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Sensing H⁺ with conventional neural probes

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In this paper, we demonstrate a technique for transforming commercially available neural probes used for electrical recordings, into chemical sensing devices for detection of ionic concentrations in electrolytes, with particular emphasis to pH. This transformation requires a single post-processing step to incorporate a thin indium tin oxide membrane for sensing H⁺. Measured results indicate a chemical sensitivity of 28 mV/pH, and relatively low leakage currents (2–10 nA) and drifts (1–10 mV/h). The proposed sensing device demonstrates the possibility of a low-cost implementation that can be reusable and thus versatile, with potential applications in real-time extracellular but mainly intracellular chemical monitoring. © 2013 AIP Publishing LLC.

Ever since the first Ion-Sensitive Field Effect Transistor (ISFET) initially appeared in 1970 on a custom technology,1 the evolution of chemical micro-sensors for effective monitoring of distinct modalities became a necessity. The demand to enable the integration of chemical sensors at large scales with significant benefits in cost and power requirements led to the realization of ISFETs based on commercially available complementary Metal-Oxide-Semiconductor (CMOS).2 An extension of this work enabled in vivo extracellular measurements of cardiac tissue through the use of multi-sensor silicon needles that incorporate CMOS-based ISFETs for the simultaneous detection of K⁺ and H⁺ ions.3 Nevertheless, the requirement to improve the sensors performance, reliability, and lifetime yet remained. A promising method for addressing such issues and separate chemistry from electronics has been introduced,4 where the chemical sensing site location is extended far from the active electronic parts. Another example of this approach involved appropriately functionalized ZnO nanorods grown on an Ag wire that served as an extended gate pad for glucose5 and Ca²⁺ sensing6 using commercial MOSFETs.

Previously, multichannel neural microelectrode arrays coated with an ion-sensitive membrane have been employed as dopamine chemical sensors based on protonization current measurements through voltammetry.7 In another study, a CMOS-based prototype was developed to acquire redox current signals from a 16-channel front-end sensor and deliver a single voltage output through a multiplexing scheme.8 The long-term usability of these devices based on redox current measurements though is limited due to short-time saturation of the enzyme-coated sensing membrane. Recently, our group has demonstrated H⁺ detection with discrete MOSFETs as the active transducers mounted on a universal instrumentation board.9 The insulating membrane (SiNx or TiO₂) covering the extended-gate pads electrostatically couples the ions in the electrolyte transducing the availing chemical potentials that are then conveyed through a connector to the active read-out circuitry.

In this study, we exploit a commercially available product customly used for in vivo measurements of the cells electrical activity (neural probes) and transform it to a H⁺ chemical sensor through a single-step processing. Further expansion of this work could yield a robust sensor for invasive chemical monitoring of the intracellular activity.

Throughout this work, a 16-channel neural probe was employed (A-probe, Neuronexus) with electrode sites of 15 μm in diameter (Fig. 1(a)). A photore sist blob was applied on the contact pads of the probe before coating the shank with a thin layer (200 nm) of Indium Tin Oxide (ITO) (In₂O₃:SnO₂/90:10) using a sputtering deposition. The deposition process provides a uniform coating that varies within the range of ±8 nm; therefore, the reproducibility of the proposed sensor is excellent. The processed probe was then wire-bonded to a Printed Circuit Board (PCB) to facilitate the transmission of the chemical potentials to the read-out circuitry (Fig. 1(b)). Encapsulation of the exposed wires and the contact pads was implemented through application of a photocurable epoxy resin, which also secured the wires to a standard position. A cross section of the post-processed prototypes is provided in Fig. 1(b). ITO is a material known for its dual-conducting (semiconducting) nature with a thickness-dependant resistivity, which for films of 200nm ranges between 1.85 and 5 × 10⁻⁴ Ω cm depending on the sputtering deposition type (DC, RF) and the deposition parameters (power, pressure, gas flow).10,11 The functional protocol behind the pH sensing operation is the electrostatic coupling between the ions and the gate ITO layer, facilitated by the site-binding of H⁺ to the ITO sensing membrane, as described by Grahame’s dual layer capacitor.12 Depending on the available ionic resources, the binding of H⁺ to the ITO surface in the vicinity of the sensing sites introduces a small capacitance that leads to a corresponding output voltage.

In order to evaluate the chemical behavior of the device, we employed discrete MOSFETs. An array of p-type MOSFETs was hosted on a versatile instrumentation system

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previously designed, together with an appropriate multiplexing scheme, the necessary biasing circuitry comprising of dual op-amp source-drain followers, and universal interfacing ports. The fabricated platforms were remotely connected with the instrumentation board through a connector to facilitate the transmission of the chemical potentials to the read-out circuitry. The extended-gate approach was selected in our study in order to improve the sensor’s reliability and lifetime by having the active transducer in a remote location from the chemical sensing sites. The sensing prototype was evaluated with commercially available buffer solutions of known pH (HANNA Instruments). The electrical properties of the device were determined with a Keithley semiconductor characterization system (SCS-4200) through the corresponding $I_D-V_{GS}$ curves of the MOSFETs, while the chemical properties were extrapolated with the aid of the universal instrumentation and a software platform developed in MATLAB. An Ag/AgCl reference electrode was immersed in the electrolyte and was used as a remote gate. All experiments were carried out at room temperature and in a faraday cage for minimizing noise.

To evaluate the chemical sensitivity of the device, the probe was immersed for 100 s into 20 ml of each electrolyte in the following order: pH 7, 4, 7, 10, and 7. Before testing a new electrolyte, the sensor and the Ag/AgCl electrode were rinsed with deionized (DI) water to remove any residual chemical compounds. Fig. 2 depicts the transient response (output voltage of the dual op-amp source-drain followers biasing the MOSFETs) of 5 probe channels across distinct electrolytes. The graphs illustrated correspond to uncalibrated data (top) and data that were calibrated in terms of offset (in pH 7 solution) and drift (bottom). Calibration was performed through the software in order to maintain a uniform and relative performance for all sensing sites of the array. Fig. 3 shows the average output voltages of the neural probe sensing sites acquired during the experiments, indicating a pH sensitivity of 28 mV/pH. This implies that the sensor is linear, which is important in order to extrapolate straightforward correlations between detected voltage and H$^+$ concentrations. It is also worth mentioning that the observed sensitivity is well below the Nerstian sensitivity; nonetheless, the relevant differences between the various pH values are still well distinguishable. Thinner passivations result in an increase on the electrostatic coupling of H$^+$, as we have proved previously; however, the small scale of the front-end sensor employed here, and therefore of the sensing sites, limits the pH sensitivity that can be achieved. Moreover, the substantially extended remote-gate used in this work significantly increases the floating-gate capacitance resulting in a voltage-scaling, which is demonstrated by a lower sensitivity.

The electrical functionality of the sensor was proved via an $I_D-V_{GS}$ sweep. Essentially, the sensing sites of the neural probe are extensions of the MOSFETs gates that are able to...
sense H$^+$ via the ITO membrane. The operational principle of these sensors is identical with the ISFETs, in which the threshold voltage of the transducer corresponds to different pH values. The drain and source voltages were fixed at 0.5 V and 0 V, respectively, while the gate voltage applied through the reference electrode was swept from $-C_0$ to 0.2 V. Chemical sensitivity results for three distinct buffer solutions of pH values 10, 7, and 4 are depicted in Fig. 4. The right-axis of the figure depicts the corresponding measured leakage current flowing through the reference electrode, which also serves as an indication of the encapsulation integrity of the ITO membrane. Leakage current measurements were assessed for a constant current of 100 μA that corresponds to the operational region of the MOSFETs (Table I). Interestingly, the leakage current in all cases remains in very low levels, demonstrating the excellent encapsulation quality of the device. During these measurements, no substantial changes in the leakage current were noticed over time, since the encapsulation integrity of the sensor dominating the leakage current measurements remained intact.

Apart from the short-term response, the long-term stability was also examined in terms of the voltage drift. With the same setup, the output (drain) voltage of the probe was recorded for 45 min under leaving the sensor in a constant-electrolyte environment (20 ml, pH 4, 7, and 10). The main source of drift is attributed to the chemical interaction between the ions and the membrane surface, which causes alterations on the membrane’s chemical composition and/or thickness, and is demonstrated via the drift-pH relation seen in Fig. 5. Average drift rates (mV/h) are extrapolated and presented in Table I. These results are favorably comparable with reported results derived from conventional ISFETs varying from a couple of mV to tens of mV per hour.

In this letter, we have demonstrated a method for integrating chemical sensing modalities into commercially available neural probes. ITO is a compatible material with existing neural probe arrays fabrication flowcharts, commonly employed for manufacturing the electrodes. Clearly, this approach is not limited to ITO sensing membranes and could be optimized according to specific application requirements in order to transform any electrical sensing product into chemical sensor or even facilitate the deployment of both modalities on the same probe. The proposed technique can be engaged along with the current state-of-the-art in monitoring intracellular potential recordings. An indicative example would be the application with Utah electrode arrays, in which ITO deposition on the active electrode tips before parylene encapsulation would finally yield a 3-D chemical sensing array.

The fabricated sensor has been characterized with the aid of discrete devices based on the electrostatic coupling between the H$^+$ and the insulating membrane. Binding of H$^+$ to the ITO membrane in the proximity of the sensing sites introduces local capacitances and therefore enables the monitoring of the local charge densities. Experimental measurements demonstrate that the proposed chemical sensing device exhibits good chemical sensitivity, high encapsulation quality, and a significantly small drift after long-term use. We believe that the promising results of the current device pave the way for a low-cost, versatile, and easily implementable approach towards real-time intracellular recordings of single cells activity.

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![FIG. 4. (Left axis) $I_D$-$V_{GS}$ curves of device for pH 4, 7, and 10. (Right axis) Measured reference leakage currents.](image1)

![FIG. 5. Drift trends of the neural probe device under electrolytes of pH 4, 7, and 10. Markers indicate the experimental data and full lines the respective fitting (exponential) curves.](image2)

### TABLE I. Device performance summary.

<table>
<thead>
<tr>
<th>Buffer solutions</th>
<th>Output voltage$^a$ (V)</th>
<th>Drift rate$^a$ (mV/h)</th>
<th>Leakage current$^b$ (nA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 4</td>
<td>1.03 ± 0.01</td>
<td>7.67 ± 2.15</td>
<td>9.8</td>
</tr>
<tr>
<td>pH 7</td>
<td>0.94 ± 0.01</td>
<td>1.13 ± 1.01</td>
<td>5.1</td>
</tr>
<tr>
<td>pH 10</td>
<td>0.86 ± 0.02</td>
<td>13.45 ± 4.58</td>
<td>1.9</td>
</tr>
</tbody>
</table>

$^a$Average measurements over 6 channels.

$^b$Measurements at $I_D = 100$ μA.