Continuous Monitoring of pH using Ion-selective Field Effect Transistors (ISFET’s) Operating with a Fixed Bias Applied to the Reference Electrode

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Abstract: - A method for correction of threshold voltage drift in pH-sensitive ion-selective field effect transistors (ISFET’s) is presented. The proposed method allows accurate continuous monitoring of pH under clinical conditions corresponding to rapid pH changes such as those encountered in acute metabolic acidosis and cardiopulmonary bypass operations. This method, which involves monitoring the differential of drain current in the current mode of ISFET operation with a constant potential applied to the reference electrode, can also be of advantage in telemetry applications requiring low-power consumption. In the current mode the inherent device instability resulting from a drift in the threshold voltage of the ISFET manifests as a relatively slow, monotonic decrease in the measuring signal, namely the drain current. Ordinarily, over sufficiently small intervals of time the variation in the measuring signal due to drift is essentially negligible in applications where changes in pH are abrupt. Consequently, the differential of the measuring signal represents only the changes in the pH if the device sensitivity is adequately high. The validity of the proposed method is examined using a Si$_3$N$_4$-gate pH-sensitive ISFET to monitor pH variations in the 3.5-10.0 range.

Key-Words: - ISFET, pH, Drift, Instability, Continuous monitoring

1 Introduction
In 1970 the ion-selective field effect transistor (ISFET) was introduced [1] as a solid state device linking the chemical sensitivity exhibited by a membrane with the field-sensing capability of a FET. Sensor systems employing ISFETs offer such advantages as small size, robustness, and low cost over potentiometric sensors relying on conventional chemical electrode technology exemplified by the glass pH-meter. While commercially available electrodes are small enough for in vivo applications, their fragility and relatively high cost present significant disadvantages [2]. In contrast, the ISFET is manufactured based on the CMOS integrated circuit technology, which not only provides the level of miniaturization necessary for installation of ISFET-based biosensors in catheter tips, but also offers the tremendous cost advantage resulting from batch fabrication.

Biosensors commonly rely on electrochemical transduction, either in the potentiometric or in the amperometric mode, to convert a given biological interaction into an electrical signal [3]. Generally, potentiometric sensors, whose response is represented by a potential versus concentration curve, enable measurement of the potential difference between a reference electrode and a transducing electrode. The response curve associated with an amperometric sensor, on the other hand, is represented by current versus potential variations [4]. Similarly, the response curve for ISFET-based sensors can be represented either by variations of the interfacial potential or those of the drain current as a function of the concentration of the ion of interest. In the commonly employed feedback mode of ISFET operation, a constant drain current is maintained through application of negative feedback via the reference electrode, allowing measurement of a Nernstian equilibrium interfacial potential as a function of the concentration of the ion of interest. In the feedback mode is 59mV/pH at room temperature. With a constant potential applied to the reference electrode, the drain current of an H$^+$-sensitive FET operating in the triode region varies linearly with pH, and the
sensitivity is dependent on the transconductance of the FET.

Irrespective of the specific mode of operation, threshold voltage instability commonly known as drift has presented a serious impediment to commercialization of ISFET-based biosensors. Drift is characterized by a relatively slow, unidirectional temporal variation in the threshold voltage and, hence, in the drain current of ISFET in the absence of changes in the concentration of the given ion. The high accuracy required for continuous monitoring of plasma pH imposes rigorous limitations on the tolerable drift rate in pH-sensitive ISFET’s. For example, continuous monitoring of blood pH during surgery requires an accuracy of 0.02pH unit over a 10-hour period in absence of recalibration. Assuming the ISFET is operated in the feedback mode, such stability is equivalent to a maximum tolerable drift rate of 0.002pH/hour which corresponds to an interfacial potential rate of (59mV/pH)(=0.002pH/hour)=0.12mV/hour. Typically, at pH=7, the drift rate in pH ISFETs employing inorganic gate insulators is on the order of millivolts per hour following the exposure of the insulator surface to an electrolyte, whereas the long-term drift rate is on the order of tenths of a millivolt per hour following an exposure period of 12-16 hours [6]. The present state of the art in ISFET technology has yet to satisfy the stability requirements for in vivo continuous monitoring.

To date several approaches have been suggested as potential solutions to the ISFET instability problem. The proposed remedies have included: 1) storage of the device in an aqueous environment for several hours prior to use, thereby avoiding the large initial drift rates, 2) correction of the measured pH using in vitro drift data stored in a PROM (programmable Read Only Memory) [7], and 3) differential measurement using an ISFET/REFET pair in an effort to eliminate drift as a common signal between the pH-sensitive ISFET and the ion-sensitive REFET [8]. These remedies, nevertheless, have proven to be either ineffective or impractical [14]. A physical model has been presented which provides an accurate, quantitative description of the drift behavior in Si$_3$N$_4$-gate and Al$_2$O$_3$-gate pH-ISFET’ s [9], [10]. This model has furnished useful insight into the mechanism of drift, leading to the development of the method for correction of drift reviewed in this work. This method has been verified using a pH-sensitive Si$_3$N$_4$-gate ISFET operating with a constant bias applied to the reference electrode to monitor a wide pH range. A discussion of the advantages and disadvantages associated with the given mode of ISFET operation in relation to the proposed corrective scheme is also provided.

2 Analytical Correction of Drift

Formulation of the proposed analytical method described elsewhere [15] will be outlined here in order to facilitate description of experimental results given below. In general for a biosensor suffering from drift the differential of the measuring signal (output of the transducer), $dM$, can be written as.

$$dM = dM_a + dM_{drift}$$

where $dM_a$ and $dM_{drift}$ represent the differential of the measuring signal arising from the changes in the analyte concentration and drift respectively, and are given by

$$dM_a = \frac{\partial M}{\partial a} \cdot da$$

and

$$dM_{drift} = \frac{\partial M}{\partial t} \cdot dt$$

For a biosensor with a relatively high sensitivity, over sufficiently small intervals of time, $(\Delta t \rightarrow dt)$, the variation in the measuring signal arising from drift will be small compared to that resulting from changes in the analyte concentration, if the drift rate, $\partial M/\partial t$, is negligible compared to the rate of change of the analyte concentration, $da/dt$. That is, if

$$\frac{\partial M}{\partial t} \ll \frac{\partial M}{\partial a} \cdot \frac{da}{dt}$$

then

$$dM \cong dM_a$$

This formulation can be applied to a pH-sensitive ISFET operating with a constant potential applied to its gate (reference) electrode. In this mode of operation constant voltages $V_{DS}$ and $V_{GS}$ are applied to the reference electrode and the drain electrode of the ISFET respectively, and the source electrode is maintained at the ground potential. If the ISFET is biased in the triode region of operation, the drain-to-source current, $I_{DS}$, will vary linearly with pH according to the following equations [9]:

$$\frac{\partial I_{DS}}{\partial pH} = \frac{\partial I_{DS}(lin)}{\partial \psi_0} \cdot \frac{\partial \psi_0}{\partial pH} = g_m(lin) \cdot \frac{\partial \psi_0}{\partial pH}$$

(6)

$$\frac{\partial \psi_0}{\partial pH} = -ln(10) \cdot \frac{kT}{q} = -2.30 \cdot \frac{kT}{q}$$

(7)

$$g_m(lin) = \mu C_{ox} \frac{W}{L} V_{DS}$$

(8)

In equations (6) through (8), $\psi_0$ represents the pH-dependent interfacial potential, $I_{DS}(lin)$ and $g_m(lin)$ are the drain current and the transconductance of the ISFET in the triode region of operation respectively and $k$, $T$, and $q$ represent the Boltzmann constant, the absolute temperature, and the charge of an electron.
respectively; \( \mu \) is the surface mobility of electrons (n-channel ISFET) or holes (p-channel ISFET), \( C_{ins} \) is the gate insulator capacitance, and finally \( W \) and \( L \) are the width and the length of the FET channel respectively. The method for correction of drift formulated above can be applied to a pH-sensitive ISFET operating with a constant potential applied to the reference electrode, if the drift rate is small compared to the product of the device sensitivity and the rate of pH change. That is, we must have:

\[
\frac{\partial I_{DS}}{\partial t} \ll \frac{\partial I_{DS}}{\partial pH} \cdot \frac{dpH}{dt} \quad (9)
\]

3 Mode of ISFET Operation

As noted above, according to equation (4), the validity of the proposed method requires that the product of device sensitivity and the rate of change in analyte concentration be considerably larger than the drift rate. It has been shown that, at a given instance of time following exposure of ISFET to an electrolyte, the two modes of ISFET operation are in principle equivalent to one another as far as detection of concentration changes in presence of drift is concerned [14]. In particular, for a given operating point, in both modes of operation the signal-to-drift ratio, \( S/D \), is given by [14]

\[
S/D = \left\{ -2.30 \frac{kT}{q} \left[ \frac{1}{(\partial V_{TH} / \partial t)} \right] \right\} \left[ \frac{dpH}{dt} \right] \quad (10)
\]

where \( V_{TH} \) denotes the threshold voltage of the ISFET.

4 Experimental Verification

The proposed method for correction of drift was verified using an n-channel Si\(_3\)N\(_4\)-gate pH-sensitive ISFET to monitor pH values in the 3.5-10.0 range. The ISFET had been fabricated according to a standard metal gate, p-well CMOS process [9]. Prior to use in the experiment, the drift behavior of the ISFET had been characterized at pH=7. The typical ISFET drift characteristics at pH=10 had also been examined previously, although the device used to examine the correction method had only been exposed to pH=7 prior to the experiment. Room temperature drift and pH response measurements were performed with a constant potential applied to the reference electrode. In all measurements the ISFET’s were biased in the triode region with \( V_{GS}=2.1V \), and \( V_{DS}=0.2V \). Solutions with pH values of 3.5, 5.4, 7.0, 9.0, and 10.0 were obtained by adding 1M HCl or 1M KOH to a solution with 0.05M phosphate monobasic and 0.142M KCl concentrations. pH values were measured using the a Corning semi-microcombination pH probe and the Orion Research\textsuperscript{TM} 601A pH meter with an accuracy of 0.01pH unit. A 0.142M concentration of KCl was used for the baseline solution in order to approximate plasma electrolyte concentration. However, K\(^+\) was used instead of Na\(^+\), since Si\(_3\)N\(_4\)-gate pH-sensitive ISFET’s are known to be sensitive to Na\(^+\) ions [11]. Addition of KOH altered the final osmolarity of K\(^+\) by approximately 50mOsm.

The ISFET was calibrated using the five pH values indicated above, and the calibration curve was constructed using the average of five measured drain current values at each pH. The device sensitivity (change in the triode drain current per unit change in pH) was determined based on linear regression. Five beakers were prepared each of which contained one of the solutions with the given pH value. Following device calibration, the ISFET was arbitrarily exposed to each of the solutions for various time intervals. The resulting pH response was monitored by measuring the drain current at 30-second intervals. To estimate the change in the pH value the difference between the drain current immediately prior to transfer of the ISFET from the given solution and the drain current measured after transfer to the new solution was determined. The magnitude of the drain current difference divided by the measured device sensitivity represented the change in pH value. During the transfer the ISFET and the reference electrode were manually placed in the new solution with a maximum time delay of 30 seconds. No stirring was performed following transfer of the device to the new solution.

5 Results

The drift characteristics corresponding to pH=7 for the Si\(_3\)N\(_4\)-gate pH-sensitive ISFET used in the experimental verification of the proposed method is given in Fig.1. The instantaneous drift rates following 6 hours of exposure to the solution at pH=7 and pH=10 were 0.0975\(\mu\)A/hour and 0.0648\(\mu\)A/hour respectively. A relatively large initial drift was observed at pH=10, although the given device had been previously exposed to the pH=7 solution for 12 hours. The sensitivity of the device was determined to be -4.234\(\mu\)A/pH at room temperature. The standard error was 0.0670\(\mu\)A, and the 95\% confidence interval was characterized by a 0.0125 standard deviation in the sensitivity. The pH response of the ISFET is shown in Fig.2. The pH transitions corresponded to abrupt changes in the
drain current, and the spikes are due to erroneous initial readings obtained immediately following the introduction of the ISFET and reference electrode into the new solution. The pH transitions along with the measured changes in the pH determined using the ISFET are given in chronological order in Table 1.

![Fig. 1. Si$_3$N$_4$-gate pH- ISFET Drift Characteristics, pH=7](image1)

![Fig. 2. pH Response of the Si$_3$N$_4$-gate pH- ISFET](image2)

### 6 Discussion

The experimental procedure undertaken in this work to verify the proposed method for correction of drift demonstrated that drift exhibited by pH-sensitive ISFET’s can be corrected by monitoring the measuring signal over sufficiently small intervals of time. In particular, as indicated in Table 1, with the exception of large step changes in pH (i.e. |$\Delta$P| $\geq$ 3) and the 9.0 $\rightarrow$ 10.0 pH transition, the accuracy of the estimated change in pH is within $\pm$ 0.1 pH unit of the values of change predicted by the pH meter. The inaccuracies in estimation of large step changes in pH are due to errors resulting from the hysteresis phenomenon, which occurs when the pH is ramped up and down [6],[12].

![Table 1. Estimated pH Changes based on the Proposed Correction Method](image3)

The inaccuracy associated with the 9.0 $\rightarrow$ 10.0 pH transition, on the other hand, is due to the large initial drift following exposure to high pH values, which occurs irrespective of the drift history at lower pH values. For operation in the feedback mode the equivalent sensitivity of the pH-sensitive ISFET used in the experiment was 42.7mV/pH at room temperature. Such a sub-Nernstian response may be expected in Si$_3$N$_4$-gate pH-sensitive ISFET’s, unless the nitride surface is briefly etched in 50:1 H$_2$O:HF solution prior to use [13]. Since a relatively high sensitivity is a prerequisite to the application of the correction method described, the ISFET was operated with a constant bias applied to the reference electrode. Given the measured drift rate of 0.0975 $\mu$A/hour at pH=7, for the given device sensitivity of -4.234 $\mu$A/pH the validity criterion expressed by equation (9) would be satisfied in an application such as cardiac surgery [7], where the pH changes of several tenths of pH unit can occur in a matter of minutes. Use of the device with a constant potential applied to the reference electrode, however, introduces additional errors, since the sensitivity given by equations (6)-(8) is proportional to the gate insulator capacitance, whose variation with time has been identified as the origin of the threshold voltage drift [9],[10]. Errors resulting from variations of sensitivity with temperature, however, were negligible, since the temperature of the laboratory was tightly controlled.
7 Conclusion

A method for correction of threshold voltage drift in pH-sensitive ISFET's was presented. This method was shown to be effective when large step changes in pH exceeding three units are not involved and/or the pH dependence of drift is unimportant. The proposed method, therefore, is promising for applications such as continuous monitoring of blood pH, where changes in pH are within physiological limits. This method is also expected to be of advantage in low-power applications such as telemetry.

References: