Searching for self-similarity in switching time and turbulent cascades in ion transport through a biochannel. A time delay asymmetry

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Abstract:
The process of ion transport through a locust potassium channel is described by means of the Fokker-Planck equation (FPE). The deterministic and stochastic components of the process of switching between various conducting states of the channel are expressed by two coefficients, $D^{(1)}$ and $D^{(2)}$, a drift and a diffusion coefficient, respectively. The FPE leads to a Langevin equation. This analysis reveals besides the well known deterministic aspects a turbulent, cascade type of action. The (noisy-like) switching between different conducting states prevents the channel from staying in one, closed or open state. The similarity between the hydrodynamic flow in the turbulent regime and hierarchical switching between conducting states of this biochannel is discussed. A non-trivial character of $D^{(1)}$ and $D^{(2)}$ coefficients is shown, which points to different processes governing the channel’s action, asymmetrically depending on the history of the previously conducting states. Moreover, the Fokker-Planck and Langevin equations provide information on whether and how the statistics of the channel action change over various time scales.

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1 Introduction

Ionic transport through biological membranes is one of the basic phenomenological processes necessary for maintaining a system alive (Hille, 1992; Schrempf et al., 1995). The mechanism, even after so many years and so many intense investigations is not yet fully understood nor even well known. A full picture should consist of combinations of causes with mechanical, electrical, thermodynamic and chemical origins (Hille, 1992; Cha et al., 1999). Ion channels are thought to be made of flexible transmembrane proteins (Hille, 1992). The ion transport through a biological channel is certainly a process of very mixed and complex nature, being governed by the noise as well as deterministic forces (Colquhoun and Hawkes, 1995) coming e.g. from external or endogenous field(s). A serious step forward was done by Bezrukov and Winterhalter who put forward the conjecture that it is the motion of channel structural constituents that induces channel switching between the open and closed states (Bezrukov and Winterhalter, 2000), as noise does in stochastic resonance processes (Beuzi et al., 1981). An evidence for this hypothesis has been experimentally provided recently on the basis of artificially controlled nanopores (Siwy and Fuliński, 2002). Indeed it can be now clear that a nanopore which possesses mobile elements exhibits scale dependent ion current fluctuations while the nanopore with smooth and stable walls produces stable ion current signals. The (stochastic) movement of the channel structural constituents seems therefore to be a dominant factor determining the channel behaviour. Moreover, those studies showed that the power spectrum of the ion current fluctuations is inversely proportional to a power of the frequency, which points to, but does not prove, the self-similarity in time of processes underlying the channel switching. Multiple exponentials in the lifetime distributions themselves indicate high degrees of correlations (Colquhoun and Sigworth, 1995).

Our knowledge on the random and/or deterministic character of those processes is however very limited. More or less sophisticated techniques are in fact used to identify features embedded in single-channel recordings (Fredkin and Rice, 1992; Mercik, et al., 1999; Wagner and Timmer, 2000; Mercik and Weron, 2001; Siwy et al., 2002). A difficulty stems in the fact that the whole membrane structure is of nanometer scale and can hardly be locally probed and the tiny electrical current measured through a single channel can reach $10^{-11}$ ampere order of magnitude. Yet, in the patch clamp technique (Neher and Sakmann, 1976) when constant voltages are applied, the ion current switches between regimes, be they composed of discrete or not levels is still an open question, - the switching often resembling some dichotomous noise. Let it be emphasized that even though the observed ion current fluctuations look random, a non-Markovianity, i.e. causality, of the process seems proven in a number of cases.

One of the especially extensively examined systems is a voltage-gated channel in a locust muscle (BK channel) (Gorczyńska et al., 1996). It reveals well distinguished

\[4\text{http://focus.aps.org/story/v10/st19}\]
conducting regimes: high values of ion current corresponding to the open state(s), while low currents point to channel closed state(s). In each regime, the measured currents surely fluctuate around a certain conductance level, but the fluctuation distributions, being discrete or not, of finite range or not, are far from universal but are of not the main concern here. We focus our attention on the features, which govern the switching between those (two ensembles of) states, and study the time series of their durations. The signal of ion current through a single BK channel has been previously subjected to the detailed analysis by the autocorrelation function (Mercik et al., 1999), the Hurst exponent for the long range correlations (Mercik, et al., 1999; Mercik and Weron, 2001; Siwy et al., 2001) as well as checking Markovianity on the basis of the Smoluchowski-Chapman-Kolmogorov equation (Fuliński et al., 1998). The existence of correlations and deterministic components have been found by all those methods. However it was also shown that a state memory effect is present not only between successive conducting states of the channel but also independently within the closed and open states themselves (Siwy et al., 2001). Thus the next step should be to characterize the random aspects in closing and opening of such ion channels in some way.

One rigorous way to sort out the noise from the deterministic components is to examine in details correlations at different time lag scales through the so called master equation, i.e. the Fokker-Planck equation (and derivation of the subsequent Langevin equation) for the probability distribution function (pdf) of time and space signal increments (Gardiner, 1983; Friedrich et al., 2000). This theoretical approach, based on rigorous statistical principles, is often the first step in sorting out the best model(s). In this paper we would like to derive such an FPE, directly from the experimental data of ion current fluctuations in the BK channel, whence describing the evolution of e.g. dwell time differences as a function of the number of interval events (number of closed events for differences in closed dwell times, number of open events for differences in open dwell times, etc.). In order words we examine series of dwell-times durations consisting of successive open (o) and closed (c) states $T_{o,c}(i_{o,c})$, as well as the series of durations of closed $T_c(i_c)$ and open states $T_o(i_o)$, treated separately.

Following an approach similar to (Friedrich et al., 2000; Renner et al., 2001; Ausloos and Ivanova, 2003; Ivanova et al., 2004) we show that the FPE can be well derived in terms of the first (two) moments of the experimental data probability distribution function $p(\Delta T, \Delta n)$, where $\Delta T$ is an increment of the closed or dwell-time series, and $\Delta n$ stands for the time delay between the specific states. We would like to emphasize that the method is model independent. Moreover the technique allows examination of long and short time scales on the same footing. The discussion of the results seem to induce some thinking about new features of correlations in ionic transport. Such an approach is in fact in line with unclassical ion transport models, e.g. based on fractal ideas for the geometry of such membranes (Roncaglia et al., 1994; Bassingthwaighte et al., 1994; Liebovitch and Todorov, 1996), though multifractal considerations might be ... timely. From the start let us recall however that a multifractal process in time can exist on a non-fractal geometrical network.

The solution of the FPE yields the probability distributions with high accuracy. Furthermore, the so found analytical form of both drift $D^{(1)}$ and diffusion $D^{(2)}$ coefficients appearing in the FPE has a simple physical interpretation, reflecting the
influence of the deterministic and random forces on the examined ion transport process. For instance deterministic forces can be thought to be derived from potential gradients in the case of physical or chemical fields, and originate from thermal (or other physical) noise in the case of stochastic forces.

Additionally, the time lag fluctuation probability distributions and the diffusion coefficient enable to trace the existence of hierarchy or cascade processes, underlying the switching phenomena. The analogy between the FPE for the ion transport through membranes can thus be briefly compared with the similar one performed for a hydrodynamic flow at the turbulent regime onset. It evokes nontrivial mechanisms to be included in realistic models.

2 Experimental data and variables to be analyzed

We hereby discuss a long data set of ion current recorded through a single large-conductance locust potassium channel (BK channel), as described in (Gorczyńska, 1996; Fuliński et al., 1998). The so published and selected for its length ion current data consists of 250 000 points separated by 0.1 ms, thus the total duration of the time series is 25 s. The probability density function of the ion current has been found to be distinctly bimodal, with a well marked threshold at \( I^* = 5.6 \pm 0.2 \) pA, as described in (Mercik et al., 1999). The value of \( I^* \) separates therefore two modes of the ion current action. A given ion current point is categorized as belonging to an open state if \( I > I^* \), otherwise it belongs to the closed state time series. This procedure led to formation of the dwell-time series of all durations of open and closed states, starting with open state duration, \( T_{o,c}(j_{o,c}) \), \((i_{o,c}=1, \ldots, 30604)\) as well as two series of durations of closed \( T_c(i_c) \), \((i_c=1...15302)\) and open states \( T_o(i_o) \), \((i_o=1...15302)\), treated separately. We have focused on the analysis of the dwell-times series.

Examination of the fluctuations of a time series can be performed via studies of the intervals’ fluctuations. The intervals can be expressed by calculating returns, log-returns, or increments (Ausloos and Ivanova, 2003). Here, we have used the increments

\[
\Delta T_{o,c}(\Delta n_{o,c}) = T_{o,c}(j_{o,c} + \Delta n_{o,c}) - T_{o,c}(j_{o,c}), \quad j_{o,c} = 1, \ldots, (i_{o,c} - 1),
\]

\[
\Delta T_c(\Delta n_c) = T_c(j_c + \Delta n_c) - T_c(j_c), \quad j_c = 1, \ldots, (i_c - 1),
\]

\[
\Delta T_o(\Delta n_o) = T_o(j_o + \Delta n_o) - T_o(j_o), \quad j_o = 1, \ldots, (i_o - 1),
\]

where \( \Delta T \) is a time increment of the time state duration, and \( \Delta n \) stands for the time delay between the specific states. Derivation of the Fokker-Planck equation presented in the next Section has been based on single and joint probability density functions (pdf) of \( \Delta T_{o,c}(\Delta n_{o,c}) \), \( \Delta T_c(\Delta n_c) \) and \( \Delta T_o(\Delta n_o) \).
The analysis has been performed for the experimental data and their surrogates created by random shuffling of the data positions (Bassingthwaighte et al., 1994). This enabled us checking the significance of obtained results.

3 Results and discussion

3.1 Probability density functions

Figures 1-3 show the probability density functions (pdf) of the dwell-time increments for the open – closed, closed and open series. We have used different discrete bins to obtain interval contents of similar length, needed for the statistical tests. The corresponding shuffled (sh) cases to be used for statistical tests are not shown for the sake of space. Note that the pdfs of the closed – state durations and of the time series of open and of closed dwell-times are qualitatively similar (for open states only the $\Delta T$ range is significantly shorter). Moreover, all pdf’s show a surprisingly high probability for large changes of the states duration (up to 300 ms!), so called extreme events. Additionally, in the examined time ranges, the obtained pdfs change their character very weakly, which is in a very good agreement with information given by the detrended fluctuation analysis (DFA) studies. We would like to note that the existence of positive correlations in all series of dwell-times has been previously shown in the same analyzed range of the lag $\Delta n$ (Siwy et al., 2001; Siwy et al., 2002) as the one used here.

More detailed information about the correlations present in the time series is given by joint pdf’s, depending on $N$ variables, i.e. $p^N(\Delta T_1, \Delta n_1; \ldots; \Delta T_N, \Delta n_N)$. We started to address this issue by determining the properties of the pdf for $N = 2$, i.e. $p(\Delta T_2, \Delta n_2; \Delta T_1, \Delta n_1)$. Contour plots for the equal values of $\Delta T$’s offer a clear way of presenting the results. The tilted and asymmetric (triangular) character of the pdf’s (Fig. 4(a-c)) for the examined series is quite unusual and points to the statistical dependence (correlation) between the increments in all examined time series. Negative increments especially are characterized by very high correlation, which confirms a persistency of the time series towards (negative) changes: the decrease of dwell-times durations is most probably followed by another decrease in the next time step. For the positive increments the correlation is more complex and shows two types of correlations, corresponding to an asymmetry in the peaked distributions. This effect is especially distinct for the series of $\Delta T_{o,c}$ and $\Delta T_c$. Note that these correspond to the largest $\Delta T$ ranges, thus to extreme events.

Other methods such as the hidden Markov model analysis incorporate filtering and detection of sub-threshold events on a background of noise (Colquhoun and Sigworth, 1995; Wagner and Timmer, 2000). This maybe prone to missing extreme and unusual events. Our approach, in contrast, considers that we can simply distinguish two well defined types of states. This might be a simplification, and we are aware that the number of states might be continuous rather than discrete. One might discretised (but under which criteria?) the pdf’s and look for correlations between sub-pdf’s. It is not obvious whether such an arbitrariness is presently useful. We have examined elsewhere (in a quite different context) whether such a distribution could be characterized (Ausloos and Ivanova, 2003). Application of the technique
to the present case is left for further work. The quantity of data in the present case should make the result fascinating.

3.2 Kramers-Moyal coefficients and Fokker-Planck equation

As the next step the general case of \( p^N(\Delta T_1, \Delta n_1; ...; \Delta T_N, \Delta n_N) \) has been considered. If the increments follow a Markov process a serious simplification occurs\(^5\) rigorously described by the Chapman-Kolmogorov equation

\[
p(\Delta T_2, \Delta n_2|\Delta T_1, \Delta n_1) = \int d(\Delta T_i)p(\Delta T_2, \Delta n_2|\Delta T_i, \Delta n_i)p(\Delta T_i, \Delta n_i|\Delta T_1, \Delta n_1)
\]

(4)

Considering the limiting case of \( \Delta n \) tending to zero, the (continuous time "\( \tau \)"") differential form of the Chapman-Kolmogorov equation yields a master equation, giving the Fokker-Planck equation (Gardiner, 1983; Risken, 1984). The moments \( M^{(k)} \) of the probability density distribution, the so called Kramers-Moyal coefficients, enable estimation of the drift \( D^{(1)} \) and diffusion \( D^{(2)} \) coefficients,\(^6\) respectively, such that the FPE reads

\[
\frac{d}{d\tau} p(\Delta T, \tau) = \left[ -\frac{\partial}{\partial \Delta T} D^{(1)}(\Delta T, \tau) + \frac{\partial^2}{\partial^2 \Delta T} D^{(2)}(\Delta T, \tau) \right] p(\Delta T, \tau)
\]

(5)

For completeness, in Fig. 5, we show the equal probability contours for the open-closed state conditional probability. The experimental (so called "empirical") pdf is compared with the pdf resulted from the Chapman-Kolmogorov equation for different triplets of \( \Delta n_2 < \Delta n_i < \Delta n_1 \). As shown in Fig. 5 we have obtained a fairly good agreement between the two pdf. Note however that the joint and conditional pdf differ in their approach to the assessment of the disappearance of a correlation axis for small \( \Delta T \) in the latter.

Figures 6-8 show the dependence of \( D^{(1)} \) and \( D^{(2)} \) on the increments of dwell-times \( \Delta T \). For the open-closed and open states the dependence of the coefficients is asymmetric with respect to \( \Delta T \). For positive \( \Delta T \), it is linear for \( D^{(1)} \) and quadratic for \( D^{(2)} \). Practically no dependence on \( \Delta T \) was found for \( \Delta T < 0 \). For open states the dependence of the diffusion coefficient on \( \Delta T \) is quadratic; the drift coefficient is asymmetric with respect to \( \Delta T \) and shows a linear dependance.

\[
D^{(1)}_{o,c} \propto \begin{cases} 
-1.1139\Delta T + 0.1684 & \text{for } \Delta T > 0\text{ms} \\
0.0081\Delta T - 0.3241 & \text{for } \Delta T < 0\text{ms}
\end{cases}
\]

\[
D^{(1)}_c \propto \begin{cases} 
-0.8806\Delta T + 0.1847 & \text{for } \Delta T > 0\text{ms} \\
-0.1740\Delta T + 0.1284 & \text{for } \Delta T < 0\text{ms}
\end{cases}
\]

\(^5\)The \( N \)-point pdf \( p^N \) is generated by the product of conditional probabilities, e.g. \( p(\Delta T_{i+1}, \Delta n_{i+1}|\Delta T_i, \Delta n_i) = p(\Delta T_{i+1}, \Delta n_{i+1}; \Delta T_i, \Delta n_i)/p(\Delta T_i, \Delta n_i) \) for \( i = 1, ... N-1 \)

\(^6\)\( \frac{D^{(k)}}{k!} \simeq M^{(k)} \)
Interestingly, such a quadratic scaling of $D^{(2)}$ has also been identified in the analysis of a fully developed turbulence where the velocity increments were studied over space scales (Ghashghaie, et al., 1996). Moreover, the quadratic dependence of $D^{(2)}$ has been found essential for the logarithmic scaling of intermittency (Ghashghaie, et al., 1996). This statistical behaviour has been explained in the light of cascade processes from large to small scales. In fluid flow it is the energy which is transported to the system on large scales and becomes distributed over smaller scales due to the instability of vortices at a given scale, thus making the dissipation of energy possible. Ion channels are perfect systems for the creation of such cascades, i.e. hierarchical processes, because of the large number and varied types of degree of freedom of the nonequilibrium process. Protein building the channel performs movements on a very wide time scale (Liebovitch and Todorov, 1996), which can be seen as self-similarity in time, and correlation between ion current values and dwell-states. The hierarchical energy cascade analogy thus fully holds here. Whether the multifractal spectrum can be deduced is still an open question requiring further work.

Finally, we have checked whether the diffusion coefficient for all dwell-times $D^{(2)}_{o,c}$ is related with diffusion coefficients of open and closed times, respectively: the following relation is found $D^{(2)}_{o,c} = (D^{(2)}_c + D^{(2)}_o) / 2$. Moreover for all the series examined we have found that the drift coefficient $D^{(1)}$ is dominant over diffusion $D^{(2)}$, through the ratio $D^{(2)}/D^{(1)}\Delta T$, $D^{(3)}/D^{(1)}(\Delta T)^2$, and $D^{(4)}/D^{(1)}(\Delta T)^3$, where $D^{(3)}$ and $D^{(4)}$ are the third and fourth coefficients of the Kramers-Moyal expansion, corresponding to $M^{(3)}$ and $M^{(4)}$ respectively.

Additionally, knowing that FPE is equivalent (in Ito sense) to a Langevin equation (Risken, 1984), which in the examined case would describe evolution of each type of $\Delta T$, the following equation has been found

$$\frac{d}{d\tau}\Delta T(\tau) = D^{(1)}(\Delta T(\tau), \tau) + \eta(\tau)\sqrt{D^{(2)}(\Delta T(\tau), \tau)},$$

where $\eta(\tau)$ is a fluctuating-correlated force with Gaussian statistics; here $< \eta(\tau) \eta(\tau') > = 2\delta(\tau - \tau')$. 

$$D^{(2)}_o \propto \begin{cases} -0.9679\Delta T + 0.3091 & \text{for } \Delta T > 0\text{ ms} \\ -0.0701\Delta T + 0.3139 & \text{for } \Delta T < 0\text{ ms} \end{cases}$$

$$D^{(2)}_{o,c} \propto \begin{cases} 0.3263\Delta T^2 - 3.2864\Delta T - 4.2590 & \text{for } \Delta T > 0\text{ms} \\ 0.0525\Delta T + 2.2371 & \text{for } \Delta T < 0\text{ms} \end{cases}$$

$$D^{(2)}_c \propto 0.2715\Delta T^2 + 1.1583\Delta T + 2.0903$$

$$D^{(2)}_o \propto \begin{cases} 0.3872\Delta T^2 - 0.0948\Delta T + 0.3531 & \text{for } \Delta T > 0\text{ ms} \\ -0.0547\Delta T + 0.4214 & \text{for } \Delta T < 0\text{ ms} \end{cases}$$
4 Discussion

The main objective of the paper was to examine the character of ion transport through a potassium channel by means of a master equation applied to the ion current time series. We have focused on the processes underlying switching between different conducting \((o, c)\) states of the channel. We aimed at separation of the deterministic and random components of the process. The derived Fokker-Planck and Langevin equations of the studied dwell-time series gave a straightforward answer to the posed question. The drift coefficient contains information about the deterministic forces influencing the process, while the diffusion coefficient expresses the noise present in the system (see the Langevin equation above). For all examined series a clear dominance of the drift component has been observed. This should have medical and pharmaceutical relevance and implications.

Scaling of \(D^{(1)}, D^{(2)}\), and of probability density functions confirmed rigorously the previous results that the character of closed states significantly influences the channel behaviour. The open states time intervals are usually very short, and their pdf is quite narrow whatever the time lag scale considered. Open pore configurations have been recently well described (Jiang et al., 2002). The analysis performed here suggests to perform an extra thinking on and interpretation of the results based on the time dependence. Notice that treating ion transport as a superposition of merely two processes, opening and closing of the channel, the closed state is the slowest part of the process. Its characteristics govern therefore the overall dynamics of switching between the states; it seems trivial to state that the ion current is a measure of the velocity of the ion transport through the channel, but it is worth reemphasizing because again this might have interesting physiological causes and practical impact.

The identified turbulent, cascade type of switching of open states and for the positive increments of closed dwell times is, as we believe, of crucial importance for the channel proper function. The intermittency character of this process (in the sense of Kolmogorov log-normal turbulence model (Frisch, 1995)) promotes the switching between the states, preventing therefore the channel from staying in one, closed (inactivation) or open (hyperactivation) state (Hille, 1992). We hint that this could be interpreted through the role of noise in forced (two or multi) level systems (de Oliveira et al., 2003).

We claim that we see an analogy between the turbulent variables, in fluids and the ion transport case. Hydrodynamic turbulence considered in spatial coordinates corresponds to the ion transport through a channel whose time development has been studied. In turbulence, the laminar periods are interrupted by turbulent bursts. In ion transport the intermittency is expressed in the switching between closed and open states. This is tantamount to the periods when large number of ions is transported through the channel, interrupted by the periods where the transport is seriously diminished. This leads to the charge cascade occurring in time hierarchy, similar to the energy cascade in space hierarchy observed in turbulence.

The non-Markovian nature of the closed state dwell time distribution is usually explained by postulating multiple closed states (the number and distribution of which are still in question). The interpretation of non-Markovian dwell time distributions has a bearing on what philosophy of ion channel kinetics is envisaged,
i.e. fractal vs. discrete state Markov models vs. hierarchical energy landscape, ...

In the above, we concur with the multifractal viewpoint about the existence of hierarchical processes as first suggested by the spectral analysis of the ion current time series (Siwy and Fuliński, 2002). The presence of the flicker noise pointed to the self-similarity in time of the processes governing the ion transport. Here, we confirm this conjecture by showing an unexpected high probability of large changes of dwell-times durations, revealed by pdf (compared to a Gaussian pdf). Recall that the existence of finite non-Gaussian tails for large events is usually thought to be a result of drastic evolutions e.g. financial crashes, earthquakes, heart attacks in functioning of an organism, turbulence and intermittency in fluid flow, .... In ion transport through a voltage-sensitive channel it may be the mere consequence of exciting the voltage-sensor i.e. part of the channel, responsible for the response of the channel to the applied electric field but fundamentally the result from the complex electrochemical and mechanical fluctuation couplings. We suggest that to separate the coupling energies, forces, and to quantify the parameters can be done by systematically analyzing and considering the various possible cascades, and their time scales.

5 Conclusion

To conclude, we would like to stress that the presented Fokker-Planck and Langevin equations have been derived through a model–free identification of charge transport through membranes. They provide the knowledge how the statistics of the channel action changes over various time scales. For ion channels structural changes (Jiang et al., 2002) are crucial to every aspect of their function: ion conduction, gating and pharmacology. The present report shows a rigorous way to describe the correlation and time-hierarchy in ion transport through channel within a turbulent cascade analogy.

In fine, the Fokker-Planck equation is often used in the literature to relate the Brownian motion of selective macroscopic variables (through a Langevin equation) across some free energy landscape to observables like the gating or ionic current. The FPE solution reduces to the Boltzmann distribution at equilibrium, and the noise term satisfies a simple fluctuation-dissipation theorem. Thus a usual FPE approach to ion channel kinetics might be expected to lead to simple Gaussian distribution functions for observables. It has been shown that this is the case for small variations, but the tails of the distributions (see Figs. 1-3) are not gaussian, and ”extreme” events are not negligible. Thus physical models should be improved to describe the tails. This will not be easy.
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Figure Captions

**Figure 1.** — Locust potassium channel probability densities (PDF) $p(\Delta T, \Delta n)$ of the dwell-times increments $\Delta T$ of (a) all dwell times, i.e. open and closed; (b) same as (a) but with each pdf displayed vertically to enhance the tail behaviour, all data (30604 data points) for the time lags $\Delta n$, as indicated in the figure. The discretization step of the histogram is 6 ms. (c) the portion between $\Delta T=-30$ and +30 ms is zoom out with discretization step of 0.6 ms and each pdf displayed vertically to enhance the tail behaviour, all data (30604 data points) for the time lags $\Delta n$, as indicated in the figure.

**Figure 2.** — Locust potassium channel probability densities (PDF) $p(\Delta T, \Delta n)$ of the dwell-times increments $\Delta T$ of (a) all dwell times, i.e. open and closed; (b) same as (a) but with each pdf displayed vertically to enhance the tail behaviour, all data (15302 data points) for the time lags $\Delta n$, as indicated in the figure. The discretization step of the histogram is 6 ms. (c) the portion between $\Delta T=-30$ and +30 ms is zoom out with discretization step of 0.6 ms and each pdf displayed vertically to enhance the tail behaviour, all data (15302 data points) for the time lags $\Delta n$, as indicated in the figure.

**Figure 3.** — Locust potassium channel probability densities (PDF) $p(\Delta T, \Delta n)$ of the dwell-times increments $\Delta T$ of (a) all dwell times, i.e. open and closed; (b) same as (a) but with each pdf displayed vertically to enhance the tail behaviour, all data (15302 data points) for the time lags $\Delta n$, as indicated in the figure. The discretization step of the histogram is 0.6 ms.

**Figure 4.** — Equal probability contour plots of the joint pdf for the simultaneous occurrence of the dwell-times differences $p(\Delta T_2, \Delta n_2, \Delta T_1, \Delta n_1)$ for two values of $\Delta n, \Delta n_1 = 16 \Delta n_0, \Delta n_2= 8 \Delta n_0$: (a) for all dwell times; (b) for the series consisting of durations of closed, and (c) for the series consisting of durations of open states. Contour levels correspond to $\log_{10} p=-1, -1.5, 2,-2.5, -3,-3.5$ from center to border.

**Figure 5.** — (a) Equal probability contour plots of the conditional pdf $p(\Delta T_2, \Delta n_2|\Delta T_1, \Delta n_1)$ for two values of $\Delta n, \Delta n_1 = 8 \Delta n_0, \Delta n_2= \Delta n_0=0.1$ ms, for open-closed durations signal. Contour levels correspond to $\log_{10} p=-1, 2,-4$, from center to border; (b) and (c) experimental and solution of the Chapman Kolmogorov equation for the corresponding pdf at $\Delta T_1 = -3$ and +3 ms.

**Figure 6.** — Kramers-Moyal drift and diffusion coefficients $D^{(1)}$ and $D^{(2)}$ as a function of $\Delta T$ for the time series consisting of all dwell-times. The quadratic fit of the diffusion coefficient is done for $\Delta T < 14$ ms. $\Delta T$ changes with step 2 ms.

**Figure 7.** — Kramers-Moyal drift and diffusion coefficients $D^{(1)}$ and $D^{(2)}$ as a function of $\Delta T$ for the time series consisting of closed time intervals. The quadratic fit of the diffusion coefficient is done for $\Delta T$ between -9 ms and +10 ms. $\Delta T$ changes with step 1 ms.

**Figure 8.** — Kramers-Moyal drift and diffusion coefficients $D^{(1)}$ and $D^{(2)}$ as a function of $\Delta T$ for the time series consisting of open time intervals. The quadratic fit of the diffusion coefficient is done for $\Delta T < 3$ ms and the linear fit is done for $\Delta T > -3$ ms. The linear fits for $D^{(1)}$ are obtained for $-3 < \Delta T < 0$ ms and $0 < \Delta T < 3$ ms. $\Delta T$ changes with step 0.2 ms.