A simulative method for the analysis of conduction properties of ion channels based on first-principle approaches

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Ion channels are nanometric macromolecular pores in the cell membranes which exibit two main biophysical properties: selectivity and gating. In the last years X-ray crystallographic structures have been obtained with atomic resolution [1]. This tremendous advancement in the atomistic knowledge of these proteins produced a number of computational approaches which range from the solution of coupled macroscopic equations to molecular-dynamics (MD) [2]. 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. It is well known that ions do not diffuse freely through the pore: saturation, competition, and block of ion channels as the ion concentrations are changed together with crystallographic analyses suggest that the permeation process takes place as a single-file movement of ions. The aim of this work is to study the conduction properties of selective ion channels by means of a Monte Carlo simulation that yields both current and its noise under open-gate conditions. A multi-ion model is used, where the ion binding sites around and inside the protein, the allowed transitions between different occupancy states and the associated rate constants are obtained from the atomic structure and ab-initio 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 [3]. Seven binding sites have been included in the model (see Fig. 1) and the transition rates are evaluated by means of free-energy profiles for the possible ion-occupancy configurations of the channel. A preliminary result is shown in Fig. 2.

[1] Y. Zhou, J. Morais-Cabral, A. Kaufman, and R. MacKinnon, Nature **414**, 43 (2001).
[2] For a review see, e.g.: B. Roux Curr. Opin. Struct. Biol. **12**, 182 (2002)
[3] M. Compoint, P. Carloni, C. Ramseyer, C. Girardet, Biochim. Biophys. Acta, **1661**, 26 (2004)

A full journal publication of this work will be published in the Journal of Computational Electronics.

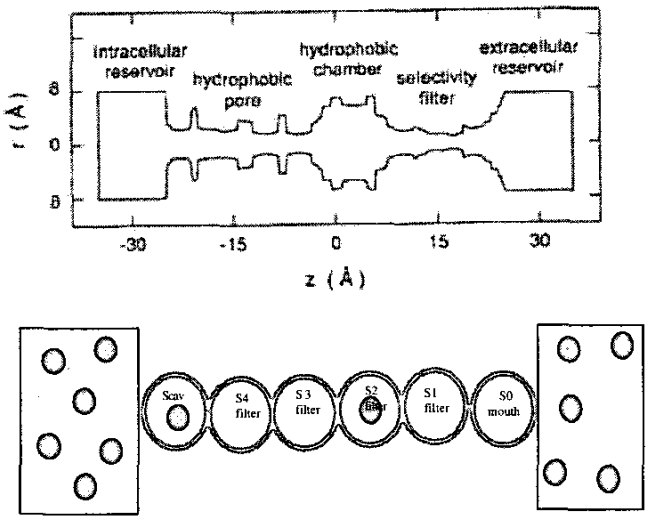

Fig. 1: scheme of the KcsA+ channel protein structure along the channel axis (upper part, from Allen et. Al, J. Chem. Phys. 112, 8191, 2000), and identification of the binding sites considered in the present simulative model (lower part).

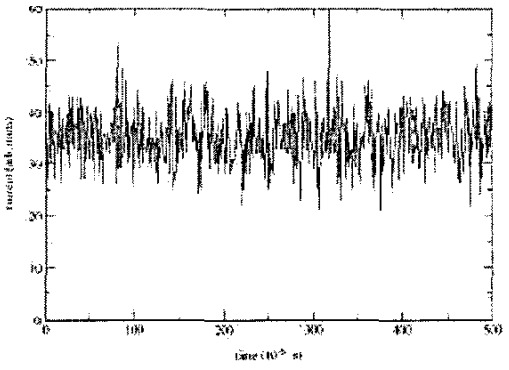

Fig. 2: preliminary result for the ion current as a function of time through a single KcsA channel.

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