

Non-Markovian character of ionic current fluctuations in membrane channels

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The Smoluchowski-Chapman-Kolmogorov functional equation presents the most basic test of Markovian character of finite stochastic chains, and is simpler in application than other tests proposed in literature. This test is used to analyze the experimental data on potassium current from single BK channel in a biological membrane. The results suggest the non-Markovian character of the analyzed data. [S1063-651X(98)12707-1]

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I. INTRODUCTION

The idea of testing of the Markov condition in ion channel recordings was put forward recently by Timmer and Klein [1]. This problem is interesting and important in itself: ionic currents belong to the group of most vitally important biophysical processes in living cells. Moreover, fluctuations induced by channel currents seem to play significant roles in several other, equally vitally important biophysical and biochemical processes [2].

Transport of different species of ions through hydrophobic lipid bilayers forming living cell membranes is governed, in most cases, by membrane-embedded specific proteins. Lipid bilayers are impermeable for electrolytes. Concentration gradients across the cell membranes are built by ATP-driven ion pumps, and their dissipation proceeds via species-specific ion channels [3]. The channel proteins continuously switch between different internal states, depending on the constantly varying environment: random thermal fluctuations, variations of the voltage difference across the cell membrane, behavior of neighboring proteins, etc. Some of the states correspond to an "open" (high current), other ones to a "closed" (low current) state of the channel. The measurements of single-channel kinetics is possible by means of the patch-clamp technique [4], which gives an output in a form of time-series (current vs time).

It is now well-established [3–7] that single ionic channels in a membrane open and close spontaneously in a stochastic way, resulting in current and voltage changes which resemble the realizations of random telegraph signals (dichotomous noise). We have recently shown [2] that existing experimental data on transport of Na⁺ and Rb⁺ by the Na⁺-K⁺-ATPase of human erythrocyte membranes [8] imply that the action of membrane-embedded enzymes depends critically on fluctuations of the membrane potential, and that the main source of these fluctuations (i.e., of the electrical noise in the vicinity of cell membrane) is not thermal, but originates in the fluctuations of ion concentrations due to the action of ion channels. This implies that the kinetics of several biophysical and biochemical processes of vital impor-

tance, governed by membrane-embedded enzymes, is sensitive to the channel-generated electrical noise. The reason is that in the membrane enzyme kinetics the membrane electric potential plays the role of activation energy (potential barrier), and it was shown [9–11] that, when a membrane enzyme is electroconformationally coupled [9] to an alternating field (either regular or random), it can transduce energy from that field to the catalyzed process. It is to be noted [10] that alternating electric fields may affect the action of membrane proteins (enzymes), because (i) such proteins are dipolar molecules embedded in a lipid bilayer of low dielectric constant, (ii) conformational changes of many proteins involve large displacements of charge, (iii) the membrane prevents the embedded enzyme from rotating and (iv) the enzymes are usually oriented asymmetrically in cell membranes.

Therefore the determination of the nature and characteristics of measured ion-channel currents will help the understanding of the character of fluctuations of transmembrane electric potentials, which determine the kinetics of many biophysical and biochemical processes. It is worth noting that these processes can become the experimentally feasible source of information for recent popular problem of *fluctuating barrier kinetics* (cf., e.g., [12], and references therein), and that barrier fluctuations and/or oscillations are implicit in models describing the kinetics of ATPases [10,11,2].

Single channel recordings are usually analyzed in terms of models assuming that the channel kinetics is a Markov process over a small number of discrete states [4,5b,13], i.e., that the basic kinetics is purely random (stochastic). However, the Markovian nature of channel currents can be questioned [1] (suggestion of non-Markovian character of channel currents can be found also in Ref. [5c]). On the other hand, there are evidently the cases where purely random, Markovian nature of the potassium current through single channels was detected [14]. Also experiments on artificial narrow pores [6] (one-exponent distribution of dwell times) seem to suggest that in the absence of specific channel proteins (enzymes) the gating process is Markovian.

Another analysis, advocated by Liebovitch [5a,15], is based on fractal scaling and on the assumption that the channel kinetics is governed by nonlinear (chaotic) dynamics, which implies, principally, the deterministic type of basic kinetics. For comparison of different models, cf. Refs. [7,16].

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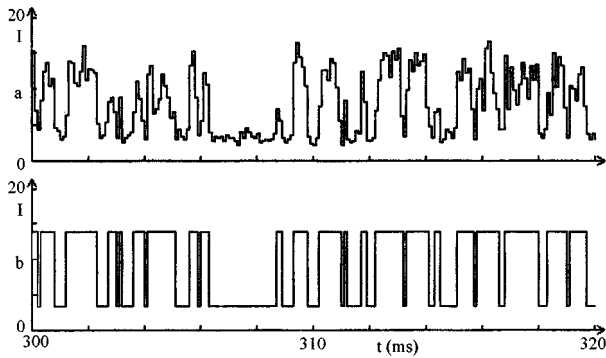


FIG. 1. Sample data of the single BK-channel current I (pA) vs time (ms), at a pipette potential of +60 mV. (a) Original recordings, (b) dichotomous representation.

The process which is partially deterministic and partially stochastic will be in most cases of non-Markovian type (cf., e.g., [17], and references cited therein). As we have said above, (i) the character of irregular ion-channel currents seems to be of importance for several reasons (cf. also below), (ii) the Markovian nature of such currents can be questioned. Therefore Markovian vs non-Markovian character of such currents seems to be worth investigating. We have mentioned that the idea of testing of the Markov condition in ion channel recordings was put forward recently by Timmer and Klein [1]. Whereas the method proposed there supplies some effective tests, it is rather indirect and not simple to use. Moreover, the authors used simulated data, not real (experimental) ones. In this paper we propose a much more direct approach to this problem, which is also more direct than the standard analysis by fits of dwell times distributions to combinations of exponential functions. The method has a purely phenomenological character, without resorting to any specific model. As an illustration of the method we present an analysis of the experimental single-channel data of a potassium current through locust muscle membrane.

The character of channel currents seems to be of importance also in the light of some related problems which recently gained attention in the literature. We have mentioned the fluctuation barrier problem [12]. Moreover, thermal fluctuations of electric fields in biological cells [18], and effects of noise on enzymatic catalysis [19,20] were recently discussed. The channels themselves are also susceptible to internal noise [21]. Besides, there is an interest in recent literature in the influence of noise on neuronal activity [22]. In this respect, it is to be noted that the nerve conduction is built by the correlated action of a multitude of specific ionic pumps and channels. To understand the mechanism of nerve conduction, the models of its constituting components are needed. Of these two modes of ion trafficking, there is now a reasonable simple working model of ionic pumps [2], checked against experimental data [8] and describing correctly the observed behavior of such pumps under stimulation by alternating electrical fields. On the other hand, of several mentioned above models of ionic channels no one is satisfactory. In the authors' opinion, before constructing realistic models of channel action, the detailed characteristics of channel currents need to be known.

The rest of the paper is organized as follows: Section II presents the experimental data on potassium channel cur-

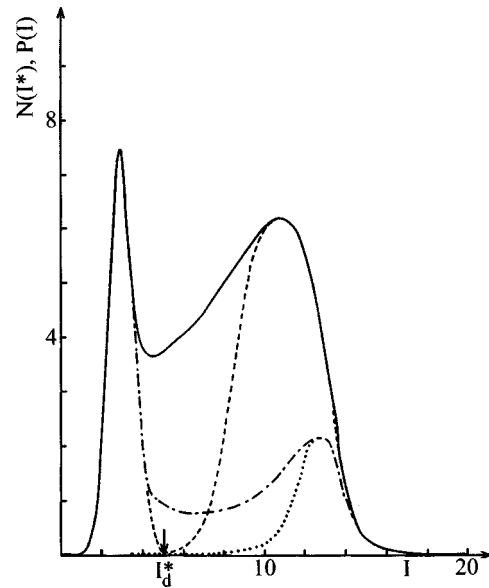


FIG. 2. Number of transitions $N(I^*)$ through threshold current I^* (solid line), the smoothed probability density $P(I)$ (dot-dashed line), and their decompositions into bimodal distributions (almost-Gaussian peaks) (dashed and dotted lines, respectively). Current in pA.

rents, and their dichotomous representation. Section III introduces the formal criterium of Markovianity: the Smoluchowski-Chapman-Kolmogorov (functional) equation. In Sec. IV this criterium is applied to the data from Sec. II. The last section contains a collection of final remarks and conclusions.

II. EXPERIMENTAL DATA

BK-channel data were recorded from cell attached patches of adult locust (*Schistocerca gregaria*) extensor tibiae muscle fibers [23]. The muscle preparation was bathed in 180 mM NaCl, 10 mM KCl, 2mM CaCl_2 , 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES), pH 6.8, and the patch pipettes contained 10 mM NaCl, 180 mM KCl, 2 mM CaCl_2 , 10 mM HEPES, pH 6.8. Channel current was recorded using a List EPC-7 patch-clamp amplifier. Output was low-pass filtered at 10 kHz, digitized at 22 kHz using a Sony PCM ES-701 and stored on standard videotape. Records were transferred to the hard disk of an IBM compatible PC via an analog-to-digital converter (Axon Instruments) sampling at 10 kHz. The complete data analyzed here consist of one record composed of 250 000 values of the channel current measured at equal intervals $\Delta t = 0.0001$ s, the whole duration being 25 s. The minimum and maximum values of the current are $I_{\min} = 0$ and $I_{\max} = 20.46$ pA. Sample data are shown in Fig. 1(a).

These data were first divided into M groups (bins) of equal width $dI = (I_{\max}/M)$ pA. The relative frequencies of visiting these groups are assumed to be equal to the probabilities $P_1(m)$ of finding the value of current in the interval $m dI < I < (m+1) dI$, $m = 0, \dots, M-1$. The stationarity of the record was checked by dividing the whole record into five smaller subrecords, and by calculating the probabilities for every subrecord separately. It is found that the results were

similar (within experimental error) for every subrecord and for the whole time series, and that there is no visible trend in the differences between subrecords.

The corresponding sample record [the same as in Fig. 1(a)], “translated” into dichotomous signal ($M=2$), with threshold determined according to the procedure described just below, is shown in Fig. 1(b).

To find the dichotomous distribution ($M=2$), the following procedure was applied: First, the probability distributions were calculated for M as high as 1000. It was found that for $M \geq 500$ the distribution shape is practically constant (because of normalization, the absolute height changes, as the whole distribution spreads over more and more bins). The resulting limiting probability density $P(I)$ is shown in Fig. 2 (dot-dashed line, arbitrary units). Next was determined the number $N(I^*)$ of transitions through the threshold current, I^* , i.e., the number of pairs of subsequent values of the current $I(t), I(t+\Delta t)$ such that one value was lower, and the second one higher than I^* . This was done for 500 values of $I^* \in (0, I_{\max})$. The result is shown also in Fig. 2 (full line). It is seen that both distributions in Fig. 2 are similar in shape. Especially, they are distinctly bimodal, and their low-current peaks coincide. Dashed and dotted lines in Fig. 2 are the reconstructions of symmetrical peaks of both distributions. These reconstructed “independent” peaks have almost empty common parts. This shows that the original experimental series can be divided into two distinct groups of states, the left one (lower values of the current) interpreted as the closed state (group of states), and the right one as the open state(s). The dichotomous threshold $I_d^* = 5.0 \pm 0.2$ pA,

indicated by the arrow in Fig. 2, and the most probable value of the “closed-state” current $I_c = 2.9 \pm 0.1$ pA can be determined uniquely from the above-described construction. The most probable value of the “open-state” current I_o is not unique: the probability distribution suggests the value $I_o = 12.5 \pm 0.2$ pA, whereas the transitions distribution— $I_o = 10.7 \pm 0.2$ pA.

The construction described above was used for the construction of the corresponding dichotomous ($M=2$) distribution, with the unequal division of current values into two groups of states: the “closed” one for $I < I_d^*$, and the “open” one for $I > I_d^*$, with $I_d^* = 5.0$ pA according to the above estimation. It is found that the stationary probabilities (relative frequencies) of both states are equal for this threshold: $P_c = P_o = 0.50 \pm 0.015$. Further analysis is conducted for this dichotomous representation.

III. CRITERIA OF MARKOVIANITY: FORMALISM

Consider a stochastic process $\xi(t)$ over M discrete states: $\xi(t) \in \{\xi_1, \xi_2, \dots, \xi_M\}$. Here these states denote the values of the current $m dI < I_m < (m+1)dI$, $m=0, \dots, M-1$, and the stochastic process is the measured time series, $\xi(t) = I(t)$, but the formulas (1)–(9) below are valid for any discrete stochastic process over any set of states.

Let $P_k(\xi_\alpha, t_1; \dots, \xi_\gamma, t_k)$ ($\alpha, \beta, \gamma, \dots = 1, \dots, M$) be the probability that the process $\xi(t)$ is in the state ξ_α at time t_1 , \dots and in the state ξ_γ at time t_k . Define *conditional probability*:

$$P_{1|k}(\xi_\alpha, t_1 | \xi_\beta, t_2; \dots, \xi_\gamma, t_{k+1}) = P_{k+1}(\xi_\alpha, t_1; \xi_\beta, t_2; \dots, \xi_\gamma, t_{k+1}) / P_k(\xi_\beta, t_2; \dots, \xi_\gamma, t_{k+1}). \quad (1)$$

Basic definition of Markovianity of the process $\xi(t)$ can be expressed as

$$P_{1|n}(\xi_\alpha, t | \xi_\beta, t_1; \dots, \xi_\gamma, t_n) = P_{1|1}(\xi_\alpha, t | \xi_\beta, t_1), \quad t > t_1 > \dots > t_n. \quad (2)$$

This criterion is to be complemented by the so-called Smoluchowski-Chapman-Kolmogorov (SCK) functional equation [24]

$$P_{1|1}(\xi_\alpha, t | \xi_\gamma, t_2) = \sum_{\xi_\beta} P_{1|1}(\xi_\alpha, t | \xi_\beta, t_1) P_{1|1}(\xi_\beta, t_1 | \xi_\gamma, t_2), \quad t > t_1 > t_2, \quad (3)$$

which follows directly from the definitions (1) and (2), and from standard properties of probability distributions. Namely [we include the known [24] derivation of Eq. (3) for the sake of completeness, and also in order to stress that for a Markovian process it is but an identity], we have from Eq. (1)

$$P_3(\xi_\alpha, t; \xi_\beta, t_1; \xi_\gamma, t_2) = P_{2|1}(\xi_\alpha, t; \xi_\beta, t_1 | \xi_\gamma, t_2) P_1(\xi_\gamma, t_2), \quad (4)$$

$$P_3(\xi_\alpha, t; \xi_\beta, t_1; \xi_\gamma, t_2) = P_{1|2}(\xi_\alpha, t | \xi_\beta, t_1; \xi_\gamma, t_2) P_2(\xi_\beta, t_1; \xi_\gamma, t_2). \quad (5)$$

From Eqs. (5), (2) (Markovianity), and (1),

$$P_3(\xi_\alpha, t; \xi_\beta, t_1; \xi_\gamma, t_2) = P_{1|1}(\xi_\alpha, t | \xi_\beta, t_1) P_2(\xi_\beta, t_1; \xi_\gamma, t_2) \quad (6)$$

$$= P_{1|1}(\xi_\alpha, t | \xi_\beta, t_1) P_{1|1}(\xi_\beta, t_1 | \xi_\gamma, t_2) P_1(\xi_\gamma, t_2), \quad (7)$$

i.e., from Eq. (4),

$$P_{2|1}(\xi_\alpha, t; \xi_\beta, t_1 | \xi_\gamma, t_2) = P_{1|1}(\xi_\alpha, t | \xi_\beta, t_1) P_{1|1}(\xi_\beta, t_1 | \xi_\gamma, t_2). \quad (8)$$

Making use of the obvious property,

$$\sum_{\xi_\beta} P_{2|1}(\xi_\alpha, t; \xi_\beta, t_1 | \xi_\gamma, t_2) = P_{1|1}(\xi_\alpha, t | \xi_\gamma, t_2), \quad (9)$$

we get the SCK equation, Eq. (3). Therefore the stochastic process $\xi(t)$ which does not satisfy either the basic definition

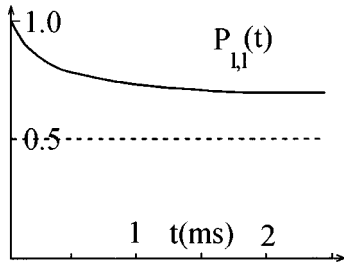


FIG. 3. Current-current conditional probability $P_{1,1}(t)$ for dichotomous representation ($M=2$). Solid line, experimental data; dashed line, randomly generated data.

Eq. (2) or the SCK equation Eq. (3) is not Markovian. Note that a non-Markovian process may satisfy one of these relations [24]: both are necessary conditions of Markovianity, but neither is sufficient.

IV. CRITERIA OF MARKOVIANITY: RESULTS

In this section we shall apply the criteria of Markovianity described above to the experimental data for ionic current, described in Section II.

A. Conditional probabilities

The two-state probabilities $P_2(m, t; n, 0) \equiv P_2(m, t_1; n, t_2)$, with $m, n = 1, 2$, $t = t_1 - t_2$ (stationary process), were calculated in a manner similar to that used for finding stationary probabilities $P_1(m)$, i.e., by counting the relative numbers of pairs of states separated by time interval t , such that $I(t_1) \in$ state m , and $I(t_2) \in$ state n . The current-current conditional probabilities $P_{m,n}(t) \equiv P_{1|1}(m, t_1 | n, t_2)$ were thus obtained from the relation $P_{m,n}(t) = P_2(m, t; n, 0) / P_1(n)$. This procedure was applied to analyzed experimental data and to randomly generated Markovian dichotomous series of the same length (control sample). The results for $P_{1,1}(t)$ are shown in Fig. 3, where the solid line denotes the experimental data, and the dashed line the Markovian control data. It is seen that the conditional probabilities for the randomly generated series are constant for all $t > 0$, whereas the conditional probabilities for the measured channel current tend to constant (asymptotic) values only after a finite time (more than $10\Delta t = 1$ ms). Note that for dichotomous series with $P_1(m) = 1/2$ we have the sum rules

$$P_{1,m}(t) + P_{2,m}(t) = 1, \quad P_{m,1}(t) + P_{m,2}(t) = 1, \quad (10)$$

therefore $P_{1,1}(t)$ represents the whole information on two-state probabilities of the examined series.

B. Smoluchowski-Chapman-Kolmogorov equation

Direct check of non-Markovianity of the process through the relation Eq. (2) for three-point ($P_{1|2}$) distributions is rather difficult. The test based on the SCK equation, Eq. (3), seems to be simpler and more accurate. Let $D_{m,n}(t, \tau)$ denote the difference between the left- and right-hand sides of Eq. (3). These functions, calculated from the functions presented in Fig. 3, are shown in Fig. 4. Note that the relations (10) imply in this case that

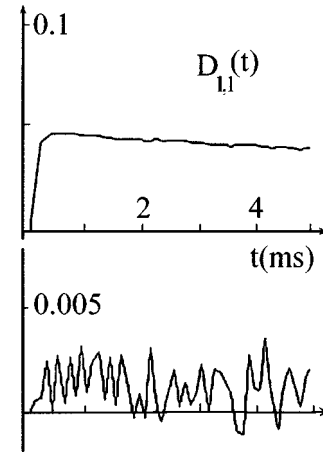


FIG. 4. Smoluchowski-Chapman-Kolmogorov differences $D_{1,1}(t, \tau)$, for $\tau = 0.1$ ms. Upper curve, experimental data; lower curve, randomly generated data. Note scale difference.

$$D_{1,m}(t) + D_{2,m}(t) = 0, \quad D_{m,1}(t) + D_{m,2}(t) = 0. \quad (11)$$

It is seen that the deviations from the SCK identity for the experimental series are more than one order of magnitude higher than these for the control Markovian series. The mean square characteristics

$$G = G(\tau, T) = \left[\frac{1}{T} \frac{1}{M^2} \sum_{m,n}^M \int_{\tau}^{\tau+T} dt D_{mn}^2(t, \tau) \right]^{1/2}, \quad (12)$$

where T is the range of the time t , τ —the shift in SCK equation, is $G_{\text{exptl}} = 0.0414$, $G_{\text{random}} = 0.0016$ for the results shown in Fig. 4 ($T = 5$ ms, $\tau = 0.1$ ms).

V. FINAL REMARKS

The main objective of the paper was to check the nature of potassium current through the locust BK channel, using the definition of the Markov process. The deviations from the SCK identity (Fig. 4, the values of G) suggest strongly that the ion channel current, in this particular case, is non-Markovian. Besides, experimental deviations have system-

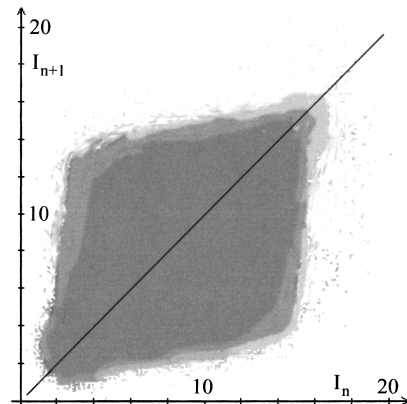


FIG. 5. Phase-space portrait of potassium current I (pA) through locust muscle BK channel. Time shift $\tau = 0.1$ ms.

atic character, whereas random ones are just random and represent numerical accuracy.

The non-Markovianity of the channel current suggests that the process generating this current is not purely random. As we have pointed out in Sec. I, non-Markovian stochastic processes contain in most cases some deterministic component [17].

In order to check the above conclusions, the nature of potassium current has also been examined by two other, independent methods, namely pseudophase portraits and power spectrum analysis. It is well known that pseudo-phase portrait of a stochastic process (here the correlation between subsequent values of the current, $I(t+\Delta t)=I_{m+1}$ vs $I(t)=I_m$) takes a dimension of an embedding space, while the dimension of an attractor in a pseudophase space of a deterministic process is lower [14]. The dimension of pseudophase portrait of the potassium current (see Fig. 5), calculated by the box counting method, is equal to 1.80 ± 0.06 , which confirms the presence of some deterministic component in the examined process. This finding has also been shown by power spectrum analysis; the decay of power spectrum with frequency f fulfills the power law behavior $f^{-\alpha}$ with exponent $\alpha=1.38 \pm 0.20$, which differs significantly from 2, the latter value being typical for the Markov processes [14]. Therefore the gating process, at least the one analyzed in this paper, seems to be a result of both random

noise and of some deterministic process, possibly chaotic with fractal characteristics.

Checking the nature of a given process is a first, very important step on the way of understanding its mechanism. Determinism suggests that some mechanical processes (atomic, molecular, electrostatic forces) play dominant roles in the phenomenon, while randomness means “no regularity” present and the dominant role of the fluctuations in the surrounding medium. This information is of crucial importance in the final step of analysis of a given phenomenon, leading hopefully to the proper theory.

This paper is but preliminary with respect to modeling of the behavior of ion channels. Its aim is to provide the means for the analysis of stochastic properties of channel currents. Deeper understanding can be gained by comparing results of such analyses for various channels in various conditions. Then the appropriate models, containing both stochastic and deterministic (mechanistic) components, can be constructed.

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