

Beyond potentiometry: robust electrochemical ion sensor concepts in view of remote chemical sensing

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Abstract

For about one hundred years, potentiometry with ion-selective electrodes has been one of the dominating electroanalytical techniques. While great advances in terms of selective chemistries and materials have been achieved in recent years, the basic manner in which ion-selective membranes are used has not fundamentally changed. The potential readings are directly co-dependent on the potential at the reference electrode, which requires maintenance and for which very few accepted alternatives have been proposed. Fouling or clogging of the exposed electrode surfaces will lead to changes in the observed potential. At the same time, the Nernst equation predicts quite small potential changes, on the order of millivolts for concentration changes on the order of a factor two, making frequent recalibration, accurate temperature control and electrode maintenance key requirements of routine analytical measurements. While the relatively advanced selective materials developed for ion-selective sensors would be highly attractive for low power remote sensing application, one should consider solutions beyond classical potentiometry to make this technology practically feasible. This paper evaluates some recent examples that may be attractive solutions to the stated problems that face potentiometric measurements. These include high amplitude sensing approaches, with sensitivities that are order of magnitude larger than predicted on the Nernst equation; backside calibration potentiometry, where knowledge of the magnitude of the potential is irrelevant and the system is evaluated from the backside of the membrane; controlled current coulometry with ion-selective membranes, an attractive technique for calibration free reagent delivery without the need for standards or volumetry; localized electrochemical titrations at ion-selective membranes, making it possible to design sensors that directly monitor parameters such as total acidity for which volumetric techniques were traditionally used; and controlled potential coulometry, where all ions of interest are selectively transferred into the ion-selective organic phase, forming a calibration free technique that would be exquisitely suitable for remote sensing applications.

1. Direct Potentiometry: The State of the Art and Promise for Remote Sensing

Ion-selective electrodes are among the oldest known types of chemical sensors [1]. In most cases, an ion-selective membrane separates the sample from an inner solution, and the electromotive force between reference electrodes in the aqueous sample and the inner solution is measured under zero current conditions (see Figure 1). The inherent promise of this arrangement in view of remote sensing is multifold. It is an extremely simple and direct form of converting chemical into electrical information. The logarithmic activity of the ion of interest is directly proportional to the observed electromotive force, or potential. In so-called direct potentiometry, this measurement is performed directly on the sample, ideally without any sample preparation steps that are often impossible in remote sensing situations. Zero current potentials measurements are also among the least power intensive measurements possible, making membrane electrodes quite promising candidates for the stated application. Ion-selective electrodes based on polymeric membranes are today the most intensively studied systems, and synthetic receptors (ionophores) that selectively bind to the target analytes have been reported for over 60 analytes [2, 3].

In recent years, the field of potentiometric sensing with ion-selective electrodes has undergone a steady transformation. Perhaps most importantly, it was found that such sensors often exhibit vastly better ion selectivities than traditionally reported [4-6], and this knowledge has allowed research teams to greatly improve on the detection limits of these electrodes [7-10]. Today, measurements at concentrations as low as nanomolar levels are not uncommon, and ion detection in small sample volumes on the order of one microliter showed that total ion quantities as low as 300 attomoles can be potentiometrically observed without any sample accumulation steps [11]. Indeed, potentiometry is a technique that, in principle, lacks so-called scaling laws [12]. A reduction in the sample or sensor size should not have an effect on the sensor output signal. Remote sensing deployments are, in principle, not difficult in terms of the actual electrochemical sensing step. Zero current potentiometry is a low power technique and can be battery operated for prolonged periods of time and linked to wireless

communications networks. The key challenges, as outlined below, are connected to the need for fluidic handling since such sensors currently need to be properly conditioned and frequently recalibrated.

2. The Trouble of Direct Potentiometry

One would think that the relatively low production costs, the simple required instrumentation and the long and established history of ion-selective electrodes would make them prime candidates for the measurement of ions in a number of situations. Indeed, these sensors are routinely used in all types of clinical analyzers to determine electrolyte concentrations in blood and other physiological samples [13, 14]. Potentiometric microelectrodes are used in physiology for single cell electrolyte detection [15]. Environmental applications are also routinely known. But widespread applications in remote sensing, requiring no human intervention, no temperature control and very little fluidic recalibration, turns out to be extremely difficult with the current state of the art. Why is this so?

Let us have a closer look at the Nernst equation, according to which ion-selective electrodes are supposed to function if all works as expected:

$$emf = K + \frac{2.303RT}{zF} \log a_i \quad (1)$$

The electromotive force, *emf*, depends on the logarithmic activity, a_i , of the analyte ion of interest. The sensitivity (slope) of this relationship primarily depends on the temperature and on the charge, z , of the ion I^z . The symbol K is, hopefully, a constant potential term, and R and F are the universal gas constant and the Faraday constant.

The logarithmic relationship between the observed potential and the sample activity means that small concentration changes translate into extremely small potential changes. Consider a 10% activity change of calcium ions at 25 °C. Equation 1 predicts a mere 1.2 mV change in the *emf*. A two-fold activity change gives a 8.9 mV signal change. In clinical analysis, microvolt reproducibilities is routinely achieved, leading to sufficiently small signal to noise levels to allow for clinically accurate results. This level of repeatability is accomplished by careful control of the temperature (T), frequent recalibrations (compensating for potential drifts) and the use of reliable reference

electrodes (keeping K as constant as possible). Needless to say, such level of control and recalibration is neither desired nor possible in a miniature remote sensing environment. Temperature compensation is, of course, possible by simultaneous measurement with temperature probes. Potential drifts will, however, lead to analytically unacceptable inaccuracies after prolonged lack of recalibration steps, which are a serious limitation of the technology.

The second principal problem is the reference electrode. To this day, established reference electrodes still require a liquid junction and an electrolyte reservoir of constant composition. This design is most likely unacceptable for remote sensing applications, and direct potentiometric sensing will only be possible with pseudo-reference electrodes, such as a second ion-selective electrode selective for a background ion whose concentration remains sufficiently constant in the course of the measurement. Overall, current technology appears to be ill suited for prolonged use of miniature sensing systems that are supposed to give reliable measuring results over prolonged periods of time on the order of days or even months.

Very similar problems have also been major stumbling blocks in the realization of implantable sensing devices that can be left inside the body for prolonged periods of times, even after decades of active research in the field [16]. Perhaps the idea of using direct potentiometry as the readout principle for sensor devices that cannot be recalibrated has been flawed all along. In this article we discuss a few innovative measurement principles involving the same type of materials used in ion-selective electrodes that may help overcome these long standing limitations.

3. High Amplitude Sensing: Chemical Alarm Systems without Reliable Reference Electrodes

The above mentioned limitation of the low sensitivity imposed by the Nernst equation and the accompanied stringent stability requirements for the reference electrode have been conceptually addressed by making use of ion fluxes [17]. Ion-selective membranes may be engineered to induce a zero-current flux of analyte ions from the sample in the direction of the membrane. This may be accomplished with electrodes containing inner solutions that exchange the analyte ion by a secondary ion at the inner membrane side.

The resulting counterdiffusion flux transports the secondary ions to the sample and syphons off the analyte ions from the sample to the membrane phase. At a critical ion concentration in the sample, the imposed flux is sufficient to deplete these ions locally at the membrane surface, and a very large potential change is observed akin to a titration endpoint. If two ion-selective electrodes are measured against each other, each engineered to exhibit slightly different fluxes, a very large peak shaped potential response may be observed at a critical concentration. This concept does not require a traditional reference electrode and gives much larger sensitivities than allowed by the Nernst equation [17].

This promising concept still has a number of potential limitations. The adjustment of inward ion fluxes by chemical means is relatively difficult because they are only accurately stable if the system is at steady-state and the concentration gradients are linear. The countertransport process that drives the inward analyte flux will eventually change the composition of the inner solution, which in turn will alter the fluxes over time. This becomes more problematic with ultraminiaturized systems, with membrane diameters on the order of micrometers, where the inner solution reservoir cannot be very large. Membrane surface fouling/adsorption processes may change the magnitude of the observed fluxes, limiting accuracy. Lastly, this concept demands a relatively high selectivity over the secondary ion and a relatively limited concentration range.

A number of the above mentioned limitations have been recently addressed by moving to an instrumentally controlled system [18, 19], illustrated in Figure 2 (top). Here, the membrane contains no added ion-exchanger, and spontaneous extraction of hydrophilic ions into the membrane is suppressed. The measurement occurs in three distinct stages (Figure 2). In step A, a short current pulse drives ions from the sample into the membrane. The current amplitude is directly proportional to the ion flux, and may now be much more accurately controlled than in the chemical mode mentioned above. In step B, the potential is measured under zero current conditions in complete analogy to traditional emf measurements. This avoids problems associated with resistance changes in the cell, which may bias the observed potential if measured during the first pulse. In step C, a potential is applied that drives all previously extracted ions back into the aqueous solution, essentially resetting the membrane. Differential measurements may be easily

accomplished with the same membrane, by either using pulses of varying magnitudes or, more simply, subtracting potentials measured at different times within a single pulse. Figure 2 (bottom) shows with a calcium-selective membrane that such a technique may yield orders of magnitude higher sensitivities than predicted on the basis of the Nernst equation. A calcium concentration change from 0.1 to just 0.24 mM, measured during pulse B at open circuit, gives a potential change of close to 200 mV [19]. The Nernst equation would predict just 11.3 mV under equilibrium conditions. Note that high apparent sensitivities only translate in higher accuracies with good potential reproducibilities, which has not yet been fully explored with the new differential modes. However, in differential measurements, the reference electrode is now only utilized to adjust the baseline potential at step C, which may also be accomplished with a second ion-selective electrode if needed. Some of the other limitations stated above still remain: A high selectivity is required, the measuring range cannot be shifted to extremely high concentrations, and surface fouling may influence the mass transport kinetics. And of course, the required instrumentation is somewhat more elaborate than in traditional potentiometry.

4. Backside Calibration Potentiometry

Very recently, a new measurement principle for ion-selective membranes has been introduced where the magnitude of the observed potential is unimportant. Moreover, changes in the sample composition for calibration or standard addition purposes are, ideally avoided as well. This principle is termed backside calibration potentiometry [20]. In backside calibration potentiometry, as the name implies, the sample side of the sensor is never altered for calibration purposes. Reference electrodes are, in some cases, unimportant as well. The concept utilizes relatively thin supported ion-selective membranes, across which steady-state concentration gradients are established in a matter of seconds [21] as illustrated in Figure 3. In this experiment, the inner solution composition is altered until the concentration gradient across the membrane reduces to zero, which can be likened to the zeroing of a Wheatstone bridge. Here, it is accomplished by changing the stirring rate of the two aqueous solutions and monitoring the potential: no influence of stirring on the emf is observed once the ion concentration

gradients disappear. What makes this technique unique is that the magnitude of the potential is unimportant in this experiment. Of course, the approach alone does not allow one to determine single ion activities, which would be thermodynamically impossible. Instead, it has been shown that one determines the activity ratio of analyte ion to its dominant interferent because the concentration gradients are dictated by ion-exchange equilibrium processes [20]. If the activity of the interferent is known, the analyte ion activity may be determined. Figure 3 (bottom) shows how this concept can be used to determine lead ions in samples buffered at pH 4, with hydrogen ions the dominant interferents [20]. Indeed, the lead concentrations found by this technique in environmental water samples corresponded well to independently measured values.

5. Constant Current Coulometry: Calibration Free Reagent Delivery

One may easily envision the accurate delivery of ionic reagents from an ion-selective membrane by current control. If spontaneous zero current ion fluxes are negligibly small, an imposed current pulse will deliver a defined quantity of material into the sample without any need for titrimetric standards or calibration procedures, with a very high degree of selectivity. This concept has just recently been demonstrated with a polymeric ion-selective membranes for the purpose of accurately delivering reagents [22]. Figure 4 demonstrates the coulometric delivery of calcium for the titration of EDTA. Here, one ion-selective membrane was electrochemically controlled to deliver calcium ions, and a second ion-selective membrane of similar composition was used as the detector electrode [22]. The simple relationship between applied number of coulombs and expelled amount of ions (Faraday's law) coupled with the high ion selectivity of such membranes makes this a very promising technique to deliver reagents without the need for maintaining accurate standard solutions.

The concept of perturbing the sample by galvanostatic control has recently been extended to allow for localized titration measurements without the need for standard solutions or bulk sample perturbations [23]. Here, pulsed galvanostatic perturbation and potential measurement are performed at the very same interface. The approach is illustrated in Figure 5 with H^+ -selective membranes for the determination of total acidity. A constant current pulse is imposed across an ion-selective membrane free of added lipophilic

cation-exchanger, and results in a defined flux of hydrogen ions from the sample in direction of the membrane. The resulting increase in the unstirred diffusion layer thickness as a function of time forces the acidity gradient to increase to maintain the imposed ion flux. Once the acid is locally depleted at the ion-selective membrane, a well defined potential change is observed that indicates the localized titration endpoint in just a few seconds [23]. The key limitations of such localized titrations relative to classical titrimetric analysis concern the kinetic nature of the measurement. Measurements on low ionic strength solutions may be affected by migration, rather than pure diffusion processes, and changes in diffusion coefficients will also give variations in the observed endpoint. Nonetheless, such principles are highly attractive for continuous monitoring purposes because they are fast, can be automated, make use of chemically selective chemistry, and do not require reagents or the need to collect sample aliquots. Many potential applications exist where the use of such direct sensing techniques may far outweigh their fundamental limitations.

6. Coulometric Ion Transfer: Calibration-Free Sensing

Controlled current coulometry was discussed above to accurately deliver reactants from ion-selective membranes. Recently, controlled potential coulometry was introduced by the group of Kihara as a very promising calibration-free analysis method in the field of ion sensing [24]. The principle is illustrated in Figure 6. A suitable potential applied between a Ag/AgCl electrode placed in the sample and a reference electrode in contact with an organic solvent containing a calcium ionophore and an inert lipophilic salt drives calcium ions from the sample solution into the organic solvent. The current associated with this process is monitored and integrated over the entire analysis time. The coulometric analysis of calcium is possible, for instance, if most calcium ions have been selectively transferred and non-Faradaic processes (charging currents) are kept insignificant [24]. To make this promising technique even more practical for routine use, the system may need to be further miniaturized for reduced analysis times and sample volumes, the direct sample contact of Ag/AgCl will have to be avoided and, perhaps most important, the simple solvent 1,2-dichloroethane used in this work may need to be replaced by a more robust and inert sensing material. While more work is certainly

required to make this direction a practical approach, coulometry may be the key solution to many of the stability problems that plague the field of ion sensing in non-traditional applications today.

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Literature Cited

- [1] M. Cremer, *Z. Biol.* 47 (1906) 562.
- [2] E. Bakker, P. Bühlmann, E. Pretsch, *Chem. Rev.* 97 (1997) 3083.
- [3] P. Bühlmann, E. Pretsch, E. Bakker, *Chem. Rev.* 98 (1998) 1593.
- [4] T. Sokalski, M. Maj-Zurawska, A. Hulanicki, *Mikrochim. Acta* 1 (1991) 285.
- [5] E. Bakker, *Anal. Chem.* 69 (1997) 1061.
- [6] E. Bakker, E. Pretsch, P. Bühlmann, *Anal. Chem.* 72 (2000) 1127.
- [7] T. Sokalski, A. Ceresa, T. Zwickl, E. Pretsch, *J. Am. Chem. Soc.* 119 (1997) 11347.
- [8] E. Bakker, E. Pretsch, *Trends Anal. Chem.* 20 (2001) 11.
- [9] E. Bakker, E. Pretsch, *Trends Anal. Chem.* 24 (2005) 199.
- [10] E. Bakker, E. Pretsch, *Angew. Chem. Int. Ed.* in press.
- [11] A. Malon, T. Vigassy, E. Bakker, E. Pretsch, *J. Am. Chem. Soc.* 128 (2006) 8154.
- [12] A. Manz, N. Graber, H.M. Widmer, *Sens. Actuators B1* (1990) 244.
- [13] M.E. Collison, M.E. Meyerhoff, *Anal. Chem.* 62 (1990) A425.
- [14] M.E. Meyerhoff, *Clin. Chem.* 36 (1990) 1567.
- [15] D. Ammann, F. Lanter, R.A. Steiner, P. Schulthess, Y. Shijo, W. Simon, *Anal. Chem.* 53 (1981) 2267.
- [16] E. Lindner, R.P. Buck, *Anal. Chem.* 72 (2000) 336A.
- [17] T. Vigassy, A. Ceresa, M. Badertscher, W.E. Morf, N.F. de Rooij, E. Pretsch, *Sens. Actuators B* 76 (2001) 476.
- [18] S. Makarychev-Mikhailov, A. Shvarev, E. Bakker, *J. Am. Chem. Soc.* 126 (2004) 10548.
- [19] S. Makarychev-Mikhailov, A. Shvarev, E. Bakker, *Anal. Chem.* 78 (2006) 2744.
- [20] A. Malon, E. Bakker, E. Pretsch, *Anal. Chem.* 79 (2007) 632.

- [21] K. Tompa, K. Birbaum, A. Malon, T. Vigassy, E. Bakker, E. Pretsch, *Anal. Chem.* 77 (2005) 7801.
- [22] V. Bhakthavatsalam, A. Shvarev, E. Bakker, *Analyst* 131 (2006) 895.
- [23] K.L. Gemene, A. Shvarev, E. Bakker, submitted.
- [24] A. Yoshizumi, A. Uehara, M. Kasuno, Y. Kitatsuhi, Z. Yoshida, S. Kihara, *J. Electroanal. Chem* 581 (2005) 275.

Figure Captions

1. Classical direct potentiometry with polymeric membrane ion-selective electrodes is widely used for the direct detection of electrolytes in clinical analysis. The potential is measured across a suitably formulated membrane that is contacted with two aqueous solutions, of which one is the sample (top). It is ideally a direct function of the ion activity on either side of the membrane, which leads to a log-linear relationship between the sample activity and the observed potential (bottom right). Since the measurement is equally dependent on the potential at the reference electrode (left), this technique requires careful maintenance, temperature control and frequent recalibrations.
2. High amplitude pulsed chronopotentiometry with ion-selective membranes [19]. This technique yields sensitivities that are drastically larger than predicted by the Nernst equation. This is accomplished by localized sample depletion at the ion-selective membrane in a three-pulse experiment (top): An applied current pulse of variable magnitude extracts ions into the membrane and may lead to localized depletion near the membrane surface (A). This may be followed by an open circuit measurement pulse to give potential readings that are independent of the sample or membrane resistance (B). The system is subsequently regenerated by a potential pulse (C). Bottom: large, nearly 200 mV observed potential responses upon changing the calcium sample concentration from 0.1 to 0.24 mM [19].
3. Backside calibration potentiometry [20]. This novel technique utilizes thin supported membranes where concentration gradients reach their steady-state in a matter of seconds [21]. The composition at the backside of the membrane may be altered and the effect of aqueous solution stirring evaluated. The stir effect disappears when the steady-state concentration gradient becomes negligibly small. Under these conditions information on the sample composition is obtained without the need for the magnitude of the potential and without requiring any alterations of the sample composition. It gives information on sample activity ratios on the basis of the underlying ion-exchange processes. Bottom:

- determination of lead concentrations at pH 4 by varying the composition at the backside and evaluating the stir effect with such thin supported membranes [20].
4. Chemically selective controlled potential coulometry with ion-selective membranes [22]. An imposed current translates into the release of a defined quantity of ions from the membrane into the sample. Unlike classical coulometry with metal electrodes, this is a chemically selective technique. It alleviates the need for standardization of titrants and volumetric delivery and is attractive for remote sensing applications. Bottom: titration of low concentrations of EDTA with coulometrically released calcium [22]. The free calcium was measured with a second calcium-selective electrode.
 5. Direct sensing of total acidity without sample perturbation or bulk sample titration [23]. In this example, a constant current pulse is imposed across a polymeric H^+ -selective membrane and the potential is observed at the very same electrode, yielding an elegant actuator/sensor combination. The current pulse results in an imposed H^+ flux in direction of the membrane, which is supported by any acid dissociation equilibria. As the diffusion layer thickness expands in the first few seconds of this experiment, the potential is monitored for the endpoint time. As shown in the bottom plot, this endpoint time is a direct function of the total acidity of the sample [23].
 6. Controlled potential coulometry with ion-selective organic phases [24]. In this new technique, all ions are exhaustively and selectively extracted from the aqueous sample to an organic phase doped with a selective receptor. The observed current is integrated over the entire experiment and yields the total number of moles of the ion of interest. This technique is inherently calibration-free and scientifically robust, and may eventually be highly suited for miniaturized, remote sensing systems.