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Theory of Transport Noise in Membrane Channels with Open-Closed Kinetics

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Abstract. A theoretical approach to transport noise in kinetic systems, which has recently been developed, is applied to electric fluctuations around steady-states in membrane channels with different conductance states. The channel kinetics may be simple two state (open-closed) kinetics or more complicated. The membrane channel is considered as a sequence of binding sites separated by energy barriers over which the ions have to jump according to the usual single-file diffusion model. For simplicity the channels are assumed to act independently. In the special case of ionic movement fast compared with the channel open-closed kinetics the results agree with those derived from the usual Master equation approach to electric fluctuations in nerve membrane channels.

For the simple model of channels with one binding site and two energy barries the coupling between the fluctuations coming from the open-closed kinetics and from the jump diffusion is investigated.

Key words: Transport-noise – Membrane channels – Single-file jump diffusion – Channel kinetics.

1. Introduction

We recently have developed a general approach to electrical fluctuations around equilibrium and nonequilibrium steady-states in discrete transport systems, where the different discrete states may be given by different binding sites for the transported particles (ions) as well as by different, e.g., chemical states [1, 2]. The general applicability of this theory of transport noise has been demonstrated, e.g., at the examples of current noise in rigid membrane pores [1], carrier noise [1] and single file noise [2]. The formalism can quite generally be extended to transport noise in Markov processes which are continuous in time and discrete in state space [3]. It can be shown that for a wide class of transport systems the microscopic electrical fluctuations also around nonequilibrium steady states are related to macroscopic properties of the system.

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In this paper we apply the general formalism to current noise in membrane channels with different conductance states. The channel kinetics may be simple two state (open-closed) kinetics or more complicated. The membrane channel is considered as a sequence of binding sites. The channel kinetics are taken into account by increasing the number of different possible states. For simplicity the channels are assumed to act independently.

The usual approaches to channel noise (see e.g. [4, 5]) are based on the assumption that the electrical current at any instant is proportional to the number of open channels for two state models and correspondingly for channels with different conductance states. This is a plausible assumption in cases where the movement of ions through the channels is fast compared with the typical times of the channel kinetics. But it should be proven because in a correct treatment the current is generated by the *movement* of ions, which in the barrier channel model is given by jumps of the ions over energy barriers separating different binding sites [6, 7]. And the ionic movement is modulated by the open-closed kinetics of the channels. The aim of this paper is to make possible the theoretical treatment of the effect of coupling between channel kinetics and ionic movement on the electrical transport noise.

The case where the ionic movement through the channels is fast compared with the channel kinetics is discussed in section 3. Generally the generated noise consists of two terms. In the frequency domain (spectral density) these two terms are: a) a shot noise term generated by the fast movement of the ions through the channels, b) a frequency dependent term which is determined by the channel kinetics. It can be shown that this term, for arbitrary channel kinetics, is equal to the channel noise which is obtained by the usual approaches, e.g., the Master equation approach [5].

In section 4 numerical results are given for the special case of channels with only one binding site, two conductance states (open-closed) and channel kinetics independent of the occupation state of the channel. The relation between the characteristic times of ion transport through the channels and of channel kinetics is varied between the limiting cases of very slow and very fast ion transport. The numerical calculations for fluctuations around equilibrium yield a low frequency white limit which is below the high frequency white limit and for fluctuations at nonequilibrium vice versa. This might be a general rule.

2. General Approach

a) Kinetic Equations

First we want to make some remarks how to arrive at equations describing the ion transport through channels with special open-closed kinetics. The single channel in a special state is considered as a sequence of binding sites [7]. In the single file model of ion transport [8, 2] through narrow channels it is assumed that the ions within the channel cannot overtake each other and each binding site can be occupied by one ion only. Hence the individual channel can be in a certain number of different states which generally depends a) on the number of ionic species which may penetrate the channel, b) on the number of binding sites within the channel, and c) on the special structure of channel kinetics, e.g., the number of different conductance states.

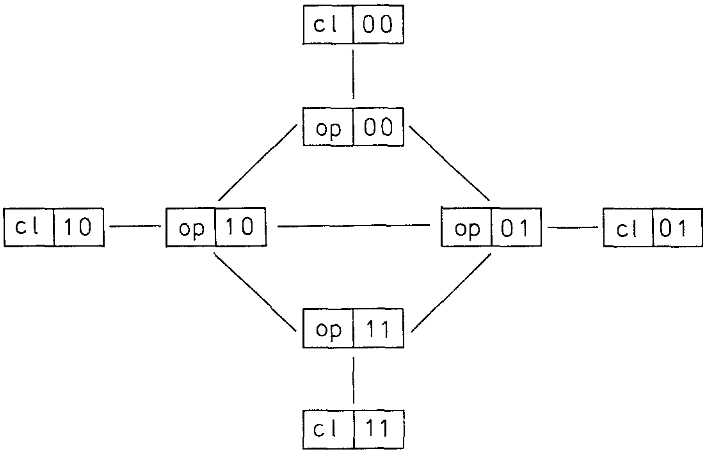

Fig. 1. State diagram for channels with two-state open-closed kinetics, two binding sites and one ion species

In general, the state diagram and the kinetic equations describing the time dependence of such a transport system may be extremely complicated. In order to illustrate how to get state diagrams for special models we have shown in Figure 1 the state diagram for transport of one ion species through channels with two binding sites and two-state (open-closed) channel kinetics. The open channel may be in four states $\boxed{op \mid 00}$, $\boxed{op \mid 10}$, $\boxed{op \mid 01}$, and $\boxed{op \mid 11}$, where $\boxed{op \mid 00}$ is the unoccupied open channel, $\boxed{op \mid 10}$ the open channel with an occupied first binding site etc. Correspondingly, the closed channel may be in four states. The interior part of the state diagram in Figure 1 is the usual single file diagram for pores with two binding sites [2, 9]. Under the assumption, that in closed channels an ionic movement is not possible, transition between the four different closed states are forbidden. On the other hand the open-closed kinetic of the channel may be dependent on its occupation state. Obviously this point can strongly influence the transport kinetics, a point which will be discussed elsewhere [10]. We omit the presentation of the kinetic transport equations.

In Figure 2 is shown the corresponding state diagram for the most simple case of pores with one binding site only. The single channel may be in four different states:

1), (occupied, open), $\boxed{1 \mid op}$
2), (unoccupied, open), $\boxed{0 \mid op}$
3), (occupied, closed), $\boxed{1 \mid cl}$ (2.1)
4), (unoccupied, closed), $\boxed{0 \mid cl}$

We distinguish between rate constants k_{cl}^{0}, k_{op}^{0} and k_{cl}^{1}, k_{op}^{1} for open-closed transitions according to the occupation state of the channel. Transitions between the open-unoccupied and open-occupied states are determined by jumps of ions from and to the left, right sides of the channel, respectively.

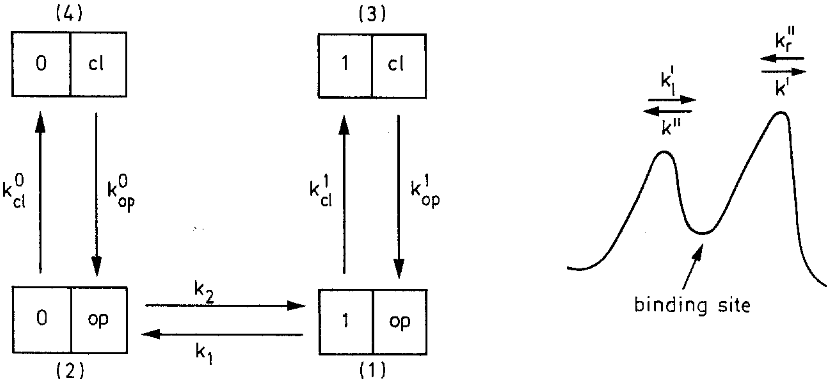

Fig. 2. State diagram for channels with open-closed kinetics and one binding site, and the corresponding potential profile within the open channel

Therefore according to Figure 2:

$$\begin{aligned} k_1 &= k' + k'' , \\ k_2 &= k_l' + k_r'' . \end{aligned} \tag{2.2}$$

If N_i denotes the number of channels in state i, the macroscopic equations describing the time dependence of N_i, are:

$$\begin{aligned} \frac{dN_1}{dt} &= -\,(k_1 + k_{cl}^1)N_1 + k_2N_2 + k_{op}^1N_3 , \\ \frac{dN_2}{dt} &= -\,(k_2 + k_{cl}^0)N_2 + k_1N_1 + k_{op}^0N_4 , \\ \frac{dN_3}{dt} &= -\,k_{op}^1N_3 + k_{cl}^1N_1 , \\ \frac{dN_4}{dt} &= -\,k_{op}^0N_4 + k_{cl}^0N_2 , \end{aligned} \tag{2.3}$$

with the conservation relation

$$N_1 + N_2 + N_3 + N_4 = N_p = \text{const.} \tag{2.4}$$

N_p is the total number of channels, which is assumed to be constant. Eq. (2.3) is solved by standard methods. The time dependence is determined by the eigenvalues of the matrix of coefficients on the right-hand side of Eq. (2.3).

If the ionic movement through the channels is fast compared with the open-closed kinetics, i.e.,

$$k_1, k_2 \gg k_{op}^0, k_{op}^1, k_{cl}^0, k_{cl}^1 , \tag{2.5}$$

we can replace Eq. (2.3) approximately by the equations

$$\begin{aligned}
\frac{dN_{op}}{dt} &= -\left(\frac{k_2}{k_1+k_2}k_{cl}^1 + \frac{k_1}{k_1+k_2}k_{cl}^0\right)N_{op} + k_{op}^1 N_3 + k_{op}^0 N_4\,, \\
\frac{dN_3}{dt} &= -\,k_{op}^1 N_3 + k_{cl}^1 \frac{k_2}{k_1+k_2} N_{op}\,, \\
\frac{dN_4}{dt} &= -\,k_{op}^0 N_4 + k_{cl}^0 \frac{k_1}{k_1+k_2} N_{op}\,,
\end{aligned} \tag{2.6}$$

with

$$\begin{aligned}
&N_{op} = N_1 + N_2\,, \qquad N_1 = \frac{k_2}{k_1+k_2}N_{op} = \frac{k_2}{k_1}N_2\,, \\
&N_{op} + N_3 + N_4 = N_p\,.
\end{aligned} \tag{2.7}$$

For channels with more than one binding site (e.g., as in Fig. 1) the more complex macroscopic kinetic equations can be derived in correspondence to Eq. (2.3). For fast ionic movement the equations are simplified analogously as Eqs. (2.6) and (2.7) by introduction of the total number N_{op} of open channels. Generally, in the fast movement case, the electric current is determined by N_{op} (see below). The kinetic transport equations are linear, because all (identical) channels act independently, and can be written in the form

$$\frac{dN_i}{dt} = \sum_{k=1}^{N} M_{ik}N_k \qquad i = 1, 2, \ldots, N\,, \tag{2.8}$$

where N is the number of different states of the channel. The N_i satisfy the conservation relation

$$\sum_{i=1}^{N} N_i = N_p\,. \tag{2.9}$$

Microscopically, the occupation numbers statistically fluctuate around mean values which are usually called the (ensemble averaged) 'expectation values' of N_i and denoted by $\langle N_i \rangle$. Because Eq. (2.8) are linear equations, they hold also for $\langle N_i \rangle$ [11]

$$\frac{d\langle N_i\rangle}{dt} = \sum_{k=1}^{N} M_{ik}\langle N_k\rangle\,. \tag{2.10}$$

The treatment of electric fluctuations generated by the described channel models can be done analogously as described in [2] for single file noise. Hence we restrict to a brief summary of the main points.

Since the kinetic Eq. (2.8) satisfy a conservation relation Eq. (2.9), they admit a steady-state solution $N_i^s \neq 0$ of the equations

$$\sum_{k=1}^{N} M_{ik}N_k^s = 0\,. \tag{2.11}$$

We introduce the deviation from the steady-state

$$\alpha_i = N_i - N_i^s\,, \quad \sum_{i=1}^{N} \alpha_i = 0 \tag{2.12}$$

which as well satisfy Eqs. (2.8) and (2.10), respectively.

Of main importance are the *fundamental* solutions $\Omega_{ik}(t)$ for the deviation $\langle \alpha_i \rangle$ from the steady-state expectation value of *one* channel, which at $t = 0$ is in state k:

$$\Omega_{ik}(t) = \langle \alpha_i(t) \rangle_{(\alpha_k(0) + N_k^s = 1,\ \alpha_j(0) + N_j^s = 0 \text{ else})}\,. \tag{2.13}$$

By the fundamental solution matrix $\boldsymbol{\Omega}(t)$ with components $\Omega_{ik}(t)$ the general solution of Eq. (2.8) is given through

$$\langle \alpha_i(t) \rangle = \sum_{k=1}^{N} \Omega_{ik}(\alpha_k(0) + N_k^s)\,. \tag{2.14}$$

Often in the standard literature (e.g. [12, 13]) the fundamental matrix includes the stationary solution N_k^s and can formally be written as the matrix exponential

$$\bar{\boldsymbol{\Omega}} = e^{-Mt}\,. \tag{2.15}$$

$$\boldsymbol{\Omega} + \boldsymbol{\Omega}^s = \bar{\boldsymbol{\Omega}}\,, \qquad \lim_{t \to \infty} \boldsymbol{\Omega} = 0\,, \qquad \lim_{t \to \infty} \bar{\boldsymbol{\Omega}} = \boldsymbol{\Omega}^s \neq 0\,, \tag{2.16a}$$

where the components

$$\Omega_{ik}^s = \Omega_i^s\,. \tag{2.16b}$$

of $\boldsymbol{\Omega}^s$ are the stationary solutions $\langle N_i^s \rangle$, i.e., the steady-state expectation value for state i of *one* pore, and independent of the initial state k.

b) Fluxes and Electric Current

In [1] we have discussed transport systems, where the occupation numbers were assumed to be the numbers of *particles* at the binding sites and the fluxes are built up by jumps of particles from one binding site to another one. On the other hand in the treatment of single-file fluctuations [2] the occupation numbers are the numbers of pores in a special state. But also in this case a transition $k \to i$ of a channel from state k to state i is connected with a jump of a particle (individual flux ϕ_{ik}, see [2]) and yields a contribution to the measured electrical current.

The situation for channels with open-closed kinetics is similar to the latter one with the slight difference, that a transition $k \to i$ between two states k and i is not necessarily connected with a jump of a particle. E.g., we can assume that the opening and closing of the channel (in the simple example in Figure 2 these are the transitions $1 \to 3$ and $2 \to 4$) does not yield a contribution to the electric current.

Though below we shall make this assumption for simplicity, we emphasize that it is not necessary. Movement of charges connected with the opening and closing of the channels, i.e., so-called gating currents and the corresponding contribution to the electrical fluctuations are included in our general approach.

Furthermore, as in [2] we shall assume for simplicity that transitions $k \rightarrow i$ are uniquely connected with one special type of jumps of particles, though this is also not necessary. But as far as we see, the only relevant exception is the case of channels with one binding site. As may be seen from Figure 2 transitions $1 \rightarrow 2$ from the occupied open channel to the unoccupied open channel can be generated by jumps of ions to the left (k'') as well as to the right (k') and transitions $2 \rightarrow 1$ correspondingly. We shall give the explicite formula for this special case below. In the general treatment we shall exclude this case and assume that transitions $k \rightarrow i$ are connected with only one type of ionic jumps and hence a unique contribution to the electric current. The reader who wants to treat more sophisticated models can do it by increasing the number of individual fluxes ϕ_{ik} and applying the formalism correspondingly.

Formally as in [1] and [2] we introduce the 'fluxes' ϕ_{ik}, i.e., number of transitions $k \rightarrow i$. ϕ_{ii} is set equal to zero. Microscopically ϕ_{ik} consists of a sum of delta-shaped contributions, each of which is generated by a transition $k \rightarrow i$ of one pore. Because interactions between different pores are neglected, the ensemble averaged expectation values $\langle \phi_{ik} \rangle$ of fluxes are given by

$$\langle \phi_{ik} \rangle = M_{ik} \langle N_k \rangle , \quad \mathrm{i} \neq k . \tag{2.17}$$

As pointed out, a transition $k \rightarrow i$ may be connected with a jump of an ion from one binding site to an adjacent one and thus may yield a contribution to the electric current J which is measured in the outer circuit. Therefore, as in [1] and [2] J is given by a linear combination

$$J = \sum_{i,k=1}^{N} \gamma_{ik} \phi_{ik} \tag{2.18}$$

with

$$\gamma_{ik} = - \gamma_{ki} . \tag{2.19}$$

For transitions $k \rightarrow i$, which yield no contribution to J, γ_{ik} is set equal to zero. A further condition, which must be satisfied by the γ_{ik} is, that the sum over a sequence of γ_{ik} must be equal to ze_0, if it belongs to a sequence of transitions by which one ion with charge ze_0 is transported across the membrane (z: valency, e_0: elementary charge).

c) Autocorrelation Function and Spectral Density of the Electric Current

The derivation of the autocorrelation function of current fluctuations around a steady-state can be done as in [1] and [2] by first regarding the correlations between the individual fluxes and then summing up over all these contributions. The result for the fluctuating part ΔJ of current J ist:

$$\langle \Delta J(0) \Delta J(t) \rangle = \sum_{i,k=1}^{N} \gamma_{ik}^2 M_{ik} N_k^s \cdot \delta(t)$$

$$+ \sum_{i,k,j,l=1}^{N} \gamma_{ik} \gamma_{jl} M_{ik} N_k^s M_{jl} \, \Omega_{li}(t) \, . \tag{2.20}$$

By Fourier transformation we get the spectral density $G_{\Delta J}$:

$$G_{\Delta J}(\omega) = 2 \sum_{i,k=1}^{N} \gamma_{ik}^2 M_{ik} N_k^s$$

$$+ 4 \sum_{i,k,j,l=1}^{N} \gamma_{ik} \gamma_{jl} M_{ik} N_k^s M_{jl} \int_0^{\infty} \Omega_{li}(t) \cos \omega t \, dt \, . \tag{2.21}$$

The first sum in Eqs. (2.20) and (2.21), which is δ-like in the time domain and frequency-independent ('white') in the frequency domain, is usual shot noise, the second time-(frequency)-dependent sum contains the correlations for $t \neq 0$.

3. Transport Kinetics fast Compared with the Channel Kinetics

a) Simplified Kinetic Equations, one Conducting State

In this and the following section we make the restricting assumption that the open-closed kinetics are not connected with (gating) currents (see remarks above). As mentioned in the preceding section, for channels with one conducting (open) state, subdivided only by the different ionic occupation states (e.g., in Fig. 1 the four states $\boxed{op \mid ik}$ with $i, k = 0,1$ and in Fig. 2 the states 1 and 2), the kinetic Eq. (2.11) can generally be simplified by introduction of the total number N_{op} of open channels, if the ionic movement across the open channels (transport kinetics) is fast compared with the channel open-closed kinetics. *Macroscopically,* the different ionic occupation states of the open channel can approximately be treated as being at any instant in an equilibrium, determined by the rate constants for jumps of the ions across the sequence of barriers in the open channel and the number of open channels N_{op}. *Microscopically,* for one channel the expectation values of the different ionic occupation states of the open channel depend on the expectation value of the channel to be open.

Hence, in the kinetic equations, which are simplified under the assumption of fast ionic movement, occurs one variable N_{op} characterizing the open channel while the other variables characterize closed states of the channel which are distincted by the different ionic occupation states. A simple example are Eq. (2.6). Generally we write these approximate equations in the form

$$\frac{dN_i^*}{dt} = \sum_{k=1}^{N} M_{ik}^* N_k^* \, , \; M < N \tag{3.1}$$

with $N_1^* = N_{op}$. They describe the channel kinetics with the time dependent fast transport kinetics being neglected.

Analogously as for Eq. (2.10) we can introduce the fundamental solution matrix $\Omega^*(t)$ which is the matrix exponential $\bar{\Omega}^*$ reduced by the steady state fundamental solution Ω^{s*} [compare Eqs. (2.12)–(2.16)]:

$$\Omega^* + \Omega^{s*} = \bar{\Omega} = e^{-M^*t}. \tag{3.2}$$

Thus the component

$$\bar{\Omega}_{11}^* = \Omega_{op} + \Omega_{11}^{s*}, \quad \Omega_{op} = \Omega_{11}^* \tag{3.3}$$

of $\bar{\Omega}^*$ is the expectation value for the single channel to be open under the initial condition to be open at $t = 0$. As we shall see below, Ω_{op} essentially determines the electrical fluctuations.

b) Current Through the Single Channel

The assumption for the validity of Eq. (3.1), that the transport kinetics are fast, implies the assumption that the expectation value $\langle j_s \rangle$ of electric current j_s through the single *open* channel may be treated as if stationary. Obviously $\langle j_s \rangle$ can be expressed by the stationary current J^s divided by the steady-state number N_{op}^s of open channels. Then according to Eqs. (2.17) and (2.18) $\langle j_s \rangle$ is given by

$$\langle j_s \rangle = \frac{J^s}{N_{op}^s} = \sum_{i,\,k\,=\,1}^{N} \gamma_{ik} M_{ik} \hat{\Omega}_k^s, \quad \hat{\Omega}_k^s = \frac{N_k^s}{N_{op}^s}. \tag{3.4}$$

If k is an ionic occupation state of the open channel, $\hat{\Omega}_k^s$ is the expectation value of this state for the open channel, which is approximately stationary.

For sufficiently small applied voltages V, where $\langle j_s \rangle$ is proportional to the applied voltage, we can introduce the single channel conductance Λ:

$$\langle j_s \rangle = \Lambda V. \tag{3.5}$$

c) Current Fluctuations

As shown above in Eqs. (2.20) and (2.21) the current fluctuations contain a shot noise contribution and a term coming from the correlations which is time-, frequency-dependent respectively. As mentioned in the introduction, it is this term which we expect to agree with the results from the usual Master equation approach [5, 12] to channel fluctuations under the condition of fast ionic movement. Under this condition the fundamental solutions $\Omega_{ll}(t)$ in Eq. (2.20) consist of terms with very fast time constants generated by the transport kinetics and terms with time constants coming from the channel kinetics. If we want to apply the approximate solution Eqs. (3.2) to (2.20), (2.21), the terms containing the fast transport kinetics yield an additional shot noise term which must be added to the first sum in Eqs. (2.20) and (2.21). We do not further consider this term. For the remaining (slower) terms we apply Eqs. (3.2) and (3.3). Under the simplifying assumption, stated at the beginning of this section, that only from jumps of the ions over the barriers of the open channel we get contributions to the electric current (nonvanishing γ_{ik}, γ_{jl}), the remaining components $\Omega_{li}(t)$ in Eq. (2.20) belong to open channel states, which approximately are given by Ω_{op} through [see Eqs. (3.3) and (3.4)]

$$\Omega_{li}(t) = \hat{\Omega}_l^s \cdot \Omega_{op}(t) \tag{3.6}$$

and independent of i. Therefore, noting that according to Eq. (3.4)

$$N_l^s = N_{op}^s \cdot \hat{\Omega}_l^s , \tag{3.7}$$

we get the approximation [c.f. Eq. (3.4)]

$$\sum_{i,\, k,\, j,\, l = 1}^{N} \gamma_{ik}\gamma_{jl}M_{ik}N_k^s M_{jl}\Omega_{li}(t) = N_{op}^s \langle j_s \rangle^2 \cdot \Omega_{op}(t) . \tag{3.8}$$

Hence with Eqs. (2.20) and (3.8) the autocorrelation function of the electric current J is

$$\langle \Delta J(0) \Delta J(t) \rangle = A \cdot \delta(t) + N_{op}^s \langle j_s \rangle^2 \Omega_{op}(t) \tag{3.9}$$

and with Eq. (2.21) the spectral density

$$G_{\Delta j}(\omega) = 2\,A + 4\,N_{op}^s \langle j_s \rangle^2 \cdot \int_0^\infty \Omega_{op} \cos \omega t \, dt . \tag{3.10}$$

The shot noise term A is composed of the first sum and the contributions from the fast terms in Ω_{li} in Eqs. (2.20) and (2.21) respectively. If Eq. (3.5) is valid, $\langle j_s \rangle$ in Eqs. (3.9) and (3.10) can be expressed by the single channel conductance Λ and the applied voltage V.

A general result, contained in Eq. (3.9) is, that in the equilibrium ($\langle j_s \rangle = 0$) the current fluctuations exhibit frequency independent white noise only. This is a consequence of the condition of fast ionic movement. In section 4 we shall see, that the spectra may become frequency dependent, if we leave this condition.

c) Comparison with the Master Equation Approach

In the usual approaches to electrical channel noise [4, 5, 14] the autocorrelation function $C_{\Delta J}$ of current is set proportional to the squared product of voltage and single channel conductance and to the autocorrelation function of fluctuations in the number of open channels. If the channel kinetic equations are approximately given by Eq. (3.1) and $N_1 = N_{op}$ is the number of open channels, the autocorrelation function for fluctuations of N_1 around the steady state N^s is the component C_{11} of the correlation matrix $\boldsymbol{C}$ [see [5, 12] and Eq. (3.14)]

$$C_{11} = \sum_{k=1}^{N} \bar{\Omega}_{1k}^{*} \sigma_{k_1}^2 . \tag{3.11}$$

Ω^* is according to Eq. (3.2) the matrix exponential and σ^2 the variance matrix belonging to the set of Markovian variables N_i (c.f. [5, 12]):

$$\sigma^2_{ik} = \langle \Delta N_i \Delta N_k \rangle\ , \quad \Delta N_i = N_i - N^s_i\ . \tag{3.12}$$

Generally the calculation of σ^2 must be done through the second order Fokker-Planck moments of the Markov process [12].

If this approach yields results which are in agreement with our more general treatment, then according to Eq. (3.9) the relation

$$\sum_{k=1}^{M} \bar{\Omega}^*_{1k}\sigma^2_{k1} = N^s_{op}\Omega_{op} \tag{3.13}$$

must be valid. Indeed a proof for the validity of this interesting relation can be derived from a result of Chen and Hill [15] (by setting $a_i = \delta_{1i}$ in Eq. (3.11) in [15]). In the following we indicate a simple proof of a somewhat more general relation, containing Eq. (3.13) as a special case.

The correlation matrix $C(t)$ has the components

$$C_{ij}(t) = \langle \Delta N_i(t)\Delta N_j(0)\rangle = \langle \langle \Delta N_i(t)\rangle_{N(0)}\Delta N_j(0)\rangle \tag{3.14}$$

$\langle \Delta N(t)\rangle \mathbf{N}(0)$ is the expectation value of $\Delta N(t)$ under the initial condition $\mathbf{N}(0)$. As generally shown in [12] C_{ij} is

$$C_{ij} = \sum_{k=1}^{M} \bar{\Omega}^*_{ik}\sigma^2_{kj}\ . \tag{3.15}$$

For σ^2_{ij} holds

$$\sigma^2_{ij} = \langle \Delta N_i \Delta N_j \rangle = \langle N_i N_j \rangle - N^s_i N^s_j\ . \tag{3.16}$$

Furthermore the fundamental solutions satisfy the following relations [compare Eqs. (2.13)–(2.16)]:

$$\sum_{k=1}^{M} \Omega^{s*}_{jk} N_k(0) = N^s_j\ , \tag{3.17a}$$

$$\sum_{k=1}^{M} \bar{\Omega}^*_{jk}(t) N_k(0) = \sum_{k=1}^{M} \Omega^*_{jk}(t) N_k(0) + N^s_j\ . \tag{3.17b}$$

With Eqs. (3.17) and (3.16) we get from Eq. (3.14)

$$C_{ij} = \left\langle \sum_{k=1}^{M} \bar{\Omega}^*_{ik} N_k(0) N_j(0) \right\rangle - N^s_i N^s_j = \left\langle \sum_{k=1}^{M} \Omega^*_{ik} N_k(0) N_j(0) \right\rangle\ . \tag{3.18}$$

Because all N_p channels are assumed to act *independently*, C_{ij} is N_p times the corresponding correlation for one pore. One pore at $t = 0$ is in *exactly one* state!

Hence we get contributions to the ensemble average in Eq. (3.18) only from pores being in state j at $t = 0$ ($N_k(0) = \delta_{kj}$). Therefore

$$C_{ij} = N_p \cdot \left\langle \sum_{k=1}^{M} \Omega^*_{ik}(t)\delta_{kj} \right\rangle = N_p \cdot P_j \Omega^*_{ij}(t) ,$$

where P_j is the probability of the single channel to be in state j. And with Eq. (3.15) we have proven the relation

$$C_{ij}(t) = \sum_{k=1}^{M} (e^{-M^* t})_{ik} \sigma^2_{kj} = N_p P_j \Omega^*_{ij}(t) . \tag{3.19}$$

With Eq. (3.19) the correlations C_{ij} can be calculated without explicit determination of the variances σ^2_{ik}. The essential condition used for derivation of Eq. (3.19) is that the channels act independently.

Setting $i = j = 1$ in Eq. (3.19) proves the validity of Eq. (3.13).

e) Extension to Channel Models with More than one Open Channel State

The extension of the results Eqs. (3.8), (3.9) and (3.10) to channel models with more than one open state can simply be done and is indicated in the following. If the channel has R different open states, denoted by greek indices ν, $\mu = 1, 2, \ldots, R$, the ion transport kinetics for all these states are fast and the channel kinetics are not connected with (gating) currents, the general kinetic Eq. (2.8) can be approximately simplified by introduction of variables N^*_ν ($\nu = 1, 2, \ldots, R$) denoting the number of channels in the ν-th open state. Then the relation Eq. (3.8) is extended to

$$\sum_{i,k,j,l=1}^{N} \gamma_{ik}\gamma_{jl} M_{ik} N^s_k M_{jl} \Omega_{li}(t) = N_p \sum_{\nu,\mu=1}^{R} P_\mu \langle j_\nu \rangle \langle j_\mu \rangle \Omega^*_{\nu\mu}(t) \tag{3.20}$$

with P_μ: probability of a channel to be in the μ-th open state; $\langle j_\nu \rangle$: expectation value of current through the single channel in the ν-th open state; $\Omega^*_{\nu\mu}$: fundamental solution of the simplified kinetic equations in analogy to Eqs. (3.2) and (3.3); ν, μ denoting the ν-th and μ-th open state.

The corresponding result of the usual Master equation approach [5] is

$$\sum_{\nu,\mu=1}^{R} \langle j_\nu \rangle \langle j_\mu \rangle C_{\nu\mu}(t) , \tag{3.21}$$

with $C_{\nu\mu}$ according to Eq. (3.15). The agreement of Eqs. (3.21) with (3.20) is shown with the use of Eq. (3.19).

4. Channels with one Binding Site

a) Equations

As a special example without restriction to fast ionic movement we discuss the case of channels with one binding site and simple open-closed kinetics shown in Figure 2 and described by the kinetic Eq. (2.3). As mentioned above for transitions 1 → 2 we must distinguish between jumps to the left and to the right and for transitions 2 → 1 correspondingly. Taking into account this fact and considering the correlations between the individual fluxes one gets similarly as Eq. (2.20) an autocorrelation function

$$\begin{aligned}\langle \Delta J(0)\Delta J(t)\rangle = {} & [\gamma_1^2(k''N_1^s + k_e'N_2^s) + \gamma_2^2(k'N_1^s + k_r''N_2^s)]\delta t \\ & + [(\gamma_1 k'' - \gamma_2 k')(\gamma_2 k_r'' - \gamma_1 k_l')(N_1^s\Omega_{22} + N_2^s\Omega_{11}) \\ & + (\gamma_2 k_r'' - \gamma_1 k_e')^2 N_2^s\Omega_{21} + (\gamma_1 k'' - \gamma_2 k')^2 N_1^s\Omega_{12}] . \qquad (4.1)\end{aligned}$$

$\pm\, \gamma_1$ is the contribution to the electric current for jumps over the first barrier and $\pm\, \gamma_2$ over the second barrier (see Fig. 2), positive sign for jumps to the right, negative sign for jumps to the left. For γ_1, γ_2 holds:

$$\gamma_1 + \gamma_2 = ze_0 . \qquad (4.2)$$

Eq. (4.1) is even valid for channels with more complex kinetics than shown in Figure 2, under the condition that the only open channels states are (1) (occupied) and (2) (empty).

Again the first term in Eq. (4.1) is the shot noise term, consisting of the contributions of the unidirectional individual fluxes over the first and second barrier. The second one is time dependent (for $t \ddagger 0$) and yields the frequency-dependent part of spectral density $G_{\Delta J}$:

$$\begin{aligned}G_{\Delta J} = {} & 2\ [\gamma_1^2(k''N_1^s + k_l'N_2^s) + \gamma_2^2(k'N_1^s + k_r''N_2^s)] \\ & + 4 \int_0^\infty dt \cos\omega t[(\gamma_1 k'' - \gamma_2 k')(\gamma_2 k_r'' - \gamma_1 k_l')(N_1^s\Omega_{22} + N_2^s\Omega_{11}) \\ & + (\gamma_2 k_r'' - \gamma_1 k_l')^2 N_2^s\Omega_{21} + (\gamma_1 k'' - \gamma_2 k')N_1^s\Omega_{12}] . \qquad (4.3)\end{aligned}$$

In the case of fast ionic movement Eqs. (4.1) and (4.3) agree with the general results Eqs. (3.9), (3.10), and (3.20).

We see from Eq. (4.3) that the fluctuations around equilibrium not necessarily yield white noise, if the characteristic times of ionic transport are comparable to the times of open-closed kinetics.

b) Numerical Results

In order to illustrate the effect of coupling between transport kinetics and channel open-closed kinetics on the current fluctuations, we give some numerical results for the spectral density (frequency-domain) for channels with one binding site and two conductance states (see Figs. 3 and 4). The spectral density $G_{\Delta J}(\omega)$ is given by Eq. (4.3), where the fundamental solutions are determined by the kinetic Eq. (2.3). In all calculations we have set

$$k_1 = k_2 = 1 \qquad (4{,}4a)$$

and

$$k_{op}^0 = k_{op}^1 = k_{op} , \quad k_{cl}^0 = k_{cl}^1 = k_{cl} . \qquad (4.4b)$$

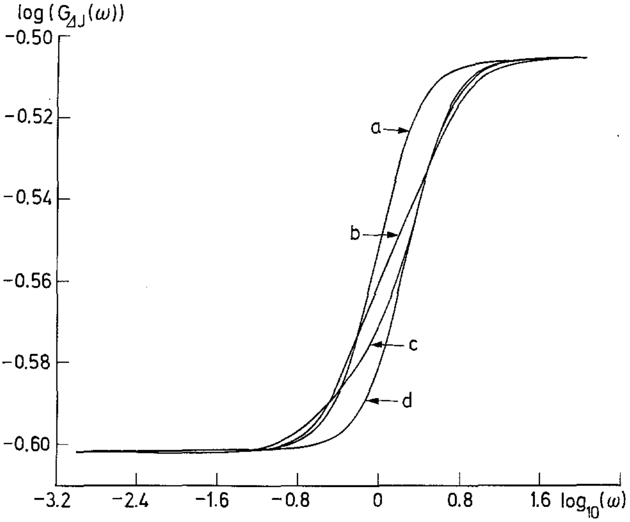

Fig. 3. Numerical results for spectral density $G_{\Delta J}$ of current fluctuations around equilibrium generated by channels with one binding site and simple open-closed kinetics. $k_1 = k_2 = 1$, $\gamma_1 = 3/4$, $\gamma_3 = 1/4$, $k' = k''$ $k_l' = k_r'' = 1/2$, $k_{op} = k_{cl}$ are 100, 1, $1/3$, $1/100$ for curves a, b, c, d, respectively

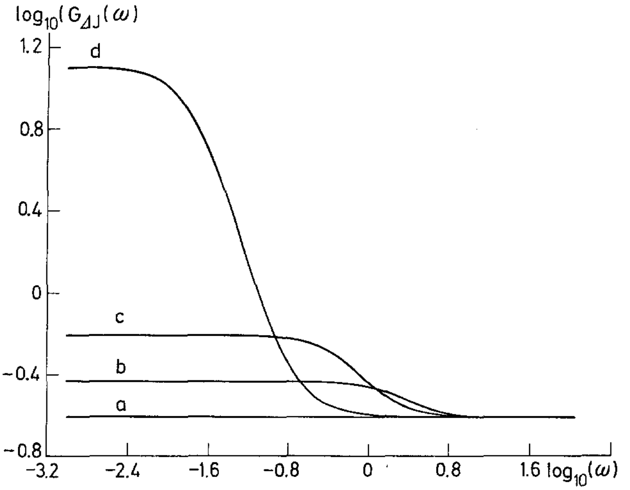

Fig. 4. Numerical results for spectral density $G_{\Delta J}$ of current fluctuations at nonequilibrium. All parameters for the four curves a, b, c, d are chosen as in Figure 3 except $\gamma_1 = \gamma_2$ and $k_1 = k'$, $k_2 = k_l'$. Note the difference between the scales of the ordinates in Figures 3 and 4

According to Eq. (4.4b) (see Fig. 2) this is a special model situation where the channel open-closed kinetics are independent of the ionic occupation state of the channel. The ratio between the characteristic times of channel kinetics and of transport kinetics is varied in Figures 3 and 4 through variation of $k_{op} = k_{cl}$ from fast open-closed kinetics (curves a) to slow open-closed kinetics (curves d). Though all rate constants occuring in Eq. (2.3) in the numerical examples in Figures 3 and 4 are equal, Figure 3 shows results for fluctuations at equilibrium ($J = 0$) and Figure 4 at nonequilibrium ($J \ddagger 0$). The equilibrium has been achieved by setting according to Eq. (2.2) (see Fig. 2) $k' = k''$ and $k'_l = k''_r$, the nonequilibrium by setting $k_1 = k'$, $k_2 = k'_l$. Furthermore in the equilibrium case we have chosen $\gamma_1 \ddagger \gamma_2$. This means that the channel has asymmetric properties and hence according to Eq. (4.3) $G_{\Delta J}$ is frequency-dependent.

Generally, the spectra show a low and high frequency white limit. If the channel kinetics are fast compared with the transport kinetics (cases a in Figs. 3 and 4) the transition between low and high frequency limit is determined by the transport kinetics. If the channel kinetics are slow (curves d), the spectrum in the nonequilibrium case shows a Lorentz-type behaviour over a wide frequency region, generated by the open-closed kinetics. It is this part of the spectrum which is usually studied in nerve channel noise experiments [4, 14].

The coupling of transport kinetics and channel open-closed kinetics is shown in the curves b, c, where the characteristic times are comparable. The high frequency limit in all cases is independent of the coupling.

Comparing the numerical results we see, that at equilibrium the low frequency limit is lower (equal) than the high frequency limit and at nonequilibrium vice versa. This possibly confirms a conjecture for a general rule which might be valid for transport fluctuations and which, apart from physical systems, could be experimentally [16–18] and theoretically (e.g. [1, 2, 19]) verified also for other biological systems as carriers, hydrophobic ions in bilayers, gating currents, pores: At equilibrium the low frequency limit is below the high frequency limit. At nonequilibrium the difference between both limits either becomes smaller, as e.g., for carrier noise [18], or even changes sign (excess noise), as in our numerical examples.

Generally, the contributions of the open-closed kinetics yield a Lorentz-type behavior, while the contributions from the transport kinetics may show Lorentz-type and inverse Lorentz-type behavior [2, 16–19]. Though in the state diagrams Figures 1 and 2 both kinetics appear in a formally equivalent way, this different behavior may be understood from a fact which has already been pointed out in the introduction: the open-closed transitions are not directly connected with contributions to the electric current, but only modulate the kinetics of the ionic movement.

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