

Final report of OTKA NN 113527

Design and synthesis of biologically inspired ion-conducting nanopores

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This project was conducted by the Hungarian research team in collaboration with a German research team in the framework of an ERA Chemistry grant. The German team was led by Paolo Carloni (Professor at GRS, Aachen and FZJ, Germany), team members are Justin John Finnerty (Postdoc of GRS, RWTH- Aachen and Forschungszentrum Juelich (FZJ) Germany), Rodrigo Casasnovas-Perera (Postdoc at GRS, RWTH-Aachen and FZJ, Germany), Emiliano Ippoliti (Postdoc at FZJ, Germany), and Jan-Philipp Machtens (Postdoc at FZJ, Germany). The Hungarian team was composed of Dezső Boda, Tamás Kristóf, Mónika Valiskó, and Zoltán Ható (Department of Physical Chemistry, University of Pannonia, Veszprém). The German team finished the project in 2016 and submitted the final report to DFG. This document reports the results of the Hungarian research team. Publications produced by this project are distinguished by linked URLs (in blue color) in the reference list.

Introduction

The goal of the project was to conduct modeling studies for ion transport through nano-scale pores with different modeling resolutions and computational methods. While the German team is an expert of all-atom models studied by molecular dynamics (MD) simulations of biological systems, the Hungarian team is an expert of reduced models and methods that are partly developed by the team. The all-atom models make it possible to focus on atomic details if necessary, while reduced models make it possible to model the device containing the pore as it functions.

By device we mean the whole non-equilibrium system including the membrane that hosts the pore, the bulk electrolytes on the two sides of the membrane, and the electrodes that provide the voltage driving the ion transport through the pore. The input signal in such a device is the voltage (if we assume that the electrolyte concentration is the same on the two sides), while the output signal is the electrical current. The response function of the device is the relationship of these two quantities.

Ion channels have been in the focus of our research team since 2000 [1–13] using reduced models. The German partner was more interested in all-atom modeling of biological systems [14–17], while, influenced by Bob Esienberg, they became more and more interested in simple models too [18–20]. The essence of our collaboration is that we develop simple models for synthetic nenopores using the knowledge of the German partner on atomic details of biological ion channels.

Although synthetic nanopores were already studied by the Hungarian team (in collaboration with American partners) [21,22], the focus of the group from natural nanopores (ion channels) towards synthetic ones has been shifted continuously during this project. By the end of the project, our attention was mainly on various nanopore-based nanodevices such as rectifying nanopores used as diodes, selective ion-binding nanopores used as sensors, and nanopores with transistor-like behavior used as switches.

Systems under investigation

The main focus of our research group is various membrane systems, where a membrane separates two bulk systems (Fig. 1). The membrane can contain pores with well-defined properties

determined by nature (ion channels) or technology (synthetic nanopores) or it can be a porous material such as crystalline aluminosilicates (kaolinite, zeolite). The special properties of the pores make the system able to function as the central unit of a device.

These special properties can be based on equilibrium processes such as selective adsorption, or dynamical processes such as regulation of ion transport through the pore with voltage (rectification), concentration (sensing), or local electric field (transistor). While we studied the behavior of ion channels with equilibrium Grand Canonical Monte Carlo (GCMC) simulations for a long time [1–12], our attention turned to non-equilibrium processes during time because both ion channels and nanopores function as little devices regulating ion transport.

Therefore, in 2012, we developed a novel simulation method, the Local Equilibrium Monte Carlo (LEMC) technique that is an adaptation of the GCMC method to non-equilibrium situations. The basic idea is that the electrochemical potential, $\mu_i(\mathbf{r})$, is not constant globally. Instead, it is assumed to be constant, but different in small subvolumes into which the system is divided [23]. This method has been coupled to the Nernst-Planck (NP) transport equation with which we compute the flux:

$$\mathbf{j}_i(\mathbf{r}) = -\frac{1}{kT} D_i(\mathbf{r}) c_i(\mathbf{r}) \nabla \mu_i(\mathbf{r}). \quad (1)$$

The resulting NP+LEMC method is our main computational technique today although we also use other techniques as described later. The NP+LEMC method proved to be efficient to study ion transport in membrane systems [23, 24], ion channels [13, 25, 26] and nanopores [27–29].

The typical simulation cell of this method is seen in Fig. 2. There are three basic components whose proper description is essential to study the whole system right. (1) There are bulk compartments on both side where the chemical potentials are constant, with which we set the boundary conditions for concentrations. (2) The solution domain of the NP equation (inside the blue line) contains the inhomogeneous regions near the membranes, where electrical double layers are formed. (3) The pore embedded in the membrane is the bottleneck for ion transport and the first-order determinant of the response of the system given to an external stimulus (voltage, for example) in the form of ionic currents.

During the project, we examined all the three components as modeled by the implicit solvent model of electrolytes with ions being charged hard spheres. Also, we examined the systems under investigation with different models of

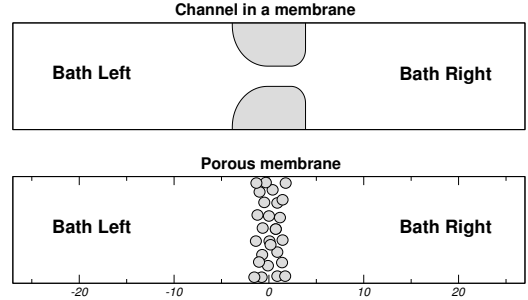


Figure 1: Membranes between baths.

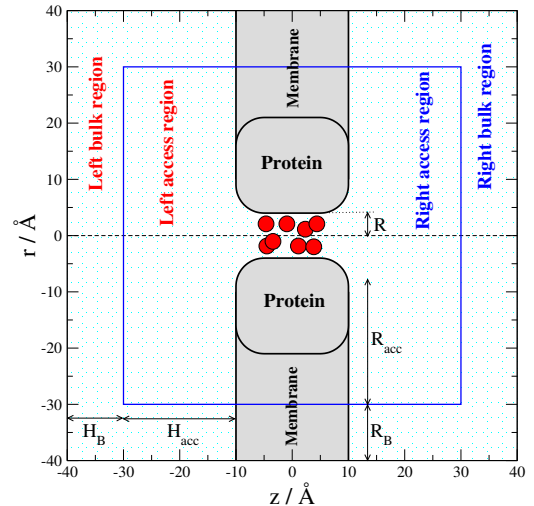


Figure 2: A typical NP+LEMC simulation cell that contains the membrane with the pore, the access regions, and the bulk regions.

varying resolutions (implicit water vs. explicit water) using various simulation techniques (LEMC vs. MD) and different computational methods on the basis of a given model, where these computational techniques applied approximations to varying degree (particle simulations vs. continuum theories).

Multiscale modeling

We call this approach multiscale modeling, because we model the systems on different length scales using models of different resolutions, but these are separate calculations (Fig. 3). This is different from another definition of multiscaling, where models/methods of different resolutions are used in a single simulation box. Although this idea is not distant from us and we intend to implement it in the future, at the present, we apply models in different scales in separate calculations. The essential part of this approach is that we connect the calculations in some intelligent way.

This requires thorough knowledge in various computational techniques. Despite its small size, our research group has a quite wide methodological arsenal that we can use: MD, MC in various ensembles, NP+LEMC, Dynamical Monte Carlo, and Brownian Dynamics (BD). We cannot be, however, experts of everything, so we recruited a wide international network whose members contribute to the common research with their own expertises. The group of Paolo Carloni (the collaborators in this grant) are MD experts as is Simone Furini (Sienna, Italy). Simone also uses BD simulations in collaboration with Claudio Berti (Rush University Medical Center, Chicago) [30]. Dirk Gillespie (Rush, Chicago) is an expert of density functional theory and a long time collaborator [31,32]. The Poisson-Nernst-Planck (PNP) theory uses the Poisson-Boltzmann (PB) theory instead of LEMC, which is a continuum theory mastered by renowned mathematicians Marie-Therese Wolfram, Bartłomiej Matejczyk (Warwick, England) and Jan Pietschmann (Münster, Germany).

In our study for the OmpF porin ion channel, we used two modeling levels [26]. The motivation of our study was the results of Miedema et al. [33] who modified the ionic pathway of the wild-type channel by point mutations and created an ion channel, where negatively charged amino acids are grouped at one part of the pore and the positively charged amino acids are grouped to the other side (Fig. 5). This way, they produced a bipolar pore with the intention of creating a rectifying ion channel. Their results coincided with their expectations: the mutant channel rectified.

Because of this, we started a project with great expectations, created an all-atom model of the mutant OmpF porin (Fig. 4), the membrane in which it is embedded, and the electrolyte around it (with explicit water molecules) and simulated this model with MD [26]. Despite our expectations and despite considerable effort (simulating large systems with millions of atoms), the all-atom channel model did not rectify. The interesting thing is that when we created a simple

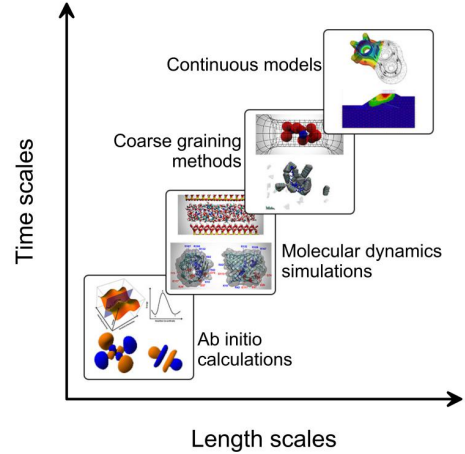


Figure 3: Multiscaling.

reduced model for this bipolar ion channel and studied it with NP+LEMC, the rectification behavior was found.

We are unsure about the source of the discrepancy. It might be that the point-mutated protein of Miedema et al. did not fold in a way we assumed (Fig. 4), the all-atom force fields or the MD simulation setup are inappropriate, or the reduced model is far from reality. In any case, it was interesting to see that a detailed model cannot reproduce experiments (not even qualitatively), while the reduced model can. This made us put more effort into the bipolar pore to understand what is going on.

Therefore, to avoid discrepancies from differences in unimportant details, we created a model bipolar nanopore on two modeling levels [27]. The basic difference between these levels was the treatment of water. Our detailed model studied with MD used explicit water, while our reduced model studied with NP+LEMC used implicit water (Fig. 5). The diffusion coefficient inside the pore (see $D_i(\mathbf{r})$ in Eq. 1) was adjusted to MD results. This is also an example how we connect various modeling levels in multiscale modeling.

Our results showed that the reduced model was able to describe the behavior of the nanopore as a device because the important degrees of freedom were taken into account in the reduced model. These are the ions under an applied field diffusing through a pore with a positive/negative charge pattern along the pore axis. If these are taken into account, the behavior of the axial concentration profiles (Fig. 5 bot-

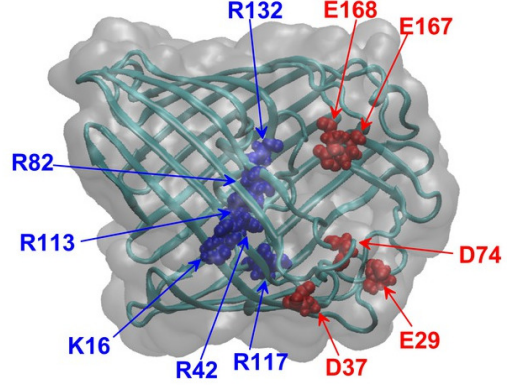


Figure 4: All-atom model for the OmpF porin.

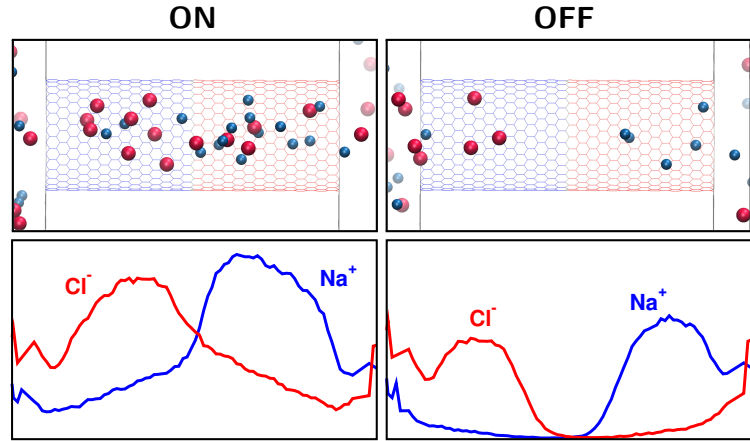


Figure 5: Bipolar nanopores at forward and reverse biased (ON and OFF) states.

tom row), and, therefore, the appearance of the depletion zones in the OFF state is reproduced. Other effects, such as the radial profiles and the mechanism of screening by water have secondary importance. Zoltán Ható was a key figure in these two studies who learned MD simulations on a professional level partly with the help of the German partner.

If electrostatic effects involving ions and pore charges have primary importance in determining the behavior of the bipolar nanopore, then the question arises whether the PNP theory can reproduce its behavior properly. PNP is a mean-field theory meaning that ions are point charges in interaction with the mean electric field produced by all charges. The comparison is made against NP+LEMC results, so the main difference between the two studies is the treatment of ion correlations. LEMC is able to compute these correlations properly because it is a

particle simulation method.

Our study with the help of Matejczyk and coworkers [28] covered a broad range of parameters and revealed where PNP can reproduce NP+LEMC data well. The overall conclusion of this study is that PNP works surprisingly well. This is against our earlier studies for ion channels [1–13], where PNP could not reproduce the selectivity behavior of the studied calcium and sodium channels. Competition based on the balance between electrostatic attraction and hard-sphere repulsion played an important role in ion channels. In the relatively wide nanopores where ion concentrations inside the pore are moderate (depletion zones are more important than peaks), PNP works fine.

This is an important finding, because PNP is much faster and can compute larger system closer to realistic sizes. The development of our own PNP code that is more appropriate to our purposes is under way.

Our series of studies in the multiscale framework is not over. BD simulations with the help of Simone Furini are under way (preliminary results have been presented at conferences [34,35]). NP+LEMC and PNP calculations have been performed for a nanofluidic transistor (a 3-region device, where the current through the nanopores is tuned by the electric field in the middle region) by Eszter Mádai — a work that earned First Prize at the Scientific Student Association (SSA, TDK in Hungarian) conference in November at the University of Pannonia.

Bulk electrolytes

Because bulk electrolytes are essential parts of the device, their proper description is also very important. It has been a debate for a while whether the implicit-solvent electrolyte (also called the Primitive Model) is able to describe the thermodynamic behavior of electrolytes. More specifically, the question is whether it can reproduce the relationship of the chemical potential and concentration.

The phenomenon that is usually under study is the non-monotonic behavior of the activity coefficient ($\gamma_i = \exp(\mu_i^{\text{EX}}/kT)$) as a function of concentration (Fig. 6). Earlier studies treated the dielectric constant concentration-independent, so this behavior could be reproduced only by using unphysically large ionic radii (a concept vividly criticized by us).

Instead of this approach, we suggested using a concentration-dependent dielectric constant, $\epsilon = \epsilon(c)$, in our 2010 work [36]. Then, the solvation term (interaction with water) also changes with concentration. Therefore, the excess chemical potential splits into two

terms describing ion-ion (II) and ion-water (IW) interactions: $\mu_i^{\text{EX}} = \mu_i^{\text{II}} + \mu_i^{\text{IW}}$. We showed that we can reproduce the $\gamma_{\pm}(c)$ behavior qualitatively without using any adjustable parameter

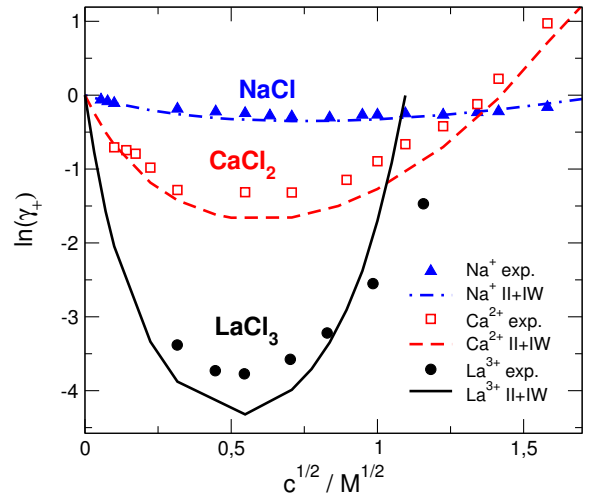


Figure 6: Cation activity coefficients in various electrolytes.

(Pauling radii for ions, experimental hydration free energies, and experimental $\epsilon(c)$ functions are all we need).

In this project, we continued these studies and showed that (1) we can reproduce the behavior of not only the mean, but also the individual activity coefficients [37], (2) compared the results given by a modified Debye-Hückel theory proposed by Shilov and Lyashchenko [38] to our simulation data also for 2:1 electrolytes [39], and (3) applied our method to a 3:1 electrolyte with surprisingly good result (see Fig. 6) [40].

From ion channels to nanopore sensors

As far as the studied systems are concerned, the shift of focus can be followed on the basis of our papers in this project. Starting with an equilibrium study of ion selectivity for a neuronal sodium channels [41], continuing through our study [26] of an expectedly rectifying OmpF ion channel (see above), we turned our attention to nanopores. Our multiscale studies on bipolar nanopores [27,28] revealed the importance of electrostatic effects in forming the depletion zones (see above). Ionic size and ionic competition played a secondary role in these systems.

Our study on biosensors, on the other hand, uses all the competitive effects in creating a sensor that we used before in calcium channels. This work was done by Eszter Máda, who got a First Prize for it at the National SSA (OTDK) conference this year. Her work has been presented at two International Conferences [42,43] and a manuscript has been written that has been submitted to *J. Chem. Phys.* [29] The reviews are positive asking only for minor revisions.

The essence of this work is that selective binding sites are placed inside a nanopore (modeled with a square-well potential in this start-up study) that bind the analyte ions, X^+ , that are present in the sample in very small ($10^{-6} - 10^{-3}$ M) concentration. These ions compete efficiently with the K^+ ions (the main charge carriers through the pore) for space inside the pore and they decrease the current of K^+ ions. The quantity of X^+ ions in the sample can be determined through calibration curves. Figure 7 shows that a detectable signal (relative current reduction, $1 - I/I_0$, where I and I_0 are the currents in the presence and absence of ion X^+ , respectively) can be observed even if ion X^+ is present in the sample in 3 orders of magnitude smaller quantity than K^+ ions.

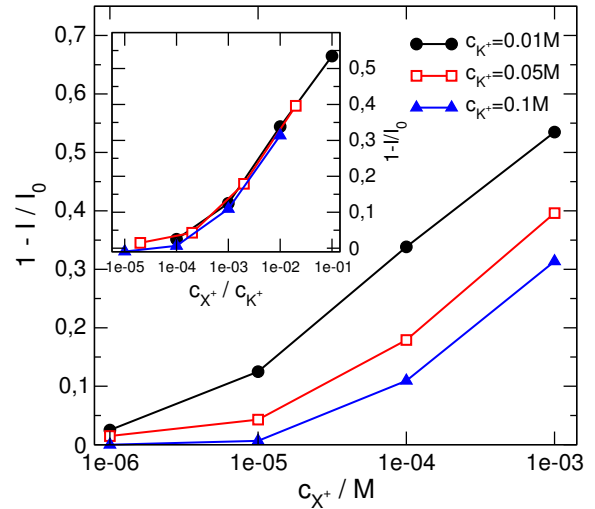


Figure 7: Calibration curves of the biosensor.

Porous crystalline aluminosilicates

In addition to single pores embedded in biological or synthetic membranes, the interest of the group continued on natural porous crystalline aluminosilicate membranes via senior researcher Tamás Kristóf. These materials have special and very useful adsorption and selectivity prop-

erties. Kaolinite, studied in this project, is sometimes used for preparing nanotubes. With all-atom MD simulations, we investigated the feasibility of one of its synthesis routes [44].

Methodological developments

The simulation of membrane systems through which the transport of some species is driven requires various methodological developments from the group. Downloadable or commercial simulation packages, although useful and well-optimized, are not always appropriate to our purposes. Therefore, we continued our efforts to develop new methods (a passion going back into the past). The NP+LEMC method is continuously under development. Coding features such as non-uniform grid and polarizable surfaces (electrodes and dielectric boundaries) is under way; unfortunately, with smaller pace than I would favor.

Driving molecules through a membrane in a steady-state MD simulation while ensuring given thermodynamic states on the two sides of the membrane was always a challenge. Ható et al. [45] proposed a novel technique, where the main control parameters are the partial pressure for the components on the input side of the membrane and the total pressure on the output side. The essential point of this scheme (called pressure-tuned, boundary-driven MD) is that this pressure control should be realised by adjusting the particle numbers in the input and output side control cells indirectly. The method was applied for simulating stationary gas transport through several nanoporous inorganic membranes (pure silica zeolites) [46].

Closing remarks

During this project two concepts became essential parts of our point of view. Multiscaling became a basic way we look at modeling and computing, while looking at the computed systems as devices is also a recent development. These happened during our collaboration with the Carloni-group whose point of view affected ours. We are grateful for the collaboration with them.

We would like to continue our research in this pragmatic direction. This will be helped by our new OTKA grant titled “Modeling nanodevices from the atomic to the mesoscopic scale”.

We would like to thank for the support of NKFI and ERA-Chemistry, and also for the common work with all the colleagues who participated in this project.

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