Chemical and biological sensors using polycrystalline silicon TFTs

Pedro Estrela* and Piero Migliorato

Over the past three decades effort has been devoted to exploit the field effect mechanism in chemical and biological sensors, due to the potential of these devices to provide large arrays of sensors that are label-free, low-cost, disposable and can be easily integrated in portable instrumentation. Most of this work concerned the development of Ion-Sensitive Field-Effect Transistors. More recently, field-effect devices have been investigated for the detection of DNA hybridization and protein interactions. Of particular interest is the use of polycrystalline silicon thin film transistors. This technology is inherently low cost and yet capable to provide complex single-use microarrays.

1. Introduction

Metal-Oxide-Semiconductor Field-Effect Transistors or MOSFETs are the key component of silicon integrated circuits. Over the past three decades effort has been devoted to exploit the field effect mechanism in chemical and biological sensors, due to the potential of these devices to meet some of the most important needs in the field: to provide large arrays of sensors that are label-free, low-cost, disposable and can be easily integrated in portable instrumentation.

Most of this work concerned the development of the Ion-Sensitive Field-Effect Transistor (ISFET) for the detection of specific ions and analytes using appropriate ion-selective or enzymatic membranes. One of the advantages of the ISFET is that it operates in equilibrium conditions. Due to the presence of the insulating layer on top of the semiconductor, no current will flow across the biological layer.

More recently, field-effect devices have been investigated for the detection of DNA hybridization and protein interactions. It is expected that a full understanding of the mechanisms involved will result in optimal device designs and create a generic platform for the detection of any biomolecular interactions that produce a change in the charge distribution at the surface of a transistor gate.

The development of commercially viable FET biosensors depends on the selection of robust (bio)sensitive layers. Typically a membrane selective to a specific (bio)species is immobilized on top of the FET gate material. Reliable surface chemistries yielding reproducible and stable (bio)membranes are required. Since for each analyte a different recognition species is to be used, the immobilization process - either covalent, polymeric entrapment or other - needs to be optimized for every single application.

Of particular interest for FET-based chemical and biological sensors is the use of polycrystalline silicon thin film transistors. This is now a mature technology, employed in the fabrication of self-scanned transistor arrays with more than 100,000 elements for LCD and Organic Light Emitting Diode screens. Application of this technology to biosensors looks very promising, as it is inherently low cost and yet capable to provide integrated circuits of a complexity comparable to conventional microchips.

Electrical Engineering Division, University of Cambridge, Department of Engineering, 9 JJ Thomson Avenue, Cambridge CB3 0FA, United Kingdom. Fax: +44-1223-748348; Tel: +44-1223-748313; E-mail: pme22@cam.ac.uk

2. Field-Effect Devices

Potentiometric chemical sensors detect the electric potential which arises at the surface of a solid material when placed in contact with an electrolyte. Field-effect semiconductor devices can be used as potentiometric chemical and biological sensors. The basic structure is the Metal-Insulator-Semiconductor Field-Effect Transistor (MISFET). The operation of a MISFET is based on the creation of a thin conducting channel at the surface of a semiconductor (typically silicon). For example, a n-channel enhancement mode MISFET, consists of a p-type semiconductor layer with two n^+ injecting contacts (named source and drain), on top of which lies an insulating layer, such as silicon dioxide (gate dielectric) and a metal electrode (gate metal). When the voltage V_G applied to the metal gate (with respect to the source) is lower than the threshold voltage V_T, no current flows between source and drain. For $V_G > V_T$ inversion occurs, a n-type channel is created at the insulator/semiconductor interface (so-called inversion) and current can flow between source and drain. Due to the presence of the insulating layer, no current flows from the gate into the semiconductor.

It was found that if the metal gate is removed from the field-effect transistor (FET) and the gate dielectric placed in contact with a liquid, ions might be adsorbed on the surface, which leads to an effect similar to applying a voltage at the gate [1]. Thus, great interest has been generated regarding the possibility of using a well understood technology to produce amplifying devices that would respond to ions and molecules in solutions and gases. Selectivity can be induced in these sensors by the appropriate incorporation of certain pH-sensitive insulators or ion-selective membranes, enzymes, antibodies or antigens, DNA, or even whole tissue layers [2-8]. More recently, FETs with a metal gate functionalized with a biological recognition layer are also being developed.

2.1. Polycrystalline Silicon Thin Film Transistors

A thin film transistor (TFT) is a metal-insulator-semiconductor field-effect transistor fabricated on an

insulating substrate by employing entirely thin-film constituents. The total thickness of the transistor is normally less than 1 µm [9]. There are variations in TFT design, but the basic device structure is depicted in Figure 1a and consists of a semiconductor layer with two injecting contacts (source and drain), a gate dielectric, and a gate electrode.

Normally TFTs are operated like enhancement-mode MISFETs. A typical drain current I_D versus gate voltage characteristic is shown in Figure 1b. When the gate voltage V_{GS} (with respect to the source) is low, very little current flows between the source and drain because of the high resistance of the active layer. When the gate voltage is high, charge is induced near the oxide-semiconductor interface, and a conductive path (channel) is established between the source and drain. Hence the TFT operates as a switch, controlled by the gate voltage.

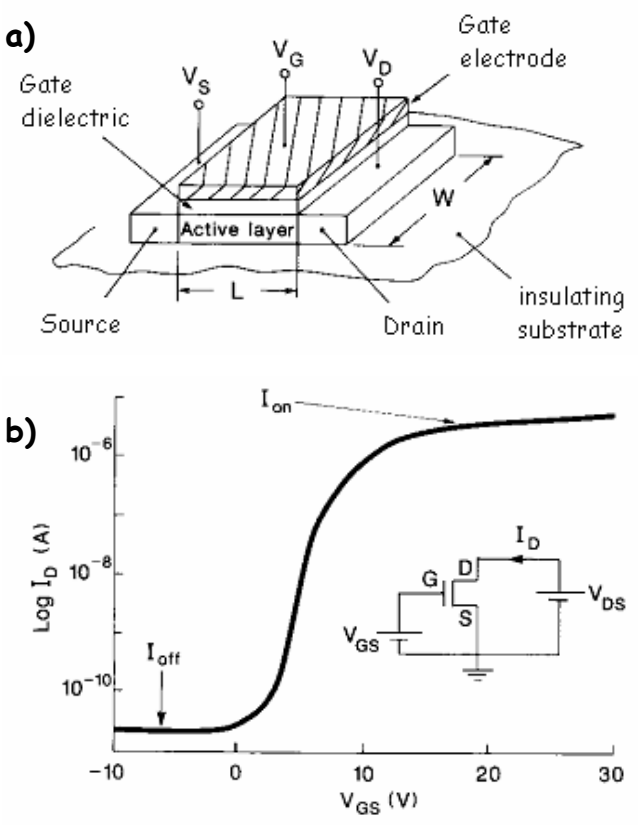

Fig. 1 - Schematic structure of a thin film transistor MISFET (a) and typical drain current versus gate-source voltage characteristics for fixed V_{DS} (b). The circuit elements are indicated in the inset.

Liquid-crystal displays (LCDs) normally employ a matrix of amorphous silicon (α-Si) TFTs to control the voltage applied to the individual pixels. However, the logic circuits driving the TFT matrix have to be made by conventional single crystal silicon microchips, since α-Si TFTs cannot provide logic drivers with the necessary speed, due to the low electron mobility (<1 $cm^2V^{-1}s^{-1}$).

To be able to monolithically integrate the logic drivers on the active matrix array plate has the great advantage of reducing the number of electrical connections between the array and the rest of the system, which is of particular relevance when compact construction is a premium to overcome space limitations. Polycrystalline silicon (poly-Si) TFTs have a much higher mobility (> 100 $cm^2V^{-1}s^{-1}$) than α-Si TFTs and can therefore be used to provide the drive logic as well as the pixel transistors [10]. The technology, now well developed, has been for long time applied in LCD displays for projectors and is now being used for mobile phones. Poly-Si TFTs have also been employed to make static random-access memories (SRAMs) and operational amplifiers. Poly-Si TFT circuits can be made on plastic substrates by using a transfer process [11].

The above properties make poly-Si TFTs a very interesting technology for the development of low cost, disposable, biosensors, with a large number of parallel channels. A micro-array of 100,000 channels, with integrated logic drivers, would require only a few tens of electrical connections to the rest of the system. These could be provided by edge connectors thereby enabling easy insertion and removal of the sensor array from the system and, therefore, single use of a complex microarray.

3. Ion-Sensitive Field Effect Transistors

The use of ion-sensitive field effect transistors (ISFETs) to measure pH and to sense a variety of ions is well known [5]. In these devices the gate insulator is in direct contact with the electrolyte solution. The high surface buffer capacity of the insulator, i.e. the ability of the insulator surface to deliver or take up protons, leads to an almost constant proton density at the surface, independent of the pH of the electrolyte. In order to equalize the free energy difference for protons at the interface and in the bulk of the solution, a pH-dependent potential drop across the double layer must arise. This results in modulation of the channel conductance. So the surface charge acts as a source or sink for protons, whereas the load of this source is the double-layer capacitance. The surface proton buffer capacity as well as the value of the double-layer capacity determine together the final value of the surface potential. The potential variation can then be related to the variation of pH of the bulk of the electrolyte. By using an ion-selective membrane on the gate dielectric, the device becomes sensitive to the presence of a particular ion in the solution.

Selective chemistry takes place at the surface of ion-selective electrodes producing an interfacial potential. Species recognition is achieved with a potentiometric chemical sensor through a chemical equilibrium reaction at the sensor surface. Therefore, the surface must contain a component which reacts chemically and reversibly with the analyte. This is achieved by using ion-selective membranes which make up the sensor surface. Some of the most common examples are PVC-based sensor membranes containing a reagent (ionophore) which selectively binds with the ion of interest. For example, the ionophore valinomycin has a cavity in its core where K^+ ions can be trapped through interactions with six ester carbonyl oxygen atoms. Polymer-based membranes have been used as the sensor surface for the detection of ions such as K^+, Ca^{2+}, NO_3^-, Na^+, Li^+, NH_4^+, Ba^{2+}, Mg^{2+}, Zn^{2+}, ClO_4^- or $FeCl_4^-$ [3].

Solid state crystalline membranes have been used for the sensing of F^-, Cl^-, S^{2+}, Br^-, I^-, CN^-, Ag^+, Cd^{2+} and Pb^{2+} [4]. Such membranes are typically ionic solids with low solubility product, which interact with their respective anions or cations.

By coating the gate insulator with enzymes as the selecting agent, highly selective sensors have been developed [6-7]. Such enzyme-modified ISFETs (EnFETs) can in principle be constructed with any enzyme that upon reaction with the analyte induces a local change of pH. When the enzymatic reaction takes place, the local change of pH is measured by the underlying ISFET. The signal can then be correlated to the concentration of analyte in the solution. EnFETs can give very sensitive measurements of different analytes. A wide range of enzymes have been used in conjunction with ISFETs, for example: the enzyme penicillinase for the detection of penicillin [12-14], urease for urea [15,16], glucose oxidase for glucose [17,18], creatinine deiminase for creatinine [19], lipase for triglycerides [20], organosphophate hydrolase for organophosphorus [21] and L-AA oxidase for L-amino acids [3].

The main disadvantage of EnFETs is that since the enzyme on the gate is not regenerated, the sensor can only measure the concentration of the analyte up to the limit when all of the enzyme is consumed. This will limit the concentration range detectable. However, different approaches can be used to incorporate on-chip mechanisms to recover the consumed enzyme either by the use of molecular mediators or electric fields [18]. For analytes where normal concentration ranges are relatively low, EnFETs are extremely useful.

ISFET biosensors are used in medical diagnostics, environmental monitoring and food quality control. One distinctive advantage of ISFETs is their suitability for miniaturization, since the signal to noise ratio is independent of the ISFET area. Therefore large multi-sensor arrays capable of detecting different species and simultaneously measuring relevant parameters (temperature, pH, etc) are possible. In all these applications cost and single-use, that is disposability, are paramount considerations.

3.1. Polysilicon TFT ISFETs

ISFETs have been fabricated on glass substrates, by using low-temperature poly-Si TFT technology [14]. An extended gate structure (EGFET) has been developed as described in Ref. 14, using Si_3N_4 as the pH sensitive area. Figure 2a shows the schematic structure of the extended gate ISFET. Si_3N_4 was deposited by plasma enhanced chemical vapour deposited (PE-CVD) on top of a tantalum extended gate. The extended gate structure facilitates the electrical and chemical isolation of the sensor, thereby increasing its stability and durability. In order to provide electrical and chemical isolation, the entire device area, except the sensitive Si_3N_4 pad, was passivated with a Si_3N_4(100 nm)/SiO_2(500 nm) layer. An external Ag/AgCl reference electrode was used.

The measured *I-V* curves are very stable and repeatable and show a rigid shift with the change of pH value. The voltage shift is proportional to the change in pH. Typical characteristics are shown in Figure 2b for a TFT with a pH sensitivity of 54 mV/pH at 300K, close to the ideal Nernstian response of 59 mV/pH [2]. In some cases a lower pH sensitivity, between 47 mV/pH and 54 mV/pH was observed. It is expected from the site-binding theory [22] that the state of the surface of the Si_3N_4 is critical for the pH sensing properties. Impurities, such as oxygen or other ions, which might exist at the Si_3N_4 surface [23] can result in a non-ideal sensitivity.

There is a temperature dependence of the ISFET characteristics. For a given current, the gate voltage shifts linearly with temperature with a coefficient of $\approx$11 mV/K. This temperature coefficient is consistent with the temperature dependence of poly-Si TFT *I-V* characteristics. This dependence is controlled by the gap density of states, which is fairly reproducible in a stable process. Therefore a reference TFT can be used as a temperature sensor and to provide the input for temperature compensation.

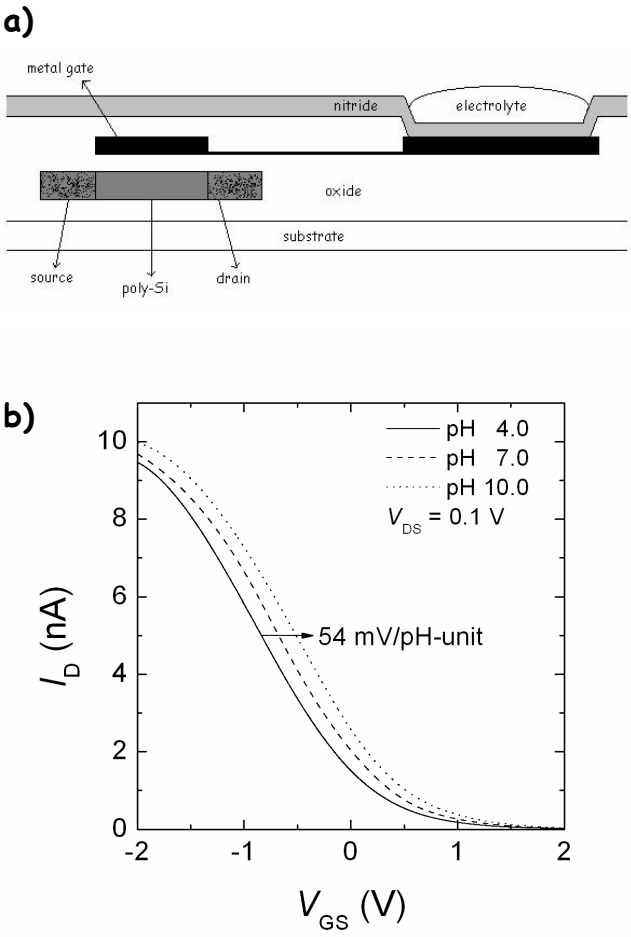

Fig. 2 - a) Schematic structure of the extended gate poly-Si TFT ISFET; b) I_D-V_{GS} curve for a p-type ISFET with transistor size W/L = 20 μm/6 μm measured with V_{DS} = 0.1 V in phosphate buffer with different pH values (from left to right: pH = 4.0, 7.0 and 10.0).

3.2. Polysilicon TFT EnFETs

A poly-Si TFT penicillin EnFET was developed by immobilizing the enzyme penicillinase on the Si_3N_4 gate

dielectric [14]. The functionalised ISFET detects the variation in H^+ concentration resulting from the catalysed hydrolysis of penicillin by penicillinase, which is dependent on the penicillin concentration in the solution. The *I-V* curves shift to negative voltages for increasing penicillin concentration as seen in Figure 3a. Figure 3b shows the voltage shift vs. penicillin G concentrations. The shift is linear with concentration until saturation is reached at about 7 mM. The sensitivity is 11 mV/mM. The enzyme penicillinase was physically adsorbed on the silicon nitride surface, which might account for a lower sensitivity than the ones reported in the literature using conventional FETs [12]. Higher sensitivities are usually expected when the enzyme is immobilized on the gate dielectric either covalently or via polymeric entrapment.

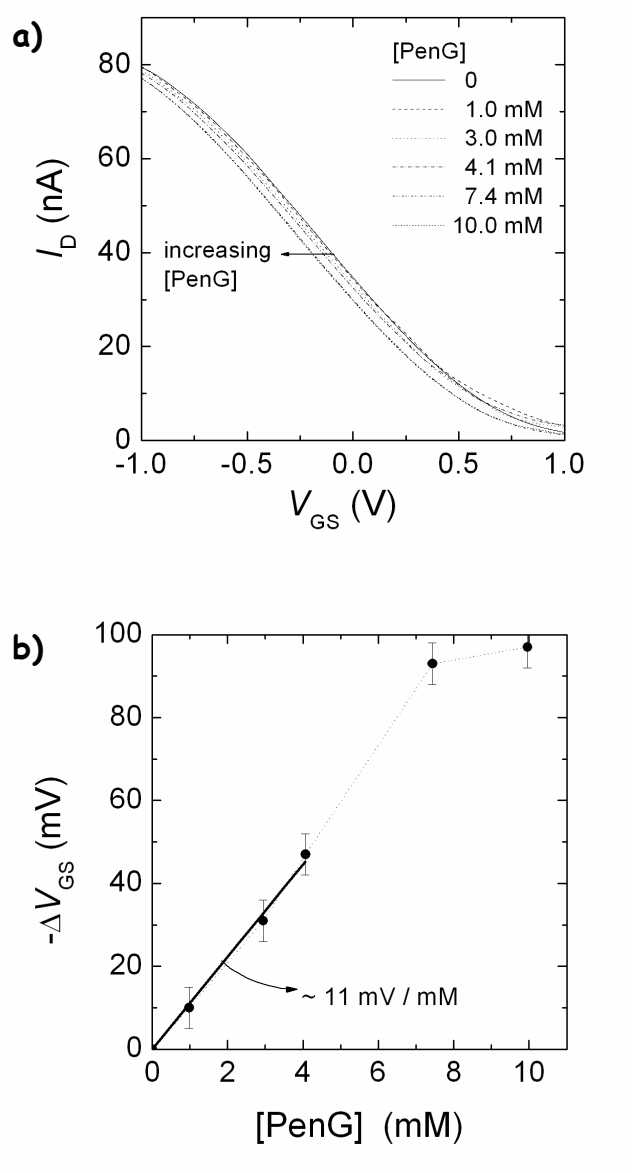

Fig. 3 - a) I_D-V_{GS} curves of a p-type EnFET with transistor size W/L = 100 µm/6 µm measured with V_{DS} = 0.1 V in a 5 mM phosphate buffer pH 7.0 obtained for different penicillin G concentrations; b) voltage shift dependence on penicillin concentration.

The development of a penicillin sensor using poly-Si TFTs shows that this technology can be used for the fabrication of other EnFETs. The development of multi-channel sensors based on arrays of poly-Si TFTs, where each channel has a different enzyme or ion-sensitive membrane, can have a significant impact in point-of-care diagnostics as well as in environmental or food monitoring. This technology, in view of the advanced level of development for mass production of poly-Si TFTs and the use of cheap substrates such as glass or plastics, shows great promise for application in single-use multi-analyte biosensors.

4. Field-effect DNA sensors

The detection of nucleic acids is of great scientific and economic importance. Applications include gene expression monitoring, pharmacogenomic research and drug discovery, clinical diagnostics, including infectious and genetic diseases, cancer diagnostics, viral and bacterial identification. It is also importantfor the detection of biowarfare and bioterrorism agents, for forensic and genetic identification. To exploit these opportunities, deoxyribose nucleic acid (DNA) biosensors are required that provide a combination of high sensitivity and selectivity, speed, low cost and portability.

One main problem with the detection of DNA at physiological levels, or for pathogen detection, is that the target is in the femtomolar or attomolar range. This requires that either the sample is amplified by polymerase chain reaction (PCR), a biochemical method to make copies of DNA, or the signal is amplified. The two basic goals of DNA sensors are to provide sufficient sensitivity to eliminate the need for PCR preamplification, which can be achieved through chemical and physical amplification, and to provide sufficient specificity for the detection of single base-pair mismatches.

A large number of transduction mechanisms have been proposed for DNA biosensors. These can be classified as: radiolabelled, optical, mass-sensitive or electrochemical transduction, and may or may not require labelling of the target DNA. Label-free techniques are of special interest since incorporation of a labelling step into a nucleic acid assay makes it more complex, cumbersome and expensive. However, a problem with label-free affinity biosensors is that there is no discrimination between specific and non-specific interactions. Other limitations of most current technologies include complex immobilization procedures and slow hybridization kinetics that require long incubation times. Details of the mentioned techniques may be found in many recent reviews [24-29].

The change in charge density in the biolayer upon hybridization of probe and target can also be exploited in field-effect sensing. Biologically sensitive FETs (BioFETs) can be constructed from ISFETs by coupling the gate with different biological recognition elements. A change in surface potential may be generated by a catalytic reaction product, surface polarization effects or the change in dipole moments occurring with bio-affinity reactions. It can be also due to potential changes arising from (bio)chemical processes in

living biological systems, such as the action potential of nerve cells [8].

The increase in negative charge in a layer of immobilized DNA probes upon hybridization with target oligonucleotides causes a change in the interface surface dipole χ_{int} and the electrochemical double-layer potential ψ_{dl}. If immobilization is on the gate of a FET, hybridization causes a shift in the flat-band potential V_{fb} of the semiconductor. This causes a shift in the current-voltage ($I-V$) characteristic of the FET [30-36]. Different theoretical models have been proposed in the literature to describe DNA sensing using FETs [37-39].

Field-effect DNA biosensors have been fabricated with very different approaches to immobilization strategies, hybridization, washing and measurement conditions. These have had varying levels of success, achieving different immobilization densities, hybridization efficiencies, amount of non-specific binding and stability. For a high sensitivity, a large voltage shift upon hybridization is needed. This requires a large increase in surface charge density upon hybridization, requiring a large surface density of probes that still allow high hybridization efficiency. To achieve a stable, high density probe layer resulting in efficient hybridization, end tethered covalent attachment is necessary. Many designs are based upon functionalization of the gate dielectric of an ISFET. However, since the pH selectivity of the gate oxide is not required, functionalization of a gate metal is an option which allows immobilization using thiol chemistry. This enables easy and reproducible fabrication of high density and highly stable mixed SAMs of thiolated oligonucleotides, using only a single biochemical step [40,41]. It also eliminates various problems that may occur using semiconductor or insulator surfaces, which are prone to uncontrolled modifications, contaminations or hydration. These may lead to a change in the intrinsic properties of the insulator, such as its dielectric constant, which are critical to the stable operation of FETs.

Polycrystalline silicon thin film transistors have also been employed for the detection of DNA hybridization [36]. A mixed self-assembled monolayer of thiolated mixed 18-base oligonucleotides and mercaptohexanol was immobilized onto the gold gate of a poly-Si TFT with an extended gate. As shown in Figure 4, a shift of the *I-V* characteristcs was obtained upon hybridization of the immobilized probe with a fully complementary strand. The shift is independent of electrode area, so microarrays can be constructed where a known DNA probe is immobilized on each FET. The inherent miniaturization and compatibility with microfabrication technologies makes the technique highly promising for the development of low-cost portable devices.

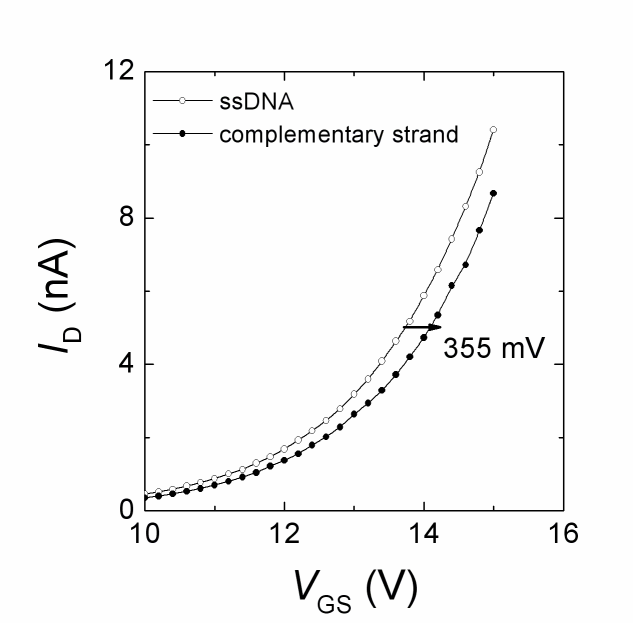

Fig. 4 - Drain current vs. gate voltage characteristics of an n-type poly-Si TFT with an extended Au gate. The figure shows the I_D-V_{GS} curves after immobilization of ssDNA and after hybridization with its complementary strand. The TFT size is W/L = 100 µm/10 µm, while the sensing pad area is 1000x1000 µm^2. The measurements were obtained with V_{DS} = 0.1 V in 5 mM PBS buffer pH 7.2 using a Ag/AgCl reference electrode.

5. Conclusions

ISFETs and enzyme-based FETs have been shown to provide sensitive detection of a wide range of analytes of interest for point-of-care diagnostics. The use of thin film transistor technology for the fabrication of FETs enables the development of low-cost disposable multi-channel sensors and microarrays. Of particular interest is the use of polycrystalline silicon TFT technology which enables the development of very large arrays with integrated logic drivers, suitable for the use with portable instrumentation.

Highly sensitive methods are required for DNA sensing. Although label-dependent methods achieve the highest sensitivities, label-free techniques are desirable in many applications. High selectivity is required to detect perfect match target DNA in solutions containing much higher concentrations of unmatched DNA and to discriminate between perfect match and mismatch sequences. In most methods the selectivity relies on the operating conditions of the assay. For example, sensitivity can be enhanced by the use of highly selective peptide nucleic acid (PNA) probes and highly stringent hybridization and measurement conditions such as high temperature or low salt concentration [42].

Miniaturization is a general trend in biosensors, and is especially important for DNA sensors where arrays with many different probe types are required. However, with most techniques, reducing the electrode surface area reduces the signal. Field-effect sensors offer many potential advantages, including a voltage shift independent of area, and a small size and weight, fast response, high reliability, low output impedance, and automated packaging at wafer level.

Field-effect DNA sensors have been reported in the literature. Very different values of voltage shifts upon hybridization have been observed. This demonstrates that immobilization, hybridization and washing protocols are crucial to success, and must be considered carefully. There are still insufficient experimental results or detailed theoretical models to fully understand the functioning of field-effect DNA sensors for the quantitation of the shift upon

hybridization, or to highlight the most important parameters in their optimization. Efforts devoted to the field-effect detection of proteins [8,43] or cells [8] are very encouraging. In the area of proteomics FETs can have a significant impact since present microarray technologies have limited applicability.

Recently, field-effect transistors using carbon nanotubes [44,45] and silicon nanowires [46] have been employed for the detection of biomolecular interactions. These technologies are not yet mature for the mass production of low-cost biosensors and multi-channel sensors. However they are expected to produce ultra-sensitive devices capable of detecting very small concentrations of sample, possibly down to the single-molecular level.

Poly-Si TFTs can be used as ISFETs, EnFETs and more generally as BioFETs. The technology is well established in the field of displays and can be easily adapted for the fabrication of self-scanning multi-channel biosensors. One of the main challenges is the development of reliable surface chemistries for the immobilization of the biolayers on the gate of the FETs. This entails the provision of reproducible enzymatic membranes, immobilized on the gate dielectric either covalently or via polymeric entrapment methods. The immobilized enzyme should retain its activity for a long period of time. The role of surface chemistry is equally, if not more critical in the use of FETs as DNA and protein sensors. Here the understanding of the microscopic mechanism controlling the device operation is still incomplete and more effort in both experiments and simulation is clearly necessary.

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