Ion sensitive Field Effect Transistors (ISFETs)
Basics and Applications

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Abstract
Microfabricated semiconductor devices are essential components of many biochemical sensors today, and show great potential for advanced devices in the future. Since the proposal of an pH sensitive device, based on the technology of field effect transistors, was made in the early seventies, these so called ISFETs have been of great interest for the application in chemical and biological sensing devices. In this report, the physical and technical basics of these systems are discussed. Starting with the introduction of MOSFETs and their operation, ion sensitivity of the oxide surface is explained by the application of the site binding model. To give an overview about recent and future applications of ISFETs for sensing and physiological measurements, modified ISFETs (ENFETs, BIOFETs, DNA-sensors) as well as sensor/actuator systems are presented. Modern research is also focusing on the application of new materials. In particular, wide bandgap semiconductors like diamond and GaN show interesting properties, with respect to biochemical sensing devices.

Introduction
Most ion sensors are potentiometric sensors, which means that the electrical potential difference $\Delta \phi$, at a solid/liquid interface as a function of the ion concentration, is measured. This is always according the Nernst equation:

$$\Delta \phi = \frac{RT}{F} \ln \frac{a_{i1}}{a_{i2}}$$

Here R is the gas constant, T the absolute temperature (K) and F the Faraday constant. Ion concentrations $c_i$ are noted in terms of activities $a_i = f_i c_i$, with $f_i$ being the activity coefficient. A typical pH electrode (slide 3, fig.1) consist of two electrodes, one in contact with the inner solution of constant concentration, the other in contact with the outer solution via a permeable membrane. This arrangement forms an electrochemical couple, whose potential difference $\Delta \phi$ is sensitive to a change in the concentration of the outer solution, since the potential drop across the inner solution is constant. [1], [3]

Although these basic devices are working well for standard pH measurements, they are not eligible for in vivo measurements, since with increasing miniaturization of these devices, they become less stable. In 1970, Bergveld proposed an ion sensitive solid state device, based on the operation of a field effect transistor, for physiological measurements, which has been the very first ISFET. [1],[2]

MOSFET

To explain the operation of an ISFET, it is very useful, to consider the basics of MOSFETs, since both devices are working due to the same principles.

If you apply a certain Voltage $V_G$ at the gate of a simple metal – oxide – semiconductor (MOS) system (sl.6, fig.1), the system behaves similar to a common capacitor, since the oxide
is an insulator, and surface charges are induced at the metal/oxide and oxide/semiconductor interfaces. These surface charges are inducing an electric field across the oxide, the so called “field effect”. The poisson equation of that charge distribution can be solved with the boundary conditions: 1) the electric field is vanishing inside the semiconductor, 2) the electric field is proportional to the induced surface charge, which is comparable to the situation in a capacitor. Calculations are leading to a modified potential landscape close to the oxide / semiconductor interface. The surface charges are inducing a “bending” of the valance- as well as the conduction band of the semiconductor (sl.7). The strength as well as the direction of this band bending depends on the surface charges, the applied $V_G$ and the doping of the semiconductor material, so that several cases have to be distinguished (for p-doped silicon).

If you apply a small, negative $V_G$, the Fermi-Level in the metal is rising, and the bands in the silicon become upward bended (sl.8, fig.1). Similar to the situation in a capacitor, negative charges are accumulating at the metal/oxide interface, whereas holes, the majority charge carriers in the p-dopes silicon, are accumulating at the oxide/semiconductor interface. In the reverse case, a low, positive applied gate voltage $V_G$ is leading to a downward band bending (sl.8,fig2). Now, the positive surface charge at the metal /oxide detracts the holes in the semiconductor, close to the interface. These holes are escaping into the bulk semiconductor, and a negative space charge, due to the neagtive charged, fixed acceptor atoms, is remaining. Thus we have a depletion zone of majority carriers near the oxide/semiconductor interface, which is acting as an insulating layer. If $V_G$ is increasing above a certain threshold value $V_{Th}$, the downward bending becomes that strong, that the Fermi-Level is getting closer to the conduction band than to the valence band. In this case, the number of electrons in the conduction band exceeds the number of holes in the valence band, which is leading to an accumulation of electrons at the semiconductor /oxide interface (“Inversion”). This inversion is the main mechanism, that enables the operation of a MOSFET. The inversion channel serves as a conducting channel between drain and source, and hence, by applying a positive drain voltage $V_D$ and connecting the source to the ground, a drain current $I_D$ can be generated. For drain voltages $V_D < V_G - V_T$ (“Pinch-Off”), the length of the inversion channel reduces with a further increase of $V_D$. Thus, due to the enhanced resistance of the inversion channel, the current $I_D$ is no longer rising and finally, it reaches a saturation value. [3],[9]

**ISFET**

The basic idea of an ISFET is to remove the metal gate electrode from a MOSFET, and to expose the oxide directly to an electrolyte, whose concentration of certain ions is wished to be determined. Instead of the fixed gate, a reference potential $V_{Ref}$ is applied to the electrolyte – oxide – semiconductor system via a reference electrode, which is dipped into the electrolyte (sl.17). [3]

The response mechanism to changes in ion concentrations of such a system has been discussed among researchers for several years. The diffusion of ion species through the oxide is a quite slow process, and can therefore be neglected for quick responses. However, effects observed on longer time scales, like the change in the drain current $I_D$ with time (“current drift”), can depend on diffusion through the oxide. But the main effect, that enables the measurement of ion concentrations with that device, is the influence of ion concentration on the potential drop at the electrolyte-oxide interface.

The following phases and interfaces are contributing to the total potential drop across the system: i) the drop across the solution $\psi_o$, with the diffuse layer, the outer as well as the inner Helmholtz plane, ii) the drop across the electrolyte-oxide interface, due to surface dipoles, iii) the drop across the oxide layer (s. capacitor), iv) the drop across the oxide semiconductor...
interface and v) the drop across the bulk semiconductor (sl.19). In good approximation, these potential drops are independent from any change of ion concentration, excepted $\psi_o$, which can be identified with the surface potential of the oxide layer (on the side of the electrolyte). Now, it becomes clear, that, with a constant $V_{Ref}$, the potential drop across the oxide-semiconductor-system (the former $V_G$) is changing with changing $\psi_o$, which leads to a relation between $V_G$ and the ion concentration. This results in an ion sensitivity of the drain current $I_D$. (In fact, it is also usual, to keep $I_D$ constant, and to measure instead the change in $V_{Ref}$).

The influence of the ion concentration on $\psi_o$ can be explained by applying the Site-Binding model (in the case of pH – sensitivity), which was introduced by Yates et al. in 1983. It proposes, that atoms in the surface layer of metal- as well as semiconductor oxides are acting as amphoteres, when they are in contact with an electrolyte. That means, that they can release protons into the electrolyte (“Donors”) an thus get negatively charged, form neutral OH sites and bind protons from the electrolyte (“Acceptors”), resulting in a negative surface charge (sl.21).

$$M - OH \leftrightarrow M - O^- + H^+ \quad \text{Donor}$$

$$M - OH + H^+ \leftrightarrow M + OH_2^+ \quad \text{Acceptor}$$

These surface reactions depend on the acidity and the basicity constant of the oxide groups, as well as the concentration of $H^+$ in the electrolyte. In the case of a high concentration of $H^+$ (low pH), the M-OH groups are rather tending to accept a proton, instead of releasing one, and thus most of them are acting as acceptors, and the oxide surface becomes positively charged. In contrast, if the concentration of $H^+$ is low (high pH), most of the M-OH groups release a proton, and the surface charge is getting negative. To determine the total change in surface charge, the sum over all surface sites $N_s$ has to be considered, which depends on the material (e.g. $N_s$(SiO$_2$) $\sim 5 \cdot 10^{14}$ cm$^{-2}$, $N_s$(Al$_2$O$_3$) $\sim 8 \cdot 10^{14}$ cm$^{-2}$). These changes in surface charge, due to the change of pH in the electrolyte, directly affect the surface potential $\psi_o$. Together with the resuts, mentioned above, we get a relation between the gate voltage $V_G$ and the pH of the electrolyte (sl.29):

$$\psi_o(pH) \rightarrow V_G(\psi_o) = V_G(pH)$$

With this relation, the pH of an electrolyte can be measured via the measurement of $I_D$ ( in case of constant $V_{Ref}$) or $V_{Ref}$ ( in case of constant $I_D$). The sensitivity factor $\beta$ ($[\beta] = mV$/pH) describes the resulting response of the ISFET to a change in the pH of the electrolyte. This factor depends among others on the total number of surface sites, and thus is specific for the used material (sl.26, 27).[[1],[2],[3],[4]]

**ENFET**

Besides basic devices for simple pH measurements, ISFETs can also be modified to enable sensing of certain biochemical substrates. Therefore, the oxide surface has to be functionalized. One option to perform this functionalisation is to deposit polymeric membranes on top of the gate oxide, which can serve as a matrix for the immobilisation of enzymes. The mechanism of immobilisation in this matrix can be pure physical, like the entrapment in the polymeric network, as well as the formation of chemical bonds to multifunctional agents or the oxide surface (sl.30).

One example of these enzyme modified ISFETs (“ENFETs”) is a device for measurements of glucose concentration (sl.31). The enzyme glucose oxidase is immobilised on the oxide surface, and enables the oxidation of glucose to gluconic acid:
Glucose + O₂ + H₂O → Gluconic acid + H⁺ + H₂O₂

Glucose oxidase

Besides the gluconic acid and the hydrogen peroxide, H⁺ is generated during this reaction. The production of H⁺ correlates with the consumption of glucose, which is depending on the concentration of glucose. Thus the electrode-oxide-semiconductor system, which is sensitive to this change in pH in the solution, is able to sense the concentration of glucose in the solution. In conclusion, ENFETs are working like ISFETs, just exploiting the well known reaction of the enzyme with the substrate, to enable an indirect measurement of its concentration. [1], [2], [3]

**Sensor/actuator systems**

The devices proposed in the previous sections are able to measure the concentration of specific ions in an electrolyte. To carry out not only the measurement of the concentration of certain ions, but to allow the control of this concentration, sensors have to be coupled to actuators. In the case of pH control, an actuator has to be able to generate H⁺ or OH⁻ ions, depending on the sensor’s output. Coulometric generation of these ions can be performed by electrochemical reactions at additional electrodes. The stochiometry of the reaction has to be known very well, and occurring side reactions have to be diminished.

The implementation of such a sensor/actuator system can be achieved with modified ENFETs, with additional generating platinum electrodes fixed on top of the enzyme layer (sl.33). The application of sensor/actuator systems with ENFETs is of great importance, since the enzyme sensitivity, and thus the sensitivity of the whole device is strongly depending on the sample’s pH. As discussed above, the enzyme supports the reaction of the substrate, which is leading to the generation of H⁺ or OH⁻, and therefore to a change in pH. Thus, the measurement of the substrate concentration itself induces a change in pH and thus a change in substrate sensitivity. Accordingly, the response of an ENFET without pH control is very nonlinear (sl.36, fig.13). Such a sensor/actuator system can be achieved with the combination of an modified ENFET, as mentioned above, with a reference ISFET (sl.36, fig.12). The ISFET is measuring the “background” pH of the solution, which has been established at the desired value for ideal enzyme sensitivity. The modified ENFET is measuring the local change of pH, due to the enzyme induced reaction of the substrate. The output voltages of both devices are transmitted into a differential amplifier. The difference between both voltages, which is an indicator for the difference between the initial pH and the changed pH due to the enzyme reaction, can be transformed into an according current via a controller. This current is used for coulometric generation of H⁺/OH⁻, to turn the pH back to its initial value. With such a feedback system, a constant enzyme sensitivity and thus a linear response of an ENFET can be achieved (sl.36, fig.13). [2],[3]

**BIOFET**

Instead of enzymes, other biological systems can be coupled to an ISFET. Such a BIOFET then exploits the interaction with a biological system for sensing special biochemical substances.

The transport of information in biological systems is working with the generation of membrane potentials. In the cell membrane, there are special ion channels embedded, which
allow ion transfer from the inner volume of the cell to the outer solution. By opening the
canals, which allow a quick transition of the specific ions, the ion concentrations of the
inner and outer solution get changed, resulting in an induced potential step $U_{\text{membrane}}$
(“Depolarisation”). When the channels, which allow a slow transition of ions, are opened, the
ion exchange takes longer, and finally, the initial concentrations can be achieved
(“Repolarisation”) (sl.37).
One example for successful biological sensing systems are the antennas of insects (sl.38). The
sensing hairs get into contact with the surrounding air, and molecules of the specific substance
are diffusing into the outer membrane (cuticula). Now, these molecules are binding to special
proteins, which can open ion channels in the cell membrane. Note, that these ion channels
have special receptors to ensure, that only proteins, which are bound to the seeked molecules,
can open these channels. This is leading to a potential drop along the sensing hairs, and since
all the sensing hairs are allocated in one direction, a total potential drop along the whole
antenna can be measured, which is depending on the substance’s concentration in the air. This
potential drop can be used for really exotic sensing devices. For instance, one option is to fix
a whole beetle on top of a FET (“Whole beetle device”). The antenna is dipped into an
electrolyte, to ensure a conducting linkage to the oxide surface of the FET. Changes in
antenna potential are affecting the applied gate voltage, which can be measured. Another,
maybe less cruel setup is to bring an isolated insect antenna in contact with two electrolytes,
one in touch with the oxide layer, the other one in contact with a reference electrode, to apply
a reference voltage (“Isolated antenna device”). In both cases, substrate concentrations can be
measured, and possible applications are fire detection in woods (with the Phaenops cyanea),
or detection of insects in agriculture (with the potato beetle Leptinotarsa decemlineata). [5]

DNA – Sensor

The sensitivity of ISFETs to surface charges, can be exploited for DNA sensing devices. It is
wellknown, that DNA posseses an intrinsnic negativ charge at its sugarphosphate backbone.
Via special treatment of the oxide layer of a FET, it can be achieved, that probe DNA gets
bound to the oxide surface. If this surface is now exposed to a solution which includes the
complementary DNA, this complementary DNA will bind to the fixed target DNA and thus
lead to a change in surface charge (sl.41, left fig.). But if the surface is exposed to a solution
with any other DNA, excepted the complementary DNA, nothing will occur, since the DNA
strands cannot get bound to the fixed DNA at the surface (s.41, right fig.).
The change in surface charge is leading to a change in the surface potential, which can be
measured. By the combination of several, surface treated FETs, with one kind of DNA
mounted on top of one of them, a whole DNA-array can be established, which is essential for
many kind of measurements in pharmacological or biochemical research. [3]

New Materials

There are several advantages of wide-bandgap semiconducting materials with respect to
advanced sensing devices. At first, the generation of unwanted charge carriers by optical or
thermal excitation is strongly depressed, due to the large bandgap. Furthermore, these atoms
form strong chemical bondings to its neighbors in the crystal grid, resulting in a strong
mechanical and thermal stability of these materials.
**GaN**

GaN is a wide bandgap semiconductor, essential for many optoelectronic devices. A typical feature of a AlGaN / GaN heterostructure (sl. 43) is the formation of a 2 dimensional electron gas near the AlGaN / GaN interface. Due to the strong electronegativity of nitrogen, dipolemoments are induced along the Ga – N as well as the Al – N bondings. But Al and Ga are possessing different electronegativities, leading to a change in the macroscopic polarisation at the AlGaN / GaN interface. In fact the macroscopic polarisation in AlGaN is larger than in GaN, \( P_{\text{AlGaN}} > P_{\text{GaN}} \). From electrostatics it is wellknown that a polarisation \( P \) is equivalent to a surface charge \( \sigma \) with opposite sign at the two interfaces perpendicular to the vector \( P \). Thus we obtain a negative surface charge \(-\sigma\) at the surface of the AlGaN, and a positive surface charge \(+\sigma\) at the AlGaN / GaN interface (sl.44). The positive charge at the interface is leading to a strong down bending of the bands in the GaN. As typical for an n-doped semiconductor, the fermi level is slightly below the conduction band, and thus, the down bending induces an accumulation of electrons near the AlGaN / GaN interface. These electrons are very well confined, since the insulating AlGaN seperates the electrons from the surface ( 2-dimensional electron gas (2DEG)). This 2DEG is very sensitive to the adsorption of ions at the AlGaN surface. If a positive ion \( X^+ \) is getting absorbed at the surface and thus is changing the surface charge, a further electron will join the 2DEG, which enlarges its conductivity (reverse in case of \( X^- \)).

ISFETs, based on GaN, show a high sensitivity. The pH sensitivity is almost reaching the ideal Nernstian Response. The high sensitivity as well as the biocompatibility of this material, offers great potential for the development of further devices for biochemical sensing.[7],[8]

**Diamond**

P- doped diamond is another wide bandgap semiconductor, which seems to be eligible for biochemical sensing, since diamond offers a very good biocompatibility. The usage of diamond for sensors is based on its surface conductivity. At a diamond surface, the dangling bonds of the atoms in the surface layer can be terminated with oxygen atoms, or with hydrogen atoms, depending on the treatment of the surface. At any surface, exposed to the air, a spontaneously formation of a thin water layer ocures (sl.49). The following redox reaction is taking place:

\[
2 \text{H}_3\text{O}^+ + 2 e^- \leftrightarrow \text{H}_2 + 2 \text{H}_2\text{O}
\]

As long as the electrochemical potential \( \mu_e \) of the electrons in the water is smaller, than the fermi level \( E_F \) in the diamond, electrons are transferring from the diamond into the liquid, until \( \mu_e \) is equal to \( E_F \). This is leading to an accumulation of holes near the diamond surface, and thus, to a conductivity of the diamond surface.

However, H-terminated diamond surfaces are not showing any sensitivity to the pH of the water layer (although Kawarada reported of a sensitivity to anions [6]). By special ozon treatment of the surface, O-termination can be achieved (sl.50). In this case, the C-OH sites show an amphoteric behaviour, wich is leading to a \( \text{pH} \)-sensitivity of O-terminated surfaces (s. Site Binding Model, p.3). To enable a measurement of \( \text{pH} \) of an electrolyte, you have to bring O-terminated regions in direct contact to H-terminated ones. When the \( \text{pH} \) of the electrolyte is high, most of the terminated sites are serving as acceptors, resulting in a positive surface charge, and reverse in case of low \( \text{pH} \). This change in surface charge affects the accumulation of holes at the H-terminated surfaces (sl.52), and thus the conductivity of the diamond surface, which can be measured. [5]
**Conclusion**

ISFETs are the basis of many biochemical sensing devices. Due to the highly developed CMOS technology, the miniaturisation of ISFETs as well as the implementation of highly integrated circuits for biochemical sensing can be achieved today. However, the great commercial breakthrough has not occurred so far. Reasons for the missing success are the problem of miniaturisation of the needed reference electrodes, as well as the, still not understood problem of current drift, which is inhibiting exact measurements on longer time scales. Furthermore, the exposure of these devices to corrosive electrolytes shortens their lifetime, so improved passivation of the surfaces has to be developed.

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**References**


