to $\tanh(u/2)$ (Läuger and Neumcke, 1973). Thus $I_e \ll I(\infty)$ and assumption 2) is fulfilled.

If pores switch randomly between open and closed positions with the frequency $1/\tau_o \approx 10^7$ Hz, an interference can only occur between the ion fluxes of pores which are less than $\sqrt{2 D\tau_0} \approx 140$ Å apart. Assuming that there are only a few pores within a circle of radius 140 Å, it is sufficient to prove assumption 3) for two neighbouring pores. The following arguments apply to the stationary state at which the deviations between the concentrations in the unstirred solution layers and the corresponding bulk concentrations assume maximum values. The stationary concentration profile in the unstirred solution layers is:

$$
c(r) = \begin{cases}
c_i - \dfrac{I(\infty)}{2\pi F D r} & \text{(intracellular solution)} \\[2mm]
c_0 + \dfrac{I(\infty)}{2\pi F D r} & \text{(extracellular solution)}.
\end{cases} \tag{45}
$$

In the special case $c_i = c_o = c$, the expression (43) can be used and the relative deviation $\Delta = |c(r) - c|/c$ of $c(r)$ from the bulk value c becomes

$$
\Delta = \frac{r_0^2}{r_0 + \varkappa} \tanh(|u|/2) \frac{1}{r} . \tag{46}
$$

Assuming $r_o = 2$ Å, $u = 3$ ($U = 75$ mV), $l = 10$ Å and using Eqs. (24) and (20) yields $\varkappa \approx 6$ Å. Thus $\Delta < 1\%$ for $r > 45$ Å. For longer pore lengths l even shorter pore distances r would be obtained at which the interferences between the ion fluxes of two neighbouring pores can be neglected.

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