J Comput Electron (2007) 6:391–394
DOI 10.1007/s10825-006-0140-4

Shot noise in single open ion channels: A computational approach based on atomistic simulations

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Published online: 18 January 2007

Abstract This paper presents a computational analysis of the noise associated with ion current in single open ion channels. The study is performed by means of a coupled Molecular Dynamics/Monte Carlo approach able to simulate the conduction process on the basis of all microscopic information today available from protein structural data and atomistic simulations. The case of potassium ions permeating the KcsA channel is considered in the numerical calculations. Results show a noise spectrum different from what is theoretically predicted for uncorrelated ion-exit events (Poisson noise), confirming the existence of correlation in ion motion within the channel, already evinced by atomistic structural analyses.

Keywords Ion channels · KcsA · Current noise · Molecular Dynamics · Monte Carlo method

1 Introduction

Rather than merely a bothersome phenomenon, noise in biological systems is a useful property. Before the patch clamp technique was developed, current noise across biological membranes provided the first experimental evidence for the existence of ion-conducting pores with discrete conductance levels. Single-channel recording techniques are nowadays widely accessible, and open-channel noise can be measured with a standard experimental set up. However a noise analysis in the frequency range corresponding to the kinetics of ions permeating a membrane channel is, at present, still a difficult task, since it is not actually possible to detect the individual shot events using the patch-clamp technique. From the computational side, X-ray crystallographic structures with atomic resolution [1] can now provide the necessary input to Molecular Dynamics (MD) analyses. MD provides further atomistic information about the system and confirms that, in nanometric pores, the permeation process takes place as a single-file concerted motion of ions. MD, however, is unable to analyse the electrical properties of ionic flux, due to the long time scale involved in the physiological process (milliseconds). The aim of this work is to study the conduction and noise properties of potassium ions in the KcsA channels by means of a coupled Molecular Dynamics/Monte Carlo (MD/MC) simulation that yields both current and its noise for a single channel under open-gate conditions and relies on input parameters based on atomistic simulations.

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2 Conduction model and computational procedure

The details of the adopted conduction model are described elsewhere [2] and will be summarized briefly below. Six stable binding sites are included, referred to as $S_0, \ldots, S_4, S_{cav}$, in which alternatively potassium ions and water molecules are found. The free-energy barriers between two ion-occupancy configurations are calculated by means of MD simulations [2, 3]. The probability per unit time $k_{A\to B}$ to undergo a transition from channel configuration A to configuration B is calculated using the transition-state theory [4]:

$$k_{A\to B} = A\exp(-\beta\epsilon_b) \tag{1}$$

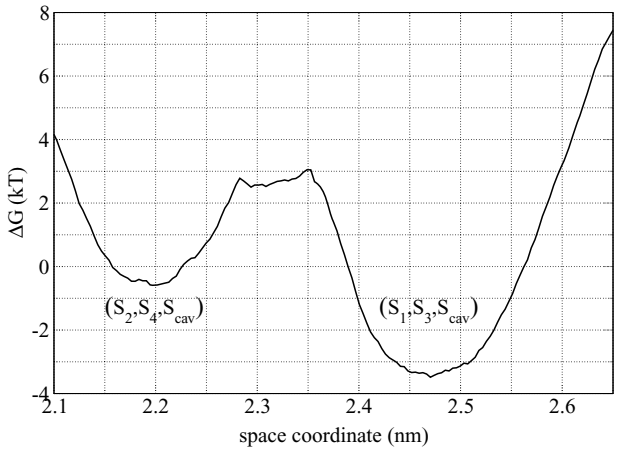

Fig. 1 Free-energy profile as a function of the center of mass coordinate of the two top ions for transition $(S_2, S_4, S_{cav}) \leftrightarrow (S_1, S_3, S_{cav})$

where ϵ_b is the free-energy barrier separating the two states and $\beta = 1/kT$.

In MD simulations the analyzed system is built by embedding the KcsA structure from Streptomices Lividans solved at 2.0 Å [1] in a water-octane-water bilayer. The free-energy barriers have been evaluated with the application of Steered MD, and validated through the implementation of Umbrella Sampling and Metadynamics [3].

An example of an equilibrium multi-ion free-energy profile is shown in Fig. 1 as a function of the center of mass coordinate of the ions initially in the 2 and 4 binding sites for the transition $(S_2, S_4, S_{cav}) \leftrightarrow (S_1, S_3, S_{cav})$. The energy barrier obtained for this transition is approximately 3.5 kT, which is consistent with that reported in the literature [5]. Similar MD calculations have been performed for all the transitions included in the conduction model.

The conduction process is simulated by generating a sequence of transitions between different channel configurations through the MC code. The available configurations and their transition rates at zero bias are reported in [2]. The ion current has been evaluated as the net flux of incoming and outgoing charges at a channel boundary in a defined time interval Δt. Power spectra have been calculated by Fourier-transforming the current fluctuations $\delta I(t)$ and averaging the results over 1000 independent sequences of 10000 time steps.

3 Noise analysis

Our noise analysis is restricted to the contribution from the electric fluctuations generated by single-file diffusion through the very narrow channel in its open configuration. These current fluctuations are expected to arise from the discrete nature of current flow (ions move in discrete steps across the membrane) yielding "shot noise" analogous to that observed in electronic devices. Additional sources of noise are associated with fluctuations of the energy barriers due to both thermal structural fluctuations of the protein and to fluctuations on the protein structure coming from the interaction between the protein and the lipid bilayer. A third source of noise is associated with the gating process of the channel. The characteristic time scales of the three fluctuations listed above are different: nanoseconds for shot noise, picoseconds to nanoseconds for protein structural fluctuations, and milliseconds for fluctuations due to gating.

Noise spectra in the frequency domain of the last two processes above have been experimentally obtained and studied in the past. The noise spectrum in the frequency domain of the shot noise is still difficult to measure and, to our knowledge, has not been studied yet. A theoretical analysis of ion current fluctuations in these nanometric biological conductors on the nanosecond time scale is feasable only through the implementation of advanced atomistic approaches. This is actually the focus of our calculations. To this purpose we assume that the channel is permanently in the open configuration. Furthermore we will not consider fluctuations which arise from internal motion of the channel protein. The autocorrelation function $C(\tau)$ of the current fluctuations $\delta I(t)$ can be numerically computed from the MC simulation assuming a stationary process. The spectral density of the current is then obtained either by Fourier transformation of $C(\tau)$ or by directly averaging the squared Fourier transform of the current fluctuations $\delta I(t)$.

The classical theory of shot noise [6] assumes that charge transport occurs by means of instantaneous processes, and that the charge movements are totally uncorrelated in time. The spectral density of the fluctuations is given by Schottky's formula: $S_{\text{shot}} = 2qI, q$ being the charge of the moving particle, if charges flow mainly in one direction, as in presence of an external bias. For cases where correlation among discrete-charge input/output exists, usually the spectral density is normalised to S_{shot}, and the Fano factor [7]: $F = S_I(\omega)/S_{\text{shot}}$ is taken as a measure of the degree of correlation in the charge motion.

4 Conduction and noise results

In order to extract $I(V)$ characteristics starting from an atomistic approach one must first deal with the problem of the effect of the external electric field on the transition rates. MD procedures at present do not explicitly include the electric field consistently with periodic boundary conditions. This has been done assuming that, after a complete cycle, the system (protein+ions inside) changes its total energy by an amount equal to qV, where V is the external applied potential

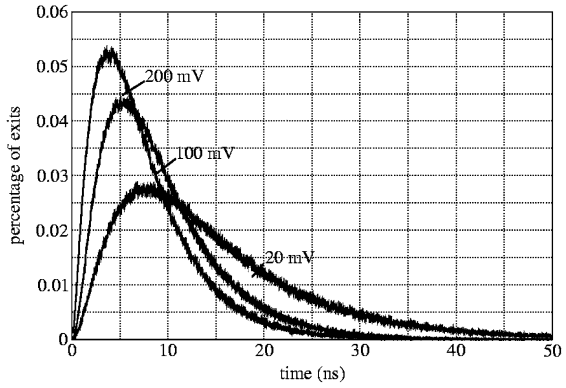

Fig. 2 Number of ion exits as a function of the time interval between two successive ion exits from the MC simulation. The mean time and most frequent time are: 14 ns and 7.8 ns at 20 mV, 9.3 ns and 5.3 ns at 100 mV and 7.4 ns and 4.1 ns at 200 mV, respectively

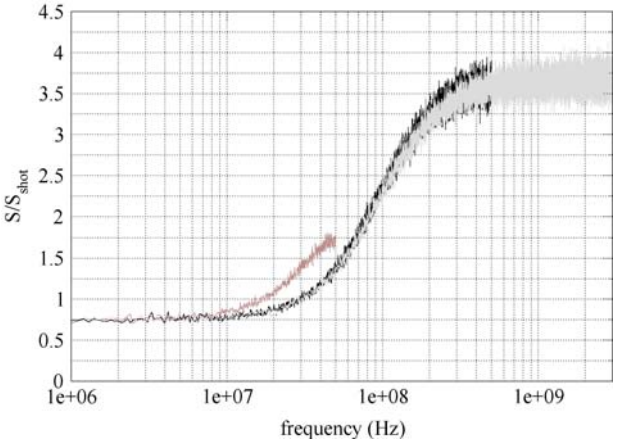

Fig. 3 Power spectrum of the current fluctuations as a function of frequency as obtained from the simulations using different sampling times for the current signal (dark line: $\delta t = 10^{-9}$ s; half tone gray line: $\delta t = 10^{-8}$ s; pale gray line: $\delta t = 10^{-10}$ s). The three results have been obtained at the same bias of 100 mV

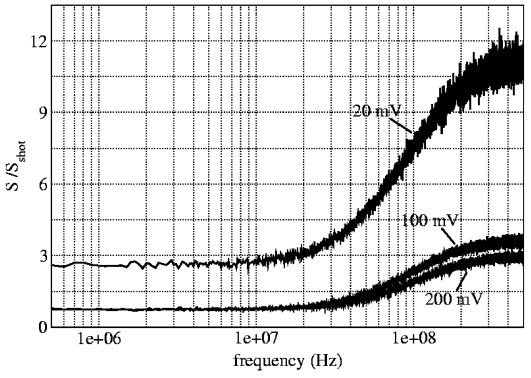

Fig. 4 Power spectrum of the current fluctuations as a function of frequency obtained with different values of the external bias, indicated in the figure. All the results refer to the same potassium concentration of 100 mM

and q the electronic charge that crossed the channel during the cycle.

We have found that the $I(V)$ characteristics are very sensitive to the fraction of the total potential energy associated with each conduction step [2]. The barriers used in our MC calculations range from 2.5 to 5.3 kT; higher values, as sometimes provided by MD simulations, lead to current saturation at voltages much higher than those suggested by experiments. Furthermore, the existence of voltage-independent transition rates dominating the ion flow is suggested above 100 mV to account for current levelling-off [2].

From the computational point of view shot noise can be analysed even at frequencies corresponding to the characteristic microscopic time of single events, provided that the current sampling time is properly chosen. In order to estimate this characteristic time for the process under investigation we have evaluated the number of ion exits as a function of the time interval between two successive exits. The distribution obtained is asymmetric; the position of its maximum value and the length of the tail depend on the external bias. Figure 2 shows examples of such a calculation. For a bias of 100 mV the peak of the curve is obtained at a time of 5.3 ns, while the average time $\langle T_{\text{exit}} \rangle$ between two successive ion exits is estimated approximately as 9.3 ns.

Figure 3 shows the power spectrum of current fluctuations normalised to S_{shot} as a function of frequency, as obtained from simulations which use a different value of the current sampling time Δt. It can be noted that the low and high-frequency ranges are not affected by the choice of Δt. On the contrary, at frequencies of the order of $1/\langle T_{\text{exit}} \rangle$ the shape of the spectrum strongly depends upon the choice of Δt, as it happens in experimental measurements, due to the limitations imposed in the frequency range of the Fourier transform.

Examples of calculated noise power spectra as functions of frequency at different external biases are shown in Fig. 4. White noise is found until about $2 \cdot 10^7$ Hz with a Fano factor F ranging from about 2.7 to 0.7, according to the choice of the external bias. This clearly indicates that the correlation in the ion motion lowers the noise spectrum with respect to the Poissonian shot-noise value. At frequencies of the order of $1/\langle T_{\text{exit}} \rangle$ an increase of the spectrum is observed, up to the highest considered frequencies, where single charge output is seen.

Finally in Fig. 5 the dependence of the Fano factor is plotted as a function of the external bias. F rapidly decreases at increasing bias until about 100 mV, where an asymptotic value of 0.75 is reached. This effect is due to the fact that, at low fields, ions exiting from one side of the channel still reside nearby and may easily enter/exit again; a strong bias drastically reduces this effect.

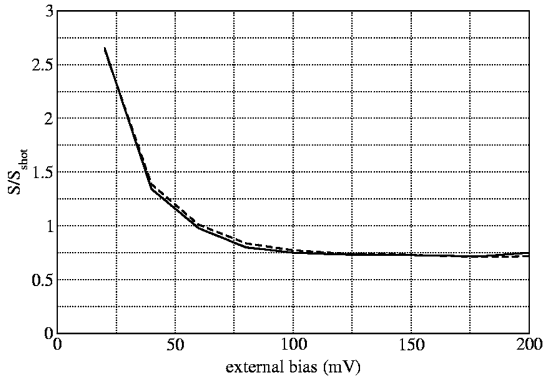

Fig. 5 Fano factor (see text) as a function of the external bias (in absolute value) for the power spectrum shown in Fig. 4. The dashed line refers to negative bias (flux from extracellular to intracellular reservoir)

5 Conclusions

We presented a study of single open-channel current fluctuations by means of a coupled Molecular Dynamics/Monte Carlo approach. The case of potassium ions permeating the KcsA protein has been considered. The mean time interval between two successive ion exits obtained from the Monte Carlo simulation is of the order of tens of nanoseconds. The peculiar features of the power spectra confirm that the ion motion within the selectivity filter is strongly correlated. The evaluation of the Fano factor yields a quantitative estimate of the degree of correlation between consecutive ion exits from the channel.

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