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Shot Noise in Single Open Ion Channels: A Computational Approach Based on Atomistic Simulations

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SOURCES OF NOISE IN ION CHANNELS

Ion channels are nanometric macromolecular pores in the cell membranes which exibit ion selectivity and gating properties. The transport of ions through a channel protein has been traditionally described as a sequence of discrete transitions over various energy barriers. In the last years X-ray crystallographic structures obtained with atomic resolution [1] confirmed this picture, but suggested that ion motion is highly correlated in the narrow segments of the pore, so that a realistic model for the permeation process is obtained considering transitions between different ion occupancy configurations along given paths on the free-energy landscape as a function of a number of specified process coordinates. Current fluctuations are expected to arise from the discrete nature of the current flow, producing a shot noise, as it is observed in electronic devices. An additional source of noise is associated with fluctuations of the energy barriers due to thermal structural fluctuations of the protein [2]. Another major source of noise is associated with the gating process of the channel. The characteristic time scales of the three fluctuations discussed above are different: ns for shot noise, ps to ns for thermal structural fluctuations, ms for gating. Noise spectra in the frequency domain of the last two processes above have been experimentally obtained and studied in the past [2,3]. The noise spectrum in the frequency domain of the shot noise is still difficult to be measured and has not been studied yet. A theoretical analysis of the time-dependent ion current fluctuations in these nanometric biological conductors is feasable through the implementation of advanced atomistic approaches. This is actually the subject of the present paper.

ATOMISTIC MODELS FOR ION CHANNELS

The tremendous advancement in the atomistic knowledge of some prototype channel proteins produced a number of computational approaches which range from the solution of coupled macroscopic equations to molecular-dynamics (MD) [4]. Even though MD provides a simulation of the dynamical motion of all atoms of the protein as a function of time, given the microscopic forces that enter the Newton's equation, the method is limited in its capability to quantitatively characterize the electrical properties of ionic flux through selective channels due to the long time scale involved in the physiological process (ms). Computational approaches able to calculate ion fluxes and including as much as possible the molecular information inside the protein in the input parameters and in the model are today one of the main challenges in computational studies of ion channels. A combined Monte Carlo-Molecular Dynamic approach [5] has been used in the present paper in order to calculate ion conduction properties.

COMBINED MONTE CARLO MOLECULAR DYNAMICS APPROACH

In selective ion channels the permeation process along the selectivity filter of the protein takes place as a single-file concerted motion of ions. Both current and its noise have been obtained from a Monte Carlo simulation of a single channel under open-gate conditions. A multi-ion model is used, where the ion binding sites around and inside the

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protein, the allowed transitions between different occupancy states and the associated rate constants are obtained from the atomic structure and atomistic MD simulations. We focused our attention on the KcsA+ channel. For such a protein recent results from MD simulations have been consistent with what is suggested from the atomic structure at high resolution of this system and provide the necessary microscopic physical input for the statistical model [6]. Six binding sites have been included in the model and the transition rates are evaluated by means of free-energy profiles for the possible ion-occupancy configurations of the channel [5].

RESULTS

In order to identify what is the frequency domain of current fluctuations produced by the discreteness of the charge carrried by the permeating ions we evaluated from the simulation the distribution of time intervals between two successive ion exits. An example for a bias of 100 mV and an ion concentration of 100mM is shown in Fig. 1. The average time $\langle T_{exit} \rangle$ between two successive ion exits is estimated to be approximately $9x10^{-9}$ s, while the most frequent time between two consecutive exits is $5x10^{-9}$ s. An example of calculated noise power spectrum as a function of frequency is shown in Fig.2. White noise is found until about $2x10^{7}$ Hz with a Fano factor of about 0.75, clearly indicating that a correlation between consecutive ion exits from the channel exists, reducing the noise spectrum with respect to the Poissonian shot-noise value. At frequencies larger than $1/\langle T_{exit} \rangle$ (corresponding to times much shorter than the current collection time) an increase of the spectrum is observed towards a plateaux which corresponds to the spectrum structure of the delta-like ion current spikes . How this correlation is sensitive to the physiological operating conditions of the channel will be discussed in the paper.

REFERENCES

[1] Y. Zhou, J. Morais-Cabral, A. Kaufman, and R. MacKinnon, *Chemistry of ion coordination and hydration revealed by a K+ channel-fab complex at 2.0 A resolution,* Nature **414**, 43 (2001).

[2] S.H. Heinemann and F. Sigworth, *Open channel noise V Fluctuating barriers to ion entry in gramicidin A channels,*Biophys. J., **57**, 499-514 (1990).

[3] Le Masurier M., Heginbotham L., and C. Miller, *KcsA: It's a potassium channel,* J. Gen. Physiol., **118**, 303-313 (2001)

[4] For a review see, e.g.: B. Roux, *Theoretical and computational modls of ion channels,* Curr. Opin. Struct. Biol. **12**, 182-189 (2002)

[5] Piccinini E., Affinito F., Brunetti R.,Jacoboni C., and Rudan M., *Physical mechanisms for ion-current levelling off in the KcsA channel through combined Monte Carlo/Molecular Dynamics simulations*, Proc. XIV Int. Conf. On Nonequilibrium carrier Dynamics in Semiconductors, in press.

[6] M. Compoint, P. Carloni, C. Ramseyer, C. Girardet, *Molecular Dynamics study of the KcsA channel at 2 .0A resolution: stability and concerted motion within the pore,* Biochim. Biophys. Acta, **1661**, 26 (2004)

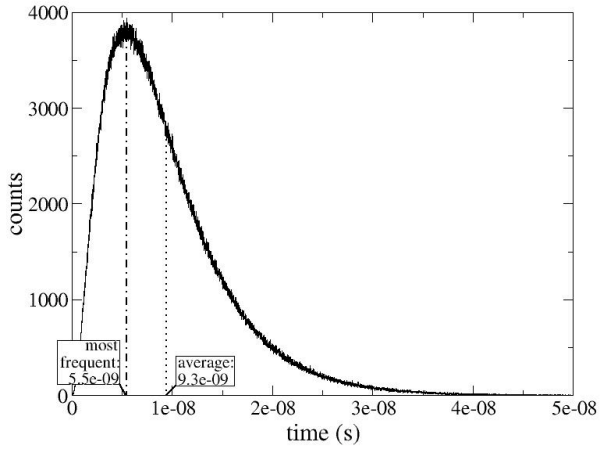

Fig. 1. Number of ion exits as a function of the time interval between two successive ion exits as obtained from the simulation (see text). A current collection time of 10^{-6} s has been used

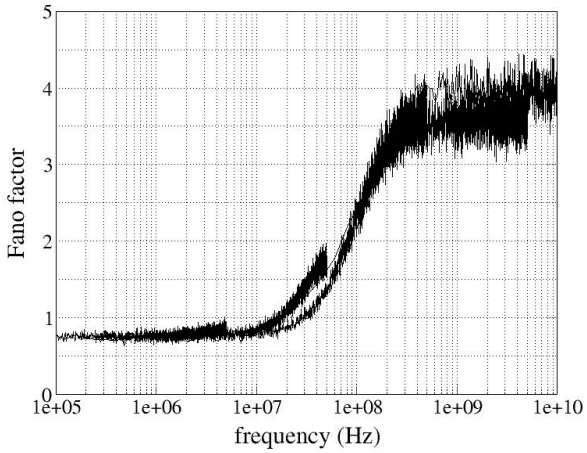

Fig. 2. Power spectrum of the current fluctuations as a function of frequency (see text) Several curves, simulated with different current collection times, have been combined together to explore a wide frequency range.