CHARACTERIZATION OF THE ASYMMETRIC ACTION OF A SINGLE PORE IN A TRACK-ETCHED MEMBRANE*

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Transport properties of a single pore in a track-etched poly(ethylene terephthalate) membrane are characterized using statistical analysis. Probability density function, autocorrelation function, power spectrum, Hurst and detrended fluctuation analysis, as well as Orey's index were the tools used to characterize the ion current behavior. The examined pore is conical in shape and has been obtained by one-sided electric field stopped etching. The pore has a highly nonlinear diode-like current-voltage characteristic, with preferential flow of ions in one direction. We show that the examined current fluctuations at −2V and +2V, however looking very similar, reflect differences in action of the system at the two polarities. The existence of longer memory for the weaker signal, recorded at −2V, has been found.

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1. Introduction

The development of the patch clamp technique [1–3] was a decisive factor in cell biology enabling the direct observation of electrical currents through biological ion channels. The technique detects ionic current through single channels and highlights local transport properties of a given membrane [4,5]. Application of the patch clamp technique to studies of ionic transport in purely synthetic membranes allowed to discover that single channel ion current fluctuations can also be observed beyond biological systems [6]. The time series of ion current recorded in biological and synthetic systems look very similar. In both systems the ion current continuously switches between various values reflecting different states of the channel [7–9]. High values of the current correspond to open states and low values to closed states (or inactive open states) of the channel. Ion-track channels in a poly(ethylene terephthalate) (PET) membranes have been studied in detail and shown to have similar transport properties as Triton- and the big conductance locust potassium channels (BK channel) [9–12]. So far, pores in PET membranes have been produced by double-sided etching of a polymer, enabling formation of pores of several ten-micrometer length, and 10–20 nm diameter [9,13]. Comparing those dimensions with a biological system one notices, however, that such pores have 10 times larger diameter and are 50 000 times longer than biological ion channels. To generate pores of smaller dimensions in PET, electric field-stopped asymmetric etching has been developed [14]. It leads to the formation of a roughly conical pore with most of its electrical resistance contained in its tip (Fig. 1). As a consequence we can now study transport properties of pores of much shorter length than before, bringing us closer to the dimensions met in biological systems. Another interesting feature of the asymmetric pore is a highly nonlinear diode-like current-voltage characteristic [14]. At neutral and basic pH values this asymmetric pore shows strong rectification, favoring a preferential flow of ions in one direction. The origin of the observed asymmetry is not yet fully understood. However, the asymmetry seems related to the asymmetry of the surface charge brought about by one-sided etching procedure [14]. The main objective of the paper is to check whether this highly asymmetric system produces also a nontrivial, asymmetric pattern of ion current behavior. The use of such techniques like probability density function, autocorrelation function and power spectrum helped us to show the main characteristics of the conical channel action. The self-similar properties of ion current have been studied by means of the Hurst and detrended fluctuation analysis as well as by the recently introduced Orey index [15].

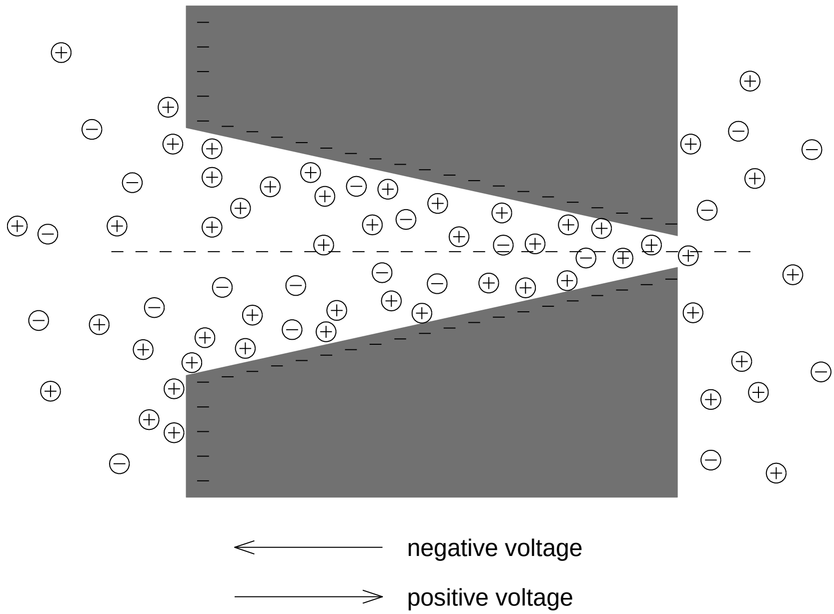

Fig. 1. Scheme of conical pore obtained through single-sided etching of a single ion irradiated foil made of poly(ethylene terephthalate). The direction of the positive ions flow is indicated in the figure.

2. Materials and methods

The examined membrane consists of poly(ethylene terephthalate) (Hostaphan, PET) of a thickness of $10\pm1\mu$m. It was penetrated with a single gold ion at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany, using the developed there single ion irradiation procedure [13,16]. Asymmetric etching of the membrane in hot aqueous sodium hydroxide solution [13] leads to a single pore membrane with highly asymmetric properties [14] (Fig. 1). The estimated diameter of the narrow part of the pore is less than 20 nm. The size exclusion technique [17] using poly(ethylene glycol) (PEG) of molecular weights between 100 and 35 000 enabled us to determine pore tip sizes smaller than 3 nm, the size of PEG molecules at which blockage of the pore occurred. The membrane has been placed in a conductivity cell whose two compartments have been filled with 0.1 M KCl solutions of pH 6 and 8, on the wide and narrow sides of the pore, respectively. Examples of ion current recordings through a conical track-etched pore for applied voltages –2V and +2V at a sampling frequency of 250 Hz are shown in Fig. 2.

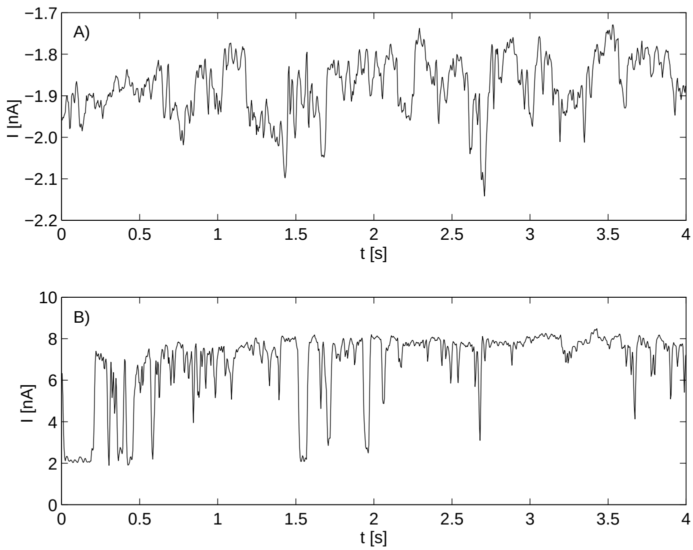

Fig. 2. The original signals of ion current recorded from a single channel in a PET membrane at the voltage −2V (A) and +2V (B). +2 V means that +2 V were applied to the electrode on the narrow side of the pore.

3. Results and discussion

3.1. Stationarity of the ionic current signals

One of the first questions asked while examining a given process is about its stationarity. Stochastic process X_t is stationary if the finite-dimensional distributions are independent of time shifts [18]. The strict mathematical definition is, however, inconvenient for a direct application. To test the stationarity of the ion current time series we have decided therefore to use a much simpler approach provided by quantiles [19]. A quantile of order $\varepsilon \in [0,1]$ is defined through a probability P being equal to ε that the recorded signal at the time t is smaller than k_ε

$$P\{X_t \leq k_\varepsilon(t)\} = \varepsilon \,.$$

In simple words, a quantile k_ε is such a number that ε-th fraction of sample's realizations are smaller than it. The quantiles of different orders calculated along the series form a family of lines by means of which one can study the properties of the investigated process [20, 21]. The stationarity is indicated by quantile lines parallel to the time axis. While investigating different processes one can also observe other patterns plotted by the quantile lines: drifts, increasing volatility, periodicity, pulsations or simply the lack of any general rule.

Quantiles are usually obtained from a large set of realizations (sample paths) of a particular stochastic process [20, 21]. Having only one time series (one realization) recorded for each voltage, to use the quantile approach, we had to apply the method shown in [19]. It is based on "production" of a set of paths by cutting the whole record into smaller subrecords (here of length 1.2 s). As the next step, for every moment t we calculated such a real number $k_\varepsilon(t)$ that ε-th fraction of the subsequent values at the moment t were smaller than $k_\varepsilon(t)$. The quantile lines for the ionic current signals recorded from a PET track-etched membrane are presented in Fig. 3. The figure shows that, in spite of the fluctuations, caused by finite lengths of the investigated samples, the lines are time invariant. Note that there is no periodic behavior or any other trend. On the basis of this observation, we may assume that the studied time series are stationary that means they have a constant mean and variance. The existence of those statistical characteristics can be checked, however, by examining the currents' probability density function, shown in the next section.

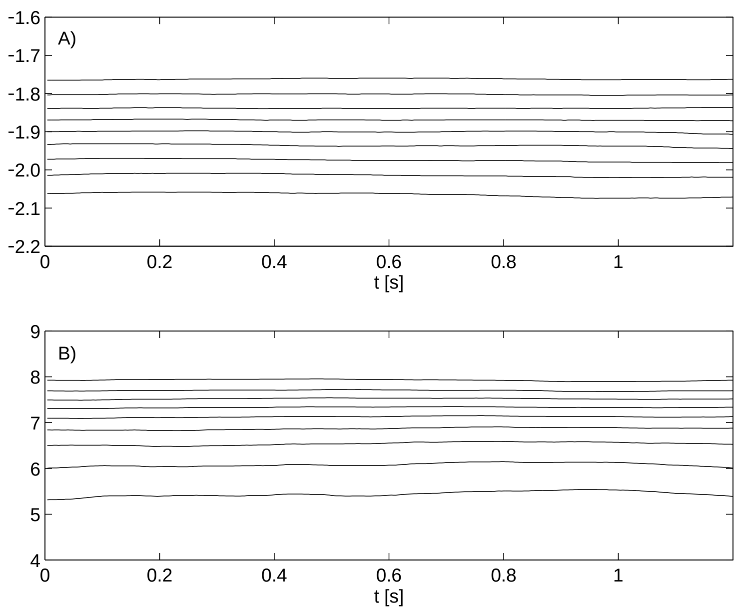

Fig. 3. The quantile lines of the signal of ionic currents recorded from a single channel in PET membrane at the voltage –2V (A) and +2V (B). The quantiles are of the order of 0.1 to 0.9 step 0.1, counting from the bottom to the top of the figure. The fluctuations result from the finite lengths of the samples.

3.2. Probability density function

A statistical analysis of ion current time series has been started from determination of the current probability density function (PDF). We have decided to use here the kernel density estimator [20,22] introduced by Rosenblatt and Parzen rather than the more popular and simpler histogram. The kernel estimator has been already successfully applied to the analysis of ion transport time series and shown to be much more effective than the widely used histogram [19,23,24].

The properties of the current probability density function (see Fig. 4) have been studied for the time series recorded at the investigated system for the two polarities. The determined PDFs clearly revealed the difference in the system behavior at positive and negative voltages. At –2V the current is smaller with weaker volatility, while positive voltage seems to enhance ion transport and fluctuations of the signal. The average current for –2V and

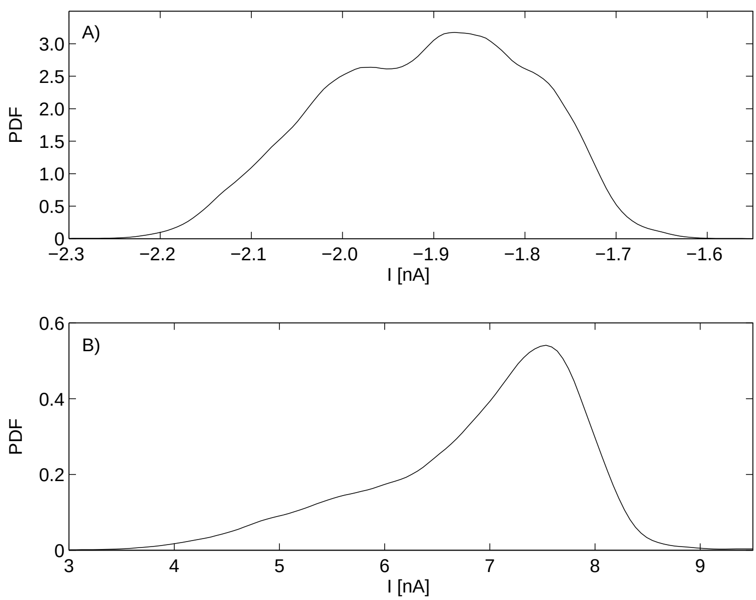

Fig. 4. The kernel estimator of probability density function of ion current time series through a single pore in a PET membrane for –2V (A) and +2V (B). Note the change of the scale.

+2V reads: $I_{-2V} = -1.91 \pm 0.12$ nA and $I_{+2V} = 6.89 \pm 1.02$ nA, respectively. This result is in accordance with earlier findings revealing an intrinsic asymmetry of a conical pore in a wide range of voltage applied [14]. The typical current-voltage characteristics measured in a conical pore has been shown in Fig. 5. Note the increase of error bars with increasing absolute value of the voltage, indicating stronger ion current fluctuations. The conductivity for the negative voltage is equal to 56 ± 1 pS while for the positive one is about five times greater. Moreover, as can be seen in Fig. 5, the behavior of the pore is ohmic only for the negative polarization showing a strong non-linearity for the positive voltage.

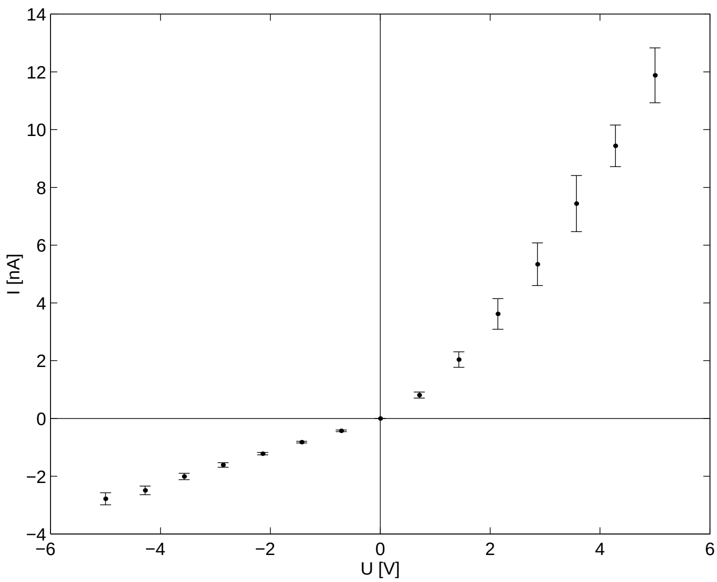

Fig. 5. Intrinsic asymmetry of a conical pore. Current-voltage characteristic in symmetric concentration and pH conditions at 0.1M KCl and pH 7. The graph presents average values with standard deviation obtained after averaging out 10 cycles of triangle voltage signal applied. The increasing size of the error bars with decreasing voltage reflects the increasing size of the electric current fluctuations of the system.

Another important feature revealed is the higher asymmetry of PDF for the current recorded at the positive voltage. This effect can be measured by so called asymmetry coefficient (skewness coefficient) [18], defined as

$$\beta = \left\langle \left(\frac{I - \mu}{\sigma} \right)^3 \right\rangle ,$$

where μ stands for the signal average value, σ is the standard deviation and $\langle \cdot \rangle$ indicates an average taken over the data. The skewness coefficient can be conveniently calculated using an estimator

$$\beta = \frac{N}{(N-1)(N-2)\sigma^3} \sum_{k=1}^{N} (I_k - \mu)^3 ,$$

where N is a length of the time series $\{I_k\}_{k=1}^N$. For symmetric (with respect to the mean value) distribution the skewness coefficient $\beta = 0$; larger absolute values of β correspond to more asymmetric distributions. The skewness coefficient β for the current through a pore in a PET membrane, recorded at –2V and +2V equals $\beta_{-2V} = -0.04 \pm 0.28$ and $\beta_{+2V} = -0.84 \pm 0.15$, respectively. This result clearly suggests higher asymmetry of PDF of the signal recorded at the positive voltage.

From the PDFs shown in Fig. 4 it is not easy and straightforward to distinguish between open and closed states. There are some fluctuations in the density around the maximum for –2V but this effect may be brought about by the superposition of several, different current states. The value of the skewness coefficient does not indicate the existence of distinct states either. The properties of PDF found for the signal recorded at the positive voltage are different. The strong asymmetry of the determined PDF can result from the existence of just two states, an open — seen as a maximum of the density for high current values — and a closed one, which appears as a flat, elongated part of the density function for low current values. The presence of two states in time series is suggested by the skewness coefficient, although it is not possible to find uniquely a minimum of the PDF function, and to distinguish clearly between open and closed states [23–25].

3.3. Autocorrelation function

Autocorrelation function gives a possibility to study an existence of memory in an examined system. Its decay gives information on the speed of correlation loss between states separated in time. The autocorrelation function $\kappa(s,t)$ of a stationary ionic current signal $\{I_k\}_{k=1}^N$ is defined as

$$\kappa(t) = \kappa(s,t) = \frac{\langle I_s \cdot I_{s+t}\rangle - \mu^2}{\sigma^2}\,,$$

where $t = k/f_{\rm ex}$, $f_{\rm ex}$ is the sampling frequency, σ is a standard deviation and μ is the mean value of the sample [18]. The stationarity of the examined process has been discussed and tested in Section 3.1. The autocorrelation function of ion current recorded in the synthetic system considered here is presented in Fig. 6 in the semilogarithmic scale. The plot reveals the existence of a long memory in the investigated system — the autocorrelation function decreases slower than exponentially. Moreover, the best fit function is not a power-law function (as in the case of an ionic current through a single channel in a biological membrane [23]) but a stretched exponential

$$\kappa(t) \propto {\rm e}^{-\left(\frac{t}{\tau}\right)^a}\,,$$

where τ and a are positive constants. The best fits obtained for the studied time series are plotted in Fig. 6. The constant a is significantly lower than 1 and equals $a_{-2V} = 0.38 \pm 0.10$ and $a_{+2V} = 0.43 \pm 0.10$. Fig. 6 reveals an asymmetry in a memory length between time series recorded at the two polarities.

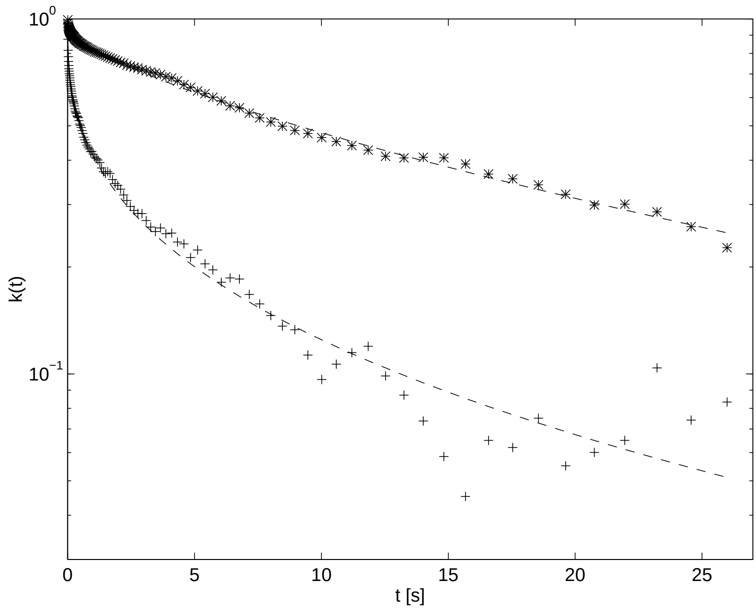

Fig. 6. The autocorrelation function of the ionic current signal through a PET membrane for −2V (crosses) and +2V (stars).

3.4. Power spectrum analysis

Power spectrum is the Fourier transform of an autocorrelation function. In our case it has been determined through a periodogram $I(f_j)$ [26]. It enables one to study the concentration of power in different frequency bands [27, 28] and for a time series $\{X_k\}_{k=1}^{N}$ is defined as

$$I(f_j) = \frac{1}{N} \left| \sum_{k=1}^{N} X_k e^{-2\pi i k f_j} \right|^2 , \tag{1}$$

where $f_j = j/N$ is called a Fourier frequency; j is an integer number such that $-0.5 < f_j \leq 0.5$. Note that in order to use a physical time t instead of the sample number k in Eq. (1) it is necessary to multiply the Fourier frequency f_j by the sampling frequency f_{ex} used in the experiment. Having the periodogram one can easily calculate the estimator of the power spectrum $S(f)$ of the series by averaging the periodogram with a proper weight function [26]. The function should be non-negative, symmetric and normalized, as *e.g.* the Bertlett kernel function

$$K(u) = \begin{cases} \frac{3}{4}(1-u^2) & \text{if } u \in [-1,1] \\ 0 & \text{if } u \notin [-1,1] \,. \end{cases}$$

The power spectrum determined for the time series recorded in the synthetic system is presented in log–log scale in Fig. 7. The two straight lines,

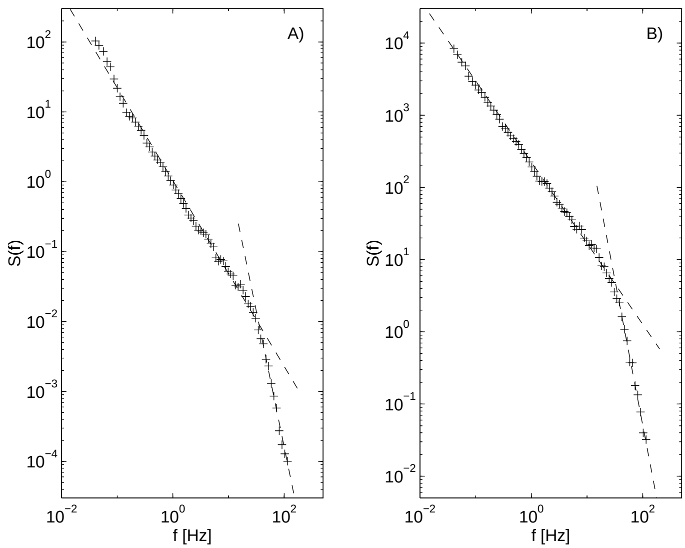

Fig. 7. The power spectrum of ion current signal through a single pore in a PET membrane for –2V (A) and +2V (B). The straight lines reveal the power-law properties of $S(f)$.

corresponding to the power law scaling can be distinguished for the positive and negative voltage applied. For the time series recorded at –2V the power law relations have the form:

$$S_{-2V}(f) \propto \begin{cases} f^{-1.32\pm0.12} & \text{for} \quad f < 40\text{Hz} \\ f^{-3.88\pm0.20} & \text{for} \quad f > 40\text{Hz} \end{cases}$$

but the significance of the two exponents is questionable. The two scaling regions found for the time recorded at the positive potential can be described by two very similar power laws:

$$S_{+2V}(f) \propto \begin{cases} f^{-1.20\pm0.12} & \text{for} \quad f < 40\text{Hz} \\ f^{-4.40\pm0.20} & \text{for} \quad f > 40\text{Hz} \end{cases} \,.$$

The result for the positive polarity reveals, therefore, slightly shorter memory compared with the signal recorded for the negative polarity. Interestingly, the two time series have the same threshold for the power laws found in their power spectra equal to 40Hz. Large values of the exponents observed for the two time series may be connected with the behavior of autocorrelation function, which does not fulfill a power law but a stretched exponential.

3.5. Self-similarity

Information about the time series structure, correlations and its fractal properties is provided by the so called self-similarity index H [29, 30]. A stochastic process $X(t)$ is called self-similar with index H if it has the following property [18]:

$$X(bt) = b^H X(t)\,, \tag{2}$$

when the equality is in a sense of finite-dimensional distributions and $b > 0$. For example, the Brownian motion is self-similar with $H = 1/2$ while the self-similarity exponent of the Lèvy flight is equal to $1/\alpha$, where $\alpha \in (0, 2)$. The self-similarity index H can be estimated by statistical methods from the realization of a stochastic process. Here we would like to show and discuss the application of the Hurst analysis and the Orey index.

Hurst analysis: The rescaled range analysis developed by Hurst [31] may be used to study correlations in the time series measured at different time scales. The detailed description of the procedure leading to the determination of the Hurst exponent has been given *e.g.* in [19, 29, 31]. The analysis is based on a power law increase of the process fluctuations $\langle R/S \rangle$ with the increase of the width of window Δt, in which the fluctuations are studied

$$\left\langle \frac{R}{S} \right\rangle (\Delta t) \propto (\Delta t)^H\,, \qquad 0 < H < 1\,. \tag{3}$$

The exponent H is known as Hurst coefficient or Hurst exponent. Its value provides information on the correlations existing in the time series measured at different time scales. When $H = 1/2$, the changes in the values of a time series are random and, therefore, uncorrelated with each other. When $0 < H < 1/2$, increases in the values of a time series are likely to be followed by decreases and, conversely, decreases are more likely to be followed by increases. Such a time series is called antipersistent. For $1/2 < H < 1$, increases in the values of a time series are more likely to be followed by increases, and, conversely, decreases are more likely to be followed by decreases. Such a time series is called persistent. Its characteristic property is a long memory [29].

For the ion current at the synthetic system recorded at –2V and +2V the Hurst exponent has been found to be equal to:

$$H_{-2V} = 0.96 \pm 0.07$$

and

$$H_{+2V} = 0.92 \pm 0.07,$$

respectively. (As Hurst exponent cannot be higher than 1, the "effective" standard deviation of H for the negative voltage is asymmetric with the upper limit 0.04.) The value of H exponent is, therefore, significantly higher than 0.5, what suggests the persistent character of ion transport through a pore in a PET membrane. We also performed detrended fluctuation analysis (DFA) which works similar to the Hurst analysis but it takes into account a local trend of the studied process [32–34]. The obtained results are however very similar. The DFA exponent is significantly larger than 0.5 and even slightly closer to 1 than the Hurst exponent. As it could not distinguish between the two time series (obtained exponents were not significantly different) the next step in the self-similarity studies was, therefore, to apply the Orey index.

Orey index: The Orey index γ is a new method of the time series analysis, which has been recently proposed for analyzing financial data sets [15] and was already used in [19] to study an ionic current fluctuations in a single biological membrane channel. The Orey index estimates the self-similarity parameter H of a stationary Gaussian stochastic processes and can be treated as a complementary technique to the Hurst analysis. Namely, the equivalence of the Orey index and the self-similarity index H (obtained by other statistical methods) suggests the Gaussian nature of the investigated process. The advantage of the Orey index is the compact formula from which it can be determined, without the necessity of application of any additional tools, like log–log plot and linear regression.

The Orey index γ can be estimated [15, 35] by means of an *ordinary least squares estimator* $\widehat{\gamma}^{\mathrm{OLS}}$. For a given time series $\{\Delta X_k; k = 1, 2, \ldots 2^m\}$ consisting of 2^m observations we have to calculate a cumulative series $\left\{X_j = \sum_{k=1}^{j} \Delta X_k; j = 1, 2, \ldots 2^m\right\}$ and an incremental variance

$$u^2(n) = \frac{1}{2^n} \sum_{j=1}^{2^n} (X_j - X_{j-1})^2 \,,$$

where $X_0 = 0$ and $n = 1, 2, \ldots m$. The Orey index estimator is given then by

$$\widehat{\gamma}^{\mathrm{OLS}} = \sum_{j=1}^{m} y_j \log_2 u(j)\,,$$

where $y_j = (x_j - \bar{x})/\sum_{j=1}^{m}(x_j - \bar{x})^2$ and $x_j = \log_2 1/2^j = -j$ for $j = 1, 2, \ldots m$. This estimator is strongly consistent with the Orey index γ.

The values of the Orey's index for the time series recorded at the synthetic system read

$$\gamma_{-2V} = 0.93 \pm 0.03$$

and

$$\gamma_{+2V} = 0.84 \pm 0.03\,.$$

The important result is that the Orey index appeared to be sensitive to the difference in the memory reflected in the two time series. It is consistent with information provided by autocorrelation function and power spectrum, which reveal existence of longer memory in case of ion current signal recorded at –2V. It is not possible to learn about the distribution of ion current increments, although the consistence of the Orey and Hurst's analysis, observed especially clearly for the negative voltage, suggests their Gaussian character.

4. Conclusions

The main objective of the paper was to study an influence of an asymmetry of a conical pore on the ion current behavior. Single conical pore is a strongly nonlinear system: the measured current-voltage characteristic shows a typical diode-like behavior with one preferred direction of ionic flow. The average current recorded at the positive voltage is almost four times larger than the signal recorded for the same absolute value of the voltage of different polarity. Higher current is characterized by larger variance, which reflects stronger ion current fluctuations. The main issue considered in the paper was, therefore, to check whether the ion current recorded for the same absolute value of the voltage but with different polarity reveals different pattern of behavior. The special emphasize has been put on the deterministic and/or stochastic nature of the process, as well as on its memory. We also asked the question about self-similar character of the observed ion current fluctuations. The performed analysis has shown that the two recorded time series, in spite of certain similarities, reveal in many respects big differences. They both have long term correlation shown by autocorrelation function, power spectrum and self-similarity studies. It follows from Hurst and Orey's analysis that the character of ion current flow in both directions is persistent. All the analysis however indicated clearly that the weaker signal possesses a stronger deterministic component, seen as a slower decrease of autocorrelation function and higher value of Orey's index. It would be, therefore, of special interest to examine the behavior of conical pore in wider span of applied voltage. Perhaps it would be possible to determine conditions for which the system could produce a desired pattern of behavior: stochastic, deterministic and mixed. These studies can also be very helpful in examination of the possible reasons of observed asymmetry of transport properties of a conical pore. Finally, the examined system, having the dimensions close to these met in a biological system can be used as an analogue of a biological channel.

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