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TRANSPORT NOISE IN MEMBRANES

CURRENT AND VOLTAGE FLUCTUATIONS AT EQUILIBRIUM

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Summary

A formulism is described for the treatment of noise resulting from the transport of ions in channels containing an arbitrary number of activation energy barriers. The analysis is based on Nyquist's theorem and is therefore restricted to fluctuations around the equilibrium state. Within this limit the spectral intensities of current and voltage noise are given by the frequency-dependent admittance, which in turn is closely linked to the relaxation-time spectrum of the transport system. Explicit expressions for the spectral intensity of current noise are derived for channels with two and three energy barriers. The analysis may be used to predict the spectral intensity of noise from the gating system in nerve.

Introduction

In recent years it has been realized that valuable information on ion transport mechanisms in biological membranes may be obtained from electrical noise studies [1—5]. Random fluctuations of membrane current and membrane voltage may originate from a number of different sources. One type of noise which has been intensively studied in the past results from the statistical opening and closing of ion channels in the membrane [1—5]. The analysis of this 'channel noise' yields information on the conductance and the mean lifetime of the different states of the channel.

This paper deals with a second source of noise which is present even in a permanently open channel and which is associated with the discrete nature of the individual ion translocation steps in the channel. The movement of an ion within the channel may be described as a series of jumps over activation energy barriers [6]. Each jump contributes with a single current pulse to the total current measured in the external circuit. Fluctuations of the total current

therefore arise from fluctuations in the number of ions crossing the individual barriers. Such noise may be called 'shot noise' (sensu stricto) [1,7,8] or, using a more general term, 'transport noise' [9]. We use the latter term here because noise associated with the transport of ions is not restricted to discrete barrier structures and occurs also in systems where the potential energy of an ion is a more-or-less smooth function of position. In contrast to the above-mentioned noise from the opening and closing of channels which depends on the lifetimes and the overall conductance of the channel states, the investigation of transport noise yields information on the rates of single transport steps within the channel.

Experimental noise studies with ion channels have been analysed up to now mainly in terms of the opening-closing behaviour of the channel; it is therefore not clear whether transport noise as defined above has been recorded from channel systems so far. On the other hand, current noise associated with the transport of hydrophobic ions through lipid bilayer membranes has been observed recently [10], which is similar to the noise analyzed here.

In a recent paper [8] a theoretical treatment of transport noise in a channel consisting of two barriers and one binding site has been given. The analysis, which was based on the generalized Carson theorem, yielded an explicit expression for the spectral intensity of current noise at arbitrary (equilibrium or non-equilibrium) voltages. The Carson method, however, is difficult to apply to channels with more than two barriers. In this paper we describe an alternative procedure which may be applied to channels with an arbitrary number of barriers. This method, which is restricted to the equilibrium state, is based on the general (frequency-dependent) Nyquist relation. The Nyquist theorem relates the spectral intensity of current and voltage fluctuations to the small-signal admittance of the system. The derivation of the spectral intensity therefore reduces to the calculation of the admittance of the channel, which in turn is related to its relaxation-time spectrum.

Barrier model of the channel

We describe the channel as an alternating sequence of n 'ion binding sites' and $(n + 1)$ activation energy barriers (Fig. 1). The 'binding sites' are the minima in the potential energy curve which result from interactions of the ion with one or several ligand groups of the channel. We assume that the membrane contains N_c channels and that the channels are permeable to a single ion species which is present in the external phases in concentrations c' and c'' (Fig. 1). If N_o is the average number of ions (referred to total membrane area) located in the outermost energy minimum at the left-hand mouth of the channel, then N_o/N_c is the probability that, for a given channel, the outer minimum is occupied by an ion. This probability is assumed to be voltage-independent and proportional to the aqueous ion concentration (a similar statement applies to the right-hand mouth of the channel). Thus

$$N_o = N_c v c'; N_{n+1} = N_c v c'' \tag{1}$$

where v is a proportionality constant.

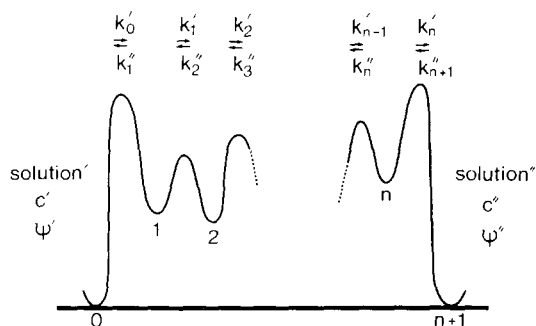The treatment which follows also applies to membranes without discrete

Fig. 1. Potential energy of an ion in the channel. k_i' and k_i'' are the rate constants for jumps from the ith energy minimum to the right and to the left. c', c'' are the concentrations of the permeable ion species and ψ', ψ'' the electrical potentials in the two aqueous solutions.

channels, where the ion permeability is distributed over the entire membrane area (this is the case, for instance, for the transport of hydrophobic ions). In this case we write (introducing another proportionality constant χ):

$$N_o = \chi c' ; N_{n+1} = \chi c'' . \tag{2}$$

We denote the number of ions present in the ith energy minimum (referred to total membrane area) by N_i, so that the probability that the ith minimum in a given channel is occupied is equal to N_i/N_c ($N_i \ll N_c$). The net ion flux Φ_i over the ith barrier is then given by

$$\Phi_i = k_{i-1}' N_{i-1} - k_i'' N_i \tag{3}$$

$$(i = 1, 2, ..., n + 1)$$

where k_{i-1} and k_i'' are the rate constants for jumps over the ith barrier from left to right and from right to left, respectively (compare Fig. 1). Implicit in Eqn. 3 is the assumption that the aqueous ion concentrations are sufficiently low so that a given channel is occupied by no more than one ion at a time. (In the above-mentioned case of a distributed permeability this corresponds to the assumption that ions move independently from each other through the membrane.) In the equilibrium state of the membrane the unidirectional fluxes over the ith barrier in either direction are equal:

$$\overline{k_{i-1}'}\,\overline{N_{i-1}} = \overline{k_i''}\,\overline{N_i} \equiv F_i \tag{4}$$

where $\overline{k_i'}$, $\overline{k_i''}$ and $\overline{N_i}$ are the equilibrium values of k_i', k_i'' and N_i, respectively, and F_i is the unidirectional flux over the ith barrier at equilibrium. Furthermore, as the concentrations N_o and N_{n+1} in the outer minima are held fixed, one may write $\overline{N_o} = N_o$ and $\overline{N_{n+1}} = N_{n+1}$.

Eqn. 4 is easily solved, starting either with $i = 1$ or $i = n + 1$, to give

$$\overline{N_i} = N_o \frac{\overline{k_o'}\,\overline{k_1'} ... \overline{k_{i-1}'}}{\overline{k_1''}\,\overline{k_2''} ... \overline{k_i''}} = N_{n+1} \frac{\overline{k_{i+1}''}\,\overline{k_{i+2}''} ... \overline{k_{n+1}''}}{\overline{k_i'}\,\overline{k_{i+1}'} ... \overline{k_n'}} \tag{5}$$

Eqn. 5 further yields, in accordance with the principle of microscopic rever-

sibility, the relationship

$$N_0 \overline{k}'_o \overline{k}'_1 \dots \overline{k}'_n = N_{n+1} \overline{k}''_1 \overline{k}''_2 \dots \overline{k}''_{n+1} \equiv P \,. \tag{6}$$

In order to describe the behaviour of the membrane in the presence of small perturbations, we assume that the total membrane voltage, $V_m = \psi' - \psi''$ (Fig. 1), is the sum of the equilibrium potential V_m^0 of the permeable ion species (valency z) plus an externally applied small voltage signal V_s:

$$V_m = V_m^0 + V_s \tag{7}$$

$$V_m^0 = \frac{kT}{ze_0} \ln \frac{c''}{c'} \tag{8}$$

$$|V_s| \ll \frac{kT}{e_0} \tag{9}$$

where k is Boltzmann's constant, T the absolute temperature and e_0 the elementary charge. In the following we denote the values of the rate constants at zero voltage ($V_m = 0$) by $\tilde{k}'_i$ and $\tilde{k}''_i$ and the corresponding values at the equilibrium voltage V_m^0 by $\overline{k}'_i$ and $\overline{k}''_i$. If α_i is the fraction of total voltage which drops across the ith barrier, then the voltage dependence of the rate constants is given by ($V_m e_0/kT \equiv u$, $V_s e_0/kT \equiv u_s$) [6]:

$$k'_i = \tilde{k}'_i \exp(\alpha_{i+1} zu/2) \approx \overline{k}'_i (1 + \alpha_{i+1} zu_s/2) \tag{10}$$

$$k''_i = \tilde{k}''_i \exp(-\alpha_i zu/2) \approx \overline{k}''_i (1 - \alpha_i zu_s/2) \tag{11}$$

$$\sum_{i=1}^{n+1} \alpha_i = 1 \,. \tag{12}$$

In the presence of a small d.c. voltage, V_s, the current I through the membrane is given by the ohmic membrane resistance R_m:

$$R_m = \left(\frac{V_s}{I} \right)_{V_s \approx 0} \tag{13}$$

As shown in Appendix A, R_m is related in a simple way to the unidirectional equilibrium fluxes F_i (Eqn. 4):

$$R_m = \frac{kT}{z^2 e_0^2} \cdot \sum_{i=1}^{n+1} \frac{1}{F_i} \tag{14}$$

Using Eqn. 14 together with Eqns. 4—6, R_m may be expressed in terms of the rate constants $\overline{k}'_i$ and $\overline{k}''_i$ [11]:

$$R_m = \frac{kT}{z^2 e_0^2} \cdot \frac{1}{P} \sum_{i=1}^{n+1} \rho_i \tag{14a}$$

$$\rho_i = \overline{k}''_1 \overline{k}''_2 \dots \overline{k}''_{i-1} \overline{k}'_i \overline{k}'_{i+1} \dots \overline{k}'_n$$

$$(\rho_1 = \overline{k}'_1 \overline{k}'_2 \dots \overline{k}'_n; \quad \rho_{n+1} = \overline{k}''_1 \overline{k}''_2 \dots \overline{k}''_n)$$

Spectral intensity of current and voltage fluctuations

The Nyquist theorem [12—15] is a general theorem connecting fluctuations with the dissipative properties of a system. Applied to electrically conducting systems it states that at equilibrium the spectral intensities $S_I(\omega)$ and $S_V(\omega)$ of current (I) and voltage (V) fluctuations are related to the frequency-dependent admittance $Y(\omega)$ of the system ($1/Y(\omega)$ is the impedance):

$$S_I(\omega) = 4kT \cdot \text{Re}[\,Y(\omega)] \tag{15}$$

$$S_V(\omega) = \frac{1}{|\,Y(\omega)|^2}\, S_I(\omega) = 4kT \cdot \text{Re}\left[\frac{1}{Y(\omega)}\right] \tag{16}$$

where ω is the angular frequency and Re signifies 'real part of'. The equilibrium condition means that $S_V(\omega)$ is measured at zero current and that $S_I(\omega)$ is measured at the equilibrium voltage V_m^0.

In order to calculate $Y(\omega)$, we assume that an a.c. voltage

$$V_s(t) = V_{s0} \cos \omega t \tag{17}$$

is applied to the membrane. The resulting current $I(t)$ is then given by

$$I(t) = I_0 \cos(\omega t - \varphi) \tag{18}$$

$$I_0 = V_{s0}\,|\,Y(\omega)| = V_{s0}\,\sqrt{\text{Re}^2[\,Y(\omega)] + \text{Jm}^2[\,Y(\omega)]} \tag{19}$$

$$\text{tg}\,\varphi = -\frac{\text{Jm}[\,Y(\omega)]}{\text{Re}[\,Y(\omega)]} \tag{20}$$

where Jm means 'imaginary part of'. The time-dependent current $I(t)$ which is measured in the external circuit results from the net ion fluxes $\Phi_i(t)$ over the single barriers; in addition, $I(t)$ contains the charging current $dV_m/dt = C_m dV_s/dt$ (C_m is the membrane capacitance). $I(t)$ is thus given by (Appendix B).

$$I(t) = ze_0 \sum_{i=1}^{n+1} \alpha_i \Phi_i(t) + C_m \frac{dV_m}{dt} \tag{21}$$

In the stationary state ($\Phi_i \equiv \Phi$, $dV_m/dt = 0$) Eqn. 21 reduces to the relation $I = ze_0\Phi$. The admittance $Y(\omega)$ may be obtained from Eqns. 17—21, as shown in Appendix C. For the formal representation of the result we define coefficients b_{ij} ($i,j = 1, 2, ..., n$) by the relations

$$b_{ij} = \begin{cases} \overline{k}'_{i-1} & (j = i - 1) \\ -(\overline{k}'_i + \overline{k}''_i) & (j = i) \\ \overline{k}''_{i+1} & (j = i + 1) \\ 0 & \text{(all other values of } j) \end{cases} \tag{22}$$

$$b_{10} = b_{n,n+1} = 0$$

Furthermore, we introduce the n relaxation times τ_k ($k = 1, 2, ..., n$) of the membrane, which are the roots of the following equation (compare Appendix

C):

$$\text{Det}(b_{ij} + \delta_{ij}/\tau) = 0 \tag{23}$$

($\delta_{ij} = 1$ for $i = j$ and $\delta_{ij} = 0$ for $i \neq j$). It may be shown that Eqns. 22 and 23 yield only real and positive roots τ_k. The real and imaginary part of the admittance $Y(\omega)$ is then obtained in the form

$$\text{Re}(Y) = \frac{z^2 e_0^2}{kT}\left(\sum_{l=1}^{n} \frac{\vartheta_l}{1 + \omega^2 \tau_l^2} + \sum_{i=1}^{n+1} \alpha_i^2 F_i\right) \tag{24}$$

$$\text{Jm}(Y) = \omega C_{\mathrm{m}} - \frac{z^2 e_0^2}{kT} \sum_{l=1}^{n} \frac{\omega \tau_l \vartheta_l}{1 + \omega^2 \tau_l^2} \tag{25}$$

$$\vartheta_l = \tau_l \sum_{i=1}^{n+1} \sum_{k=1}^{n} \alpha_i(\alpha_k F_k - \alpha_{k+1} F_{k+1})p_{lk}(\overline{k'_{i-1}} q_{i-1,l} - \overline{k''_i} q_{il}) \tag{26}$$

$$q_{0l} = q_{n+1,l} = 0$$

The n^2 quantities q_{il} are defined (apart from a common multiplicative factor) by the following n^2 equations:

$$\sum_{j=1}^{n} (b_{ij} + \delta_{ij}/\tau_k)q_{jk} = 0 \tag{27}$$

$$(i, k = 1, 2, ..., n)$$

The quantities p_{lk} in turn are defined as the elements of the inverse matrix $(q_{jk})^{-1}$:

$$\sum_{k=1}^{n} p_{ik} q_{kj} = \delta_{ij} \tag{28}$$

$$(i, j = 1, 2, ..., n)$$

From Eqns. 24—26 together with Eqns. 15 and 16 the spectral intensities $S_{\mathrm{I}}(\omega)$ and $S_{\mathrm{V}}(\omega)$ may be calculated. In the following we shall mainly discuss the spectral intensity of current noise, $S_{\mathrm{I}}(\omega)$:

$$S_{\mathrm{I}}(\omega) = 4z^2 e_0^2\left(\sum_{l=1}^{n} \frac{\vartheta_l}{1 + \omega^2 \tau_l^2} + \sum_{i=1}^{n+1} \alpha_i^2 F_i\right) \tag{29}$$

$S_{\mathrm{I}}(\omega)$ has the following properties:

a. S_{I} is independent of membrane capacitance C_{m} (as may be expected) whereas the expression for S_{V} contains C_{m}.

b. For a channel with n internal binding sites the spectral intensity $S_{\mathrm{I}}(\omega)$ has n dispersion regions (regions where S_{I} changes steeply with frequency) which are centered at angular frequencies $\omega_l = 1/\tau_l$ ($l = 1, 2, ..., n$). In the limit $\omega = 0$ the admittance approaches the membrane conductance $1/R_{\mathrm{m}}$:

$$S_{\mathrm{I}}(0) = \frac{4kT}{R_{\mathrm{m}}} = 4z^2 e_0^2\left(\sum_{l=1}^{n} \vartheta_l + \sum_{i=1}^{n+1} \alpha_i^2 F_i\right) \tag{30}$$

This means, according to Eqn. 14, that the following relation must be fulfilled:

$$\sum_{j=1}^{n+1} \frac{1}{F_j} \left(\sum_{l=1}^{n} \vartheta_l + \sum_{i=1}^{n+1} \alpha_i^2 F_i \right) = 1 \tag{31}$$

This relation is easily verified for small values of n. At high frequencies, S_I approaches a finite limit

$$S_I(\infty) = 4z^2 e_0^2 \sum_{i=1}^{n+1} \alpha_i^2 F_i \tag{32}$$

From Eqns. 30 and 32 it is seen that the channel acts as a white-noise source both at low and high frequencies.

c. For a completely regular potential profile with identical barrier heights, for which $\bar{k}_i' = \bar{k}_i'' \equiv \bar{k}^*$, $F_i \equiv F^*$ and $\alpha_i \equiv 1/(n+1)$ holds, the term $(\alpha_k F_k - \alpha_{k+1} F_{k+1})$ in Eqn. 26 vanishes so that $\vartheta_l = 0$ and

$$S_I(\omega) = 4z^2 e_0^2 \frac{F^*}{n+1} = \frac{4kT}{R_m} \tag{33}$$

(It may be shown that the coefficients p_{lk} and q_{il} in Eqn. 26 remain finite.) In this case only white noise is observed at equilibrium.

In the following section we illustrate the general result by considering some special cases.

Special cases

a. n = 1

In the case of a channel with only one binding site (and two barriers) the relaxation time is given by $\tau_1 = 1/(\bar{k}_1' + \bar{k}_1'')$ and Eqns. 27 and 28 may be satisfied by $p_{11} = q_{11} = 1$. Furthermore, the unidirectional fluxes are $F_1 = \bar{k}_0' N_c v c'$ and $F_2 = \bar{k}_2'' N_c v c''$.

This yields, after some rearrangement:

$$S_I(\omega) = \frac{4kT}{R_m} \cdot \frac{1 + Q\omega^2 \tau_1^2}{1 + \omega^2 \tau_1^2} \tag{34}$$

$$\frac{1}{R_m} = \frac{z^2 e_0^2}{2kT} \cdot N_c v \cdot \frac{c' \overline{k_0' k_1'} + c'' \overline{k_1'' k_2''}}{\bar{k}_1' + \bar{k}_1''} \tag{35}$$

$$Q = (\bar{k}_1' + \bar{k}_1'') \left(\frac{\alpha_1^2}{\overline{k_1'}} + \frac{\alpha_2^2}{\overline{k_1''}} \right) \tag{36}$$

Eqns. 34—36 agree with the result of a previous calculation which was based on Carson's theorem [8]. We further note that for a symmetrical channel ($\alpha_1 = \alpha_2 = 1/2$, $\bar{k}_1' = \bar{k}_2''$) one finds $\vartheta_1 = 0$, $Q = 1$, so that S_I becomes independent of frequency.

To give a specific example: In the symmetrical case ($\bar{k}_1' = \bar{k}_1'' \equiv \bar{k}_1$) and for an activation energy barrier of $E = 50$ kJ·mol^{-1} ($\simeq 12$ kcal·mol^{-1}) the jump frequency $\bar{k}_1 \simeq (kT/h) \exp(-E/kT)$ becomes of the order of $1 \cdot 10^4$ s^{-1} (h is

Planck's constant). This yields a time constant $\tau_1 = 5 \cdot 10^{-5}$ s, corresponding to a frequency $f_1 = 1/2\pi\tau_1 \simeq 3$ kHz. Thus, in the case considered here the spectrum exhibits a strong frequency dependence around $f_1 = 3$ kHz and becomes frequency independent both below and above this frequency range.

b. n = 2

For a channel with two binding sites the relaxation times are given by

$$1/\tau_1 = a + \sqrt{r} \tag{37}$$

$$1/\tau_2 = a - \sqrt{r} \tag{38}$$

$$a = \tfrac{1}{2}(\overline{k}_1' + \overline{k}_1'' + \overline{k}_2' + \overline{k}_2'') \tag{39}$$

$$b = \tfrac{1}{2}[(\overline{k}_1' + \overline{k}_1'') - (\overline{k}_2' + \overline{k}_2'')] \tag{40}$$

$$r = b^2 + \overline{k}_1' \overline{k}_2'' \tag{41}$$

From Eqns. 27 and 28 the coefficients p_{ij} and q_{ij} are obtained in the form

$$q_{11} = \overline{k}_2'' ; \qquad q_{12} = -\overline{k}_2'' \tag{42}$$

$$q_{21} = b - \sqrt{r} ; \qquad q_{22} = -b - \sqrt{r}$$

$$p_{11} = \frac{b + \sqrt{r}}{2\overline{k}_2''\sqrt{r}} ; \qquad p_{12} = -\frac{1}{2\sqrt{r}} \tag{43}$$

$$p_{21} = \frac{b - \sqrt{r}}{2\overline{k}_2''\sqrt{r}} ; \qquad p_{22} = -\frac{1}{2\sqrt{r}}$$

Instead of writing down the rather cumbersome expression for $S_I(\omega)$ which is obtained by inserting Eqns. 37—43 into Eqn. 29, we consider the special case of a symmetrical channel ($n = 2$) and identical aqueous solutions. This means that $c' = c'' \equiv c$, $\overline{k}_0' = \overline{k}_3'' \equiv k_{am}$, $\overline{k}_1'' = \overline{k}_2' \equiv k_{ma}$, $\overline{k}_1' = \overline{k}_2'' \equiv k_i$, $\alpha_2 \equiv \alpha$ and $\alpha_1 = \alpha_3 = 1 - \alpha$.

Under these conditions one finds $\vartheta_2 = 0$ and

$$S_I(\omega) = \frac{4kT}{R_m} \cdot \frac{1 + Q\omega^2\tau_1^2}{1 + \omega^2\tau_1^2} \tag{44}$$

$$\frac{1}{R_m} = \frac{z^2e_0^2}{kT} N_c \upsilon c \frac{k_{am}k_i}{k_{ma} + 2k_i} \tag{45}$$

$$Q = \frac{k_{ma} + 2k_i}{2k_{ma}k_i} [k_{ma}(1 - \alpha)^2 + 2k_i\alpha^2] \tag{46}$$

$$1/\tau_1 = k_{ma} + 2k_i \tag{47}$$

Here again (as in the case $n = 1$) the spectral intensity $S_I(\omega)$ increases from the low-frequency value $S_I(0) = 4 kT/R_m$ to a high-frequency limit $S_I(\infty) = Q \cdot S_I(0)$ in the vicinity of $\omega = 1/\tau_1$. This simple behaviour (one single dispersion region) is observed only for a symmetrical channel, whereas in the general case two dispersions occur for $n = 2$.

c. Gate noise

Recent experiments suggest that the operation of the gate which controls the sodium channel in nerve is associated with the displacement of charges in the membrane dielectric [18—20]. A simple model for the description of the gate current consists in the assumption that membrane-bound, electrically charged 'gate-particles' exist which may distribute themselves between two potential energy minima in the membrane [19]. Studies of electrical noise from the gating mechanism have not been reported so far, but is is nevertheless interesting to give an estimate of the noise spectrum which may be expected on the basis of the above model. In the case considered here, the rate constants for the movement over the outer barriers are zero $(\bar{k}_0' = \bar{k}_1'' = \bar{k}_2' = \bar{k}_3'' = 0)$, as the gate particles are assumed to be confined to the membrane. This means that at any membrane voltage V_m an equilibrium state is reached for $t \to \infty$ in which the gate particles are distributed between the two energy minima according to a Boltzmann distribution [19]. We may therefore apply Nyquist's theorem at any value of V_m. If $N = \bar{N}_1 + \bar{N}_2$ is the total number of gate particles in the membrane and if $k' = \bar{k}_t'$ and $k'' = \bar{k}_2''$ are the rate constants for the translocation across the central barrier, then

$$\bar{N}_1 = N \frac{k''}{k' + k''} \; ; \bar{N}_2 = N \frac{k'}{k' + k''} \tag{48}$$

The spectral intensity of gate noise may be obtained by evaluating the general expressions for $S_I(\omega)$ and $S_V(\omega)$ for $n = 2$ in the limit $\bar{k}_0' \to 0$, $\bar{k}_1'' \to 0$, $\bar{k}_2' \to 0$, $\bar{k}_3'' \to 0$ or, more easily, by calculating $Y(\omega)$ directly according to the method described in Appendix C. This yields

$$\mathrm{Re}[\,Y(\omega)\,] = \frac{(\alpha z e_0)^2}{kT} \, N \cdot \frac{k'k''}{k' + k''} \cdot \frac{\omega^2 \tau^2}{1 + \omega^2 \tau^2} \tag{49}$$

$$\mathrm{Im}[\,Y(\omega)\,] = \frac{1}{\omega \tau} \, \mathrm{Re}[\,Y(\omega)\,] + \omega C_m \tag{50}$$

$$S_I(\omega) = (2\alpha z e_0)^2 \, N \, \frac{k'k''}{k' + k''} \cdot \frac{\omega^2 \tau^2}{1 + \omega^2 \tau^2} \tag{51}$$

$$\tau = \frac{1}{k' + k''} \tag{52}$$

Thus, the spectral intensity of current noise from gate particles may be expected to have the form of an inverted Lorentz spectrum, $S_I(\omega)$ increasing proportional to ω^2 at low ω and approaching a finite limit at high ω. Relation 51 is formally identical with the current-noise spectrum of a membrane containing hydrophobic ions which has been derived (using the Langevin method) for the limiting case of vanishing exchange between membrane and water [10].

If the voltage dependence of the rate constants is described by $k' = k_0' \exp(\alpha z u/2)$, $k'' = k_0'' \exp(-\alpha z u/2)$ then Eqn. 51 may be written in the form

$$S_I(\omega) = (\alpha z e_0)^2 \, \frac{2N/\tau}{1 + \cosh[\alpha z(u - u^*)]} \cdot \frac{\omega^2 \tau^2}{1 + \omega^2 \tau^2} \tag{53}$$

where u* is the reduced voltage at which the gate particles are symmetrically distributed ($\overline{N}_1 = \overline{N}_2$, $k' = k''$). From Eqn. 53 one infers that an upper limit of S_I is given by $S_I \leqslant (\alpha z e_0)^2 N/\tau$.

Conclusion

In the preceding sections a formulism has been described for the treatment of noise resulting from the random movement of ions over a series of activation barriers. In such a transport system the individual barriers behave as coupled shot-noise sources, the coupling being given by the potential energy minima between the barriers, which act as storage elements for the transported ions. Accordingly, the resulting noise shows a characteristic frequency dependence which is closely linked to the relaxation-time spectrum of the transport system. The analysis has been based on Nyquist's theorem and is therefore restricted to fluctuations around the equilibrium state. In this limit the spectral intensities of current and voltage noise are given by the frequency-dependent admittance of the system. Because of the very general nature of Nyquist's theorem, a similar treatment seems possible for electrical noise from ion carriers. Another possible application concerns transport noise in systems where the potential energy of the ion is a more or less smooth function of position so that a Nernst-Planck (or electrodiffusion) treatment is more appropriate.

Future extensions of the present analysis should deal with non-equilibrium states of the channel; noise studies under non-equilibrium conditions would give additional information on microscopic parameters of the channel not already contained in the admittance.

Acknowledgements

Appendix A

Derivation of Eqn. 14

In the presence of a d.c. voltage V_s the membrane assumes a stationary state in which the net ion fluxes Φ_i over all barriers are equal:

$$\Phi_i = k'_{i-1}N_{i-1} - k''_i N_i = \Phi \tag{A1}$$

$$(i = 1, 2, ..., n + 1)$$

For $|V_s| \ll kT/e_0$ the N_i remain close to their equilibrium values $\overline{N}_i$, so that we may write $N_i = \overline{N}_i (1 + h_i)$ with $|h_i| \ll 1$. Using Eqns. 4, 10 and 11 and neglecting terms proportional to $h_i u_s$, Eqn. A1 gives

$$\frac{\Phi}{F_i} = h_{i-1} - h_i + \alpha_i z u_s \tag{A2}$$

$$h_0 = h_{n+1} = 0$$

Summation over i yields, together with Eqn. 12:

$$\Phi \sum_{i=1}^{n+1} \frac{1}{F_i} = zu_\mathrm{s} \tag{A3}$$

Introducing the electric current $I = ze_0\Phi$ into Eqn. 13 and using Eqn. A3 then leads to relation 14 for R_m.

Appendix B

Derivation of Eqn. 21

The derivation of Eqn. 21 may be based on the following model. We assume that the internal energy minima are located at positions s_i $(i = 1, 2, ..., n)$ and that the membrane surfaces have the coordinates s_0 and s_{n+1} (Fig. 1). If the membrane is a homogeneous dielectric, the fraction α_i of the total voltage droping across the ith barrier (which is to the left of the ith energy minimum) is given by

$$\alpha_i = \frac{s_i - s_{i-1}}{d} \tag{B1}$$

where $d = s_{n+1} - s_0$ is the membrane thickness. If a charge ze_0 is displaced in the membrane over the distance $(s_i - s_{i-1})$ a corresponding charge-displacement of magnitude $ze_0\,(s_i - s_{i-1})/d = ze_0\alpha_i$ occurs in the external circuit at constant voltage V_m (for the present purpose the aqueous electrolyte solutions may be considered as ideal conductors and as part of the external circuit). Therefore, if Φ_i charges per unit time pass over the ith barrier the resulting current in the external circuit is equal to $ze_0\alpha_i\Phi_i$. The total current I is obtained by summing over all barriers and adding the charging current $C_\mathrm{m}dV_\mathrm{m}/dt$ (C_m is the membrane capacitance). This yields Eqn. 21. The above derivation may be generalized to the case of an inhomogeneous membrane dielectric [16].

Appendix C

Derivation of Eqns. 22—28

In the presence of a small a.c. voltage $V_\mathrm{s} = V_{\mathrm{s}0}\cos\omega t$ with $|V_{\mathrm{s}0}| \ll kT/e_0$, the quantities N_i, k_i', k_i'' are given by (compare Eqns. 10 and 11):

$$N_i(\mathrm{t}) = \overline{N}_i + x_i(\mathrm{t}) \tag{C1}$$

$$k_i'(\mathrm{t}) = \overline{k}_i'\left(1 + \alpha_{i+1}\,\frac{zu_{\mathrm{s}0}}{2}\cos\omega t\right) \tag{C2}$$

$$k_i''(\mathrm{t}) = \overline{k}_i''\left(1 - \alpha_i\,\frac{zu_{\mathrm{s}0}}{2}\cos\omega t\right) \tag{C3}$$

with $|x_i| \ll \overline{N}_i$, $|u_{\mathrm{s}0}| = |V_{\mathrm{s}0}e_0/kT| \ll 1$. Introduction of Eqns. 3, 4, 17 and

C1—C3 into Eqn. 21 and neglection of terms proportional to $x_i\, u_{s0}$ yields

$$I(t) = ze_0 \sum_{i=1}^{n+1} \alpha_i (\overline{k}_{i-1} x_{i-1} - \overline{k}_i'' x_i + \alpha_i F_i z u_{s0} \cos \omega t) - C_m V_{s0}\, \omega \sin \omega t \qquad (C4)$$

$$x_0 = x_{n+1} = 0$$

The rate of change of N_i is given by

$$\frac{dN_i}{dt} = \Phi_i - \Phi_{i+1} \qquad (C5)$$

This equation, together with Eqns. 3, 4, 17 and C1—C3 yields the following system of differential equations for the n functions $x_i\,(t)$:

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} b_{ij} x_j + g_i \cos \omega t \qquad (C6)$$

$$g_i = z u_{s0} (\alpha_i F_i - \alpha_{i+1} F_{i+1}) \qquad (C7)$$

The coefficients b_{ij} are given by Eqn. 22. Using the transformation

$$y_i = \sum_{k=1}^{n} p_{ik} x_k ; \qquad x_j = \sum_{k=1}^{n} q_{jk} y_k \qquad (C8)$$

Eqn. C6 may be obtained in the form [17]:

$$\frac{dy_i}{dt} = -\frac{1}{\tau_i} y_i + \sum_{k=1}^{n} p_{ik} g_k \cos \omega t \qquad (C9)$$

The τ_i are the relaxation times of the membrane and are given by the roots of the equation

$$\text{Det}(b_{ij} + \delta_{ij}/\tau) = 0 \qquad (C10)$$

where δ_{ij} is Kronecker's delta. In order to transform Eqn. C6 into Eqn. C9 the coefficients q_{jk} have to be chosen such that

$$\sum_{j=1}^{n} (b_{ij} + \delta_{ij}/\tau_k) q_{jk} = 0 \qquad (C11)$$

By virtue of Eqn. C10 this equation has a non-trivial solution. We now replace the functions y_i by complex functions η_i with Re $(\eta_i) = y_i$:

$$\frac{d\eta_i}{dt} = -\frac{1}{\tau_i} \eta_i + \sum_{k=1}^{n} p_{ik} g_k \exp(j\omega t) \qquad (C12)$$

where j is the imaginary unit. It is easily verified that the solution of Eqn. C12 is given by

$$\eta_i = A_i \exp(j\omega t) \qquad (C13)$$

$$A_i = \tau_i \frac{1 - j\omega\tau_i}{1 + \omega^2\tau_i^2} \sum_{k=1}^{n} p_{ik}g_k \tag{C14}$$

Instead of the real current I (Eqn. C4) we introduce a complex current J with Re $(J) = I$:

$$J(t) = Y(\omega)V_{s0} \exp(j\omega t) \tag{C15}$$

$$J(t) = ze_0 \sum_{i=1}^{n+1} \alpha_i[\overline{k'_{i-1}}\,\xi_{i-1} - \overline{k''_i}\xi_i + \alpha_i F_i z u_{s0} \exp(j\omega t)] + C_m V_{s0} j\omega \exp(j\omega t) \tag{C16}$$

$$\text{Re}(\xi_i) = x_i \; ; \qquad \xi_0 = \xi_{n+1} = 0$$

The complex quantities ξ_i are obtained from the functions η_i by the transformation C8:

$$\xi_i = \sum_{l=1}^{n} q_{il}\eta_l = \sum_{l=1}^{n} q_{il}A_l \exp(j\omega t) \tag{C17}$$

After introduction of the ξ_i from Eqns. C17 and C14 into Eqn. C16 and separate comparison of the real and imaginary parts of Eqns. C15 and C16 the relations 24—26 are obtained.

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