Molecular Transport Through Nanopores: Bridging Simulations and Experiment.

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Abstract

Single-channel electrophysiology is a powerful technique to sense the interaction of single molecules with ion-conducting nanopores. The ion current through a nanopore incorporated into an artificial lipid membrane and induced by an applied potential is modulated by the substrate while entering, binding and leaving the channel. The ion current may be partially or completely blocked (so-called induced channel gating) during the time the substrate molecules stay inside the pore. The resulting substrate-induced ion-current fluctuations are the observable which contains the information on the pore-molecule kinetics. Besides, by using the reversal potential at concentration gradient conditions, one may estimate the permeability of charged molecules through the pore.
Typical time resolution in the electrophysiology allows one to reliably detect channel gating events longer than 10 μs. On the other hand, direct all-atom simulations of the system of few hundreds of thousand atoms (the pore, the membrane, the solute and the molecules of interest) can be used routinely these days to study non-equilibrium processes at up to the microsecond time scale. Thus, there is a gap of one order of magnitude, from 1 to 10 μs between the experimental and the theoretical capabilities to address the transport kinetics through nanopores.

We will discuss recent advancements achieved in our group, in collaboration with experimentalists in order to bridge this time-scale gap from the both sides.

To quantify small molecule penetration into and eventually permeation through nanopores we applied an improved excess-noise analysis [1] of the ion current fluctuation caused by entering molecules. The kinetic parameters of substrate entry and leave are derived from a two-state Markov model analyzing the substrate concentration dependence of the average ion current, its variance and the power spectral density (PSD). Including filter corrections allows one to detect the kinetic rates constants far beyond the cutoff frequency of the instrumental ion-current filter and to extend the applicability of the electrophysiology to the diffusion time scale of few hundreds nanoseconds.

From the simulation side, we will discuss two approaches. First, a multi-scale protocol includes the evaluation of the potential of pean force (PMF) of the substrate molecule in the pore and the local diffusion constants. The diffusion flux and, in principle, pore/substrate kinetic rates constants are calculated by solving the corresponding diffusion-drift equation [2].

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The second method is the "from metadynamics to dynamics" approach [3]. The latter assumes location of the binding sites of the substrate in the pore and the corresponding saddle points using an enhanced sampling technique; evaluation of the average effective transition times in the metadynamics runs with subsequent scaling to the real transition times.

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