Eur Biophys J (1985) 11:167–178

European Biophysics Journal

Non-equilibrium voltage noise generated by ion transport through pores

E. Frehland* and P. Solleder

Fakultäten für Biologie und Physik, Universität Konstanz, Postfach 5560, D-7750 Konstanz, Federal Republic of Germany

Received June 19, 1984/Accepted October 29, 1984

Abstract. In this paper, we describe a systematic approach to the theoretical analysis of non-equilibrium voltage noise that arises from ions moving through pores in membranes. We assume that an ion must cross one or two barriers in the pore in order to move from one side of the membrane to the other. In our analysis, we consider the following factors: a) surface charge as a variable in the kinetic equations, b) linearization of the kinetic equations, c) master equation approach to fluctuations. To analyze the voltage noise arising from ion movement through a two barrier (i.e., one binding site) pore, we included the effects of ions in the channel's interior on the voltage noise. The current clamp is considered as a white noise generating additional noise in the system. In contrast to what is found for current noise, at low frequencies the voltage noise intensity is reduced by increasing voltage across the membrane. With this approach, we demonstrate explicity for the examples treated that, apart from additional noise generated by the current clamp, the non-equilibrium voltage fluctuations can be related to the current fluctuations by the complex admittance.

Key words: Voltage noise, steady-state fluctuations, current clamp, ion pores, Nyquist relation

1. Introduction

In the last 15 years the analysis of membrane noise has become a well established method in the study of ion transport through biological membranes (Verveen and De Felice 1974; Chen 1978; for further references see De Felice 1981). The need for a satisfactory analysis of noise measurements, and the fact that the most interesting states to be analyzed are states far from thermodynamic equilibrium, has stimulated theoretical work on non-equilibrium fluctuations in membranes. Most of this experimental and theoretical work has been concerned with *current* fluctuations. It has been possible to develop a theoretical formalism (Frehland 1982) by which current fluctuations in membranes can be described very generally. The application to a number of different charge transport processes, e.g., carrier-mediated ion transport, transport through pores, channels with open-close kinetics or electrogenic pumps (Läuger 1984) has shown that such directed (vectorial) transport processes exhibit non-equilibrium fluctuation properties which are basically different from steady-state fluctuations of (scalar) quantities such as, for example, density fluctuations. An important finding is that it is impossible to generalize the Nyquist relation (fluctuation dissipation theorem) for non-equilibrium states (Frehland 1980). This theoretical result has been confirmed by experimental studies (Fishman et al. 1983; Kolb and Frehland 1980).

There is also a need for a theoretical description of voltage fluctuations. Apart from the general interest in finding a satisfactory analysis for this type of electric fluctuation, the occurrence of voltage fluctuations may be important for the control of processes in biological membranes on the molecular level. On the one hand the fluctuations give rise to a limit in the sensitivity of such processes. On the other hand, processes may be stochastically switched on or off by fluctuations. Furthermore, there is a need to show which types of information can be obtained from voltage noise experiments.

In this paper we start a systematic approach to the theoretical treatment of voltage noise at non-equilibrium steady states. At equilibrium, the spectral densities $G_{\Delta J}(\omega)$, $G_{\Delta V}(\omega)$ of current and voltage fluctuations are related to the complex admittance $Y(\omega)$ through the Nyquist relations (Nyquist 1928; Callen and Welton 1951; Callen and Greene 1952; Bell 1960).

* To whom offprint requests should be addressed

$$G_{\Delta J}(\omega) = 4\,kT\,\mathrm{Re}\,Y(\omega) \tag{1.1}$$

$$G_{\Delta V}(\omega) = 4\,kT\,\mathrm{Re}\left(\frac{1}{Y(\omega)}\right). \tag{1.2}$$

(J: electric current, V: voltage, ω: circular frequency, k: Boltzmann constant, T: absolute temperature).

Hence the spectral densities are related by the expression

$$G_{\Delta V}(\omega) = G_{\Delta J} \cdot \frac{1}{|Y(\omega)|^2}. \tag{1.3}$$

Though the Nyquist relations are not valid under non-equilibrium conditions it is nevertheless not clear if the relation (1.3), between current and voltage noise, is invalid. If Eq. (1.3) could be proved, the theoretical description of non-equilibrium voltage noise could be based on the well-developed current noise approach and raises no further fundamental problems. Indeed, based mainly on the linear theory of electric networks it has been argued that Eq. (1.3) might generally be valid (Verveen and De Felice 1974; De Felice 1981).

Starting with the most simple example of ions crossing the membrane by jump diffusion over one barrier we derive a basic concept for the description of voltage noise: a) introduction and theoretical treatment of current clamp, b) inclusion of surface charge as a further variable in the kinetic equations, c) dependence of voltage on charge densities and membranes capacitance, d) linearisation of the kinetic equations via the linearisation of the voltage dependent rate constant and e) calculation of voltage noise with the use of well established approaches to scalar density fluctuations. This approach to voltage noise is basically different from the approach to current noise. Nevertheless, in the examples, treated, one-barrier pores and pores with one binding site, the relation in Eq. (1.3) is valid, if one considers only the noise inherent to the system and neglects additional noise generated by the current clamp.

In contrast to current noise, the voltage noise intensity at low frequencies is reduced for increasing voltage, behaviour which seems to be typical for voltage noise in rigid transport system, and which is shown to be valid for voltage noise generated by the current clamp.

2. Voltage noise for a simple one-barrier model

2.1 Current clamp

While the fluctuations of electric current are usually analyzed under the condition of *constant voltage* applied to the system, for definition and analysis of

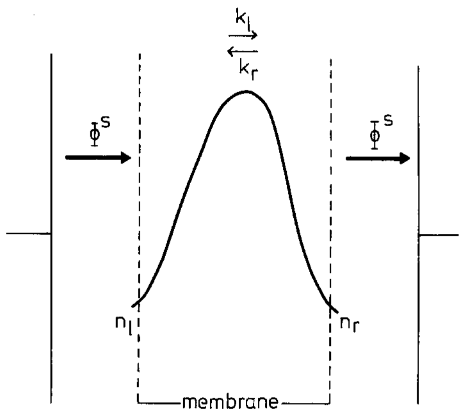

Fig. 1. One barrier model of the membrane under non-equilibrium current clamp, generating a constant flux, ϕ^s, of charges to the left and from the right side of the membrane

voltage fluctuations we have to introduce the *constant current* condition. Thus, in a voltage noise experiment at non-equilibrium steady-state a constant net flux, ϕ^s, of charge (ions) has to be delivered to one side and a constant efflux has to be drained from the other side of the transport system (membrane) (c.f. Fig. 1). Because of the discrete nature of charge carriers this constant current source may exhibit its noise in addition to the transport system being analyzed. The most realistic way is to treat the current clamp as a white voltage noise source because the constant current is imposed on the system independently of the (transport) processes occurring within the system to be analyzed. Below we shall see that the current clamp noise yields an additive term to the total voltage noise.

2.2 *Surface density of charge carriers and voltage*

In the simple case that is the subject of this section the transport of charges is assumed to involve jump diffusion over one barrier and the charges are located at both sides of the membranes (c.f. Fig. 1). The voltage, V, across the membrane is composed of a constant voltage, V^s, and a fluctuating part ΔV:

$$V = V^s + \Delta V. \tag{2.1}$$

Introducing the membrane capacitance C, the voltage, V, is directly related to the difference

$$n = n_l - n_r \tag{2.2}$$

between surface densities n_r and n_l of the charges q on the right and left sides of the membrane, respectively.

$$V = \frac{q}{2\,C} \cdot n. \tag{2.3}$$

Then the fluctuating part, ΔV of V, is given by the difference Δn from the steady-state value n^s of n.

$$\Delta V = \frac{q}{2\,C}\Delta n\,. \tag{2.4}$$

2.3 Kinetic equations for surface density

According to Eq. (2.4) the voltage fluctuations are linearly coupled to the fluctuations in the surface density of charges. The equation governing the time dependent averaged (expected) behavior $\langle \Delta n \rangle$ of Δn is a standard rate equation:

$$\frac{d\,\langle \Delta n \rangle}{dt} = -2\,(k_l \langle n_l \rangle - k_r\,\langle n_r \rangle) + 2\,\phi^s\,. \tag{2.5}$$

The first two terms on the RHS of Eq. (2.5) are the rates for jumps to the right and left, respectively. The last term takes into account the constant fluxes, ϕ^s, to and from the membrane on the left and right sides, generated by the current clamp. The rate constants are voltage dependent:

$$k_l = \bar{k}_l \cdot e^{\frac{\Delta u}{2}}\,, \qquad k_r = \bar{k}_r \cdot e^{-\frac{\Delta u}{2}}$$

$$\Delta u = \frac{q}{kT}\Delta V\,, \qquad \bar{k}_l = k_l(V^s)\,, \qquad \bar{k}_r = k_r(V^s)\,. \tag{2.6}$$

According to Eq. (2.4) the voltage dependence can be expressed by Δn. Linearization of Eq. (2.6) for small Δu yields

$$k_l \approx \bar{k}_l(1 + q^2\,\alpha\,\Delta n)$$

$$k_r \approx \bar{k}_r(1 - q^2\,\alpha\,\Delta n) \tag{2.7a}$$

with $\alpha = \dfrac{1}{4\,kTC}$.

Left and right surface densities are given by

$$n_l = \bar{n}_l\left(1 + \frac{\Delta n}{\bar{n}_l}\right), \qquad n_r = \bar{n}_r\left(1 - \frac{\Delta n}{\bar{n}_r}\right). \tag{2.7b}$$

In the following we shall neglect $\dfrac{\Delta n}{n_l}$ and $\dfrac{\Delta n}{n_r}$. This is justified if in Eqs. (2.7a) and (2.7b) $\dfrac{\Delta n}{\bar{n}}$ is small compared with $q^2\alpha \cdot \Delta n$ and hence for the surface densities, c_n, of ions [cm^{-2}] on the membrane surfaces the following relation holds

$$c_n\,[\text{cm}^{-2}] \gg \frac{1}{q^2\alpha} \approx 6 \cdot 10^{11}\,[\text{cm}^{-2}]\,. \tag{2.8}$$

We have set a value for the membrane capacitance of $\sim 10^{-6}$ [$F \cdot \text{cm}^{-2}$]. Assuming maximum transport rates of $\sim 10^9\,\text{s}^{-1}$ per channel the corresponding diffusion length is $\sim 1.5 \cdot 10^{-7}$ cm. Then for ionic concentrations of $\sim 10^{-1}\,\text{M}^{-1}$ the number of ions available per cm^2 membrane area is indeed ~ 2 orders of magnitude greater than $6 \cdot 10^{11}$.

Furthermore, we take into account the fact that the following relation holds in the stationary state

$$\phi^s = \bar{k}_l\bar{n}_l - \bar{k}_r\bar{n}_r\,. \tag{2.9}$$

Then, we get from Eq. (2.5) the linearized kinetic equations

$$\frac{d\,\langle \Delta n \rangle}{dt} = -\,K \cdot \langle \Delta n \rangle\,,$$

$$K = 2\,q^2\alpha\,(\bar{k}_l\bar{n}_l + \bar{k}_r\bar{n}_r) \tag{2.10}$$

with the solution

$$\langle \Delta n(t) \rangle = \langle \Delta n(0) \rangle\,\Omega(t)\,, \quad \Omega(t) = \mathrm{e}^{-t/\tau}\,,$$

$$\frac{1}{\tau} = \frac{q^2}{2\,kTC}(\bar{k}_l\bar{n}_l + \bar{k}_r\bar{n}_r)\,. \tag{2.11}$$

2.4 Autocorrelation, variance, Fokker-Planck moment

The steady-state fluctuations of (scalar) quantities in discrete systems can be calculated with the use of a general approach developed by Lax (1960), Van Vliet and Fassett (1965) and others. As far as is necessary this approach is briefly summarized in Appendix A1.

According to Eq. (A.8) the autocorrelation function $C_{\Delta n}(t)$ of the fluctuating quantity, Δn, is given by the fundamental solution Ω in Eq. (2.11) of the linearized kinetic Eq. (2.10):

$$C_{\Delta n}(t) = \langle \Delta n(0)\,\Delta n(t) \rangle = \Omega(t)\,\sigma^2_{\Delta n}$$

and the variance $\sigma^2_{\Delta n}$ is given by:

$$\sigma^2_{\Delta n} = \langle \Delta n\,\Delta n \rangle\,. \tag{2.12}$$

The variance is determined with Eq. (A.6) by the Fokker-Planck moment, $B(n^s)$, of the steady-state

$$\sigma^2_{\Delta n} = \frac{B(n^s)}{2\,K} \tag{2.13}$$

with

$$B(n^s) = \sum_{\Delta n} \Delta n^2\,Q(n^s + \Delta n\,; n^s)\,. \tag{2.14}$$

$Q(n^s + \Delta n\,; n^s)$ are the transition probabilities per unit time from the steady-state to states $n^s + \Delta n$. We have to sum over all states, $n^s + \Delta n$, with nonvanishing $Q(n^s + \Delta n\,; n^s)$.

First, transitions from the steady-state may be generated by jumps of charges to the right and to the left, each jump connected with a change, $\Delta n = -2$ or $\Delta n = +2$. Therefore

$$Q(\Delta n = +2; n^s) = \bar{k}_r \bar{n}_r ,$$

$$Q(\Delta n = -2; n^s) = \bar{k}_l \bar{n}_l . \tag{2.15}$$

Second, the current clamp may generate transitions from the steady-state. If ϕ^s is generated by discrete jumps of charges q to the left side and away from the right side (unidirectional fluxes), the corresponding change, Δn, is $+1$, with a transition probability:

$$Q(\Delta n = +1; n^s) = 2\,\phi^s . \tag{2.16}$$

Using Eqs. (2.15) and (2.16) the Fokker-Planck moment $B(n^s)$ follows from Eq. (2.14)

$$B(n_s) = 4(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r) + 2\,\phi^s \tag{2.17}$$

and the variance is obtained from Eqs. (2.13), (2.10) and (2.17)

$$\sigma^2_{\Delta n} = \frac{1}{q^2 \alpha} + \frac{\phi^s}{2\,q^2 \alpha(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r)} . \tag{2.18}$$

Thus, the autocorrelation function of fluctuations, Δn, in Eq. (2.12) is completely determined by Eqs. (2.11) and (2.18).

Because of the linear coupling of voltage to n, according to Eqs. (2.3) and (2.4), the autocorrelation function of voltage fluctuations, $C_{\Delta V}(t)$, is given by $C_{\Delta n}(t)$ through:

$$C_{\Delta V}(t) = \frac{q^2}{4\,C^2}\, C_{\Delta n}(t) . \tag{2.19}$$

Hence we get from Eqs. (2.19), (2.11), (2.18), and (2.7)

$$C_{\Delta V}(t) = \mathrm{e}^{-t/\tau} \cdot \sigma^2_{\Delta V} ,$$

$$\sigma^2_{\Delta V} = \frac{kT}{C}\left(1 + \frac{\phi^s}{2(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r)}\right) . \tag{2.20}$$

The spectral density, $G_{\Delta V}(\omega)$, follows from the Wiener-Khintchine relations by Fourier transformation of $C_{\Delta V}(t)$

$$G_{\Delta V}(\omega) = 4 \int_0^\infty C_{\Delta V}(t) \cos\, \omega t dt . \tag{2.21}$$

Therefore:

$$G_{\Delta V}(\omega) = \sigma^2_{\Delta V} \cdot \frac{4\,\tau}{1 + \omega^2 \tau^2}$$
$$= \frac{kT}{C}\left(1 + \frac{\phi^s}{2(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r)}\right) \frac{4\,\tau}{1 + \omega^2 \tau^2} . \tag{2.22}$$

The voltage noise is composed of two terms, the first term is generated by the transport system and the second by the current clamp. Generally, this additional second term depends on the special properties of the current clamp. In Sect. 2.6 it will be discussed further.

2.5 *Comparison with current noise*

The spectral density of current noise, $G_{\Delta J}(\omega)$, in this simple case is (Frehland 1982)

$$G_{\Delta J}(\omega) = 2\,q^2 (\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r) . \tag{2.23}$$

It is frequency-independent white noise, while the frequency dependence of voltage noise comes from the dependence of voltage on the capacitance C. In order to examine the validity or invalidity of Eq. (1.3) we need the complex admittance $Y(\omega)$, which can be determined by calculating the linear current response, J, to a (small) periodic voltage applied to the system in addition to stationary voltage, V^s:

$$V = V^s + \varepsilon_0\, \mathrm{e}^{\mathrm{i}\omega t} \tag{2.24}$$

$$J = J^s + Y(\omega)\, \varepsilon_0\, \mathrm{e}^{\mathrm{i}\omega t} . \tag{2.25}$$

The current $J(t)$ is given by the net flux over the central barrier and by the membrane capacitance

$$J = q(k_l \langle n_l \rangle - k_r \langle n_r \rangle) + C\frac{dV}{dt} . \tag{2.26}$$

Introducing the voltage dependence of the rate constants [Eq. (2.6)] the linear response of J results in an admittance

$$Y(\omega) = (\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r)\frac{q^2}{2\,kT} + \mathrm{i}\omega C , \quad \mathrm{i}^2 = -1 \tag{2.27}$$

and with Eq. (2.11)

$$|Y(\omega)|^2 = \frac{C^2}{\tau^2}(1 + \omega^2 \tau^2) . \tag{2.28}$$

Hence we get

$$\frac{G_{\Delta J}(\omega)}{|Y(\omega)|^2} = \frac{kT}{C}\left(\frac{4\,\tau}{1 + \omega^2 \tau^2}\right) . \tag{2.29}$$

Comparison with Eq. (2.22) shows that, apart from the additional noise generated by the current clamp, the relation (1.3) is satisfied.

2.6 *The noise contribution of the current clamp*

The additional contribution to the variance of voltage noise that the current clamp imposes on the transport system comes in via the Fokker-Planck moments and strongly depends on the special properties of the clamp. If for instance the net fluxes, ϕ^s, on both sides are composed of unidirectional fluxes ϕ', ϕ'' in both directions

$$\text{left:} \quad \phi^s = \phi_l' - \phi_l''$$

$$\text{right:} \quad \phi^s = \phi_r' - \phi_r'' \tag{2.30}$$

the transition probabilities in Eq. (2.16) become

$$Q(\Delta n = +1; n^s) = \phi_l' + \phi_r'$$

$$Q(\Delta n = -1; n^s) = \phi_l'' + \phi_r'' . \tag{2.31}$$

The Fokker-Planck moment is

$$B(n^s) = 4(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r) + \phi_l' + \phi_l'' + \phi_r' + \phi_r'' . \tag{2.32}$$

Hence in Eqs. (2.18), (2.20) etc., $2\,\phi^s$ is to be replaced by the sum $(\phi_l' + \phi_l'' + \phi_r' + \phi_r'')$.

Furthermore, by step-wise diffusion to (from) the membrane surface the discrete charges, q, might effect a change of voltage, V, in fractions of $\frac{q}{2\,C} \cdot \Delta n$. For example, if on both sides Δn is divided into N equal steps in one direction, Eq. (2.16) is replaced by

$$Q = \left(\Delta n = \frac{1}{N};\ n^s\right) = N \cdot \phi^s . \tag{2.33}$$

And from Eq. (2.14) it follows that

$$B(n^s) = 4(\bar{k}_l \bar{n}_l + \bar{k}_r \bar{n}_r) + \frac{1}{N} \phi^s . \tag{2.34}$$

Therefore, with this assumption, the additional contribution to voltage noise from the current clamp is proportional to $\frac{1}{N}$. It vanishes in the limit $N \to \infty$, where the charge carriers diffusing to (from) the membrane cause a continuous change of membrane voltage.

It is interesting to note that in the limiting case $N \to \infty$ we have done a stochastic analysis of a function of n, which is a superposition of two parts: a step function with random steps, $\Delta n = \pm 2$, and averaged negative slope, $-2\,\phi^s$, and a (deterministic) straight line with slope $+2\,\phi^s$. Both parts are non-stationary, but the superposition results in a stationary random process.

3. Voltage noise in pores with one binding site

In this section we consider the voltage noise generated by ion transport through pores with one binding site and shall investigate the way in which the internal structure of the system modifies the voltage noise. The current fluctuations in such systems have been discussed extensively (Läuger 1975; Frehland 1978).

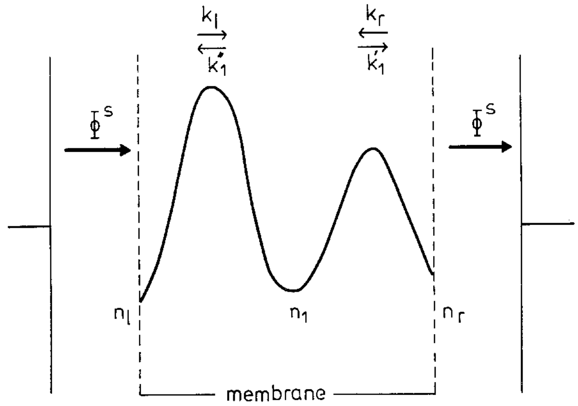

Fig. 2. Two barrier model for pores with one binding site, with the membrane under constant current clamp

We first treat the case with vanishing ionic interactions where the ionic motion is free jump diffusion over the two barriers within the system (c.f. Fig. 2). The current clamp is treated as described in the preceding section. It generates an additional noise term, which can be discussed in complete analogy to Sect. 2.

3.1 Voltage

The voltage across the membrane is given not only by the charges at the membrane surfaces but also by the charges in the internal binding site. If Δn_1 denotes the deviation from the steady-state density, n_1^s, of charges, q, in this site the relation (2.4) for ΔV has to be replaced by

$$\Delta V = \frac{1}{2\,C}[q\Delta n + (\gamma_2 - \gamma_1)\,\Delta n_1] \tag{3.1}$$

with

$$\gamma_1 + \gamma_2 = q . \tag{3.2}$$

Equation (3.1) can be derived as follows: If an ion jumps from the left side into the binding site, the voltage is changed by

$$\Delta V_1 = -\frac{\gamma_1}{C} \Delta n_1 , \qquad \Delta n_1 = +1 . \tag{3.3a}$$

Correspondingly, the voltage change, ΔV_2, arising from an ionic jump from the right side into the membrane is

$$\Delta V_2 = +\frac{\gamma_2}{C} \Delta n_1 , \qquad \Delta n_1 = +1 . \tag{3.3b}$$

Because the transport of an ion across the membrane is connected with a voltage change

$$\Delta V_1 - \Delta V_2 = -\frac{q}{2\,C}\cdot \Delta n\,, \qquad \Delta n = -2$$

relation (3.2) is valid. Furthermore, ΔV_1 and ΔV_2 are connected with changes, $\Delta n = +1, -1$, respectively. Hence with Eq. (3.2) we can write for Eq. (3.3)

$$\Delta V_1 = \frac{q}{2\,C}\Delta n + \frac{1}{2\,C}(\gamma_2 - \gamma_1)\,\Delta n_1, \qquad \Delta n = +1, \quad \Delta n_1 = +1$$

$$\Delta V_2 = \frac{q}{2\,C}\,\Delta n + \frac{1}{2\,C}\,(\gamma_2 - \gamma_1)\,\Delta n_1, \qquad \Delta n = -1, \quad \Delta n_1 = +1\,. \tag{3.4}$$

For jumps from the binding site to the left and to the right the corresponding relations hold. Therefore Eq. (3.1) is generally valid. We note that the constant factor γ_1, γ_2 are the same as we have used in the theoretical description of current noise (Frehland 1978). In the current noise experiment under voltage clamp conditions an ionic jump over the first barrier generates a current pulse proportional to γ_1 and similarly for the second barrier.

The constants γ_1, γ_2 depend on the geometric and dielectric properties of the system. The relation of Eq. (3.1) for voltage, and further relations, are simplified in the symmetric case, $\gamma_1 = \gamma_2$.

3.2 Kinetic equations

In contrast to Sect. 2 we now arrive at two kinetic equations, one for the difference, $\langle n\rangle$, of surface densities and another for the number, $\langle n_1\rangle$, of ions in the binding site. One gets

$$\frac{d\,\langle n\rangle}{dt} = -\,(k_l\langle n_l\rangle - k_r\langle n_r\rangle) + k_1''\,\langle n_1\rangle - k_1'\langle n_1\rangle + 2\,\phi^s$$

$$\frac{d\,\langle n_1\rangle}{dt} = -\,(k_1'' + k_1')\,\langle n_1\rangle + k_l\langle n_l\rangle + k_r\langle n_r\rangle\,. \tag{3.5}$$

The voltage dependence of the rate constants depends on the fractions $\frac{\gamma_1}{q}\Delta V$, $\frac{\gamma_2}{q}\Delta V$ of voltage over the first and second barrier, respectively.

$$k_l = \bar{k}_l\,e^{\gamma_1\Delta u}\,, \qquad k_1'' = \bar{k}_1''\,e^{-\gamma_1\Delta u}\,,$$

$$k_1' = \bar{k}_1'\,e^{\gamma_2\Delta u}\,, \qquad k_r = \bar{k}_r\,e^{-\gamma_2\Delta u} \tag{3.6}$$

with Δu as in Eq. (2.6) and $\bar{k}_l$, $\bar{k}_r$, $\bar{k}_1'$, $\bar{k}_1''$ denoting the steady-state values ($\Delta u = 0$) of rate constants. With (3.1), linearization, and α as in Eq. (2.7) we get the linearized voltage dependences

$$k_l \approx \bar{k}_l\;[1 + \gamma_1\alpha q\Delta n - \gamma_1\alpha(\gamma_1 - \gamma_2)\,\Delta n_1]$$

$$k_r \approx \bar{k}_r\;[1 - \gamma_2\alpha q\Delta n + \gamma_2\alpha(\gamma_1 - \gamma_2)\,\Delta n_1]$$

$$k_1'' \approx \bar{k}_1''\,[1 - \gamma_1\alpha q\Delta n + \gamma_1\alpha(\gamma_1 - \gamma_2)\,\Delta n_1]$$

$$k_1' \approx \bar{k}_1'\;[1 + \gamma_2\alpha q\Delta n - \gamma_2\alpha(\gamma_1 - \gamma_2)\,\Delta n_1]\,.$$

This yields, as in the preceding section for $\langle\Delta n\rangle$, the linearized kinetic equations for $\langle\Delta n\rangle$ and $\langle\Delta n_1\rangle$, which form the basis for the analysis of voltage noise:

$$\frac{d\langle\Delta n\rangle}{dt} = -\,q\,[m_1 + m_2]\,\langle\Delta n\rangle + \{(\gamma_1 - \gamma_2)\,[m_1 + m_2] - (\bar{k}_1' - \bar{k}_1'')\}\,\langle\Delta n_1\rangle$$

$$\frac{d\langle\Delta n_1\rangle}{dt} = q\,[m_1 - m_2]\,\langle\Delta n\rangle - \{(\gamma_1 - \gamma_2)\,[m_1 - m_2] - (\bar{k}_1' + \bar{k}_1'')\}\,\langle\Delta n_1\rangle$$

with

$$m_1 = \alpha\gamma_1(\bar{k}_l\bar{n}_l + \bar{k}_1''\bar{n}_1)$$

$$m_2 = \alpha\gamma_2(\bar{k}_r\bar{n}_r + \bar{k}_1'\bar{n}_1) \tag{3.8}$$

or in matrix notation

$$\frac{d\langle\alpha\rangle}{dt} = -\mathbf{K}\cdot\langle\alpha\rangle \tag{3.9}$$

with the vector α

$$\alpha = \begin{pmatrix}\Delta n\\ \Delta n_1\end{pmatrix} \tag{3.10}$$

and the matrix of coefficients $\mathbf{K}$ to be seen from Eq. (3.8).

3.3 Fluctuations

As in the preceding section, for the calculation of voltage noise the approach summarized in Appendix A1 is used. Because of Eqs. (3.1) and (3.2) the autocorrelation of voltage fluctuations is coupled to the correlation matrix $\langle\alpha(t)\,\alpha(0)\rangle$ as follows

$$C_{\Delta V}(t) = \frac{1}{4\,C^2}\,\{q^2\langle\Delta n(t)\,\Delta n(0)\rangle + (\gamma_2 - \gamma_1)^2\,\langle\Delta n_1(t)\,\Delta n_1(0)\rangle + q\,(\gamma_2 - \gamma_1)\,[\langle\Delta n(t)\,\Delta n_1(0)\rangle + \langle\Delta n_1(t)\,\Delta n(0)\rangle]\} \tag{3.11}$$

and the spectral density $G_{\Delta V}(\omega)$ is given by the spectral density matrix $\mathbf{G}_\alpha(\omega)$ through

$$G_{\Delta V}(\omega) = \frac{1}{4\,C^2}\{q^2[\mathbf{G}_\alpha(\omega)]_{11} - 2\,q(\gamma_1 - \gamma_2)[\mathbf{G}_\alpha(\omega)]_{12} + (\gamma_1 - \gamma_2)^2\,[\mathbf{G}_\alpha(\omega)]_{22}\}\,. \tag{3.12}$$

From the general formula of Eq. (A.10) follow the components of the symmetric spectral density matrix, $\mathbf{G}_\alpha(\omega)$, as functions of the matrix of coefficients, $\mathbf{K}$, and the variance matrix, $\boldsymbol{\sigma}^2$.

In Appendix A.2 the Fokker-Planck moments, $\mathbf{B}$, and the variances, $\boldsymbol{\sigma}^2$, are derived. As a result of rather lengthy calculations one gets the variance, $\sigma^2_{\Delta V}$, and spectral density, $G_{\Delta V}(\omega)$, of voltage fluctuations

$$\begin{aligned}\sigma^2_{\Delta V} = \frac{\delta}{2\,C^2}\{&B_{22}[(\gamma_1^2 + \gamma_2^2)\det\mathbf{K} + q^2(m_3^2 + m_4^2)]\\ &+ B_{12}q^2[(m_3^2 - m_4^2)\\ &- 2(\gamma_1 - \gamma_2)(m_1m_4 + m_2m_3)]\\ &+ \phi^s q^2[\det\mathbf{K} + (m_3 + m_4)^2]\}\end{aligned} \tag{3.13}$$

$$\begin{aligned}G_{\Delta V}(\omega) = \frac{1}{C^2\det(\mathbf{K}^2 + \omega^2\mathbf{E})}\cdot\{&B_{22}[q^2(m_3^2 + m_4^2)\\ &+ (\gamma_1^2 + \gamma_2^2)\omega^2] + B_{12}[q^2(m_3^2 - m_4^2)\\ &- (\gamma_1^2 - \gamma_2^2)\omega^2] + \phi^s q^2[(m_3 + m_4)^2 + \omega^2]\}\end{aligned} \tag{3.14}$$

with

$$m_3 = \bar{k}_1''$$

$$m_4 = \bar{k}_1'\,.$$

$$\delta^{-1} = 2(K_{11} + K_{22})\det\mathbf{K}\,.$$

3.4 Comparison with current fluctuations

The spectral density, $G_{\Delta J}(\omega)$, of current fluctuations has been calculated (Läuger 1975; Frehland 1978) to be

$$\begin{aligned}G_{\Delta J}(\omega) = 2[&\gamma_1^2(\bar{k}_l\bar{n}_l + \bar{k}_1''\bar{n}_1) + \gamma_2^2(\bar{k}_r\bar{n}_r + \bar{k}_1'\bar{n}_1)]\\ &+ (\gamma_1\bar{k}_l\bar{n}_l - \gamma_2\bar{k}_r\bar{n}_r)(\gamma_2\bar{k}_1' - \gamma_1\bar{k}_1'')\frac{4\,\tau}{1 + \omega^2\tau^2}\end{aligned} \tag{3.15}$$

with

$$\frac{1}{\tau} = (\bar{k}_1' + \bar{k}_1'')\,. \tag{3.16}$$

The real and imaginary parts of the admittance are (c.f. Läuger 1978; Frehland 1980)

$$\begin{aligned}\operatorname{Re} Y(\omega) &= 2\,C\{\gamma_1m_1 + \gamma_2m_2 + \frac{\tau}{1 + \omega^2\tau^2}(m_1 - m_2)(\gamma_2\bar{k}_1' - \gamma_1\bar{k}_1'')\}\\ \operatorname{Im} Y(\omega) &= \omega C - 2\,C\frac{\omega\tau^2}{1 + \omega^2\tau^2}(m_1 - m_2)(\gamma_2\bar{k}_1' - \gamma_1\bar{k}_1'')\end{aligned} \tag{3.17}$$

with m_1, m_2 defined in Eq. (3.8). From Eq. (3.17) one gets

$$|Y(\omega)|^2 = \operatorname{Re}^2 Y(\omega) + \operatorname{Im}^2 Y(\omega) = \frac{C^2\tau^2}{1 + \omega^2\tau^2}\cdot\det(\mathbf{K}^2 + \omega^2\mathbf{E})\,. \tag{3.18}$$

Using Eqs. (3.17) and (3.18) the spectral density, $G_{\Delta V}(\omega)$, of the voltage noise can be written in the form

$$G_{\Delta V}(\omega) = 4\,kT\operatorname{Re}\left(\frac{1}{Y(\omega)}\right) + \frac{2\,J^s(\gamma_2\bar{k}_1' - \gamma_1\bar{k}_1'')(\bar{k}_1' + \bar{k}_1'')}{C^2\det(\mathbf{K}^2 + \omega^2\mathbf{E})} + \frac{\phi^s q^2[(\bar{k}_1' + \bar{k}_1'')^2 + \omega^2)]}{C^2\det(\mathbf{K}^2 + \omega^2\mathbf{E})} \tag{3.19}$$

with the steady-state current

$$J^s = q(\bar{k}_l\bar{n}_l - \bar{k}_1''\bar{n}_1) = q(\bar{k}_1'\bar{n}_1 - \bar{k}_r\bar{n}_r)\,. \tag{3.20}$$

And from Eqs. (3.15), (3.18) it follows that

$$\begin{aligned}\frac{G_{\Delta J}}{|Y(\omega)|^2} = \frac{1}{C^2\det(\mathbf{K}^2 + \omega^2\mathbf{E})}\cdot\{&B_{22}[q^2(\bar{k}_1''^2 + \bar{k}_1'^2)\\ &+ (\gamma_1^2 + \gamma_2^2)\omega^2] + B_{12}[q^2(\bar{k}_1''^2 - \bar{k}_1'^2)\\ &- (\gamma_1^2 - \gamma_2^2)\omega^2]\}\,.\end{aligned} \tag{3.21}$$

As for the simple example in the preceding section, neglecting noise generated by the current clamp, the relation of Eq. (1.3) between $G_{\Delta J}(\omega)$ and $G_{\Delta V}(\omega)$ is satisfied. Current clamp noise under different conditions can be treated in complete analogy to Sect. 2.6 and is not further considered.

3.5 Consideration of ionic interaction

We will now extend our results to pores with the ionic interaction condition that each site can be occupied by only one ion. In this case, the "single-file" effect concerning the ratio of unidirectional fluxes

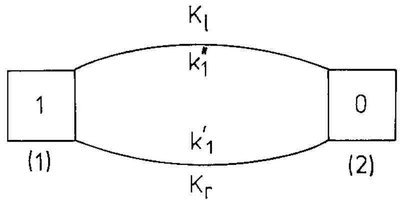

Fig. 3. Two-state (empty, occupied) model for a pore with one binding site

(Hodgin and Keynes 1955; Heckmann 1972) is not yet observed, because the maximum number of ions in one pore is only 1. On the other hand, the non-equilibrium fluctuation properties could be shown to be influenced by the interaction condition: the current noise intensity is reduced (Frehland 1984).

Therefore it is interesting to investigate the voltage noise in this case. The single pore can be described by a two-state diagram according to Fig. 3, where the two states are empty and occupied pore, and N_1, N_2 are the number of occupied, empty pores, respectively. The kinetic equations for $\langle N_1 \rangle$ and $\langle N_2 \rangle$ are

$$\frac{d\langle N_1\rangle}{dt} = -\frac{d\langle N_2\rangle}{dt} = M_{12}\langle N_2\rangle - M_{21}\langle N_1\rangle \quad (3.22\text{a})$$

with

$$M_{12} = K_l + K_r, \qquad M_{21} = k_1' + k_1''$$

or

$$\frac{d\langle N_1\rangle}{dt} = -(M_{12} + M_{21})\langle N_1\rangle + M_{12} N_p \qquad (3.22\text{b})$$

with the constant total number of pores, N_p, given by

$$N_p = N_1 + N_2 . \qquad (3.22\text{c})$$

The kinetic equation for the difference $\langle n \rangle$ of surface densities has the form

$$\frac{d\langle n\rangle}{dt} = (k_1'' - k_1' + K_l - K_r)\langle N_1\rangle - (K_l - K_r) N_p + 2\,\phi^s . \qquad (3.23)$$

Closer inspection shows that the analysis of the preceding section for the non-interaction case can be applied if we replace, in all relations, the m_i $(i = 1, \ldots, 4)$ by

$$m_1 = \alpha\gamma_1[\bar{K}_l(N_p - N_1^s) + \bar{k}_1'' N_1^s]$$

$$m_2 = \alpha\gamma_2[\bar{K}_r(N_p - N_1^s) + \bar{k}_1' N_1^s]$$

$$m_3 = \bar{K}_l + \bar{k}_1''$$

$$m_4 = \bar{K}_r + \bar{k}_1' . \qquad (3.24)$$

The Fokker-Planck moments for this case are listed in Appendix A3.

Even the result of Eq. (3.21) can be shown to be valid. Hence, apart from the current clamp noise, the relation of Eq. (1.3) between the spectral densities of current and voltage noise is also valid in this simple case which includes ionic interaction.

4. Discussion

In order to get more insight into the properties of non-equilibrium voltage fluctuations we have performed some numerical evaluations of our results.

First, omitting the contribution of the current clamp itself the voltage noise in the one-barrier model has been calculated for varying capacitance C. According to Eqs. (2.11) and (2.22) the intensity of low frequency voltage noise, $G_{\Delta V}(0)$, in the one-barrier model does not depend on the membrane capacitance, C, while the characteristic frequency, $\frac{1}{\tau}$, becomes smaller for increasing C. This behaviour, which is similar for one binding site pores, is demonstrated in Fig. 4.

The voltage dependence of the pseudo first-order rates $\bar{k}_l\bar{n}_l$, $\bar{k}_r\bar{n}_r$ is treated as in Sect. 2.3, i.e., the (voltage dependent) change of surface densities $\bar{n}_l$ and $\bar{n}_r$ is neglected because it is small compared with the voltage dependent change of $\bar{k}_l$ and $\bar{k}_r$. The same arguments are valid for the voltage dependence of the rate constants in the two-barrier models.

On the other hand, the noise intensity at low frequencies in Eq. (2.22) is inversely proportional to the sum, $(\bar{k}_l\bar{n}_l + \bar{k}_r\bar{n}_r)$, of jumping rates. As a consequence, for increasing voltage, the low frequency voltage noise decreases. Again, omitting the current clamp contributions, Fig. 5 shows the frequency

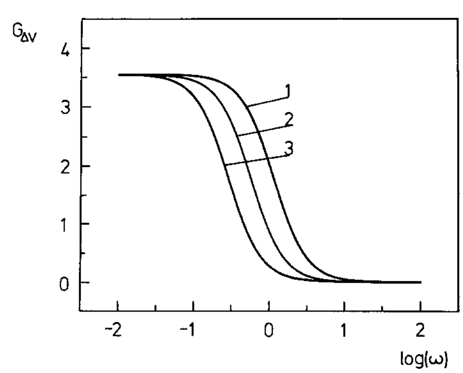

Fig. 4. Frequency-dependence of voltage noise for varying membrane capacitance C for voltage $u = 1 \triangleq 25$ mV. kT, q and $\bar{k}_l\bar{n}_l$ $(u = 0)$, $\bar{k}_r\bar{n}_r$ $(u = 0)$ are set equal to one. 1, 2, 3 correspond to a capacitance $C = 1, 2, 4$, respectively

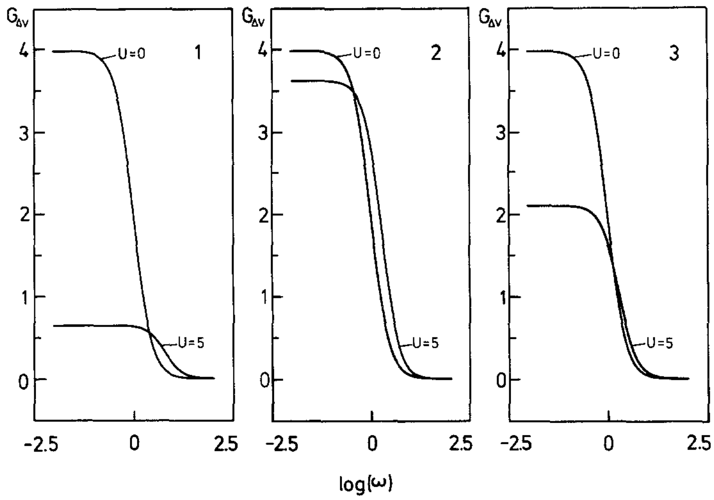

Fig. 5. Frequency-dependence of voltage noise for varying voltage u: **1)** One barrier model, $\bar{k}_l\bar{n}_l$ $(u = 0) = \bar{k}_r\bar{n}_r$ $(u = 0) = 1$. **2)** One binding-site-pores without ionic interaction, $\bar{k}_l\bar{n}_l$ $(u = 0) = \bar{k}_r\bar{n}_r$ $(u = 0) = 2$, $\bar{k}_1'$ $(u = 0) = \bar{k}_1''$ $(u = 0) = 2, \gamma_1 = \gamma_2 = \frac{1}{2}$. **3)** One binding-site-pores with ionic interactions as described in Sect. 3.5 $\bar{K}_l$ $(u = 0) = \bar{K}_r$ $(u = 0) = 4$, $\bar{k}_1'$ $(u = 0) = \bar{k}_2''$ $(u = 0) = 4, \gamma_1 = \gamma_2 = \frac{1}{2}$. kT, q and C are set equal to 1

dependent noise intensities for one binding site pores (without and with interaction). The rate constants are chosen in such a way that for small voltages the conductances are equal. Apart from a small increase for small voltage in the case of one binding site pores without interactions the noise intensity tends to decrease for increasing voltage and current. This tendency seems to be characteristic of voltage fluctuations in *rigid* transport systems. It is planned to investigate theoretically these fluctuations in more complex systems, expecially in systems where the transport units are movable (e.g., ion-carriers) or may exhibit conformational changes (nerve channels, ion-pumps).

In previous sections, especially Sect. 2.6, it has been shown that the noise contribution of the current clamp strongly depends on the special properties of the current clamp itself, acting as a white noise source. In non-equilibrium noise experiments it might be an essential point to identify the contribution of the current clamp to the measured noise. Possibly, in current noise experiments, the problem of a noise generating voltage clamp should be carefully rediscussed. In order to get some idea we have evaluated the second term in Eq. (2.22), which has been derived as explained in Sect. 2.1 from Eq. (2.16). Under these special conditions both terms are compared for the one-barrier model (Fig. 6). Under equilibrium conditions (vanishing currents) the current clamp term vanishes. But for increasing voltage both terms behave similarly. Asymptotically $\left(\text{i.e., } \frac{k_r n_r}{k_l n_l} \ll 1\right)$ the current clamp intensity is half the system-inherent noise intensity. The essential property of voltage noise in decreasing with increasing driving force is preserved.

Different behaviour of voltage and current noise is shown in Fig. 7, where the low frequency noise as a function of steady-state current, J^s, is shown. In contrast to voltage noise, the current noise intensity

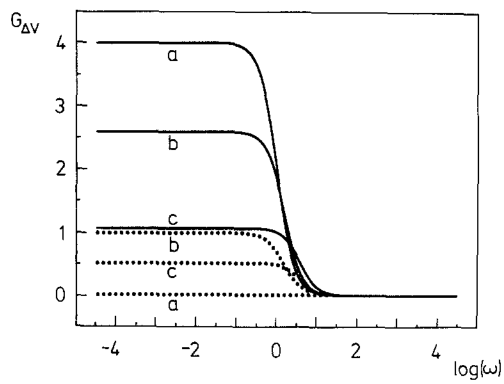

Fig. 6. Comparison between system-inherent voltage noise, i.e., first term of equations (2.22)-(solid line), and current clamp generated noise, i.e., second term of (2.22).(dotted line), for the one barrier model. a, b, c refer to the voltage $u = 1, 2, 4$, respectively, $C = 1$

increases for increasing voltage. For both types of noise the ordering effect of ionic interactions (Frehland 1984) leads to a reduction of low frequency noise intensities at high voltages.

In view of the physiological importance of voltage noise it is interesting to try some predictions of the expected noise intensities for cells, though our results are derived only for rigid pores. Considering Eq. (2.20) we see that, apart from the current clamp term, the variance of voltage fluctuations in the one-barrier model for pores depends only on the capacitance, C, and is independent of the transport rates, i.e., the resistance (conductivity) of the pores and the applied voltage. As seen from Fig. 5.1 and as discussed above the frequency-dependent noise intensity decreases with increasing voltage at low frequencies and increases at higher frequencies so that the variance according to Eq. (2.21),

$$\sigma_{\Delta V}^2 = C_{\Delta V}(0) = \int G_{\Delta V}(f)\, df \tag{4.1}$$

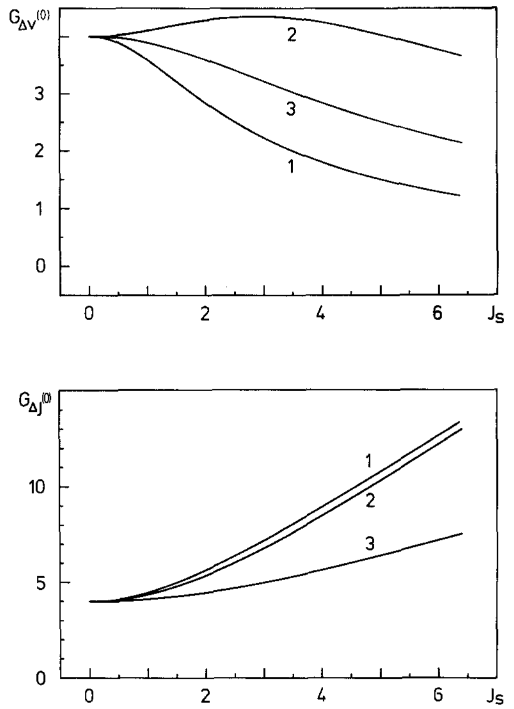

Fig. 7. Comparison of low frequency voltage and current noise $G_{\Delta V}(0)$, $G_{\Delta J}(0)$ in dependence on the applied voltage u. Curves 1, 2, 3 correspond to the parameters and transport models 1, 2, 3 in Fig. 5. Parameters as in Fig. 5

remains constant. Similar behaviour is observed for the one binding site pores. This result can readily be understood: for low transport rates the averaged relaxation time, τ, of a disturbance is greater and thus the contribution of a disturbance to the variance increases as the number of disturbances (jumps) decreases.

Quantitatively for cells with a surface area of $\sim 10^{-6}$ cm^2 and a capacitance of $\sim 10^{-6}$ Farad $\cdot$ cm^{-2} we get a variance

$$\sigma^2_{\Delta V} = 40 \cdot 10^{-10}\ V^2$$

i.e.,

$$\sqrt{\sigma^2_{\Delta V}} \approx 10^{-1}\ \text{mV}\,. \tag{4.2}$$

For smaller cells of $\sim 10^{-10}$ cm^2 surface area ($\sim 10^3$ Å diameter) the mean fluctuation $\sqrt{\sigma^2_{\Delta V}}$ takes a relatively high value of 10 mV. We emphasize that this estimation for *rigid* transport channels is independent of the number and conductivity of the channels. We plan to investigate the important problem of how more complex transport mechanisms (i.e., open-close kinetics, carriers, pumps) influence (reduce) the non-equilibrium voltage fluctuations.

Appendix

A.1 Master equation approach to steady-state fluctuations of scalar quantities

This approach (Lax 1960; van Vliet and Fassett 1965; Chen 1978) starts from the linearized phenomenological equations

$$\frac{d\,\langle \mathbf{N} \rangle}{dt} = -\mathbf{K}\,\langle \mathbf{N}(t) \rangle + \mathbf{Y} \tag{A.1}$$

($\mathbf{N}$: set of Markovian variables; $\mathbf{K}$: matrix of coefficients; $\mathbf{Y}$: inhomogenities), which can be derived from the Master-equation. With the deviations

$$\boldsymbol{\alpha} = \mathbf{N} - \mathbf{N}^s \tag{A.2}$$

from the steady-state one gets for $\boldsymbol{\alpha}$

$$\langle \boldsymbol{\alpha}(t) \rangle = \boldsymbol{\Omega}(t)\,\langle \boldsymbol{\alpha}(0) \rangle\,, \tag{A.3}$$

where the fundamental solution matrix $\boldsymbol{\Omega}(t)$ is given by the matrix exponential

$$\boldsymbol{\Omega}(t) = \exp(-\mathbf{K}t)\,. \tag{A.4}$$

The variance matrix

$$\sigma^2 = \langle \boldsymbol{\alpha}\,\tilde{\boldsymbol{\alpha}} \rangle$$

$$\sigma^2_{ik} = \langle \alpha_i\,\alpha_k \rangle \tag{A.5}$$

has to be determined from the equations

$$\sigma^2 \tilde{\mathbf{K}} + \mathbf{K}\sigma^2 = \mathbf{B}(\mathbf{N}^s) \tag{A.6}$$

with $\tilde{\mathbf{K}}$ as the transpose of $\mathbf{K}$ and the components B_{ik} of the symmetric matrix $\mathbf{B}$ called the second order Fokker-Planck moments

$$B_{ik}(\mathbf{N}^s) = \sum_{\text{all}\,\mathbf{N}} \alpha_i \alpha_k\, Q(\mathbf{N}; \mathbf{N}^s) \tag{A.7}$$

$Q(\mathbf{N}; \mathbf{N}^s)$ is the transition rate per unit time from $\mathbf{N}^s$ to $\mathbf{N}$.

The correlation matrix $C(t)$ is

$$\mathbf{C}(t) = \langle \boldsymbol{\alpha}(t)\,\tilde{\boldsymbol{\alpha}}(0) \rangle = \boldsymbol{\Omega}(t)\sigma^2\,. \tag{A.8}$$

The noise spectrum matrix

$$\mathbf{G}_\alpha(\omega) = \operatorname{Re} \int_0^\infty [\mathbf{C}(t) + \tilde{\mathbf{C}}(t)]\, e^{i\omega t} dt \tag{A.9}$$

becomes

$$\mathbf{G}_\alpha(\omega) = 2\,[\mathbf{K}^2 + \omega^2 \mathbf{E})^{-1} \mathbf{K}\sigma^2 + \sigma^2 (\tilde{\mathbf{K}}^2 + \omega^2 \mathbf{E})^{-1} \tilde{\mathbf{K}}]\,. \tag{A.10}$$

According to Chen (1975, 1978), in Eq. (A.8), σ^2 may be replaced by **B** with the use of Eq. (A.6):

$$\mathbf{G}_\alpha(\omega) = 2\,[(\mathbf{K}^2 + \omega^2\mathbf{E})^{-1}\,\mathbf{KB\tilde{K}}(\mathbf{\tilde{K}}^2 + \omega^2\mathbf{E})^{-1} + \omega^2(\mathbf{K}^2 + \omega^2\mathbf{E})^{-1}\,\mathbf{B}(\mathbf{\tilde{K}}^2 + \omega^2\mathbf{E})^{-1}] \quad (A.11)$$

A.2 Pores with one binding site: Fokker-Planck moments, variances and noise spectrum matrix

According to Eq. (A.7) the second-order Fokker-Planck moments contain the transition rates for transitions from the steady-state, $\Delta n = 0$, $\Delta n_1 = 0$. The transitions are generated by ionic jumps into and out of the binding site, and the current clamp. The corresponding transition rates are

$$Q(\Delta n = -1, \Delta n_1 = +1; \mathbf{N}^s) = \bar{k}_l\bar{n}_l \quad (A.12a)$$

$$Q(\Delta n = +1, \Delta n_1 = +1; \mathbf{N}^s) = \bar{k}_r\bar{n}_r \quad (A.12b)$$

$$Q(\Delta n = +1, \Delta n_1 = -1; \mathbf{N}^s) = \bar{k}_1''\bar{n}_r \quad (A.12c)$$

$$Q(\Delta n = -1, \Delta n_1 = -1; \mathbf{N}^s) = \bar{k}_1'\bar{n}_1 \quad (A.12d)$$

and

$$Q(\Delta n = +1, \Delta n_1 = 0; \mathbf{N}^s) = 2\,\phi^s\,. \quad (A.13)$$

In Eq. (A.13) the current clamp is assumed to be generated by unidirectional discrete jumps of charges to the left side and away from the right [c.f. Eq. (2.16)]. From Eqs. (A.12), (A.13), and (A.7) one gets the Fokker-Planck moments as follows:

$$B_{11} = \bar{k}_l\bar{n}_l + \bar{k}_r\bar{n}_r + (\bar{k}_1' + \bar{k}_1'')\,\bar{n}_1 + 2\,\phi^s$$

$$B_{12} = B_{21} = -(\bar{k}_l\bar{n}_l - \bar{k}_r\bar{n}_r) - (\bar{k}_1'' - \bar{k}_1')\,\bar{n}_1$$

$$B_{22} = \bar{k}_l\bar{n}_l + \bar{k}_r\bar{n}_r + (\bar{k}_1' + \bar{k}_1'')\,\bar{n}_1\,. \quad (A.14)$$

The variances, σ_{ik}^2, are determined from Eq. (A.6) with the use of Cramer's rule. With K_{ik} as components of the matrix of coefficients **K** in (A.1) the result is

$$\sigma_{11}^2 = \delta[(B_{22} + 2\,\phi^s)\beta_1 - 2\,B_{12}K_{12}K_{22} + B_{22}K_{12}^2]$$

$$\sigma_{21}^2 = \sigma_{12}^2 = -\delta[B_{22}(K_{11}K_{12} + K_{22}K_{21}) - 2\,B_{12}K_{11}K_{22} + 2\,\phi^s K_{22}K_{21}]$$

$$\sigma_{22}^2 = \delta[(B_{22} + 2\,\phi^s)\,K_{21}^2 - 2\,B_{12}K_{21}K_{11} + B_{22}\beta_2]$$

with

$$\beta_1 = \det\mathbf{K} + K_{22}^2$$

$$\beta_2 = \det\mathbf{K} + K_{11}^2$$

$$\delta^{-1} = 2\,(K_{11} + K_{22})\det\mathbf{K}\,. \quad (A.15)$$

The noise spectrum matrix can now be derived with the use of (A.10) or (A.11):

$$[\mathbf{G}_\alpha(\omega)]_{ij} = \frac{4}{\det(\mathbf{K}^2 + \omega^2\mathbf{E})}\,[\chi_{ij}^- \det\mathbf{K} + \chi_{ij}^+\,\omega^2] \qquad i,j = 1,2$$

with

$$\chi_{11}^\pm = \sigma_{11}^2 K_{11} \pm \sigma_{12}^2 K_{12}$$

$$\chi_{12}^\pm = \chi_{21}^\pm = \sigma_{12}^2(K_{11} + K_{22}) \pm (\sigma_{11}^2 K_{21} + \sigma_{22}^2 K_{12})$$

$$\chi_{22}^\pm = \sigma_{22}^2 K_{11} \pm \sigma_{12}^2 K_{21}\,. \quad (A.16)$$

A.3 Fokker-Planck moments for ionic interactions

Considering the different notations in the interaction case the transition rates Eq. (A.12) are

$$Q(\Delta n = -1, \Delta N_1 = +1; \mathbf{N}^s) = \bar{K}_l(N_p - N_1^s) \quad (A.17a)$$

$$Q(\Delta n = +1, \Delta N_1 = +1; \mathbf{N}^s) = \bar{K}_r(N_p - N_1^s) \quad (A.17b)$$

$$Q(\Delta n = +1, \Delta N_1 = -1; \mathbf{N}^s) = \bar{k}_1''N_1^s \quad (A.17c)$$

$$Q(\Delta n = -1, \Delta N_1 = -1; \mathbf{N}^s) = \bar{k}_1'N_1^s \quad (A.17d)$$

and

$$Q(\Delta n = +1, \Delta N_1 = 0; \mathbf{N}^s) = 2\,\phi^s\,. \quad (A.18)$$

In Eq. (A.18) we assume unidirectional jumps of charges [c.f. Eqs. (A.13) and (2.16)].

From Eqs. (A.17), (A.18), and (A.7) one gets the Fokker-Planck moments as follows:

$$B_{11} = (\bar{k}_1' + \bar{k}_1'')\,N_1^s + (\bar{K}_l + \bar{K}_r)\,(N_p - N_1^s) + 2\,\phi^s$$

$$B_{12} = B_{21} = (\bar{k}_1' - \bar{k}_1'')\,N_1^s - (\bar{K}_l - \bar{K}_r)\,(N_p - N_1^s)$$

$$B_{22} = (\bar{k}_1' + \bar{k}_1'')\,N_1^s + (\bar{K}_l + \bar{K}_r)\,(N_p - N_1^s)\,. \quad (A.19)$$

Acknowledgements. We wish to thank Dr. P. Läuger for interesting discussions on this subject. This work has been financially supported by the Deutsche Forschungsgemeinschaft (E.F., Heisenberg-Fellowship; P.S., FR 509/5-1).

References

Bell DA (1960) Electrical noise. Van Nostrand, London

Callen HB, Welton TA (1951) Irreversibility and generalized noise. Phys Rev 83: 34–40

Callen HB, Greene RF (1952) On a theorem of irreversible thermodynamics. Phys Rev 86: 702–710

Chen Y (1975) Matrix method for fluctuations and noise in kinetic systems. Proc Natl Acad Sci USA 72: 3807–3811

Chen Y (1978) Noise analysis of kinetic systems and its applications to membrane channels. Adv Chem Phys 37: 67–97

De Felice LJ (1981) Introduction to membrane noise. Plenum Press, New York

Fishman HM, Leuchtag HR, Moore LE (1983) Fluctuation and linear analysis of Na-current kinetics in squid axon. Biophys J 43: 298–307

Frehland E (1978) Current noise around steady-states in discrete transport systems. Biophys Chem 8: 255–265

Frehland E (1980) Current fluctuations in discrete transport system far from equilibrium – Breakdown of the fluctuation dissipation theorem. Biophys Chem 12: 63–71

Frehland E (1982) Stochastic transport processes in discrete biological systems. Springer, Berlin Heidelberg New York

Frehland E (1984) Non-equilibrium current noise generated by ordered ion transport processes in biological membranes. In: Frehland E (ed) Synergetic. From microscopic to macroscopic order. Springer Series in Synergetics, vol 22. Springer, Berlin Heidelberg New York

Heckmann K (1972) Single file diffusion. Biomembranes 3: 127–153

Hodgkin AL, Keynes RD (1955) The potassium permeability of giant nerve fibre. J Physiol 128: 61–88

Kolb HA, Frehland E (1980) Noise-current generated by carrier-mediated ion transport at non-equilibrium. Biophys Chem 12: 21–34

Lax M (1960) Fluctuations from the non-equilibrium steady-state. Rev Mod Phys 32: 25–64

Läuger P (1975) Shot noise in ion channels. BBA 413: 1–10

Läuger P (1978) Transport noise in membranes – Current and voltage fluctuations at equilibrium. BBA 507: 337–349

Läuger P (1984) Current noise generated by electrogenic pumps. Eur Biophys J 11: 117–128

Nyquist H (1928) Thermal agitation of electrical charge in conductors. Phys Rev 32: 110–113

Verveen AA, De Felice LJ (1974) Membrane noise. Prog Biophys Mol Biol 28: 189–265

Vliet KM van, Fassett JR (1965) Fluctuations due to electronic transitions and transport in solids. In: Burgess RE (ed) Fluctuation phenomena in solids. Academic Press, New York