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# FRACTIONAL BROWNIAN MOTION AS A MODEL OF THE SELF-SIMILAR ION CHANNEL KINETICS*

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The correspondence of the fractional Brownian motion to the statistically self-similar on different time scales kinetics of a single locust potassium channel is discussed. The parameters of the non-Markovian long-memory process, modelling the ionic transport, are derived in terms of the main statistical characteristics of the recorded current signal.

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## 1. Introduction

Ionic currents are one of the basic processes in living cells [1–3]. They enable living cells to control its volume, to generate and conduct electrical and chemical impulses, to maintain ionic concentration desired for biochemical reactions, *etc.* The problem of determination of the ion current nature is hence of great importance [4–12]. Its solution may provide a clue to better understanding of the membrane channels action.

A subject of intensive discussions is the question of the stochastic origins of the ionic current fluctuations. However the single channel recordings are often analyzed in terms of models assuming that the basic channel kinetics is a Markov process [13–15], such an assumption can be questioned [16–20]. It was already reported [16–20] that the non-Markovian nature of the ionic currents recorded from a single channel can be also observed. The non-Markovian properties of the investigated signals have been brought to light by means of different statistical tools [18–21]. The most effective of them are: the Hurst, detrended fluctuation, and autocorrelation analyses. The

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detailed statistical studies (including the dwell-time distributions) have revealed, for example, the non-Markovian long-memory nature of the current signal recorded from a single locust potassium channel [18–20]. Such properties are currently interpreted as an example of the fractional Brownian motion (fBm). The long-range correlations were also observed in membrane potential fluctuations of human T-lymphocytes [22], bacteria DNA sequences [23], cardiac rhythm [24], Ethernet traffic [25], and insurances [26]. Despite some theoretical studies include mathematical justification [25, 26], a lack of rigorous mathematical proofs is often observed in the relationship between the long-range correlations of a signal and the fBm.

In this paper we show how the dynamics of a dichotomous stationary process with the long-range correlation, such as underlying the ionic current fluctuations recorded from a single locust potassium channel, is related to the fBm. The proposed model is compatible with the known biological and physical constraints, and also consistent with the information on channel kinetics obtained by the detailed statistical analysis of the experimental data [18–20].

## 2. Basic statistical properties of the experimental signal

The statistical analysis presented recently, for details see [18–20], concerns a data set that was recorded from cell attached patches of adult locust (*Schistocerca gregaria*) extensor tibiae muscle fibres [18, 27]. The complete data consists of one record composed of $N = 250\ 000$ values of the channel current measured at equal intervals $\Delta t = 0.1$ ms, the whole duration being 25 s. The error of measurements of ionic current is equal to $\Delta I = 1$ pA. A sample of the data set is shown in Fig. 1.

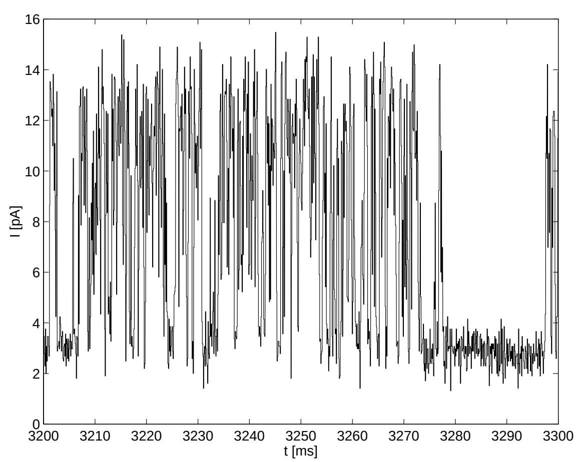


Fig. 1. A part of patch clamp recording of the single BK channel current I(pA) *vs* time (ms), at a pipette potential of +100 mV.

The ionic current signal recorded from a single membrane channel, Fig. 1, reflects the fact that the channel is not permanently open for conduction of ions but continuously switch between closed and open states. The changes are of random nature resulting from *e.g.* thermal fluctuations, variations of the voltage difference across the cell membrane, or from conformational changes of channel proteins. The states of low and high currents correspond to the closed and open channel states, respectively [18–20, 27]. Dividing the investigated signal into periods of closed and open states one can get the periods of closed- and open-states and their distributions. It was shown [19, 20] that the closed-time distribution has a power tail

$$P\{T_{\mathrm{c}} > t\} = 1 - F_{\mathrm{c}}(t) \propto t^{-D_{\mathrm{c}}}, \tag{1}$$

with $D_{\mathrm{c}} = 1.24 \pm 0.06$. As it is seen in Fig. 2 the tail of the closed-time distribution is heavier than the tail of the open-time distribution, *i.e.*, it holds

$$P\{T_{\mathrm{c}} > t\} \gg P\{T_{\mathrm{o}} > t\}.$$

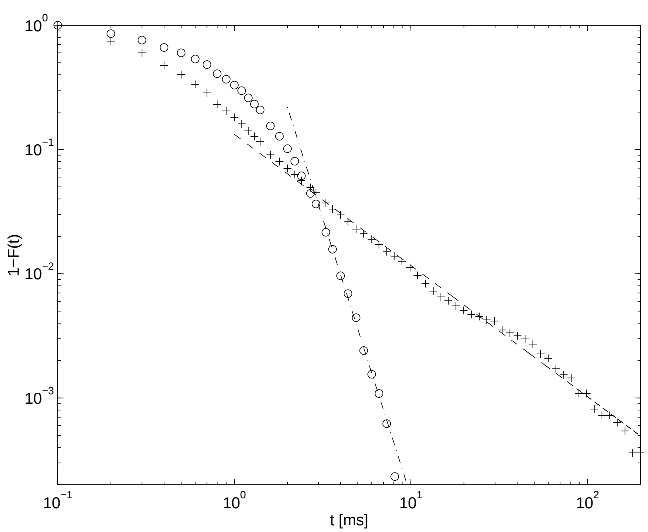


Fig. 2. The tails of the closed- (crosses) and open-time (circles) distributions in log–log scale. The tail of the closed-time distribution is heavier than the tail of the open-time distribution: $P\{T_{\mathrm{c}} > t\} \gg P\{T_{\mathrm{o}} > t\}$.

The time structure of the ionic current time series $\{I_n\}_{n=1}^{N}$ recorded in a sequence of moments $\{t_n = n\Delta t\}_{n=1}^{N}$ yields the autocorrelation function $\kappa(t)$ [20] decaying in time with a power-law

$$\kappa(t) \propto K\, t^{-\alpha_\kappa}, \qquad \text{as} \qquad t \to \infty, \tag{2}$$

where $\alpha_\kappa = D_c - 1$. The constant $K$ reads

$$K = \frac{\langle T_c \rangle^2 (M-m)^2}{(D_c - 1)(\langle T_c \rangle + \langle T_o \rangle)^3}, \tag{3}$$

where $\langle T_c \rangle$ and $\langle T_o \rangle$ is the mean of closed- and open-time, and $m$ and $M$ is the mean of ion current flow in closed and open state, respectively. As it has been already shown [19], the means are finite and take the following values: $\langle T_c \rangle = 0.84 \pm 0.01$ ms, $\langle T_o \rangle = 0.79 \pm 0.01$ ms, $m = 3.2 \pm 0.1$ pA, and $M = 11.0 \pm 0.1$ pA.

The non-Markovian long-memory property of the investigated signal has been confirmed [20] by the self-similarity index $H$ obtained from the Hurst, detrended fluctuation and Orey analyses. The values of $H$ are equal, respectively,

$$\begin{aligned} H_H &= 0.84 \pm 0.08\,, \\ H_D &= 0.89 \pm 0.07\,, \\ H_O &= 0.84 \pm 0.04\,. \end{aligned}$$

The Hurst exponent $H$ provides information on the correlations in the time series measured at different time scales. It is related to the autocorrelation power exponent $\alpha_\kappa$ [13] by means of the following relation

$$H = 1 - \frac{\alpha_\kappa}{2}. \tag{4}$$

## 3. Fractional Brownian motion and its main properties

Fractional Brownian motion $B_H(t)$, introduced by Mandelbrot and van Ness [28], can be simply considered as an extension of the Markovian Brownian process into the non-Markovian case. For every moment $t > 0$ the fBm is defined as

$$B_H(t) = \frac{1}{\Gamma(H + \frac{1}{2})} \times \left\{ \int_{-\infty}^{0} \left[ |t-s|^{H-1/2} - |s|^{H-1/2} \right] dB(s) + \int_{0}^{t} |t-s|^{H-1/2} dB(s) \right\}, \tag{5}$$

where $H \in (0,1)$ is the self-similarity index and $B(t)$ is the Brownian motion with mean 0 and variance $\sigma^2(t) = t$. The process defined in (5) has mean

0 and variance $\sigma_H^2(t) = t^{2H}$. Increments of the fBm (5) are Gaussian and stationary, and its autocovariation function $\rho(t)$ decays with a power law

$$\rho(t) \sim t^{2H-2}. \tag{6}$$

Let us note that the fBm is the only Gaussian self-similar process with the self-similarity index $H$ [29], *i.e.* for all $a > 0$ it holds

$$B_H(at) = a^H B_H(t). \tag{7}$$

Eq. (7) denotes the equality of the finite-dimensional distributions of the process on the right- and left-hand side of the equation [30]. Brownian motion is a special case of the fBm when $H = 1/2$ (its increments are then purely random and therefore uncorrelated with each other). When $0 < H < 1/2$, every positive increment is likely to be followed by a negative one and, conversely, decreases of the $B_H(t)$ value are more likely to be followed by increases. Such a case is called antipersistent. When $1/2 < H < 1$, increases in the values of a process are more likely to be followed by increases, and, conversely, every negative increment is more likely to be followed by another negative one. Such a process is called persistent and it has a long-memory property [13].

Fractional Brownian motion can be obtained via summation of Gaussian and correlated random variables [31]. If the sequence $\{X_i\}_{i=1}^{\infty}$ is Gaussian and stationary with mean 0 and autocovariation $\rho(i-j) = \mathrm{E}X_iX_j$ satisfying the following condition

$$\sum_{i=1}^{N}\sum_{j=1}^{N}\rho(i-j) \sim KN^{2H}L(N) \tag{8}$$

for $N \to \infty$, $H \in (0,1)$, and $K > 0$, then

$$\lim_{N\to\infty}\frac{1}{d_N}\sum_{i=1}^{[Nt]}X_i = \sqrt{K}B_H(t) \tag{9}$$

for $d_N \sim N^H\sqrt{L(N)}$; $[Nt]$ denotes the largest integer number less or equal $Nt$. Function $L$ denotes a slowly varying in infinity function, *i.e.*

$$\lim_{x\to\infty}\frac{L(ax)}{L(x)} = 1$$

for every $a > 0$. The convergence in (9) is weak in the Skorokhod topology [26, 31]; for every bounded continuous functional $f$ it holds

$$\lim_{N\to\infty}\mathrm{E}\left[f\left(\frac{1}{d_N}\sum_{i=1}^{[Nt]}X_i\right)\right] = \mathrm{E}\left[f\left(\sqrt{K}B_H(t)\right)\right], \tag{10}$$

where E denotes the expected value. The condition (8) is fulfilled if the correlation $\rho(n) = \mathrm{E}X_i X_{i+n}$ between two observations $X_i$ and $X_{i+n}$ separated by $n$ time lags decays as

$$\rho(n) \sim K n^{2H-2} L(n) \tag{11}$$

for large $n$ [31]. The presence of the slowly varying in infinity function $L$ in Eqs (8) and (11) enables one to use the above theorem in the case when the power-law condition (6) is slightly disturbed due to the limited length of the time series. Let us note that from the point of relationship between the channel kinetics and the fBm the stationarity of the experimental sequence $\{X_i\}_{i=1}^{N}$ is of great importance. In case of the signal examined (see Chapter 2), it has been tested by means of quantile lines [20, 32].

## 4. Fractional Brownian motion of the effective charge

On the basis of experimental data analysis [19, 20] we can construct a stationary sequence of Gaussian random variables satisfying condition (11). Taking into account that recordings were made with the experimental frequency $f_{\mathrm{ex}} = \frac{1}{\Delta t}$, we may assume that the current flow between the moments of sampling can be approximated by an interpolation. We assume the current to be constant between two consecutive recordings (one can also apply another linear approximation of the current in time interval $\Delta t$ but it does not affect the construction proposed below). Let us also assume that the considered ion channel has constant cross section $S$ and is filled up with an electrolyte with constant volume concentration $c$ of $x$-valued ions (see Fig. 3). The current $I_n$ flowing through the channel in $n$-th moment corresponds to a shift $r_n$ of the effective charge inside the channel

$$r_n = \lambda I_n \Delta t, \tag{12}$$

where $\lambda$ is the linear concentration of ions

$$\lambda = \mathrm{F} S x c \tag{13}$$

and F is the Faraday constant. The current recorded in experiment is of order 1–10 pA with the sampling frequency 10 kHz. The single current recording corresponds hence to flow of about $10^2$–$10^4$ potassium ions. This suggests that we can only track a path of a mean charge representing the ions and not a single ion itself.

It follows from (12) and power-law property of the current autocorrelation function $\kappa(t)$, see Eq. (2), that the covariation of two shifts separated by $n$ time lags $\Delta t$ has also the power-law property

$$\rho_r(n) \propto \sigma_r^{2H} (\Delta t)^{2H} n^{2H-2}, \tag{14}$$

where $2H = 3 - D_{\rm c}$ and $\sigma_r^{2H} = \lambda^2 K$. A total shift $R(t)$ of the effective charge in the channel is then a sum of all shifts until moment $t$

$$R(t) = \sum_{n=1}^{\left[\frac{t}{\Delta t}\right]} r_n . \tag{15}$$

The random process $R(t)$ converges to the fBm if the frequency of recordings increases, *i.e.* the duration of the time lag decreases $\Delta t \to 0$ [26].

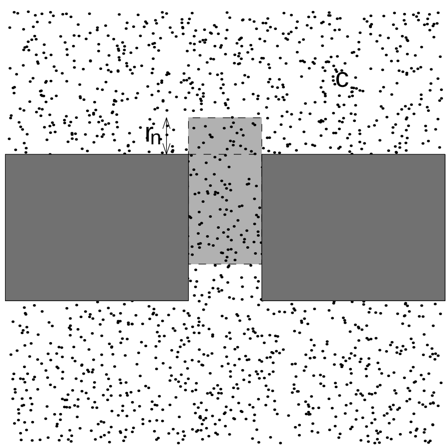


Fig. 3. Shift $r_n$ of the effective charge in a channel with constant cross section (see Eq. (11)).

In order to show the convergence let us consider the sum at the right-hand side of Eq. (15). One can rewrite it in the form

$$\sum_{n=1}^{\left[\frac{t}{\Delta t}\right]} r_n = t\nu - \left(\frac{t}{\Delta t} - \left[\frac{t}{\Delta t} + 1\right]\right)\mu + (\sigma_r \Delta t)^H \sum_{n=1}^{\left[\frac{t}{\Delta t}\right]} y_n , \tag{16}$$

where $\left\{ y_n = \frac{r_n - \mu}{(\sigma_r \Delta t)^H} \right\}_{n=1}^{\infty}$ denotes a stationary series with mean 0 and covariation function of the form

$$\rho_y(n) \propto n^{2H-2} , \tag{17}$$

following from Eq. (14). The parameter $\mu$ denotes the mean value of $r_n$ and reads

$$\mu = \nu \Delta t = \lambda \frac{M \langle T_{\rm o} \rangle + m \langle T_{\rm c} \rangle}{\langle T_{\rm o} \rangle + \langle T_{\rm c} \rangle} \Delta t \, .$$

The first term on the right-hand side of Eq. (16) is a constant $\nu$ multiplied by time and denotes the process drift. The second one converges to 0 while $\Delta t$ tends to 0. If we assume that the experimental frequency increases $k$-times we have to substitute $\Delta t$ in Eq. (16) by $\frac{\Delta t}{k}$. It follows from Eq. (9) that the third term in (16) converges to the fBm for fixed $t$ and $k \to \infty$

$$(\sigma_r \Delta t)^H \frac{1}{k^H} \sum_{n=1}^{\left[k\frac{t}{\Delta t}\right]} y_n \longrightarrow (\sigma_r \Delta t)^H B_H \left(\frac{t}{\Delta t}\right).$$

Due to the self-similarity property (7) of the fBm, we get

$$(\sigma_r \Delta t)^H B_H \left(\frac{t}{\Delta t}\right) = B_H (\sigma_r t).$$

The considerations presented above have shown that with an increase of the experimental frequency the shift $R(t)$ of the effective charge in a single ionic channel is well described by the fBm

$$R(t) = \nu t + B_H (\sigma_r t) \tag{18}$$

with the self-similarity index

$$H = \frac{3 - D_{\rm c}}{2},$$

the drift

$$\nu = \lambda \frac{M \langle T_{\rm o} \rangle + m \langle T_{\rm c} \rangle}{\langle T_{\rm o} \rangle + \langle T_{\rm c} \rangle},$$

and the scale parameter

$$\sigma_r^{2H} = \lambda^2 \frac{\langle T_{\rm c} \rangle^2 (M - m)^2}{(D_{\rm c} - 1)(\langle T_{\rm c} \rangle + \langle T_{\rm o} \rangle)^3}.$$

The fBm is not, however, observed in an experiment. It is only a mathematical, idealized construction with properties similar to those observed in real data. The agreement follows from the fact that applying the statistical tools (such as the Hurst, detrended fluctuation and Orey analyses, or quantiles) we simply calculate mean values of different functionals. Since the convergence holds in the Skorokhod topology, see Eq. (10), we get the statistical properties similar to that calculated for the fBm.

## 5. Conclusions

The main objective of the paper was to present a rigorous mathematical basis for the interpretation of the non-Markovian long-memory nature of ionic current signals as an example of a fractional Brownian motion. Our aim was to explain why the statistical properties of the investigated data seem to be compatible with the properties of this self-similar stochastic process and also to find the experimental conditions under which the correspondence of the fractional Brownian motion to the single channel kinetics holds.

The analysis presented in this paper shows that the total shift of an effective charge in the ionic membrane channel can be well approximated by the fractional Brownian motion if the recorded current signal is stationary and exhibits long-range correlations. The higher the sampling frequency is the better approximation can be made.

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