

A Scientific Journey with Ionophore-based Sensors

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Simon-Widmer Award 2019

Abstract: This article describes selected historical milestones in the field of neutral ionophore-based sensors, starting with the first discovery by Wilhelm Simon and their impact to analytical sciences despite the initial difficulty to understand their function. The reader is then guided through topics in which the author has been involved over the years, from understanding thermodynamic aspects to the field of non-equilibrium potentiometry, polyion sensors, trace level potentiometry, instrumentally controlled ion sensors and finally potentiometry involving local perturbations and transient currents that allow for new readout possibilities. Discussed applications include clinical diagnostics, environmental *in situ* sensing/profiling and speciation analysis. The article loosely follows the content of the Simon-Widmer Award lecture of the same title presented by the author at the CHAnalysis 2019 conference in Beatenberg, Switzerland.

Keywords: Clinical analysis · Environmental analysis · Ionophores · Ion sensors · Membrane electrodes · Potentiometric sensing



Eric Bakker was born in Switzerland into a Dutch family and spent his childhood both in the French- and German-speaking parts of the country. He studied chemistry at ETH Zurich and pursued his doctoral studies at the same place with Wilhelm Simon on optical sensors, then moved to the University of Michigan for separate parallel postdocs with Mark Meyerhoff and Raoul Kopelman. Auburn University in the deep south of the

USA, where he stayed for a period of 10 years, welcomed him to pursue his independent academic career, after which time he moved to Purdue University in Indiana, then to Curtin University in Perth, Western Australia to be director of the Nanochemistry Research Institute, and in 2010 to the University of Geneva. He has published extensively in the field of chemical sensors, electroanalysis and optical sensing, and serves as the Executive Editor for the journal ACS Sensors. He is married to Eva Jüngling and has one daughter, Colette, who of course has been his biggest project.

1. Simon's Discovery

At the Meeting of the Swiss Chemical Society in 1966, Wilhelm Simon (ETH Zurich) presented results on the electrochemical behavior of the macrotetrolides (Actin homologs) that would trigger a dramatic paradigm shift in the clinical diagnostics of blood electrolytes. As published in a short communication with Stefanac in *Chimia* (!) in the same year,^[1] the use of these compounds in an organic membrane gave a remarkable response to potassium ions relative to other tested ions, including Li⁺ and Na⁺. The preference of potassium over sodium was claimed to be about a factor of 750, which surpassed the best potassium glass

electrodes (the state of the art at that time) by more than one order of magnitude.

This discovery was a watershed moment for the Analytical Sciences, in Switzerland and across the world. It triggered extensive synthetic, mechanistic and analytical research that propelled the Simon group to the forefront of ion-selective electrode research, a direction that formed an exciting new wave in analytical science. It coincided with the birth of supramolecular chemistry, and compounds such as cryptands (originally: cryptates, for cavity) introduced by Dietrich, Lehn and Sauvage^[2] served as an inspiration to the Simon group in the quest of finding new molecules that might exhibit unique binding characteristics. One may consider Fig. 1 for its synthetic pathway where the initial step involves the condensation of a diamine with a diacid chloride to give a cyclic diamide. Reduction then yields the diamine compound which is then further reacted to form a third diether bridge. Unfortunately, cryptands turned out to be unsuccessful compounds for ion-selective membranes. They tend to bind to metal ions too tightly and are too hydrophilic for their effective retention in an organic sensing phase. If we step back along the synthetic pathway, the cyclic diamine is still not attractive because the basicity of the amine groups would introduce significant interference from hydrogen ions. Therefore, the diamide was most promising and served as the basis for a range of compounds in Simon's group that eventually resulted in a lipophilic, non-cyclic diamide that showed remarkable selectivity for calcium ions, see Fig. 1.^[3] It was proudly named ETH 1001 and is still in routine use (Sigma Aldrich Product, CAS 58801-34-6).

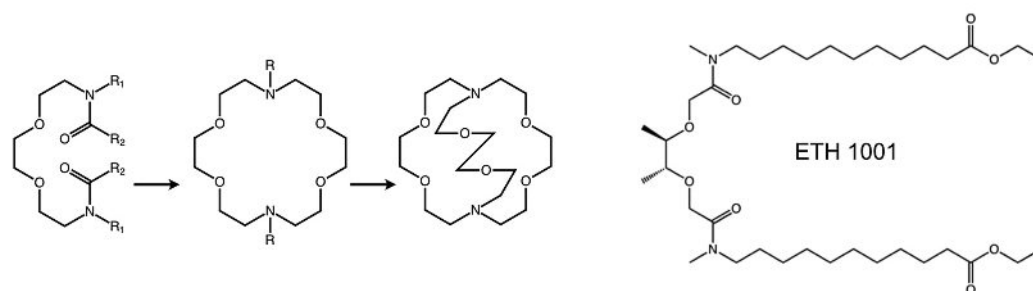
So-called ionophores for the selective recognition of sodium, potassium and calcium, along with a membrane containing an anion-exchanger salt for measuring chloride were introduced in rapid order and applied for quantitative blood electrolyte mea-

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Fig. 1. Pathway for the synthesis of cryptands as reported by Dietrich *et al.* (left),^[2] which served as an inspiration to design the noncyclic diamide ionophore ETH 1001 (right).^[3]

FROM CRYPTANDS TO THE CALCIUM IONOPHORE ETH 1001



measurements in clinical analyzers using solution flow, in partnership with industry.^[4] It was shown to exhibit improved reproducibility compared to the state of the art at the time, flame photometry, atomic absorbance and colorimetry, and cross-correlation was excellent after correcting for hematocrit.^[4] The cited review was published just a decade after that first oral presentation in 1966, showing how rapidly this fundamental discovery translated into a routine tool that would be used for the measurement of undiluted whole blood samples in hospitals all over the world.

2. Theoretical First Steps, and Pitfalls

Early on, the practical work was accompanied with efforts to understand how these membranes work and how the reversible recognition of the guest ion with the ionophore host molecule could translate into a potential change across an organic membrane phase doped with said ionophore.^[5] Here, the Simon group initially relied on work by Eisenman and co-workers in the US who had developed a comprehensive model to account for electrical migration and boundary potentials for a number of cases of practical relevance.^[6] Two questions needed to be answered: 1) what is the origin of the Nernstian response slope? 2) How can one understand selectivity over competing ions?

Eisenman and co-workers considered all known species, the ion of interest, the electrically neutral ionophore, and any counterion in solution. The partitioning of all these species including their complexes and ion pairs between solution and membrane phase were taken into account. It turns out that a Nernstian response slope was only possible by assuming a concentration gradient of

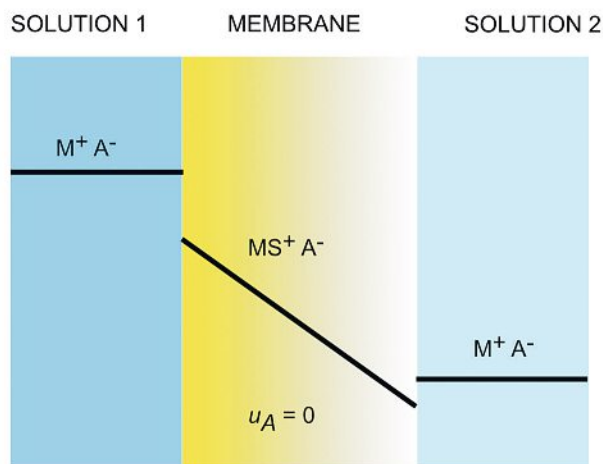
the electrically charged ion-ionophore complex across the membrane, caused by an asymmetrical extraction of the complex with its counterion from solution (Fig. 2). Moreover, the counterion, once in the membrane, must have a mobility of zero. Knowing that in potentiometric measurements the overall current is zero, the diffusional flux from the ion-ionophore complex and the flux originating from electrical migration have to compensate each other. The measured potential was therefore thought to originate from electrical migration and called a diffusion potential. Once this was explained, the potential E for a system containing two competing ions was developed in the same way, resulting in equations of the following type:

$$E = E_i^0 + \frac{RT}{F} \ln \left(a_i + \frac{u_{JS} k_{JS} K_{JS}}{u_{IS} k_{IS} K_{IS}} a_j \right) - \frac{RT}{F} \ln (1 + K_{IS} a_i + K_{JS} a_j) \quad (1)$$

where R , T and F have their established meanings, u_{IS} and u_{JS} are the mobilities of the two ion-ionophore complexes (I is the analyte while J is the interference), K_{IS} and K_{JS} the respective complex formation constants in solution and $k_{species}$ the relative partition coefficients.

However, it turned out that this theoretical framework was wrong. Eisenman considered a lipid bilayer and Simon an artificial liquid membrane of larger thickness, but both assumed an organic solvent just containing a neutral ionophore because this was the way the membranes had been prepared. With time,

A) EISENMAN MODEL



B) ION-EXCHANGE MEMBRANE

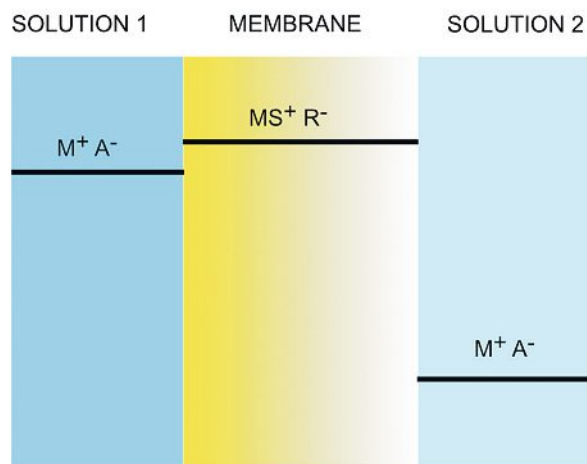


Fig. 2. Left, historical view:^[6] the assumption of a concentration gradient across the membrane was required in the early days of ionophore-based potentiometric sensors to explain the observed Nernstian slope, along with a zero mobility for the co-diffusion counter ion ($u_A = 0$), which was rather unreasonable. The membrane potential is given by the diffusion potential in the membrane. Right, modern view:^[9] ionic impurities render the membranes permselective. In the absence of interference there is no substantial concentration gradient across the membrane. The membrane potential is dictated by changes at the two phase boundary potentials.

mounting evidence pointed to the existence of ionic impurities in ion-selective membranes. In an elegant example, Philippe Buhlmann, then with Yoshio Umezawa in Tokyo, carefully purified the solvents and ionophores used to make ion-selective membranes that perfectly agreed with the model assumptions used by Eisenman.^[7] Surprisingly, he found that the potential vs. logarithmic ion activity now exhibited a negligible slope. This meant that, one, the original theory was incorrect, and that, two, most original work with ion-selective membranes containing electrically neutral ionophores was successful only because of the components contained ionic impurities.^[8] Had the researchers used perfectly purified compounds and solvents they would not have found a potassium response in the 1966 paper cited above.^[1] However, they did, and despite this initial lack of understanding, the technology conquered clinical laboratories all over the world.

These types of insights allowed the field to move to a thermodynamic model not unlike that originally used to explain the response of precipitate-based membranes of the type AgX (where X is a halide).^[8] The membranes behave as ion-exchangers, either purposely added or initially present as impurities, imposing a constant concentration of analyte ions in the membrane phase. A Nernstian response is expected for a simple salt in solution if the concentration of ions co-extracted with their counter ions from solution remains significantly smaller than the concentration of ions initially present in the membrane by the ion-exchange capacity.^[9] Such membranes are called permselective.

3. Membrane Selectivity

The ill-fated diffusion potential response model of Eisenman also served to describe how competing co-ions cause a deviation from Nernstian behavior, but only for ions of the same monovalent charge. The actual form of the equation had been developed by Nikolskii for glass electrodes^[10] and maintained for ionophore-based membranes as:

$$E = E_i^0 + \frac{RT}{F} \ln(a_i + K_{i,j}^{pot} a_j) \quad (2)$$

where $K_{i,j}^{pot}$ is the selectivity coefficient. In Eisenman's early model,^[6] this selectivity coefficient was related to ion mobilities in the membrane as well as complex formation constants. Smaller values of the selectivity coefficient mean a better selectivity and a smaller deviation from Nernstian behavior.

It is said that Eisenman urged Nicolsky to offer a similar description for ions of different charge, because ion-selective electrodes for divalent ions, including calcium, had become available and needed to be described adequately. Initial versions of this treatment were more complicated, but in Simon's 1970 review^[5] we find the following description for a divalent ion-selective electrode exhibiting interference from monovalent ions:

$$E = E_i^0 + \frac{RT}{2F} \ln(a_i + K_{i,j}^{pot} a_j^2) \quad (3)$$

while the response for a monovalent ion-selective electrode with interference from divalent ions is described by:

$$E = E_i^0 + \frac{RT}{F} \ln(a_i + K_{i,j}^{pot} a_j^{1/2}) \quad (4)$$

These relationships correctly predict Nernstian behaviour if just one of the two ions is present in solution. It gives guidance to develop ion sensors for a given application, such as in clinical

diagnostics of whole blood samples. If the upper concentration limit of an interfering species is known, the required selectivity to give an acceptable error can be calculated.^[11] Unfortunately, however, the two equations given above are semi-empirical and were never derived from first principles and Morf had long ago recognized that the two equations are incompatible with each other.^[12] If one treats the analyte as the interference, one should be able to use Eqn. (3) interchangeably with Eqn. (4) but unfortunately this does not give the same potential change (see Fig. 3). Ion-exchange theory would be later used to introduce a thermodynamically sound and consistent treatment of ion-selectivity for many cases of interest.^[13] While its mathematical form is more complicated than the equations stated above it gives different required selectivities compared to what had been proposed earlier. Recently, however, it was found that computing the average of the two semi-empirical Eqns (3) and (4) gives a reasonably close agreement with the thermodynamic model (Fig. 3) and its practical use is better recommended.^[14]

MONOVALENT ION-SELECTIVE ELECTRODE

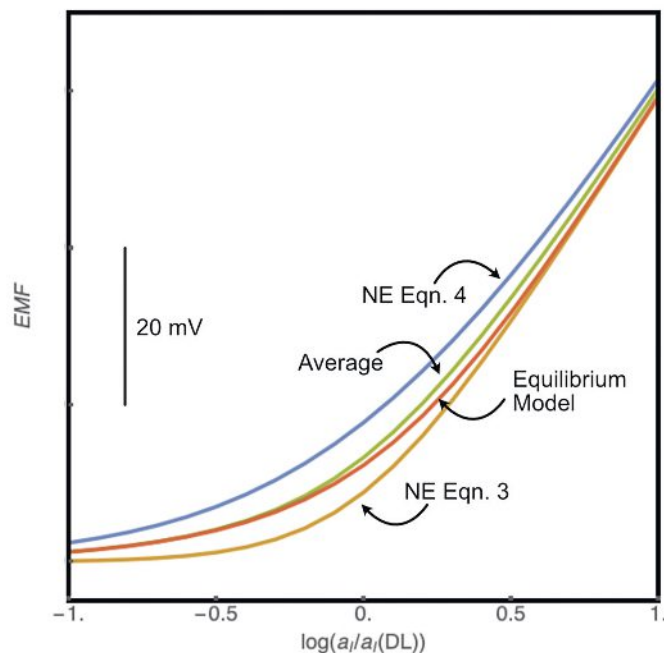


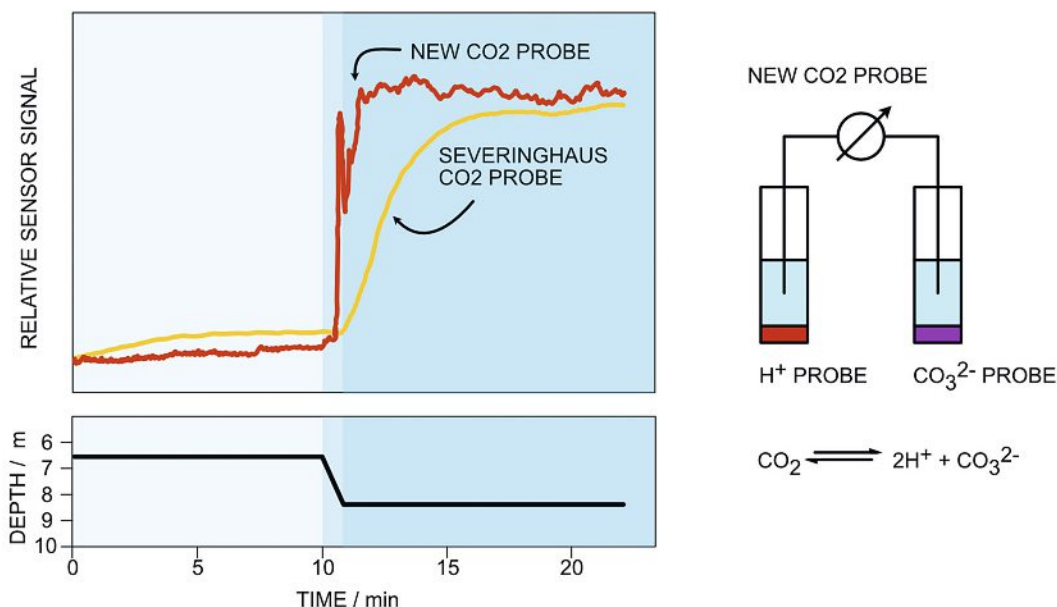
Fig. 3. Calculated potential response of a monovalent ion-selective electrode exhibiting interference from a divalent ion, based on the two semi-empirical Nikolskii-Eisenman Eqns. (3) and (4) (which are inconsistent), the thermodynamically sound description (Equilibrium Model), and the behavior calculated from computing the average of Eqns (3) and (4) (Average), which better agrees with the thermodynamic model.^[14]

4. Environmental Applications

Our group at the University of Geneva has explored the use of ion-selective electrodes in environmental analysis, especially for the monitoring of aquatic systems *in situ*, partially thanks to Marylou Tercier-Waeber, a senior scientist with Jacques Buffle, who joined our group upon his retirement. Potentiometry is especially attractive for this purpose because these sensing probes are responsive to ion activity and are best placed to assess dynamic systems where chemical speciation is important. Often, the delicate balance between species is perturbed by traditional sampling because the interplay between the solution and gas phase, colloidal matter and microorganisms as well as light and temperature cannot be maintained by withdrawing an aliquot for laboratory testing. We have co-developed submersible probes as part of a European Project and deployed them in the Arcachon Bay in France.^[15]

An interesting example is given here that is a result of a collaboration with Bernhard Wehrli at EAWAG where we demonstrate the rapid profiling of carbon dioxide in a stratified lake (Rotsee near Lucerne) by potentiometry.^[16] Carbon dioxide can be measured in various ways, but most methods require its equilibrium partitioning across a membrane where it can be detected by a number of techniques. This equilibration step is slow and carbon dioxide probes tend to exhibit slow response times. If detection is by changing solution pH, it also does not involve a direct chemical recognition of the gas and other species, such as hydrogen sulfide, can interfere. This has been overcome by a carbonate-selective electrode based on an ionophore originally developed by Nam and Cha in Korea that contains two trifluoroacetyl groups to recognize this divalent anion in a tweezer action.^[17] The selectivity is outstanding, even in high saline samples such as seawater.^[18] So, how can a carbonate-selective electrode be used to directly detect carbon dioxide? Carbon dioxide, through its equilibrium with carbonic acid, acts a diprotic acid and is in equilibrium with carbonate and hydrogen ions. If one is able to directly detect pH and the activity of carbonate, detection of carbon dioxide should be possible. So, a potentiometric measurement cell containing a pH electrode measured against a carbonate-selective electrode can be shown to give a potential change that indicates directly carbon dioxide,^[19] assuming that the acid dissociation constants remain constant. Fig. 4 shows a rapid profiling experiment of carbon dioxide at the interface of the aerated surface water (epilimnion) and the oxygen-poor hypolimnion of lake Rotsee,^[16] comparing the newly developed principle with a commercially available Severinghaus probe that requires membrane equilibration. It is clear that the fine structure of carbon dioxide fluctuations is not visible with the commercial probe.

Fig. 4. Rapid carbon dioxide profiling in a stratified lake (Rotsee near Lucerne),^[16] using a rapidly responding pH electrode measured against a carbonate-selective electrode to directly detect CO₂, and a slow responding commercial Severinghaus probe that requires equilibration across a gas permeable membrane.



5. Dynamic Potentiometry: Polyion Sensors

The considerations above suggest that ion-selective membranes can be adequately understood with equilibrium models where, ideally, the composition of the membrane remains effectively unchanged during measurement. It was accepted that non-idealities introduce concentration changes in the membrane, for example by ion-exchange with interfering ions (see *Selectivity* above) or co-extraction with counter ions from solution at higher concentration.^[20] However, in the early 90s Meyerhoff and Yang explored the possibility of detecting polyionic species, especially heparin, a polysulfated anticoagulant drug administered during surgical procedures to keep the blood from clotting. They found

an unlikely potentiometric response to heparin in physiological levels of NaCl with seemingly simple ion-selective membranes containing tridodecylammonium chloride.^[21] At the time it was not clear why heparin should give a response, as its polysaccharide backbone is already hydrophilic, the high anionic charge (about -70) should render extraction into an organic phase in high saline concentration impossible. Moreover, even if selectivity would be adequate, the high valency should give extremely low sensitivity: the Nernstian slope is expected to be inversely proportional to charge, giving less than 1 mV per 10-fold concentration change. Yet, the promising experimental evidence was in contradiction to these anticipated limitations.^[21]

The solution to this theoretical challenge^[22] started the direction of non-equilibrium potentiometry, which served as a trigger for numerous new advances in the field. For heparin detection, it was recognized that extraction does occur,^[23] but the heparin concentration is sufficiently low that it prevents quantitative displacement of chloride ions from the membrane by ion-exchange.^[22] The rate of extraction is assumed to be diffusion limited, with the flux from the solution bulk to the membrane surface equal to that from the membrane surface to its interior (see Fig. 5). This simple model was able to explain why the potentiometric response to heparin is seemingly non-Nernstian and dependent on kinetic parameters such as plasticizer content of the membrane (affecting mobility) and sample convection (stirring rate). It also gave guidance on how to regenerate the membranes after use to strip the heparin back out of the membrane.^[24] The Meyerhoff group went on to develop a selective probe for the detection of protamine, the polycationic antidote to heparin, and demonstrated that the heparin concentration in whole blood could be followed during open heart surgery, using protamine as

titrant.^[25] Heparin was confirmed to metabolize during surgery, demonstrating that heparin levels must be monitored directly at the point of care for accurate neutralization after surgery to avoid complications.

6. Suppressing Ion Fluxes: Potentiometry at Trace Levels

Ion-selective electrodes have long been associated with relatively high detection limits in the micromolar range. The reason for this was often thought to originate in the need to have a sufficiently high ion-exchange current density to result in a stable, measurable potential, although scientific studies on the topic were

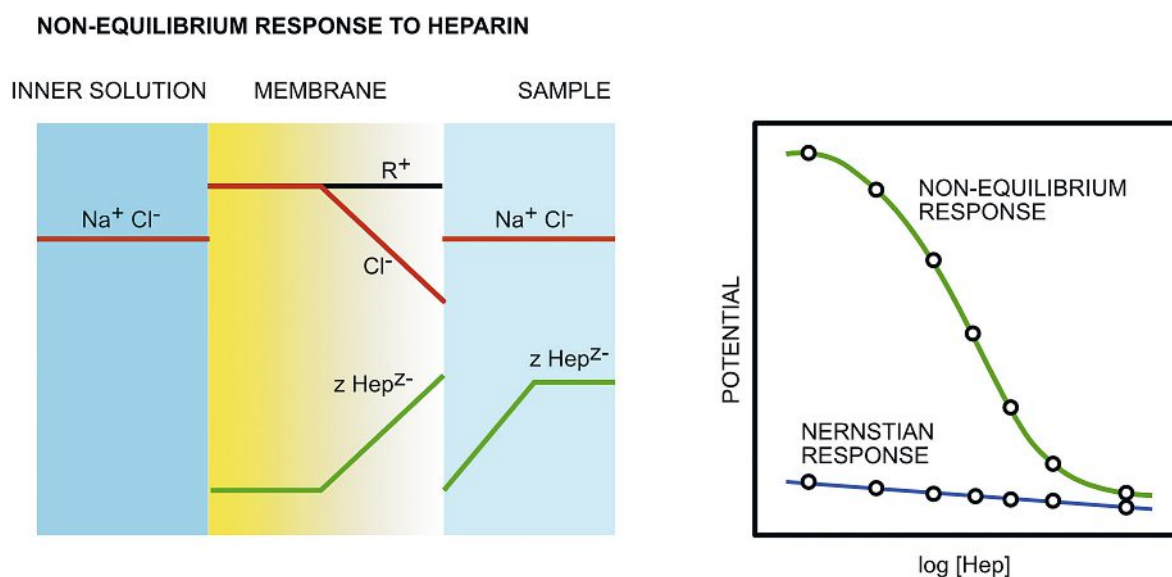


Fig. 5. Response mechanism of potentiometric polyion sensors for the detection of heparin or protamine.^[22] Left: Incomplete ion-exchange with chloride at the sample–membrane interface results in a transient response (shown schematically in green on the right plot) that depends on mass transport of the polyion to the membrane. This gives much larger sensitivities than expected from the Nernst equation (flat line shown in blue).

largely lacking. Once optical ion sensors (ion optodes) on the basis of the same recognition elements of the corresponding potentiometric probes were developed,^[26] it was realized that orders of magnitude lower detection limits could be achieved with those devices.^[27] Ionophore-based optodes were initially spin coated on a flat support and later further miniaturized to microparticles^[28] and to the nanoscale.^[29] They could be quite simply understood with ion-exchange extraction principles, displacing a reference ion (typically H^+) from the sensing phase upon extraction of a cationic analyte from solution.^[30] For this, two ionophores were required, one for the analyte and an indicator ionophore for the reference ion. With adequate selectivity and dynamic measuring range, the lower concentration limit was found to be given by mass transport, sometimes reaching values in the nano- to picomolar concentration range.^[28,31] Parallel potentiometric experiments with otherwise the same selective components did not give the same performance.^[32] Still, it was found that avoiding initial exposure to the most preferred ion resulted in dramatically improved selectivity values,^[33] which suggested that the relatively high detection limit was caused by the presence of the analyte ion in the membrane.

In a joint effort with Erno Pretsch, these findings initiated a quest to find the mechanistic reasons that resulted in a dramatic improvement of the detection limits of ion-selective membrane electrodes. The initial breakthrough came from our two respective groups, with Sokalski and Pretsch demonstrating ultra-low detection limits for a Pb^{2+} -selective membrane by adding EDTA to the inner solution.^[34] In parallel work, we showed that a high concentration of salt in the inner solution results in higher detection limits that can be modulated by solution stirring.^[35] As shown in Fig. 6a this can be understood in some analogy to the heparin sensor discussed above. The asymmetric extraction of ions and their counter ions from the two contacting solutions into the membrane creates a concentration gradient that results in a flux of electrolyte in direction of the more dilute solution. Ironically, this corresponds rather closely to Eisenman's ill-fated model shown in Fig. 1 but here the counter ion is not assumed to exhibit zero mobility but diffuses along with the ion-ionophore complex. Diffusion of electrolyte gives an outward flux into the dilute sample, increasing the concentration of analyte ions at the membrane surface relative to the bulk sample. This renders the electrode insensitive to small concentration changes in the sam-

ple because the potential is a function of ion activity at the phase boundary, not the sample bulk. This concentration gradient and associated outward flux is also possible by partial ion-exchange with interfering ions from solution, giving rise to a counterdiffusion flux at zero current. With perfectly adjusted inner solution compositions and membranes of high selectivity, the attainable detection limit may be predicted by the following relationship, valid for monovalent ions:^[36]

$$c_i(DL) = \left(\frac{D_{IL}^m \delta_{aq}}{D_I^{aq} \delta_m} c_R^m K_{I,J}^{pot} c_J \right)^{1/2} \quad (5)$$

where $D_{species}^{phase}$ is the diffusion coefficient of the indicated species in the respective phase, δ_{phase} is the diffusion layer thickness in the indicated phase (membrane and solution), and c_R^m is the ion-exchanger concentration in the membrane. This gives important guidance to the design of potentiometric sensors exhibiting trace-level detection limits.^[37] The ion-exchanger concentration should be kept low, the mobility of the membrane matrix should be minimized, sample convection should be maximized, and the membrane thickness should be large. Fig. 6b shows a classical example of detecting $Pb(II)$ at trace levels (10 ppb) in freshwater samples as a function of pH,^[38] demonstrating the power of potentiometry to detect the uncomplexed ionic species in solution.

Clearly, the reason that potentiometry gives higher detection limits than optical sensors is caused by the fact that the inner solution introduces an asymmetry that aims to equilibrate with the sample solution. More recent work has therefore focused on eliminating this limitation by exploring all-solid-state sensor configurations, for example with lipophilic conducting polymers such as poly(octyl thiophene).^[39] Experimental evidence suggests that only the surface layer of this polymer can be oxidized.^[40] This is because the resulting positive polymer charge requires ion association with the bulky lipophilic ion-exchanger from the overlying membrane, which however cannot penetrate deeper into the film for steric reasons. This appears to spontaneously create a mixed redox state for the conducting polymer, thereby resulting in a stable potential. Many other ion-to-electron transducing materials have since been explored for various applications that cannot be discussed here.

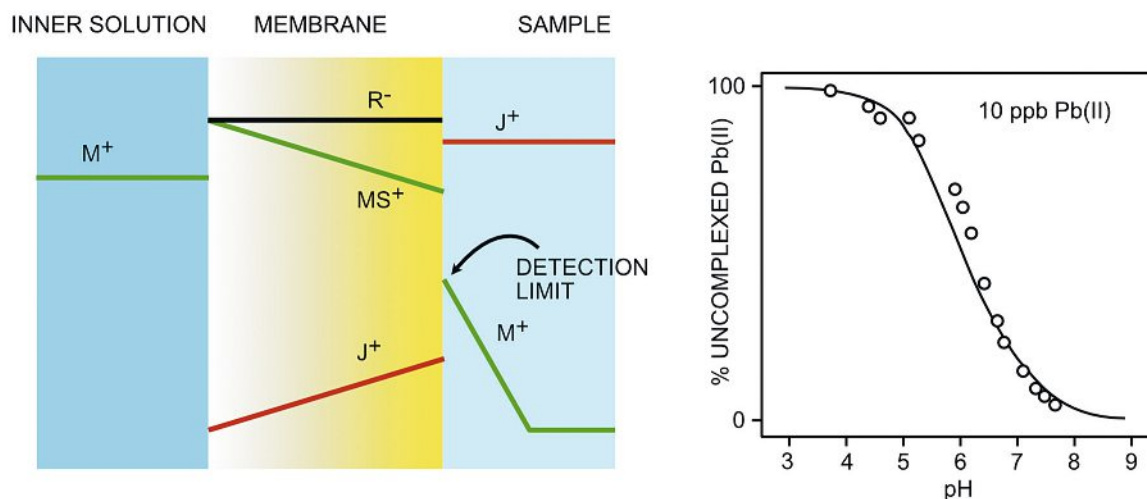


Fig. 6. Detection limit of ISEs. Left: asymmetrical solutions on either side of the ion-selective membrane result in undesired co- and counterdiffusion processes that transport analyte ions in direction of the sample solution, giving rise to a higher local concentration than in the sample bulk. The potential depends on this local concentration, biasing the experiment. Right: optimized ion-selective electrode response to trace Pb^{2+} levels in tap water as a function of pH, demonstrating that these probes can be used in speciation analysis to detect the so-called free ion concentration.^[38]

7. Controlling Ion Fluxes by Dynamic Electrochemistry

Zero current ion fluxes across the membrane, generated by counter or co-diffusion processes, could also be used to one's advantage to improve analytical characteristics. One such example involves the realization of large potential changes upon reaching a critical concentration with membranes that exhibit an inward ion flux.^[41] This is made possible because the membrane effectively consumes low concentrations of ions present in the sample. Research then began to control these fluxes not only by chemical, but by instrumental control. With ion conductors, an applied current imposes a net flux of ionic species that can be quantitatively adjusted by its amplitude. Early uses of this approach aimed to eliminate the outward ion flux to reach ultra-low detection limits by applying a small current.^[42] Larger current densities were found to be very interesting because the amplitude and sign of the current could be used in membranes containing no ion-exchanger to control the phase boundary concentration as well as the type of extracted ions.^[43] Reversible polyion sensors were realized in this manner, where the extraction is not spontaneous but imposed by the applied current, making it possible to regenerate the membrane by electrochemical control.^[44] The undesired ohmic drop during the applied current period was eliminated by measuring at zero current immediately after the pulse, giving rise to so-called 'pulstrodes'.^[45]

An adequate current density was also used to locally deplete the ions of interest during measurement, giving a potential change at a so-called transition time that serves as analytical signal.^[46] This technique, chronopotentiometry, was found to be especially attractive with permselective membranes containing ion-exchangers.^[47] The very same membrane can be interrogated by zero current potentiometry, giving information on so-called free ion concentration, while a subsequent current pulse indicates total available concentration that includes labile complexes. Such a tandem technique has been found attractive for speciation analysis and has been demonstrated for the measurement of free and total concentration as exemplified for the detection of phenytoin.^[48] An interesting example is given in Fig. 7 where the results from a potentiometric/chronopotentiometric detection with a polymeric pH electrode during the volumetric titration of acetic acid is shown.^[47] While the observed pH change during titration is as expected, the chronopotentiometric data give information on the unreacted acid (total acidity) of the sample, which is found to decrease linearly with added hydroxide. Ion-selective membranes interrogated in this way can give information that is not accessible with zero current potentiometry.

Inward ion fluxes controlled by dynamic electrochemistry can be imposed onto thin layer samples (of thicknesses less than the diffusion layer), resulting in an exhaustive depletion of ionic species. This idea was first proposed with liquid membranes by Kihara who used ion transfer voltammetry principles to quantitatively remove the ions of interest from a sample.^[49] The approach is attractive because the resulting charge gives direct information about the quantity originally present in solution by using Faraday's law. Such thin layer coulometric methods are potentially calibration free and may be much more robust than traditional electroanalytical techniques. While this was explored with ionophore-based membranes,^[50] an attractive example of this approach is the exhaustive removal of halides (chloride and bromide) by electrochemical plating onto a silver electrode, with the counterions forced to migrate through a cation-exchange membrane to an otherwise symmetrical solution.^[51] This approach was shown to be useful in detecting the concentration of chloride and bromide in samples as complex as seawater.^[52] Additionally, it represents an efficient technique (99.9% salt removal) to desalinate seawater in order to make it available for downstream detection. This approach was successfully used for the measurement of nitrate in seawater by potentiometry with submersible probes.^[15a]

8. New Approaches for Ion-selective Membranes

More recently, our group has been involved in the combination of different membranes, readout principles and electronic components to further broaden the scope of ion-selective membranes. In a recent example the time-dependent potential change during a chronopotentiometric measurement was directly translated into a cell potential to generate electrochemiluminescence.^[53] As a result, the change of potential that normally serves as signal is transformed into a visible light pulse. Note that the quantity that serves as signal is the time at which the light pulse occurs, not the light intensity. This is easy to measure, even with smartphones.

We have also explored thin layer gap electrodes where two membrane electrodes face each other, separated just by a thin space that allows for rapid equilibration.^[54] One membrane perturbs the solution by an instrumentally imposed ion flux while the opposite membrane serves as detection electrode. This principle has been used to detect total alkalinity in environmental samples without the need for volumetric titration.^[55] It has also been demonstrated for the adjustment of pH to detect anionic species in aquatic samples where the optimal measurement pH should be higher than the natural pH,^[56] or in the detection of

TANDEM SPECIATION ANALYSIS

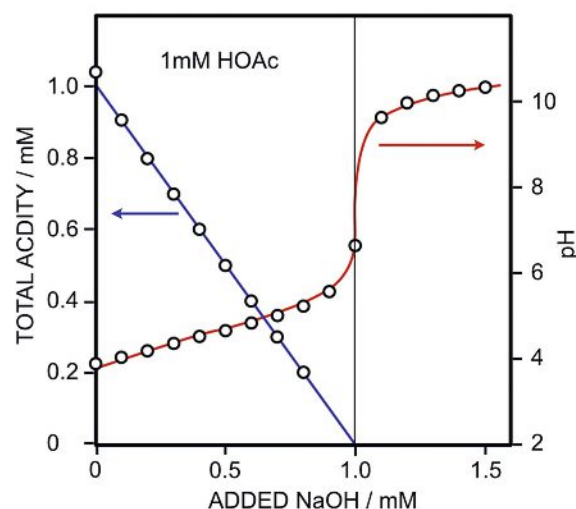
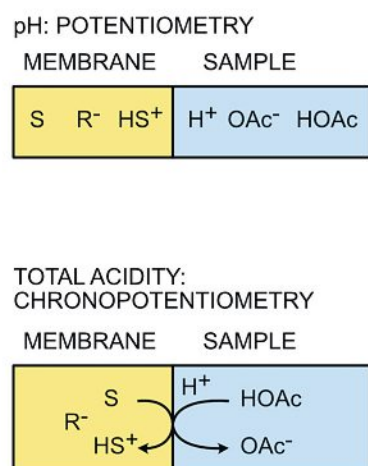


Fig. 7. Tandem potentiometric/chronopotentiometric experiment with a pH responsive membrane to detect pH and total acidity at the same time (adapted from ref. [47]). Shown is the volumetric titration of acetic acid, where the pH probe not only detects pH but also the remaining concentration of the acid in solution. To reach this, the membrane is subjected to subsequent zero current and applied current pulses to interrogate the sample.

total carbonate by transforming all inorganic carbon species to ionic carbonate.^[57]

More recent work has explored the placement of an electronic capacitive element in series with an ion-selective electrode.^[58] The approach was originally introduced by Bobacka with capacitive ion-to-electron transducing materials.^[59] If the cell potential is held at the open circuit value determined for a reference solution, a subsequent activity change will result in potential change that must be compensated over the capacitive element. This results in a transient charging current that can be conveniently measured as a peak and integrated, which is in contrast to zero current potentiometry. This allows one to better correct for baseline drifts and give unsurpassed precision. In the measurement of stabilized seawater samples, this technique gave a precision (standard deviation) in the order of tens of micro-pH, which is very attractive for the assessment of ocean acidification (see Fig. 8^[58]).

Similar to the capacitive element placed in series we have also explored the use of electrochromic materials, which can give an optical readout for ion-selective membranes and that can be placed in parallel for the construction of large sensing arrays.^[60] Such optical sensors are spatially removed from the sample, elim-

inating optical interference arising from opaque, turbid or colored samples. They are traceable because they report fundamentally on a potentiometric measurement. And they form the basis for sensors that do not require any external power source, which is one of our current research directions.

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ULTRASENSITIVE SEAWATER pH MEASUREMENT

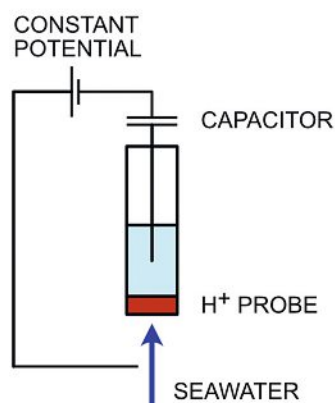
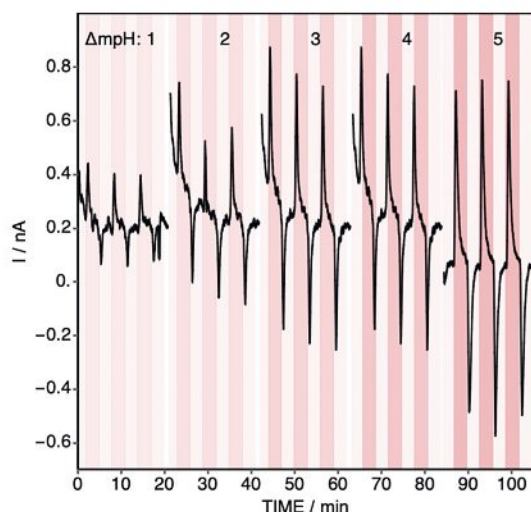


Fig. 8. Ultra-sensitive detection of pH in stabilized seawater by placing a capacitive electronic element in series with the pH probe and holding the potential at its initial open circuit potential.^[58] Any small pH change results in a potential change at the pH probe that is compensated with an opposite potential change over the capacitor. This results in a current transient to charge the capacitor, which is easily identified, baseline corrected and integrated. The resulting precision is orders of magnitude better than observed by potentiometry with the same probe and may be very attractive for monitoring ocean acidification at short time scales.

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