*Biochimica et Biophysica Acta*, 557 (1979) 283—294


BBA 78538

# DIELECTRIC NOISE IN MEMBRANES

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(Received February 12th, 1979)

*Key words: Membrane noise; Electric fluctuation; Gating noise; (Bilayer membrane)*

## Summary

Most theoretical and experimental studies of electrical fluctuations in membranes so far have been devoted to noise associated with conduction processes. In this paper a different type of noise is described which results from dipolar transitions in the membrane. Two mechanisms for the generation of such dielectric noise are analyzed: (a) conformational transitions of membrane proteins involving changes in dipolar moment and/or polarizibility, and (b) rotation of dipolar molecules dissolved in the lipid. The spectral intensity of current noise calculated for the two models exhibits a characteristic dependence on frequency $\omega$ with a decrease proportional to $\omega^2$ towards low frequencies and an approach to a frequency-independent (white noise) limit at high frequencies. For a given number of dipolar molecules in the membrane, the spectral intensity is inversely proportional to the square of the membrane thicknesss.

## Introduction

Valuable information on elementary processes in membranes may be obtained from the analysis of electrical fluctuations [1—5]. Current and voltage noise have been studied with biological membranes and with artificial lipid bilayer membranes, and theoretical investigations have been carried out relating the observed noise to the microscopic parameters of the membrane. Most of these studies have dealt with noise resulting from conduction processes in the membrane, such as opening-closing noise [6,7] and transport noise [8,9] in ion channels, as well as noise from carrier-mediated ion transport [10].

Processes in which free charges move within the membrane are not the only source of electrical fluctuations, however. In the following we deal with a different type of noise which results from dipolar transitions in the membrane. If a membrane constituent, such as a protein, is able to assume a number of

conformational states differing in the dipolar moment and/or the polarizibility, then transitions between the states will cause electrical fluctuations in an external measuring circuit. Such transitions involving a change of dipolar moment may be the basis of the gating process in nerve [11]. A similar situation arises when the membrane contains polar molecules which are able to rotate. In this case noise in the external circuit will be generated by random rotational motions of the dipolar molecules. The noise resulting from dipolar transitions or from rotation of permanent dipoles may be termed 'dielectric noise', as these processes are closely related to the macroscopic dielectric properties of the membrane.

**Transitions between discrete conformational states**

We assume that the membrane contains a protein species P which may be present in different conformational states $P_1, P_2, ..., P_n$. We denote the component of the dipolar moment of state $P_i$ in a direction perpendicular to the membrane surface by $\mu_i$ and the component of the polarizibility in the same direction by $\alpha_i$. The value of $\mu_i$ is taken at an applied voltage of zero and contains any contribution arising from the polarization of state $P_i$ under the influence of an intrinsic field in the membrane. (If the membrane is asymmetric, a non-zero electrical field may be present even without an externally applied voltage). If $E$ is the field strength due to the external voltage, the change $m_{ij}$ of the total (permanent and induced) dipolar moment during the transition $P_i \rightarrow P_j$ is given by

$$m_{ij} = \mu_j - \mu_i + (\alpha_j - \alpha_i)E \tag{1}$$

Implicit in Eqn. 1 is the assumption that $E$ is independent of position and directed perpendicular to the membrane surface and that dielectric saturation effects are absent. In the following we discuss the behaviour of the system under the condition that the applied voltage $V$ is composed of a stationary voltage $V_0$ and a superimposed small a.c. voltage $V_s$:

$$V(t) = V_o + V_s(t) = V_o + V_{so} \cos \omega t \tag{2}$$

$$|V_{s0}| << |V_0|$$

where $\omega$ is the angular frequency. The corresponding values of the electric field are then given by $E = V/d$, $E_o = V_o/d$ and $E_s = V_s/d$ ($d$ is the membrane thickness).

Denoting the average number of protein molecules in state $P_i$ by $N_i$ and the rate constant for the transition $P_i \rightarrow P_j$ by $k_{ij}$, the rate of change of $N_i$ is given by

$$\frac{dN_i}{dt} = -\sum_{j=1}^{n} k_{ij}N_i + \sum_{j=1}^{n} k_{ji}N_j \tag{3}$$

($k_{ii} \equiv 0$). Here we have assumed (for generality) that transitions from any state $P_i$ to any other state $P_j$ are possible. The net rate $\Phi_{ij}$ of transitions between $P_i$ and $P_j$ is given by

$$\Phi_{ij} = k_{ij}N_i - k_{ji}N_j \tag{4}$$

According to the principle of microscopic reversibility, the transition rate $\Phi_{ij}$ vanishes in the equilibrium state of the system:

$$(\Phi_{ij})_{eq} = \bar{k}_{ij}\bar{N}_i - \bar{k}_{ji}\bar{N}_j = 0 \tag{5}$$

$N_i$ and $N_j$ are the equilibrium values of $N_i$ and $N_j$, and $k_{ij}$ and $k_{ji}$ are the rate constants at the voltage $V_0$. Introducing the equilibrium constant

$$\bar{K}_{ij} = \frac{\bar{k}_{ij}}{\bar{k}_{ji}} = \frac{\bar{N}_j}{\bar{N}_i} \tag{6}$$

it is easy to show (using Eqn. 6) that the equilibrium concentrations may be represented by

$$\bar{N}_i = \frac{N}{\sum_{j=1}^{n} \bar{K}_{ij}} \tag{7}$$

($\bar{K}_{ii} \equiv 1$). $N = N_1 + N_2 + \ldots + N_n$ is the total number of protein molecules.

Both the equilibrium constants $K_{ij}$ as well as the rate constant $k_{ij}$ depend on the field strength $E$. As the electrostatic contribution to the change of free energy in the transition $P_i \rightarrow P_j$ is given by $-[(\mu_j - \mu_i)E + (\alpha_j - \alpha_i)E^2/2] \equiv w_{ij}$, the relation

$$K_{ij} = \tilde{K}_{ij} \exp\left[\frac{(\mu_j - \mu_i)\,E + (\alpha_j - \alpha_i)\,E^2/2}{kT}\right] \equiv \tilde{K}_{ij} \exp\left(-\frac{w_{ij}}{kT}\right) \tag{8}$$

holds, where $k$ is Boltzmann's constant, $T$ the absolute temperature and $\tilde{K}_{ij}$ the value of $K_{ij}$ at zero applied voltage. In order to describe the dependence of $k_{ij}$ and $k_{ji}$ on $E$, we may assume that the transition rate is limited by an activation energy barrier which, in the presence of a field $E$, is changed by $a_{ij}w_{ij}$ for the transition $P_i \rightarrow P_j$ and by $-(1 - a_{ij})w_{ij}$ for the reverse transition ($a_{ij}$ is a dimensionless factor smaller than unity, $0 < a_{ij} < 1$). Thus,

$$k_{ij} = \tilde{k}_{ij} \exp\left[-a_{ij}\frac{w_{ij}}{kT}\right] \tag{9}$$

$$k_{ji} = \tilde{k}_{ji} \exp\left[(1 - a_{ij})\frac{w_{ij}}{kT}\right] \tag{10}$$

$\tilde{k}_{ij}$ and $\tilde{k}_{ji}$ are the values of $k_{ij}$ and $k_{ji}$ for $E = 0$.

The spectral intensities $S_I(\omega)$ and $S_V(\omega)$ of current ($I$) and voltage ($V$) fluctuations generated by dipolar transitions may be calculated using the Nyquist theorem [12—15] which relates $S_I(\omega)$ and $S_V(\omega)$ to the frequency-dependent admittance $Y(\omega)$ of the system:

$$S_I(\omega) = 4kT \cdot \mathrm{Re}[Y(\omega)] \tag{11}$$

$$S_V(\omega) = 4kT \cdot \mathrm{Re}\left[\frac{1}{Y(\omega)}\right] \tag{12}$$

Re means 'real part of'. Nyquist's theorem is valid for equilibrium states; it may even be applied to nonequilibrium situations here if it is assumed that the

dipolar molecules represent an equilibrium subsystem which is not affected by simultaneously present dissipative processes (such as ion-flow through the membrane).

In the presence of a voltage $V(t) = V_o + V_{so} \cos \omega t$ the current $I(t)$ in the external circuit resulting from the dielectric polarization of the membrane may be represented by

$$I(t) = I_o \cos(\omega t - \phi) \tag{13}$$

$$I_o = V_{so} \sqrt{\mathrm{Re}^2 [Y(\omega)] + \mathrm{Im}^2 [Y(\omega)]} \tag{14}$$

$$tg\phi = -\frac{\mathrm{Im}[Y(\omega)]}{\mathrm{Re}[Y(\omega)]} \tag{15}$$

where Im means 'imaginary part of'. $I(t)$ is given by the time derivative of the dielectric displacement $D$:

$$I(t) = A \frac{dD}{dt} = A \frac{d}{dt} (\epsilon_0 E + P) \tag{16}$$

$A$ is the membrane area, $P$ the polarization and $\epsilon_0 = 8.85 \cdot 10^{-12}\ \mathrm{C} \cdot \mathrm{V}^{-1} \cdot \mathrm{m}^{-1}$ the permittivity of free space. The calculation of $P$ may be based on a simple model in which the membrane is described as a mosaic consisting of lipid regions and embedded proteins. The proteins may be represented as cylinders oriented normal to the surface and bridging the hydrophobic thickness of the membrane. If the polarizations of the lipid and protein phases are denoted by $P_l$ and $P_p$, respectively, and if $\beta$ is the fraction of membrane area occupied by lipid, then the average polarization $P$ may be written as

$$P = \beta P_l + (1 - \beta) P_p \tag{17}$$

The lipid may be treated as a nonpolar medium of dielectric constant $\epsilon_l$. Thus,

$$P_l = \epsilon_0 (\epsilon_l - 1) E \tag{18}$$

The polarization $P_p$ of the protein phase is obtained as the ratio of the electric moment $M_p$ divided by the volume $(1 - \beta) Ad$ of the protein phase [16]:

$$P_p = \frac{M_p}{(1 - \beta) Ad} = \frac{1}{(1 - \beta) Ad} \sum_{i=1}^{n} N_i (\mu_i + \alpha_i E) \tag{19}$$

($d$ is the membrane thickness). As shown in Appendix A, the following expressions are obtained from Eqns. 1—10 and 16—19 for the real and imaginary part of the admittance $Y(\omega)$:

$$\mathrm{Re}(Y) = \frac{1}{\boldsymbol{k}Td^2} \sum_{l=1}^{n-1} \frac{\omega^2 \tau_l^2 \theta_l}{1 + \omega^2 \tau_l^2} \tag{20}$$

$$\mathrm{Im}(Y) = \frac{1}{\boldsymbol{k}Td^2} \sum_{l=1}^{n-1} \frac{\omega \tau_l \theta_l}{1 + \omega^2 \tau_l^2} + \omega C_m^* \tag{21}$$

$$\theta_l \equiv \tau_l \sum_{i,k=1}^{n-1} \sum_{j,r=1}^{n} q_{il} p_{lk} \bar{k}_{rk} \bar{N}_r (m_{nj} \bar{k}_{nj} - m_{ij} \bar{k}_{ij}) \bar{m}_{rk} \tag{22}$$

$$C_m^* \equiv \frac{\epsilon_0 A}{d}\left[1 + \beta(\epsilon_l - 1) + \frac{1}{\epsilon_0 A d}\sum_{i=1}^{n} \bar{N}_i \alpha_i\right] \tag{23}$$

$\bar{m}_{ij}$ is the value of $m_{ij}$ (Eqn. 1) for $E = E_0$, and $\bar{k}_{ii} \equiv 0$. The quantities $\tau_l$ are the $(n-1)$ time constants describing the relaxation behaviour of the system of the $n$ conformational states $P_1, P_2, ..., P_n$ after a macroscopic perturbation (Eqn. A15). The coefficients $q_{il}$ and $p_{lk}$ are functions of the rate constants as defined by Eqns. A13 and A16. According to Eqn. A5, the quantity $C_m^*$ is the membrane capacitance in the limit of vanishing transition rates ($k_{ij} \equiv 0$).

The spectral intensity $S_I(\omega)$ of current noise is obtained from Eqns. 11 and 20 as

$$S_I(\omega) = \frac{4}{d^2}\sum_{l=1}^{n-1} \theta_l \frac{\omega^2 \tau_l^2}{1 + \omega^2 \tau_l^2} \tag{24}$$

It is seen that $S_I(\omega)$ declines with $\omega^2$ toward low frequencies. This behaviour results from the fact that the membrane is considered as a dielectric with vanishing stationary conductance [$Y(0) = 0$]. (In a real membrane other noise components from conduction processes will predominate in the limit $\omega \to 0$). On the other hand, the spectral intensity approaches a finite value at high frequencies. According to Eqns. A25 and A26:

$$S_I(\infty) = \frac{4}{d^2}\sum_{l=1}^{n-1} \theta_l = \frac{2}{d^2}\sum_{i,j=1}^{n} \bar{k}_{ij} \bar{N}_i \bar{m}_{ij}^2 \tag{25}$$

Between $\omega = 0$ and $\omega \to \infty$, the spectral intensity has $(n-1)$ dispersion regions centered at frequencies $\omega_l = 1/\tau_l$.

In the following, we illustrate the general result by considering a special case.

*The case n = 2*

We assume that the protein P has only two conformational states:

$$P_1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} P_2$$

with permanent dipolar moments $\mu_1$, $\mu_2$ and polarizabilities $\alpha_1$, $\alpha_2$. In this case the relations

$$\tau_1 \equiv \tau = \frac{1}{\bar{k}_{12} + \bar{k}_{21}} \tag{26}$$

and $N_1 = N\bar{k}_{21}\tau$, $N_2 = N\bar{k}_{12}\tau$ hold, and Eqns. A13 and A16 may be satisfied with $p_{11} = q_{11} = 1$. This gives (with $\mu_2 - \mu_1 \equiv \Delta\mu$ and $\alpha_2 - \alpha_1 \equiv \Delta\alpha$):

$$S_I(\omega) = \frac{4N}{d^2} \cdot \frac{(\Delta\mu + E_0\Delta\alpha)^2}{(1/\bar{k}_{12}) + (1/\bar{k}_{21})} \cdot \frac{\omega^2\tau^2}{1 + \omega^2\tau^2} \tag{27}$$

The spectral intensity has components resulting from changes of the permanent dipolar moment and of the polarizibility. These two components differ in their dependence on the applied voltage $V_0 = E_0 d$. If only the

polarizibility changes in the conformational transition ($\Delta\mu = 0$), the relation

$$S_I(\omega) \propto V_0^2 \tag{28}$$

is predicted from Eqn. 27 (at low field-strength $E_0$, the rate constants $\bar{k}_{12}$ and $\bar{k}_{21}$ may be replaced by their voltage-independent values $\tilde{k}_{12}$ and $\tilde{k}_{21}$). On the other hand, if the two states $P_1$ and $P_2$ have different permanent moments ($\Delta\mu \neq 0$), the spectral intensity approaches a finite value in the limit $V_0 \to 0$.

Field-dependent transitions between two conformational states $P_1$ and $P_2$ of a membrane protein have been proposed as a mechanism for the gating process of the sodium channel in nerves [11]. In order to estimate the spectral intensity of current noise generated by the gating systems, we assume $\Delta\alpha = 0$ and $\Delta\mu \sim 400$ debye $\approx 1.3 \cdot 10^{-27}$ C · m$^{-1}$ (this value of $\Delta\mu$ is required in order to account for the voltage-dependence of the sodium conductance in the squid giant axon [11]). With $N = 500\ \mu\text{m}^{-2} = 5 \cdot 10^{10}$ cm$^{-2}$ [18], $\bar{k}_{12} \approx \bar{k}_{21} \approx 2 \cdot 10^3$ s$^{-1}$ [18], and $d \sim 5$ nm, one obtains

$$S_I(\infty) \approx 1.4 \cdot 10^{-23}\ A^2\ \text{s} \cdot \text{cm}^{-2}$$

This value may be compared with the spectral intensity $S_I^*$ of current noise resulting from the resting conductance $g_r$ of the axon membrane. With $g_r \sim 1$ mS · cm$^{-2}$ [19] one finds

$$S_I^* = 4\,kTg_r \approx 1.5 \cdot 10^{-23}\ A^2\ \text{s} \cdot \text{cm}^{-2}$$

This comparison shows that, although the separation from other noise sources seems difficult in general, gating noise may be measurable under favourable conditions.

**Rotation of dipolar molecules**

As a further possibility for the occurrence of dielectric noise we consider here the case that the membrane contains dipolar molecules which are able to rotate. In order to describe the rotation of molecules within a lipid matrix, one generally has to take into account the shape of the rotating molecule and the anisotropic nature of the lipid medium [20]. For an estimate of the order of magnitude of the spectral intensity and in order to simplify the discussion we consider in the following the special case of spherical molecules which rotate isotropically. Furthermore, we assume that all orientations of the rotating molecules in the membrane are equally probable (in the absence of an external electric field), thus neglecting, for instance, the influence of image forces near the membrane-solution interface. The rotation of molecules in a viscous medium is described by a frictional coefficient $f_r$ which relates the torque $M_r$ acting on the molecule to the resulting angular frequency of rotation $\omega_r$, in the stationary state:

$$\omega_r = \frac{M_r}{f_r} \tag{29}$$

$f_r$ in turn is related to the relaxation time $\tau$ of the orientational distribution

function [21]:

$$\tau = \frac{f_r}{2kT} \tag{30}$$

The dielectric behaviour of a dilute solution of dipolar molecules in a nonpolar medium has been treated by Debye [21]. Using the Debye equations (Appendix B), the real and imaginary part of the admittance $Y(\omega)$ are obtained as

$$\mathrm{Re}(Y) = \frac{\mu^2 N}{3kTd^2\tau} \cdot \frac{\omega^2\tau^2}{1+\omega^2\tau^2} \tag{31}$$

$$\mathrm{Im}(Y) = \frac{\mu^2 N}{3kTd^2\tau} \cdot \frac{\omega\tau}{1+\omega^2\tau^2} + \omega C_m^{\infty} \tag{32}$$

$\mu$ is the permanent dipolar moment, $N$ the number of dipolar molecules in the membrane, and $C_m^{\infty}$ the membrane capacitance in the limit of high frequencies ($\omega\tau >> 1$).

The spectral intensity of current noise, as obtained from Eqns. 11 and 31:

$$S_I(\omega) = \frac{4\mu^2 N}{3d^2\tau} \cdot \frac{\omega^2\tau^2}{1+\omega^2\tau^2} \tag{33}$$

shows the same frequency dependence as the two-state system considered above (Eqn. 27), i.e. an increase with $\omega^2$ at low frequencies and an approach to a frequency-independent value in the limit $\omega \to \infty$. If the rotation of the dipole is described, to a first approximation, in the same way as the rotation of a macroscopic sphere in a medium of viscosity $\eta$, the relaxation time $\tau$ becomes [21]:

$$\tau \simeq \frac{4\pi\eta a^3}{kT} \tag{34}$$

where $a$ is the radius of the sphere. Taking $\eta \approx 3$ P $= 0.3$ J $\cdot$ m$^{-3}$ $\cdot$ s$^{-1}$ as representative for the microviscosity of a lipid bilayer [22], the relaxation time of a molecule of radius $a = 0.5$ nm becomes of the order of $\tau \sim 0.1$ $\mu$s (at $T =$ 300 K). This means that up to frequencies of 100 kHz the relations $\omega^2\tau^2 << 1$ and

$$S_I(\omega) \approx \frac{4\mu^2 N\tau}{3d^2}\omega^2 \tag{35}$$

hold. For small polar molecules (such as nitrobenzene) the dipolar moments may be of the order of 5 debye $\approx 2 \cdot 10^{-29}$ C $\cdot$ m. If we assume that $N = 10^{12}$ dipolar molecules are dissolved in 1 cm$^2$ of a lipid-bilayer membrane of thickness $d = 5$ nm (corresponding to about one dipole per 300 lipid molecules), the spectral intensity at a frequency of $f = \omega/2\pi = 1$ kHz becomes

$$S_I(1\text{ kHz}) \approx 1 \cdot 10^{-28} A^2\,\mathrm{s} \cdot \mathrm{cm}^{-2} \tag{36}$$

This value is too small to be detectable with the present sensitivity of current-

noise measurements. This means that the observations of dielectric noise from freely rotating small dipolar molecules in a bilayer will be extremely difficult. The possibility remains, however, to observe the restricted rotation of polar molecules bound to the membrane-solution interface. In this case the rotation may be slowed down by activation energy barriers so that the relaxation time $\tau$ in Eqn. 35 becomes larger.

## Conclusion

In the preceeding sections two mechanisms have been analyzed by which dielectric noise may be generated in lipid bilayers, namely: (a) conformational transitions of proteins involving changes in dipolar moment and/or polarizibility, and (b) rotation of dipolar molecules dissolved in the lipid. A further potential source of dielectric noise not considered here consists of fluctuations in the conformation of the polar head-groups of lipid molecules [23]. The spectral intensity of current noise calculated for the two processes exhibits a characteristic frequency dependence with a decrease proportional to $\omega^2$ towards low frequencies and an approach to a frequency-independent (white noise) limit at high values of $\omega$. The spectral characteristic of dielectric noise is thus completely different from the familiar Lorentzian behaviour of noise resulting from open-close processes of ion channels [2,3], but similar to the noise observed with hydrophobic ions in lipid bilayer membranes [24]. So far, dielectric noise in membranes has not been studied experimentally. Interesting potential applications concern the gating system in nerve [11,18], as well as transition between conducting and non-conducting states of synthetic ion channels involving changes of dipolar moments [26,26]. At a given number $N$ of dipolar molecules in the membrane, the spectral intensity is inversely proportional to the square of the membrane thickness $d$ (Eqns. 24, 27 and 33), and therefore very thin membranes may be used for such experiments. Numerical estimates of the spectral intensity given in the previous sections show that dielectric noise will be rather difficult to observe. Artificial lipid bilayer membranes with a low level of background noise from conduction processes seem to be the most favourable system for the study of dielectric noise.

## Appendix A

*Derivation of Eqns. 20—23*

In the presence of a small a.c. field $E_s(t)$, the total field strength is given by

$$E(t) = E_o + E_s(t) = E_o + E_{so} \cos \omega t \tag{A1}$$

For $|E_s| << |E_o|$ the values of $N_i$ remains close to the equilibrium value $\bar{N}_i$, so that we may write

$$N_i(t) = \bar{N}_i + x_i(t);\ |x_i| << \bar{N}_i \tag{A2}$$

Neglecting the term proportional to $x_i E_s$ (which is small to the second order), Eqn. 19 is obtained in the form (with $\mu_i + \alpha_i E_o \equiv \bar{m}_i$):

$$(1 - \beta)\, P_p = \frac{1}{Ad} \sum_{i=1}^{n} (N_i \bar{m}_i + \bar{N}_i \alpha_i E_s) \tag{A3}$$

Using the identity

$$\sum_{i,j=1}^{n} \bar{m}_i k_{ji} N_j = \sum_{i,j=1}^{n} \bar{m}_j k_{ij} N_i \tag{A4}$$

as well as Eqns. 3, 16—18 and A4, the current $I(t)$ is obtained as

$$I(t) = \frac{1}{d} \sum_{i,j=1}^{n} \bar{m}_{ij} k_{ij} N_i + C_m^* \frac{dV}{dt} \quad (k_{ii} \equiv 0) \tag{A5}$$

$$C_m^* \equiv \frac{\epsilon_0 A}{d} \left[1 + \beta(\epsilon_l - 1) + \frac{1}{\epsilon_0 A d} \sum_{i=1}^{n} \bar{N}_i \alpha_i\right] \tag{A6}$$

where $\bar{m}_{ij} = \bar{m}_j - \bar{m}_i$ is the value of $m_{ij}$ (Eqn. 1) for $E = E_o$, and $k_{ii} \equiv 0$. According to Eqns. 1, 9 and A1 the dependence of the rate constants $k_{ij}$ on the a.c. field $E_s(t)$ may be expressed by (for small $|E_s|$):

$$k_{ij} \approx \bar{k}_{ij} \left(1 + \frac{a_{ij} \bar{m}_{ij}}{kT} E_s\right) \tag{A7}$$

With the relations $\bar{k}_{ij} \bar{N}_i = \bar{k}_{ji} \bar{N}_j$ (Eqn. 5), $\bar{m}_{ij} = -\bar{m}_{ji}$ and $\bar{m}_{ii} \equiv 0$, it is easily seen that the identity

$$\sum_{i,j=1}^{n} \bar{m}_{ij} \bar{k}_{ij} \bar{N}_i = 0 \tag{A8}$$

holds. Using Eqns. 2, A1, A2, A5, A7, A8 as well as the relation $a_{ji} = 1 - a_{ij}$ (Eqns. 9 and 10), the current $I(t)$ is obtained in the form

$$I(t) = \frac{V_{so} \cos \omega t}{2kTd^2} \sum_{i,j=1}^{n} \bar{k}_{ij} \bar{N}_i \bar{m}_{ij}^2 + \frac{1}{d} \sum_{i,j=1}^{n} \bar{m}_{ij} \bar{k}_{ij} x_i - C_m^* V_{so} \omega \sin \omega t \tag{A9}$$

A set of differential equations for the quantities $x_i$ is obtained from Eqns. 3 and A2. As the sum of all $N_i$ is constant, the relation $x_1 + x_2 + \ldots + x_n = 0$ holds. This means that only $n - 1$ variables $x_i$ are independent. By elimination of $x_n$ on finds

$$\frac{dx_i}{dt} = g_i \cos \omega t + \sum_{j=1}^{n-1} b_{ij} x_j \qquad (i = 1, 2, \ldots, n-1) \tag{A10}$$

$$g_i = -\frac{V_{so}}{kTd} \sum_{j=1}^{n} \bar{k}_{ij} \bar{N}_i \bar{m}_{ij} \tag{A11}$$

$$b_{ij} = \begin{cases} \bar{k}_{ji} - \bar{k}_{ni} & (i \neq j) \\ -\bar{k}_{ni} - \sum_{l=1}^{n} \bar{k}_{il} & (i = j) \end{cases} \tag{A12}$$

Using the transformation

$$y_i = \sum_{k=1}^{n-1} p_{ik} x_k \; ; \qquad x_j = \sum_{k=1}^{n-1} q_{jk} y_k \tag{A13}$$

Eqn. A10 may be obtained in the form [17]:

$$\frac{dy_i}{dt} = -\frac{y_i}{\tau_i} + \sum_{k=1}^{n-1} p_{ik} g_k \cos \omega t \tag{A14}$$

The relaxation times $\tau_i$ are given by the roots of the equation

$$\mathrm{Det}(b_{ij} + \delta_{ij}/\tau) = 0 \tag{A15}$$

where $\delta_{ij}$ is Kronecker's delta. In order to transform Eqn. A10 into Eqn. A14, the coefficients $q_{jk}$ have to be chosen in such a way that

$$\sum_{j=1}^{n-1} (b_{ij} + \delta_{ij}/\tau_k)\, q_{jk} = 0 \tag{A16}$$

By virtue of Eqn. A15 this equation has a non-trivial solution. We now replace the functions $y_i$ by complex functions $\eta_i$ with $\mathrm{Re}(\eta_i) = y_i$:

$$\frac{d\eta_i}{dt} = -\frac{\eta_i}{\tau_i} + \sum_{k=1}^{n-1} p_{ik} g_k \exp(j\omega t) \tag{A17}$$

where $j$ is the imaginary unit. It is easily verified that the solution of Eqn. A17 is given by

$$\eta_i = A_i \exp(j\omega t) \tag{A18}$$

$$A_i = \tau_i \frac{1 - j\omega\tau_i}{1 + \omega^2\tau_i^2} \sum_{k=1}^{n-1} p_{ik} g_k \tag{A19}$$

Instead of the real current $I$ (Eqn. A9) we introduce a complex current $J$ with $\mathrm{Re}(J) = I$:

$$J(t) = Y(\omega)\, V_{so} \exp(j\omega t) \tag{A20}$$

$$J(t) = \frac{V_{so} \exp(j\omega t)}{2kTd^2} \sum_{i,j=1}^{n} \bar{k}_{ij} \bar{N}_i \bar{m}_{ij}^2$$

$$+ \frac{1}{d} \sum_{i=1}^{n-1} \sum_{j=1}^{n} (\bar{m}_{ij}\, \bar{k}_{ij} - \bar{m}_{nj} \bar{k}_{nj})\, \xi_i + j\omega C_m^*\, V_{so} \exp(j\omega t) \tag{A21}$$

The complex quantities $\xi_i(\mathrm{Re}(\xi_i) = x_i)$ are obtained from the functions $\eta_i$ by the transformation A13:

$$\xi_i = \sum_{l=1}^{n-1} q_{il} \eta_l = \sum_{l=1}^{n-1} q_{il} A_l \exp(j\omega t) \tag{A22}$$

Introduction of the $\xi_i$ from Eqn. A22 into Eqn. A21 and comparison of the real and imaginary parts of Eqns. A20 and A21 leads to the following relations:

$$\mathrm{Re}[Y(\omega)] = \frac{1}{kTd^2} \left( Q - \sum_{l=1}^{n-1} \frac{\theta_l}{1 + \omega^2\tau_l^2} \right) \tag{A23}$$

$$\mathrm{Im}[Y(\omega)] = \frac{1}{kTd^2} \sum_{l=1}^{n-1} \frac{\omega\tau_l\theta_l}{1+\omega^2\tau_l^2} + \omega C_m^* \tag{A24}$$

$$Q \equiv \tfrac{1}{2} \sum_{i,j=1}^{n} \bar{k}_{ij}\bar{N}_i\bar{m}_{ij}^2 \tag{A25}$$

$\theta_l$ is given in Eqn. 22. Under the assumptions of the model, the d.c. conductance of the membrane is zero: $\mathrm{Re}[Y(0)] = 0$. This means that

$$\sum_{l=1}^{n-1} \theta_l = Q \tag{A26}$$

$$\mathrm{Re}[Y(\omega)] = \frac{1}{kTd^2} \sum_{l=1}^{n-1} \frac{\omega^2\tau_l^2\theta_l}{1+\omega^2\tau_l^2} \tag{A27}$$

## Appendix B

*Derivation of Eqns. 31 and 32*

The frequency-dependent orientation of dipolar molecules in an alternating field $E^c = (V_0/d)\exp(j\omega t)$ is usually described by introducing a complex dielectric constant $\epsilon$ [16,21]:

$$\epsilon = \epsilon' - j\epsilon'' \tag{B1}$$

The (complex) displacement $D^c$ is then equal to

$$D^c = \epsilon_0\epsilon E^c \tag{B2}$$

According to Eqn. 16, the electric current $J$ in the external circuit is given by $J = A(dD^c/dt)$. Comparison with $J = Y(\omega)V_0\exp(j\omega t)$ shows that

$$\mathrm{Re}(Y) = \frac{A}{d}\omega\epsilon_0\epsilon'' \tag{B3}$$

$$\mathrm{Im}(Y) = \frac{A}{d}\omega\epsilon_0\epsilon'. \tag{B4}$$

For a dilute solution of spherical molecules with permanent dipolar moment $\mu$ in a nonpolar medium, $\epsilon'$ and $\epsilon''$ are given by the Debye equations [15,20]:

$$\epsilon' = \epsilon_\infty + \frac{\mu^2 n}{3kT\epsilon_0} \cdot \frac{1}{1+\omega^2\tau^2} \tag{B5}$$

$$\epsilon'' = \frac{\mu^2 n}{3kT\epsilon_0} \cdot \frac{\omega\tau}{1+\omega^2\tau^2} \tag{B6}$$

$\epsilon_\infty$ is the dielectric constant of the solution at high (optical) frequencies, $n$ the number of dipoles per unit volume and $\tau$ the relaxation time defined by Eqn. 30. Introducing the membrane capacitance $C_m^\infty = \epsilon_0\epsilon_\infty A/d$ at infinite frequency and the number $N = nAd$ of dipoles in the membrane and inserting Eqns. B5 and B6 into Eqns. B3 and B4 yields Eqns. 31 and 32.

## Acknowledgements

I wish to thank Drs. E. Frehland and H.-A. Kolb for interesting discussions. This work has been financially supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 138).

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