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# Towards an automated, standardized protocol for determination of equilibrium potential of ion-selective electrodes

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ABSTRACT

An automated real-time method for determination of ISE steady state value and response time is developed, following most recent IUPAC recommendations. Specifically, detection of the 'steady state' is related to (1) the time derivative of the emf as it reaches a limiting value ($\Delta E/\Delta t_{\mathrm{limit}}$, e.g., 0.1–1.0 mV min$^{-1}$) and (2) the duration of time for which the absolute value of the time derivative remains less than this limiting value (stability window, denoted win$_{\mathrm{st}}$). A suite of representative ISEs, including glass, solid state, and polymer-based electrodes, is examined to determine sensitivity of results to parameterization choice. Measurements taken over a wide range of concentration values and in un-processed samples (i.e., without use of ionic strength adjustment) provide insight into behavior of ISEs in applications where analyte concentrations span a wide range and/or sample pre-processing may not be an option, e.g., use of sensors for in situ environmental sampling. Results show that declared steady state emf is strongly sensitive to variations in $\Delta E/\Delta t_{\mathrm{limit}}$ but relatively unaffected by changes in the stability window when win$_{\mathrm{st}}$ ≥30 s. Linearity of calibration curves produced, quantified by root mean squared error (RMSE) against a linear fit, improves as $\Delta E/\Delta t_{\mathrm{limit}}$ decreases, however the percentage of measurements which reach a declared steady state within the prescribed sample window (~6.5 min) falls with corresponding decreases in the $\Delta E/\Delta t_{\mathrm{limit}}$ parameter. Response time, defined as the time required to reach declared steady emf, is also a strong function of parameterization. Dependence of response times on sample composition and/or ISE membrane composition and type are also discussed; results for ISEs in samples comprised exclusively of interfering ions are included. In general, limiting emf derivatives of {0.25–0.4 mV min$^{-1}$} and stability windows of {30–40 s} achieve both good analytical accuracy and compliance with potentially short sampling window requirements. Methodology based on use of these parameters can improve sampling speed and accuracy as well as promote inter-comparison of data and ISE characterizations among research teams.

## 1. Introduction

Ion selective electrodes (ISEs) now exist for measurement of a great number of both cations and anions. Their simplicity, small size, and low power requirements make them particularly attractive for a wide range of applications where real-time and/or in situ analysis is beneficial. The electromotive force (emf), or electrical potential, produced by an ISE varies with the logarithm of ionic activity over a substantial portion of the ISE's usable range and is typically described by the Nernst equation equilibrium model. However, because several tens of seconds, or even minutes, may elapse before this emf reaches a sufficiently steady value, any measurement by ISE necessarily involves determining the time at which this sufficiently steady (sometimes designated "equilibrium") electrode emf is declared. This can be problematic, given that ISE response characteristics vary by electrode and membrane type, manufacturer, history of usage and storage, and aqueous solution composition and ionic strength. In addition, solution properties and accuracy requirements vary widely between applications in medicine, industry, and environmental chemistry. As a result, ISE measurement technique is often customized by field, practitioner, or application.

The steady or "equilibrium" emf value is often subjectively judged by the analyst, values being detected by eye as signals "level off" or "look flat" on a graph. While such a protocol can be entirely adequate under the eye of an experienced analyst in applications within a constrained range of concentrations and at nearly constant ionic strengths, other applications within industrial and environmental chemistry may face wide ranges of analyte concentration or highly varied (and sometimes very weak) ionic strengths and/or

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cases where sample pre-processing may not be an option, e.g., use of sensors for in situ sampling. In these cases, electrode emf can approach stable values quite slowly and/or have a non-monotonic approach to steady state [1,2], making subjective or ad hoc means of declaring ISE "equilibrium" particularly problematic. Further, use of automation, which can be highly beneficial or even mandatory in the case of measurement from an autonomous mobile platform, requires an explicit algorithm for "equilibrium" emf detection. More broadly, lack of a uniform protocol likely undermines reproducibility and weakens comparability of data across differing dates, times, sample solutions, or laboratories.

A corollary to the lack of a uniform protocol for determination of "equilibrium" emf is the lack of a standardized criterion for determining electrode response time, a key metric used to characterize ISEs, which limits the extent to which the published response times of competing electrode technologies is meaningful. Various guidelines for determination of ISE response time have been proposed and supported by the IUPAC in the past. Early recommendations included use of $t_{90}$ or $t_{95}$ (time at which emf reaches 90% or 95% of final stable emf) and $t^*$ (time at which emf reaches final stable value within +/−1 mV) [3]. Three drawbacks of these methods have been previously identified [2]:

1 Both methods require knowledge of the 'final stable emf,' which by definition is not known during live data readings, making automation difficult to impossible;
2 The log-linear relation of concentration and voltage dictates that a 1 mV change in emf corresponds to an approximately 4% change in concentration for singly-charged ions (more for doubly-charged ions), which may not be acceptable in all applications;
3 Somewhat counter-intuitively, these definitions necessitate that the response time *is not* the time at which a stable emf is reached/recorded.

In 1994 the IUPAC updated the recommended method for determination of ISE response time [4], proposing a method based on the slope of emf/time ($\Delta E/\Delta t$), specifically the "time which elapses between immersion in a sample and the first instant at which the emf slope reaches a pre-determined limiting value." In addition to providing a more functional methodology (in the sense that it can be automated), this has the benefit of creating a methodology within which the response time is by definition the time at which the steady state emf is reached. While this steady state emf is not necessarily identical to the value for a true chemical equilibrium in the Nernstian sense, $\Delta E/\Delta t$ would in practice be chosen such that the emf would be sufficiently stable and repeatable for most analytical purposes. Use of such a method is also likely to avoid very long equilibration times, which are both inconvenient in a practical sense and may increase the exposure of the methodology to low frequency noise or signal drift.

Adoption of this method has not been widespread, however, as noted by other researchers in the field [5]. This may be due to (1) interest in presenting statistics which are easily compared with historical publications and work, or (2) ambiguity in defining an appropriate, standardized $\Delta E/\Delta t$ value, as the IUPAC recommendations simply indicate selection "on the basis of the experimental conditions and/or requirements concerning the accuracy (e.g., 0.6 mV min$^{-1}$.)" [4].

Further, this $\Delta E/\Delta t$ method may not be robust or determinate when faced with real-world signals that inherently contain some amount of noise. Ion selective electrodes in particular may be vulnerable to noise due to (1) their high output impedance and consequent sensitivity to electromagnetic noise, (2) potential drift in output signals, e.g., due to leaching, and (3) their sensitivity to temperature changes. Because even small amounts of noise may lead to non-idealized (i.e., non-monotonic) $\Delta E/\Delta t$ time series, this issue must be considered in the development of an automated implementation of these IUPAC recommendations.

We address these problems by systematically examining the approach to steady state emf of a representative suite of ISEs over a large range of solution concentrations and compositions, with the goal of characterizing a reliable, reproducible, and fully automatable detection methodology. The specific choice of ISEs, solution compositions, and ionic strength range in this work is guided by the objective of making in situ, real-time measurement of the major ion composition of natural waters, however the approach to assessing ISE protocols for their means of declaring steady emf is independent of application. Our method is consistent with the 1994 IUPAC recommendations but also provides for automated detection of a steady state emf and response time from a dynamic ISE time series *in real time*. Optimization with respect to response time (minimization), steady state emf error (minimization), and method robustness (e.g., sensitivity of results to a small change in parameterization) is detailed. Cases where signals do not follow the traditionally-expected exponential-like approach to "equilibrium," i.e., are not monotonic, are considered, along with restrictions that may prevent steady state conditions from being detected within an acceptable sampling window or at all. Typical response times recorded when using this method, along with the parameters that most strongly affect the response time are presented. Finally calibration curves for electrodes considered in this work are shown, along with discussion of the sensitivity of RMSE error to parameterization choice, demonstrating that this method leads to robust calibration curves, with near-Nernstian slope, high $R^2$ value, and linear response down to μM levels.

## 2. Materials and methods

### 2.1. Theory

Development of a practical algorithm for determining the emf at which an ISE could be considered sufficiently steady was based on the following assumptions:

1. The time at which steady state is reached can be related to a specific value of $\Delta E/\Delta t$ (here termed $\Delta E/\Delta t_{\text{limit}}$), following IUPAC recommendations;
2. Once meeting the criterion of (1), recording the emf value at the soonest possible time point is the most accurate (as longer immersion may lead to drift or signal change due, e.g., to leaching or slow surface processes), also following IUPAC recommendations;
3. Automatically-detected steady state emf should be consistent with values declared by an experienced analyst inspecting the same data.

Additional challenges posed by real (non-idealized) data which are not addressed by IUPAC recommendations include the following:

4. Noise in data often leads to non-monotonic $\Delta E/\Delta t$ signals;
5. ISE response itself may be in the form of a non-monotonic time-series signal (see Fig. 1), e.g., for measurements in low-concentration standards where slow surface reactions (order minutes) can cause the standard electrode potential and selectivity coefficients to change over time [2], where surface processes changing the chemical composition and/or morphology of the electrode membrane surface can change the surface potential over time [2], or before the liquid junction potential has stabilized [6,7].

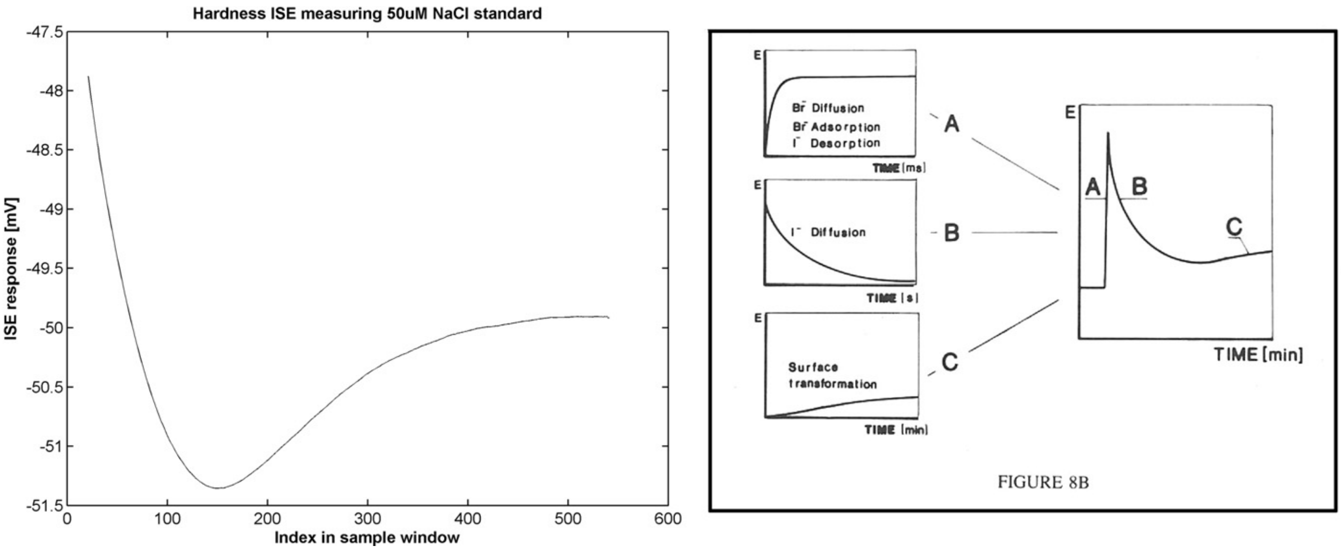


**Fig. 1.** Typical non-monotonic ISE response signal as seen in this study (left) and as elucidated by Lindner et al. [2] (right).

These latter issues are worthy of consideration as data with non-monotonic characteristics can lead to erroneous identification of steady state conditions by automated systems, primarily due to transient minima in $\Delta E/\Delta t$ signals or irregularities in overall $\Delta E/\Delta t$ signal shape. Signal smoothing (e.g., running average or boxcar averaging) typically mitigates small transients caused by relatively high-frequency noise, however, not all signals will produce a monotonic derivative signal even after smoothing. For instance, conditions such as those shown in Fig. 1 require identification of a steady state emf at a non-limiting point in the curve (the dip between "B" and "C" as shown on the right) to avoid bias caused by slow surface processes [2].

To address these issues, our automated method incorporates a $\Delta E/\Delta t$ *stability condition* to qualify the IUPAC recommendation of defining "equilibrium" on the basis of the first instance at which a limiting $\Delta E/\Delta t$ is reached. Specifically this stability conditions is defined by a stability window, being met at the first window of time of duration $\text{win}_{\text{st}}$ during which the absolute value of the emf slope remains less than the designated limiting value, $\Delta E/\Delta t_{\text{limit}}$. Declared steady emf is subsequently determined as the average emf value within the designated stability window.

### 2.2. Sensitivity analysis

The sensitivity of resulting *steady state emf* and *response time* values to the choice of parameterization was examined for values of $\Delta E/\Delta t_{\text{limit}}$ and $\text{win}_{\text{st}}$ consistent with those seen in published research [2,5] and with the level of signal stability expected from ISEs. Specifically, all combinations of parameters within the following ranges were considered:

$$\Delta E/\Delta t_{\text{limit}} = \left\{0.1,\ 0.2,\ 0.4,\ 0.8,\ 0.1\right\}\ \left[\text{mV min}^{-1}\right]$$

$$\text{win}_{\text{st}} = \left\{10,\ 20,\ 30,\ 40,\ 50\right\}\ [\text{s}]$$

The mid-range parameter set $\{0.4\,\text{mV}\,\text{min}^{-1}, 30\,\text{s}\}$ was chosen as a convenient baseline for viewing trends over parameterization variation, presented below. For all cases, recall that the declared steady emf is determined as the average emf value within the designated stability window.

Resulting steady state values were subsequently used to produce linear calibration curves over as much of the concentration range as possible, i.e., with the linear range determined by a maximization of $R^2$ for the linear fit. Slope, slope margin of error, intercept, intercept margin of error, $R^2$, and RMSE for the linear fits were compared for the range of parameterizations. RMSE values were judged to be the most informative, producing the largest spread among varying parameter sets. RMSE is thus used below to quantitatively differentiate calibration curves produced using different parameterizations.

### 2.3. Experimental setup

#### 2.3.1. Materials

Salt solutions used for electrode characterization are listed in Table 1, along with the concentration levels of the 13 standards which each contained the indicated concentration *of a single salt only*, producing a total of 52 different salt standards. Concentrations from 0.1 μM to 0.1 M were chosen to simulate the widest possible range of analytes expected in environmental fresh water applications while salt solutions were chosen to correspond to primary specificity and to expected or known interferences of the electrodes. Consequently, for many salt/electrode combinations the electrode response was determined solely by *interfering* ions to which the response was substantially sub-Nernstian (or, perhaps, not well defined, as in the case of divalent ISE responses to univalent ions).

Standards were made using Millipore Milli-Q water (18.2 MΩ cm) and Reagent A.C.S. grade salts (NaCl and $NH_4Cl$, Fisher Scientific; KCl, MCB Reagents; $CaCl_2 \cdot 2H_2O$, Mallinckrodt). Salts were dried overnight at 55 °C before being weighed out using an Ohaus Precision Standard TS4KD balance. Standards were made via serial dilution from 100 mM (for 1.0 μM to 10 mM) or 100 μM (for 0.1–0.5 μM) in Class A Pyrex volumetric flasks. Glass and plasticware used in this process were first acid washed for at least 24-h in 10% $HNO_3$ and rinsed 7–10 times in Milli-Q water.

#### 2.3.2. Instrumentation

Nine ion selective electrodes (6 solid-state, 1 plastic, 2 glass membrane) were characterized in the single-salt solutions described above. Electrodes were selected both to maximize relevance to environmental applications, measuring ions typically found in surface and ground waters, and to provide some general insight into behavior of different ISE technologies. All electrodes were configured as half-cells and simultaneously referenced to a single double-junction reference electrode. A list of ISEs used is given in Table 2.

**Table 1**
Single-salt standards used for electrode characterization, producing a total of 52 standard salt solutions.

| Analyte | Membrane | Manufacturer | Published LOD |
|---|---|---|---|
| $Ca^{2+}$ | Solid-state PVC polymer matrix | ELIT 8041 | 0.50 μM (0.02 ppm) |
| $K^+$ | Solid-state PVC polymer matrix | ELIT 8031 | 10 μM (0.4 ppm) |
| $Na^+$ | Solid-state PVC polymer matrix | ELIT 8230 | 2.0 μM (0.05 ppm) |
| $NH_4{}^+$ | Solid-state PVC polymer matrix | ELIT 8051 | 2.0 μM (0.03 ppm) |
| $Cl^-$ | Solid-state poly-crystalline | ELIT 8261 | 30 μM (1 ppm) |
| $Cl^-$ | Solid-state (unspecified) | Hanna Instruments 4007 | 50 μM (1.8 ppm) |
| Hardness (divalent cation) | Plastic (unspecified) | Thermo Sci. 9332BNWP | 6.0 μM |
| pH | Glass | Thermo Sci. 9101BN | pH 0–14 |
| $Na^+$ | Glass | Ross 8411BN | 1 μM (0.02 ppm) |
| Reference | Double junction $CH_3COOLi$ | ELIT 003N | |

**Table 2**
Ion selective electrode hardware; information on membrane composition and published detection limit (LOD) as given by manufacturers where available.

| Salt |
|---|
| NaCl |
| KCl |
| $NH_4Cl$ |
| $CaCl_2$ |

| Concentration | |
|---|---|
| 0.10 | μM |
| 0.25 | μM |
| 0.50 | μM |
| 1.0 | μM |
| 2.5 | μM |
| 5.0 | μM |
| 10 | μM |
| 25 | μM |
| 50 | μM |
| 100 | μM |
| 1 | mM |
| 10 | mM |
| 100 | mM |

### 2.3.3. Procedures

Time course data was collected simultaneously from all 9 electrodes for each standard via a custom LabVIEW interface (LabVIEW 2009), receiving input from a National Instruments USB-6218 Data Acquisition device. A custom-built low-pass filter stage (active 2-pole Butterworth filter, cutoff frequency of 10 Hz) was installed between electrode outputs and data acquisition inputs to reduce high-frequency noise coupled into the system via high-impedance electrodes. Note that results should not be dependent on the specific filter or analog-to-digital hardware used as long as it is properly implemented, i.e., where ISE leads are connected via a high input impedance interface, internal circuitry, filters and amplifiers have low leakage currents, etc.

During data collection, standards were measured from low to high concentration, with seven replicates of each standard measured sequentially for each concentration; the electrode circuit was broken by removal from the solution into air between measurements. A complete set of data for each single salt solution (13 standards × 7 replicates) was recorded in a single day to minimize potential environmental or electrode drift effects. Each sample time-course was recorded for approximately 6.5 min at 1.3 Hz, yielding time sequences of 500–600 samples. This produced a total of 3276 (4 salts × 13 standards × 7 replicates × 9 ISEs) full time course measurements (each of 500–600 instantaneous samples) recording ISE approach to steady state.

Measurements of approximately 75 mL of sample were recorded under unstirred batch conditions in a temperature controlled setting (less than 2 °C range) to minimize electromagnetic noise and to reproduce expected environmental in situ sampling conditions. Note that while the magnitude of response times under unstirred conditions is likely to be greater than under stirred conditions [2], it is expected that the proposed methodology and demonstrated trends will pertain equally to other experimental conditions.

## 3. Results and discussion

### 3.1. Steady state determination

Fig. 2 shows the mean absolute difference (mV) in declared steady state emf for all parameterizations relative to the baseline case ($0.4\,mV\,min^{-1}$, 30 s). These data are averages over time series for 9 electrodes, 4 salts, 13 standards, and 7 replicates ($N > 3200$ samples). For reference, a second set of axis values is shown on the colorbar to indicate the corresponding percent change in concentration values for a monovalent Nernstian relationship. While not all electrode responses are expected to be monovalent or Nernstian, e.g., responses to interfering analytes, this provides an indication of the *minimum corresponding concentration change* expected for a given voltage change. This data clearly demonstrates that within this range, sensitivity to parameterization choice itself may introduce greater than 2% difference in declared concentration for this set of electrodes.

Manual review of the results indicated that the highest and the lowest $\Delta E/\Delta t_{limit}$ parameterizations (0.1, 0.8, and $1.0\,mV\,min^{-1}$) frequently selected a steady state emf that differed significantly from that chosen visually by an experienced analyst; the same was true for the shortest stability windows (e.g., 10 s). Consequently, a second, more tightly clustered, sensitivity analysis ($0.3–0.5\,mV\,min^{-1}$, 20–40 s) was undertaken to investigate sensitivity to parameterization in the range where manual interpretation of the plots suggested that the results would likely be

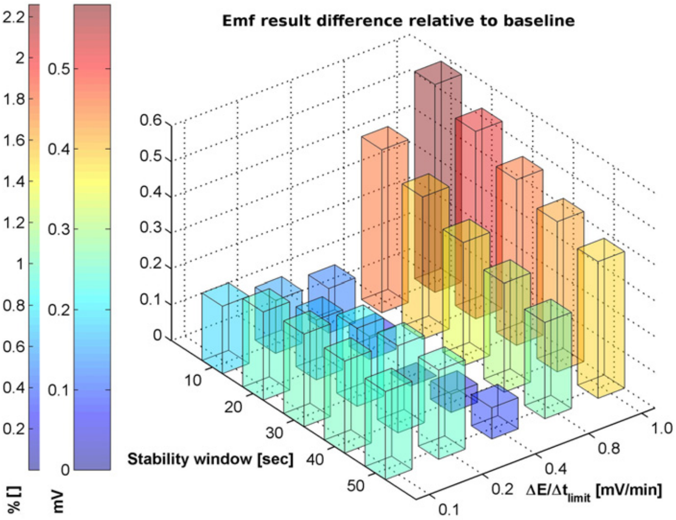


**Fig. 2.** Mean absolute change in determined steady state emf [mV] for a range of parameterizations relative to the baseline case of {$0.4\,mV\,min^{-1}$, 30 s}. Difference in bar heights indicates that emf declared for a specific time series may vary significantly with parameter choice.

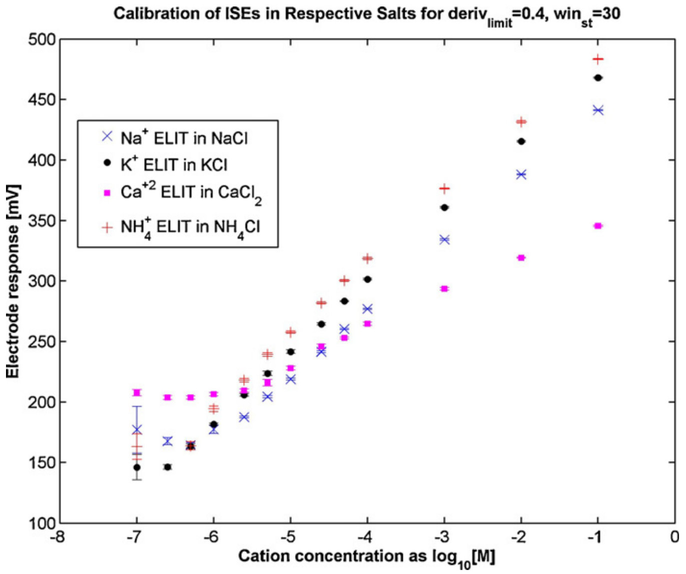


**Fig. 3.** Calibration curves for four ELIT ISEs in their respective salts (3$\sigma$ error bars). Linear fits with near-Nernstian slopes and $R^2 > 0.99$ are found for concentrations down to 1 μM in all cases (down to 0.25 μM for K$^+$).

consistent with an analyst's judgment. Maximum difference in average declared concentration values for these parameterizations was less than 0.7%., indicating that sensitivity to parameterization choice in this range is minimal (data not shown).

### *3.2. Linearity of electrode response*

Choice of appropriate parameterization must also result in acceptable calibration curves demonstrating reproducibility and ideally a high degree of linearity over a usable range of concentrations. The response of most modern commercial ISEs to primary ions is expected to be approximately Nernstian over a substantial range of ionic concentration. Shown in Fig. 3 are calibration curves for four solid state electrodes (ELIT Na$^+$, K$^+$, NH$_4$$^+$, Ca$^{2+}$) each in their corresponding salt solution (e.g., Na$^+$ ISE measuring NaCl solution). When using parameter values of {0.4 mV min$^{-1}$, 30 s}, all four electrodes produce linear responses ($R^2 > 0.99$) with near Nernstian slopes (Na$^+$: 54.8 ± 0.6; K$^+$: 58.0 ± 0.4; Ca$^{2+}$: 29.3 ± 0.7; NH$_4$$^+$: 58.1 ± 0.6) down to at least the 1 μM level (shown with 3$\sigma$ error bars). Activity corrections do not change these values for singly-charged ion solutions; for calcium-containing solutions, however, inclusion of the activity correction (Debye–Huckel) increases the slope to 31.4 ± 0.3.

Many other metrics of goodness, including slope, slope margin of error, intercept, intercept margin of error, $R^2$, and RMSE were also inspected to compare calibration curves resulting from differing parameterizations. Of these, RMSE was identified as the most differentiating indicator for quality of fit of ISE data to the Nernstian ideal. Importantly, however, this introduces a necessary tradeoff between (1) producing the most accurate data (which typically requires using the most stringent limitations) and (2) producing usable results in a practical time frame (typically requires relaxing requirements to maximize number of results). The nature of this trade-off and resulting findings are discussed further below.

### *3.3. Rate of failure to declare equilibrium as a function of parameterization*

In practice it may be necessary to choose a parameterization that will lead to a declared steady state emf within a prescribed maximum time. For example, in the case of data gathered by a moving underwater vehicle, sample time directly translates into spatial resolution of the chemical mapping, and longer sample periods result in lower spatial resolution. Maximum sampling time for many applications could thus be less than 10, or even 5, min; for the purpose of the present study, a sample period of approximately 6.5 min was used. Results were then analyzed to determine the number of samples which did not reach a declarable steady state in this sample period, expressed as the equilibrium failure rate, $\lambda_{\text{failure}}$. This rate was then examined as a function of parameterization; more 'stringent' values were expected to increase the failure rate.

Fig. 4 shows the observed $\lambda_{\text{failure}}$ (as a fraction of ~3200 samples) as a function of solution composition and probe type. From this figure, it is clear that the fraction of samples which do not reach steady state is a strong function of $\Delta E/\Delta t_{\text{limit}}$, with as few as 50% of the samples reaching a declared steady state for parameterizations

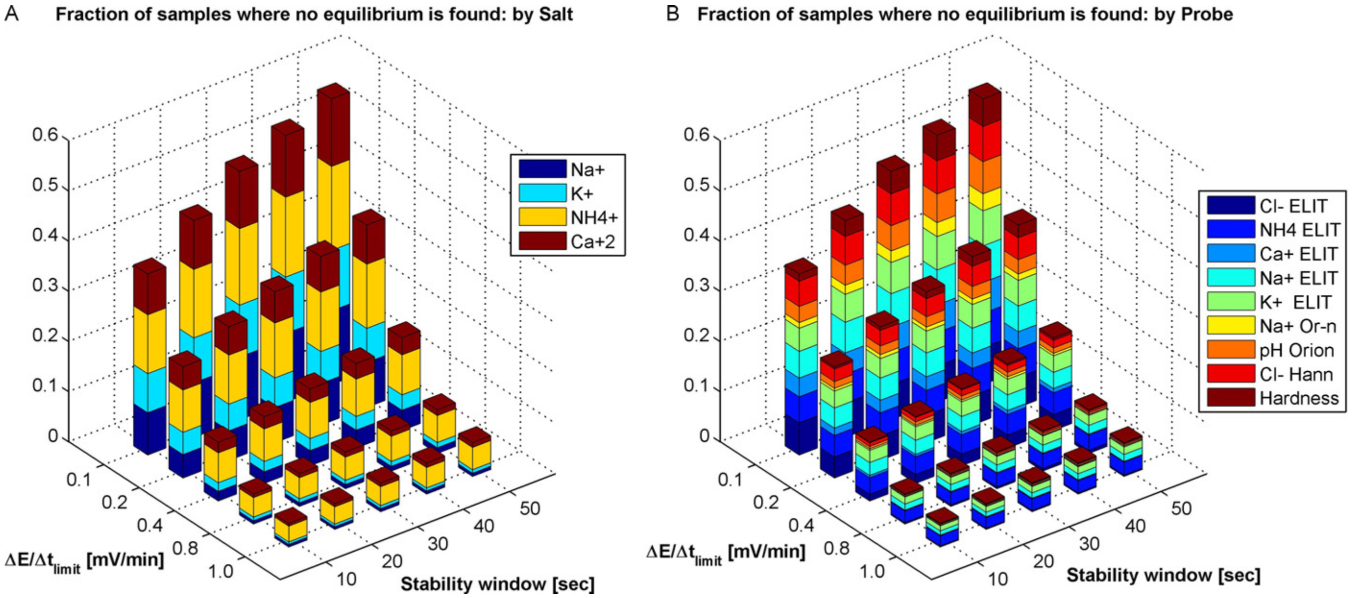


**Fig. 4.** Effect of parameterization on equilibrium failure rate, $\lambda_{\text{faiure}}$, for a sample period of ~6.5 min. Bars are subdivided by solution content (A) and probe (B) to demonstrate the range of characteristics affecting the response time of electrodes.

where $\Delta E/\Delta t_{\mathrm{limit}} \leq 0.2\,\mathrm{mV\,min^{-1}}$. This favors adoption of the maximum $\Delta E/\Delta t_{\mathrm{limit}}$ value that is consistent with acceptable analytical accuracy for applications where sample time is a constraint.

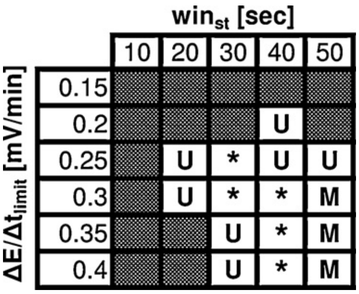
### *3.4. Optimization against system constraints*

In order to determine an optimal choice of parameterization, it is necessary to consider both analytical accuracy and $\lambda_{\mathrm{failure}}$ minimization. To do so, RMSE (against the optimal linear fit) was plotted against the *equilibrium success rate* ($\lambda_{\mathrm{success}} = 1 - \lambda_{\mathrm{failure}}$) for each of 45 parameterizations, including those listed in Section 2.1 and several additional values for $\Delta E/\Delta t_{\mathrm{limit}}$ in the 'most promising' mid-range identified above. The resulting 36 plots (one for each combination of salt solution and ISE probe) were examined for visible trends or trade-offs in accuracy vs. equilibration success rate. Although overall plot shape showed significant variability, three features were generally identifiable:

(1) *Existence of an RMSE baseline for parameterizations*: Below some cutoff, further lowering of $\Delta E/\Delta t_{\mathrm{limit}}$ results in a drop in $\lambda_{\mathrm{success}}$ without a corresponding drop in RMSE;
(2) *An approximately linear trade-off region*: Increasing $\Delta E/\Delta t_{\mathrm{limit}}$ produces an increase in $\lambda_{\mathrm{success}}$ that is coupled with an increase in RMSE;
(3) *An equilibrium success rate saturation region*: Further increase of $\Delta E/\Delta t_{\mathrm{limit}}$ produces an increase in RMSE without a corresponding increase in the $\lambda_{\mathrm{success}}$.

In many cases, $\Delta E/\Delta t_{\mathrm{limit}} < 0.2\,\mathrm{mV\,min^{-1}}$ corresponded to condition (1) while $\Delta E/\Delta t_{\mathrm{limit}} > 0.4\,\mathrm{mV\,min^{-1}}$ corresponded to condition (3). Exact curve shape was unique for each salt solution/probe combination, however, with some demonstrating clear parametric optima and others showing parameterizations which would not be desirable even under conditions where an increase in RMSE could be tolerated. Generally, these trends reinforced the conclusions stated above regarding unacceptable parameterization values.

Results for $\Delta E/\Delta t_{\mathrm{limit}} = \{0.15\text{–}0.4\}\,\mathrm{mV\,min^{-1}}$ are qualitatively summarized and shown in Fig. 5. Note that (*) indicates *acceptable results* (not necessarily optimal results) *for all salt/probe combinations in the present study* while hashing indicates poor results. Results were further evaluated to identify acceptable parameterizations separately for selectivity matched (M) salt/probe pairs (e.g., NaCl as measured by the Na+ ELIT ISE) and un-matched (U) pairs (e.g., $CaCl_2$ as measured by the Na+ ELIT ISE).



| ΔE/Δt_limit [mV/min] | win_st [sec] 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|
| 0.15 | ▨ | ▨ | ▨ | ▨ | ▨ |
| 0.2 | ▨ | ▨ | ▨ | U | ▨ |
| 0.25 | ▨ | U | * | U | U |
| 0.3 | ▨ | U | * | * | M |
| 0.35 | ▨ | ▨ | U | * | M |
| 0.4 | ▨ | ▨ | U | * | M |

**Fig. 5.** Summary of parameterization 'goodness' as judged by simultaneous minimization of RMSE and maximization of equilibrium success rate. Cross-hatching = poor results; * = good results for all probes; M/U = good results for the subset of selectivity matched (M) or un-matched (U) salt/ISE probe pairs.

Overall, parameterizations of $\Delta E/\Delta t_{\mathrm{limit}} = \{0.25\text{–}0.4\,\mathrm{mV\,min^{-1}}\}$ and $\mathrm{win_{st}} = \{30\text{–}40\,\mathrm{s}\}$ produced the best results over the large range of solution compositions, concentrations, and ISE technologies that were studied. When jointly optimizing for analytical results and equilibration success rate, the parameter set of $\{0.4\,\mathrm{mV\,min^{-1}}, 40\,\mathrm{s}\}$ is thus determined to be optimal for the electrode set tested.

### *3.5. Quantification of response time*

The effect of parameterization was also investigated for its effect on the response times assigned to each electrode under the conditions of this study. Fig. 6 (left) shows the relative difference in determined response time with respect to the $\{0.4\,\mathrm{mV\,min^{-1}}, 30\,\mathrm{s}\}$ parameterization baseline; additional sensitivity analysis in a tighter parameterization range are shown in Fig. 6 (right). Note that cool colors indicate parameterizations producing shorter response times than baseline (generally $\Delta E/\Delta t_{\mathrm{limit}} > 0.4\,\mathrm{mV\,min^{-1}}$), while hot colors indicate longer response times (generally $\Delta E/\Delta t_{\mathrm{limit}} < 0.4\,\mathrm{mV\,min^{-1}}$). Dot size is proportional to the magnitude of this difference in all cases.

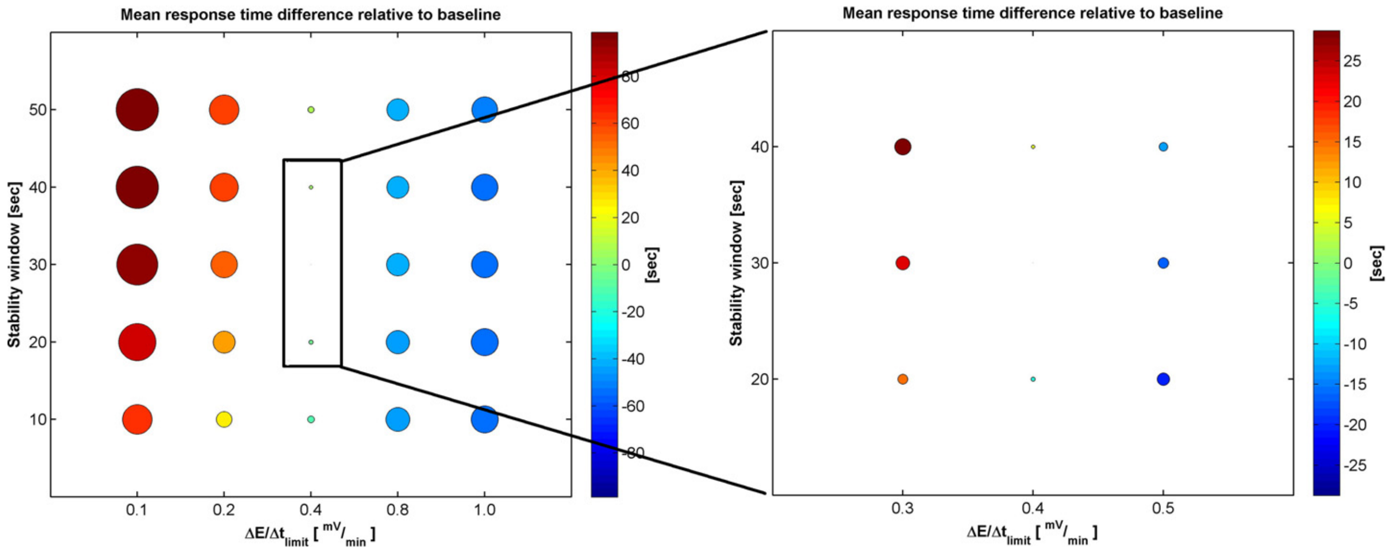


**Fig. 6.** Mean difference in determined response time [s] relative to the $\{0.4\,\mathrm{mV\,min^{-1}}, 30\,\mathrm{s}\}$ baseline over a range of parameterizations; plot on the right shows results for a more constrained parameterization set (referenced to plot on left). Blue tones indicate that parameterization produces shorter response times than baseline while red tones indicate longer response times (note colorbar scale change from left to right). Note total difference of almost 3 min across parameterizations shown in plot on left as compared to a difference of less than 1 min on the right.

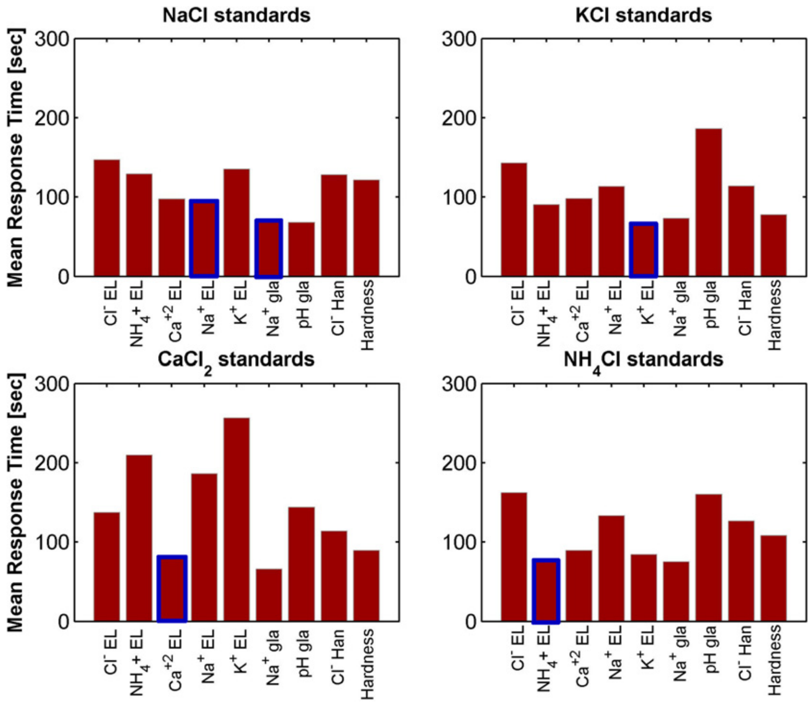


**Fig. 7.** Effect of electrode sensitivity and membrane type on mean response time for baseline parameter values.

In general, response time determinations were more sensitive to parameterization, and to $\Delta E/\Delta t_{\text{limit}}$ in particular, than were ionic concentrations. Response time varied by nearly 3 min over the extended parameter set, suggesting that use of a standardized value for $\Delta E/\Delta t_{\text{limit}}$ in comparisons of ISE time responses may be important.

Systematic response time differences among membrane types and identity of ions were also seen (Fig. 7). Bars outlined in blue in the figure indicate electrodes that are specifically marketed for sensitivity to the given salt cation. Response times for most electrodes to their indicated analyte were in the range of 80–100 s; response times to other analytes (i.e., interfering ions or those to which the electrode was not strongly responsive) were often more than double that value. Response time also varied as a function of salt solution concentration, changing by a factor of three or more over the concentration range from 0.1 μM to 0.1 M (data not shown). In general, the data indicate that a number of characteristics, including specificity of the ISE to the ions in solution, the total concentration of ions in the solution, and possibly the membrane type, strongly contribute to the response time of the electrode, as has been noted previously by other researchers, e.g., [2].

These data point to the need for a uniform testing protocol to support intercomparability of published response times for different ISEs. They also have important implications for ISE sampling methodologies where, for example, electrodes are simply allowed to equilibrate for a pre-specified number of minutes before taking a reading; depending on the sample composition and specific ISE membrane type, surface reactions may cause the electrode emf to diverge from an accurate reading before the reading, or the emf may not yet have reached adequate stability.

## 4. Conclusions

Time series emf measurements from a variety of ISEs measuring a wide range of sample compositions and concentrations demonstrate the value of determining steady state using a standardized method employing both $\Delta E/\Delta t_{\text{limit}}$ and $\text{win}_{\text{st}}$ criteria. Quantitative trade-offs were also found between (1) obtaining analytically optimal results and (2) obtaining results within a constrained sampling period. In this study, analytical accuracy was preserved for values of $\Delta E/\Delta t_{\text{limit}} = \{0.25\text{–}0.4\ \text{mV min}^{-1}\}$ and $\text{win}_{\text{st}} = \{30\text{–}40\ \text{s}\}$, while at least 90% of samples reach a declared steady state within the sampling time of 6.5 min for values of $\Delta E/\Delta t_{\text{limit}} > 0.3\ \text{mV min}^{-1}$. Variability in declared emf as a function of parameterization choice was not strongly dependent on the choice of $\Delta E/\Delta t_{\text{limit}}$ within this range, while highly linear Nernstian calibration curves are attained, demonstrating the utility of this method for use in analytical applications.

For a given value of $\Delta E/\Delta t_{\text{limit}}$, steady state emf was not strongly dependent on the width of the stability window, $\text{win}_{\text{st}}$, with individual acceptable results being observed for windows as short as 20 s. Because stability window width strongly influences the calculated response time for the ISEs (longer windows corresponding to longer response times), however, choice of $\text{win}_{\text{st}}$ may influence utility of the ISE for some time-critical applications. Analytical results are not shown to greatly improve for $\text{win}_{\text{st}} > 40$ s but are shown to degrade for $\text{win}_{\text{st}} < {\sim}20\text{–}30$ s; values of $\text{win}_{\text{st}} = \{30\text{–}40\ \text{s}\}$ are thus generally recommended for the ISEs used in this study. For applications where minimization of response time is essential, however, a parameter set of $\{0.4\ \text{mV min}^{-1}, 40\ \text{s}\}$ is recommended.

Finally, determined response times were more sensitive to the choice of method parameters than were steady state emfs, being generally proportional to the value chosen for $\Delta E/\Delta t_{\text{limit}}$. Response time was also strongly dependent on ion/ISE sensitivity and membrane type. This further supports use of a standardized method for ISE characterization to promote reliability and inter-comparability of results, such as the real-time, standardized method described here.

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