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# Paper-Based Potentiometric Ion Sensing

Wen-Jie Lan<sup>a</sup>, Xu U. Zou<sup>b</sup>, Mahiar M. Hamed<sup>a</sup>, Jinbo Hu<sup>b</sup>, Claudio Parolo<sup>a</sup>, E. Jane Maxwell<sup>a</sup>,  
Philippe Bühlmann<sup>b\*</sup>, and George M. Whitesides<sup>a,c\*</sup>

<sup>a</sup>Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street,  
Cambridge, MA 02138, <sup>b</sup>Department of Chemistry, University of Minnesota, 207 Pleasant Street  
SE, Minneapolis, MN 55455, <sup>c</sup>Wyss Institute for Biologically Inspired Engineering, Harvard  
University, 60 Oxford Street, Cambridge, MA 02138

\*Corresponding authors' E-mail: [gwhitesides@gmwhgroup.harvard.edu](mailto:gwhitesides@gmwhgroup.harvard.edu); [buhlmann@umn.edu](mailto:buhlmann@umn.edu)

## **Abstract**

This paper describes the design and fabrication of ion-sensing Electrochemical Paper-based Analytical Devices (EPADs) in which a miniaturized paper reference electrode is integrated with a small ion-selective paper electrode (ISPE) for potentiometric measurements. Ion-sensing EPADs use printed wax barriers to define electrochemical sample and reference zones. Single-layer EPADs for sensing of chloride ions include wax-defined sample and reference zones that each incorporates a Ag/AgCl electrode. In EPADs developed for other electrolytes (potassium, sodium, and calcium ions), a PVC-based ion-selective membrane is added to separate the sample zone from a paper indicator electrode. After the addition of a small volume (less than 10  $\mu\text{L}$ ) of sample and reference solutions to different zones, ion-sensing EPADs exhibit a linear response, over three orders of magnitude, in ranges of electrolyte concentrations that are most relevant medically, with a slope close to the theoretical value ( $59.2/z$  mV). Ion-selective EPADs provide a portable, inexpensive, and disposable way of measuring concentrations of electrolyte ions in aqueous solutions.

## Introduction

The selective quantitation of electrolyte ions in solution is an important task for clinical diagnosis, environmental monitoring, and quality control.<sup>1,2</sup> Measurements of this type are routinely performed in laboratory settings by recording the potential difference between an ion-selective electrode (ISE) and a reference electrode;<sup>3</sup> the cost and fragility of conventional ISEs, however, limit their application in the field, or in resource-limited environments. Portable analyzers designed for clinical settings, such as the i-STAT<sup>®</sup> handheld blood analyzer<sup>4</sup>, facilitate sample preparation and miniaturize potentiometric measurements by using wafer-scale, high-volume, planar, thin-film microfabrication techniques, but the price of these devices (~\$10,000 per device, and ~\$15 per single-use cartridge) limits their accessibility. Low-cost and disposable potentiometric sensors could bring much-needed diagnostic capabilities to remote and resource-limited environments.

In this article, we demonstrate that Electrochemical Paper-based Analytical Developments (herein after referred to as EPADs) that combine a paper reference electrode and an ion-selective paper electrode (ISPE) with a conventional ion-selective membrane (ISM). These devices provide a simple, affordable, and disposable tool for measuring the concentration of specific ions in solution using potentiometry.

Potentiometry is an electrochemical method that passively measures the difference in potential between an indicator electrode and a reference electrode (Figure S1a, Supporting Information, SI).<sup>5</sup> The indicator electrode used when measuring ions (often referred to as ion-selective electrode, or ISE), is selective in its response to species (*i*) of interest due to the presence of an ISM, whereas the reference electrode is not. The observed potential changes with the phase boundary potential across the interface between the sample and the ISM that separates

the analyte solution from an inner reference solution (Figure S1a). The analyte concentration in the sample is determined through the Nernst equation, which relates the measured potential (electromotive force, EMF) to the ion activity,<sup>6</sup> by calibrating the device before the measurement with a standard solution that has a known activity of the analyte.

The development of ISEs based on ionophore-doped ISMs in the 1960s allowed potentiometry to replace flame photometry (flame atomic emission spectroscopy) as the standard technique for the measurement of electrolyte ions in physiological fluids and other environmental or industrial samples.<sup>7</sup> For example, valinomycin, the most widely used ionophore for potassium, is an electrically uncharged macrocyclic antibiotic that has a very high selectivity for potassium ions. Valinomycin forms complexes with the target ions ( $K^+$ ) that are carried across the solution-membrane boundary; this partitioning causes the separation of charge, and results in a Nernstian response of potential to ionic activity. Valinomycin-based membrane electrodes are used in many automated devices, such as the i-STAT<sup>®</sup> portable clinical analyzer. Today, well over a billion measurements are performed annually with potentiometry.<sup>8</sup> A wide variety of conventional ISEs are available from commercial sources, and these electrodes permit selective determination of numerous cations and anions by direct potentiometric measurements.

Paper soaked with an electrolyte solution has been historically used as a salt bridge to connect two electrochemical half-cells.<sup>9</sup> Paper has also been used to provide mechanical support for ISMs and electrolyte solutions. For example, in the 1990s, Knoll and co-workers developed a strip type sensor in which paper was used as a mechanical matrix for an ISM. To prevent direct contact between the sample and the paper with the coated silver lead, the device was encapsulated using a heat-sealing film made of polyethylene and polyester.<sup>10</sup> More recently, Novell et al. reported the use of filter paper that was impregnated with carbon nanotubes and

coated with an ISM. A plastic mask prevented the sample from circumventing the ISM and wetting the filter paper directly. Measurements were performed with a commercial Ag/AgCl reference electrode for samples having a large volume,<sup>11</sup> or, for small volumes, by use of a neoprene rubber gasket in combination with a separate miniaturized reference electrode<sup>12</sup>. In another report, Bobacka and co-workers performed potentiometric measurements by pressing solid-contact electrodes against sample-impregnated filter paper.<sup>13</sup> Neither of these approaches used wax-imprinted paper to define a more fully integrated paper-based potentiometric cell.

We have developed paper-based voltammetric/amperometric devices that are capable of quantifying the concentrations of heavy-metal ions, glucose, cholesterol, lactate, and ethanol in aqueous solutions.<sup>14</sup> EPADs are also able to provide accurate measurements that are referenced by an electrode with a constant, well-defined potential.<sup>15</sup> The devices are easy to fabricate, portable, and inexpensive.

Here, we describe the development of ion-sensing EPADs that incorporate a reliable paper Ag/AgCl reference electrode with a small, ion-selective paper electrode (ISPE). The realization of paper-based potentiometric ion sensors enables a method for measuring concentrations of electrolyte ions ( $\text{Cl}^-$ ,  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Ca}^{2+}$ ) in very small sample volumes and at very low cost.

## **Experimental Section**

*Chemicals:* Ag/AgCl ink (E2414) was purchased from Ercon (Wareham, MA). Valinomycin (Potassium ionophore I) was purchased from Sigma-Aldrich or A.G. Scientific. 4-*tert*-butylcalix[4]arene-tetraacetic acid tetraethyl ester (Sodium ionophore X),

[*N,N,N',N'*-tetracyclohexyl-3-oxapentanediamide] (ETH 129, Calcium ionophore II), potassium tetrakis(4-chlorophenyl)borate (KTPCIPB), 2-nitrophenyl octyl ether (*o*-NPOE), poly(vinyl chloride) high molecular weight (PVC), and tetrahydrofuran (THF) were all purchased from Sigma-Aldrich or Fluka. The organic silane 3-aminopropyldimethylethoxysilane (APDES) was purchased from Gelest. PVC tubing (Tygon<sup>®</sup>, formulation R-3603) and rubber caps were purchased from VWR International.

*Electrochemical Supplies:* A double-junction type external reference electrode (DX200; 3.0 M KCl saturated with AgCl as inner reference solution and 1.0 M LiOAc as bridge electrolyte) was purchased from Mettler Toledo. Ag/AgCl reference electrodes with 1 M KCl internal filling solution were purchased from CH Instruments (Austin, Texas).

*Fabrication of the Paper Devices:* Paper-based zones and microfluidic channels were fabricated by patterning chromatography paper (Whatman 1 Chr) by wax printing. The width of the printed wax line is  $\sim 2$  mm. We placed the paper in an oven (100 °C) to melt the wax and let it penetrate the full thickness of the paper. We fabricated the electrodes by stencil-printing Ag/AgCl ink on the wax-printed paper devices. We generated a stencil for printing by designing patterns of electrodes using AutoCAD<sup>®</sup> 2012, and cutting the pattern into frisket film (Grafix, low tack) using a laser-cutter (VersaLASER VLS3.50, Universal Laser Systems). We adhered the stencil on top of the paper, and filled the openings of the stencil with ink. We cured the ink by baking the electrodes in an oven at 100 °C for 10 min. We treated the electrode zones of the EPAD with a solution of 2 wt% APDES in water (1  $\mu$ L in each zone) to enhance their hydrophilicity.

*Fabrication of the Ion-Selective Membranes (ISMs):* The ISM typically contains a lipophilic ion receptor (an ionophore) and, in an optimized molar ratio,<sup>16</sup> a lipophilic ion

exchanger, both incorporated into a polymeric membrane matrix such as a plasticized poly(vinyl chloride) (PVC). All components are dissolved into tetrahydrofuran (THF), giving an ISM cocktail.<sup>4</sup> After spotting the cocktail solution onto a substrate, the THF evaporates and the ionophore-containing PVC membrane is formed (Figure S2a). We prepared all ISMs following established literature protocols.<sup>17</sup> The K<sup>+</sup> ISM contained 1.4 wt% of valinomycin, 0.3 wt% of KTpCIPB, 32.8 wt% of PVC, and 65.5 wt% of *o*-NPOE. The Na<sup>+</sup> ISM contained 1.0 wt% of sodium ionophore X, 0.3 wt% of KTpCIPB, 32.9 wt% of PVC, and 65.8 wt% of *o*-NPOE. The Ca<sup>2+</sup> ISM contained 1.0 wt% of ETH 129, 0.6 wt% of KTpCIPB, 32.8 wt% of PVC, and 65.6 wt% of *o*-NPOE.<sup>18</sup> The membranes were prepared by dissolving ~0.2 g of the mixture into 1.5 mL of THF for K<sup>+</sup> and Na<sup>+</sup>, and ~0.4 g of the mixture into 4 mL of THF for Ca<sup>2+</sup>. We poured the THF solution into a petri dish and allowed the THF to evaporate over 24 h. We then cut the membrane into small circular pieces (10 mm in diameter) and conditioned them by soaking overnight in chloride solutions of the corresponding ions (10<sup>-3</sup> M K<sup>+</sup>, 10<sup>-1</sup> M Na<sup>+</sup>, and 10<sup>-2</sup> M Ca<sup>2+</sup>).

*Fabrication of Conventional ISEs:* We wetted the bottom of the PVC electrode body (Tygon<sup>®</sup> tubing) with several microliters of THF solution. The circular ISM was then attached to the tubing to seal the bottom.

*Potentiometric Measurements:* The inner reference, sample, and the external reference solutions were spotted onto the corresponding zones of the EPAD. All potential measurements were performed at room temperature with an EMF 16 channel potentiometer (Lawson Labs, Malvern, PA). This instrument has a high input impedance (10<sup>13</sup> Ω) that is suitable for potentiometric measurements in which the ISM has a large resistance. Activity coefficients were



calculated according to a two-parameter Debye–Huckel approximation.<sup>19</sup> All EMF values were corrected for liquid-junction potentials with the Henderson equation.<sup>20</sup>

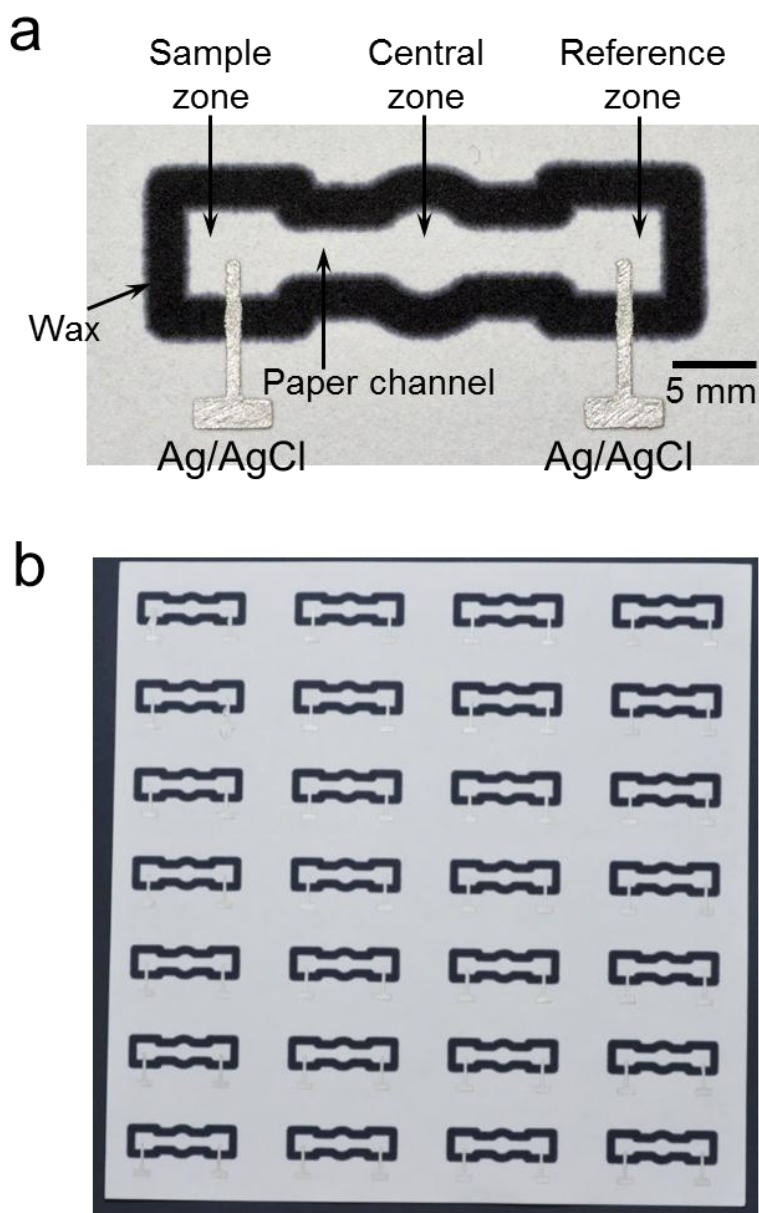
## Results and Discussion

### *Design of EPADs for Sensing Chloride Ions ( $Cl^-$ )*

The ion-sensing EPADs include wax-patterned sample and reference zones that each contain a stencil-printed Ag/AgCl electrode (see Experimental Section for details on the fabrication process). The measurement zones are connected by a paper-based microfluidic channel that includes a central contact zone (Figure 1a). When sample and reference solutions are added to the appropriate zones of the EPAD, the geometry of the EPAD (shown in Figure 1) allows ionic conductivity between the two solutions, but—due to slow diffusive transport of ions and solvent in liquid-filled paper channels—prevents large-scale convective mixing that would shift the potential of the reference electrode or change the concentration of the analyte, and thereby affect the accuracy of the potentiometric measurement.<sup>15</sup> The contact zone in the EPAD thus has a function similar to that of a salt bridge (typically an electrolyte-filled porous tip<sup>21</sup>) in conventional reference electrodes.

Devices for sensing chloride ions required no further modification, as the potential of the Ag/AgCl electrode is proportional to the logarithm of the activity of chloride ions, as defined by the redox reaction ( $AgCl(s) + e^- \rightleftharpoons Ag(s) + Cl^-(aq)$ ) and the Nernst equation. Thus, the  $Cl^-$  concentration in the sample can be obtained by measuring the potential difference between the two Ag/AgCl electrodes that are in contact with a sample solution on the sample zone and a reference solution of KCl with a known concentration on the reference zone.

**Figure 1.** (a) Photograph of a  $\text{Cl}^-$ -sensing Electrochemical Paper-based Analytical Device (EPAD). The chromatography paper (Whatman 1 Chr) was patterned by wax printing to define the sample zone, central contact zone, reference zone, and microfluidic channels. The sample and reference zones include stencil-printed Ag/AgCl electrodes. (b) Photograph of 28 potentiometric  $\text{Cl}^-$ -sensing EPADs fabricated on one page of wax-printed paper (20 cm by 20 cm).



The ion-sensing EPADs are fabricated in a planar structure, and are thus appropriate for mass fabrication. As shown in Figure 1b, one page of chromatography paper (Whatman 1 Chr, 20 cm by 20 cm) can be used to fabricate 28 devices. It takes less than 30 minutes to fabricate one page of EPADs manually (28 or more devices, depending on the device configuration; *vide infra*). The efficiency of fabrication would be greatly improved by machine-based roll-to-roll printing.

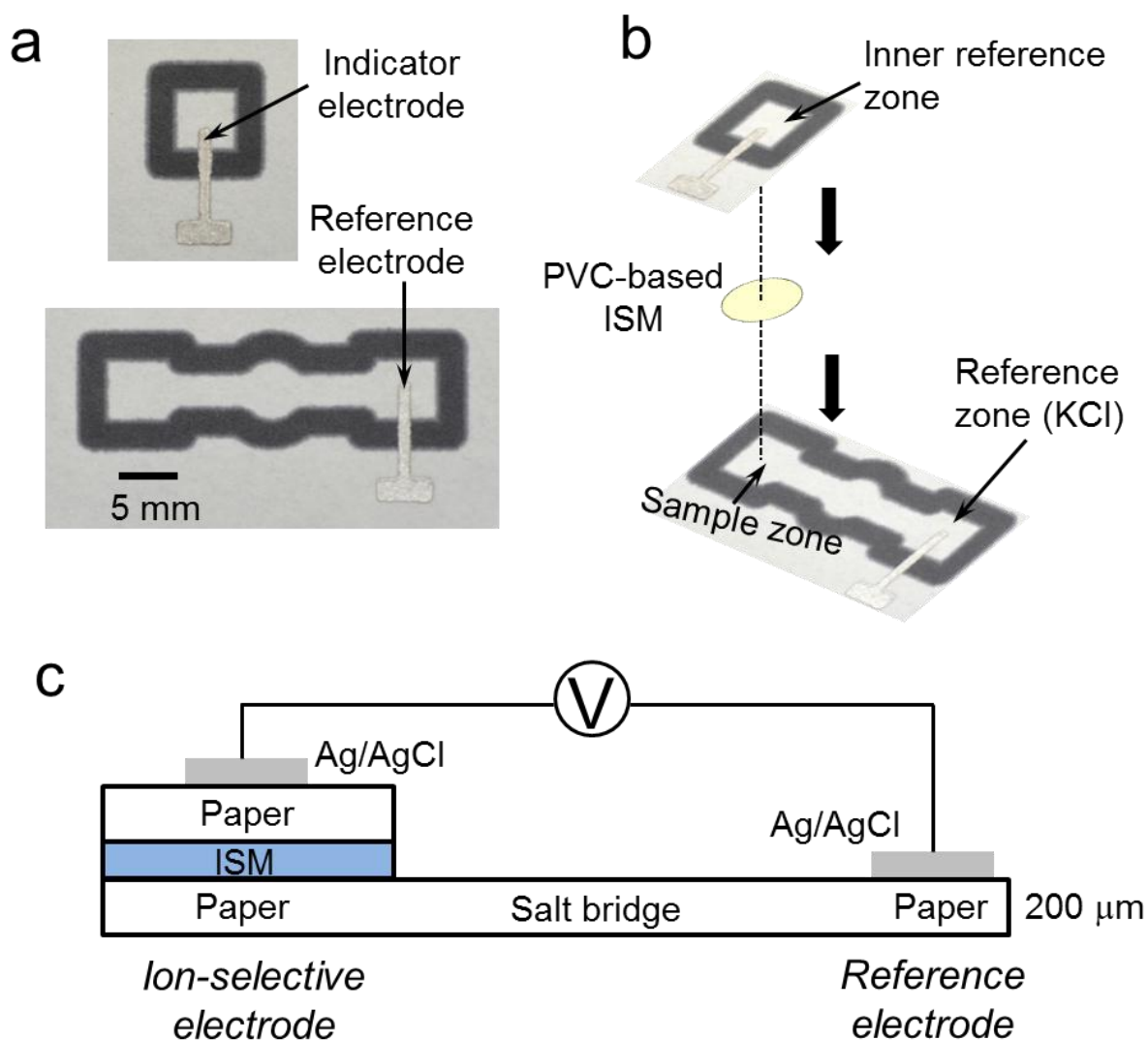
#### *EPADs for Sensing Potassium ( $K^+$ ), Sodium ( $Na^+$ ), and Calcium Ions ( $Ca^{2+}$ )*

The potentiometric measurements of other electrolytes such as  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$  require the addition of an ISM that separates the indicator electrode (ISE) from the sample solution. We used a conventional ISM that contains an ionophore and ionic sites in a thin PVC membrane matrix (<400  $\mu\text{m}$ ). The ISMs are sensitive to specific ions of interest.

We chose conventional ISMs because (i) they can be easily fabricated by addition of a small volume (1.5 to 4.0 mL) of a cocktail solution into a Petri dish and evaporation of the solvent (Figure S2a, see Experimental Section for detailed formulations), (ii) they have been well investigated and commercialized, (iii) they are small (typically smaller than 1 cm in diameter) and easy to handle, (iv) the PVC membrane matrix has the mechanical robustness required for it to be incorporated into paper devices, and (v) conventional ISMs have the potential for low-cost mass fabrication.

We used an additional wax-printed paper layer with a Ag/AgCl electrode printed on top to serve as the indicator electrode, as shown in Figure 2a. The wax barriers operate in a manner similar to the plastic electrode body used in conventional ISEs with polymeric sensing membranes (Figure S1, arrows 3 and 3'). Other parts in the paper device (labeled by the arrows)

**Figure 2.** (a) Photograph of two wax-printed paper layers in an ion-sensing EPAD for  $K^+$ ,  $Na^+$ , or  $Ca^{2+}$ . Ag/AgCl ink was stencil-printed on paper to make the indicator and reference electrodes. (b) The PVC-based ion-selective membrane and the indicator electrode were attached sequentially to the sample zone of the EPAD. (c) Schematic illustration (cross-sectional view) of an assembled paper-based potentiometric device.



perform functions similar to those of their conventional counterparts. Analogously, paper components in the ion-sensing EPADs for  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$  can also be mass fabricated (Figure S3).

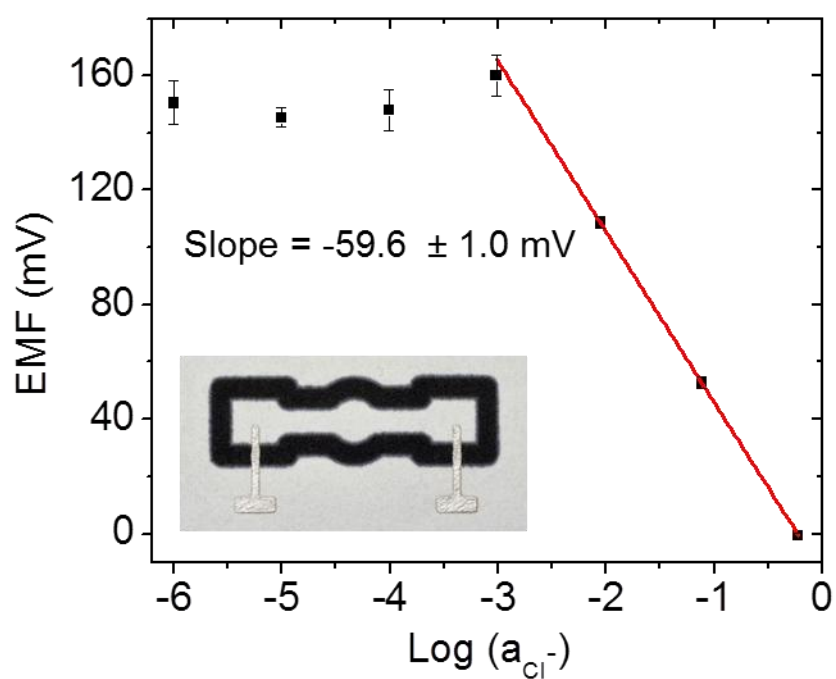
The ISM and the indicator electrode were attached sequentially to the sample zone of the EPAD (Figure 2b). The configuration of the assembled paper device resembles a scaled-down version of a conventional potentiometric measurement setup, as shown in Figure S1. Figure 2c provides a schematic illustration (cross-sectional view) of the assembled ion-sensing EPAD. We estimate that the costs of paper components and printing ink (*e.g.*, Ag/AgCl) in one ion-sensing EPAD to be ~\$0.092, which is only ~12% of the cost of a conventional ISM (~\$0.8, see SI for more details).

#### *Potentiometric Measurement of $Cl^-$*

We used a potentiometer to measure the EMF between the two paper electrodes for aqueous KCl samples with different concentrations of  $Cl^-$ . Aqueous 1 M KCl was used as the reference solution. We applied solutions to respective zones (~6  $\mu$ L in each), and solutions wicked into the central mixing zone in less than 20 s. We used two PVC sheets to sandwich the device and slow the rate of evaporation of water. EPADs alone—that is, without the sandwiching film—can also be used for measurements that take only short intervals (< 10 min) of time without introducing significant loss of accuracy. We recorded the potential for ~15 min at a sampling rate of two data points per second (see Figure S4 for one example).

Figure 3 shows that  $Cl^-$ -sensing EPADs with a 1 M KCl reference solution exhibit a linear response to the concentration of  $Cl^-$  ion in solutions, over three orders of magnitude in concentration ( $10^{-3}$  to 1 M KCl), with a slope that is close to the theoretical value ( $-59.6 \pm 1.0$

**Figure 3.** Potentiometric response obtained from  $\text{Cl}^-$ -sensing EPADs (inset). The calibration plot after addition of the reference solution (1 M KCl) and various sample solutions is shown. The red solid line represents a linear fit to data (■) between  $10^{-3}$  and 1 M KCl with regression equation:  $y = -13.6 - 59.6x$  ( $R^2 = 0.999$ ). Each point (■) was averaged from potentiometric readings from at least 3 paper devices, which each produced over 1,800 readings in ~15 minutes.



mV/decade vs. a theoretical value of -59.2 mV/decade). Additional experiments employing reference solutions with lower KCl concentrations ( $10^{-3}$  M or  $10^{-1}$  M) obtained similar linear trends with a slope ( $\sim$ -51 mV), which is slightly lower than the theoretical value. Our results indicate that EPADs can be used to measure the concentration of  $\text{Cl}^-$  over a range that is relevant to various industrial, environmental, and clinical samples (98-109 mM in blood serum).<sup>22</sup>

The potentiometric reading of  $\text{Cl}^-$ -sensing EPADs leveled off when the concentration of KCl sample is decreased to lower than  $10^{-3}$  M. We speculate that this plateau is due to the solubilization of a small amount of chloride ions from the Ag/AgCl ink during the measurements. The selectivity of Ag/AgCl electrodes does not render  $\text{Cl}^-$ -sensing EPADs an ideal device for measuring  $\text{Cl}^-$  concentrations in the presence of interfering ions, in which case a  $\text{Cl}^-$  ISM may be desired.<sup>17</sup> The  $\text{Cl}^-$ -sensing results of EPADs shown here, however, demonstrate the capability of quantifying  $\text{Cl}^-$  in aqueous samples with a simple and disposable paper-based device. We discuss ion-sensing EPADs that incorporate an ISM in the next section.

#### *Potentiometric Measurement of $\text{K}^+$ , $\text{Na}^+$ , and $\text{Ca}^{2+}$*

We integrated the ISMs with a conventional PVC-based cylindrical electrode body in order to test their performance independently from that of a paper device. The electrode body was filled with an inner reference solution (depending on the type of ISM), and a Ag/AgCl wire was placed in contact with this solution to serve as the indicator electrode (Figure S2b). We then immersed the resulting ISE and a commercial double-junction Ag/AgCl reference electrode in a sample solution that contained relevant ions of interest (Figure S1a). We measured the EMF between two electrodes, and used a two-fold serial dilution to obtain the calibration curve of this conventional ISE. As shown in Figure S5, the potentiometric responses from three ISMs of

different types of ions ( $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Ca}^{2+}$ ) in the conventional configuration are in excellent agreement with the Nernst equation ( $59.2/z$  mV per decade).

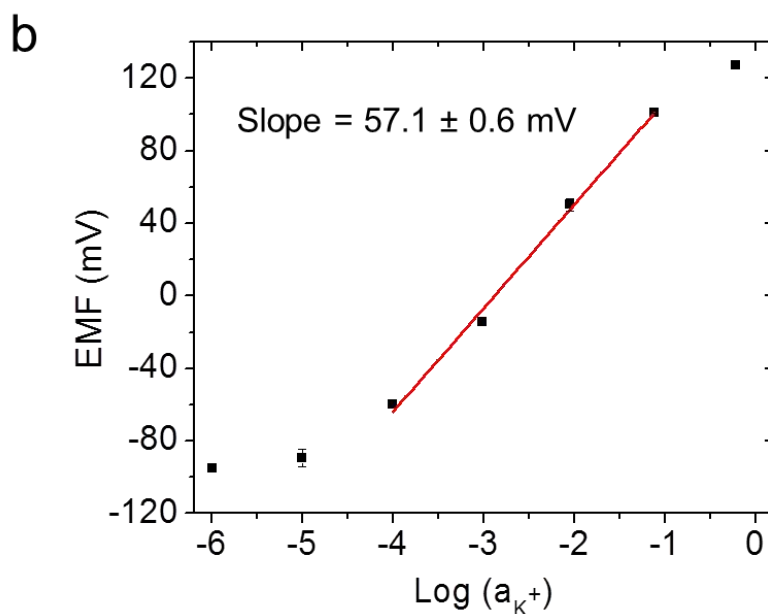
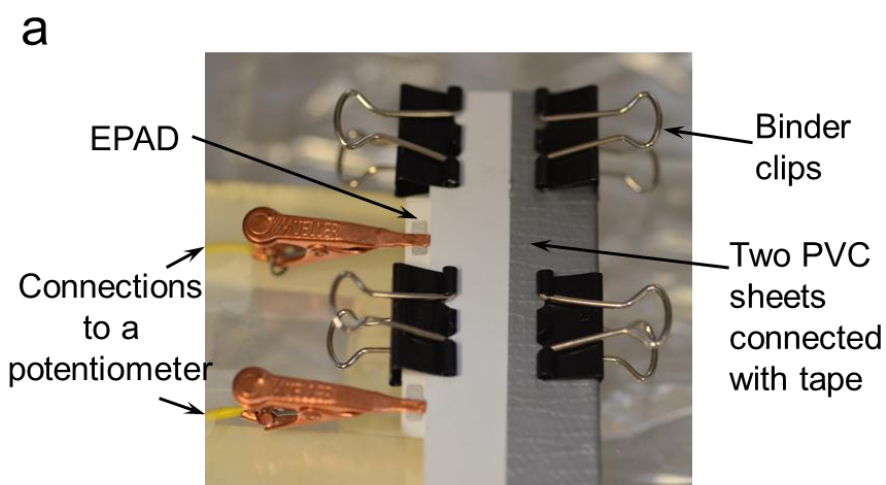
Having determined that the PVC-based ISMs exhibit the anticipated Nernstian behavior, we incorporated the ISMs into paper devices and performed measurements of  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Ca}^{2+}$  using ion-sensing EPADs. We spotted several microliters of the inner reference solution ( $10^{-3}$  M KCl for  $\text{K}^+$ ,  $10^{-1}$  M NaCl for  $\text{Na}^+$ , and  $10^{-2}$  M  $\text{CaCl}_2$  for  $\text{Ca}^{2+}$ ), the sample, and the reference solution ( $10^{-3}$  M KCl for  $\text{K}^+$ , 1 M KCl for  $\text{Na}^+$ , and 1 M KCl for  $\text{Ca}^{2+}$ ) to respective zones of the EPADs shown in Figure 2. The sample and reference solutions wicked through the device and made contact in less than 20 s. We then sandwiched the device between two PVC sheets using binder clips, and recorded the potential difference between the paper reference electrode and the ISPE (Figure 4a).

We chose PVC sheets and binder clips for this proof of concept because (i) they allow reversible attachment and easy disassembly between the ISM and paper layers, so that a single ISM can be calibrated and measured by multiple paper devices that are impregnated with calibrant or sample solutions, (ii) the PVC cover slows the rate of solvent evaporation, and (iii) the PVC sheets keep the EPAD in a flat, horizontal position, thus minimizing the gravity-driven fluid flow, which might cause contamination of sample or reference zones.

Figure 4b shows the response of the  $\text{K}^+$ -sensing EPADs to varying concentrations of  $\text{K}^+$  in aqueous KCl samples. We observed a linear dependence between the measured EMF and the logarithm of the activity of  $\text{K}^+$  ranging from  $10^{-4}$  to  $10^{-1}$  M, with a slope of  $57.1 \pm 0.6$  mV/decade, in accordance with the Nernst equation (59.2 mV) and the calibration of the conventional ISE ( $60.1 \pm 0.3$  mV, Figure S5a). Repetitive experiments produced calibration curves with similar slope under the same experimental condition. In addition, the linear



**Figure 4.** (a) Photograph of an assembled ion-sensing EPAD for potentiometric measurement of  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$ . The EPAD was sandwiched between two PVC sheets using binder clips. (b) Potentiometric response of EPAD to different concentrations of  $K^+$  in an aqueous KCl solution. A  $10^{-3}$  M KCl solution was used as the inner reference and the reference solution. The red solid line represents a linear fit to data (■) within the range between  $10^{-4}$  and  $10^{-1}$  M KCl with regression equation:  $y = 164.5 + 57.1x$  ( $R^2 = 0.997$ ).



(dynamic) range of the paper devices ( $10^{-4}$  to  $10^{-1}$  M) is comparable to that of the conventionally assembled device ( $\sim 10^{-5}$  to  $10^{-1}$  M, Figure S5a); this observation indicates the wax-printed paper layers and the paper reference electrode function as well as the plastic/glass electrode bodies used in commercial reference electrodes.

Measurements of  $\text{Na}^+$  with a  $\text{Na}^+$  ISM and paper devices also resulted in a Nernstian relationship that had a slope of  $60.9 \pm 1.4$  mV between  $10^{-3}$  and 1 M (Figure 5a). Similarly, the measurement of the EMF with different  $\text{Ca}^{2+}$  concentrations and a  $\text{Ca}^{2+}$  ISM led to a slope of  $29.0 \pm 1.0$  mV between  $10^{-4}$  and  $10^{-1}$  M (Figure 5b), compared to an ideal value of 29.6 mV/decade for a doubly charged species.

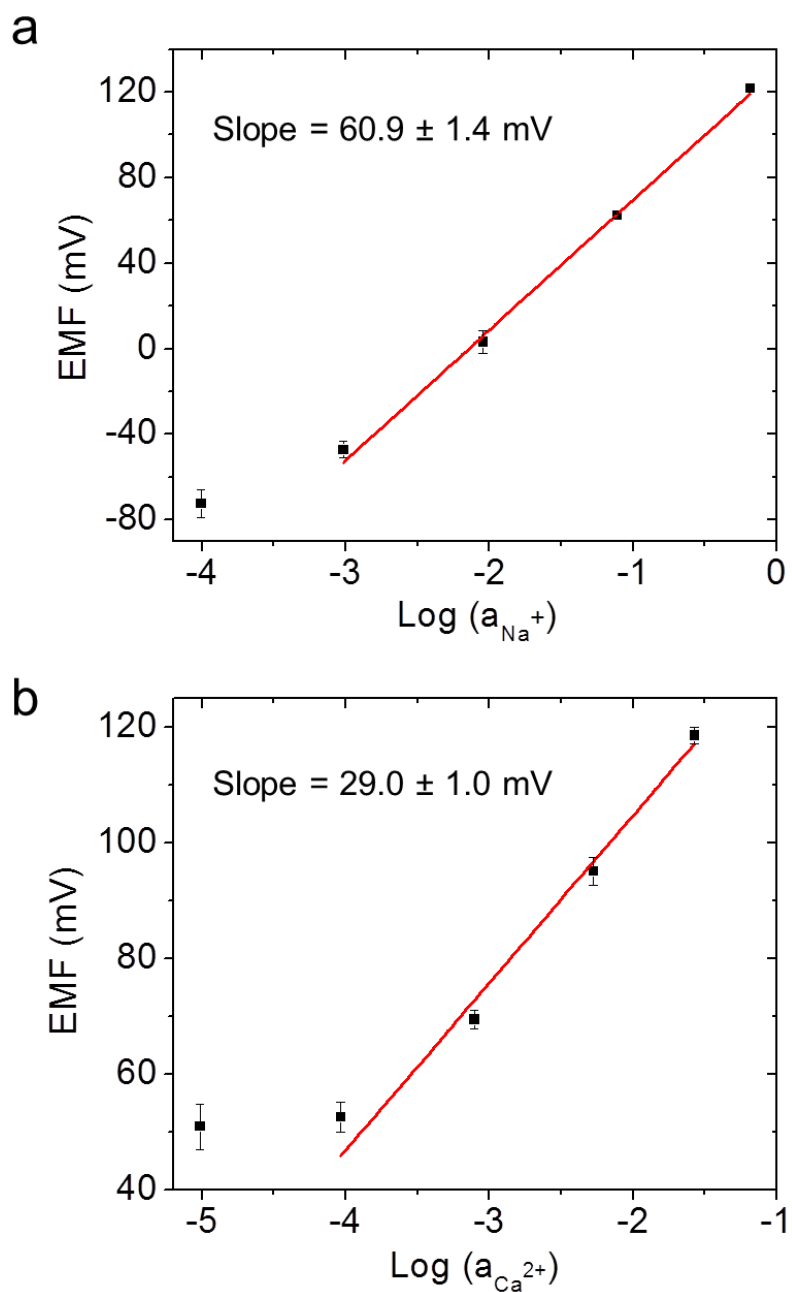
The linear ranges of these ion-sensing EPADs cover medically relevant concentrations of  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Ca}^{2+}$  in physiological fluids. These results suggest that EPADs have the potential to be applied to diagnostic uses. For example, the concentrations of  $\text{K}^+$ ,  $\text{Na}^+$ , and ionized  $\text{Ca}^{2+}$  in human blood are, respectively, 3.5-4.9 mM<sup>22</sup>, 138-146 mM<sup>22</sup>, and 1.12-1.32 mM.<sup>23</sup>

The EPAD-based measurements sometimes resulted in a small deviation from the Nernstian response (59.2 and 29.6 mV per decade for  $\text{Na}^+$  and  $\text{Ca}^{2+}$ , respectively) and conventional measurements. The deviation may be due to the difficulty in assembling EPADs that have an ideal, homogeneous interface between the ISM and the fluid-filled paper layers (*i.e.*, an interface with an evenly distributed pressure and no air trapped in between these layers).

## Conclusions

With the objective of adapting the paper electrochemical platform to a broader range of electrochemical analyses, we have developed ion-sensing EPADs. These devices comprise a

**Figure 5.** Potentiometric responses of ion-sensing EPADs to (a)  $\text{Na}^+$  in aqueous  $\text{NaCl}$  solutions and (b)  $\text{Ca}^{2+}$  in aqueous  $\text{CaCl}_2$  solutions. We incorporated a  $\text{Na}^+$  ISM and a  $\text{Ca}^{2+}$  ISM in corresponding EPADs. A  $10^{-1}$  M  $\text{NaCl}$  solution (for  $\text{Na}^+$  sensing) and a  $10^{-2}$  M  $\text{CaCl}_2$  solution (for  $\text{Ca}^{2+}$  sensing) were used as the inner reference solution. 1 M  $\text{KCl}$  solutions were used as the reference.



small paper- and PVC-based ISE, and a miniaturized paper-based reference electrode. Potentiometric measurements between these two electrodes make it possible to measure concentrations of electrolyte ions ( $\text{Cl}^-$ ,  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Ca}^{2+}$ ) in aqueous solutions over ranges that are clinically useful.

The ion-sensing EPADs have many potential advantages. (i) They are portable, disposable, and environmentally friendly. (ii) They combine the selectivity and sensitivity of ISMs and potentiometric measurements with the low cost of paper-based devices.<sup>24</sup> (iii) They do not require complicated microfabrication techniques. (iv) They are less subject to biofouling or biological interference than their conventional counterparts, because they are designed and intended for single-use applications. (v) They can be readily interfaced with almost any portable electrochemical reader that measures differences in potential. (vi) They are, in principle, adaptable to other biomedically or environmentally relevant ions (*e.g.*,  $\text{Li}^+$ ,  $\text{H}^+$ ,  $\text{Mg}^{2+}$ , and  $\text{NO}_3^-$ ) so long as an appropriate ISM has been developed.

The disadvantages of ion-sensing EPADS, at this stage of development, include (i) the three layers of components needing to be manually assembled each time, prior to potentiometric measurements, and (ii) the stability of the device being worse than that of conventional device. For example, the drift of the EMF reading (several mV in minutes) is larger than that of the conventional measurements. Current efforts are focused on improvements of the design and performance of ion-sensing EPADs, and their further applications in multiplexed, real-sample measurements.

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# TOC Graphic

