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NONEQUILIBRIUM VOLTAGE FLUCTUATIONS IN BIOLOGICAL MEMBRANES

I. GENERAL FRAMEWORK OF CHARGE TRANSPORT IN DISCRETE SYSTEMS AND RELATED VOLTAGE NOISE

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This paper continues our work on the theory of nonequilibrium voltage noise generated by electric transport processes in membranes. Introducing the membrane voltage as a further variable, a system of kinetic equations linearized in voltage is derived by which generally the time-dependent behaviour of charge-transport processes under varying voltage can be discussed. Using these equations, the treatment of voltage noise can be based on the usual master equation approach to steady-state fluctuations of scalar quantities. Thus, a general theoretical approach to nonequilibrium voltage noise is presented, completing our approach to current fluctuations which had been developed some years ago. It is explicitly shown that at equilibrium the approach yields agreement with the Nyquist relation, while at nonequilibrium this relation is not valid. A further general property of voltage noise is the reduction of low-frequency noise with increasing number of transport units as a consequence of the interactions via the electric field. In a second paper, the approach will be applied for a number of special transport mechanisms, such as ionic channels, carriers or electrogenic pumps.

1. Introduction

Electric fluctuations can be observed depending on the experimental conditions, either as current noise under constant voltage or as voltage noise under constant current. Most of the experimental and theoretical work on nonequilibrium electric noise in biological membranes has been concerned with current fluctuations (refs. 1–6; for further references see the work cited therein). Current-noise experiments are usually preferable since they are not limited by the RC time constant of the membrane. Especially at high frequencies the available operational amplifiers have advantages for current-noise experiments. Moreover, the theoretical analysis of current-noise spectra can be carried out in a straightforward way using a general approach to nonequilibrium transport fluctuations developed some years ago [7,8] while, until recently, such a general approach to voltage noise was not available.

On the other hand, a number of cellular membrane processes such as nerve excitation and sensory transduction are controlled or influenced by the electric field. Thus, fluctuations of membrane potential may have direct consequences for the safety of signal detection, processing and transduction in biological cells. For safe signal detection the voltage-noise amplitude in the relevant frequency interval must be smaller than the threshold values of the cellular process.

In a recent paper we have commenced investigation of nonequilibrium voltage noise arising from ionic transport processes in biological membranes [9]. In continuation of this work we now present a general theoretical framework by which

electric membrane transport processes can be analyzed under varying conditions: voltage-clamp, periodic voltage, or current clamp. In particular, an approach to nonequilibrium voltage noise is presented in this paper thus completing our former on nonequilibrium current noise.

Thus, it is now possible to analyze and compare both types of fluctuations for a wide range of applications and models of charge transport.

This program, its application to and discussion of basic passive and active transport mechanisms will be the subject of a second paper.

2. General treatment of charge-transport processes in biological membranes

In modelling active and passive charge-transport processes in biological membranes, such as carrier-mediated transport [10–12], transport through narrow ionic channels [12–17], channels with additional conformational transitions [18,19] or electrogenic pumps [20–23], a discrete description turned out to be most adequate mainly for the following reasons: The transport processes take place in small regions of molecular dimensions with a discontinuous structure. According to their biological functions conformational transitions of the transport units (proteins), coupling to chemical reactions or ionic interactions have to be included.

2.1. Transport under voltage-clamp conditions

Under constant-voltage conditions (voltage-clamp) it is often convenient to treat the whole transport system as consisting of a number of independent noninteracting transport units (carriers, channels, pumps). The transport through a single unit can be regarded as taking place in a sequence of discrete steps or transitions between a finite number of substates of this unit. Then the central point in modelling the processes is the construction of a state diagram (graph) being as simple as possible but containing the essential characteristics of the process.

For characterization of states μ of a discrete system (transport unit) the variables N_μ are introduced. The N_μ are step functions:

$$N_\mu = \begin{cases} 1 & \text{if the system is in state } \mu \\ 0 & \text{if the system is not in state } \mu \end{cases} \tag{1}$$

The time derivative $\mathrm{d}N_\mu/\mathrm{d}t$ is a sequence of δ-pulses with alternating sign determined by the transitions from states ν into state μ (positive sign) and from state μ to states ν (negative sign). If at times $t_{i,\mu,\nu}$ the transitions $\nu \to \mu$ occur, the fluxes $\phi_{\mu\nu}$ are introduced through [8]

$$\phi_{\mu\nu} = \sum_i \delta(t - t_{i,\mu,\nu}), \quad \mu \neq \nu \tag{2}$$

Then the balance relation holds

$$\frac{\mathrm{d}N_\mu}{\mathrm{d}t} = \sum_{\substack{\nu \\ \mu \neq \nu}} (\phi_{\mu\nu} - \phi_{\nu\mu}). \tag{3}$$

In analogy to continuum systems the fluxes $\phi_{\mu\nu}$ are vectorial quantities, while the time derivatives $\mathrm{d}N_\mu/\mathrm{d}t$ are scalar fluxes.

The transitions between different states are governed by probabilistic laws and the N_μ are random variables. Introducing the probability P_μ of the system being in state μ, one obtains with eq. 1 the averaged or expectation value $\langle N_\mu \rangle$

$$\langle N_\mu \rangle = P_\mu \tag{4}$$

And with eq. 2 the expected flux $\langle \phi_{\mu\nu} \rangle$ is the mean transition rate, being the transition probability (transition moment) $M_{\mu\nu}$ per unit time multiplied by the probability P_ν of finding the system in state ν

$$\langle \phi_{\mu\nu} \rangle = M_{\mu\nu} P_\nu \tag{5}$$

Hence, by averaging the balance relation (eq. 3), one obtains as fundamental stochastic equation the master equation

$$\frac{\mathrm{d}P_\mu}{\mathrm{d}t} = \sum_{\substack{\nu \\ \nu \neq \mu}} (M_{\mu\nu} P_\nu - M_{\nu\mu} P_\mu) \tag{6}$$

The steady state, given by the steady-state solution P_μ^s of eq. 6 is called an equilibrium state if the steady-state fluxes $\langle \phi_{\mu\nu}^s \rangle$ satisfy the detailed balance

$$\langle \phi_{\mu\nu}^s \rangle = \langle \phi_{\nu\mu}^s \rangle \quad \text{for all } \mu, \nu, \quad \text{with} \quad \mu \neq \nu \tag{7}$$

Otherwise, the steady state is a nonequilibrium state.

Up to now we have considered a single subunit. Treatment of a transport system consisting of N_0 identical subunits can similarly be done as follows: N_μ is now a step function which assumes the values 0, 1, 2,..., N_0 if 0, 1, 2,..., N_0 subunits are in state μ. The times $t_{i,\mu,\nu}$ in eq. 2 as well as the fluxes $\phi_{\mu\nu}$ now refer to all transitions $\nu \to \mu$ in any one of the subunits and eq. 3 is valid for the whole system. Furthermore, it is now assumed that all subunits act independently and under identical conditions. Then the expected values $\langle N_\mu \rangle$ and $\langle \phi_{\mu\nu} \rangle$ have simply to be replaced by

$$\langle N_\mu \rangle = N_0 P_\mu \tag{4a}$$

and

$$\langle \phi_{\mu\nu} \rangle = M_{\mu\nu} \langle N_\nu \rangle \tag{5}$$

From eq. 6 follow the kinetic equations

$$\frac{\mathrm{d}\langle N_\mu \rangle}{\mathrm{d}t} = \sum_{\substack{\nu \\ \nu \neq \mu}} \left(M_{\mu\nu} \langle N_\nu \rangle - M_{\nu\mu} \langle N_\mu \rangle \right). \tag{8}$$

or

$$\frac{\mathrm{d}\langle N_\mu \rangle}{\mathrm{d}t} = \sum_\nu M_{\mu\nu} \langle N_\nu \rangle \tag{8a}$$

with the diagonal elements $M_{\mu\mu}$ of M according to

$$M_{\mu\mu} = -\sum_\nu M_{\nu\mu} \tag{9}$$

For experimental applications concerning the measurement of the electric current J under voltage-clamp the transport observable J is defined within the general framework as a linear mapping of the fluxes

$$J = \sum_{\mu,\nu} \gamma_{\mu\nu} \phi_{\mu\nu} \tag{10}$$

The underlying idea is that the observed current is generated by transitions in the system and special transitions yield special contributions to J. As an example we consider the ion carrier (cf. fig. 1): only the transitions of the charged carrier-ion complex MS^+ of charge q between states 3 and 4 contribute to J. Hence

$$\gamma_{43} = -\gamma_{34} = q, \quad \gamma_{\mu\nu} = 0 \quad \text{otherwise} \tag{11}$$

Generally, the matrix γ is antisymmetric, $\gamma_{\mu\nu} = -\gamma_{\nu\mu}$, $\gamma_{\mu\mu} = 0$, because transitions $\mu \to \nu$, $\nu \to \mu$ yield contributions to the electric current of equal absolute value but opposite sign.

2.2. Extension to systems under varying voltage

In case the system is not kept under constant-voltage conditions, the framework of section 2.1 has to be extended because first the voltage dependence of the transition moments $M_{\mu\nu}$ and second the additional contribution of the membrane charging current $C\mathrm{d}V/\mathrm{d}t$ as a function of the membrane capacitance C have to be taken into account.

In order to express the dependence of the transition moments on varying voltage around an average values V^s, we replace M in eq. 8 by $\hat{M}(\Delta V)$, where

$$\Delta V = V - V^s \tag{12}$$

is the deviation of V from V^s. Hence, we obtain from eq. 8

$$\frac{\mathrm{d}\langle N_\mu \rangle}{\mathrm{d}t} = \sum_{\substack{\nu \\ \mu \neq \nu}} \left(\hat{M}_{\mu\nu} \langle N_\nu \rangle - \hat{M}_{\nu\mu} \langle N_\mu \rangle \right),$$

$$\hat{M}_{\mu\nu}(V^s) = M_{\mu\nu} \tag{13}$$

For the voltage dependence of $\hat{M}$ we set [8]:

$$\hat{M}_{\mu\nu}(\Delta V) = M_{\mu\nu} \exp\left(\frac{\gamma_{\mu\nu}}{2k_B T} \Delta V \right), \quad \mu \neq \nu \tag{14}$$

(k_B, Boltzmann constant; T, absolute temperature).

The expression (eq. 10) for current J has to be replaced by

$$J = \sum_{\substack{\mu,\nu \\ \mu \neq \nu}} \gamma_{\mu\nu} \phi_{\mu\nu} + C \frac{\mathrm{d}V}{\mathrm{d}t} \tag{15}$$

For small deviations ΔV from V^s the voltage dependence can be linearized:

$$\hat{M}_{\mu\nu}(\Delta V) = M_{\mu\nu} \left(1 + \frac{1}{2k_B T} \gamma_{\mu\nu} \Delta V \right), \quad \mu \neq \nu \tag{16}$$

Eqs. 13–15 represent a set of equations describing the time-dependent (averaged) behavior of the transport system. In case only small deviations are considered, these equations can be linearized with respect to ΔV with the use of eq. 16.

Furthermore, assuming that for $t \to \infty$ the system tends to a stable steady state with voltage V^s, we arrive at the linearized equations for the deviations α_μ, ΔV from the steady state N_μ^s, V^s.

$$\frac{d\langle\alpha_\mu\rangle}{dt} = \sum_\nu M_{\mu\nu}\langle\alpha_\nu\rangle + \frac{1}{2k_BT}\sum_{\substack{\nu \\ \nu\neq\mu}} \gamma_{\mu\nu}\left(\langle\phi^s_{\mu\nu}\rangle + \langle\phi^s_{\nu\mu}\rangle\right)\cdot\langle\Delta V\rangle \tag{17a}$$

$$\langle J - J^s\rangle = \sum_{\substack{\mu,\nu \\ \nu\neq\mu}} \gamma_{\mu\nu} M_{\mu\nu}\langle\alpha_\nu\rangle + \frac{1}{2k_BT}\sum_{\mu,\nu}\gamma^2_{\mu\nu}\langle\phi^s_{\mu\nu}\rangle\langle\Delta V\rangle + C\frac{d\langle\Delta V\rangle}{dt} \tag{17b}$$

This system of equations serves as basis for further treatment. As well as, for example, eqs. 8 and 13 it describes the expected (or averaged) kinetic behavior, which will be observed in macroscopic experiments if the number N_0 of subunits is sufficiently large. For the treatment of stochastic behavior, such as the electric current or voltage noise, it is necessary to consider in more detail the microscopic properties of the transport processes. This will be done in section 3 of this paper.

The general system (eq. 14) of $n+1$ equations cannot be solved uniquely unless a further condition, e.g., on voltage or current, is imposed. Under the constant voltage condition $\Delta V = 0$, from eq. 17a follow the kinetic equations (eq. 8) and from eq. 17b the (expected) electric current $\langle J\rangle$ in agreement with eq. 10.

2.3. Transport under current-clamp

In experimental applications, an alternative method is relaxation measurement under constant-current conditions where the system is driven away from a stationary state, e.g., by a charge pulse [23,24], and then is subject to relaxation (of voltage) under constant current.

The constant-current condition imposed on eq. 14b means that

$$\langle J - J^s\rangle = 0 \tag{18}$$

Thus, from eq. 14 one obtains the kinetic equations

$$\frac{d\langle\alpha_\mu\rangle}{dt} = \sum_\nu M_{\mu\nu}\langle\alpha_\nu\rangle + \frac{1}{2k_BT}\sum_{\substack{\nu \\ \nu\neq\mu}}\gamma_{\mu\nu}\left(\langle\phi^s_{\mu\nu}\rangle + \langle\phi^s_{\nu\mu}\rangle\right)\langle\Delta V\rangle \tag{19a}$$

$$\frac{d\langle\Delta V\rangle}{dt} = -\frac{1}{C}\sum_{\substack{\mu,\nu \\ \mu\neq\nu}}\gamma_{\mu\nu}M_{\mu\nu}\langle\alpha_\nu\rangle - \frac{1}{2k_BTC}\sum_{\substack{\mu,\nu \\ \mu\neq\nu}}\gamma^2_{\mu\nu}\langle\phi^s_{\mu\nu}\rangle\langle\Delta V\rangle \tag{19b}$$

This set of $n+1$ linear kinetic equations can be solved by standard methods similarly to the constant-voltage case, eq. 8. Eq. 8 as well as eq. 19 satisfies the balance

$$\frac{d\sum_\mu\langle\alpha_\mu\rangle}{dt} = 0 \tag{20}$$

Hence, because the α_μ are defined as the deviation from the steady state:

$$\sum_\mu\langle\alpha_\mu\rangle = 0 \tag{20a}$$

Eq. 20 follows directly for eq. 8 and for the sum over the first terms on the right-hand side of eq. 19a from the definition (eq. 9) of $\boldsymbol{M}$:

$$\sum_{\nu,\mu} M_{\mu\nu}\langle\alpha_\nu\rangle = 0 \tag{21}$$

The sum over the second term on the right-hand side of eq. 19a vanishes because $\boldsymbol{\gamma}$ is antisymmetric.

For the further treatment it is favorable to write the eqs. 19 in matrix notation:

$$\frac{d\langle\boldsymbol{\beta}\rangle}{dt} = -\boldsymbol{K}\langle\boldsymbol{\beta}\rangle \tag{22}$$

with $\beta_\mu = \alpha_\mu$ for $\mu = 1, 2, \ldots, n$, $\beta_{n+1} = \Delta V$

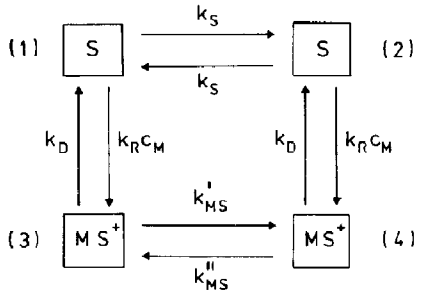

Fig. 1. State diagram for modelling carrier-mediated ion transport: S and MS^+ are the concentrations of the free carrier and the carrier-ion complex within the membrane, respectively. k_R and k_D are the rate constants for association and dissociation of the carrier-ion complex. k_S described the movement of the free carrier, whereby k'_{MS} and k''_{MS} are the rate constants for the ion transport. c_M is the ion concentration in the aqueous solutions.

and

$$K_{\mu\nu} = -M_{\mu\nu},$$

$$K_{\mu,n+1} = -\frac{1}{2k_BT}\sum_{\nu}\left(\langle\phi^s_{\mu\nu}\rangle + \langle\phi^s_{\nu\mu}\rangle\right)\gamma_{\mu\nu},$$

$$K_{n+1,\nu} = \frac{1}{C}\sum_{\mu}\gamma_{\mu\nu}M_{\mu\nu}, \quad \mu,\ \nu = 1, 2, \ldots, n$$

$$K_{n+1,n+1} = \frac{1}{2k_BTC}\sum_{\mu,\nu}\gamma^2_{\mu\nu}\langle\phi^s_{\mu\nu}\rangle \tag{24}$$

Because of eq. 9 or 20a the rank of the matrix $\boldsymbol{M}$ is smaller than n. Generally, if the graph of the system is simply connected it is $n-1$. Correspondingly, the rank of $\boldsymbol{K}$ is n. For applications, where the inverse of the matrix of coefficients is needed, it is favorable to reduce the system (eq. 22) of $n+1$ equations to a system of n equations by eliminating one α_μ $(\mu = 1, 2, \ldots, n)$ with the use of (eq. 20a)

$$\frac{d\langle\bar{\beta}\rangle}{dt} = -\bar{\boldsymbol{K}}\langle\bar{\beta}\rangle \tag{22a}$$

for example, if one eliminates α_n according to

$$\alpha_n = -\sum_{\nu=1}^{n-1}\alpha_\nu \tag{25}$$

one obtains explicitly for $\mu,\ \nu = 1, 2, \ldots, n-1$

$$\bar{\beta}_\mu = \bar{\alpha}_\mu = \alpha_\mu, \quad \bar{\beta}_n = \Delta V$$

$$\bar{M}_{\mu\nu} = M_{\mu\nu} - M_{\mu n} \tag{26}$$

and hence according to eqs. 19

$$\bar{K}_{\mu\nu} = \bar{M}_{\mu\nu}$$

$$\bar{K}_{\mu,n} = K_{\mu,n+1}, \quad \bar{K}_{n,n} = K_{n+1,n+1}$$

$$\bar{K}_{n,\nu} = K_{n,\nu} + \frac{1}{C}\sum_{\rho=1}^{n}\gamma_{\rho n}M_{\rho n} \tag{24a}$$

2.4. Periodic voltage, admittance

If additionally to constant voltage V^s a macroscopic periodic voltage of small amplitude ϵ_0 is applied to the system, the linear response yields the complex admittance $Y(\omega)$ of the system [8]. We set

$$\langle\Delta V\rangle = \epsilon_0 e^{i\omega t} \tag{25}$$

and for the response of current

$$\langle\Delta J\rangle = \epsilon_0 Y(\omega) e^{i\omega t} \tag{26}$$

with (eq. 25) eqs. 17a yield

$$\langle\boldsymbol{\alpha}\rangle = (i\omega\boldsymbol{E} - \boldsymbol{M})^{-1}\boldsymbol{R}\epsilon_0 e^{i\omega t} \tag{27}$$

$$R_\mu = \frac{1}{2k_BT}\sum_{\substack{\nu\\ \nu\neq\mu}}\gamma_{\mu\nu}\left(\langle\phi^s_{\mu\nu}\rangle + \langle\phi^s_{\nu\mu}\rangle\right) \tag{28}$$

of $\boldsymbol{R}$. From eq. 27 together with the general relation (eq. 15) for current J, we obtain a general expression for the complex admittance $Y(\omega)$ of discrete transport systems:

$$Y(\omega) = \frac{1}{2k_BT}\left\{\sum_{\mu,\nu}\gamma^2_{\mu\nu}\langle\phi_{\mu\nu}\rangle + \sum_{\mu,\nu,\kappa,\rho}\gamma_{\mu\nu}M_{\mu\nu}\left[(i\omega\boldsymbol{E} - \boldsymbol{M})^{-1}\right]_{\nu\kappa}R_\kappa\right\} + i\omega C \tag{29}$$

3. Electric fluctuations around steady states

In section 2 we have formulated the framework of kinetic equations (eqs. 17), which may serve as a basis for the analysis of macroscopic experiments: current relaxation after a voltage-jump (eq. 8), the response to a periodic voltage (admittance)

and the voltage relaxation after a charge pulse (eq. 22). The stochastic analysis of electric (current or voltage) noise can be based on these kinetic equations.

3.1. Current noise

As described elsewhere the treatment of current noise starts from the flux-flux correlations under voltage-clamp for which the following general relation holds [7,8,24]:

$$\langle \phi_{\mu\nu}(0)\phi_{\kappa\rho}(t)\rangle = \langle \phi^s_{\mu\nu}\rangle \{ \delta_{\mu\nu,\kappa\rho}\cdot\delta(t) + M_{\kappa\rho}\bar{\Omega}_{\rho\mu}(t)\} \tag{30}$$

with

$$\delta_{\mu\nu,\kappa\rho} = \begin{cases} 1 & \text{for} \quad \mu,\nu = \kappa,\rho \\ 0 & \text{otherwise} \end{cases}$$

and the matrix exponential

$$\bar{\Omega} = e^{\mathbf{M}t} = \Omega(t) + \lim_{t\to\infty} e^{\mathbf{M}t} \tag{31}$$

as the fundamental solution matrix of eq. 8. Then, because the current J is linearly dependent on the fluxes (cf. eq. 10), the autocorrelation function $C_{\Delta J}(t)$ of current fluctuation is

$$C_{\Delta J}(t) = \sum_{\substack{\mu,\nu,\kappa,\rho \\ \mu\neq\nu \\ \kappa\neq\rho}} \gamma_{\mu\nu}\gamma_{\kappa\rho}\{\langle \phi_{\mu\nu}(0)\phi_{\kappa\rho}(t)\rangle - \langle \phi^s_{\mu\nu}\rangle\langle \phi^s_{\kappa\rho}\rangle\} \tag{32}$$

According to the Wiener-Khintchine relations [25,26] one obtains from eq. 32 by Fourier transformations the spectra density $G_{\Delta J}(\omega)$ as a function of circular frequency ω

$$G_{\Delta J}(\omega) = 2\sum_{\substack{\mu,\nu \\ \mu\neq\nu}} \gamma^2_{\mu\nu}\langle \phi^s_{\mu\nu}\rangle + 4\sum_{\substack{\mu,\nu,\kappa,\rho \\ \mu\neq\nu \\ \kappa\neq\rho}} \gamma_{\mu\nu}\gamma_{\kappa\rho}\langle \phi^s_{\mu\nu}\rangle \times M_{\kappa\rho}\int_0^\infty \Omega_{\kappa\rho}(t)\cos\omega\, dt \tag{33}$$

Thus, also at nonequilibrium the current noise is determined by the solutions of the phenomenological equations. In earlier papers [8,24] we have shown that at nonequilibrium the current noise is determined not only by the macroscopic admittance (Nyquist relation) but also by a second term, which in many cases exhibits a so-called excess noise with an intensity proportional to the square of the steady-state current.

It should be emphasized that at nonequilibrium via the individual fluxes $\langle \phi^s_{\mu\nu}\rangle$ in eq. 33 there is contained information about the system which is not contained in the macroscopic response properties, although $G_{\Delta J}(\omega)$ can be calculated with the use of the solution of the phenomenological equations (eqs. 13). Below (cf. eq. 39a) we will see that by the steady-state fluxes the steady-state second-order Fokker-Planck moments are determined from which, on the other hand, the variances can be derived.

Because the discrete description of transport processes seems to be a very general framework, the formulation of nonequilibrium transport noise according to eqs. 30–33 is a rather general tool for the analysis of current noise. On the other hand, such a general framework for nonequilibrium voltage noise has been lacking so far, but will now be derived.

3.2. Second-order Fokker-Planck moments and voltage noise

Considering the kinetic current-clamp equations (eqs. 19) with the voltage occurring as the $(n+1)$-th (scalar) variable, it is sensible to treat voltage noise formally by the so-called master equation approach to fluctuations [6,27,28]. In this approach eqs. 19 and 22 may be considered as the linearized phenomenological equations derived from a master equation, in which voltage V occurs as a further Markovian variable and the states must be further distinguished according to voltage V.

Then generally the correlations $\langle \boldsymbol{\beta}(t)\tilde{\boldsymbol{\beta}}(0)\rangle$ are given by

$$\langle \boldsymbol{\beta}(t)\tilde{\boldsymbol{\beta}}(0)\rangle = e^{\mathbf{K}'t}\boldsymbol{\sigma}^2 \tag{34}$$

with the variance matrix

$$\boldsymbol{\sigma}^2 = \langle \boldsymbol{\beta}(0)\tilde{\boldsymbol{\beta}}(0)\rangle \tag{35}$$

Hence, the autocorrelation function of voltage noise is

$$C_{\Delta V}(t) = [\langle \boldsymbol{\beta}(t)\tilde{\boldsymbol{\beta}}(0)\rangle]_{n+1,n+1}$$

and the variance

$$\langle \Delta V^2 \rangle = C_{\Delta V}(0) = \left[\langle \boldsymbol{\beta}(0)\tilde{\boldsymbol{\beta}}(0) \rangle \right]_{n+1,n+1} \tag{36}$$

Thus, for calculation of voltage noise it is not sufficient to solve the kinetic (macroscopic) equations (eqs. 19). One needs additional information on microscopic properties which is contained in the variance matrix according to

$$\boldsymbol{\sigma}^2 \tilde{\boldsymbol{K}} + \boldsymbol{K}\boldsymbol{\sigma}^2 = \boldsymbol{B}(\boldsymbol{\beta} = 0) \tag{37}$$

with the second-order Fokker-Planck moments $B_{\mu\nu}(0)$ of the steady state $\boldsymbol{\beta}^s = 0$ defined by

$$B_{\mu\nu}(0) = \sum_{\text{all}\boldsymbol{\beta}} \beta_\mu \beta_\nu Q(\boldsymbol{\beta}; \boldsymbol{\beta}^s = 0) \tag{38}$$

$Q(\boldsymbol{\beta}; \boldsymbol{\beta}^s = 0)$ is the transition rate per unit time from the steady state $\boldsymbol{\beta}^s = 0$ to the state $\boldsymbol{\beta}$. Within the framework described in section 3.1 the transition rates are given by the fluxes $\phi_{\mu\nu}$. Hence, the Fokker-Planck moments for $\mu, \nu = 1 \ldots n$ are easily determined by

$$B_{\mu\nu}(0) = -\left(\langle \phi^s_{\mu\nu} \rangle + \langle \phi^s_{\nu\mu} \rangle \right), \quad \mu \neq \nu, \quad \mu, \nu = 1, \ldots, n$$

$$B_{\mu\mu}(0) = \sum_{\substack{\mu \\ \mu \neq \nu}} \left(\langle \phi^s_{\mu\nu} \rangle + \langle \phi^s_{\nu\mu} \rangle \right) \tag{39a}$$

because transitions from the steady state $\boldsymbol{\beta}^s = 0$ generate changes of β_μ, $\beta_\nu = \pm 1$.

For the remaining components $B_{\mu,n+1} = B_{n+1,\mu}$, $B_{n+1,n+1}$ we have to take into account that under current-clamp conditions a transition $\nu \to \mu$ in one transport unit is connected with a change

$$\Delta V_{\mu\nu} = -\frac{1}{C}\gamma_{\mu\nu} \tag{40}$$

of voltage (cf. eq. 15 under the current-clamp condition $J = J^s$). Therefore one obtains from eq. 38

$$B_{\mu,n+1} = -\frac{1}{C} \sum_{\substack{\nu \\ \nu \neq \mu}} \gamma_{\mu\nu} \left(\langle \phi^s_{\mu\nu} \rangle + \langle \phi^s_{\nu\mu} \rangle \right)$$

$$B_{n+1,n+1} = \frac{1}{C^2} \sum_{\substack{\mu,\nu \\ \mu \neq \nu}} \gamma^2_{\mu\nu} \langle \phi^s_{\mu\nu} \rangle \tag{39b}$$

with eqs. 39 and eqs. 23 and 34–37 we are in a position to calculate the nonequilibrium voltage noise in a very straightforward way. According to Chen [6], it is even possible to avoid the explicit and lengthy calculation of the variance matrix and replace $\boldsymbol{\sigma}^2$ directly by $\boldsymbol{B}$. The result for the spectral density matrix which may be used in explicit calculations is [6]

$$G = 2(\boldsymbol{K}^2 + \omega^2 \boldsymbol{E})^{-1} \boldsymbol{K}\boldsymbol{B}\tilde{\boldsymbol{K}} (\tilde{\boldsymbol{K}}^2 + \omega^2 \boldsymbol{E})^{-1} + 2\omega^2 (\boldsymbol{K}^2 + \omega^2 \boldsymbol{E})^{-1} \boldsymbol{B} (\tilde{\boldsymbol{K}}^2 + \omega^2 \boldsymbol{E})^{-1} \tag{41}$$

In the limit $\omega \to 0$ it is favorable to use the reduced equations (eq. 22a) with the reduction according to eq. 24. Then, the Fokker-Planck moments are simply

$$\bar{\boldsymbol{B}}_{\mu\nu} = \boldsymbol{B}_{\mu\nu} \quad \mu, \nu = 1, \ldots, n-1$$

$$\bar{\boldsymbol{B}}_{\mu,n} = \boldsymbol{B}_{\mu,n+1}, \; \bar{\boldsymbol{B}}_{n,n} = \boldsymbol{B}_{n+1,n+1} \tag{42}$$

and eq. 41 is replaced by

$$G = 2(\bar{\boldsymbol{K}}^2 + \omega^2 \boldsymbol{E})^{-1} \bar{\boldsymbol{K}}\bar{\boldsymbol{B}}\tilde{\bar{\boldsymbol{K}}} (\tilde{\bar{\boldsymbol{K}}}^2 + \omega^2 \boldsymbol{E})^{-1} + 2\omega^2 (\bar{\boldsymbol{K}}^2 + \omega^2 \boldsymbol{E})^{-1} \bar{\boldsymbol{B}} (\tilde{\bar{\boldsymbol{K}}}^2 + \omega^2 \boldsymbol{E})^{-1} \tag{41a}$$

4. Discussion of the general approach to voltage noise

With eqs. 23, 34–37, 39 and 41 a general theoretical approach to voltage fluctuations in discrete membrane transport systems at nonequilibrium states has been derived, thus completing the approach to current fluctuations to a general framework. In both cases the fluctuations can be derived in a very straightforward way. The explicit application to a number of different transport models (channels, carriers, pumps) will be the subject of a second paper. Here we wish to discuss some general points.

4.1. Variance of voltage fluctuations at equilibrium

As shown in appendix A, at equilibrium (cf. eq. 7) it is possible to solve generally eqs. 37 for the variance matrix $\boldsymbol{\sigma}^2$ with the result for the variance of voltage fluctuations

$$\langle \Delta V^2 \rangle = \frac{k_B T}{C} \tag{43}$$

This result is in agreement with the equipartition theorem: Regarding voltage V as one degree of freedom, its averaged contribution to the energy of the system is

$$\tfrac{1}{2}C\langle \Delta V^2 \rangle = \tfrac{1}{2}k_B T \tag{44}$$

4.2. Nyquist relation at equilibrium

At equilibrium the spectral density of current noise according to eq. 33 satisfies the Nyquist relation

$$G_{\Delta J}(\omega) = 4k_B T Re\, Y(\omega) \tag{45}$$

with $Y(\omega)$ according to eq. 29 [8,24]. Correspondingly, the voltage noise as derived in section 3 should satisfy the relation

$$G_{\Delta V}(\omega) = 4k_B T Re \frac{1}{Y(\omega)} \tag{46}$$

In order to verify the validity of eq. 46 at equilibrium within our framework, we use the fact that at equilibrium eq. 41 can be reduced to the simplified expression

$$\boldsymbol{G}(\omega) = 2(\boldsymbol{K}^2 + \omega^2 \boldsymbol{E})^{-1}\boldsymbol{B} \tag{47}$$

Hence, the spectral density of voltage noise $G_{\Delta V}(\omega)$ is

$$G_{\Delta V}(\omega) = \boldsymbol{G}_{n+1,n+1}(\omega) = 2\sum_{\nu}\left[(\boldsymbol{K}^2 + \omega^2 \boldsymbol{E})^{-1}\right]_{n+1,\nu} B_{\nu,n+1} \tag{48}$$

Comparison of eq. 39b with the matrix of coefficients $\boldsymbol{K}$ shows that

$$B_{\nu,n+1} = \frac{2k_B T}{C} K_{\nu,n+1} \tag{49}$$

Therefore, from eq. 48 follows

$$G_{\Delta V}(\omega) = \frac{4k_B T}{C}\sum_{\nu}\left[(\boldsymbol{K}^2 + \omega^2 \boldsymbol{E})^{-1}\right]_{n+1,\nu} K_{\nu,n+1}$$

or

$$G_{\Delta V} = \frac{4k_B T}{C} Re(\boldsymbol{Z}^{-1})_{n+1,n+1} \tag{50}$$

with

$$\boldsymbol{Z} = (\boldsymbol{K} + i\omega \boldsymbol{E}) \tag{51}$$

Thus, according to eqs. 46 and 50, the matrix of coefficients $\boldsymbol{K}$ of the system of $n+1$ linear kinetic equations (eqs. 19) under current-clamp is directly related to the complex admittance via eq. 51.

In appendix B, the validity of the relation

$$(\boldsymbol{Z}^{-1})_{n+1,n+1} = C/Y(\omega) \tag{52}$$

is explicitly derived, thus showing the agreement between the Nyquist relation at equilibrium and the framework presented in this paper.

It can be shown explicitly that eqs. 45 and 46 are not valid at nonequilibrium steady states [8,24]. However, it remains an open question whether and under which conditions the relation

$$G_{\Delta V} = G_{\Delta J}\frac{1}{|Y|^2} \tag{53}$$

can be generalized to nonequilibrium states.

4.3. Dependence of noise intensity on the number of transport units

In a following paper we shall present a number of numerical calculations of voltage noise generated by different transport mechanisms. In all these calculations the variance of voltage noise at nonequilibrium states does not deviate essentially from the equilibrium value $k_B T/C$. On the other hand, the frequency dependence of voltage noise strongly depends on the number of transport units in the system in a way which is completely different from the behavior of current noise.

If under constant voltage (voltage-clamp) the transport units act independently, the current-noise intensity is directly proportional to the number N_0 of independent units. Under constant current (current-clamp) the transport interacts through the electric field. This interaction is expressed in the second term on the right-hand side of eq. 19a. It leads to statistics being completely different from that of independent events. The variance is not proportional to the number N_0 as it would be for independent events. Furthermore, the noise intensity for low frequencies ($\omega \to 0$) is inversely proportional to N_0

$$G_{\Delta V}(\omega \to 0) \propto \frac{1}{N_0} \tag{54}$$

The validity of eq. 54 is shown in appendix C. Thus, the low-frequency noise is reduced, while generally the high-frequency intensity increases. This can be understood in the following way: The probability of relaxation of a spontaneous fluctuation in membrane voltage generated in one transport unit is greater if the number of transport units is greater because the electric field equally acts on all transport units.

This result is in agreement with the Nyquist relation (eq. 46) at equilibrium expressing the fact that the spectral density is inversely proportional to the (real part of the) admittance, which increases with increasing number of transport units.

On the other hand, the frequency of stochastic voltage fluctuations in the system increases with increasing number of transport units. As a consequence, the variance being kept at an approximately constant value $k_B T/C$, the spectral intensity of voltage noise is shifted to higher frequencies.

Appendix A: Variance at equilibrium

At equilibrium states the relation

$$\boldsymbol{\sigma}^2 \tilde{\boldsymbol{K}} = \boldsymbol{K}\boldsymbol{\sigma}^2 \tag{A1}$$

holds [27,28], simplifying eq. 37 to

$$2\boldsymbol{K}\boldsymbol{\sigma}^2 = \boldsymbol{B}(\boldsymbol{\beta}=0) \tag{A2}$$

i.e.

$$2\sum_{\rho=1}^{n+1} K_{\nu\rho}\sigma^2_{\rho\mu} = B_{\nu\mu}(\boldsymbol{\beta}=0) \tag{A2a}$$

For solving eq. A2 we make the ansatz that

$$2\sum_{\rho=1}^{n} K_{\nu\rho}\sigma^2_{\rho\mu} = B_{\nu\mu}(\boldsymbol{\beta}=0), \quad (\nu, \mu = 1,\ldots,n) \tag{A3}$$

holds for the reduced system of equations. The validity of eq. A3 would mean that the equilibrium fluctuations of the number of states and of voltage are uncoupled.

From eq. A3 follows with eq. A2

$$K_{\nu,n+1}\sigma^2_{n+1,\mu} = 0, \quad (\nu, \mu = 1,\ldots,n)$$

or

$$\sigma^2_{n+1,\mu} = \sigma^2_{\mu,n+1} = 0, \quad (\mu = 1,\ldots,n) \tag{A4}$$

With eq. A4 we obtain

$$2K_{n+1,n+1}\sigma^2_{n+1,n+1} = B_{n+1,n+1}(\beta=0) \tag{A5}$$

Comparison of eq. 39b with eq. 24 yields the relation

$$K_{n+1,n+1} = \frac{C}{2k_B T} B_{n+1,n+1} \tag{A6}$$

Then, from eqs. A5 and A6 one obtains for the variance of voltage fluctuations $\langle \Delta V^2 \rangle = \sigma^2_{n+1,n+1}$

$$\langle \Delta V^2 \rangle = \frac{k_B T}{C} \tag{A7}$$

Finally, insertion of eqs. A3–A6 in eq. A2 shows that the ansatz (eq. A3) leads to a solution of the complete set of equations (eq. A2).

Appendix B: Derivation of eq. 52

If eq. 52 is valid, the complex admittance $Y(\omega)$ is related to the matrix $\boldsymbol{K}$ by

$$C[Y(\omega)]^{-1} = \left[(\boldsymbol{K} + i\omega\boldsymbol{E})^{-1}\right]_{n+1,n+1} \tag{B1}$$

With

$$\boldsymbol{Z} := (\boldsymbol{K} + i\omega\boldsymbol{E}) \tag{B2}$$

and the general relation for calculation of inverse matrices we are able to rewrite eq. B1

$$C[Y(\omega)]^{-1} = \frac{\det(-\boldsymbol{M} + i\omega\boldsymbol{E})}{\det \boldsymbol{Z}} \tag{B3}$$

$\boldsymbol{M}$ is defined by eq. 8 and related to $\boldsymbol{K}$ by eq. 24. $\det \boldsymbol{Z}$ can be written in the following way

$$\det \boldsymbol{Z} = \sum_{j=1}^{n} (-1)^{n+1+j} K_{n+1,j}(\det \boldsymbol{Q}^j) + (K_{n+1,n+1} + i\omega)\det(-\boldsymbol{M} + i\omega\boldsymbol{E}) \tag{B4}$$

with the matrix $\boldsymbol{Q}^j$ following from $\boldsymbol{Z}$ by omitting

the j-th column and $(n+1)$-th row

$$\boldsymbol{Q}^{j}=\begin{Bmatrix} Z_{11} & \cdots & Z_{1,j-1} & Z_{1,j+1} & \cdots & Z_{1,n+1} \\ \vdots & & \vdots & \vdots & & \vdots \\ Z_{n1} & \cdots & Z_{n,j-1} & Z_{n,j+1} & \cdots & Z_{n,n+1} \end{Bmatrix} \tag{B5}$$

Furthermore, defining a matrix $\boldsymbol{Q}^{ji}$ by omitting in $\boldsymbol{Q}^{j}$ the i-th row and $(n+1)$-th column

$$\boldsymbol{Q}^{ji}=\begin{Bmatrix} Z_{11} & \cdots & Z_{1,i-1} & Z_{1,i+1} & \cdots & Z_{1n} \\ \vdots & & \vdots & \vdots & & \vdots \\ Z_{i-1,1} & \cdots & Z_{i-1,j-1} & Z_{i-1,j+1} & \cdots & Z_{i-1,n} \\ Z_{i+1,1} & \cdots & Z_{i+1,j-1} & Z_{i+1,j+1} & \cdots & Z_{i+1,n} \\ \vdots & & \vdots & \vdots & & \vdots \\ Z_{n1} & \cdots & Z_{n,j-1} & Z_{n,j+1} & \cdots & Z_{nn} \end{Bmatrix} \tag{B6}$$

we obtain from eq. B4

$$\det \boldsymbol{Z}=\sum_{\substack{i=1\\ j-1}}^{n}(-1)^{n+1+j+n+i}K_{n+1,j}K_{i,n+1}(\det\boldsymbol{Q}^{ji}) + (K_{n+1,n+1}+i\omega)\det(-\boldsymbol{M}+i\omega\boldsymbol{E}) \tag{B7}$$

Closer inspection yields

$$(-1)^{i+j}(\det\boldsymbol{Q}^{ji})=\left[(-\boldsymbol{M}+i\omega\boldsymbol{E})^{-1}\right]_{ji} \times\det(-\boldsymbol{M}+i\omega\boldsymbol{E}) \tag{B8}$$

With eqs. B7 and B8 we obtain

$$C\left[Y(\omega)\right]^{-1}=\left((K_{n+1,n+1}+i\omega) - \sum_{i,j=1}^{n}K_{n+1,j}K_{i,n+1}\left[(-\boldsymbol{M}+i\omega\boldsymbol{E})^{-1}\right]_{ji}\right)^{-1} \tag{B9}$$

Comparison of eq. B9 with eqs. 28 and 29 yields eq. 52.

Appendix C: Derivation of eq. 54

From eq. 41a we obtain in the low-frequency limit

$$G_{\Delta V}(\omega\to 0)=2\sum_{i,j=1}^{n}(\bar{K}^{-1})_{ni}B_{ij}(\bar{K}^{-1})_{nj} \tag{C1}$$

According to eq. 24 only the $K_{i,n+1}$, $\bar{K}_{i,n}$ (cf. eq. 41b) are linearly dependent on the steady-state fluxes and hence on N_0, while the remaining components are not. Therefore

$$\det\bar{\boldsymbol{K}}\propto N_0 \tag{C2}$$

is valid.

The elements $(\boldsymbol{K}^{-1})_{ni}$ of the inverse matrix $\boldsymbol{K}^{-1}$ are given by

$$(\bar{K}^{-1})_{ni}=\frac{(-1)^{i+n}}{\det\bar{\boldsymbol{K}}}A_{in} \tag{C3}$$

with

$$A_{in}=\det\begin{Bmatrix} \bar{K}_{1,1} & \cdots & \bar{K}_{1,n-1} \\ \vdots & & \vdots \\ \bar{K}_{i-1,1} & \cdots & \bar{K}_{i-1,n-1} \\ \bar{K}_{i+1,1} & \cdots & \bar{K}_{i+1,n-1} \\ \vdots & & \vdots \\ \bar{K}_{n,1} & \cdots & \bar{K}_{n,n-1} \end{Bmatrix}$$

A_{in} is the determinant of a $(n-1)\times(n-1)$ matrix with components A_{in} $(i=1,\ldots,n)$ not depending on N_0. According to eq. 39 all Fokker-Planck moments $B_{\mu\nu}$ are linearly dependent on N_0. Hence, eq. C1 becomes with eqs. C3 and C2

$$G_{\Delta V}(\omega\to 0)\propto\frac{1}{N_0}2\sum_{i,j=1}^{n}(-1)^{2n+i+j}A_{in}A_{jn} \tag{C4}$$

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