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Quantitative Measurement of Sweat as a Diagnostic

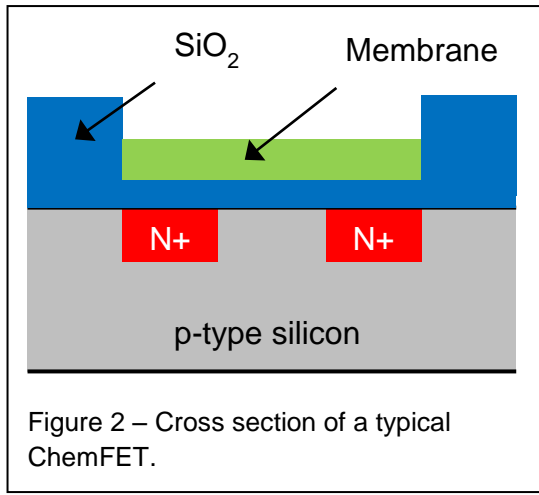
Abstract

The metal oxide field-effect transistor (MOSFET) structure is exploited to create a precise chemical sensor able to track the concentration of selected analytes in sweat droplets. A membrane similar to the cell wall allows transport of Na^+ ions to the gate insulator, inducing a change in threshold voltage measurable as a current between the drain and source. This can be used to detect the presence/concentration of Na^+ . Membranes with a variety of desirable characteristics, including durability, sensitivity, selectivity, thickness and uniformity were manufactured. This paper is mainly concerned with methods to improve the thickness and uniformity of these membranes

Introduction

Over the last 30 years much research has been done investigating the potential of chemically sensitive field-effect transistors, or CHEMFETS, as potential chemical sensors [3]. Advantages include miniaturization, low-cost production, and straight-forward integration into modern electronics [3]. To this end we have created a CHEMFET to detect the presence and concentration of Na^+ in sweat. A CHEMFET is essentially a metal-oxide-semiconductor field-effect transistor (MOSFET) with the gate metal removed and replaced with an ion-selective membrane. The ion-selective membrane replaces the function of the gate metal. When a known voltage is applied to the surface of the membrane, the selected analyte forms a concentration gradient within the membrane. This concentration gradient in turn modulates the charge carrier density between the source and drain, changing the 'threshold voltage' at which a current from drain to source occurs. The threshold voltage can then be used to

determine the concentration of the ion. A schematic of the structure of the CHEMFET can be found in figure 1.



The membranes constructed consisted of 2 layers, an ion-selective layer made with plasticized PVC infused with a sodium-selective ionophore and a poly(hydroxyethylmethacrylate) (POLYHEMA) hydrogel inner layer. The POLYHEMA hydrogel layer was introduced to resolve many issues identified by Haak et al. in [1] and [4]. The poor

bonding between the hydrophobic ionophore layer and the hydrophilic SiO_2 gate leads to the membrane becoming easily detached. It is also known that water can penetrate the ionophore layer and can seep underneath the layer, contributing to this detachment and limiting lifespan [1]. Additionally, a problem with PVC as the membrane is the penetration of CO_2 and subsequent interaction with SiOH surface groups on the gate surface, interfering with the surface potential and adversely affecting response [1], [4]. Also, the SiOH groups are amphoteric and surface potential can be strongly affected by pH [1]. Finally, it is claimed that the ionophore-gate interface lacks a common charge carrier species, and thus the surface potential is not thermodynamically defined in terms of an equilibrium interaction, leading to chaotic surface potentials [1].

The introduction of the POLYHEMA layer pre-treated with the selected analyte allows for a common charge carrier species between the two membranes, and the surface potential is subsequently defined through the equilibrium of this interaction. The presence of hydroxyethyl functional groups allows the ionophore to be covalently bonded with the POLYHEMA layer, and silylation of the gate oxide with methacryloxypropyltrimethoxysilane (MPTS) covers the gate with methacryl groups, allowing the POLYHEMA to be covalently bonded to the oxide surface [1]. Elimination of CO_2 interference was observed for this membrane after covalent attachment, as well as a general increase in the durability of the sensor [1]. The silylation of the SiOH surface groups also reduces the pH sensitivity of the device [1].

Procedure

MOSFETS with a missing metal gate were manufactured in-house. The devices were then encapsulated with epoxy resin with the source, drain, and gate region left open. This

allows the membrane to be draped across the gap without short-circuiting the channel from source to drain. The surface of the devices were then silyated according to the procedure in [1] and [2]. The devices were submerged in a mixture of 22.5 ml Tuolene, 2.5 ml MPTS, and 1% v/v deionized water and placed on a hot plate at 30^o C for 4 hours. The devices were then submerged in Butanone and washed by sonication for 15 minutes, then left overnight to dry. For the deposition of POLYHEMA several protocols were used. The basic protocol was as outlined by Brunink et al. in [4]. POLYHEMA solution was prepared by dissolving POLYHEMA crystals in 95% ethanol to a concentration of 12 mg/ml, then drop-casted on the surface of the device and allowed to dry overnight. However, we questioned whether drop-casting was suitable for our purposes, as it produces a membrane of non-uniform thickness. The thickness observed using this method was between 5-10 microns. Thus, spin-casting was done in an attempt to create a uniform POLYHEMA layer. For ease of measurement, this was done on blank wafer of SiO₂. POLYHEMA at 12 mg/ml was spun at speeds of 500, 1000, and 2000 rpm for 40 seconds. The POLYHEMA was filtered with either 0.2 or 0.45 μm filter to prevent agglomerates from creating streaks in the membranes. Membrane thickness was measured using an ellipsometer and a profilometer. Thicknesses between 0.9-1.9 μm were observed. However, at 500 RPM the POLYHEMA evaporated prior to the formation of a uniform layer, leading to chaotic patterns. As 1/10 μm was already deemed too thin, 1000 rpm was used. To increase the thickness POLYHEMA was made at concentrations of 15 and 18 mg/ml, and the 12 mg/ml was allowed to evaporate for several days, settling at 13.6 mg/ml. Membrane thickness for these can be seen in table 1. The 18 mg/ml could only be completely dissolved by heating the solution to 40^o C and sonicating. However, when the solution cooled the POLYHEMA would condense out and the mixture would become cloudy, which would subsequently clog the filter. Filtering prior to the mixture cooling simply delayed this result, as sufficient cooling happens during spinning, leading to visible agglomerate streaking after spin-casting. Multiple applications and spins were also attempted in an effort to increase membrane thickness, with each application adding ~.02 μm for the first few layers, however after the 3rd layer fairly negligible amounts were deposited. With 4 layers a membrane thickness of ≈.17 μm was achieved using a POLYHEMA mixture of 15 mg/ml.

POLYHEMA density	Membrane Thickness (μm)
12 mg/ml	0.1
13.6 mg/ml	0.12
15 mg/ml	0.14
15 mg/ml 2nd layer	0.16
15 mg/ml 3rd layer	0.16
15 mg/ml 4th layer	0.17

Table 1.

Some unfiltered membranes were also spun cast to gauge the effect of filtering on membrane thickness. A thickness of $.11\ \mu\text{m}$ was measured from a mixture of 12 mg/ml using the ellipsometer, which indicates that filtration did not significantly impact membrane thickness.

The POLYHEMA layer was finally treated with 0.1M NaCl solution for four hours to ensure a common charge carrier species and molarity with the analyte. Then the ionophore layer was made using the method described in [3]. 33mg Polyvinyl chloride (PVC) and 2mg synthetic sodium ionophore are plasticized in 65 mg dioctyl sebacate (DOS) and 1 ml tetrahydrofuran (THF). The ionophore was then drop cast onto the POLYHEMA layer. Spin casting was also attempted with the ionophore layer. Measurement with the ellipsometer indicated a layer of $4.2\ \mu\text{m}$, though confirmation with the profilometer is still needed to ensure uniformity and confirm thickness. All measurements using the profilometer were done by scratching the surface with a razor blade and measuring the depth.

An additional consideration was measuring the changing threshold voltage with time while the membrane is in contact with the analyte solution. This introduces difficulty due to the conductivity of NaCl. Previously this had been attempted by submerging the top of the CHEMFET in analyte while leaving to source and drain open. However, shorts were still difficult to avoid. To solve this problem a can of superhydrophobic spray NeverWet[®] was applied in two thin strips on either side of the membrane region. A sodium water droplet could then be applied to the membrane without danger of short-circuit. The application was done by spray, using the instructions on the can. A mask would be ideal, and a pattern was attempted using photolithography techniques to remove unnecessary hydrophobic spray, but it was ultimately unsuccessful. The hydrophobic coating was tolerant of the developer, but there was another issue (you'll have to ask Jun Young). However, it was successfully applied by using two glass slides pressed close together with a narrow gap in between. Two lines of superhydrophobic were then sprayed and deposited on either side of the sensing region, and a sodium water droplet was successfully suspended over the region without interfering with the source or drain.

Conclusion

Despite some progress towards full fabrication and testing of a device that fits our specifications, much work still needs to be done. Several avenues were explored to improve POLYHEMA layer uniformity and thickness. Unfortunately, none of the strategies used significantly increased membrane thickness. It is, however, unclear as to how strongly this will affect device performance. In Janata's paper [3] it is questioned whether the POLYHEMA layer is necessary at all. He states that the original membrane-gate interface is already

thermodynamically defined, eliminating one of its main motivations. He also states that even small differences between the molarity of the analyte and the molarity of the POLYHEMA pre-treatment result in the transport of water across the membrane and subsequent damage or destruction of device [5]. However, there were several improvements in device performance reported Haak et al. in [1] attributed to the POLYHEMA layer. Still, the concern regarding the transport of water across the membrane, if valid, pose some serious limitations on the device, as ion concentration in the analyte is something we would like to measure and hence would not be pre-determined. Additionally, the covalent attachments of the ionophore to the POLYHEMA layer and the POLYHEMA layer to the gate oxide described in [1],[4] were done with photopolymerization. In the case of POLYHEMA, the HEMA monomer was polymerized into POLYHEMA in situ at the same time covalent bonding occurred, and it should be confirmed that covalent anchoring still occurs without photopolymerization.

References

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