BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

Investigation and modeling the mass transport properties of ionophore based liquid membrane electrodes and nanopore sensors

Summary of PhD thesis

Author: Höfler Lajos
Supervisor: Dr. Gyurcsányi E. Róbert

Budapest University of Technology and Economics
Faculty of Chemical and Bioengineering
Department of Inorganic and Analytical Chemistry

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1 Introduction

Chemical and biosensors are usually based on multiple membrane layers with different functionalities. The definition of membrane in biology is: "phase that acts as a barrier to the flow of matter or heat". The role of these membranes can be diverse: selective recognition, controlling the mass transport, assuring the biocompatibility, protecting the sensor components. Thus with the application of proper membranes differentiated mass transport or sorption can be achieved for the different components of the sample, that establishes the selectivity, sensitivity and the dynamic range of the sensor.

My research focused on the development and mathematical interpretation of the response of ionophore based, liquid membrane ion-selective electrodes and chemically modified synthetic nanopore based ion-channel sensors. Recently both areas experienced a dramatic progress that forecasted new highly important applications in various analytical fields. However the transition from proof-of principle experiments to real word applications needs significant further refinements. This includes the need for a better control over the sensor properties and the development of mathematic models that enable to predict their response as well to implement rational approaches in the development.

The progress in lowering the detection limit of ionophore based ion-selective membranes invigorated the area of ion-selective potentiometry.[1] The practical significance of this finding becomes clear if one realize that one of the simplest instrumental methods, with cost effective electrode fabrication technologies and inexpensive instrumentation, has been conferred with ultra-trace analysis capabilities. It has been realized that the detection limit of ion-selective electrodes is determined by the transmembrane primary ion flux, which contaminates the sample solution layer in the immediate vicinity of the sensing membrane.[2] As result of this contamination the primary ion activity in the sample solution layer adjacent to the membrane will elevate with respect of the bulk value. As the ion-selective electrodes are surface sensors they will respond to the activity of this superficial solution layer and not to that of the bulk resulting in this case in an apparent sub-nernstian potential response.[3] This transmembrane primary ion flux is a consequence of the non perfect selectivity and permselectivity of the ion-selective membranes. Thus there is always a minor primary ion flux through the membrane, which at low primary ion concentrations of the sample bulk can become potential determining. The detection limit of ion-selective electrodes can be improved by lowering/eliminating the transmembrane ion fluxes. This proved to be in practice harder than it was thought in the beginning. This can be explained by the continuous reconditioning of membranes during experiments, which depends on the composition of the sample and the contact time of the membrane with the sample solutions. The time dependent transport processes cannot be interpreted with the simple steady-state models, which had replaced the empirical approach in electrode design.

[1] Sokalski, T.; Ceresa, A.; Zwickl, T.; Pretsch, E. *Journal of the American Chemical Society* **1997**, *119*, 11347-11348.

[2] Gyurcsányi, R.; Pergel, E.; Nagy, R.; Kapui, I.; Lan, B.; Tóth, K.; Bitter, I.; Lindner, E. *Analytical Chemistry* **2001**, *73*, 2104-2111.

[3] Bakker, E.; Bühlmann, P.; Pretsch, E. *Talanta* **2004**, *63*, 3-20.

Hence our main goal was to build numerical models which are capable of describing restrictions and prospects of mass transport controlled sensors. These numerical models allowed us to interpret the water uptake of polymer membrane based ion-selective electrodes. Currently it is little known about the effect of water uptake to the potential response, but in the case of solid contact electrodes its significance has been proven.[4] FTIR-ATR spectroscopy was used to study the water uptake. With this technique it is possible to track the diffusion of different forms of water.[5]

Nanopore sensors are in the forefront of life sciences due to their single molecule detection capability. The driving force of this interest is the pioneering results which forecasted the possibility of ultra-fast DNA sequencing with nanopores.[6] In case of successful realization nanopore based sequencing would have revolutionary effects on bioanalysis owing to the dramatically decreased analysis time and costs.[7] Moreover, nanopore based molecule and particle counting as well as selective label-free detection are also in the forefront of bioanalysis and nanotechnology. The first nanopore based sensors were biological ion-channels,[8] the wide-spread analytical use of which is greatly hampered by the lack of stability and the difficulty in varying their pore sizes and geometries.

Thus there is an effort to replace biological origin ion-channels with robust solid-state nanopores. However the transition from natural to synthetic nanopores is not necessarily straightforward, but rather it raises numerous challenges in terms of fabrication, (bio)chemical modification and processes governing the response mechanism.[9] Our group has made significant contributions to the field with the introduction of biological receptor modified nanopores to biosensing.[P8] My work in the area of nanopore sensing aimed at the coarse grained modeling of electromechanic rectification effects observed with single stranded DNA modified solid-state conical nanopores. By using random-walk and multiphysiscs simulation I have investigated how single molecule detection capability of single nanopores based sensors translates to concentration-based detection limit. As the detection limit was determined by the probability of finding the sensing nanopores by the detected compound means to reduce the escape (encountering) time by using an external force field were addressed as well.

2 Methods

Numerical methods used in my PhD dissertation can be divided in three groups: coarse grained molecular dynamics, random walk simulations, and finite difference calculations. Multiphysical software (Comsol) was used to solve numerically the Nernst-Planck-Poisson

[4] Cha, G.; Liu, D.; Meyerhoff, M.; Cantor, H.; Midgley, A.; Goldberg, H.; Brown, R. *Analytical Chemistry* **1991**, *63*, 1666-1672.

[5] Sutandar, P.; Ahn, D. J.; Franses, E. I. *Macromolecules* **1994**, *27*, 7316-7328.

[6] Kasianowicz, J.; Brandin, E.; Branton, D.; Deamer, D. *Proceedings of the National Academy of Sciences of the United States of America* **1996**, *93*, 13770-13773.

[7] Service, R. *Science* **2006**, *311*, 452-452.

[8] Bayley, H.; Braha, O.; Gu, L. *Advanced Materials* **2000**, *12*, 139-142.

[9] Jirage, K. B.; Hulteen, J. C.; Martin, C. R. *Science* **1997**, *278*, 655-658.

and the Navier-Stokes equations. Coarse grained molecular dynamics were used to model the effect of external force field on the ionic current in single stranded DNA modified conical nanopores. The calculations were done with GROMACS molecular dynamics software.[10] The detection limit and the escape time of single nanopore sensors were determined by random walk simulations. One-dimensional finite difference calculations were used to define the potential response and water uptake of ion-selective electrodes.

2.1 Finite difference numerical model to describe the potential response and water uptake of ion-selective electrodes

While the generally used steady-state treatment is a valuable tool to describe the long-term behavior of the ion-selective electrodes (ISE), it is incapable of predicting practical response transients under rapidly changing conditions. Our goal with the finite difference based numerical model was to describe and influence the potential response of ISEs near the detection limit. In this model the small difference between the neighboring elements is calculated. Each phase is divided into N segments of thickness δ, and the number of ions, $n_{i,\nu}$, in a segment, ν, after each time step, Δt, is given by:

$$n_{i,\nu}(t+\Delta t) = n_{i,\nu}(t) + \frac{D_i}{\delta^2}\left(n_{i,\nu-1}(t) + n_{i,\nu+1}(t) - 2n_{i,\nu}(t)\right)\Delta t \tag{1}$$

According to the phase-boundary potential model, the potential is determined by the boundary concentrations of ions. In the presence of one dominating interfering ion, J^z, with valency z equal to that of the primary ion, a fast equilibrium at the phase boundary relates the concentrations, c_I and $[IL^z]$, to each other by:

$$K_{IJ}^{pot} = \frac{c_I}{c_J}\frac{[JL^z]}{[IL^z]} \tag{2}$$

where c_I, c_J and $[I^{z_I}]$, $[J^{z_I}]$ are the boundary concentrations of the primary an interfering ions in the aqueous and organic phases, respectively; these concentrations are used as an approximation of activities.

For reasons of electroneutrality, the total amount of cations in the membrane is constant. The concentration of interfering ions in the aqueous phase is assumed to be sufficiently high so that the ion exchange across the membrane does not significantly alter it. ($c_J = c_{J,bulk}$):

$$K_{IJ}^{pot} = \frac{n_I^{aq}(t+\Delta t)}{n_J^{aq}(t+\Delta t)}\frac{n_J^{mem}(t+\Delta t)}{n_I^{mem}(t+\Delta t)} = \frac{n_I^{aq}(t)+\Delta n_I}{n_J^{aq}(t)}\frac{n_J^{mem}(t)+\Delta n_I}{n_I^{mem}(t)-\Delta n_I} \tag{3}$$

and the amount of exchanged primary cations at the interface, Δn_I, is given by solving Eq. 3:

$$\Delta n_I = \frac{1}{2}\left(-n_I^{aq} - K_{IJ}^{pot}n_J^{aq} - n_J^{mem} + \sqrt{-4n_I^{aq}n_J^{mem} + 4K_{IJ}^{pot}n_J^{aq}n_I^{mem} + \left(n_I^{aq} + K_{IJ}^{pot}n_J^{aq} + n_J^{mem}\right)^2}\right) \tag{4}$$

Migrational fluxes can be calculated using the current density (j).

[10] Van Der Spoel, D.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J. C. *Journal of Computational Chemistry* **2005**, *26*, 1701-1718.

3 Results

3.1 Opportunities and constraints in detection limit of ion-selective electrodes

Ion fluxes across polymeric ion-selective membrane are a decisive parameter dictating the detection limit of potentiometric ion sensors. An applied current has been earlier proposed to counterbalance such fluxes and extend the detection limit to ultra-trace levels. So far, however, the method has not been able to be used in practical situations since the correct current amplitude requires prior knowledge of the sample solution. We explored the use of stir effect to evaluate the optimal current by theory and experiments. Ion fluxes can be detected by observing the presence of potential drifts upon changing the stirring rate in the sample. The stirring effect disappears when the primary ion concentration in the bulk and the superficial sample solution layer are equal. The improvements obtained in the lower detection limit are much less pronounced than expected on the basis of the steady-state model (Figure 1A). This is apparently a consequence of the non-steady-state situation during the measurements. In all cases, before each measurement at the concentration shown, the membrane was conditioned until steady-state in a solution of 10^{-4} M Ag^+ and 10^{-4} M NH_4^+ on both sides. Then, the optimal current (i.e., the current at which the stir effect disappears) was applied for 5 min, 60 min, or infinitely long. It is apparent that the achievable lower detection limit is significantly worse at short times than at steady state. In Figure 1B, the zero-current ion flux of Ag^+ from the membrane into the sample (calculated in current units) is shown together with the optimal external current for each concentration. It is apparent that much larger external currents are required to compensate for ion fluxes than the zero-current value (note the logarithmic scale of the y-axis). As also evidenced in Fig. 1B, concentrations below ca. 10^{-9} M become measurable only by inducing a strong ion flux from the sample solution in direction of the membrane. This results in an ever increasing inward flux of the interference with increasing current density for the situation where concentration polarization of the primary ion is perfectly compensated.
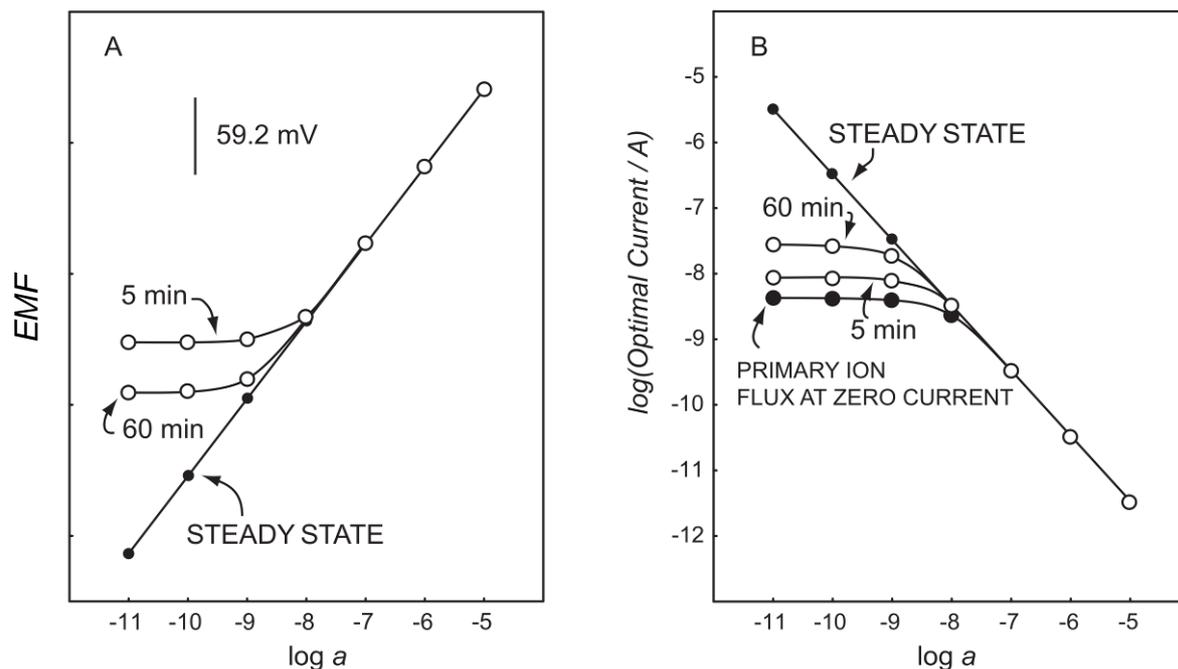
Figure 1   A) Finite difference calculations of the responses of a Ag^+-selective electrode with different measuring times. Before each measurement, the membrane was conditioned until steady-state in a solution of 10^{-4} M Ag^+ and 10^{-4} M NH_4^+ on both sides and then the optimal current (i.e., the current at which the stir effect disappears) was applied during the measurement time indicated. B) Zero-current ion flux of Ag^+ from the membrane into the sample (calculated in current units) and optimal external current for each concentration.

The numerical results suggest that stir effects may be used to find optimal currents, but that the detection limit of an electrode already properly optimized chemically cannot be significantly improved galvanostatically.

3.2 Potentiometric ion-breakthrough experiment to determine the unbiased selectivity coefficient and the diffusion coefficient of ions in

The unbiased selectivity coefficient and the diffusion coefficient of ions in membrane can be assessed in a single ion-breakthrough experiment. The *EMF* of a primary ion-free membrane is measured in a symmetrical electrochemical cell. In the beginning there is a constant concentration of interfering ions on both sides of the membrane. After a stable membrane potential is reached a high concentration of primary ion (10^{-3} M) is set in the sample solution. By finite difference simulations of the potential response it become clear that the slope of the potential response curve only depends on the diffusion coefficient in the membrane and the thickness of the membrane.
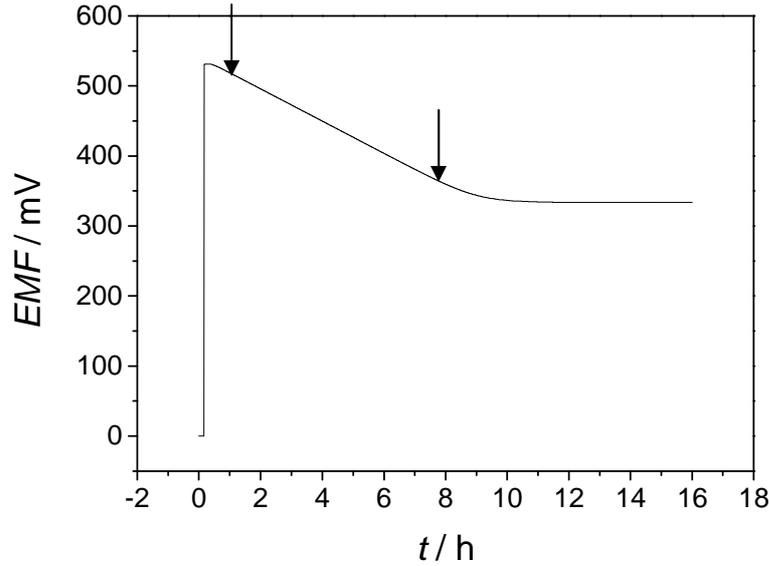
Figure 2 Potential response curve of a typical membrane. The membrane is conditioned in 10^{-4} M interfering ion solution. At 10 min the primary ion concentration is set to 10^{-3} M in the sample solution. Arrows show the range used for the linear fitting.

The larger the slope of the linear range, marked in Fig. 2, the faster the ion transport through the membrane. The *EMF* value of a symmetrical electrochemical cell according to the phase-boundary potential theory is given by the following expression:

$$EMF = E_f - E_b = \frac{RT}{z_I F}\left(\ln \frac{c_{I,f}}{\left[IL^{z_I} \right]_f} - \ln \frac{c_{I,b}}{\left[IL^{z_I} \right]_b} \right) \tag{5}$$

Since the primary ion concentration in the sample solution is high, its boundary concentration is equal to the bulk concentration ($c_{I,f} = c_I$), while $\left[IL^{z_I} \right]_f$ equals the in exchanger concentration (R_T). Finally taking into account that in the inner compartment the interfering ion concentration is high ($c_{J,b} = c_J$), the ion-ionophore complex concentration at the inner membrane boundary, $\left[IL^{z_I} \right]_b$, can be expressed from Fick's second law. Thus for $z_I = z_J$ the EMF can be described by a first order equation as a function time:

$$EMF = A + B \cdot t = \frac{RT}{z_I F} \ln\left(\frac{4}{\pi} \frac{c_I}{K_{IJ}^{pot} c_J} \right) + \frac{RT}{z_I F}\left(\frac{-\pi^2 D_{org}}{\left(2d_{org} \right)^2} \right) t \tag{6}$$

The unbiased selectivity (K_{IJ}^{pot}) can be calculated from the intercept of the linear expression (*A*) while the diffusion coefficient in the membrane (D_{org}) from the slope of the line (*B*).

3.3 Rational design of solid-contact ion-selective electrodes for ultra-trace analysis

There is no inner solution in the case of solid contact ISEs that could sustain the transmembrane flux of primary ions. Therefore, constant flux of ions cannot evolve and the main experimental tool to lower the detection limit is the membrane conditioning. With proper preconditioning flat primary ion concentration profile can be reached in the membrane, which means that there is no flux of ions through the phase boundary. Preconditioning is optimal when the detection limit is the lowest. The detection limit is defined as the primary ion activity in the sample for which the potential deviates more than $(RT / z_I F) \ln 2$ from the linear nernstian response (Fig. 3).
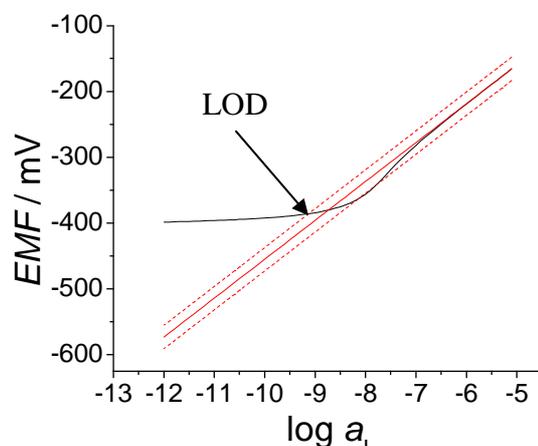

Figure 3   Calibration curve by exponential dilution[11] after optimal preconditioning of the ion-selective membrane.

To find the parameters of optimal preconditioning procedure several thousand simulations were made with different input parameters (diffusion coefficient in the sample solution and membrane, diffusion layer thicknesses, selectivity coefficient, ion-exchanger content, interfering ion concentration).   After evaluating these simulations we got this empirical equation to the lower detection limit for fully conditioned solid contact ISE-s.

$$\log c_{I,LOD} = -2,0 + 0,5\left(\log K_{IJ}^{pot} + \log c_J + \log d_{aq} - \log D_{aq} + \log R_T\right) + 0,25\log D_{org} + 0,294\log\left(\frac{\partial \log c_I}{\partial t}\right) \quad (7)$$

where d_{aq} is the thickness of the diffusion layer, D_{aq} and D_{org} are the diffusion coefficients in the sample and membrane, respectively, R_T is the concentration of ion exchanger, and $\frac{\partial \log c_I}{\partial t}$ is the rate of concentration change in the exponential dilution.

Evaluating the outcome of the simulations in terms of the composition of the optimal preconditioning solution results in the following expression:

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[11] G. Horvai, K. Toth, E. Pungor, Analytica Chimica Acta 1976, 82, 45

$$\log \frac{c_{\text{I,pre}}}{c_{\text{J,pre}}} = 1,25 + 0,5\left(\log K_{\text{IJ}}^{\text{pot}} + \log c_{\text{J}} + \log d_{\text{aq}} - \log D_{\text{aq}} + \log R_{\text{T}}\right) + 0,25\log D_{\text{org}} + 0,212\log\left(\frac{\partial \log c_{\text{I}}}{\partial t}\right) \quad (8)$$

$$- 0,560\log\left(4,12 + \log c_{\text{I,start}} - 0,5\left(\log K_{\text{IJ}}^{\text{pot}} + \log c_{\text{J}} + \log d_{\text{aq}} - \log D_{\text{aq}} + \log R_{\text{T}}\right)\right)$$

Thus the lengthy, empirical optimization of preconditioning solution can be avoided by using a solution with the proper primary ion/interfering ion composition calculated from Eq. 8.

3.4 Water uptake of ion-selective membranes

The water uptake significantly affects the potentiometric response of ion-selective membranes. In case of solid contact ion-selective electrodes an aqueous layer might form between the membrane and the substrate electrode. The ionic composition of this layer is constantly changing with changes in the sample solution composition, which leads to potential instability. As the main source of water for the aqueous layer formation is the transmembrane water flux we have subjected membranes based on most commonly used polymeric materials (plasticized PVC, poly(acrylate) and silicon rubber) to FTIR-ATR analysis. Monomeric, dimeric, clustered and bulk water could be distinguished by deconvolution of the FTIR-ATR spectra, which is provides additional information to understand the water uptake mechanism. The best fits of the time dependent water concentration changes in the membrane upon water uptake were obtained with a model consisting of two diffusion coefficients describing fast and slow diffusion of water in the ion-selective membranes (Fig. 4).
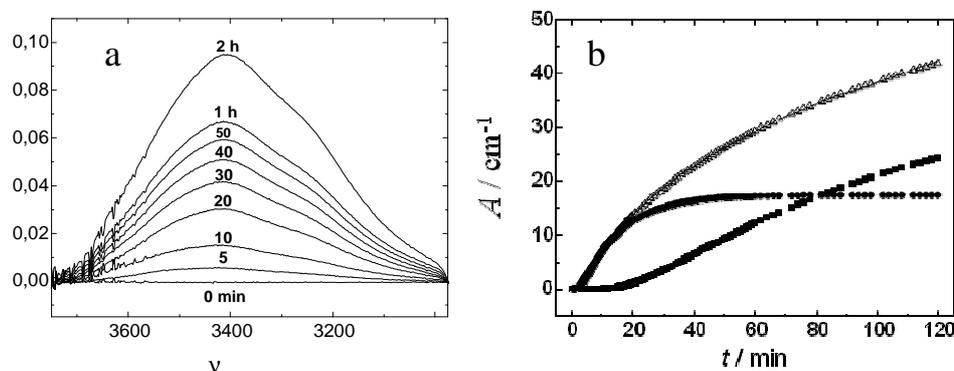

Figure 4   FTIR-ATR spectra of a) a PVC:DOS (1:2) membrane (thickness: 281 µm) and b) integrated band areas of the OH stretching bands Experimentally measured band areas (——) and mathematically simulated band areas for (●) fast and (■) slow diffusion of water through the membranes. The sum of the "fast" and "slow" water is indicated with (Δ).

It was found that the water uptake of the plasticized PVC and poly(acrylate) membranes was considerably decreased by the incorporation of lipophilic salts and ionophore in the membrane matrix. Among the studied membranes those based on poly(acrylate) took up water

with the smallest diffusion coefficients while the equilibrium water content of silicon rubber membranes was the smallest.

Table 1. Diffusion coefficients and integrated absorbances at infinite time (A_∞) for different types of membranes. $A_{1,\infty}$ and $A_{2,\infty}$ are the absorbances at infinite time for the quickly (D_1) and slowly (D_2) diffusing water, respectively. $A_{\text{tot},\infty}$ is the sum of these two absorbances, indicative of the equilibrium water content.

membrane	D_1 (cm^2·s^{-1})	$A_{1,\infty}$ (cm^{-1})	D_2 (cm^2·s^{-1})	$A_{2,\infty}$ (cm^{-1})	$A_{\text{tot},\infty}$ (cm^{-1})
plasticized PVC[1]	$(1,3 - 3,3)\cdot10^{-7}$	5,3 – 30,4	$(0,8 - 6,0)\cdot10^{-8}$	10,7 – 84,9	15,4 – 115,3
PA[2]	$(1,7 - 8,9)\cdot10^{-8}$	7,3 – 68,4	$(2,1 - 7,4)\cdot10^{-9}$	54,7 – 128,1	76,7 – 196,5
SR[3]	$(2,0 - 2,3)\cdot10^{-7}$	3,5 – 5,9	$(0,9 - 2,0)\cdot10^{-8}$	4,9 – 7,7	10,1 – 12,0

[1] Plasticized PVC membranes without additives or containing ionophore and/or lipophilic anion.

[2] Poly(acrilate) membranes without additives or containing ionophore and/or lipophilic anion. The measured copolymers were: poly(methyl metacrylate):poly(decyl metacrylate), poly(methyl metacrylate):poly(nbuthyl metacrylate) és poly(methyl metacrylate):poly(isodecyl acrylate)

[3] Silicon rubber (RTV 3140, Dow Corning) membranes without additives or containing ionophore and/or lipophilic anion.

3.5 Coarse grained modeling of electromechanic rectification effects in DNA modified conical nanopores

Nanopore based devices are emerging as tools for single molecule manipulation, characterization and chemical analysis. However, it is little known about the orientation, coverage and behavior of surface tethered species in the nanopore environment as function of applied transpore voltages. Coarse grained modeling of short DNA modified conical gold nanopores subjected to electrical field gradients of 5 and 50 mV/nm were performed. An electromechanical gating effect in the single stranded DNA modified conical nanopores is predicted, which is due to the obstruction of the tip entrance by DNA strands oriented by the external electrical field. The magnitude of the rectification effect increases with increasing DNA length and decreasing tip diameter of the conical nanopore. The direction of on/off switching was found to be dependent on the location of the immobilized DNAs on the membrane supporting the nanopore (Fig. 5).
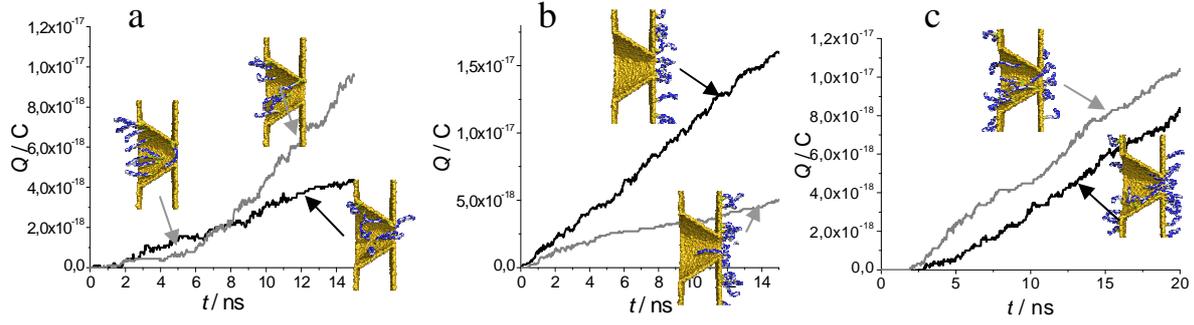
Figure 5: Cumulated charge transients recorded at +0.05 V/nm (black curve) and -0.05 V/nm (grey curve) for the same membrane geometry having either only the pore inner surface (a), only the membrane outer surface (b) or the entire surface (c) modified with 15-mer CG ssDNA.

Since the rectification effect and the direction of the on/off switching is very much influenced by the surface coverage of DNA and whether the entire, only the outer membrane surface or the inner of the nanopore is modified, it may provide information on the surface modification process as well.

3.6 Detection limit of single nanopore sensors

Even one molecule can affect the ion transport through a single nanopore sensor. However it is important to know what is their detection limit in terms of concentration. To find it out we performed random walk simulations to determine the probability of a molecule to encounter the nanopore. The simulation space was cubic with one nanopore in the center of one of the faces. A single molecule was placed in the simulation environment which using the constant volume resulted of the cube can be scaled to a concentration value. We calculated the escape (encounter) time, which is the time the molecule needs to encounter the nanopore. The molecule was rendered to random locations in the simulation space, and in one step it could move to the neighboring six grid points randomly but with equal probability. By using the Einstein-Smoluchowski equation and the distance between two neighboring grid points the simulation environment can be conferred with real space and time values. Evaluating the simulations the escape time could be described by the following semi-empirical equation:

$$t = \frac{4{,}1 \cdot 10^{-15}}{C \cdot D \cdot r_{V}} \tag{9}$$

where C is the concentration of sample solution, D is the diffusion coefficient of the molecule, and r_{V} is the radius of the nanopore.

If the molecule is spherical Stokes-Einstein equation can be used to calculate the escape time.

$$t = 1{,}7 \cdot 10^{-9} \frac{r_{\text{mol}}}{r_{V} C} \tag{10}$$

where r_{mol} is the hydrodynamic radius of the molecule.

Based on our calculations at pM concentrations the escape time (1000 s) is near the experimentally feasible analysis time. Thus the detection limit for single nanopore sensors is constrained by the time needed for the detected component to encounter the nanopore. However, charged particles can be directed into the nanopore using an electric field, which results in a considerable shortening of the escape time (Fig. 6). At larger potentials there is a reciprocal dependence of escape time to potentials.
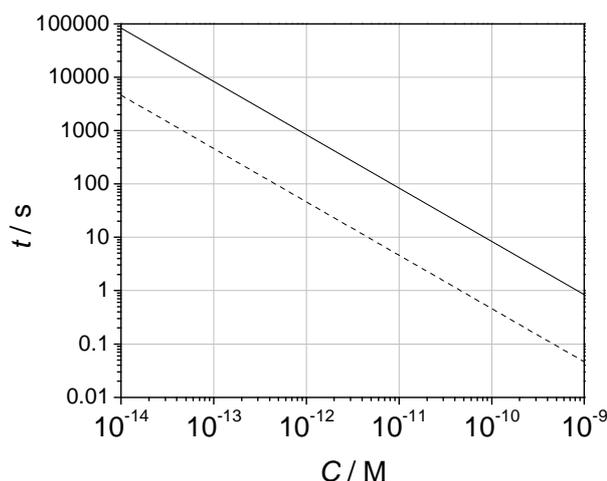

Figure 6   Escape time of a 30-mer DNA, from 1 μm^3 volume through a 10 nm diameter nanopore: in the absence of external force field (solid line) and when 0.5 V transpore potential is applied (dashed line)

4 Novel scientific results

1. A numerical method based on the finite difference method was developed which is capable of describing the potential response of ion-selective electrodes under convective, migrational and diffusional perturbations. With this method, among others, by knowing the previous history of the ion-selective electrode it is possible to predict its time dependent potential response.[P2]

2. The thermodynamic detection limit for ion-selective electrodes cannot be reached with the current polarization method, as it was suggested in earlier publications.[P2]

3. The potential response during potentiometric ion breakthrough experiments could be properly described with the introduced numerical method. A new expression was introduced that can be used to calculate the unbiased selectivity coefficient and diffusion coefficients of ions in the membrane from the experimental potential traces recorded in a single potentiometric ion breakthrough experiment.[P6]

4. An empirical equation was introduced to rationally determine the composition of preconditioning solution needed to reach the optimal detection limit (Eq. 8). Using this equation the lengthy, experimental optimization of preconditioning can be avoided.[P5]

5. By finite difference modeling of FTIR-ATR data it was shown that the water uptake of ion-selective membranes (plasticized poly(vinyl chloride), poly(acrylate) and silicon rubber) can be described with a two diffusion coefficients.[P3,P4]

6. Based on the determined diffusion coefficients the water uptake is the slowest in poly(acrylate) membranes while the equilibrium water concentration is the smallest in silicon rubber membranes. Furthermore, it was proven that the water uptake of the plasticized PVC and poly(acrylate) membranes is decreased by the incorporation of lipophilic salts and ionophore in the membrane matrix.[P3,P4]

7. A coarse grained molecular representation was introduced for the molecular dynamics simulation of ion currents within DNA modified conical nanopores. Based on coarse grained molecular dynamics simulation the electromechanical rectification originating from the orientation of immobilized DNA strands in the applied transpore electric field could be explained. [P1]

8. The detection limit of single nanopore sensors is dependent on the probability of the detected molecule to reach the pore. Based on random walk simulation results a semi-empirical expression (Eq. 9) was introduced to predict the concentration and pore size dependence of the escape (encountering) time.[P7]

9. Combining force fields calculated using multiphysical simulations and random-walk simulations it was shown that the escape time of a charged molecule can be significantly reduced by applying a transpore electrical field.[P7]

5 List of scientific publications

5.1 Publications directly related to the PhD thesis

P1   Coarse grained molecular dynamics simulation of electromechanically-gated DNA modified conical nanopores (**Höfler, L**; Gyurcsányi, RE; Electroanalysis; 20(3) 301-307; Published: 2008; Impact Factor: 2.949; Times Cited: 1)

P2   Limitations of current polarization of lowering the detection limit of polymeric membrane potentiometric sensors (**Höfler, L**; Bedlechowicz, I; Vigassy, T; Gyurcsányi, RE; Bakker, E; Pretsch, E; Analytical Chemistry; 81(9) 3592-3599; Published: 2009; Impact Factor: 5.287; Times Cited: 1)

P3   FTIR-ATR study of water uptake and diffusion through ion-selective membranes based on plasticized poly(vinyl chloride) (Lindfors, T; Sundfors, F; **Höfler, L**; Gyurcsányi, RE; Electroanalysis; Accepted; Published: 2009; Impact Factor: 2.949; Times Cited: 1)

P4   FTIR-ATR study of water uptake and diffusion through ion-selective membranes based on poly(acrylates) and silicone rubber (Lindfors, T; Sundfors, F; **Höfler, L**; Bereczki, R; Gyurcsányi, RE; Analytical Chemistry; Submitted; Publish: 2009; Impact Factor: 5.287)

P5   Rational design of solid-contact ion-selective electrodes for ultra-trace analysis (**Höfler, L**; Szűcs, J; Gyurcsányi, RE; Electroanalysis; Under preparation; Publish: 2009; Impact Factor: 2.949)

P6   Mathematical model to assess the apparent diffusion coefficient and unbiased selectivity of ion-selective electrodes from a single potentiometric ion-breakthrough experiment (**Höfler, L**; Bodor, S; Gyurcsányi, RE; Electroanalysis; Under preparation; Publish: 2009; Impact Factor: 2.949)

P7   Detection limit of single nanopore sensors. A semi-empirical treatment. (**Höfler, L**; Cserkaszki, A; Gyurcsányi, RE; Analyst; Under preparation; Publish: 2009; Impact Factor: 3.553)

5.2 Other publications

P8   Hybridization-modulated ion fluxes through peptide-nucleic-acid-functionalized gold nanotubes. A new approach to quantitative label-free DNA analysis (Jágerszki, G; Gyurcsányi, RE; **Höfler, L**; Pretsch, E; NANO LETTERS; 7(6) 1609-1612; Published: 2007; Impact Factor: 9.627, Times Cited: 5)

5.3 Presentations in English

Non-steady state model to predict the potential response of solid contact ion-selective electrodes (**Höfler, L**; Pretsch, E; Gyurcsányi, RE; Event: Mátrafüred'08 International Conference on Electrochemical Sensors, Dobogókő 2008,)

5.4 Presentations in Hungarian

Transzportfolyamatok molekula dinamikai számítása kémiailag módosított szintetikus nanopórusok esetében (**Höfler Lajos**; Gyurcsányi E. Róbert; Esemény: Kémiai Szenzorok Kutatásának Eredményei II. Workshop, Pécs 2006)

Iondiffúzió vizsgálata szintetikus nanocsöveken keresztül molekuladinamikai számításokkal (**Höfler Lajos**; Esemény: VII. Téli Iskola, Balatonfüred 2007)

Transzportfolyamatok molekuladinamikai számítása kémialilag módosított szintetikus nanocsövek esetében (**Höfler Lajos**; Esemény: Doktoráns Konferencia, Budapest 2007)

Szintetikus nanocsövek iontranszport tulajdonságainak vizsgálata molekuladinamikai számítások segítségével (**Höfler Lajos**; Gyurcsányi E. Róbert; Esemény: Centenáriumi Vegyészkonferencia, Sopron 2007)

5.5 Other presentations and posters

Chemically modified solid-state nanopores for sensing (Róbert E. Gyurcsányi, **Lajos Höfler**, Áron Cserkaszky, Tamás Varga, Gergely Lautner, Gyula Jágerszki, Péter Fürjes, Attila L. Tóth; Event: Mátrafüred'08 International Conference on Electrochemical Sensors, October 5-10, 2008, Dobogókő, Hungary)

Diffusion of water through polymeric ion-selective membranes monitored by FTIR-ATR spectroscopy and multispectral optical imaging (Tom Lindfors, Fredrik Sundfors, **Lajos Höfler**, Gyula Jágerszki, Róbert E. Gyurcsányi; Event: Mátrafüred'08, International Conference on Electrochemical Sensors, Dobogókő, 2008, October 5-10)

Bioassays with potentiometric detection (Róbert E Gyurcsányi, Ernő Pretsch, **Lajos Höfler**, Júlia Szűcs, Tamás Vigassy; Event: Pittcon 2008, March 1-7, New Orleans, USA.)

Hybridization-modulated ion fluxes through peptide nucleic acid functionalized nanotubules. A new approach for label-free DNA analysis (Róbert E. Gyurcsányi, Gyula Jágerszki, **Lajos Höfler**, Tamás Vigassy, Ernő Pretsch; Event: International Conference on Electrochemical Sensors, November 13-18, 2005, Mátrafüred, Hungary)

Hybridization-modulated ion fluxes through peptide-nucleic-acid-functionalized gold nanotubes. A new approach to quantitative label-free DNA analysis (Róbert E. Gyurcsányi, Gyula Jágerszki, **Lajos Höfler**, Ernő Pretsch; Event: Development and Application of Chemical Sensors A conference held in honor of Ernö Pretsch June 28 – 29, 2007, Zürich, Switzerland By The Swiss Chemical Society)