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Current noise generated by electrogenic ion pumps

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Abstract. Active ion transport by ATP- or light-driven pumps involves a sequence of elementary steps such as binding and release of ions, as well as conformational transitions of the pump protein. At the microscopic level the individual reaction steps occur at random intervals, and therefore the current generated by electrogenic pumps fluctuates around a mean value. In this paper, a theoretical treatment of the electrical noise associated with active ion transport is given. The analysis, which is based on the calculation of the correlation function, yields the spectral intensity S_I of current noise as a function of frequency, f. The shape of $S_I(f)$ contains information on the rate constants as well as on the magnitude of the charge displacements occuring during single reaction steps. The contribution of electrogenic pumps to the total voltage noise of the cell may be estimated from $S_I(f)$ and from the frequency-dependent impedance of the cell membrane.

Key words: Electrical noise, membranes, ion pumps, active transport, fluctuations

Introduction

Cellular membranes contain a number of active ion transport systems capable of accumulating or extruding ions against a gradient of electrochemical potential. Examples of ATP-driven ion pumps are the sodium-potassium pump in the plasma membranes of animal cells (Hoffman and Forbush 1983), the calcium pump in sarcoplasmatic reticulum (Hasselbach and Oetliker 1983) and the proton-translocating ATPase in fungal membranes (Goffeau and Slayman 1981). Light as an energy source is utilized by bacteriorhodopsin, a proton pump of *Halobacterium halobium* (Stoeckenius et al. 1979).

Most ion pumps so far known are electrogenic, i.e., they translocate net electric charge across the membrane. For example, the Na,K pump of erythrocytes translocates three sodium ions outward and two potassium ions inward during one pumping cycle. Electrogenic ion pumps may strongly influence the potential difference between the cytoplasm and the extracellular medium. For instance, the proton pump in the plasma membrane of the fungus *Neurospora* is capable of maintaining a large intracellular potential of about −200 mV (Warncke and Slayman 1980). In this way, electrogenic ion pumps may modulate other cellular activities such as secondary (gradient-coupled) active transport or electrical excitation.

The molecular mechanisms of active ion transport are still incompletely understood, but it is clear that ion pumping is a multistep process, involving a series of binding, dissociation and translocation reactions. At the microscopic level the pumping cycle proceeds through a sequence of elementary steps which occur at random intervals and in random directions. That is, an ion pump operates in a stochastic way, carrying out a sort of biased random walk among the states of the reaction cycle. While there is an average net flow in the forward direction, single steps will always occur in which the cycle moves backward. As a result of the statistical nature of the transport process, the transmembrane pump current fluctuates around a mean value. In this way electrogenic ion pumps contribute to the electrical noise of the cell membrane. Voltage noise in sensory cells ultimately limits the threshold for signal transduction, since stimulus-evoked potential changes can only be detected if they are larger than the average noise amplitude (Hagins et al. 1970; Fain et al. 1977).

By analysing membrane noise, information on ion transport mechanisms may be obtained (Verveen and De Felice 1974; Conti and Wanke 1975; Neher and Stevens 1977; De Felice 1981). Such studies have been carried out, for instance, with acetylcholine-activated channels in the neuromuscular junction (Katz and Miledi 1970; Anderson and Stevens 1973), with gramicidin A channels (Neher and Zingsheim 1974; Kolb et al. 1975) and with ion carriers in artificial lipid bilayer membranes (Kolb and Läuger 1978; Kolb and Frehland 1980). While ionic channels with large transport rates can now conveniently be studied using the patch-clamp technique (Hamill et al. 1981), the method of single-channel analysis is not applicable to transport systems having small turnover numbers, such as ion pumps. An experimental study of electrical fluctuations associated with active ion transport has been described by Segal (1972), but the interpretation of these experiments has been questioned (Fishman and Dorset 1973; Segal 1974). Current fluctuations from light-driven proton transport by bacteriorhodopsin have been observed by Bamberg et al. (1984).

In this paper a theoretical treatment of the frequency behaviour of current noise associated with active ion transport is given. The analysis is based on the theory of transport noise under non-equilibrium conditions developed by Frehland (1978, 1982). Assuming that the pumping cycle consists of a sequence of conformational transitions and ion translocation steps, the spectral intensity, S_I, of the current noise can be predicted as a function of the frequency, f. The shape of $S_I(f)$ contains information on the rate constants as well as on the magnitude of the charge displacements associated with single reaction steps.

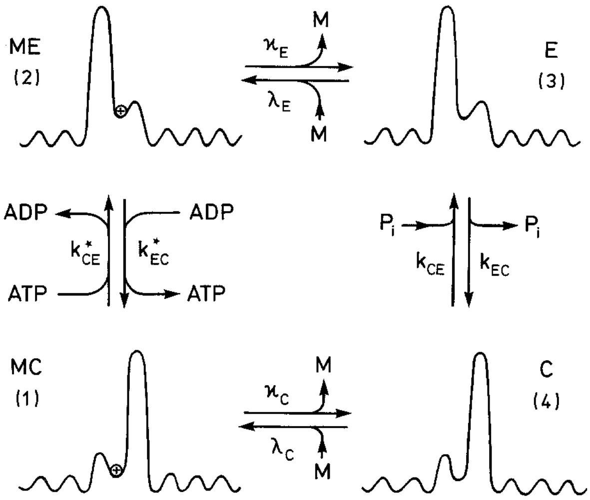

Fig. 1. ATP-driven active transport of ion species M. The pathway of the ion through the pump molecule is described as a series of energy wells and barriers. In the dephosphorylated state (MC/C) the ion binding site is accessible from the left (cytoplasmic) side, but separated from the extracellular site by an energy barrier of virtually infinite height. In the phosphorylated state the binding site is exposed to the right (extracellular) side. During the cycle $MC \rightarrow ME \rightarrow E \rightarrow C \rightarrow MC$ an ion M is translocated from the cytoplasm to the extracellular medium. k^*_{CE}, k^*_{EC}, and k_{CE}, k_{EC} are the rate constants for the conformation transitions in states with occupied and empty binding site, respectively. $\varkappa_C$, $\varkappa_E$, λ_C, and λ_E are rate constants for the exchange of ions between binding site and aqueous media

Description of the pump model

We consider a pump which is driven by ATP hydrolysis or light absorption and which translocates an ion M from the cytoplasm to the extracellular medium during each pumping cycle. In order to describe ion movement across the pump molecule, it is convenient to introduce the potential energy profile of the ion along the transport pathway, consisting of a series of potential wells separated by activation barriers (Läuger 1984). According to Fig. 1 the pump is represented as an ionic channel with an ion binding site and two rate-limiting barriers on either side. Towards the aqueous phases a number of smaller barriers may be present which allow fast diffusion of ions, so that the outer energy wells are always in equilibrium with the respective aqueous phases. We assume that in the ground state of the pump (state MC/C) the binding site is accessible from the left (cytoplasmic) side, but separated from the extracellular side by a barrier of virtually infinite height (Fig. 1). In state MC the pump protein may be phosphorylated or activated by light, resulting in a transition to state ME, in which the binding site is accessible only from the right (extracellular) side. State ME may either return directly to MC (which would short-circuit the pump) or through the intermediate states E and C ($ME \rightarrow E \rightarrow C \rightarrow MC$). During this cycle an ion is released to the extracellular side, followed by rebinding of another ion from the cytoplasmic side.

If the pump is driven by ATP hydrolysis, state ME/E may be assumed to represent a phosphorylated form and state MC/C an unphosphorylated form of the protein. The rate constants k^*_{CE}, k^*_{EC}, and k_{CE} then depend on the concentrations of ATP, ADP, and inorganic phosphate (P_i). If the pump is tightly coupled (no spontaneous hydrolysis of the phosphorylated form ME), the following relations hold:

$$k^*_{CE} = pc_T \tag{1}$$

$$k^*_{EC} = rc_D \tag{2}$$

$$k_{CE} = wc_P\,, \tag{3}$$

where c_T, c_D, and c_P are the concentrations of ATP, ADP, and P_i, respectively and p, r, w, and k_{CE} are concentration-independent quantities. Implicit in Eqs. (1)–(3) is the assumption that phosporylation/dephosphorylation and conformation transition takes place simultaneously. This assumption, which has been introduced merely for mathematical convenience, may be omitted in a more detailed treatment.

In the following we assume that conformational transitions are possible only if the binding site is either empty (states C and E) or fully occupied (states MC and ME). Transitions between C and MC take place by exchange of ions with the cytoplasm (denoted by $'$), transitions between E and ME by exchange with the extracellular medium (denoted by $''$):

$$C + \mathrm{M}' \underset{\varkappa_C}{\overset{\lambda_C}{\rightleftarrows}} MC \tag{4}$$

$$E + M'' \underset{\varkappa_E}{\overset{\lambda_E}{\rightleftarrows}} ME \,. \tag{5}$$

The rate constants $\varkappa_C$, $\varkappa_E$, λ_C, and λ_E are overall rate constants which are used for an approximate description of the binding/dissociation reactions; in reality, reactions 4 and 5 are multistep processes. λ_C and λ_E depend on the cytoplasmic (c') and extracellular (c'') ion concentrations:

$$\lambda_C = \varrho'_C c' \,; \quad \lambda_E = \varrho''_E c'' \tag{6}$$

where ϱ'_C, ϱ''_E, $\varkappa_C$, and $\varkappa_E$ are concentration-independent quantities.

According to the principle of microscopic reversibility (or detailed balance) the rate constants of the reaction scheme (Fig. 1) are not independent, but connected by a relation containing the thermodynamic driving forces (Appendix A):

$$\frac{k_{EC} k^*_{CE}}{k_{CE} k^*_{EC}} \cdot \frac{\varkappa_E \lambda_C}{\varkappa_C \lambda_E} = \exp\left(\frac{\Delta\bar{\mu} - \Delta G}{RT}\right), \tag{7}$$

where R is the gas constant and T the absolute temperature. $\Delta\bar{\mu} \equiv \bar{\mu}' - \bar{\mu}''$ is the electrochemical potential difference of the transported ion (cytoplasm minus extracellular medium), and ΔG the Gibbs free energy of ATP hydrolysis:

$$\Delta\bar{\mu} = zF(\psi' - \psi'') + RT \ln(c'/c'') \tag{8}$$

$$\Delta G = -RT \ln\left(\frac{c_T/c_D c_P}{\bar{c}_T/\bar{c}_D \bar{c}_P}\right), \tag{9}$$

where z is the valency of the ion, F the Faraday constant, ψ' and ψ'' are the electrical potentials in the cytoplasm and the extracellular medium, and $\bar{c}_T$, $\bar{c}_D$, and $\bar{c}_P$ are the equilibrium concentrations of ATP, ADP, and P_i, respectively.

For the pump model described above, the mean (time-averaged) pump current in the stationary state may be easily calculated using standard methods (Läuger 1984). In the following we introduce the assumption that the rate of binding and dissociation of ions is fast compared with the rate of conformational transitions ($\varkappa_C$, $\varkappa_E$, λ_C, $\lambda_E \gg k_{CE}$, k_{EC}, k^*_{CE}, k^*_{EC}). Under these conditions the binding sites are always in equilibrium with the respective aqueous phase. Introducing the dissociation constants K_C and K_E, the binding equilibria are described by

$$\frac{K_C}{c'} = \frac{N_C^{eq}}{N_{MC}^{eq}} = \frac{\varkappa_C}{\lambda_C} \equiv C \tag{10}$$

$$\frac{K_E}{c''} = \frac{N_E^{eq}}{N_{ME}^{eq}} = \frac{\varkappa_E}{\lambda_E} \equiv E \tag{11}$$

where N_X^{eq} is the number of pump molecules in state X at equilibrium. The mean pump current $\bar{I}$ in a membrane containing N independent pump molecules is then obtained as

$$\bar{I} = Nze_0 \, \sigma k^*_{EC} k_{CE} C \left[\exp\left(\frac{\Delta\bar{\mu} - \Delta G}{RT}\right) - 1\right] \tag{12}$$

$$= Nze_0 \sigma (k^*_{CE} k_{EC} E - k^*_{EC} k_{CE} C) \tag{12a}$$

$$\sigma \equiv [(1 + C)(k^*_{EC} + E k_{EC}) + (1 + E)(k^*_{CE} + C k_{CE})]^{-1}, \tag{13}$$

where e_0 is the elementary charge. The current $\bar{I}$ vanishes when the electrochemical potential difference of the transported ion is equal to the chemical driving force ($\Delta\bar{\mu} = \Delta G$).

Spectral intensity $S_I(\omega)$ of current fluctuations at constant voltage

A transition of a pump molecule from state i to state j is, in general, associated with a charge displacement in the membrane dielectric. This in turn leads to a charge translocation in the external measuring circuit, if the voltage across the membrane is kept constant. The externally measured current results from the superposition of a large number of current pulses generated by the elementary charge movements. If $q_{ji} = -q_{ij}$ is the charge which is translocated in the external circuit as a result of a single transition $i \rightarrow j$, and if $\Phi_{ji}(t)$ is the rate of the transition $i \rightarrow j$ at time t, the pump current $I(t)$ across the membrane is given by (Frehland 1978; Läuger et al. 1981):

$$I(t) = \sum_{i,j} q_{ij} \Phi_{ij}(t) \qquad (q_{ii} \equiv 0) \,. \tag{14}$$

For the four-state reaction scheme of Fig. 1 one obtains

$$I(t) = q_{21}[\Phi_{21}(t) - \Phi_{12}(t)] + \cdots + q_{14}[\Phi_{14}(t) - \Phi_{41}(t)] . \tag{15}$$

The mean (time-averaged) current $\bar{I}$ at steady-state is given by the net transition rate between any two neighbouring states in the cycle:

$$\bar{I} = ze_0(\bar{\Phi}_{21} - \bar{\Phi}_{12}) = \cdots ze_0(\bar{\Phi}_{14} - \bar{\Phi}_{41}) \tag{16}$$

Considering Eq. (15), this means that

$$q_{21} + q_{32} + q_{43} + q_{14} = ze_0 , \tag{17}$$

where ze_0 is the total charge translocated through the membrane per pumping cycle. As a result of the stochastic nature of the transport process, the transition rates Φ_{ij} and the electric current I fluctuate around their mean values:

$$\Phi_{ij}(t) = \bar{\Phi}_{ij} + \delta\Phi_{ij}(t) \tag{18}$$

$$I(t) = \bar{I} + \delta I(t) . \tag{19}$$

According to Eq. (14), the fluctuating part of the current is given by

$$\delta I(t) = \sum_{i,j} q_{ij}\, \delta\Phi_{ij}(t) . \tag{20}$$

Under equilibrium conditions, the frequency behaviour of the electrical noise is described by Nyquist's theorem (Kubo 1966), stating that the spectral intensity of the current noise is proportional to the real part of the complex admittance. However, in a non-equilibrium situation, the Nyquist treatment is no longer applicable. In this case, the correlation matrix of the system has to be used for a calculation of the spectral intensity (Frehland 1978). The correlation function $C_I(t)$ of current fluctuations is defined by the relation

$$C_I(t) \equiv \overline{\delta I(0)\delta I(t)} . \tag{21}$$

In a similar way, cross-correlations between fluctuations of transition rates may be described by a correlation matrix with elements $C_{ij,kl}(t)$:

$$C_{ij,kl}(t) \equiv \overline{\delta\Phi_{ij}(0)\delta\Phi_{kl}(t)} . \tag{22}$$

According to Eqs. (20) and (21), $C_I(t)$ is obtained as

$$C_I(t) = \sum_{i,j,k,l} q_{ij}q_{kl}C_{ij,kl}(t) . \tag{23}$$

As has been shown by Frehland (1978), the correlation matrix may be calculated from the average time behaviour of the system after an external perturbation. For this purpose one considers a statistical ensemble of many identical membranes, each containing N pump molecules. If $\langle N_i^s \rangle \equiv N_i^s$ the ensemble average of the number of pump molecules in state i in the stationary state, the following relation holds

$$N = \sum_i N_i^s . \tag{24}$$

After an external perturbation at time $t = 0$, the $\langle N_i(t) \rangle$ relax toward the stationary values N_i^s, according to

$$\frac{d\langle N_i \rangle}{dt} = \sum_j M_{ij} \langle N_j(t) \rangle . \tag{25}$$

The quantities M_{ij} are given by the rate constants for the transitions between the different states of the cycle.

A convenient way to represent the time behaviour of the $\langle N_i \rangle$ for different initial conditions consists of introducing a set of fundamental solutions $\Omega_{ij}(t)$ which are defined by

$$\Omega_{ij}(t) \equiv [\langle N_i(t) \rangle - N_i^s] \quad \text{for} \quad \langle N_j(0) \rangle = 1,$$

$$\langle N_{k \neq j}(0) \rangle = 0 . \tag{26}$$

The correlation matrix is then obtained as (Frehland 1978, 1982):

$$C_{ij,kl}(t) = M_{ij}N_j^s [\delta_{ij,kl}\delta(t) + M_{kl}\Omega_{li}(t)] \tag{27}$$

with

$$\delta_{ij,kl} = \begin{cases} 1 \ (ij = kl) \\ 0 \ (ij \neq kl) \end{cases} ,$$

where $\delta(t)$ is the delta function which has the property $\delta = 0$ $(t > 0)$ and $\delta \to \infty$ $(t \to 0)$. The term $\delta_{ij,kl}\delta(t)$ describing the self-correlation of fluctuations represents the shot-noise contribution to the correlation matrix.

The spectral intensity $S_I(\omega)$ of current fluctuations is related to the autocorrelation function $C_I(t)$ by the Wiener-Khintchine theorem (van der Ziel 1970):

$$S_I(\omega) = 4 \int_0^\infty C_I(t) \cos \omega t dt , \tag{28}$$

where $\omega = 2\pi f$ (f is the frequency). Using the relation

$$\int_0^\infty \delta(t) \cos \omega t dt = \frac{1}{2} \tag{29}$$

one obtains from Eqs. (23) and (27)

$$S_I(\omega) = 2 \sum_{i,j,k,l} q_{ij} q_{kl} M_{ij} N_j^s \times \left[\delta_{ij,kl} + 2\, M_{kl} \int_0^\infty \Omega_{li}(t) \cos \omega t dt \right] . \tag{30}$$

Calculation of $S_I(\omega)$

In the following we apply the general relation, represented by Eq. (30), to the pump model of Fig. 1. In order to calculate the translocated charges q_{ij}, we assume that an ion entering the binding site in conformation *C*, from the left-hand (cytoplasmic) solution, has to move a certain distance through the membrane dielectric. Accordingly, for the transition $4 \rightarrow 1$ in which an ion of charge ze_0 enters the site, the translocated charge becomes $q_{14} = ze_0\gamma$. The dimensionless quantity γ depends on the location of the binding site and on the local dielectric constant. (For a homogeneous dielectric film of thickness d, γ would be equal to a/d, where a is the distance of the binding site from the surface). An an analogous way, the charge q_{23} which is translocated during the binding of an ion from the extracellular medium (state *E* of the pump) can be expressed as $q_{23} = -ze_0\varepsilon$. Conformational transitions of the pump molecule are, in general, associated with displacements of charges and rotation of dipoles. For the transition $C \rightarrow E$ (binding site empty) the translocated charge may be described by the quantity $q_{34} = e_0\eta$ representing the sum over all individual charge movements. Using Eq. (17) one then has

$$q_{21} = -q_{12} = e_0\eta + ze_0(1 - \gamma - \varepsilon) \equiv e_0\theta$$

$$q_{32} = -q_{23} = ze_0\varepsilon$$

$$q_{43} = -q_{34} = -e_0\eta$$

$$q_{14} = -q_{41} = ze_0\gamma \tag{31}$$

The rate constants M_{ij} which are defined by Eq. (25) may be immediately obtained from Fig. 1; thus, $M_{11} = -(k^*_{CE} + \varkappa_C)$, $M_{21} = k^*_{CE}$, $M_{32} = \varkappa_E$, $M_{31} = 0$, etc. The steady-state quantities N_i^s and the fundamental solutions $\Omega_{ij}(t)$ are given in Appendix *B*, assuming (as discussed previously) that the binding/dissociation reactions are much faster than the conformational transitions. The result is then obtained in the form

$$S_I(\omega) = S_I^\infty + \frac{A_1}{1 + \omega^2\tau_1^2} + \frac{A_2}{1 + \omega^2\tau_2^2} + \frac{A_3}{1 + \omega^2\tau_3^2} \tag{32}$$

$$\tau_1 = (\varkappa_C + \lambda_C)^{-1} ; \qquad \tau_2 = (\varkappa_E + \lambda_E)^{-1} \tag{33}$$

$$\tau_3 = [(k^*_{CE} + Ck_{CE})/(1 + C) + (k^*_{EC} + Ek_{EC})/(1 + E)]^{-1} \tag{34}$$

$$\begin{aligned} S_I^\infty = 2\, N\sigma[&(e_0\theta)^2 (k^*_{CE}k_{EC}E + k^*_{EC}k_{CE}C + 2\, k^*_{CE}k^*_{EC}) \\ &+ (e_0\eta)^2 (k^*_{CE}k_{EC}E + k^*_{EC}k_{CE}C + 2\, k_{CE}k_{EC}CE) \\ &+ 2\, (ze_0\gamma)^2 \varkappa_C (k^*_{EC} + Ek_{EC}) \\ &+ 2\, (ze_0\varepsilon)^2 \varkappa_E (k^*_{CE} + Ck_{CE})] . \end{aligned} \tag{35}$$

The frequency-independent quantities A_1, A_2, and A_3 are long expressions (containing the rate constants and the fractional charges q_{ij}) which can be obtained from Eq. (30) but which are not explicitly given here.

For the discussion of the meaning of Eq. (32) we consider the special case in which the ion binding site moves across the entire membrane dielectric in the conformational transition $C \rightleftarrows E$. Assuming further that the charge displacement associated with the transition $C \rightleftarrows E$ is negligible, the only contribution to the current signal results from the transition $MC \rightleftarrows ME$. This means that $\gamma = \varepsilon = \eta = 0$ and $\theta = z$. Under these conditions the following relations hold (Appendix B):

$$S_I^\infty = 2\, Nz^2e_0^2\sigma(k^*_{CE}k_{EC}E + k^*_{EC}k_{CE}C + 2\, k^*_{CE}k^*_{EC}) \tag{36}$$

$$A_1 = -4\, Nz^2e_0^2\sigma\tau_1 k^*_{CE}k^*_{EC}(k^*_{CE} + Ck_{CE})C/(1 + C) \tag{37}$$

$$A_2 = -4\, Nz^2e_0^2\sigma\tau_2 k^*_{CE}k^*_{EC}(k^*_{EC} + Ek_{EC})E/(1 + E) \tag{38}$$

$$\begin{aligned} A_3 = -4\, Nz^2e_0^2\sigma^2\tau_3[&k^*_{CE}(1 + E) \\ &+ k^*_{EC}(1 + C)]\, [k^*_{EC}(k^*_{CE} + Ck_{CE})^2/(1 + C) \\ &+ k^*_{CE}(k^*_{EC} + Ek_{EC})^2/(1 + E)] . \end{aligned} \tag{39}$$

The frequency dependence of spectral intensity S_I, as given by Eqs. (32) and (36)–(39), may be described in the following way. At low frequencies ($\omega \rightarrow 0$) the spectral intensity approaches a finite value $S_I(0) = S_I^\infty + A_1 + A_2 + A_3$. For $\omega > 0$, $S_I(\omega)$ monotonically increases towards the limiting value, S_I^∞, representing the shot-noise contribution (Läuger 1975). At intermediate frequencies there are three dispersion regions, centered at $\omega = 1/\tau_3$, $\omega = 1/\tau_2$ and $\omega = 1/\tau_1$, where $S_I(\omega)$ strongly varies with frequency. τ_1, τ_2, and τ_3 are identical with the time constants that can be observed in a relaxation experiment. Equation 32 has the same form as the relationship for the spectral intensity of current noise associated with carrier-mediated ion transport (Kolb and Läuger 1978; Kolb and Frehland 1980). This is not surprising in view of the general similarity of carrier and pump mechanisms (Läuger 1980).

When the electrochemical potential difference $\Delta\tilde{\mu}$ is equal to the free energy ΔG of ATP hydrolysis, the net current $\bar{I}$ vanishes, i.e., the system is in equilibrium. Under this condition the relation

$$k^*_{CE} k_{EC} E = k^*_{EC} k_{CE} C \tag{40}$$

holds, according to Eqs. (7), (10), and (11). It is seen from Eqs. (32) and (36)–(39) that the general form of the equation for the spectral intensity $S_I(\omega)$ is the same for equilibrium and non-equilibrium conditions and that $S_I(\omega)$ remains finite for $\bar{I} = 0$. In the equilibrium state the current $I(t)$ fluctuates around zero, with the same general frequency behaviour as under non-equilibrium conditions.

If the chemical driving force is large ($k^*_{CE} k_{EC} E \gg k^*_{EC} k_{CE} C$), the pump cycle (Fig. 1) proceeds almost exclusively in a forward direction ($MC \rightarrow ME \rightarrow E \rightarrow C \rightarrow MC$). Under this condition Eqs. (12a) and (36) reduce to

$$\bar{I} \approx N z e_0 \sigma k^*_{CE} k_{EC} E \tag{41}$$

$$S_I^\infty \approx 2\, z e_0 \bar{I} \left(1 + \frac{2\, k^*_{EC}}{k_{EC} E}\right) . \tag{42}$$

It is interesting to note that the first term in Eq. (42) is equal to the shot-noise intensity of a thermionic diode, which is given by Schottky's relation: $S_I^\infty = 2ze_0\bar{I}$ (van der Ziel 1970). Equation (42) shows that, depending on the value of $2k^*_{EC}/k_{EC}E$, the high-frequency limit of S_I can be much larger than $2ze_0\bar{I}$.

A numerical example for S_I is represented in Fig. 2 with the following values of the kinetic parameters: $C = E = 1$, $k_{CE} = k_{EC} = k^*_{EC} = 500\ \mathrm{s}^{-1}$, $\tau_1 = \tau_2 = 10^{-5}$ s, $N = 5 \cdot 10^8$. The value of N corresponds to the density of Na,K-ATPase molecules of about 750 $\mu\mathrm{m}^{-2}$ in heart-muscle cells (Daut and Rüdel 1981; Baker and Willis 1972), assuming a cylindrical cell 200 μm in diameter and 1,000 μm in length. The rate constant k^*_{CE} is determined by the total driving force ($\Delta\tilde{\mu} - \Delta G$), according to Eq. (7). In Fig. 2 the spectral intensity S_I is plotted as a function of frequency, $f = \omega/2\pi$, for zero driving force, $V_p = 0$, and for $V_p = 100$ mV (for convenience, the driving force is expressed as a voltage V_p which is defined by $V_p \equiv (\Delta\tilde{\mu} - \Delta G)/\mathrm{F}$). At a driving force of $V_p = 100$ mV the pump current, according to Eq. (12), is $\bar{I} = 18$ nA. It is seen from Fig. 2 than both the low-frequency as well as the high-frequency (shot-noise) limit of $S_I(f)$ increase with the driving force. Furthermore, the characteristic frequency, $f_3 = 1/2\pi\tau_3$, fo the slow process is shifted upwards with increasing V_p. The dispersions at $f_1 = 1/2\pi\tau_1$ and $f_2 = 1/2\pi\tau_2$ which are predicted from Eq. (32) are not visible in Fig. 2, since the amplitudes A_1 and A_2 are too small.

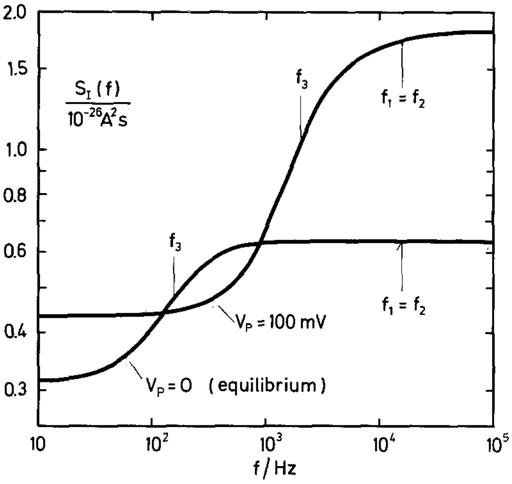

Fig. 2. Spectral intensity S_I of current noise as a function of frequency $f = \omega/2\pi$. $S_I(f)$ has been calculated from Eqs. (32) and (36)–(39) using the following values of the kinetic parameters: $C = E = 1$, $k_{CE} = k_{EC} = k^*_{EC} = 500\ \mathrm{s}^{-1}$, $\tau_1 = \tau_2 = 10^{-5}$ s, $N = 5 \cdot 10^8$, $z = 1$, $e_0 = 1.60 \cdot 10^{-19} C$. The total driving force is expressed as a voltage V_p which is defined by $V_p \equiv (\Delta\tilde{\mu} - \Delta G)/F$. The rate constant k^*_{CE} is determined by V_p, according to Eq. (7). The set of kinetic parameters given above corresponds to a maximum turnover rate ($k^*_{CE} \rightarrow \infty$) of $v_{max} = k_{EC}E/(1 + E) = 250\ \mathrm{s}^{-1}$. At a driving force of $V_p = 100$ mV, the mean pump current is $\bar{I} = 18$ nA (T = 25° C)

In the example chosen here, spectral intensities of the order of $10^{-26}\ \mathrm{A}^2 \cdot \mathrm{s}$ are predicted for a single large cell. This value may be compared with the intensity $S_{I,b}$ of background thermal noise of the cell membrane, which is calculated from Nyquist's relation: $S_{I,b} = 4\ \mathrm{kT}/R_m$. For a cell with a resistance of 10^4 $\Omega\ \mathrm{cm}^2$, $S_{I,b}$ becomes $1 \cdot 10^{-26}\ \mathrm{A}^2 \cdot \mathrm{s}$, which is of the same order as the intensity of pump noise. Thus, in order to measure current noise from ion pumps, conditions must be chosen under which the specific membrane resistance is large.

Light-driven ion pumps

Certain bacteria, such as *Halobacterium halobium* contain light driven pumps for H^+ (bacteriorhodopsin) or Cl^- (halorhodopsin) (Stoeckenius et al. 1979; Schobert and Lanyi 1982). In this case light absorption creates an excited state of very high energy (compared to kT); accordingly, most (or all) reaction steps leading back to the ground state are virtually irreversible. This means that the reaction cycle assumes the form

$$P_1 \xrightarrow{h\nu} P_2 \longrightarrow \cdots \longrightarrow P_n \longrightarrow P_1 . \tag{43}$$

As shown in Appendix C for the case $n = 3$, the current-noise intensity of a light-driven (irreversible) pump may again be represented by a relation with the form of Eq. (32) (with $A_3 = 0$ for $n = 3$).

Discussion

The treatment of current noise of ion pumps given here is based on the assumption that the overall transport process can be divided into a number of elementary steps, such as binding and release of ions and conformational transitions of the transport protein. The pump current may then be described as a superposition of many small current pulses associated with the elementary reaction steps. From this model the pump is predicted to act as a shot-noise source in the limit of high frequency, exhibiting frequency-independent ("white") current noise. Toward lower frequencies a decrease in noise intensity occurs in a frequency region which corresponds to the characteristic time constants of the reaction system. This dispersion results from correlations between the current pulses.

In the pump model considered above the pump cycle was assumed to proceed through four (main) states, meaning that the reaction system is described by $4 - 1 = 3$ independent state variables. Accordingly, three time constants τ_1, τ_2, τ_3 enter into the relationship for the spectral intensity (Eq. 32). If the pump molecule assumes n states in the cycle, the autocorrelation function of the current noise contains $n - 1$ time constants. A more general form of Eq. (32) thus reads

$$S_I(\omega) = S_I^\infty + \sum_{i=1}^{n-1} \frac{A_i}{1 + \omega^2 \tau_i^2}. \tag{44}$$

Mean amplitude of current noise

In order to estimate the average contribution of electrogenic pumps to the total current-noise of a cell, we calculate the mean square amplitude of current fluctuations (the variance of I) in a given frequency interval $(0, f^0)$:

$$\overline{(\delta I)^2_{f^0}} = \int_0^{f^0} S_I(f)df\,. \tag{45}$$

If the limiting frequency is chosen such that it is far outside the dispersion region ($f^0 \gg 1/2\pi\tau_i$), one obtains from Eq. (32)

$$\overline{(\delta I)^2_{f^0}} = S_I^\infty f^0 + \frac{1}{4}\left(\frac{A_1}{\tau_1} + \frac{A_2}{\tau_2} + \frac{A_3}{\tau_3}\right). \tag{46}$$

Since A_1, A_2, and A_3 are negative quantities (Eqs. 37–39), an upper limit for the variance is given by the shot-noise term S_I^∞:

$$\overline{(\delta I)^2_{f^0}} < S_I^\infty f^0\,. \tag{47}$$

This relationship holds for any value of f^0. The variance of I depends, of course, on the average pump current, $\bar{I}$, and it is therefore meaningful to consider the relative amplitude of current fluctuations. Assuming that the pump runs at large driving force ($[\Delta\tilde{\mu} - \Delta G]/RT \gg 1$, $k^*_{CE}k_{EC}E \gg k^*_{EC}k_{CE}C$), the average current is given by $\bar{I} \approx Nze_0\sigma k^*_{CE}k_{EC}E$, according to Eq. (41). Introducing the turnover rate $\nu = \bar{I}/Nze_0$ of the pump, one obtains from Eq. (42)

$$\chi \equiv \sqrt{\overline{(\delta I)^2}/\bar{I}^2} < \sqrt{\frac{2f^0}{\nu N}\left(1 + \frac{2k^*_{EC}}{Ek_{EC}}\right)}\,. \tag{48}$$

For instance, under the condition $k^*_{CE} = 5 \cdot 10^3\ \mathrm{s}^{-1}$, $k^*_{EC} = k_{CE} = k_{EC} = 500\ \mathrm{s}^{-1}$, $C = E = 1$, the turnover rate becomes $\nu = 170\ \mathrm{s}^{-1}$, which is in the range of values found for Na,K-ATPase in different types of cells (Baker and Willis 1972). If the cell membrane contains $N = 10^4$ pump molecules, the limiting value of χ in the frequency range between 0 and 10 kHz is predicted by Eq. (48) to be $\chi < 0.19$. (The exact value of χ, as obtained from Eqs. (12) and (46), is nearly the same in this case). According to Eq. (48) the relative current-noise amplitude decreases with increasing number of pump molecules and with increasing turnover rate.

Voltage-noise and threshold of sensory transduction

Fluctations in the rate of active ion transport can be observed, depending on the experimental conditions, either as current noise at constant voltage or as voltage noise at constant current. Current noise measurements are usually preferable, since they are not limited by the RC time constant of the membrane and therefore can be performed with higher time resolution. Moreover, as shown above, the theoretical analysis of current-noise spectra can be carried out in a straightforward way, starting with Eq. (27), whereas direct calculation of the spectral intensity of voltage noise is much more difficult.

On the other hand, fluctuations of membrane potential may directly interfere with a number of cellular processes such as sensory transduction, and therefore voltage noise is particularly interesting from the standpoint of physiology. In an intact cell (in the absence of intracellular electrodes) the external current is zero, meaning that in the membrane the sum of displacement currents and ionic currents vanishes. In order to estimate the amplitude of voltage fluctuations at zero current, we use the following relationship between the spectral intensities $S_V(\omega)$ and $S_I(\omega)$ of voltage and current noise (De Felice 1981):

$$S_V(\omega) = \frac{S_I(\omega)}{|Y(\omega)|^2} \qquad (49)$$

$Y(\omega)$ is the complex admittance of the cell membrane ($1/Y(\omega)$ is the impedance). Equation (49) is usually assumed to hold both for equilibrium and non-equilibrium systems; under non-equilibrium conditions it may, however, be valid only in an approximate sense.

The admittance $Y(\omega)$ is, in general, a complicated function of frequency, containing the time constants of the different ionic transport systems present in the membrane. For the purpose of obtaining an estimate of $S_V(\omega)$ we assume that $Y(\omega)$ is approximately given by a frequency-independent membrane resistance R_m and a frequency-independent membrane capacitance C_m (Fig. 3). This assumption implies that the electrogenic pumps do not significantly contribute to the admittance of the cell membrane; this is usually the case, at least for animal cells (De Weer 1984). The absolute value of the admittance is then given by:

$$|Y(\omega)| = \frac{1}{R_m}\sqrt{1+\omega^2\tau_m^2}\,, \qquad \tau_m \equiv R_m C_m\,, \qquad (50)$$

where τ_m is the time constant of the membrane. From Eqs. (49) and (50) it follows that the intensity of voltage noise is damped by the frequency-dependent factor $1/(1+\omega^2\tau_m^2)$:

$$S_V(\omega) = \frac{R_m^2 S_I^\infty}{1+\omega^2\tau_m^2} + \sum_i \frac{R_m^2 A_i}{(1+\omega^2\tau_i^2)(1+\omega^2\tau_m^2)}\,. \qquad (51)$$

The mean square amplitude of voltage noise in the frequency range $(0, \infty)$ then becomes

$$\overline{(\delta V)^2} = \int_0^\infty S_V(f)\,df = \frac{R_m^2}{4}\left(\frac{S_I^\infty}{\tau_m} + \sum_i \frac{A_i}{\tau_i+\tau_m}\right). \qquad (52)$$

Comparison of Eqs. (52) and (46) shows that (as a result of the filtering effect of the membrane capacitance) $\overline{(\delta V)^2}$ remains finite in the whole frequency range $(0, \infty)$, whereas $\overline{(\delta I)^2}$ increases indefinitely for $f^0 \to \infty$.

Numerical values of the mean amplitude of voltage fluctuations are given in Fig. 4 as a function of driving force V_p for different membrane areas A. The specific membrane resistance and capacitance were assumed to be $R_M = R_m A = 10\ \mathrm{k}\Omega \cdot \mathrm{cm}^2$ and $C_M = C_m/A = 1\ \mu\mathrm{F/cm}^2$. For the density N/A of pump molecules a mean value of $10^3\ \mu\mathrm{m}^{-2}$ was used, which corresponds to the average density of Na,K-ATPase molecules in the plasma membrane of a variety of cell types (Baker and Willis 1972). It is seen from Fig. 4 that the voltage-noise amplitude increases towards a limiting value with increasing driving force. At constant density, N/A, of pump molecules, $\sqrt{\overline{(\delta V)^2}}$ is inversely proportional to the square root of the membrane area. For small cells with membrane areas of 10^2–$10^3\ \mu\mathrm{m}^2$ the voltage noise amplitude may be of the order of 10–100 μV (Fig. 4). In addition to the noise generated by ion pumps, the total voltage noise of cells contains contributions from passive pathways, in particular from the statistical opening and closing

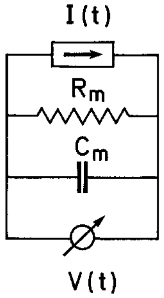

Fig. 3. Equivalent circuit for the calculation of $S_V(\omega)$. The time-dependent pump current $I(t)$ produces voltage fluctuations across the cell membrane under open-circuit conditions. R_m and C_m are the membrane resistance and membrane capacitance, respectively

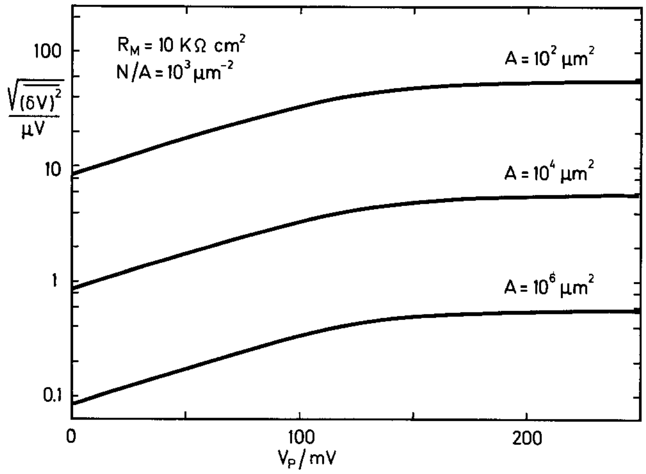

Fig. 4. Mean amplitude of voltage noise (Eq. 53) as a function of driving force V_p for different membrane areas A. The specific membrane resistance and capacitance were assumed to be $R_M = 10\ \mathrm{k}\Omega \cdot \mathrm{cm}^2$ and $C_M = 1\ \mu\mathrm{F/cm}^2$. For the mean density N/A of pump molecules a value of $10^3\ \mu\mathrm{m}^{-2}$ was used (Baker and Willis 1972). The other kinetic parameters were $C = E = 1$, $k_{CE} = 10\ \mathrm{s}^{-1}$, $k_{EC} = k_{EC}^* = 500\ \mathrm{s}^{-1}$, $\tau_1 \approx \tau_2 \approx 0$, $z = 1$. Under these conditions the contribution of the pumps to the total membrane resistance is $66\ \mathrm{k}\Omega \cdot \mathrm{cm}^2$ according to Eq. (12) ($V_p = 0$, $c' = c''$, $V \approx 0$)

of ionic channels. Since the pump current flows back through passive pathways, conductance fluctuations of the cell membrane represent a kind of indirect contribution of pumps to the total noise.

It is interesting to compare the noise amplitudes given by Fig. 4 with estimated threshold values of stimulus-induced voltage changes in sensory cells. For instance, experiments with vertebrate photoreceptors have shown that a voltage change of 10 μV is sufficient for synaptic transmission and generation of an action potential in the neighbouring second-order neuron (Fain et al. 1977). For safe signal detection the voltage noise of the receptor cell must be smaller than the threshold value of 10 μV. Even lower thresholds have been observed in electroreceptors (Bennet 1971; Bennet and Clusin 1979; Bullock 1982).

A possible way to minimize noise effects in signal transduction consists in a bandwidth limitation of the detecting system (Hagins et al. 1970; Oosawa 1975). Consider the case where a voltage-dependent transition between two states A and B of a membrane protein is a critical step in signal transmission between receptor cell and neuron:

$$A \underset{k''}{\overset{k'}{\rightleftarrows}} B\,.$$

For instance, A may be the closed and B the open state of a channel which regulates Ca^{2+} influx into the receptor cell and thereby modulates transmitter release. After a step change in voltage the population of channels would respond with a finite time constant $\tau = 1/(k' + k'')$ where k' and k'' are the rate constants of the transitions $A \rightarrow B$ and $B \rightarrow A$. This means that only slow voltage-fluctuations with frequencies $f^* \lesssim 1/2\pi\tau$ can lead to fluctuations in the number of open channels. Accordingly, the threshold voltage ΔV for signal detection is given by

$$\Delta V \lesssim \left(\int_0^{f^*} S_V(f) df \right)^{1/2}. \tag{53}$$

In this way ΔV can become much smaller than $\sqrt{\overline{(\delta V)^2}}$.

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Appendix A

Derivation of Eq. (7)

We consider an equilibrium situation in which both the electrochemical potential difference $\Delta\tilde{\mu}$ of the transported ion (Eq. 8) as well as the free energy ΔG of ATP hydrolysis (Eq. 9) vanish. This means that the membrane voltage $\psi' - \psi'' \equiv (RT/F)u$ is equal to the Nernst potential $(RT/F)u_0$ of the transported ion:

$$zu_0 = \ln(c''/c')\,. \tag{A1}$$

Introducing the equilibrium probability $P(X)$ that a given pump molecule is in state X and denoting values of the rate constants at the equilibrium voltage u_0 by a bar, one has

$$\frac{P(ME)}{P(MC)} = \frac{\bar{p}\bar{c}_T}{\bar{r}\bar{c}_D} \tag{A2}$$

$$\frac{P(C)}{P(E)} = \frac{\bar{k}_{EC}}{\bar{w}\bar{c}_P} \tag{A3}$$

$$\frac{P(E)}{P(ME)} = \frac{\bar{\varkappa}_E}{\bar{\varrho}''_E\bar{c}''} \tag{A4}$$

$$\frac{P(MC)}{P(C)} = \frac{\bar{\varrho}'_C\bar{c}'}{\bar{\varkappa}_C} \tag{A5}$$

The product of the left-hand sides of Eqs. (A2) to (A5) is equal to unity. Thus,

$$\frac{\bar{p}\bar{c}_T\bar{k}_{EC}}{\bar{r}\bar{c}_D\bar{w}\bar{c}_P} \cdot \frac{\bar{\varkappa}_E}{\varkappa_C} \cdot \frac{\bar{\varrho}'_C}{\bar{\varrho}''_E} = \frac{\bar{c}''}{\bar{c}'} = e^{zu_0}\,. \tag{A6}$$

Since any value of u_0 can be achieved by a suitable choice of c' and c'' and since the rate constants p, r, w, k_{EC}, $\varkappa_C$, $\varkappa_E$, ϱ'_C and ϱ''_E do not explicitly depend on c' and c'', Eq. (A6) must hold at any voltage u:

$$\frac{p\bar{c}_T k_{EC}}{r\bar{c}_D w\bar{c}_P} \cdot \frac{\varkappa_E}{\varkappa_C} \cdot \frac{\varrho'_C}{\varrho''_E} = e^{zu}\,. \tag{A7}$$

Combining Eq. (A7) with Eqs. (1)–(3), (6), (8) and (9) then yields Eq. (7).

Appendix B

Calculation of the fundamental solutions $\Omega_{ij}(t)$ and derivation of Eqs. (32) and (36)–(39)

In the following we describe the transient behaviour of the ensemble averages $\langle N_i(t) \rangle$ using the assumption that the rate constant of the association-dissociation reactions $M + C \rightleftarrows MC$ and $M + E \rightleftarrows ME$ are much larger than the rate constants of the conformational transitions $MC \rightleftarrows ME$ and $C \rightleftarrows E$:

$$\varkappa_C, \varkappa_E, \lambda_C, \lambda_E \gg k_{CE}, k_{EC}, \overset{*}{k}_{CE}, \overset{*}{k}_{EC}\,. \tag{B1}$$

Under this condition the reactions $M + C \rightleftarrows MC$ and $M + E \rightleftarrows ME$ are always in equilibrium at the steady state. Denoting the steady-state values of $\langle N_i \rangle$ by N_i^s, the relationships

$$\frac{N_4^s}{N_1^s} = \frac{\varkappa_C}{\lambda_C} \equiv C\,; \qquad \frac{N_3^s}{N_2^s} = \frac{\varkappa_E}{\lambda_E} \equiv E \tag{B2}$$

hold (compare Fig. 1). Introducing $y \equiv \langle N_1 \rangle + \langle N_4 \rangle$, the quantities N_i^s are obtained from the steady-state condition

$$\frac{dy}{dt} = -\overset{*}{k}_{CE} \langle N_1 \rangle + \overset{*}{k}_{EC} \langle N_2 \rangle - k_{CE} \langle N_4 \rangle + k_{EC} \langle N_3 \rangle = 0 \tag{B3}$$

Using $\langle N_2 \rangle + \langle N_3 \rangle = N - y$ together with Eqs. (B2), one finds

$$N_1^s = N\sigma(\overset{*}{k}_{EC} + Ek_{EC})\,; \qquad N_4^s = CN_1^s \tag{B4}$$

$$N_2^s = N\sigma(\overset{*}{k}_{CE} + Ck_{CE})\,; \qquad N_3^s = EN_2^s \tag{B5}$$

$$\sigma \equiv [(1 + C)(\overset{*}{k}_{EC} + Ek_{EC}) + (1 + E)(\overset{*}{k}_{CE} + Ck_{CE})]^{-1}\,. \tag{B6}$$

If at time $t = 0$ the ensemble is perturbed by a sudden change of an external parameter, the association-dissociation reactions will quickly and independently relax toward new quasi stationary states, the time constants of these fast processes being given by

$$\tau_1 = \frac{1}{\varkappa_C + \lambda_C}\,; \qquad \tau_2 = \frac{1}{\varkappa_E + \lambda_E}\,. \tag{B7}$$

If $\langle N_i(0) \rangle \equiv \langle N_i^0 \rangle$ are the initial values immediately after the perturbation, the quasi-stationary values $\langle N_i^* \rangle$ which are reached at the end of the fast relaxation processes are given by the relation $\langle N_1^* \rangle + \langle N_4^* \rangle = \langle N_1^0 \rangle + \langle N_4^0 \rangle$ and $\langle N_2^* \rangle + \langle N_3^* \rangle = \langle N_2^0 \rangle + \langle N_3^0 \rangle$.

This yields:

$$\langle N_1^* \rangle = (\langle N_1^0 \rangle + \langle N_4^0 \rangle)/(1 + C)\,; \qquad \langle N_4^* \rangle = C\langle N_1^* \rangle \tag{B8}$$

$$\langle N_2^* \rangle = (\langle N_2^0 \rangle + \langle N_3^0 \rangle)/(1 + E)\,; \qquad \langle N_3^* \rangle = E\langle N_2^* \rangle \tag{B9}$$

According to Eq. (B3) (together with $\langle N_4 \rangle = C\langle N_1 \rangle$ and $\langle N_3 \rangle = E\langle N_2 \rangle$ the process is described by:

$$\frac{dy}{dt} = -(\overset{*}{k}_{CE} + Ck_{CE})\langle N_1 \rangle + (\overset{*}{k}_{EC} + Ek_{EC})\langle N_2 \rangle\,. \tag{B10}$$

Using the relation $y = (1 + C)\langle N_1 \rangle = N - (1 + E)\langle N_2 \rangle$ the solution of Eq. (B10) is obtained in the form

$$y(t) = [y(0) - y(\infty)]\exp(-t/\tau_3) + y(\infty) \tag{B11}$$

$$\tau_3 = \sigma(1 + C)(1 + E)\,. \tag{B12}$$

Introducing the notation

$$h_i \equiv \exp(-t/\tau_i) \tag{B13}$$

$$x_i(t) \equiv \langle N_i(t) \rangle - N_i^s\,; \qquad x_{io} \equiv x_i(0) \tag{B14}$$

the total solution (including fast and slow processes) reads

$$x_1(t) = [(Cx_{10} - x_{40})h_1 + (x_{10} + x_{40})h_3]/(1 + C) \tag{B15}$$

$$x_2(t) = [(Ex_{20} - x_{30})h_2 + (x_{20} + x_{30})h_3]/(1 + E) \tag{B16}$$

$$x_3(t) = [(x_{30} - Ex_{20})h_2 + E(x_{20} + x_{30})h_3]/(1 + E) \tag{B17}$$

$$x_4(t) = [(x_{40} - Cx_{10})h_1 + C(x_{10} + x_{40})h_3]/(1 + C) \tag{B18}$$

The fundamental solutions $\Omega_{ij}(t)$ are defined by

$$\Omega_{ij}(t) \equiv [\langle N_i(t) \rangle - N_i^s] \text{ for } \langle N_j(0) \rangle = 1,\ \langle N_{k \neq j}(0) \rangle = 0\,. \tag{B19}$$

This is equivalent to

$$\Omega_{ij}(t) \equiv x_i(t) \text{ for } x_j(0) = 1 - N_j^s/N,\ x_{k \neq j}(0) = -N_k^s/N \tag{B20}$$

where N_j^s/N and N_k^s/N have to be taken from Eqs. (B4) and (B5). This yields:

$$\Omega_{11} = Ch_1/(1 + C) + [1/(1 + C) - \sigma(\overset{*}{k}_{EC} + Ek_{EC})]h_3 \tag{B21}$$

$$\Omega_{12} = \Omega_{13} = -\sigma(\overset{*}{k}_{EC} + Ek_{EC})h_3 \tag{B22}$$

$$\Omega_{21} = -\sigma(\overset{*}{k}_{CE} + Ck_{CE})h_3 \tag{B23}$$

$$\Omega_{22} = Eh_2/(1 + E) + [1/(1 + E) - \sigma(\overset{*}{k}_{CE} + Ck_{CE})]h_3 \tag{B24}$$

and so forth.

Under the condition $\gamma = \varepsilon = \eta = 0, \theta = z$ all terms in Eq. (30) except those with i,j and k,l equal to 1, 2 or 2, 1 vanish. Introducing N_j^s from Eqs. (B4) and (B5) into Eq. (30) together with $M_{12} = \overset{*}{k}_{EC}$, $M_{21} = \overset{*}{k}_{CE}$ and using the relation

$$\int_0^\infty \exp(-t/\tau)\cos\omega t\,dt = \frac{\tau}{1 + \omega^2\tau^2} \tag{B25}$$

yields Eqs. (32) and (36)–(39).

A further case in which a simple expression for $S_I(\omega)$ is obtained is when in the transition $C \rightleftarrows E$, the charge displacement is small and the binding site does not move appreciably. Under this condition the relations $\eta \approx \theta \approx 0$ and $\gamma + \varepsilon \approx 1$ hold. The quantities S_I^∞, A_1, A_2 and A_3 of Eq. (32) then assume the form

$$A_1 = -4\,Nz^2 e_o^2 \gamma^2 \sigma \lambda_C C(k_{EC}^* + Ek_{EC}) \tag{B26}$$

$$A_2 = -4\,Nz^2 e_0^2 \varepsilon^2 \sigma \lambda_E E(k_{CE}^* + Ck_{CE}) \tag{B27}$$

$$A_3 = 0 \tag{B28}$$

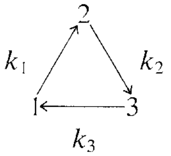
$$S_I^\infty = -A_1 - A_2\,. \tag{B29}$$

In this case $S_I(0)$ is zero, meaning that mainly high-frequency noise is observed.

Appendix C

Light-driven (irreversible) ion pumps

We consider a cyclic reaction among three states 1, 2, and 3 with virtually irreversible transitions:



The cycle is associated with the transport of an ion of charge ze_0 across the membrane. If reaction 1 → 2 is driven by light, the rate constant k_1 may be assumed to be proportional to the light intensity J:

$$k_1 = \gamma J\,. \tag{C1}$$

In the notation which we use in the following, ijk stands for 123, or 231, or 312 (cyclic permutation). The transient behaviour of the system is described by (with the same abbreviations as used in Appendix B):

$$\frac{dx_i}{dt} = -k_i x_i + k_k x_k\,. \tag{C2}$$

The solution reads:

$$\begin{aligned} x_i(t) = {} & \frac{1}{\sqrt{W}}\,[(k_i + \lambda_2)x_{jo} - (k_j + \lambda_1)x_{ko}]\exp(\lambda_1 t) \\ & + \frac{1}{\sqrt{W}}\,[-(k_i + \lambda_1)x_{jo} + (k_j + \lambda_2)x_{ko}]\exp(\lambda_2 t) \end{aligned} \tag{C3}$$

$$\lambda_1 = -\frac{1}{\tau_1} = -\frac{1}{2}\,(k_1 + k_2 + k_3 - \sqrt{W}) \tag{C4}$$

$$\lambda_2 = -\frac{1}{\tau_2} = -\frac{1}{2}\,(k_1 + k_2 + k_3 + \sqrt{W}) \tag{C5}$$

$$W \equiv k_1^2 + k_2^2 + k_3^2 - 2(k_1k_2 + k_1k_3 + k_2k_3)\,. \tag{C6}$$

It is seen from Eq. (C6) that W can become negative for certain combinations of the k_i. In this case the eigenvalues λ_1 and λ_2 are complex, meaning that the system carries out damped oscillations after a perturbation (Frehland and Läuger 1974). In the following we consider only situations with $W > 0$. The fundamental solutions $\Omega_{ij}(t)$ can be obtained from Eq. (C3), as discussed in Appendix B, using the stationary values N_i^s:

$$N_i^s = Nk_o/k_i \tag{C7}$$

$$\frac{1}{k_o} \equiv \frac{1}{k_1} + \frac{1}{k_2} + \frac{1}{k_3}\,. \tag{C8}$$

Introducing the electrostatic coefficients α_i:

$$q_{21} = ze_o\alpha_1\,, \quad q_{32} = ze_o\alpha_2\,, \quad q_{13} = ze_o\alpha_3 \tag{C9}$$

$$\alpha_1 + \alpha_2 + \alpha_3 = 1 \tag{C10}$$

the spectral intensity of current noise is obtained in the form

$$S_I(\omega) = S_I^\infty + \frac{A_1}{1 + \omega^2\tau_1^2} + \frac{A_2}{1 + \omega^2\tau_2^2} \tag{C11}$$

$$S_I^\infty \equiv S_I(\infty) = 2\,ze_o\bar{I}\,(\alpha_1^2 + \alpha_2^2 + \alpha_3^2) \tag{C12}$$

$$A_1 = -2\,ze_o\bar{I}\,\frac{k_o}{\lambda_1\sqrt{W}}[2\lambda_2(\alpha_1^2 + \alpha_2^2 + \alpha_3^2) + B_1] \tag{C13}$$

$$A_2 = 2\,ze_o\bar{I}\,\frac{k_o}{\lambda_2\sqrt{W}}[2\lambda_1(\alpha_1^2 + \alpha_2^2 + \alpha_3^2) + B_2] \tag{C14}$$

$$\begin{aligned} B_{1/2} = \sum_{ijk}\alpha_i\alpha_j \Bigg[& \frac{k_j}{k_i}(k_k \pm \sqrt{W}) + \frac{k_j}{k_k}(k_i \pm \sqrt{W}) \\ & + (k_i + k_k \mp \sqrt{W}) - \frac{k_j^2}{k_0} + 2\,\frac{k_ik_k}{k_j}\Bigg]\,. \end{aligned} \tag{C15}$$

The upper sign in $B_{1/2}$ refers to B_1. The summation has to be carried out over ijk = 123, 231 and 312. As before, $\bar{I}$ is the mean current:

$$\bar{I} = ze_oNk_o \tag{C16}$$

Equation (C11) for the spectral intensity $S_I(\omega)$ has the same form as Eq. (32). It may be shown from Eqs. (C11) to (C15) that the low-frequency limit of S_I is given by:

$$S_I(0) = 2\,ze_o\bar{I}\cdot\frac{(k_1k_2)^2 + (k_1k_3)^2 + (k_2k_3)^2}{(k_1k_2 + k_1k_3 + k_2k_3)^2}\,. \tag{C17}$$

Comparison with Eq. (C12) shows that $S_I(\infty)$ may be smaller or larger than $S_I(0)$, depending on the values of the rate constants k_i and the electrostatic coefficients α_i.

At low light intensity, where k_1 is much smaller that k_2 and k_3, the time constants τ_i and the amplitudes A_i become

$$\tau_1 = 1/k_2\,; \qquad \tau_2 = 1/k_3 \tag{C18}$$

$$A_1 = 4\, ze_o\bar{I}\, \alpha_3[\alpha_2 + \alpha_1 k_2/(k_2 - k_3)] \tag{C19}$$

$$A_2 = 4\, ze_o\bar{I}\, \alpha_1[\alpha_2 + \alpha_3 k_3/(k_3 - k_2)]\,. \tag{C20}$$

Furthermore, according to Eq. (C17) the low-frequency limit of S_I is given by Schottky's relation for a shot-noise source:

$$S_I(0) = 2\, ze_o\bar{I}\,. \tag{C21}$$

The same result as represented in Eqs. (C18)–(C21) may be obtained by an entirely different method, using the generalized Carson theorem (to be published).

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