# 1/f Noise in Membranes*

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**Abstract.** The present situation of $1/f$ noise in the passage of ions across membranes is examined. A survey of biological and synthetic membranes is given at which a $1/f$ frequency dependence has been observed in the spectrum of voltage or current fluctuations. Empirical relations and theories of $1/f$ noise in membranes are critically discussed.

**Key words:** $1/f$ Noise — Biological membrane — Synthetic membrane — Membrane pore — Diffusion.

## Introduction

A standard method in the analysis of random processes is the determination of the spectral density $S$ of the fluctuating variable at various frequencies $f$. The process is said to produce "$1/f$ noise" if $S(f)$ varies approximately inversely to $f$ over a wide frequency range. $1/f$ noise is a well known phenomenon in a great number of different systems and has been extensively studied in semiconductor devices. An introduction into the properties and problems of $1/f$ noise may be found in several monographs, for instance in Bell (1960), chapter 10 and Pfeiffer (1962), § 8. Hooge (1976) has given a survey of recent literature on $1/f$ noise in semiconductors and metals.

   This review concentrates on $1/f$ noise in the passage of ions across membranes and only occasionally refers to work on other systems. $1/f$ noise in membranes was first detected in myelinated nerve (Verveen and Derksen, 1965) and subsequently described for a variety of other biological and synthetic membranes. Despite many attempts the occurance of $1/f$ noise in membranes is still unexplained and it is not even known whether $1/f$ noise in different membranes has a common origin (Derksen, 1965; Verveen and DeFelice, 1974; Conti and Wanke 1975; deGoede and Ver-

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veen, 1977). To examine the present situation a survey of membranes is given where a $1/f$ frequency dependence was observed in the spectrum of voltage or current fluctuations. Then empirical relations and various theories of $1/f$ noise in membranes are discussed.

## General Properties of $1/f$ Noise

The term "$1/f$ noise" does not imply an exact inverse relationship between the spectral density $S$ and the frequency $f$. Instead all fluctuation phenomena are called $1/f$ noise which exhibit a proportionality between $S$ and $1/f^n$ over several frequency decades with a uniform exponent $n$ close to 1. For example in voltage clamped lobster axons Poussart (1971) determined from 250 spectra values $n$ with a range between 0.8 and 1.3, a mean of 1.002, and a standard deviation of 0.076. Dorset and Fishman (1975) reported exponents $n$ between 0.7 and 1.4 for noise in artificial porous membranes, again with a mean close to 1. All these fluctuations are considered as $1/f$ noise. In the following mainly a constant exponent $n = 1$ for $1/f$ noise will be assumed.

The experiments of Moore (1974) on carbon resistors suggest that the observed $1/f$ noise in this system is produced by a stationary normally distributed process with a time independent variance. Since this variance also must be finite, an exact $1/f$ frequency dependence cannot extend from $f = 0$ to $f = \infty$ because the integration would lead to infinite results at both limits. The necessary deviations from the $1/f$ behaviour at low and high frequencies often cannot be observed. Caloyannides (1974) performed measurements at semiconductors down to $10^{-6}$ Hz without finding deviations from a $1/f$ dependence. Only in the fluctuations of the density of grains flowing through an hourglass a $1/f$ spectrum with a low frequency white noise limit could be detected (Schick and Verveen, 1974). At the high frequency end as well deviations from $1/f$ behaviour can hardly be observed, the $1/f$ spectrum then vanishes in the thermal noise level.

The uncertain frequency dependence at low and high frequencies makes it difficult to assign a unique autocorrelation function to $1/f$ noise. This is demonstrated by the following example: It was shown (Neumcke, 1975) that randomly occuring pulses of the form

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

generate a spectrum which is flat at low frequencies, proportional to $1/f$ in the frequency range $1/(2\pi b) < f < 1/(2\pi a)$ and which decays as $1/f^2$ at higher frequencies. Calculating the autocorrelation function

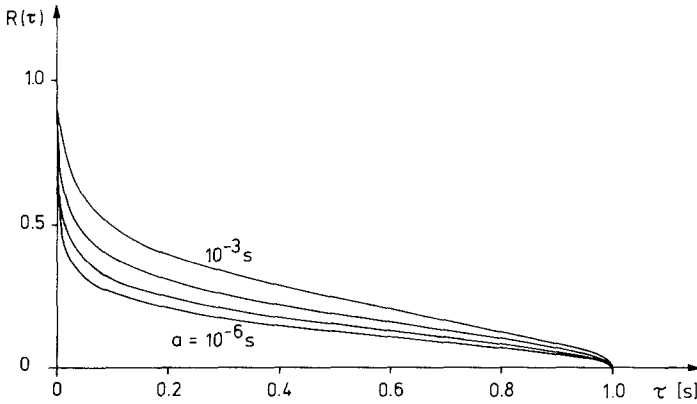$$C(\tau) = \int_0^\infty g(t)\, g(t + \tau)\, dt \tag{2}$$

**Fig. 1.** Normalized autocorrelation function $R(\tau)$ of the pulse sequence (1) for the parameters $a = 10^{-6}$, $10^{-5}$, $10^{-4}$, $10^{-3}$ s (from bottom to top) and $b = 1$ s

of the pulse sequence yields

$$C(\tau) = \begin{cases} 2 \ln \dfrac{\sqrt{b} + \sqrt{b - \tau}}{\sqrt{a} + \sqrt{a + \tau}}, & 0 \leqslant \tau \leqslant b - a \\ 0, & \tau > b - a \end{cases} \tag{3}$$

Figure 1 shows the normalized function $R(\tau) = C(\tau)/C(0)$ for $b = 1$ s and various parameters $a$ between $10^{-6}$ and $10^{-3}$ s. The characteristic sharp decline of $R(\tau)$ near $\tau = 0$ is also seen in Figure 3.4.1b of Derksen (1965) where the normalized autocorrelation function is plotted for a similar truncated $1/f$ spectrum as obtained form the pulse sequence of Equation (1).

Though for all parameters $a$, $b$ chosen in Figure 1 a $1/f$ frequency dependence results between 0.16 and 160 Hz, the functions $R(\tau)$ are clearly different in the corresponding time interval $10^{-3}$ s $< \tau < 1$ s. This explains that the autocorrelation function of $1/f$ noise critically depends on the behaviour of the spectral density outside the $1/f$ range. The same result can be deduced from the investigations of DeFelice (1976) on high and low pass filtered $1/f$ noise. In this case the autocorrelation function $C(\tau)$ can be represented as products of exponential integrals and exponential functions. Equation (7) of his publication then reveals that $C(\tau)$ depends on the corner frequencies and the transfer characteristics of both filters at any time $\tau$. Similar complications may arise when relaxation noise is studied in terms of autocorrelation functions (DeFelice and Sokol, 1976a).

DeFelice and Sokol (1976b) have developed another method to analyse fluctuation phenomena which seems to be particularly suitable for $1/f$ noise. In their so called integral spectrum pure $1/f$ noise appears as a frequency independent quantity and thus can easily be separated from other noise components. Disadvantages of the integral spectrum method are that thermal noise now becomes frequency dependent and that the integral spectrum of $1/f^n$ noise with exponents $n$ close to 1 is no longer flat (Poussart, 1977).

## 1/f Noise in Biological Membranes

1/f noise in a biological system was for the first time detected in myelinated nerve (Verveen and Derksen, 1965; Derksen, 1965). In the early experiments of the Leiden group voltage fluctuations were studied in single myelinated nerve fibres under current clamp conditions. The analysis revealed an almost pure 1/f spectrum between 1 Hz and several kHz which could be related to the flux of $K^+$ ions through the nodal membrane but was apparently not affected by the flow of $Na^+$ ions or active transport processes (Derksen and Verveen, 1966; Verveen et al., 1967; Verveen and Derksen, 1968). The 1/f noise intensity was minimal at the potassium equilibrium potential and increased steadily with depolarization. At the resting potential the amplitude distribution of the 1/f fluctuations was found to be Gaussian. Deviations from this normal distribution were seen at other membrane potentials. Negatively skewed noise at hyperpolarizations could be related to bursts of $Na^+$ influx, whereas no interpretation was given for positively skewed noise at large depolarizations (Verveen and Derksen, 1969).

Subsequent spectral analyses at depolarizing membrane potentials indeed revealed an additional noise component arising from conductance fluctuations due to the statistical opening and closing of gates in ionic channels. This component has been called conductance noise, shot noise or channel noise. Following the first publications on this new type of membrane noise (Siebenga and Verveen, 1971, 1972), little information has been added to the properties of 1/f noise. Exceptions are the reports on the temperature independence of the 1/f noise intensity between 7 and 17° C (Siebenga and Verveen, 1971) and the reduction of 1/f noise by tetraethylammonium ions (Siebenga et al., 1974). The last publication also describes an independence of 1/f noise on tetrodotoxin blocking sodium channels in nerve. However, in a later study of van den Berg et al. (1975) a small 1/f component presumably originating from the ion flux through sodium channels could be detected.

Figure 2 is reproduced from the work of Siebenga et al. (1973) and shows the superposition of 1/f noise and channel noise at different membrane potentials. The shape of the curves and a model experiment of the authors suggest that the two noise sources are not correlated. Hence their spectral densities may be added to give the compound spectrum.

Voltage fluctuations under current clamp conditions may be filtered by a frequency dependent membrane impedance $Z$. A frequency dependence of $Z$ indeed has been detected by Cole and collaborators (see Cole, 1968) for squid giant axons. Also, from linearized Hodgkin Huxley equations sharp resonances of $|Z(f)|$ are predicted around 100 Hz for squid giant axons (Mauro et al., 1970) and between $10^2$ and $10^3$ Hz for myelinated nerve (Clapham and DeFelice, 1976). Since the spectral density $S_V(f)$ of voltage fluctuations under constant current is related to the spectrum $S_I(f)$ of current fluctuations at constant voltage through

$$S_V(f) = |Z(f)|^2 \cdot S_I(f) \tag{4}$$

(Verveen and DeFelice, 1974), the spectrum $S_V(f)$ may be modified by $Z(f)$ (Wanke et al., 1974). On the other hand, the spectral density $S_I(f)$ under voltage clamp conditions is not affected by a possible frequency dependence of the membrane
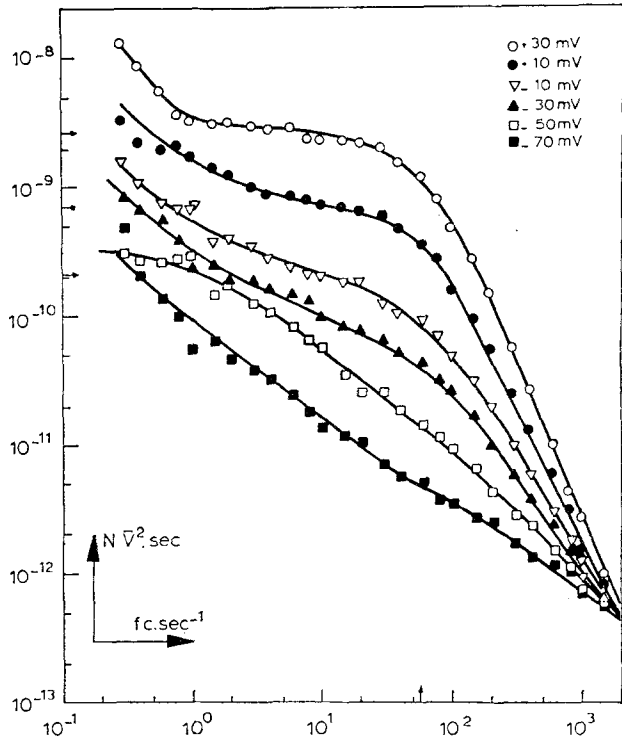
**Fig. 2.** Voltage noise spectra of a myelinated nerve fibre at different membrane potentials (from Siebenga et al., 1973; by permission)

impedance and thus yields more direct information on the underlying fluctuations. In a recent report by van den Berg et al. (1977) the fluctuations of the potassium currents in voltage clamped myelinated nerve were recorded during an early and a late phase after a depolarizing voltage step. In the spectra of both phases a 1/*f* noise component is visible which was not further analysed in their report. However, the authors have found (van den Berg, personal communication) that the spectral density of 1/*f* noise was largest in the late phase at which the potassium currents were partly inactivated (Schwarz and Vogel, 1971) and that it steadily decreased at earlier times. This suggests structural changes of the potassium channels during the process of potassium inactivation. More data of 1/*f* potassium current noise in myelinated nerve may be found in a recent report by van den Berg et al. (1977).

A 1/*f* component was also seen at voltage clamped myelinated nerve in the difference between the current spectra without and with external application of tetrodotoxin (TTX) (Conti et al., 1976a). Since TTX exclusively blocks sodium channels, induces no additional current fluctuations, and gives negligible impedance changes of the nodal membrane, the difference may be regarded as the spectrum of sodium current fluctuations. The spectral density $S_I(f)$ of 1/*f* sodium current noise was roughly proportional to the square of the steady-state sodium current $I_{Na}$. The quantity $S_I(1)/I_{Na}^2$ was of the order of $10^{-4}$ s in normal nodes and remained practically unchanged after modification of sodium inactivation by external treatment with *Leiurus* scorpion venom, *Anemonia* Toxin II or internal application of iodate (Conti et al., 1976b).

In unmyelinated nerve fluctuation measurements were immediately done under voltage clamp conditions. The first investigations of Poussart (1969, 1971) on lobster giant axons revealed an almost pure $1/f$ spectrum between 20 Hz and 5 kHz for current fluctuations. The dependence of the $1/f$ spectral density $S_I$ on the mean potassium current $I_K$ could be described by the empirical relation

$$S_I(f) = \frac{A + kI_K^m}{f},$$
(5)

where $A$ was a positive constant and the exponent $m$ in the range between 1.1 and 2.1 with a mean of 1.5. This relation and the observed change of $S_I(f)$ with the external potassium concentration suggested that the $1/f$ noise was produced by the flow of $K^+$ ions as in myelinated nerve. No clear indications for a correlation between $1/f$ noise and sodium or leakage current could be found.

In squid giant axons small membrane areas for fluctuation measurements may be isolated by three different methods, by an external sucrose patch (Fishman, 1973, 1975; Fishman et al., 1975, 1977b), by two internal air bubbles (Wanke et al., 1974) or by external air gaps (DeFelice et al., 1975; Conti et al., 1975; Fishman et al., 1975). All investigations cited above revealed a $1/f$ component in the spectra of current fluctuations between 1 Hz and several kHz. Since the main emphasis of all studies was on channel noise, only few results for $1/f$ noise were reported which can be summarized as follows: A minimum of the $1/f$ spectral densities $S_V(f)$ and $S_I(f)$ was observed near the potassium equilibrium potential. At increasing displacements from the equilibrium potential $S_V(f)$ increased superlinearly (Fishman et al., 1975, Fig. 3) and $S_I(f)$ was proportional to the square of the potassium current $I_K$ at positive displacements (Conti et al., 1975, Fig. 15). From this figure $S_I(1)/I_K^2 \approx 2 \cdot 10^{-8}$ s may be calculated. Almost the same value follows from the data of Fishman (1973) and Fishman et al. (1975). Hence the quantity $S_I(1)/I_K^2$ seems to be independent of the area of the axon surface from which fluctuations are recorded (about 0.38 cm$^2$ in the experiments of Conti et al., 1975; $10^{-4}–10^{-5}$ cm$^2$ in the patch method of Fishman et al., 1975). Since $S_I(f)$ was strongly dependent on the external $K^+$ concentration but not affected by tetrodotoxin (TTX), the main part of the observed $1/f$ noise should be due to the flow of $K^+$ ions through the membrane. However, a small $1/f$ component was also seen in the difference spectra without and with application of TTX and contributed to $1/f$ sodium current noise (Conti et al., 1975). For a discussion of possible errors in such subtraction procedures compare Fishman et al. (1977a). Finally, $S_I(f)$ was not significantly influenced by temperature within the range from 9.5–20° C (Conti et al., 1975).

In addition to nerve membranes, $1/f$ noise in biological systems has been described for the ciliated protozoan *Paramecium* (Moolenaar et al., 1976) and for cultured neuroblastoma cells (Moolenaar, 1975). Whether the voltage fluctuations in algae cells are $1/f$ like is not yet clear. In a preliminary report on *Nitella*, Warncke (1974) described a spectral density proportional to $1/f^2$ at low frequencies which passed into a $1/f$ dependency above 1 Hz. However, in a later investigation on *Chara braunii* no $1/f$ noise component was observed between 1 and 100 Hz (Roa and Pickard, 1976, Fig. 2).

In general $1/f$ noise from biological systems exhibits a large scatter both in the

spectral density and in the parameter $n$ of the $1/f^n$ frequency dependence. In addition the correlation with the flux of specific ions is sometimes difficult. For example the $1/f$ spectral density $S_I(f)$ was found to depend on the physiological state of the squid giant axons, $S_I(f)$ being much larger in axons of poor condition (Conti et al., 1975, page 71). Stevens (personal communication) observed no $1/f$ noise in good preparations of myelinated nerve. These results indicate that a part of the recorded $1/f$ noise was procuded by unspecific leakage currents which are particularly high in poor axon preparations.

## 1/*f* Noise in Artificial Membranes

Fluctuation measurements in artificial membranes could help to solve open problems of $1/f$ noise in biological systems. But even for synthetic membranes sometimes controversial reports on $1/f$ noise have appeared. The first investigations on thick ion exchange membranes (Green and Yafuso, 1968; Yafuso and Green, 1971; Green, 1974) revealed a $1/f$ spectrum of voltage fluctuations up to several kHz in anion membranes, but only at certain concentrations of the permeant anions and at certain imposed current densities through the membrane. On the other hand no $1/f$ frequency dependence was found for the spectra of cation membranes. From their studies the authors concluded that the voltage fluctuations were produced not in the interior of the membrane but at the boundary between the membrane and the aqueous depletion layers. This interesting result could be of relevance to an explanation of $1/f$ noise as will be shown below in the discussion of diffusion polarization effects.

In another series of experiments with synthetic membranes DeFelice and Michalides (1972a, b), Michalides et al. (1973) found an almost pure $1/f$ spectrum for voltage fluctuations in excess of the thermal noise. Figure 3 illustrates their results. The $1/f$ spectral density $S_V(f)$ at various current levels could be described by the empirical relation

$$S_V(f) = \frac{g \cdot W \cdot ReZ}{f}, \tag{6}$$

in which $ReZ$ is the real part of the equivalent membrane impedance $Z$, $W$ the average power being dissipated in the membrane, and $g$ a constant. Different $g$ values of $3 \cdot 10^{-10}$ and $9 \cdot 10^{-12}$ were obtained for collodion and PVC membranes respectively which suggests that the parameter $g$ depends on the internal structure of the membrane. However, no relation between $g$ and membrane parameters could be given.

Voltage fluctuations in various porous membranes have been extensively studied by Dorset and Fishman (1975). All spectral densities above the thermal level were found to be of the type $1/f^n$ with a mean value of $n$ near 1. Of particular interest are their measurements on pores of constant, known dimensions in mica sheets. Here $n$ values of 1.38 and 1.23 were obtained at 100 and 50 mV applied potential respectively (Fig. 6 of Dorset and Fishman, 1975). Similar studies on pores of fixed diameter and length were reported by Green (1976). The spectra shown correspond to an $1/f^{1.5}$ spectrum and thus are no longer of the $1/f$ type. Green
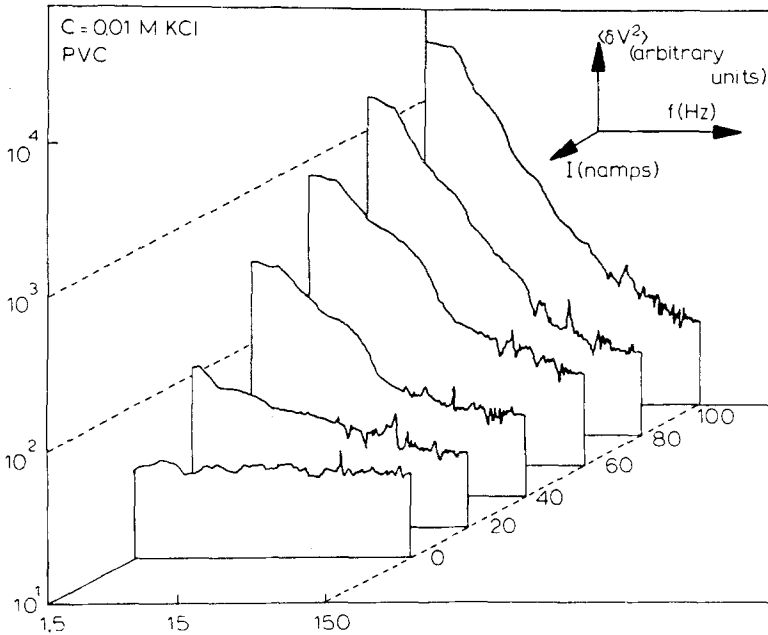
**Fig. 3.** Noise spectra at different current levels from a PVC membrane in 0.01 M KCl (from Michalides et al., 1973; by permission)

considered this result as indication for a diffusion process producing the observed noise. This point will be discussed further in the section on diffusion theories of $1/f$ noise.

Other investigations have failed to detect any $1/f$ noise in single pores in polycarbonate films (Bean and Golibersuch, 1977) and in gramicidin $A$ pores in lipid bilayer membranes (Neher, personal communication). But in these systems a $1/f$ component might not be detectable. As an example consider a gramicidin $A$ pore. In 1 M KCl solutions the current through a single pore is approximately $i = 2$ pA at an applied voltage of 100 mV (Neher and Zingsheim, 1974, Fig. 1a). A possible $1/f$ current noise should be visible in small fluctuations on top of the level $i$. Such fluctuations at frequencies above 0.1 Hz have been estimated to be smaller than 5% of $i$ (Neher, personal communication). The spectral density $S_I(f)$ of a possible $1/f$ noise at a single pore thus should be less than $(0.05 \cdot 2 \cdot 10^{-12})^2 = 10^{-26}$ A²/Hz at $f = 0.1$ Hz or less than $10^{-27}$ A²/Hz at $f = 1$ Hz. If a sodium channel in the nerve membrane and a gramicidin $A$ pore in a lipid bilayer had the same $1/f$ properties, the above estimate would predict $S_I(1) < 10^{-22}$ A²/Hz for a possible $1/f$ current noise from $10^5$ sodium channels in a node of myelinated nerve. The measured value of $S_I(1)$ is smaller than $10^{-23}$ A²/Hz (Conti et al., 1976a), thus below this limit. Hence the analysis of fluctuations seen in the current through a single pore might not be sufficient to exclude the presence of $1/f$ noise in multi-pore membranes.

There are two preliminary reports on $1/f$ like current fluctuations at lipid bilayers containing a large number of pores formed by nystatin (Wanke, 1975) or by alamethicin (experiments by Kolb, see Läuger, 1977). However, Romine et al.

(1977), could not confirm the nystatin results. In general 1/*f* studies on pores in lipid bilayers will be difficult since the density $S_I(1)$ at 100 mV membrane potential expected for one sodium channel like pore will be in the order of $10^{-28}$ A$^2$/Hz or even less. Hence high numbers of pores would be required to obtain reliable spectra.

## Empirical Relations for 1/*f* Noise

Already in early experiments of 1/*f* noise it was found, that its spectral density $S_I(f)$ is proportional to the square of the steady current *I*, at least for small currents. Subsequent investigations also revealed an inverse relationship between $S_I(f)$ and the total number *N* of mobile charge carriers in the system. Such a dependency was reported for 1/*f* noise at semiconductors, thermo- and concentration cells (Hooge, 1972) and also for carbon composition resistors (DeFelice, 1976). As empirical relation for 1/*f* current noise one may then write

$$S_I(f) = \alpha \cdot \frac{I^2}{N} \cdot \frac{1}{f}, \tag{7}$$

where the dimensionless parameter $\alpha$ depends on the type and concentration of charge carriers. For ions in water $\alpha$ is approximately 10 for 1-molar solutions and roughly proportional to the concentration (Hooge, 1972). The parameter $\alpha$ is temperature dependent as well (DeFelice, personal communication), but systematic studies of this point have not yet been reported.

From their measurements of 1/*f* noise in single membrane pores Dorset and Fishman (1975) could not derive a unique relationship between the parameter $\alpha$ of Equation (7) and the ion concentration in the aqueous solutions. Hence they questioned the applicability of this empirical relation and the concept that 1/*f* noise is solely dependent on the number of charge carriers. The origin of this discrepancy with Hooge's results is not clear since the pores employed in both investigations were approximately of the same geometry, the only difference seems to be the ionic species (HCl, AgNO$_3$, CuSO$_4$, Cu(NO$_3$)$_2$, NiSO$_4$ and Ni(NO$_3$)$_2$ in Hooge's investigations, KCl in the experiments of Dorset and Fishman).

Instead of pursuing a possible inadequacy of Equation (7), we want to assume in the following its applicability to 1/*f* noise produced by the ion flux through microscopic pores in nerve membranes. From the measurement of current fluctuations in myelinated nerve under voltage clamp conditions Conti et al. (1976a) obtained a mean value of $1.1 \cdot 10^{-4}$ s for the quantity $S_I(1)/I_{Na}^2$ of 1/*f* sodium current noise per node. Similar values were found after the process of sodium inactivation had been modified (Conti et al., 1976b). Taking $\alpha = 1$ for 0.1 M solutions gives an average number $N = 9 \cdot 10^3$ of mobile Na$^+$ ions in the system. This value is one order of magnitude below the number M = $10^5$ of Na channels per node calculated from Na conductance fluctuations (Conti et al., 1976b). Hence the effective number $n_t$ of mobile Na$^+$ ions per channel would be approximately 0.1. The same number was derived by van den Berg and Beekman (1977) using data of van den Berg et al. (1975). For the number of mobile K$^+$ ions per potassium channel significant higher values $n_t$ between 4 and 10 were estimated (van den Berg and Beekman, 1977; van

den Berg et al., 1977). This may support the hypothesis of a short sodium channel and a long potassium channel.

The above estimates for $n_t$ do not consider the gating of ionic channels in nerve. In the conventional interpretation of the Hodgkin Huxley formalism only the fractions $m_\infty^3 \cdot h_\infty$ and $n_\infty^4$ of Na and K channels are open in the stationary state ($m_\infty$, $h_\infty$, $n_\infty$ denote the steady state values of Na activation, Na inactivation and K activation respectively). In particular for the sodium system this fraction assumes very small values because Na inactivation under normal conditions is almost complete in the stationary state and at the depolarizations at which fluctuation measurements were performed. Calculating $m_\infty = \alpha_m/(\alpha_m + \beta_m)$ and $h_\infty = \alpha_h/(\alpha_h + \beta_h)$ for normal nodes from Equations (3)–(6) of Conti et al. (1976a) yields a maximum number of about 300 open sodium channels per node in the steady state near a depolarization of 30 mV. From this one would arrive at more than 30 mobile $Na^+$ ions per open sodium channel. Possible reasons for this unrealistic high number are:

(i) As pointed out by Conti et al. (1976a), their low frequency sodium current noise data scattered appreciably and were also subject to systematic errors. Hence the actual $1/f$ spectral density could be lower than reported.

(ii) The number of mobile ions estimated from Equation (7) could not only include ions within the pore but also ions entering or leaving the pore through the unstirred solution layers.

(iii) Each individual ionic channel could have multiple conductance states between fully open and closed (Hill and Chen, 1972, Appendix III). The factors $m_\infty^3 \cdot h_\infty$ and $n_\infty^4$ then no longer would represent the fraction of open channels but would merely give the ratio between the observed conductance and its maximum available value. The fraction of conducting channels at all membrane potentials would then be higher than the factors $m_\infty^3 \cdot h_\infty$ and $n_\infty^4$. In the extreme case all sodium and potassium channels would conduct, and the $n_t$ values for sodium and potassium channels would become 0.1 and 4–10 as cited above. Multiple conductance levels of the sodium channel could also explain that the quantity $S_I(1)/I_{Na}^2$ of $1/f$ sodium current noise would be hardly affected by a drastic increase of the parameter $h_\infty$ after modification of sodium inactivation (Conti et al., 1976b).

Hooge (1972) also investigated whether $1/f$ noise is produced by fluctuations in the number or in the mobility of charge carriers. He compared the voltage fluctuations of a concentration cell, in which the solutions of the two compartments had different concentrations, with the conductance fluctuations in the same cell but now with equal concentrations. The experimentally observed $1/f$ noise in both situations could only be explained by mobility fluctuations of the charge carriers and not by fluctuations of their number. If this result is applicable to $1/f$ noise in artificial and biological membranes, it has important implications with respect to a realistic theory of $1/f$ noise as will be shown in the following section.

### Theories of $1/f$ Membrane Noise

Experimental data and empirical relations for $1/f$ noise in various membrane systems give valuable information on the origin of these fluctuations. But a definitive theory of $1/f$ noise in membranes has not yet emerged, and it is even unknown

whether the observed noise in different systems has a common origin. Some basic unsolved questions of 1/*f* noise are:

(i) Is this noise produced by a stationary or a nonstationary process? We already mentioned the evidence for a stationary process in carbon resistors (Moore, 1974). But 1/*f* noise in other systems could still be produced by nonstationary fluctuations.

(ii) Can 1/*f* noise occur in equilibrium or only under non-equilibrium conditions? For an equilibrium system the spectral density of current fluctuations is given by the Nyquist formula

$$S_I(f) = 4\,kT\,\frac{Re\,Z(f)}{|Z(f)|^2}\,.$$

(8)

(*k*: Boltzmann constant, *T*: absolute temperature, *Z(f)*: complex impedance, *Re Z*: real part of *Z*). From this equation no 1/*f* dependence over several frequency decades can be obtained for a simple equivalent circuit of *Z*. Hence, 1/*f* current noise should occur in general only under non-equilibrium conditions. However, in experiments with small semiconductor and metal films, Voss and Clarke (1976) have demonstrated that 1/*f* resistance fluctuations do exist in equilibrium. But it is unknown whether these results apply also to 1/*f* noise in membranes.

(iii) Is 1/*f* noise a bulk or surface effect? In the empirical relation (7) the spectral density $S_I(f)$ of 1/*f* current noise depends on the total number *N* of mobile charge carriers in the system. This suggests that 1/*f* noise is a bulk effect. On the other hand, the model of McWhorter (see below) explains 1/*f* noise merely by charge transfer processes in the surface layer. The distinction between bulk and surface effects becomes irrelevant for thin membranes with a large ratio between surface area and membrane thickness (e.g. lipid bilayers and biological membranes).

Due to the uncertainties described above no solid basis for a description of 1/*f* fluctuation phenomena exists at present. This explains the numerous and often controversial theories on 1/*f* noise published so far. In the following we will only review 1/*f* theories with relevance to fluctuations of the ion passage across membranes. The mechanisms proposed to generate 1/*f* noise in membranes may be grouped into the following classes:

### A) Ion Jumps Over a Single Barrier

If the ion transport across a membrane is idealized as a jump over a single activation energy barrier, fluctuations of the ion concentration *c* on either side of the barrier relax exponentially with a time constant $\tau$. The corresponding spectral density $S_c$ of concentration fluctuations is then of the Lorentzian form:

$$S_c(f) \sim \frac{\tau}{1 + (2\pi f\tau)^2}\,.$$

(9)

In general the current *I* across the membrane is proportional to the time derivative *dc/dt*. The spectrum $S_I$ of current fluctuations thus contains an additional factor $f^2$ (Kolb and Läuger, 1977):

$$S_I(f) \sim \frac{f^2 \cdot \tau}{1 + (2\pi f\tau)^2}\,.$$

(10)

Neither of the two spectra shows a $1/f$ behaviour over a sufficiently large frequency range. $S_c(f)$ is flat at low frequencies $f \ll 1/(2\pi\tau)$ and decays as $1/f^2$ for $f \gg 1/(2\pi\tau)$, whereas $S_I(f)$ approaches monotoneously a plateau value at increasing frequencies. Ion jumps over a single specified barrier thus do not produce $1/f$ noise. Monte-Carlo simulations of a random walk across a single barrier which apparently revealed a $1/f$ dependence (Offner, 1970, 1971a, b, 1972) have been shown to yield actually a Lorentzian spectrum in the limit of an infinite number of walk steps (Bird, 1974a, b).

For a population of single barriers of different height with a distribution $g(\tau)$ of time constants $\tau$ Equation (9) must be replaced by

$$S_C(f) \sim \int g(\tau) \cdot \frac{\tau}{1 + (2\pi f\tau)^2}\, \mathrm{d}\tau \,. \tag{11}$$

Now a $1/f$ behaviour is obtained in the frequency interval $1/(2\pi\,\tau_2) \ll f \ll 1/(2\pi\,\tau_1)$ if $g(\tau) = 1/\tau$ for $\tau_1 < \tau < \tau_2$ (Kingston and McWhorter, 1956). For semiconductors the authors also proposed a mechanism which produces the special distribution $1/\tau$ of time constants $\tau$. In their model electron traps in the surface layer are assumed which may be filled by electrons from outside. If the concentration of traps is constant throughout the layer and if the probability of occupation by electrons decreases exponentially with the distance from the interface, a $1/\tau$ distribution of relaxation times $\tau$ is indeed observed. While such a trap model for $1/f$ noise could be designed for thick ion exchange membranes, it does not seem to be applicable to thin membranes where the ion adsorption can only occur at the membrane/solution interfaces.

## B) Random Diffusion Processes

In general the ion transport through a membrane cannot be treated as a jump over only one energy barrier. For example, single file effects in potassium channels of nerve suggest that $K^+$ ions have to cross several barriers in passing through the channel (Bezanilla and Armstrong, 1972). For sodium channels of nerve Hille (1975) has constructed a four-barrier model to account for the observed deviations from simple flux independence. Hence a migration of ions over a series of barriers seems to be often more appropriate than a single ion jump in a description of membrane transport. However, the theory of fluctuations in a multi-barrier system is rather complex in general since the statistics of penetration the whole membrane can only be formulated by joint probabilities depending on the transition rates of all barriers in the series. Läuger (1975) has solved this problem for two consecutive energy barriers, but it seems hopeless to extend his formalism to more. Fortunately, the limiting case of ion transport over an infinite number of identical and symmetrical activation energy barriers leads to well known diffusion (Glasstone et al., 1941) whose fluctuation properties have been studied in great detail. In the following it will be shown that random diffusion processes may yield $1/f$ spectra.

For a uniform diffusion coefficient $D$, the kinetics of the concentration $c$ are governed by the ordinary diffusion equation

$$\frac{\partial c}{\partial t} = D \cdot \Delta c \tag{12}$$

($\Delta$: Laplace operator). This equation describes diffusion in a concentration gradient. For electrodiffusion of ions in an external electric field another term describing the electrical driving force has to be added on the right-hand side. Particular solutions of Equation (12) depend on the dimension $n$ of space, the symmetry of the diffusion process and on the initial and boundary conditions. As an example consider one-dimensional diffusion $\partial c/\partial t = D \, \partial^2 c/\partial x^2$ with the initial condition $c(x, 0) = a \cdot \delta(x)$ and no boundary conditions imposed at finite coordinates $x$. The solution reads:

$$c(x, t) = \frac{a}{2\sqrt{\pi Dt}} \exp\left(-\frac{x^2}{4\,Dt}\right). \tag{13}$$

At $x = 0$ the concentration $c$ relaxes proportional to $1/\sqrt{t}$. Since pulses of the form $1/\sqrt{t}$ produce $1/f$ noise (Schönfeld, 1955; Neumcke, 1975), this frequency dependence may be found in the spectrum of concentration fluctuations from one-dimensional diffusion processes. The same kinetics and spectral behaviour are obtained for the fluctuations of the current $I \sim \partial c/\partial x$. Though Equation (13) gives $\partial c/\partial x = 0$ at $x = 0$, $I(t)$ is actually proportional to $1/\sqrt{t}$ at sufficiently large times $t$ if more realistic initial and boundary conditions are imposed than formulated above [Neumcke, 1971, Eq. (28)].

Kinetics of the type $1/\sqrt{t}$ are also observed for diffusion in three dimensions with spherical symmetry. In polar coordinates Equation (12) assumes the form

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r} \cdot \frac{\partial c}{\partial r}\right), \tag{14}$$

where $r$ is the distance from the origin. As a particular example we consider the spherical influx into a sink of radius $r_0$. For the initial condition $c(r > r_0, t = 0) = c_0$ and the boundary conditions $c(r_0, t > 0) = 0$, $c(\infty, t > 0) = c_0$ the integration of Equation (14) yields:

$$c(r, t) = c_0 \left\{1 - \frac{r_0}{r} \, \text{erfc} \, \frac{r - r_0}{2\sqrt{Dt}}\right\} \tag{15}$$

where erfc denotes the complement error function. Again the kinetics of the concentration at $r > r_0$ and at sufficiently large times and of the flux $\partial c/\partial r$ at the sink $r = r_0$ are proportional to $1/\sqrt{t}$.

Spherical diffusion in three dimensions is an exceptional case, since the kinetics of diffusion in two or three dimensions are normally not of the type $1/\sqrt{t}$. For example, in Cartesian coordinates the solution of the $n$-dimensional diffusion Equation (12) may be factorised into $n$ one-dimensional solutions. Assuming the same initial and boundary conditions in each dimension gives solutions of the form $(1/\sqrt{t})^n$. Such pulses only produce a $1/f$ frequency dependence for $n = 1$, whereas for $n = 2$ a spectral density proportional to $(\log f)^2$ and for $n = 3$ a constant are obtained in the low frequency limits.

So far we have only studied the kinetics of diffusion at sufficiently large times and the corresponding fluctuation spectra at low frequencies. At the high frequency end diffusion spectra are often of the type $f^{-3/2}$ (van Vliet and Fassett, 1965). This frequency dependence is universal for diffusion in an infinite domain regardless of the geometry or number of dimensions and for step function singularities in the

spatial weighting function (Lax and Mengert, 1960). In a finite diffusion range the "universal inverse 3/2 power law" holds only for a variety of boundary conditions (see Lax and Mengert, 1960, section 4; van Vliet and Fassett, 1965, page 340, for exceptions). Another modification of the $f^{-3/2}$ high frequency dependence may be introduced by various singularities in the fluctuation weighting function. Weissman (1977) has analysed a class of singularities producing $1/f$ noise at high frequencies. Of particular interest to $1/f$ noise in membranes are singularities of the type $1/r$ in two-dimensional systems ($r$: distance to the singularity) which result in a $1/f$ spectrum almost independently of the transport mechanism.

Despite the restricted validity of the "universal inverse 3/2 power law" the spectra of the form $f^{-3/2}$ reported by Green (1976) for the ion passage through membrane pores give some evidence for an underlying diffusion mechanism. Green could not observe the flattening of the $f^{-3/2}$ spectra at low frequencies. If the transition frequencies would be a function of the pore length, a $1/f$ spectrum could be constructed as superposition of noise from pores of variable length (Green, 1976).

The $1/\sqrt{t}$ kinetics observed in one-dimensional and spherical three-dimensional diffusion suggest that $1/f$ noise may be generated already by a uniform diffusion process. In principle $1/f$ noise in diffusion could be due to fluctuations in the number or in the mobility of the charge carriers. Mikulinsky and Mikulinsky-Fishman (1976) and Frehland (1976) have invoked the first possibility. Both theories start from electrodiffusion equations but differ in the dimension of the diffusion process and the imposed boundary conditions. Mikulinsky et al. (1976) have claimed to obtain a $1/f$ spectrum in systems extended in all three dimensions. However, an analysis of their end formula (8) gives a flat spectrum at low frequencies which changes rather abruptly into a $f^{-3/2}$ dependence at increasing frequencies. Hence the authors actually have studied a specific example of the "universal inverse 3/2 power law" and did not present a theory of $1/f$ noise. Frehland (1976) demonstrated possible differences between the spectra of concentration fluctuations and current fluctuations. For a further discussion of this point see Frehland (1977) and Green (1977). In Frehland's models of one-dimensional electrodiffusion a $1/f$ behaviour for current fluctuations was observed only in a semi-infinite medium with a flux-controlling boundary between the diffusion range and a domain of constant ion concentration and vanishing electric field. Open questions are whether this boundary condition may be applied to the ends of membrane pores and whether the density of $1/f$ noise calculated from the model would be in agreement with experimental data.

The diffusion theories discussed above explain $1/f$ noise by fluctuations in the number of charge carriers. Instead, fluctuations in the mobility of ions seem to be more likely to produce $1/f$ noise, at least in concentration cells (Hooge, 1972). In general mobility fluctuations will occur in the ion transport over a series of activation energy barriers and through membrane pores switching randomly between different conductance levels. By identifying $1/f$ noise at myelinated nerve with the conductance noise of potassium channels, Cole and Lecar (see Cole, 1968, page 535) have estimated the resistance of a channel and the average distance between two channels. Though their values ($2 \cdot 10^{12}$ $\Omega$ at the resting potential, 20 nm) are surprisingly close to present data, channel noise spectra are of the Lorentzian form rather than $1/f$ like. But random switches of the pore conductance do not only modulate the current through the membrane, they also change the concentration
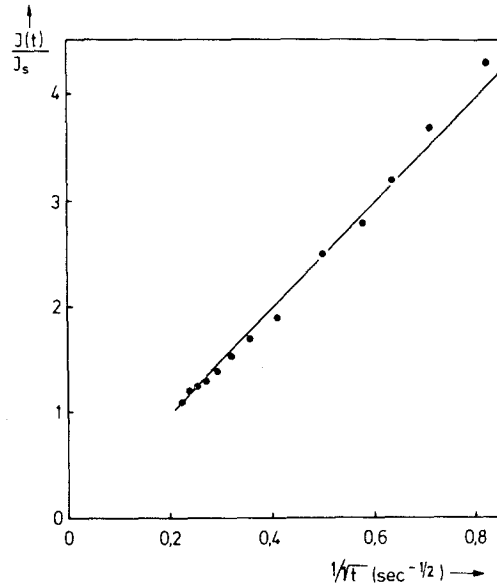
$$\frac{J(t)}{J_s}$$

Fig. 4. Kinetics of diffusion polarization at a lipid bilayer membrane. $I(t)/I_s$ as a function of $1/\sqrt{t}$ for tetraphenylborate as permeant ion ($c = 4.5$ μM) (from Neumcke, 1971; by permission)

$$1/\sqrt{t} \; (\text{sec}^{-1/2}) \longrightarrow$$

profile in the aqueous solution layers near the pore ends. The ion concentration is uniform in the unstirred solution layers only under zero-current conditions. If current flows through the membrane, the charge carrier concentration will decrease at one membrane surface and increase at the other. Since the potential created by these concentration gradients is opposite to the externally applied voltage, the current will decrease with time. The kinetics of the so called diffusion polarization will be proportional to $1/\sqrt{t}$ in the one-dimensional case and for spherical three-dimensional diffusion. Hence diffusion processes in the unstirred solution layers may produce $1/f$ noise. The experiments of Green and Yafuso (1968) on synthetic membranes could support the idea that the source of $1/f$ membrane noise might be located at the boundary between the membrane and the unstirred solution layers.

Kinetics of the type $1/\sqrt{t}$ have already been discussed for diffusion in the Schwann cell layer around squid giant axons (Frankenhaeuser and Hodgkin, 1956). But in this system no evidence for a non-exponential time course could be detected. Later in experiments with lipid bilayer membranes strong diffusion polarization effects have been observed in the transport of hydrophobic ions (Le Blanc, 1969). Figure 4 illustrates that the ratio between the current $I(t)$ at time $t$ and the steady-state current $I_s$ is indeed proportional to $1/\sqrt{t}$ up to several seconds. Hence diffusion polarization could in principle produce $1/f$ noise at frequencies below 1 Hz. Similar $1/\sqrt{t}$ kinetics at lipid bilayers have been described for the ion transport mediated by alkali ion carriers (Ciani et al., 1975, Fig. 7) and by uncouplers of oxidative phosphorylation (Smejtek et al., 1976, page 331).

Diffusion polarization effects at homogeneous lipid bilayers are due to one-dimensional diffusion in the unstirred solution layers. For heterogeneous porous membranes this symmetry is no longer observed because ions will flow at different angles towards a pore mouth. The situation may be idealized by spherical diffusion in three dimensions (Hille, 1968, Appendix) if the conductance of the pore is much higher than that of the membrane phase and if the pores are sparsely distributed over

the membrane surface. The kinetics of diffusion polarization then become again proportional to $1/\sqrt{t}$. Hence random switches between different pore conductance levels will produce a $1/f$ spectrum for current fluctuations under voltage clamp conditions. Recently we have calculated the spectral density of $1/f$ noise for this situation assuming simple open-close transitions of the pore and treating the ion passage through an open pore as a single ion jump (Neumcke, 1975). With this model $1/f$ noise at nerve membranes could be explained only by very rapid open-close transitions whose frequencies had to exceed even the rate of ion transport through an open pore. Another shortcoming of the model was pointed out by Weissman (personal communication): In a simple two-state system the current responses after a pore opening and after a subsequent closing are not independent of each other since a permeable pore can only switch to nonpermeable, and vice versa. The correlations between different conductance states lead to a flat power spectrum in the low frequency limit. Since the two-state model is entirely characterized by the life time $\tau$ of the open pore, the deviation from the $1/f$ behaviour must occur around the frequency $1/\tau$. Hence $1/f$ noise below 1 Hz can no longer be obtained in the stationary state with time constants $\tau < 1$ s. This argument also suggests two possible generalizations of the theory to introduce more and longer time constants into the model. From the analysis of channel noise at nerve membranes some evidence for multiple conductance states was obtained for potassium channels in squid giant axons (Fishman, 1973; Conti et al., 1975) and for sodium channels in myelinated nerve (Conti et al., 1976a). A corresponding multi-state pore model would be characterized not only by the life times of the individual states but also by longer time constants describing the reoccurrance of a given state. In a second generalization one may replace a single ion jump through an open pore by a migration over a series of $n$ energy barriers. Again the kinetics would no longer be determined by one relaxation time but by a discrete spectrum of $n$ time constants (Frehland and Läuger, 1974).

A critical test of all diffusion theories of $1/f$ noise in membranes would be measurements of its temperature dependence. Since the $Q_{10}$ values of aqueous conductivity of $Na^+$ and $K^+$ ions are about 1.3 between 0 and 25° C (Robinson and Stokes, 1955, Appendix 6.2), the spectral density of $1/f$ noise should vary accordingly. In two investigations with nerve membranes no significant temperature dependence of $1/f$ noise was found within a temperature interval of 10° C (Siebenga and Verveen, 1971; Conti et al., 1975). But measurements over a larger temperature interval would be required to clarify a possible temperature dependence of $1/f$ noise in membranes.

## C) Non-Poisson Pulse Sequences

In the theories described so far $1/f$ noise was explained by a random superposition of independent events. A characteristic feature of such Poisson pulse sequences is an exponential distribution of time periods between two subsequent pulses. We now turn to a discussion of $1/f$ theories based on non-Poisson sequences with various correlations between the parameters of an individual pulse or between different pulses. If a coupling exists between pulse parameters, different events still may be uncorrelated and the whole pulse sequence then belongs to the class of Markov processes. Heiden (1969) has analysed the power spectrum of such stochastic events

assuming that an individual pulse may be characterized by three parameters: amplitude $h$, duration $\tau$, and time period $\vartheta$ following a pulse. A 1/*f* frequency dependence was found for the couplings $\tau \cdot h$ = const (constant pulse area) and $\vartheta \sim \tau \cdot h$ (time interval between pulses proportional to the area of previous pulse). If the ion transport through membranes would occur in such pulses, the observed 1/*f* noise could be easily explained (Schick, 1974). But it is not clear which mechanisms should produce the specific couplings between pulse parameters.

In another 1/*f* theory with non-Poisson sequences interactions between a membrane channel and its lipid environment were postulated. The theory was developed for liquid crystals of the smectic $A$ type (Lundström et al., 1973) and subsequently applied to nerve membranes (Lundström and McQueen, 1974). The authors assume that the conductivity of a membrane channel would be determined by the orientation of the hydrocarbon chains of the neighbouring lipid molecules and that the propagation of fluctuations in the chain orientation may be described by a two-dimensional diffusion equation. Since spatially uncorrelated two-dimensional diffusion processes do not produce 1/*f* noise (see above), correlations have to be introduced to obtain a 1/*f* spectrum of the fluctuations in the current through the channel. In their end result the spectral density of 1/*f* noise is proportional to the square of the membrane current. Motivated by the empirical relation (5) for 1/*f* noise at lobster axons, Clay and Shlesinger (1976, 1977) have tried to extend the model of Lundström and McQueen to explain 1/*f* noise also under zero-current conditions. But a positive parameter $A$ in Equation (5) does not necessarily imply the occurance of 1/*f* noise in equilibrium. Instead the residual 1/*f* noise found at the potassium equilibrium potential is most probably due to the flow of other ions than $K^+$.

In the theories of Lundström and McQueen, Clay and Shlesinger 1/*f* noise is produced already in one ionic channel vibrating in the membrane phase. Hence the sentence in Clay and Shlesinger's (1976) paper: "The current flowing through a single channel does not produce 1/*f* noise in this model" is misleading since it suggests interactions between different channels. Weissman (1976) clarified this apparent contradiction and also critically analysed the treatment of correlations in lipid-channel interactions. As Weissman points out the final spectrum is determined by the product of two types of weighting functions: (i) A function giving the spectral distribution of lipid orientation fluctuations (which may often be ignored in other types of fluctuation problems) and (ii) a vector function of position which gives the coupling between the orientation fluctuations over the observed region and the conductance fluctuation (which has not been considered by Lundström and McQueen, Clay and Shlesinger). Although Weissman's note contains an outline of a revised model, a complete theory of 1/*f* noise from channels vibrating in the membrane phase would require many unmotivated postulates.

While in the previous 1/*f* theories a single membrane channel in its lipid environment was considered, Holden (1976) and Holden and Rubio (1976) explicitly studied interactions between different channels. The authors assumed that the opening of any channel produces a structural change in the surrounding membrane which propagates radially and modifies the opening of neighbouring channels. For the simple case of three interacting channels the power spectrum of the current was found to have a frequency dependence $1/f^n$ where $n$ could have any value between 0 and 1. This result is promising, but it remains to be shown that the exponent $n$ is close to 1

over several frequency decades, that this frequency dependence also holds for the more realistic case of interacting pores arranged in a two-dimensional lattice, and that the spectral density of $1/f$ noise calculated from the model is in agreement with experimental data.

To summarize, no satisfactory theory describing the phenomenon of $1/f$ noise in membranes has been presented so far. To reduce the number of acceptable models more fluctuation measurements at single membrane pores are needed. It would be of eminent importance whether Green's (1976) $f^{-3/2}$ spectra for µm thick and long pores would also be observed with smaller pores. In this case $1/f$ noise in biological membranes might then be explained only as superposition of noise from pores of variable size or by interactions of ionic channels with the membrane matrix or with neighbouring channels.

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